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Chapter 2

Gelatin and Collagen Nanofiber Scaffolds for Tissue Engineering

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Abstract

One of the main complications that can present a person with second and third degree burns is the possibility of being infected by opportunistic bacteria or viruses that are present in the environment. Nowadays, the majority of the burn injuries are treated with conventional gauze, which involves a high probability of infection and pain for the patient being treated with this method. In order to obtain low-cost scaffolds, natural and abundant polymers were used such as gelatin (GEL) and collagen (COL). The GEL functions as a base scaffold, stable and flexible, and also biocompatible because it is a byproduct of the partial hydrolysis of COL, which is an indispensable component for the stability of the cell membrane and it is present in great extent in the human epithelium.

Keywords: cutaneous dressings, polymer, gelatin, collagen, bioactivity

1. Introduction

Electrospinning technique is used for the production of fibers at nanometer scale, which has been used previously for the production of cutaneous dressings and a great variety of scaffolds with biomedical interest. It consists of the injection of a polymer solution properly homogenized in a polar solvent, in order to obtain a conductive material; by applying a current of the order of kilovolts (kV), it allows the solution to form a Taylor cone, which permits the formation of fibers. Another widely used technique is the electrospray that starts from the same principle of electrospinning but through a solution that allows the formation of suspended nanoparticles in the solvent, so that they are deposited on the collector (**Figure 1**) [1].

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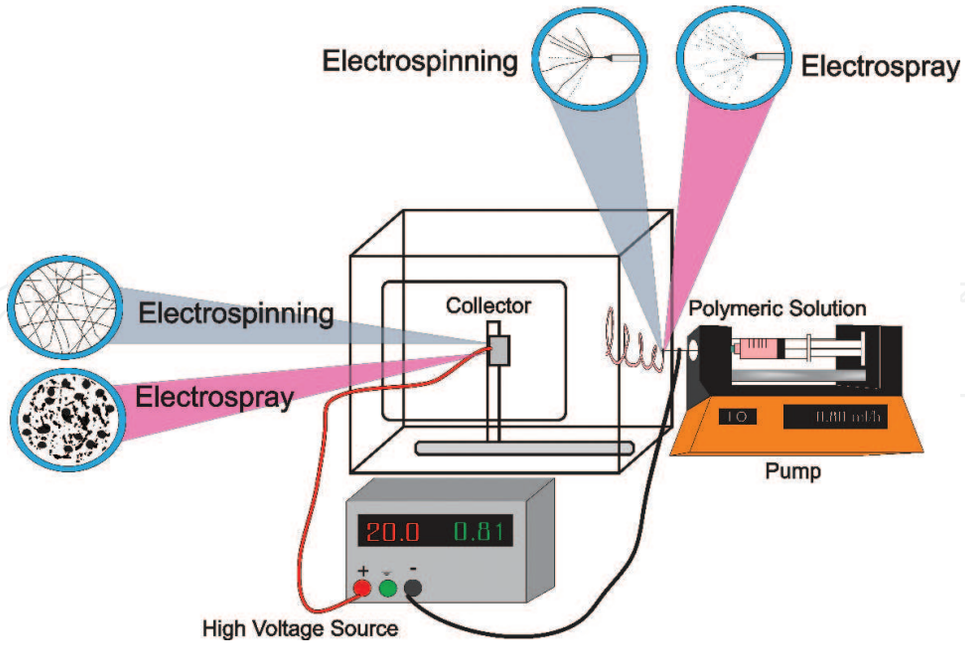


Figure 1. Electrospinning/electrospray scheme with polymer solutions.

Generally, the polymers used in electrospinning for biomedical applications are biodegradable and biocompatible; thus, they can be in contact with physiological medium without generating undesired reactions. Among them is GEL, which is a natural polymer obtained from collagen (COL) which is a protein obtained from the connective tissue of animals when boiled in water, GEL is a very useful polymer in electrospinning because of its ability to produce fibers of nanometric scale independently of the changes in the temperature and humidity of the environment, for this reason it was used as a base for the formation of bioactive electrospun [2].

Electrospinning has recently been extensively studied; it is a well-known technique for the manufacture of nanoscale fibers because of its various advantages such as high surface-volume ratio, adjustable porosity, and ease of surface functionalization. The resulting fibers are extremely useful for applications in the fields of tissue engineering, drug delivery, and wound dressing. In addition to the morphological, physical, and chemical properties, electrospun scaffolds are often evaluated through various cell studies. Researchers have adopted approaches such as surface modification and drug loading to improve scaffold ownership and function [3].

The electrospinning technique has been used as an efficient and accessible method for the manufacture of nanofibers with a wide variety of applications in the fields of pharmaceutics and medicine. Among the most outstanding applications, we can see wound dressings, drug delivery systems, or tissue engineering scaffolds [4]. Animal polysaccharides such as chitosan, hyaluronic acid, heparin, and collagen have been studied with this technique; these compounds are natural biopolymers with numerous advantages for biomedical applications such as biocompatibility, biodegradability, nonantigenicity, and nontoxicity [5].

2. Gelatin electrospun scaffolds

GEL nanofibers have been prepared using an electrospinning process in previous studies. To improve water-resistant capacity and thermomechanical performance for potential biomedical applications, GEL nanofibers were cross-linked with glutaraldehyde-saturated steam at room temperature. Exposure of this nanofibrous material to the glutaraldehyde vapor was performed for 3 days to provide sufficient cross-linking to preserve the fibrous morphology assayed by immersion at 37°C warm water. On the other hand, cross-linking also led to improved thermostability and substantial improvement in mechanical properties. The denaturation temperature corresponding to the transition from the helix to the coiled structure of the air-dried samples increased by about 11°C and the tensile strength and modulus were nearly 10 times greater than those of the electrospun GEL fibers. In addition, cytotoxicity was evaluated based on a cell proliferation study by culturing human dermal fibroblasts on the fibrous scaffolds of cross-linked GEL for 1, 3, 5, and 7 days. It was found that cell growth occurred and increased almost linearly over the course of the entire cell culture period. Initial inhibition of cell growth on the cross-linked fibrous substrate of GEL suggested some cytotoxic effect of residual glutaraldehyde on cells [6].

The GEL was successfully electrospun using a solvent based on ethyl acetate, acetic acid, and water. Since natural polymers including GEL have limited solubility in water, toxic or highly acidic solvents are usually used to dissolve them for electrospinning. Instead of using such solvents, ethyl acetate was used with acetic acid in water; the beneficial effect of its use was investigated in terms of the spinning capacity of the nanofiber and the acidity of the solvent. It was found that the substitution of acetic acid with ethyl acetate improved the spinning capacity of the nanofiber by reducing the surface tension of the solution, as well as increasing the pH of the solvent significantly. The optimum composition of the co-solvent was found to correspond to a ratio of ethyl acetate to acetic acid in a ratio of 2:3. Under this solvent condition, the GEL could be dissolved at concentrations up to 11% by weight and successfully electrospun to produce nanofibers of various diameters (47–145 nm on average) depending on the GEL concentration. The water-based co-solvent method proposed herein may be useful for generating other natural nanofibrous polymers, as well as being applicable in delivery systems for bioactive molecules within the nanofiber matrices [7].

In another study, electrospinning was performed in aqueous GEL solution, increasing the spinning temperature. To improve stability and mechanical properties in the wet state, the GEL nanofibrous membrane is chemically reticulated by 1-ethyl-3-dimethylaminopropylcarbodiimide hydrochloride and N-hydroxyl succinimide. The crosslinker concentration was optimized by measuring the degree of swelling and weight loss. The nanofibrous structure of the membrane was maintained after lyophilization, although the fibers were crimped and conglutinated. The tensile test revealed that the hydrated membrane becomes flexible and provides predetermined mechanical properties [8].

It can be said that electrospinning has been one of the simplest, most versatile, and promising processes for producing continuous nanofibers. In the case of GEL, this polymer has been

widely used in food for the purpose of thickening and stabilization. At nanometer scale, electrospun nickel/GEL nanofibers can be used in food for the same purpose in smaller quantities that give more results that are efficient. A study investigated the influence of the parameters that affected during electrospinning on the properties of the electrospun GEL. GEL concentrations of 7 and 20% (w/v) were electrospun under 28 or 35 kV applied voltage. The feed rate was 1 or 0.1 ml/h. Before electrospinning, the electrical conductivity, surface tension, and rheological properties of the feed solutions were determined. Morphological analysis showed that only the 20% GEL solution produced nanofibers. The electrical conductivity, surface tension, consistency index, and flowability of the 20% GEL solution were 4.77 mS/cm, 34.91 mN/m, 1.37 Pa, and 0.93 sn, respectively. The range of diameters of nanofibers increased with the applied voltage. The zeta potential and diffusion coefficients of dispersions containing the GEL and the electrospun GEL were determined. Both values were higher for dispersions containing electrospun GEL than for dispersions with GEL at the same concentration. The zeta potential and diffusion coefficient values of dispersion coefficients containing electrospun GEL decreased as the voltage applied during the electrospinning increased. The applied low voltage resulted in higher values of the diffusion coefficient and zeta potentials for dispersions containing electrospun GEL nanofibers, which may indicate that these nanofibers can be used for the stabilization of food emulsions, as compared to the smooth nanofiber morphology without pearl formation obtained at the highest stress [9].

On the other hand, electrospinning is a very useful technique for producing polymeric nanofibers by the application of electrostatic forces. It has been reported that the modeling and optimization of the GEL/chitosan electrospinning process have been achieved, where the interaction effects of the GEL/chitosan blend ratio (50/50, 60/40, and 70/30) were investigated, the applied voltage (20, 25, and 30 kV), and the feed rate (0.2, 0.4, and 0.6 ml /h) on the optical fiber diameter and the standard deviation of the fiber diameter by scanning electron microscopy. To manufacture the GEL/chitosan nanofibers mixture, trifluoroacetic acid/dichloromethane was selected as the solvent system. The model obtained for the hinge diameter has a quadratic relation with the applied voltage and the feed rate. The interaction between the applied voltage and the flow rate was found to be significant, but the interactions of the mixing ratio and the flow and the mixing ratio and the applied voltage were insignificant. Scanning electron micrographs of human dermal fibroblast cells in the structure of gel/chitosan nanofibers show coupling and proliferation on the surface of fabricated scaffolds. These microfibers have great potential to be used as scaffolding for the engineering of cutaneous tissues [10].

In another study, poly (lactic-co-glycolic acid) (PLGA) and PLGA/GEL nanofibrous sheet materials embedded with mesoporous silica nanoparticles were fabricated using an electrospinning method. The mean diameters of the nanofibers were 641 ± 24 nm for pure PLGA scaffolds versus 418 ± 85 and 267 ± 58 nm for PLGA scaffolds/silica nanoparticles at 10% w/w PLGA/GEL silica nanoparticles to 10% w/w, respectively. The results of the contact angle measurement (102°± 6.7 for the pure PLGA scaffold versus 81 ± 6.8 and 18 ± 8.7 for PLGA/silica nanoparticles and the PLGA/GEL scaffolds/silica nanoparticles revealed improved hydrophobicity of scaffolds by the incorporation of GEL and silica nanoparticles. In addition, the incorporation of scaffolds with silica nanoparticles resulted in better tensile mechanical properties. The culture of PC12 cells in the scaffolds showed the

introduction of silica nanoparticles into the matrices. The DAPI staining results indicated that cell proliferations in the PLGA/silica and PLGA/GEL/silica nanoparticle matrices were surprising (almost 2.5%), and the proliferation of PLGA and PLGA/GEL leads to improved cell attachment and proliferation (three times, respectively) higher than in pure aligned PLGA scaffolds. These results suggest superior properties of mesoporous silica nanoparticles incorporated into electrospun PLGA/GEL scaffolds for stem cell culture and tissue engineering applications [11].

On the other hand, we studied the mass production of GEL nanofibers by spiral electrospinning and investigated the performance of different cross-linking methods such as glutaraldehyde vapor and liquid phase cross-linking. Compared with conventional single-needle electrospinning, spiral electrospinning nanofibers were finer, where an increase of more than 1000 times over the productivity of traditionally obtained nanofibers was obtained. Mechanical tests showed that the tensile strength of nanofiber membranes increased from 1.33 to 2.60 MPa after cross-linking of glutaraldehyde vapor and from 1.33 to 5.08 MPa after liquid phase cross-linking. In addition, the SEM and FTIR analysis indicated that the membrane of nanofibers obtained by liquid phase cross-linking presented better properties, resulting in an ideal material for wound dressing applications [12].

A study where GEL scaffolds were prepared by electrospinning using aqueous acetic acid and thermally cross-linked with glucose showed the effect of the amount of glucose used as the cross-linking agent on the mechanical properties of the GEL fibers, and it was found that cross-linking with glucose increases the elastic modulus of GEL fibers from 0.3 GPa to 0% glucose content at 1.1 GPa with 15% glucose. This makes fibrous GEL scaffolds cross-linked by glucose, a promising material for biomedical applications [13].

In another study, GEL nanofibers were prepared from ternary mixtures of GEL/acetic acid/water with the aim of studying the feasibility of making GEL nanofiber membranes at room temperature using an alternative benign solvent by significantly reducing the concentration of acetic acid. The results showed that GEL nanofibers can be optimally electrospun with a low concentration of acetic acid (25%, v/v) combined with GEL concentrations above 300 mg/ml. GEL mats made from low acetic acid solutions had some advantages such as maintaining the decomposition temperature of the pure GEL (230°C) and the reduction of the acid content in the electrospun mats, which allowed a cellular viability of more than 90% [14].

The manufacture of fibroin nanofibers/silica GEL loaded with ceftazidime without the loss of structure and bioactivity of the drug was demonstrated using the electrospinning method. The results show that the average diameter of the drug-loaded nanofibers at the optimum ratio of polymer to drug [10, 1] was 276.55 ± 35.8 nm, while increasing the feed ratio to 1:1 increased the mean diameter at 825.02 ± 70.3 nm. In FTIR analysis of drug loaded on the nanofibers revealed that the drug ceftazidime was successfully encapsulated in the nanofibers while the feasibility study approved the cytocompatibility of the system. The drug was released from the nanofibers for 6 h, and the formation of the zone of inhibition in the diffusion test demonstrated the antibacterial effect of the drug-loaded nanofibers. Together, the fibroin/GEL/ceftazidime nanofibrous system can enhance drug effectiveness particularly in the prevention of postsurgical adhesions and wound dressing infections [15].

Since GEL undergoes a gelation process, Furuike et al., used a new dry spinning process for GEL. In this case, the nonwoven GEL fabrics were electrospun by applying dry spinning principles. The diameter of the fibers, the viscosity, and flow rate of the solution depended directly on the GEL concentration. Spunted nonwoven fabrics with a concentration of 25% (w/w) GEL exhibited a nanoscale diameter. In order to improve the properties of the nonwoven fabrics, they were cross-linked with glutaraldehyde vapor after spinning by the addition of N-acetyl-d-glucosamine to the GEL solution before spinning followed by heating of these fibers. Nonwoven fabrics cross-linked by glutaraldehyde vapor exhibited improved mechanical properties compared to those without cross-linking or cross-linking of N-acetyl-d-glucosamine. Swelling and water absorption did not produce morphological changes in glutaraldehyde cross-linked fibers. The thermogravimetric analysis (TGA) thermogram did not confirm any phase change in the composite structure. In addition, in vitro cytocompatibility studies using human mesenchymal stem cells showed the compatible nature of the developed nonwoven fibers, where they demonstrated that these nonwoven fibers could be useful in medical care [16].

Delivery of hydrophobic drug into the hydrophilic polymer matrix as a carrier is usually a challenge. Therefore, in one study, the synthesis of GEL nanofibers by electrospinning was presented, which were evaluated as a potential carrier for the oral system of hydrophobic drugs, piperine. GEL nanofibers were cross-linked by exposing to saturated glutaraldehyde vapor, to improve their water-resistive properties. An exposure of only 6 min was not only adequate to control early degradation with intact fiber morphology, but also significantly marginalized any adverse effects associated with the use of glutaraldehyde. The results illustrated good compatibility of the hydrophobic drug in GEL nanofibers with promising patterns of controlled drug release by varying the cross-linking time and the pH of the release medium [17].

3. Collagen electrospinning

Collagen (COL) is the most widely distributed class of proteins in the human body. The use of COL-based biomaterials in the field of tissue engineering applications has been growing strongly during the last decades. It is for this reason that multiple cross-linking methods have been investigated and different combinations with other biopolymers have been explored to improve tissue function. The COL has a great advantage, as it is biodegradable, biocompatible, readily available, and highly versatile. However, since COL is a protein, it remains difficult to sterilize without alterations in its structure [18].

We have investigated the possibility of preparing COL-inspired nanofibers by electrospinning aqueous suspension of telopeptide-free COL molecules avoiding organic solvents and blends with synthetic and natural polymers. The results underscored the need for a basic atmosphere between the needle and the ground collector in order to increase the pH of the environment during auto-assembly of COL molecules along the electrostatic force lines in order to prepare a biomimetic component of reinforcement of new biomaterials for medical and surgical use [19].

It has been reported that he designed a durable sandwich wrap preparation system with high liquid absorption, biocompatible, and with antibacterial properties. For this purpose, various weight ratios of the COL solution to chitosan were used to immobilize on the polypropylene

nonwoven fabric, which was pre-grafted with acrylic acid or N-isopropyl acrylamide to construct a durable wound sandwich liner membrane with high water absorption, easy removal, and antibacterial activity in an animal skin model. The results indicated that tissue immobilized with N-isopropyl acrylamide and COL/chitosan/PP/N-isopropyl acrylamide-COL/chitosan) showed a better healing effect than COL/chitosan immobilized polypropylene tissue. The poly (propylene)/N-isopropyl acrylamide/COL/chitosan-treated wound showed an excellent remodeling effect on histological examination with respect to the construction of the vein, epidermis, and dermis at 21 days post-cutaneous lesion. The water absorption values and water diffusion coefficient for polypropylene/N-isopropyl acrylamide/COL/chitosan were higher than those of polypropylene /acrylic acid/COL/chitosan under a weight-volume ratio of COL/chitosan. Both polypropylene/N-isopropyl acrylamide/COL/chitosan and poly (propylene)/acrylic acid/COL/chitosan showed antibacterial activity [20].

Electrospinning is a process that is used to create nanofibers, which have the potential to be used in many medical and industrial applications. The molecular structure of the raw material is an important factor in determining the structure and quality of the electro-chip fibers. COL has been extracted from a cold-water hoki species (*Macruronus novaezelandiae*), and this was prepared in several different molecular formats (triple helical CO, denatured whole chains, denatured atelocollagen chains, and GEL) for electrospinning. When denatured COL chains were used, 10% acetic acid proved to be an aqueous solvent effective to produce uniform fibers. This information is useful for the development of a nontoxic aqueous solvent system suitable for the industrial enlargement of the electro-silting process [21].

Nerve tissue engineering is one of the most promising methods in nerve tissue regeneration. The development of combined scaffolds of COL and glycosaminoglycans can potentially be used in many soft tissue-engineering applications. In a study by Timnak *et al*. developed two types of randomized and aligned electro-alloying. Their cellular tests showed that the scaffold acted as a positive factor to support the growth of connective tissue cells. These results suggested that scaffolding of nanostructured porous COL-glycosaminoglycans is a potential cell carrier in nerve tissue engineering [22].

On the other hand, COL and hyaluronic acid are the main components of the extracellular matrix naturally and have been successfully used in the electrospinning. In this case, a solution of COL/hyaluronic acid polymer was electrospun creating a scaffold for patients with osteoporosis who have reduced bone strength. The membranes were cross-linked to render them insoluble and conjugated to gold nanoparticles to promote biocompatibility. Their results showed that COL/hyaluronic acid scaffolds were insoluble in aqueous solutions and promoted cell fixation that could be used as a tissue engineering framework to promote cell growth [23].

Zulkifli *et al*. [24] focused on the degradation behavior of nanofibrous scaffolds composed of HEC/PVAL (alcohol hydroxyethyl cellulose/polyvinyl alcohol) and HEC/PVAL/COL as potential substrates for the engineering of cutaneous tissues in two media (PBS) and Dulbecco's modified Eagle's medium (DMEM) for a period of 12 weeks of incubation. Once the scaffolds were characterized, the HEC/PVAL/COL scaffolds showed a slower degradation rate in both media compared to the HEC/PVAL blend nanofibers. All fibers showed irregular and rough surfaces toward the final week of incubation in PBS and DMEM solution. As the degradation time increased, there were few changes in the chemical structure determined

by the FTIR spectra, while the thermal studies revealed that the melting and crystallinity temperatures of the scaffolds were slightly shifted to a lower value. Both HEC/PVAL and HEC/PVAL/COL fibers showed a significant decrease in Young's modulus and tensile stress during the 12 weeks of degradation. Their results demonstrate that these nanofibrous scaffolds showed degradation behavior that meets the requirements as a degradable biomaterial potential for dermal replacement.

The development of biomaterials with the capacity to induce the healing of cutaneous wounds is a great challenge in biomedicine. In one study, COL sponges were developed from tilapia skin and electro-nylon nanofibers for wound dressing. It was found that nanofibers could significantly promote the proliferation of human keratinocytes and stimulate epidermal differentiation through the expression of regulated genes involved, filaggrin and type I transglutaminase in human keratinocytes. In addition, COL nanofibers could also facilitate the regeneration of rat skin, in one study, electrolyzed nanofibers of COL were prepared from biomimetic tilapia skin and were shown to have a good bioactivity and could accelerate the healing of wounds from rat quickly and efficiently. These biological effects can be attributed to the structure of the biomimetic extracellular matrix and to the multiple amino acids of the COL nanofibers. Therefore, tilapia COL nanofibers could be used as a new wound dressing, effectively avoiding the risk of transmitting diseases in future clinical application [25].

Another study using the double-extrusion electrospinning technique prepared with multilayer 3D scaffolds stacking poly-lactic-co-glycolic acid (PLGA) microfiber membranes alternately to micro- /nano-mixed fibrous membranes of PLGA and COL. The density of the COL fibers in multilayered scaffolds obtained was able to control the adhesion, proliferation, and osteogenic differentiation of MC3T3-E1 cells. Demonstrating that the homogeneous dispersion of glutamic acid-modified hydroxyapatite nanoparticles (nHA-GA) in the COL solution improved the osteogenic properties of the multilayer scaffolds fabricated. In addition, it found that PLGA-COL-HA micro-nano fibrous scaffolds were highly bioactive compared to pristine microfibrous PLGA and PLGA and COL micro/nano-mixed fibrous platforms [26].

The development of biomimetic scaffolds represents a promising direction in the engineering of bone tissue. This was demonstrated by Ma *et al.* [27], when they designed a two-step process to prepare a type of biomimetic hybrid hydrogels that were composed of COL, hydroxyapatite, and alendronate, the latter as anti-osteoporosis drug. These hybrid hydrogels of collagen, hydroxyapatite, and alendronate exhibited remarkably improved mechanical properties (G: 38–187 kPa storage modulus), higher gel contents, and lower swelling proportions compared to hydrogels prepared from COL only under similar conditions. In addition, they showed degradable behaviors against collagenase. The hybrid hydrogels of COL-hydroxyapatite-alendronate well supported the adhesion and growth of MC3T3-E1 osteoblastic cells. Such resistant but enzymatically degradable hybrid hydrogels hold the potential as scaffolds for bone tissue engineering.

The hybrid constructs from marine organism material for porous scaffolds of COL, such as fibrillated jellyfish and alginate hydrogel, mimic the two major components of cartilage,

thus being a promising approach as a model for the chondrogenic differentiation of mesenchymal stem cells human beings. This is why Pustlauk *et al.* [28] investigated their potential for joint cartilage repair. They studied the expression of the COL 2 gene and found that its expression was comparable in all scaffold types examined. However, the COL 2/COL 1 ratio was higher for pure alginate disks and alginate-cell suspension scaffolds compared to alginate-embedded stem cells. In addition, they found that the secretion of sulfated glycosaminoglycans was comparable in the suspension of alginate cells and cells embedded in alginate scaffolds. They conclude that hybrid COL constructs of jellyfish and alginate support the chondrogenic differentiation of stem cells and provide more stable constructs compared to pure hydrogels.

4. Electrospinning with the GEL/COL system

Angarano *et al.* [29] synthesized GEL and COL cross-linked fibers by the reactive electrospinning technique using a mixture of nontoxic solvents: acetic acid, ethyl acetate, and water (5, 3, and 2 w/w/w), eliminating fluorinated solvents, which require post-treatment and purification by the implementation of glyoxal, represented an easy, versatile, and one-step procedure. Enabling the expansion and fabrication of synthetic fabrics of COL based on nanofiber cross-linked GEL in situ. This in situ cross-linking renders the water soluble GEL fibers water resistant without adversely affecting the hydrophilicity, excellent wetting of fibers, cell compatibility, reabsorption, cell adhesion, and proliferation typical of COL nonwoven nanofibers cross-linked.

Tylingo *et al*. [30] prepared and characterized new porous scaffolds composed of chitosan, COL, and GEL for the preparation of GEL and COL scaffolds isolated from fish skin with various physicochemical properties. All biomaterials obtained showed homogeneous porosity. The type of protein polymer determined the rheology and mechanical properties of the preparation of the preparations. The use of protein polymers decreased the swelling ability of the materials by about 30% compared to the materials obtained from chitosan. GEL-containing materials showed the highest solubility (approximately 30%). Scaffolds obtained in 100% chitosan were found to be harder than COL materials by an average of 30% and less flexible more than twice. In addition, materials containing protein polymers showed good antioxidant properties.

In **Table 1**, other studies with the electrospinning technique are summarized.

Polymers	Application	Characteristics	References
GEL (type B porcine)	Food industry	Soft nanofibers without pearl formation	[9]
GEL (type B porcine)	Tissue engineering Cell regeneration in fibroblasts (BJ-5ta) and human embryonic kidney cells (HEK 293 T)	Nanofibers with up to 90% cell proliferation	[14]
GEL (type A porcine)	Tissue engineering Cell regeneration in fibroblasts (3 T3)	Nanofibers cross-linked in glutaraldehyde.	[5]

Polymers	Application	Characteristics	References
GEL (25.43 kDa)	Regeneration of Periodontal Tissues.	Reticulated membrane, hydrated and flexible.	[8]
GEL (bovine Type B)	Delivery system for bioactive molecules in nanofiber matrices	Nanofibers between 47 and 147 nm.	[7]
GEL	Scaffolds for cell regeneration in human gingival keratinocytes and human gingival fibroblasts.	Water-resistant glyoxal cross-linked nanofibers.	[29]
GEL/fibroin	Tissue engineering Cell regeneration in human fibroblasts	Nanofibers loaded with ceftazidime as an antimicrobial agent.	[15]
COL (type I)/poly (lactic-co-glycolic acid)/hydroxyapatite	Tissue engineering Osteogenic differentiation of MC3T3-E1 cells	Micro/nano-bioactive scaffolds	[26]
COL/hyaluronic acid	Tissue Engineering Regeneration of bone tissues in murine fibroblasts (L - 929)	Fibers insoluble in aqueous solutions that promote cell binding.	[23]
COL Free telopeptide type I (equine tendon)	Biomedical and Surgical	Simple molecular set of nanometric size	[19]

Table 1. Gelatin and collagen uses in biomedical applications.

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