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Original Research Article

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Preparation of Antibiotics-containing Electrospinning Chitosan/Gelatin Nanofibers

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Abstract: The electrospun nanofibers-based systems have opened new windows on drug delivery systems. Antibiotic treatment and drug resistance in infectious disease management have introduced some potential applications of using electrospun nanofibers. In this respect, chitosan/gelatin nanofibers can be considered a reliable source for drug delivery. This study aimed to synthesize antibiotics-containing electrospinning chitosan/gelatin nanofibers. To this end, electrospinning was performed using different concentrations of chitosan and gelatin, followed by adding ceftriaxone to the corresponding solutions. Afterward, nanofibers were crosslinked through ceftriaxone loading. The nanofiber was characterized in terms of its morphology via scanning electron microscopy (SEM) analyses. In addition, spectrophotometrical analysis was performed to examine the amount of released ceftriaxone at 280 nm wavelength. Eventually, SPSS version 21 was used to perform statistical analyses. Based on the obtained results, the mean Gelatin diameters before and after crosslinking were 154.5±286 and 162.3±27, respectively; the mean Chitosan/gelatin (95:5) diameters before and after crosslinking were 192±25 and 208±11.6 respectively. Finally, the mean Chitosan/gelatin (80:20) diameters before and after crosslinking were 188.2±34.7 and 212.1±54.8, respectively. Overall, the obtained results indicate that the fiber diameters increase after crosslinking and by adding chitosan. This increase can be attributed to polymer chain entanglement in the gelatin chain reaction with glutaraldehyde's aldehyde group. In addition, despite the short drug release time (i.e., 240 min). In general, chitosan lowered the drug release rate in comparison to gelatin nanofibrous. In conclusion, the fiber diameters rise with adding chitosan, followed by its glutaraldehyde crosslinking. The nanofibers showed a considerably higher drug release compared to polymeric films. Nevertheless, gelatin nanofibers such as chitosan decline the ceftriaxone release rate compared to gelatin nanofibers. Furthermore, prolonging the buffer solution immersion time enhances the drug release percentage.
Keywords: Electrospinning; Chitosan/Gelatin nanofibers; Antibiotics; Ceftriaxone; Drug delivery

1. Introduction

Recently, a growing interest has been witnessed in applications of polymeric nanofibers synthesized using electrospinning. These nanofibers show great properties, including high porosity with perfect interconnected pores, a large surface-to-volume ratio, and great mechanical features. Accordingly, they are a suitable option for multiple usages in various field[1-3].

Electrospinning has been the subject of intense interest in nanofiber studies. This technique offers a straightforward and powerful mean to synthesize nonwoven fibrous substances with beneficial properties. For instance, they have a fine diameter, large surface area for each unit of mass, small interfibrous pore diameter, high porosity, and high gas permeability[4,5]. Typically, an electrospinning design consists of a polymer solution reservoir with a metallic capillary attached to a metallic collector with high voltage. Charges accumulated on the surface destabilize the droplet's hemispherical geometry at the tip of a needle[6-8]. At critical voltages, the droplet's surface tension is overweighed by the electric forces, thereby producing a jet of ultra-fine fibers from the Taylor cone's tip. Gelatin (polyelectrolyte) is a polypeptide with a high molecular weight synthesized through the collagen's controlled hydrolysis[9-11]. Gelatin's primary amino acids include glycine (30%) and proline/hydroxyproline (25%). Gelatin is an efficient particle-forming material and a good film with numerous applications in medicine. For example, it can be used in controlled drug delivery, wound dressing, plasma expanders, and adhesives[12-14].

To date, numerous attempts have been made to prepare polysaccharides nanofibers regarding their high availability in nature, low cost, and several industrial applications (e.g., novel scaffolding and separating materials for tissue cultures. Chitosan (generated through chitin's alkaline N-deacetylation) is a poly-aminosaccharide and among the cationic polyelectrolyte natural functional biopolymer in which the structural unit of 2-acetomido-2-deoxy-b-D-glucose is repeated. This poly-aminosaccharide has interesting properties, including hydrophilicity, biocompatibility, nonantigenicity, nontoxicity, and bioactivity. Besides, it produces natural metabolites as its degradation products[15-17].

The electrospun nanofiber-based materials have opened new windows on drug delivery. So far, some therapeutic agents have been used to electrospun fibers. For instance, some biological materials (e.g., proteins, antibiotics, growth factors, RNA, living cells, and DNA) and fine molecular drugs have been used for this purpose[18-20]. These materials are incorporated through surface modification post-electrospinning or encapsulation during electrospinning (e.g, emulsion electrospinning, coaxial electrospinning, and blended electrospinning). The electrospun nanofiber scaffolds provide efficient structures for different modes of drug delivery, including transdermal, topical drug, and oral[21-23]. In addition, short nanofibers/fragments are great candidates for local injection into diseased sites with the minimum degree of invasion. Furthermore, electrospun nanofibers provide excellent benefits in drug release rate control via changing the composition (e.g., hydrophilic and hydrophobic substances), microstructure (e.g., multilayered, homogenous, and core-sheath structures), or macrostructure (such as stacked meshes)[24-27]. In recent years, the emergence of stimuli-responsive nanofibers has offered new techniques for controlled drug release and delivery spatially and temporally.

Electrospun scaffolds loaded with antibiotic nanoparticles may provide multiple benefits as they allow antibiotics' sustained and controlled release at effective concentrations locally. In addition, they can actively prevent biofilm formation and infection during healing and after implantation. Adding antibacterial agents to electrospun scaffolds may prevent infection during wound healing Moreover, the agent's controlled and sustained release can prevent implant rejection caused by minimized stress in the microenvironment. Release kinetics control of biomolecules and drugs from the electrospun fibers is essential in regenerative tissue engineering[28-30]. Antimicrobial agents are incorporated by several techniques in electrospun fibers during electrospinning. For instance, coaxial electrospinning, blending, and emulsion electrospinning are used for the agent's controlled release. These methods lead to the antibiotic's encapsulation in the electrospun fibers, whose release is a function of polymeric nanofibers degradation. These strategies use a fast degrading polymer to reach the antibiotic's sustained release[31-33].

Cephalosporins are a group of beta-lactam

antibiotics for cell wall synthesis that inhibit a broad spectrum of pathogens. These antibiotics are typically used to treat common microbial infections, including skin and soft tissue infections, pneumonia, meningitis, and bacteremia. Today, resistance to third-generation cephalosporins poses substantial pressure on the health systems worldwide. Also, resistant microbial strains show multidrug resistance. Consequently, they pose serious challenges in the treatment of infectious diseases. Hence, looking for more efficient delivery modalities and materials is necessary[34-36]. Ceftriaxone was first introduced in 1982 to treat severe infections or those induced by multi-drug-resistant strains. Since its launch, ceftriaxone has been a frequently used antibiotic because of its high antibacterial performance, wide activity spectrum, and minimum toxicity. This antibiotic is considered for respiratory bacterial infections (e.g., bronchitis) and bacterial infections in the urinary tract, abdomen, and the bone[37-39]. This study aimed to prepare antibiotics-containing chitosan/gelatin nanofibers through electrospinning.

2. Material and Methods

2.1 Materials

Gelatin was bought from Merck (Germany). Chitosan (M = 1000 g/mol and deacetylation degree of 85%) was bought from Qingdao Baicheng Biochemical Corp (China). Also, fetal bovine serum (FBS), DMEM culture medium, ceftriaxone sodium, and phosphate-buffered saline (PBS) were supplied from the Chinese Pharmaceutical and Biological Test. Finally, the aqueous glutaraldehyde solution and formic and acetic acids were obtained from Merck (Germany).

2.2 Electrospinning solutions preparation

Gelatin (GEL) was dissolved in 10% and 33% of formic acid. In addition, chitosan (chitosan) was dissolved in 45% acetic acid solution and mixed. Afterward, electrospinning was performed at different concentrations of chitosan and gelatin at flow chitosan/gelatin ratios of 100:0, 95:5, and 80:20. Eventually, the ceftriaxone was added to the solutions and held at room temperature.

2.3 Electrospinning methods

The solutions were separately put in a plastic syringe (10 mL), put in a syringe pump, and injected through a plastic needle attached to a high voltage supply (20 kV) with a needle-to-collector distance of 85 mm. The solution's flow rate and relative humidity (RH) were 4 $mL.h^{-1}$ and 55%, respectively, at room temperature. The collector had a horizontal board that was covered with aluminum foil. In the end, the obtained ceftriaxone-contained electrospun nanofibers were crosslinked in glutaraldehyde vapor for 120 min.

2.4 Microscopy

Scanning electron microscopy (SEM) was performed to visualize the nanofiber's morphology at an accelerating voltage of 20 kV after gold coating for 250 s using a sputter coater.

2.5 Drug release evaluation

Ceftriaxone from chitosan-G was released at a pH of 7.4 conditioned medium to simulate the blood pH. The amount of the released ceftriaxone was analyzed via the spectrophotometric modality at a wavelength of 280 nm.

2.6 Statistical analysis

Statistical analyses were performed using SPSS version 21 at a significance level of $p \leqslant 0.05$.

3. Results

3.1 Morphology of nanofibers

According to the obtained results, the randomly oriented ceftriaxone-loaded gelatin and gelatin/chitosan nanofibers had smooth surfaces with no beads (**Figure 1**). The mean gelatin diameters before and after crosslinking were 154.5±286 and 162.3±27, respectively. Also, the mean chitosan/gelatin (95:5) diameters before and after crosslinking were 192±25 and 208±11.6, respectively. Finally, the mean chitosan/gelatin (80:20) diameters before and after crosslinking were 188.2±34.7 and 212.1±54.8, respectively. These results suggest that the fiber diameters increase with chitosan incorporation and also after crosslinking. This diameter increase can be attributed to the polymer chains entanglement and gelatin chains reaction with glutaraldehyde's aldehyde group (**Figure 2**).

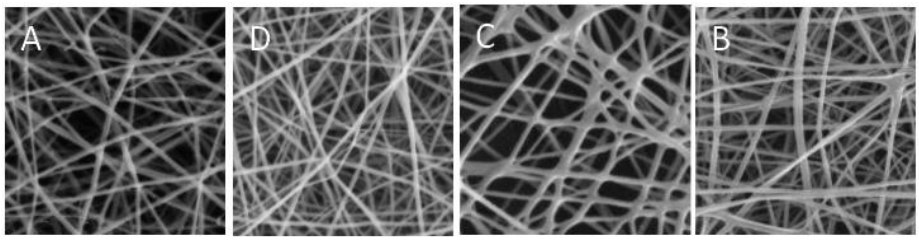

Figure 1. ceftriaxone-loaded gelatin and gelatin/chitosan nanofibers before and after crosslinking. A: ceftriaxone-loaded gelatin before crosslinking; B: ceftriaxone-loaded gelatin after crosslinking; C: gelatin chitosannanofibers before crosslinking; D: gelatin chitosannanofibers after crosslinking.

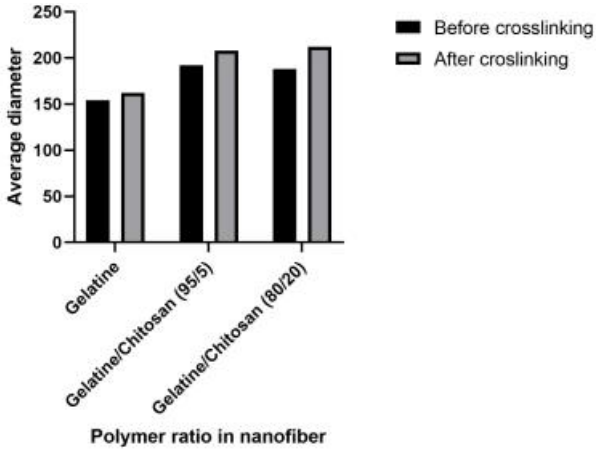

Figure 2. The average of fiber diameters

3.2 Results of drug release

Drug release from nanofibrous mats increased by prolonging the immersion time in buffer solution. In comparison, drug release from gelatin nanofibrous mats declined by adding chitosan to the soliton, particularly when it is immersed in buffer solution for 240 min. A sudden release was noticed in the release profile of gelatin nanofibrous mats loaded with ceftriaxone. It is inferred that chitosan lowers the drug release rate As can be seen in the **figure 3**, a slower drug release rate occurs in comparison to the nanofibrous mats. Also, drug release is slower because of the greater surface-to-volume ratio of nanofibers to films. Despite the short time of drug release (i.e., 240 min), chitosan's effect is well demonstrated on drug release from chitosan/gelatin nanofibrous mats. Generally, chitosan lowers the drug release rate compared to gelatin nanofibrous mats (**Figure 3**).

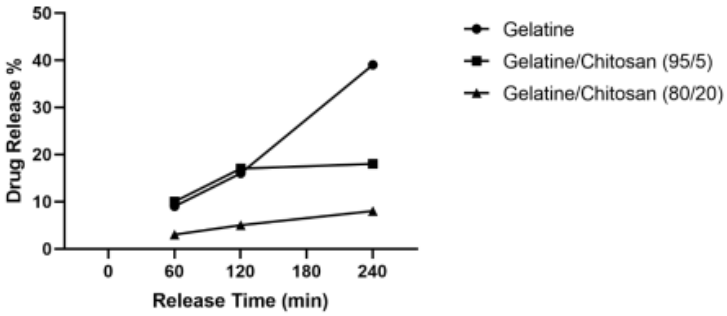

Figure 3. Drug release from nanofiber

4. Discussion

Antibiotics delivery directly to the site of infection instead of applying an oral dosage is more advantageous. The explanation is that the oral

ingested dosage distributes at the infection site and non-specifically around the body. the term non-specificity means that a high dosage must be used to ensure concentration sufficiency at the infection site for an effective treatment. When directly delivered to the site of infection, the dosage can be reduced, thereby lowering complications and side effects. Despite lowering the dosage compared to the oral dosage, the concentration of antibiotics loaded in the infection site may still be higher[40-42]. Accordingly, the bacteria do not sustain and induce bacterial resistance problems. The antibiotics can be delivered to a specific site by immobilizing the antibiotics on a scaffold. To this end, they are embedded into a fibrous mesh synthesized through the electrospinning approach[43,44]. Electrospinning has received intense interest in the biomedical community because of its promising results in countless applications such as drug delivery, antibiotic coating, and wound management. In the electrospinning technique, a polymer dissolved in a volatile solvent is put in a syringe[45,46]. Afterward, a high voltage is applied between the collector plate and the needle attached to the syringe.

Nanocomposite nanofibrous matrices produced by electrospinning and containing nanoscale polymer matrix and inorganic fillers enjoy the benefits of both the inorganic materials (e.g., chemical resistance, high strength, and thermal stability) and the polymer materials (e..g, good moldability, flexibility, and low weight)[47,48]. Therefore, these composite nanofibers may offer improved magnetic, optical, mechanical, electrical, and thermal properties without transparency loss. Furthermore, they can be used in several multifunctional applications such as filtration, membranes, storage systems, textile coating, energy conversion, and catalysis. Furthermore, they can be used in biomedical applications, including tissue engineering scaffolds, drug delivery, and wound healing[49-51].

Electrospinning is widely used in synthesizing polymers reinforced with various nanofillers and nanofiber made of one polymer and blended polymers. Nanofiller reinforcements improve the properties of the produced electrospun nanofibers, including their electrical and mechanical properties, porosity, and antibacterial activity[52,53]. Nanofillers can be carbon-based materials (such as cellulose nanocrystals, carbon nanotubes, and graphene nanosheets) or metals and metal oxides (such as titanium dioxide and silver nanoparticles). Graphene is a two-dimensional (2D) conformational crystalline structure with one-atom-layer thickness. This nanofiller is a biocompatible matter in multiple biomedical applications, including biosensors, imaging, and drug delivery. Also, it shows antimicrobial activity against Escherichia coli[54,55]. Chitosan, as the second most abundant polysaccharide, is generated via chitin's partial deacetylation in the presence of either deacetylase enzyme or NaOH. This natural polymer shows promising results in biomedical applications regarding its good biodegradability, high biocompatibility, antimicrobial activities, and high swellability[56,57].

As another natural FDA-approved polymer, gelatin has high biodegradability, biocompatibility, hydrophilicity, low antigenicity, irritability, and immunogenicity. Besides, it does not have any toxicity or carcinogenicity. Gelatin is generated via collagen's acid or alkaline hydrolysis. Due to many functional groups on the surface of gelatin, it can easily be crosslinked to other molecules or ligands or modified chemically. Subsequently, it increases cell proliferation and fluid diffusion within its structure[58,59]. Previous research has shown that combining gelatin and chitosan leads to the formation of a composite matter with promising features for biomedical engineering applications. The excellent properties of this material are primarily owing to the electrostatic interactions between the positive moieties on the chitosan surface and the negative functionalities on the gelatin surface. These features prevent chitosan's interaction with the negative moieties existing on the surface of the cellular membrane. Hence, the cellular migration capacity increases on the biomaterial surface. Besides, hydrophilic gelatin enhances the hydrophilicity of chitosan-containing materials, thereby increasing the cell adhesion and spread on the surface of fabricated matters[60-62]. The increasing emergence and spread of drug resistance to antimicrobial agents pose serious threats to the global health system, alarming the hazard of surrendering to bacterial infections and entering an era of post-antibiotic. Many studies are underway on antimicrobial resistance (AMR) contaminants worldwide regarding these tremendous threats. In this respect, nanotechnology, particularly nanostructures

with antimicrobial capability, has emerged as a new possibility to combat infectious multidrug-resistant organisms (MDRs)[63-65].

In this respect, debates are hot on using nanomaterials to control microbial resistance or conducting further fundamental studies on detecting the molecular processes that lead to nanomaterials' antimicrobial activity. Current developments in using nanotechnology in medical fields indicate new hopes for new drug formulations applying different distinctive properties of nanomaterials, including their intrinsic antimicrobial activity, size, and shape. In this regard, nanoparticles may provide reliable solutions by acting as carrier systems for antimicrobial compounds or directly detecting the bacteria[66-68].

Several nanomaterials are already used in a wide spectrum of antimicrobial agents. In this respect, nanoengineered systems provide superior and advanced methodologies to deal with antibiotic drug therapy restrictions and combat different drug resistance mechanisms. Apart from their antimicrobial activities, nanostructures may effectively detect antimicrobial drugs, control drug resistance processes, interfere with plasmid curing and quorum sensing, and prevent the formation of biofilm or other vital processes. Notwithstanding, the practical use of various nanocarriers is restrained, although an increased real-world demand is witnessed due to incomplete biodegradability, insufficient biocompatibility, and lower sensitivity to pH and temperature.

In the present research, physiochemical and antibiotic characteristics of gelatin/chitosan nanofibers were investigated. The results indicate an increase in fiber diameters increase with adding chitosan and also after crosslinking because of the polymer chains entanglement and gelatin chains reaction with glutaraldehyde's aldehyde group. Moreover, the results showed that the drug release percentage from nanofibrous mats enhances by prolonging the immersion time in buffer solution. Nevertheless, drug release from these mats declined after adding chitosan to the system, particularly when immersing for 240 min in a buffer solution. The release profile of ceftriaxone from gelatin/chitosan and gelatin films represents a slower drug release rate in comparison to the nanofibrous mats and much more drug release thanks to the considerably higher surface-to-volume ratio of nanofibers to films. Despite the short drug release time (240 min), the chitosan's effect on drug release from chitosan/gelatin nanofibrous mats was demonstrated effectively. Accordingly, the drug release rate decreased compared to gelatin nanofibrous mats.

Conducting these experiments on ceftriaxone, Behbood *et al.*[69] indicated that the proposed system is suitable to shorten the Van infusion time and boost Van blood concentration, thereby increasing patient compliance and bio-availability. Elsewhere, Özkahraman *et al.*[70] examined the suitability of nanofibers for hyaluronic acid and verified the compatibility of chitosan-G/HA-NPs hydrogels to control drug delivery systems. These results are consistent with those of us, suggesting that conducting similar studies is useful in reaching more reliable results in employing nanotechnology in drug release, especially in antibiotics delivery. Overall, our results revealed that the fiber diameters increase by adding chitosan and followed by crosslinking by glutaraldehyde. Nanofibers showed a considerably higher drug release percentage compared to polymeric films. However, gelatin nanofibers, including chitosan, lower the ceftriaxone release compared to gelatin nanofibers. Finally, prolonging the immersion time in buffer solution enhances the drug release.

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