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Review Article

Electrospinning of Collagen: Formation of Biomedical Scaffold

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Abstract

In order to mimic the cellular microenvironment, several techniques using both synthetic and natural polymer were considered. Electrospinning of collagen is one of the most successful and useful techniques: it produces scaffolds that could be used especially in the human body. Thanks to being biocompatible, low antigenic, promoter of cell attachment and non-immunogenic, collagen is considered the best biomedical device. Depending on its application field, collagen generally couldn't be used alone. To ameliorate its performance, the scaffolds of the collagen-based scaffold are normally composed also of another kind of polymer nanofibers such as chitosan, Silk fibroin, Poly (Lactic Acid) (PLA), Polycaprolactone (PCL). In this review article, we will introduce the novelties in solving and Electrospinning collagen, evaluation of scaffold properties and their application fields.

Keywords: Electrospinning; Collagen; Benign solvent; Crosslinking; Collagen-based scaffold

Introduction

In our days, the study of material at nano level acquires a lot of interest. In fact, it is one of the rapidly growing scientific disciplines due to its enormous potential in creating novel materials. This technology, named "Nanotechnology", has hugely impacted many different sciences and engineering fields, such as electronics, materials science, and polymer engineering. Indeed, when the diameters of polymer fiber materials are contracted from micrometers to nanometers, several amazing characteristics loom up such as: 1) Smaller pores and higher surface area. 2) Flexibility in surface functionalities. 3) Superior mechanical performance compared with any other known form of material.

A number of techniques such as drawing, phase separation, template synthesis, self-assembly, electrospinning, etc. have been recently used to prepare polymer nanofibers. Only "electrospinning" has gained the most interest as a developing technique to obtain nanometer diameter polymer fibers collected to make a nonwoven scaffold. In addition, Electrospinning is adopted to produce ultra-fine fibrous scaffolds using natural and synthetic polymers to imitate the microcellular organism.

The benefit of using collagen scaffold over normal scaffolds resides on the fact that Collagen substance has a lot of special characteristics as the ability to be resorbed into the body, the non-toxicity , the production of only a minimal immune response (even between different species). Also, it is a premium for connection and biological interaction along cells. Collagen could also be treated into several formats as porous sponges, gels, and sheets, in addition to being capable to cross-link with chemicals in order to make it stronger or to ameliorate its degradation rate. Collagen has been utilized in multiple biomedical applications such as various types of surgery, cosmetics, drug delivery, bioprosthetic implants and tissue-engineering of multiple organs [1]. Moreover, for the duplication of natural tissue, collagen is the best polymer since it often comes close to behave as it does within the body.

Presentation of Collagen

Collagen is the most abundant protein in mammalian (including the human body). It is found specifically in the Extracellular Matrix (ECM) [2] and it constitutes 30 % of all vertebrate body protein [3]. In general, Collagen is considered as a tissue scaffold and a drug release material. Owing to be the major structural protein, it conferees strength to tissues such as dermis, bone, cartilage, tendon, ligament, and internal organs. In addition, thanks to its biocompatibility, low antigenicity, promotion of cell attachment and growth, and being relatively non-immunogenic, it is the best material for biomedical devices [4-6].

Collagen, as a biopolymer, is defined by its unique structure, size, and amino acid sequence. Its molecules are characterized by being reunited in three polypeptide chains twined around one another as in a three-stranded rope. Those cordages are held together primarily by hydrogen bonds between adjacent (-CO) and (-NH) groups, and secondly by covalent bonds (See Figure 1). The basic collagen molecule is rod-shaped with a length of 3000A°, a width of 15A° and has an approximate molecular weight of 300 kD [7].

The collagen family is made of a high variety of molecular combination, supramolecular structure, and function. Basing on its structural organization and sequence homologies, Collagens are grouped into different categories. As an example, we could cite the human body, which comprehends 29 types of collagen. Those proteins can be distributed into different subfamilies such as fibrillar collagens, fibril-associated and related collagens, beaded filament-forming collagen, basement membrane and associated collagens, transmembrane collagens, and hexagonal network collagens (Table 1) [8] .

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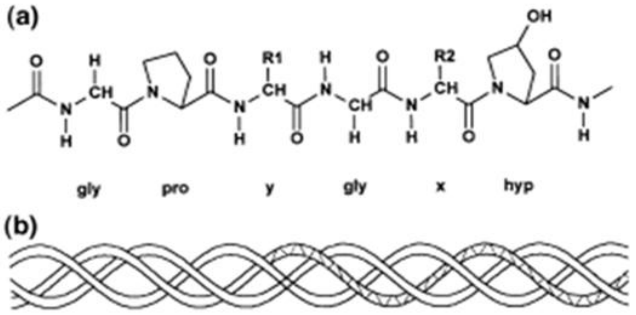

Figure 1: Chemical structure of collagen (a) Primary amino acid sequence, (b) secondary left handed helix and tertiary right handed triple-helix structure [3].

Table 1: Classification of Collagen types.

Categories of collagen	Type of collagen	Diameter of fibers	Arrangement of fibers	Placement of fibers
Fibrillar collagens	I, II, III, V, XI, XXIV, XXVII	50 to few hundred nm	Parallel bundles (in tendons and ligaments), Orthogonal lattices (in the cornea) Concentric weaves (in bone).	In the ECM of connective tissues such as tendon, skin, and bone
Fibril-associated and related collagens	IX, XII, XIV, XVI, XIX, XX, XXI,XXII	Non-fibrillar collagens as they do not form fibrils by themselves, but they are associated with the surface of **Collagen fibrils:** they are found in the basement membrane junctions between tissues.		
Network-Forming Collagens	IV, VI, VIII, X	It makes linear and lateral associations to form open networks rather than fibrils. Collagen networks act as supporting structures for cells and tissues, serve as selective molecular filters and barriers, function as anchorage for neighboring cells, contain and protect the developing embryos.		
Multiplexins	IV, VII, XV, XVIII	These collagens occur in the endothelial and epithelial basement membrane zones of a wide variety of tissues.		
Transmembrane collagens	XIII, XVII, XXIII, XXV	The transmembrane collagens are widely expressed and participate in cell adhesion, epithelial–mesenchymal interactions during morphogenesis, neuromuscular signaling, and host defense against microbial agents.		

Electrospinning of Collagen

History of "electrospinning"

The origin of electrospinning dated back to the early 1930s. In 1934, Formhals invented his first invention relating to this process. Here, the used apparatus for producing artificial filaments utilized electric charges [9]. Though this method, which has been used for a long time, had not gain any importance .This was due to the technical difficulties related to spinning methods such as fiber drying and collection. This earlier process consisted of a movable collecting device to collect the threads in a stretched condition. Also, the process was capable of producing aligned and parallel threads into the receiving device. In his first patent, Formhals introduced the spinning of 'Cellulose Acetate Fibers' using 'Acetone' as a solvent [9]. However, this first spinning method had some technical disadvantages that consist essentially on difficulties relating to the complete dry of fibers after spinning which was influenced by the shortness of the distance 'Spinning zone- Collection zone'.

In a second patent, Formhals revised his earlier approach in order to correct the aforementioned drawbacks [10]. In the corrected process, the distance 'feeding nozzle- fiber collecting device' was increased to give more chance to the electrospun fibers to dry. After that in 1940, Formhals introduced another method to produce composite fiber from multiple polymers by electrostatically spinning [11]. In the 1960s, Taylor started his studies on the jet forming process [12] and in 1969 he examined the shape of the polymer droplet that took place at the tip of the needle when an electric field is applied. His experiences showed that the jets are pitched out from the vertices of the cone [12]. This conical shape of the jet took later his name and be referred as the "Taylor Cone". The importance of this trick resides on defining the onset of the extensional velocity gradients in the fiber forming process. So, after examining different kinds of viscous fluids, he found that an angle of 49.3 degrees is required to keep the balance between the surface tension of the polymer and the electrostatic forces [13].

In subsequent years, focuses shifted to studying the structural morphology of nanofibers. Researchers went over the structural characterization of fibers and its relationships with the process parameters. Scanning Electron Microscopy (SEM), Wide-Angle X-ray Diffraction (WAXD), Differential Scanning Calorimetry (DSC) and Transmission Electron Microscopy (TEM) have been used in order to characterize electrospun nanofibers. In 1971, Baumgarten reported the electrospinning of acrylic microfibers with diameters ranging from 500 to 1100 nm [14]. In addition to that, he detected the spinnability limits of a Polyacrylonitrile/Dimethylformamide (PAN/DMF) solution and noticed a specific dependence of fiber diameter with the viscosity of the solution. He also proved that after an initial increase in the applied field, the diameter of the jet shrunk to a minimum value then it increases as the electric fields increases. Larrondo and Mandley made polyethylene and polypropylene fibers from the melt. They found that the use of this method produces fibers with a larger diameter than the process using solvent [15,16]. Consequently, they were interested in studying the relationship between the fiber diameter and the melt temperature and they found that the diameter decreases as the melt temperature increases. Moreover, according to them, fiber diameter decreases by 50% when the applied voltage doubled which also shows the importance of applied voltage on fiber characteristics. In 1987, Hayati et al. discussed the effects of the electric field, experimental conditions, and the factors affecting the fiber stability: They found that liquid conductivity has a major role in the electrostatic disruption of liquid surfaces. In fact, the obtained results showed that the combination of highly conducting

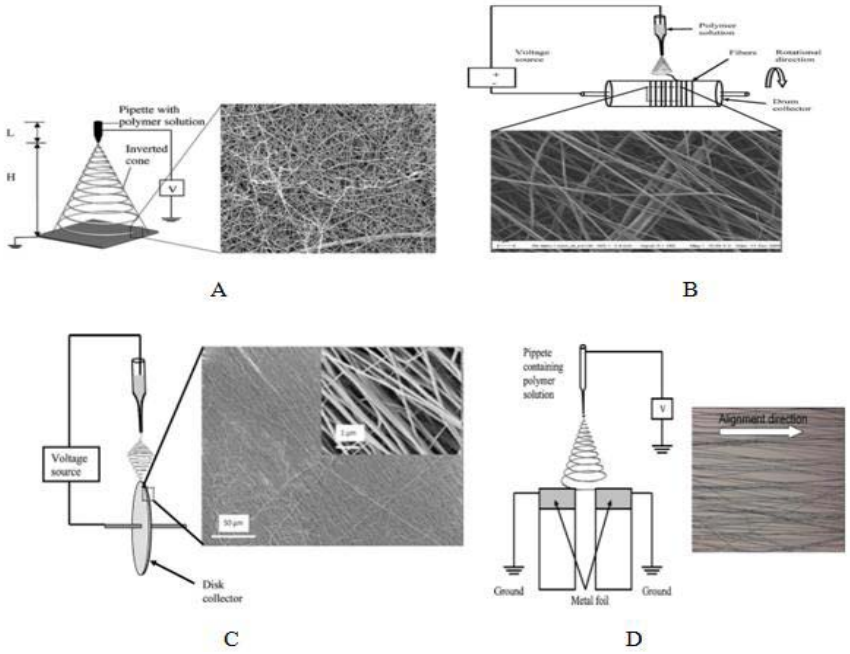

Figure 2: A-Schematic of the Static metal plate used for fiber collection. The inset SEM micrograph shows the randomly arranged fibers obtained B- Schematic of the rotating drum used for fiber collection. The inset SEM micrograph shows the aligned fibers obtained using the rotating drum. C- Schematic of the disk collector used for fiber collection. The SEM micrograph shows the alignment of the fibers obtained using the disk collector. D- Schematic of static electrodes used for collecting aligned fiber bundles. The optical micrograph shows the aligned fibers collector using this technique.

fluids with a highly applied voltage produced a highly unstable jet that whipped around in different directions. Relatively, the production of stable ones requires the use of semi conducting liquids [17]. After a break up of a more than a decade, a major renaissance in research on electrospinning raised due to the increased knowledge of the powerful application of nanofibers in different fields, such as catalyst substrates, protective clothing, high-efficiency filter media, and adsorbent materials. Research on nanofibers gained a big attention due to the work of Doshi and Reneker [18] who studied the characteristics of Polyethylene Oxide (PEO) nanofibers by changing the solution concentration and applied electric potential values. The Jet diameters were measured as a function of distance from the top of the cone (Distance=f (concentration, voltage)). They observed that to decrease the jet diameter an increase in distance is required. Relatively, they found that the PEO solution having a viscosity less than 800 centipoises (cP) is considered too dilute to form a stable jet whereas solutions with viscosity more than 4000 cP were too thick to form fibers. Jaeger et al. studied the process of the fibers thinning when the extrusion progressed in PEO/water electrospun fibers. They noticed that the diameter of the flowing jet was shrunk to 19 μm after traveling 1 cm from the orifice, 11 μm after traveling 2 cm, and 9 μm after 3.5 cm [19]. Their experiments showed also that, solutions with conductivities in the range of 1000–1500 μs.cm-1 heated up the jet due to the present electric current which ranges between 1 to 3 μA. Deitzel et al. proved that since the shape of the jet is linked to the increase/decrease in the bead defects then any modification in the applied voltage alters the shape of the surface [20]. Also, they tried to control the deposition of fibers by using a multiple types of electrospinning apparatus that provide an additional field of polarity to the jets [21]. Shin et al. patented a new apparatus capable of giving enough control over the experimental parameters in order to quantify the electrohydrodynamics of the process [22]. Gibson et al. examined the transport properties of electrospun fiber mats, and they concluded that nanofiber layers give very small resistance toward the moisture vapor [23,24].

Principe of electrospinning in general

The technique of electrospinning is composed of two major divisions:

Melt Electrospinning.

Solution Electrospinning

In general, the process of 'Electrospinning technique' consists of using high electrostatic forces to produce fiber: in fact, this method is about electrically charging the polymer solution/melt using a high voltage (about 10–20 kV) in order to produce ultra-fine fibers [25]. Figure 2A shows the basic electrospinning setup which especially consists of:

A pipette or a syringe filled with polymer solution/melt

A high voltage source

A grounded conductive collector screen

Firstly, the polymer solution/melt placed in the syringe pump. After that, it is forced to the tip in order to form a pendant drop. Secondly, free charges are induced inside the polymer as a result of the application of the voltage potential using the immersed electrode in the syringe. Thirdly, the formed pendant elongates due to the presence of the electric field. Finally, when the applied potential reaches the critical value that allows it to overcome the surface tension

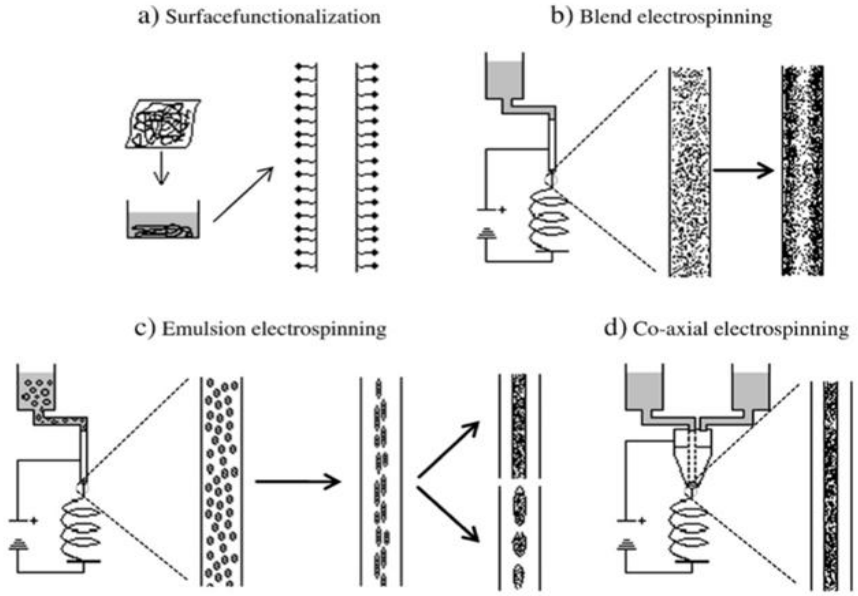

Figure 3: The different strategies for functionalization of electrospun fibers [31].

of the liquid, a jet of liquid is ejected from the cone tip toward the charged collector. During its trip, the jet undergoes a chaotic motion or bending instability which allows it to evaporate the solvent and to leave behind just a dry fiber situated in the collector device.

Electrospinning's method and their relation with the arrangement of fibers

The degree of charge dissipation upon fibers affects essentially: "fibers density per unit area on the collector" and "fibers arrangement on the collector". However, the collector nature influences fundamentally:

The morphological of the spun fibers

The physical characteristics of the spun fibers

The arrangement and packing density of the fibers

As an example, the use of conductive collectors helped in dissipating the charges and reducing the repulsion between the fibers. Therefore, in this case, the fibers collected are smooth and densely packed. Inversely, the fibers collected on non-conductive collectors do not disperse the charges which cause the repeal of each other, so the obtainment of loosely packed fibers [26].

Recently, in order to better control the Electrospinning process, researchers look toward getting highly ordered and aligned fibers using mechanical and electrostatic methods. Aligned fibers have found interest in several engineering applications, such as nanocomposites, tissue engineering, sensors, filters, electronic devices [27].

Rotating drum collector: This kind of collector is generally used to produce aligned arrays of fibers in addition to enabling not only the control of the fiber's diameter but also the rotational speed of the drum. (See Figure 2B) The cylindrical drum is capable to:

Rotate at high speeds (a few 1000 rpm)

Orient the fibers circumferentially

It is fundamental that the linear speed of the rotating drum matches with the evaporation rate of the solvent, which enable the control of the fiber's deposition and their taken up on the surface of the drum [27]: In fact, when the rotational speed is slower than the fiber take-up speed, the fibers collected on the durum will be randomly oriented. Contrary if the application of higher speeds took place, a centrifugal force will be developed near the vicinity of the circumference of the rotating drum, which provokes the elongation of the fibers before being placed on the drum [27]. Moreover, the continuous increase of the speed at much higher level induces the take-up velocity which drags to break the depositing fiber jet so no continuous fibers will be collected.

Rotating disk collector: About 'The rotating disk collector', it could be presented as a derivative of the rotating drum collector. It is used to obtain uniaxially aligned fibers (See Figure 2C). The advantage of using a rotating disk collector comparing with the use of the normal drum collector is that the fibers are presented on the sharp-edged disk then are collected as aligned patterned nanofibers [27]. This method consists of applying an electric field which is concentrated on the tapered edge of the disk so the charged polymer jet is attracted toward this locality. Comparing the quality of the fibers obtained using this method and the others using the rotating drum, the ones obtained by the Rotating disk collector are much better, but the only problem here that a few aligned fibers could be produced since there is only a small area at the tip of the disk.

Static parallel electrodes: The benefits of using this technique are in relation with:

The simplicity of its setup

The facility of collecting single fibers for mechanical testing

The phenomenon is as follows; the air gap found between the two electrodes contributes of creating a residual electrostatic repulsion between the spun fibers which helps their alignment

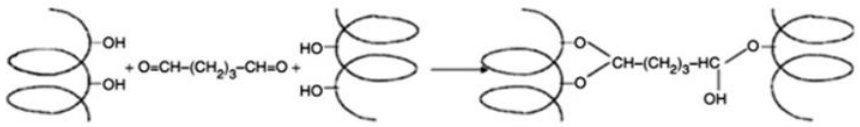

Figure 4: Cross linking reaction of collagen with glutaraldehyde.

Table 2: Overview of studies investigating the effect of pore size and cell infiltration of collagen.

Year	Study\Author	Reference	Scaffold material	Cell type	Cell diameter [μm]	Duration [days]	Fiber diameter [μm]	Measured porosity [%]	Measured pore size [μm]	Calculated pore size [μm]	±51% of cell diameter [μm]	Cell in growth
2009	Yang et al	[63]	PLGA+ Collagen	hDF	~15	7	1.02-1.14	82-91	86.7-130.7	5.9-11.2	7.5-22.6	+/−
2008	Lee at al	[64]	Collagen I	Bsmc/bEC	_	2	0.52	-	22.7	_	_	+/−
2005	He at al	[65]	P(LLA-CA)+Collagen I	hCAEC	~15	7	0.1-0.2	68-76	-	0.45-0.63	7.5-22.5	-

[28] (See Figure 2-D). This technique allows fibers to be deposited at the end of the strips so that the fibers join the strips in a variant fashion and be collected as aligned paintings of fibers. Speaking about collagen's Electrospinning, the only applicable method here is 'Solution Electrospinning" since melt Electrospinning, which consists of heating the polymer presented in the syringe in order to melt it, causes the denaturation of the collagen molecule.

The process of "Solution Electrospinning" technique starts always with the preparation of solution as a first step: choosing the suitable solvent to solve some kind of polymer could be the most critical move in this procedure since it depends on four critical factors: The dielectric constant, Volatility, Surface tension, Solvent conductivity [29].

Functionalization of fiber strategies

Although having normally the ability to functionalize the fibers produced by it and allowing the introduction or the deliberation of the bioactive molecule to the cell over a long duration, electrospinning could have a problem in the functionalization of fibers produced using organic solvents which are incompatible with their bioactive molecules. To solve this malfunctioning, several strategies are used.

Surface functionalization: This method uses physical or chemical immobilization of the bioactive molecule post electrospinning. It is composed essentially of adsorbing biologically functional nanoparticles or drug encapsulated polymeric nanoparticles layer by layer assembly of polyelectrolyte or chemical immobilization of bioactive molecules on the fiber surface [30]. An example of chemical functionalization of fiber surface is presented in Figure 3A [31].

Blend electrospinning: Generally, this technique is used for drug released functionality [32-35]. It consists of mixing the target bioactive molecule with the polymer solution prior to electrospinning (See Figure 3B).

Emulsion electrospinning: Emulsion electrospinning could be considered as an extension of blend electrospinning since it demands the same basic set up. This technique requires the spinning of two immiscible solutions simultaneously. The fiber forming polymer involves an organic solvent and makes the continuous phase whereas the bioactive molecules are dissolved in aqueous solution and formulate the dispersed phase. This method was used in producing functionalized fibers with different morphologies for regenerative therapies [36-42] (See Figure 3C).

Coaxial electrospinning: This technique consists of electrospinning fibers issued from two different solutions: The process here involves pumping separately those solutions through two nozzles connected to a high voltage source (See Figure 3D), which results in a core- sheath fiber morphology. Hence, coaxial electrospinning provides functionalizing fibers with bioactive molecule [43].

Electrospinninmg of collagen

As a historical view, we could shortly admit that the first experiences of Electrospinning collagen-based scaffolds were executed by Huang et al. in 2001. Those tests consist of combining the Electrospinning of collagen and Polyethylene Oxide (PEO) to form nanofibers [6]. The diameter range of those descendant products was between 100 and150 nm. In 2002, the Electrospinning of pure collagen was successfully observed using type I and type III collagen. The solving of those proteins was provided by HFP which is considered as a very suitable solvent for those types of collagen: HFP is considered as an organic and volatile solvent which has a boiling point at 61°C. This low value permits it to initiate the evaporation of the solvent under normal atmospheric conditions so facilitating the deposition of the fiber in the required dry state. Speaking about viscosity, the parameter concentration could be mentioned: the perfect concentration of collagen was found at 0,083g/ml since above this value the polymer solution presents droplet and leaked from the syringe tip. The cause of those defects is the dissolving of acid extracted from collagen in HFP. Matthews et al. announced that the average diameter of electrospun fibers is ranging between 100 and 730 nm and mentioned that the source of the used collagen influences it [5].

In this context, the effect of polymer concentration on collagen fiber morphology was explained by Li et al [27]: They affirmed that by decreasing the collagen concentration a decrease in the fiber diameter is noticed. However, if the concentration goes below 5%, beaded fibers will be obtained. So to get a successful electrospun collagen, the procedure has to be unrolled under a concentration above 5 %. The tensile modulus of the obtained collagen nanofibers was under 262±18 Mpa.

In addition to using HFP as a solving agent, 2,2,2-Trifluoroethanol

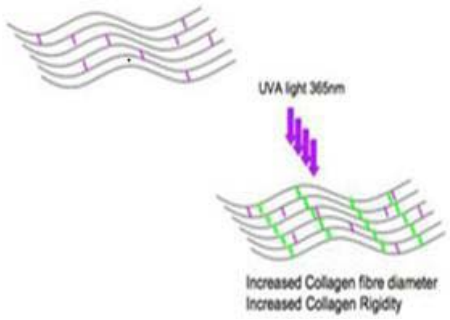

Figure 5: Cross linking of collagen using UV radiation.

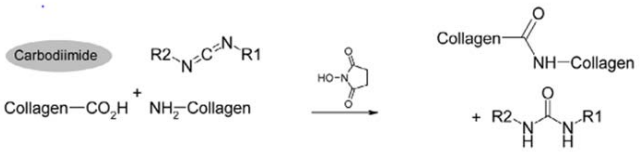

Figure 6: collagen cross linking using 1-Ethyl-3-Diaminopropyl-Carbodiimide (EDC) and N-hydroxysuccinimide (NHS).

(TFE) is also commonly used to solve collagen for electrospinning. However HFP and TFE, due to their corrosive nature, can decrease the water stability of collagen scaffolds. This drawback pressed researchers to find more suitable solvents which could mimic both the nature of HFP and effectively disturbs hydrophobic and hydrogen bonding interaction. They find that a combination of water\ethanol\ salt worked well since the presence of ethanol facilitates this mission. After that, researchers found the combination of Buffer\ethanol which was considered even better because it helps to overcome the high surface tension of water that used to give limited electrospinning quality to water-based polymer solution. Using this combination contributes also in facilitating the formation of a stable Taylor cone due to its high conductivity. In this context, it was noticed that increasing the salt concentration in buffer contributes in decreasing the average fiber diameter [44]. A system composed of water/alcohol/ salt system such as the combination of Phosphate Buffered Saline (PBS) and ethanol was developed, and due to its high salinity, it could adversely affect the strength, water stability, and cytocompatibility of fibers [45]. Also, we could cite the experience marked by Liu et al. which consists of developing an acetic acid aqueous solvent system but still causing a 70% decrease in the triple helical fraction of collagen [46]. As a conclusion, we could report here that collagen dissolves well in acidic conditions. In addition, the use of a benign binary solvent of acetic acid and DMSO [47] could lead to a successful collagen electrospinning.

Collagen Cross-Linking

Cross-linking of collagen scaffolds is the next step after electrospinning to produce scaffolds with enhanced mechanical properties [44]. There are four major approaches for cross-linking collagen.

Covalent chemical cross-linking of neighboring fibrils

This method consists of covalently coupling neighboring collagen fibrils using the combination of reactive groups in the collagen fibrils and the cross-linking molecules. As an example of those agents, we cite Glutaraldehyde, epoxy compounds, and isocyanates. The disadvantage to these compounds consists on being included within the cross-link as strange chemical species toward biological tissues, and as a consequence, it may cause several kinds of unfavorable conditions, such as inflammation, foreign body response, immunogenic reactions, etc. To clarify more, Glutaraldehyde could be mentioned here as the most used cross-linking agent: it is characterized by its low cost, availability, rapid reactivity, and solubility in aqueous solution. The cross-linking of collagen-based tissues using glutaraldehyde diminishes especially biodegradation which makes them biocompatible and non-thrombogenic while conserving anatomic integrity, leaflet strength, and flexibility [48]. Although, it has received criticism as a crosslinking agent for implants since it promotes calcification and releases toxic molecules from the implant [49]. The reaction of Crosslinking collagen with glutaraldehyde is presented in Figure 4.

Physiochemical cross-linking methods

The basic principle of these methods consists of exciting the reactive amino acid side chain found already in the collagen fibrils in order to create a covalent cross-link without the addition of foreign chemical substances into the scaffold. These processes include microwave irradiation, photooxidation, dehydration, and dehydrothermal treatment. The use of this method is preferred over covalent chemical crosslinking agents such as Glutaraldehyde since no chemicals are required and the risk of producing a toxic species decreases. As an example, we cite the exposition of collagen scaffold to UV irradiation with a wavelength light around 254 or 514 nm. The UV treatment is capable of improve the mechanical integrity of the scaffolds [50]. However, overexposing the collagen has damaging effects on fibril structure (See Figure 5).

Intermolecular cross-linking of amino acid side chains

Launching intermolecular cross-linking of the reactive amino acid side chains needs the addition of a catalyst, such as a carbodiimide or azyl acid which will not be a part of the cross-link like glutaraldehyde, epoxies, and isocyanates. This method aims as a zero-length crosslinking procedure. The catalyst and its byproducts can be easily washed out of the scaffold after crosslinking.

Carbodiimide cross-linking is now preferred over glutaraldehyde owing to its increased biocompatibility. The most common carbodiimide compound is 1-ethyl-3- (3-dimethylaminopropyl) carbodiimide. It reacts with the carboxyl groups of side chains in collagen which generates the amide cross-link and ejects made wastes of the carbodiimide. Those derivatives can be easily pitched out from the scaffold by the use of a simple rinse. The produced isopeptide bond imitates the native peptide bond present in proteins (see figure 6). The carbodiimide reaction was found to be optimized at *p*H 5 [50].

Polymerizing compounds

The feature of those compounds consists of not being chemically reacted with the collagen fibrils. It has the role to interact with the fibrils in order to reinforce it. Since the collagen and polymer matrix hold separate, attentions must be considered to define any ill effect produced by the polymer matrix *in vivo*.

Characterization of Electrospun Collagen Fibers and Scaffold

Geometrical characterization

Scaffold microstructure is described by its fiber diameter, fiber orientation, porosity and pore size: fiber diameter and fiber orientation are estimated directly and with a good reliability from SEM image. Contrary, porosity and pore size are frequently evaluated by a various type of techniques. For pore size, we cite image analysis [51,52], capillary flow porometry [53-56], liquid instruction\ extraction porosimetry [53,57,58].

Electron Microscopy: To evaluate the morphology of the collagen electrospun fiber, both Scanning Electron Microscopy (SEM) [13] and Transmission Electron Microscopy (TEM) are used [48]. SEM has the advantages of being a quick method for observing the produced fibers and using small samples size for its operations (See Figures 2-A, 2-B, 2-C, and 2-D). But the disadvantage of having a reduce resolution at extreme magnification. In the other hand (TEM) is another alternative for observing fiber with extremely reduced diameters (<300 nm) [59,60].

Porosity measurement: Scaffold porosity is known as the void volume related to the total volume of a scaffold. Therefore, it shows the part of the scaffold available for cell infiltration and tissue formation. The ideal porosity values for electrospun scaffold range from 70 to 95% and may be determined gravimetrically [31,60,61].

Scaffold porosity could be determined using those equations:

D_s=Scaffold mass/Scaffold thikness×Scaffold area; P_s=1-Scaffold density/Bulk material density

Where D_s: scaffold density

P_s: Scaffold porosity

For unknown bulk density

V_{pt}=wet weight×dry weight/Liquid density; P_s= Total pore volume/Scaffold thikness×Scaffold area

Where V_{pt} Total pore volume

The porosity of the collagen scaffold was also tested using the SEM instrument. The image issued from this last is examined using ImageJ software [47]. This program transforms the gray scale level of 256 into binary images by calculating the threshold. The equation used in this measurement is;

$P = (1 - n/N) \times 100$

where: n is the number of white pixels

N is the total number of pixels in the binary image

P is the porosity percentage of the binary image

Determination of pore size: Several methods are used to characterize the pore size of an electrospun scaffold:

Capillary flow porometry is a characterization technique which provides the measure of pore size with respect to gas flow on the scaffold. It is broadly used to measure minimum, maximum and mean flow pore sizes in addition to pore size distribution. This method is usually used in filtration application but it proves its usability also in perfusion seeding of cells [53-56].

SEM base analysis [51,52] uses a small representative sample of the scaffold where all fibers are projected in the same plane and the void area between them is measured. The pore diameter distribution is estimated from the area distribution.

Liquid instruction\extrusion porosimetry [53,57,58] provides the measure of the pore diameter and volume which is more relevant to cell scaffold interaction. Pore characterization is realized by introducing mercury or excluding the wetting liquid out of pore while a pressure application.

In order to study the effect of porosity and pore size on cell proliferation and infiltration by varying the fiber diameter, researchers were done on scaffold based collagen and results are given in the Table 2.

Surface contact measurement: Wettability is an important factor to characterize either scaffold for wound healing or skin or tissue engineering since they are exposed to water blood or even other body fluids. This test is generally done by estimating the contact angle of a liquid applied on the surface of the scaffold or tissue using a contact angle meter [60,65].

Chemical characterization

To determine the surface chemistry of the collagen electrospun nanofibers, FTIR analysis is used [60,66]. This test is critical for tissue engineering scaffold to provide a cellular growth, physiological function and keep normal states of cellular differentiation. To examine those characteristics a RCCS Bioreactor was used in order to give a nutrient environment to cells. After that, a Microscopic examination was considered [5].

Mechanical characterization

The use of the produced collagen electrospun nanofiber scaffold is directed toward the biomedical application that is why the precise measurement of the mechanical properties is vital. Generally, the tensile and elongation tests are carried out here [28,47,60,66].

Collagen-Based Scaffold: Possible Combinations

In order to enhance mechanical and structural properties of the collagen-based scaffold, a mixture of natural or\ and synthetic polymer are used.

Combination of Collagen with natural polymer

Blending collagen with a natural polymer is widely used in tissue engineering. In this review, the combinations with chitosan and fibroin are taken as examples:

Chitosan: As owing a low toxicity, being non-immunogenic and biodegradable, chitosan is considered a good choice for the biomedical application. Also, being a positively charged polymer makes its combination with collagen, which is an anionic polymer, perfect to form a two component scaffold with ameliorated mechanical and biological properties. This kind of scaffold, which is characterized by its satisfying porosity, provides a good grow to 'Mesenchymal Stem Cells' (MSCs) with pseudopodia spreading into the scaffold with

shows the good cytocompatibility between (MSCs) and the scaffold [67].

Silk fibroin: Silk fibroin shows a good biocompatibility, biodegradability, and mechanical properties which make it a suitable biomaterial for scaffold fabrication. Experiences show that the combination Collagen-Silk fibroin is beneficial in corneal tissue engineering application [68].

Combination of Collagen with synthetic polymer

As like blending with a natural polymer, blending collagen with synthetic collagen has been largely used for tissue engineering. Examples of these synthetic polymers are; Poly (ε-caprolactone) (PCL), Polylactic Acid (PLA), Poly (Ethylene Glycol) (PEG), Polyglycolide (PGA), Poly (Lactide-Co-Glycolide) (PLGA) and Polyvinyl Alcohol (PVA).

In addition to being a non-toxic, low cost, bioresorbable polymer which has a good mechanical properties and slow degradation rate, the combination of PCL with collagen fibrous scaffold is characterized by a low crystallinity, a small size and an ameliorated dehydration temperature (50 to 60°C) comparing to 32, 5°C for collagen. This kind of scaffold proves its efficacy in repairing large skeletal muscle tissue defects [69].

The blended collagen\PLA scaffolds own open pores throughout the scaffold and better stiffness rate comparing to collagen scaffold. These characteristics permit it to be used in cartilage tissue engineering [70].

Besides, the multi-component scaffolds, that use the combination of natural and\or synthetic polymers such as; collagen\chitosan\PLA, hyaluronic acid\collagen\PEG [71] and PCL\PLGA\collagen, prove their potential application in vascular tissue engineering [72], repair of central or peripheral nervous system [71] and regeneration of bone or liver tissue [73].

Combination of collagen with inorganic hybrid scaffold

The examination of PLLA\collagen\ HA scaffold shows a good cytocompatibility and superior osteoinductivity [74]. This scaffold proves also its efficacy as a supportive for steam cell-based therapies for bone repair and reconstruction. Besides, Shin et al [75] showed that GO\PLGA\Collagen hybrid fibrous scaffold has a good attachment, proliferation and myogenic differentiation of C2C12 skeletal myoblasts.

Applications of Collagen Scaffolds

As being the major component of ECM in many tissue and organs, multiple typical applications of collagen scaffold are found.

Nerve tissue

The use of collagen-based scaffold facilitates the regeneration of injured nerves. This is thanks to their good platform for nerve regeneration and repair. Liu et al [76] showed the possibility of fabricating 3D scaffolds utilizing collagen fibers and their related application potential for SCI repair. Boecker et al. [77] proved that this method improves axonal regeneration by linking seeding cells with scaffolds.

Cartilage tissue

A recent technology named 'Matrix-Induced-Autologous chondrocyte implantation' (MACI) has been developed. It is composed of two surgical processes: Extraction, Purification, and Expansion *in vitro* of chondrocytes; seeding of chondrocytes on a 3D matrix, which can later be re-implanted. This method was evaluated by Basad et al [78] who proved its safety, efficacy, and usefulness in surgical operations for treating damaged cartilage.

Tendon\Ligament tissue

The electrospun fibers can mimic the fibrous structure of tendon and ligament tissue repair. A study done by Cardwell et al [79] showed that the use of large diameter fiber is preferred in tendon\ ligament tissue engineering. Another study [80] proved that the use of oriented structure can promote the repairing efficacy of tendon\ ligament due to the anisotropy of native tissue.

Vascular graft

Lee et al [63] showed that PCL\Collagen scaffold has the ability to resist high degrees of pressure and flow for a long time in addition to providing a suitable environment for the growth of the vascular cell. The characteristics of this kind of fibrous scaffolds were: Elasticity: 2.7±1.2 MPa, Tensile strength: 4.0±0.4 MPa and Burst pressure: 4912±155 mmHg, which were considered appropriate to use. Tests of biocompatibility give also satisficing results.

Skin

Ma et al. [81] presented GA-treated collagen/chitosan scaffolds as an owner of a good cytocompatibility and able to promote a good cell infiltration and effective proliferation. Moreover, the scaffolds are capable of pushing along the infiltration of the fibroblasts from the surrounding tissue *in vivo*, which marks their ability in dermal repair. Rho et al. [82] showed that in open wound healing tests, the collagen scaffold speeded up the disappearance of the surface tissue debris, proliferation of fibroblasts and young capillaries in the early stage of wound healing.

Conclusion

In this paper, we presented collagen as an owner of a tremendous potential to make tissue engineering scaffold. We also proved that electrospinning is a powerful mean of processing collagen into nanofibrous scaffolds for biomedical usage thanks to its biocompatibility. In addition, the use of collagen could be blended with other natural or\and synthetic electrospun polymer fibers. The fabrication of these composites can produce mechanically stable and highly durable materials for a lot of medical applications.

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