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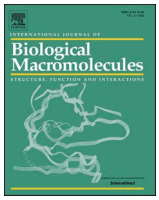

Review

Comparing solution blow spinning and electrospinning methods to produce collagen and gelatin ultrathin fibers: A review

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ABSTRACT

Ultrathin fibers have been used to design functional nanostructured materials for technological and biomedical applications. Combining the use of renewable and compatible sources with the emerging alternative SBS (solution blow spinning) technique opens new opportunities for material applications. In this review, we introduce the benefits of SBS over the classical electrospinning technique by following studies that use collagen or gelatin. SBS offers distinct advantages over electrospinning in the preparation of ultrathin fibers based on natural proteins, including the absence of high-voltage sources and the possibility of using fewer toxic solvents. Notably, there is also the prospect of using SBS directly in injured tissues, opening new strategies for *in situ* structure assembly SBS is a suitable approach to produce fibers at the nanoscale that can be tailored to distinct diameters by blending or simply adjusting experimental conditions. The focus on producing collagen or gelatin fibers contributes to designing highly biocompatible mats with potential for promoting cellular growth and implantation, even though their applications can be found also in food packaging, energy, and the environment. Therefore, a comprehensive analysis of the topic is essential to evaluate the current strategies regarding these materials and allow for their expanded production and advanced applications.

1. Introduction

Polymeric ultrathin fibers display potential use in several areas due to their unique properties, such as tailored fiber size and a high surface-to-volume ratio. Usually, they are described as acting materials in fields like biosensors [1], thermoregulating dressings [2], electrically conductive fibers [3], drug delivery platforms [4], food production, analysis and packaging [5] and tissue engineering [6], among others. The ultrathin fibers employed in tissue engineering are mainly used in the production of scaffolds, developed to act as structures that facilitate the growth and proliferation of cells, sometimes used as artificial extracellular matrices (ECMs). These biomaterials seek to promote interactions of the artificial tissue with the implanted organism which avoid the recognition of this material as foreign and promote a cellular response that results in cell adhesion, proliferation, and, sometimes, differentiation [7,8].

The dimensions of natural protein fibers (from 50 to 500 nm in diameter) contributes to their interaction with cells (typically from 10 to 100 μm), since they allow direct contact of cells with multiple fibers, promoting cell anchoring and facilitating cell motility. Various methods can be employed to produce scaffolds, such as freeze drying, 3D printing, solvent casting, and others [9]. However, the use of techniques for producing nano-, micro- and submicron-scale fibers has emerged as a promising alternative, as these dimensions resemble natural fibers found in the ECM of various tissues. Among the techniques for producing fibers on a micro- to nanoscale are conventional methods like self-assembly, phase separation, melt blowing, wet spinning, and electrospinning (ES), along with more recent methods such as centrifugal spinning and solution blow spinning (SBS) [8,10,11].

Each of the above-mentioned techniques has its advantages and

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disadvantages in the preparation of polymeric fibers on a submicron scale. The melt blowing technique, for example, requires the polymer used to be thermoplastic (which makes it difficult to use natural polymers) and rarely produces fibers on a nanometric scale. Wet spinning, in turn, produces fibers by their precipitation in a coagulation bath, and fiber formation is slow because it depends on solvent drainage [12]. The other conventional methods, self-assembly and phase separation, present low yields and the polymers that can be prepared using these techniques are limited. On the other hand, many studies involving the production of scaffolds by the ES of natural polymers can be found [11,13,14], which is in part due to the versatility and low cost of this technique. The SBS technique resembles the well-established ES technique in some aspects, but uses a pressurised gas instead of an electric field to promote the formation of polymeric fibers [15,16] and is also largely applied for scaffold production using biopolymers, among other applications.

The main constituent of the ECM in various tissues is collagen, an animal protein with structural functions that promotes resistance to deformation, preventing mechanical failures in the tissues it composes, and transmitting biological signals to cells responsible for specific functions [13,17]. An approach employed in biomaterials development is to mimic the ECM of some tissues, aiming to closely approximate its composition and architecture of each living tissue, producing scaffolds that are designed as artificial ECMs [7]. In this scenario, collagen and gelatin, the natural protein and its denatured form are two biopolymers largely applied in scaffold production by the fiber formation techniques electrospinning and solution blow spinning. Here we present the recent studies (2019–2024) that applied these ultrathin fiber production techniques to spin collagen or gelatin, first discussing the materials produced by both processes and then focusing on their main applications and properties of the fibers produced by solution blow spinning.

2. Spinning methods for fiber formation

The concept of fiber production has been reported since early in history, starting from the representation of a mechanical device for twisting a series of parallel fibers into a yarn, described by the ancient Egyptians, to the Saxony wheel, which expressed a considerable advance in the art of spinning [18].

Nevertheless, the well-known characteristics of fibers for sensors, filters, and tissue engineering applications raised interest in developing techniques to produce and reduce their scale to a nano-size range. The use of electrostatic force as a method for fabricating fibers was first described and patented by Formhals in 1934 [19]. Considerable interest in this process expanded in the 1990s [20], mainly focusing on the use of ES to fabricate fibers from a variety of polymers and blends, including poly(vinyl pyrrolidone), and poly(lactic acid)/poly(ethylene glycol) (PLA-PEG) block copolymers [21,22]. Recently, due to advances in the tissue regeneration area, natural proteins and polysaccharides are used to produce ultrathin fibers-based patches that are highly biocompatible and with low antigenicity [23].

In parallel, solution blow spinning emerged as an alternative method for fabricating fibers in micro and nano lengths. The technique resembles ES in some aspects but is mainly distinct by using a pressurised gas instead of an electrical field to promote the formation of the fibers [24].

2.1. Electrospinning

A conventional ES setup comprises a high-voltage power supply, a conductive collector, a spinneret with a capillarity needle, and a syringe pump (Fig. 1). A high voltage creates an electrical field, usually between 5 and 30 kV [25]. The created opposite charges lead to an electrically charged jet of polymer solution, where the polymer fiber is created during the travel between electrodes (designated as the spinneret and the collector) by drying or solidifying the polymer solution [26].

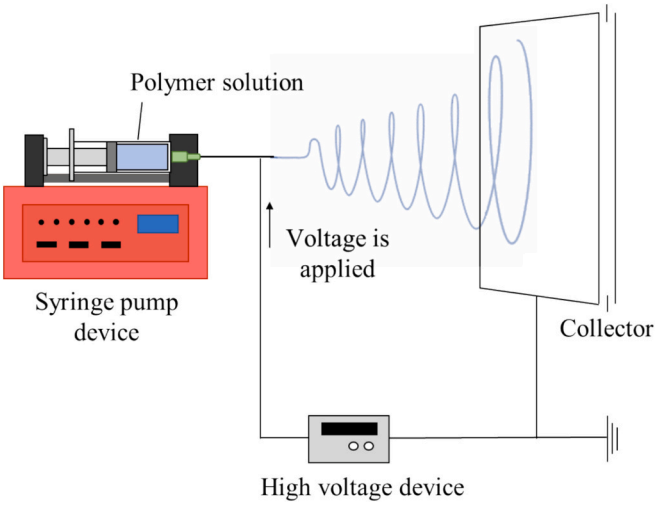

Fig. 1. Schematic structure of the electrospinning apparatus (Adapted from [25]).

A charge on the surface of the liquid is induced by the connection of the spinneret needle and the collector to a high voltage, which causes a particular shape of the liquid at the end of the needle controlled by surface tension, viscosity, and electrostatic field. Due to the mutual charge repulsion, a force created causes an elongation of the spherical surface of the drop, forcing it to form a conical shape known as the Taylor cone [27]. Along with this, a repulsive electrostatic force overcomes the surface tension at a specific high voltage between the electrodes, ejecting the charged jet from the tip of the Taylor cone. With an increase in the interaction between the electrical field and the charged surface of the drop, the jet becomes very thin. In parallel, the surface-to-volume ratio of the jet grows quickly, the solvent evaporation is facilitated, and the solidification of the fiber is observed [26]. These fibers are usually collected on a flat metal plate or on the surface of a rotating collector, allowing the creation of aligned fibers through a specific direction [171].

2.2. Solution blow spinning (SBS)

The SBS approach is a new technology for preparing ultrathin fibers, first reported by Medeiros et al. [16]. Its development was based on the combination of ES and traditional melt-blowing methods. A simplified SBS setup consists of a gas cylinder (providing the gas flow), a pressure regulator, a syringe pump, a nozzle represented by an apparatus that integrates both streams into a simple device (airbrush), and a collector (Fig. 2a).

The fabrication process requires a pair of concentric fluid streams in which a polymer is dissolved in a volatile solvent and a pressurised gas is pumped. The gas is responsible for flowing around the polymer solution, forcing it to assume the flow direction. Usually, a commercially available airbrush combines both streams, the polymer solution delivered by the syringe pump and the compressed gas source (Fig. 2b) that provides the flow at a specific rate [16].

The nozzle is designed with an inner part where the polymer solution is pumped and an outer stream where the pressurised gas is conducted. The high-pressure gas at P_1 is pumped out of the outer nozzle, decreasing the pressure to P_{atm}. At the same time, the jet flow energy increases, which leads to an enhancement in gas velocity. This promotes a drop in the pressure P_2 in the centre of the jet, creating the driving force to accelerate the polymer solution [16].

Unlike ES, the fibers are produced without any electrical source, as the airflow controls the process. The theoretical basis of the SBS technique is based on the high-speed stretching principle occurring in the inner nozzle and the Bernoulli principle [28]. The Bernoulli principle

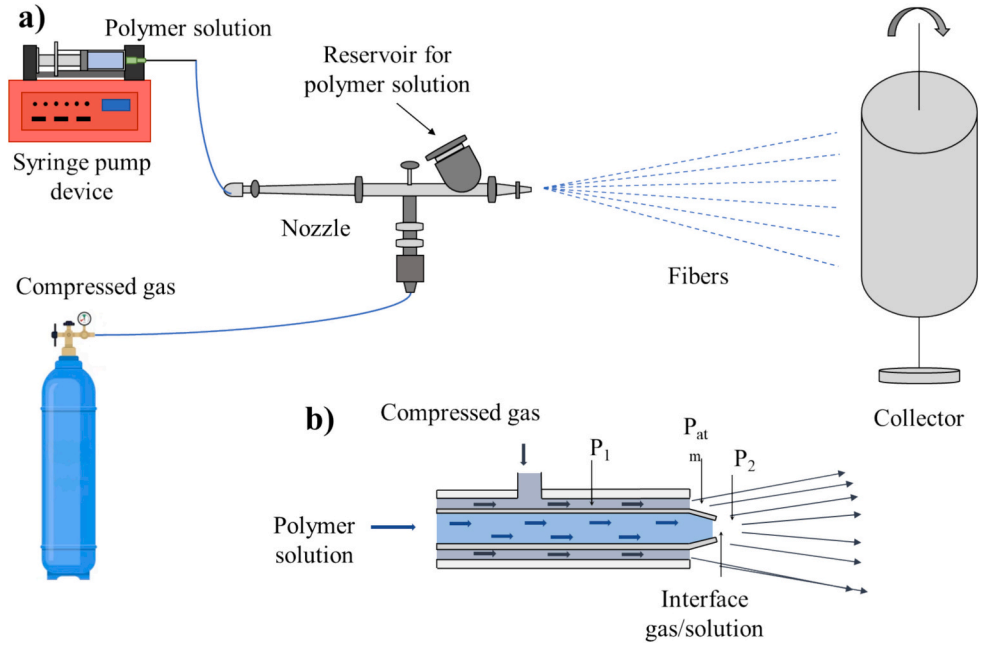

Fig. 2. In a), a simplified SBS setup, indicating the main components.
In b), a schematic picture of the airbrush system and how the pressurised gas acts in the polymer flow direction (Adapted from [16]).

describes the phenomena that occur in the outer concentric nozzle, wherein changes in the air pressure are converted into kinetic energy [29]. The nozzle geometry is responsible for the formation of a region of low pressure around the inner part, and the polymeric drop at the tip of the nozzle is stretched into a cone comparable to a Taylor cone, as observed in the ES technique. As soon as an ultrathin jet is formed, the polymer drop is released in the direction of the collector, followed by a quick solvent evaporation before the fiber deposition [16].

2.3. Factors that affect spinning processes

Despite the methods appearing straightforward in forming fibers, relevant factors are involved in providing uniform morphology of the fibers. The literature constantly reports the observation of beads, which disrupt the homogeneous fiber structure. This is caused by using a polymer solution with a viscosity below a certain threshold, creating an additional instability known as Rayleigh instability [30]. Nevertheless, the absence of those beads and the manipulation of the diameter and morphology of the fibers are directly influenced by different parameters.

The characteristic of the polymer solution controls the formation of smooth and uniform ultrathin fibers. As mentioned, a specific viscosity condition must be accomplished to avoid the appearance of beads. This condition is governed by Berry's number (Be), which is described as the product of intrinsic viscosity and polymer concentration [31]. The solution forms smooth fibers when *Be* exceeds a specific critical value. On the other hand, when *Be* is lower than that critical value, jet fragments are obtained, and instead of fibers, drops and beads are formed. Associated with this, beads or even non-dried fibers are observed when polymer solutions at a low concentration are used, as the solvent in a high amount is not fully evaporated during the path to the collector. Oppositely, a polymer solution at a high concentration obstructs the end of the needle, restricting the formation of the Taylor cone and, consequently, the acquisition of fibers.

Still, regarding the viscosity of the polymer solution, other authors prefer to describe the performance of the production of the fiber in terms of the critical concentration of chain entanglement (C*) instead of Berry's number [32]. Both parameters are related to the conformation the polymer assumes in the presence of a solvent in a semi-diluted system. To achieve and form fibers, the polymer solution needs to overlap this C* and reach an entanglement system, mainly described by using an appropriate solvent to promote a good polymer-solvent interaction [33]. Srinivasan et al. [34] confirmed that polymer solutions above this C* strongly stabilise the polymer jet, which conducts the formation of fibers. Another study suggested that no beads are formed when the entanglement concentration is approximately 10 times the C* [35]. Independent of the parameter applied, it is important to understand the role of viscosity and concentration in controlling the production of homogeneous fibers.

Surface tension is another important property of polymer solutions that should be controlled, since in electrospinning the applied electric voltage needs to overcome this property, inducing charge repulsion to distort the solution droplets at the nozzle and generate the Taylor cone, propelling the solution jet to the collector. For solution blow spinning, surface tension must be overcome by pressurised gas, which lowers the pressure around the nozzle, stretching the polymer droplet to form a Taylor cone-like structure. Additionally, this factor can affect fiber morphology, as surface tension controls the shear forces at the interface between the polymer solution and the atmosphere. Higher surface tension values, for example, can even result in unstable jets in the SBS method [32,36,37].

The instrument parameters, such as the minimum applied voltage in the case of ES, must be considered to promote the Taylor cone formation. Even though a reduction in the fiber diameter is noticed with an increase in the electrical field due to the stretching of the polymer jet, a further rise in the voltage above a critical value is related to the formation of beads in the structure of the fibers [38]. A high flow rate used to eject the polymer solution out of the spinneret directly impacts the formation of beads in ultrathin fibers as a result of the Taylor cone deformation [39].

In the case of SBS, the gas pressure and polymer flow rate affect the morphology of the fibers, especially their diameter. In a study by Oliveira et al. [40], the fiber diameter was only affected by the polymer solution flow rate at low gas pressure. Other studies suggested a polymer solution flow rate ranging from 0.02 to 1 mL h^{-1}, confirming the influence of this variable in the SBS operation conditions, as a low rate is related to jet instability while a high rate causes nozzle clogging [41,42]. A consistent fiber morphology, with a narrow diameter distribution, is formed when the SBS system is operated at a high gas pressure, as reported earlier [40,43,44]. Nevertheless, an incorrect modulation of the

pressure above an optimal range creates a temperature decrease in the SBS device due to gas expansion. Consequently, the solvent is poorly evaporated, and no homogeneous fiber structures are formed [43].

Besides gas pressure and polymer flow rate, other variables that can affect the diameter of the fibers produced by SBS are the nozzle design and the speed of the gas at its exit: the nozzle is constituted by an inner section (where the polymeric solution is pumped) and an outer section, which provides pressurised air. The geometry of the nozzle creates a region of low pressure around the inner nozzle, helping to draw the polymer solution into a cone. The increase in the air velocity creates a driving force that stretches the polymer solution out of the nozzle. The narrower the nozzle, the smaller the diameter of the fiber produced [45].

Another variable commonly related to both processes is the distance between the spinneret and the collector. An optimized gap is required to allow solvent evaporation before reaching the collector, and long distances are generally related to the obtention of non-uniform ultrathin fibers [46].

Regardless of the extensive impact of the solution properties and instrument parameters on ultrathin fibers synthesis, ambient parameters must be carefully adjusted for the obtention of homogeneous structures. Temperature and relative humidity are parameters that indirectly influence the performance of the spinning method. For instance, an enhancement in the temperature reflects a reduction of viscosity, affecting the production of fibers [30,32]. Additionally, the solvent evaporation rate is dependent on the relative humidity. Generally, a higher humidity leads to the polymer jet absorbing ambient water, reducing the solvent evaporation in the path between the spinneret and the collector [46].

Complex fibers can be produced by the use of multiple nozzles, which represents a way to combine the properties of immiscible polymer solutions in the development of multicomponent mixtures immediately before solvent drying and fiber formation, instead of directly blending the components in one solution. The arrangement of two or more concentric nozzles results in coaxial fibers, a strategy applied, for example, to coat fibers applied in drug delivery, to generate self-healing fibers, or simply to enable the production of fibers that are not spinnable alone and are stabilised by their shell. Also, the outer layer(s) of these core-shell or core-shell-shell fibers can be selected to modulate the swellability, air permeability, diameter, morphology and other fiber properties [32,36]. When applying parallel nozzles in a side-by-side spinneret, Janus nanofibers can be produced, resulting in an interface connected material along the fiber that also can be applied in advanced functions, such as sensors and catalysis [47,48].

2.4. Comparing both methods

The production of polymer fibers using ES and the SBS methods permits the adjustment of experimental conditions concerning the raw material and its interaction with the solvent and operation systems, displaying advantages and disadvantages regarding each technique (Fig. 3).

One of the main challenges of producing commercial materials by spinning techniques is to scale up the production to fulfill the requirements of industries such as pharmaceuticals. Electrospinning is often reported as a technique to produce uniform and aligned fibers with diameters at the micrometer scale [49]. Nonetheless, ES exhibits limitations as a method for industrial use, as its scalability finds obstacles due to high energy consumption, long production times, and potential safety hazards [50]. Adjustments like multiple needles and additional energy sources have been studied to improve the ES production rate, typically around 0.01–1 g/h [51]. Despite that, many fibrous materials produced by ES can be found on the market; more specifically, focusing on collagen and gelatin-based materials, we can cite the BioPaperTM technology, 3D fibrous scaffolds designed for 3D-cell culture (Dipole [52]).

In this context, SBS represents a competitive and industrially scalable

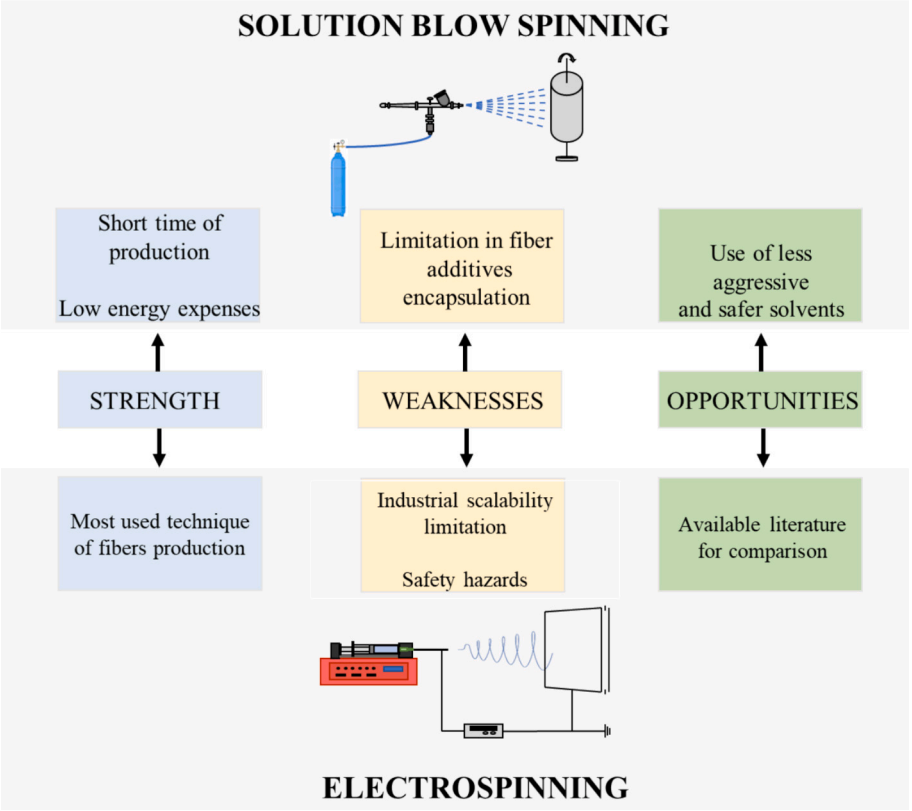

Fig. 3. Comparison of the advantages and disadvantages of electrospinning and solution blow-spinning methods.

method of producing ultrathin fibers patches in a short time and without high energy expenses. Since there is no interference between the nozzles, thus allowing multiple nozzles to be used simultaneously, the blown fibers can be collected by any type of collector, and various forms of fibers can be obtained (sponges, mats, papers, films) [53]. Although not yet commercially available, Yang et al. [54] recently developed collagen-based nerve guidance conduits (NGCs) by multi-needle SBS, aiming for materials with better permeability and mechanical properties, as well as improved cell attachment, when compared to similar materials found on the market.

Another advantage of SBS is not being limited to solvents with a high dielectric constant, as it commonly affects heat or voltage-sensitive polymers, like proteins [16]. This characteristic expands the use of less aggressive and safer solvents, also known as green solvents, reducing toxicity concerns in health and environmental areas. This is especially relevant in the production of materials for tissue regeneration, as the possibility of substituting such solvents for less-risk ones improves the biocompatibility of the fibers and non-woven polymer webs [55]. For example, concerns about the proper solvent for producing collagen ultrathin fibers as an inappropriate selection are reflected in the denaturation of the protein structure, interfering with essential biological properties [56].

Concerning the innovation feature, SBS displays a remarkable impact on ES and the direct deposit of the fibers onto the target of interest, particularly biological substrates. It prospects the use of SBS in biomedical applications and broader the significance of the method.

One disadvantage related to SBS is the limitation of encapsulation of additives in the fibers compared to the ES process. Daristotle et al. [32] and Oliveira et al. [57] reported that particularly liquid and solid drugs emerge on the surface of the fibers due to the high evaporation rate of solvent in the SBS method, disturbing the release kinetics and the possibility of using the fibers in a sustainable release over the time. Nevertheless, antimicrobial active compounds were incorporated in ultrathin fibers of gelatin derived from fish skin using the SBS technique. The compounds cinnamaldehyde and carvacrol were included in the gelatin-acetic acid system and showed an increase in action against *Escherichia coli, Salmonella enterica,* and *Listeria monocytogenes* [58,59].

3. Biocompatible and bio-based polymers for SBS fibers production

The polymers used in the production of fibers by SBS can be synthetic or bio-based. Polymers of synthetic origin may or may not be biocompatible, that is, safe for applications involving contact and interactions with biological systems, such as biomedical and food. Bio-based polymers, on the other hand, come from readily available and sustainable sources and, in most cases, are biocompatible [12].

Regardless of their source and biocompatibility, both synthetic and bio-based polymers can be functionalized or have their properties improved by mixing them with other materials, such as precursor polymers (which may or may not be biocompatible), producing the so-called composite fibers [12]. Among the main synthetic polymers that are non-biocompatible and used for SBS fibers production, stand out poly (acrylonitrile) (or PAN, the most used one), poly (vinylidene fluoride) (PVDF), poly (vinylpyrrolidone) (PVP), poly (methyl methacrylate) (PMMA), and poly (vinyl chloride) (PVC).

The choices of bio-based and/or biocompatible polymers are wider: PLA is a bio-based and biocompatible polymer derived from lactic acid and is one of the most common polymers used for the fabrication of SBS fibers. Its copolymerization with glycolic acid produces poly (lactic acid-*co*-glycolic acid) (PLGA), which is also used in SBS. The biocompatibility and nontoxicity of poly (ethylene oxide) (PEO) and polyurethane (PU) make the fibers based on these polymers also widely used for the production of biomaterials. Other common polymers which are synthetic but biocompatible and commonly used are Nylon (polyamide 6), poly (vinyl acetate) (PVAc), poly (vinyl alcohol) (PVA), poly (styrene) (PS), and poly (caprolactone) (PCL).

Among the main natural polymers used for the production of fibers by SBS, we can cite cellulose and lignin, from vegetal origin, and proteins such as collagen and gelatin, from animal origin. Collagen is widely used in tissue engineering due to its biodegradability, absorptivity, excellent cell compatibility, and promotion of tissue regeneration, all of these properties related to the stability of its triple helix [17]. Collagen also promotes cell adhesion and proliferation, due to its interaction with receptors located on the cells surface [60].

3.1. Collagen

Collagen is the most abundant structural protein in tissues of animal origin, constituting about 30 % of all proteins found in the human body. In total, 29 types of collagenous proteins are known, which are composed of trimeric molecules with primary amino acid structures based on the glycine-X-Y pattern; the amino acids most commonly found after glycine are proline and hydroxyproline. This pattern of trimeric molecules is responsible for the formation of the triple helices that are characteristic of all collagenous proteins [17,61].

Due to the predominance of acidic, basic, and hydroxylated amino acids, collagen can be considered a hydrophilic molecule. The molecular arrangement of collagen fibers is dependent on their type: in adult tissues, the predominant collagens are type I (80 %, $(\alpha_1)_2\alpha_2$) and type III (10 %, $(\alpha_1)_3$). The unit of type I collagen is the tropocollagen, composed of three polypeptide chains with about 1000 amino acids in length (300 nm); tropocollagen is stabilised by hydrogen bonds between glycine and hydroxyproline from adjacent chains, van der Waals intermolecular interactions, and also covalent bonds [62,63]. These interactions are responsible for the poor solubility of collagen, which is overcome by its extraction in an acidic medium or by the use of enzymes such as pepsin and trypsin. The molecular arrangement of these units of type I collagen in fibrils and fibers results in a striated pattern known as D-period bands, which repeat every 67 nm. This pattern is identifiable by techniques such as transmission electron microscopy, scanning transmission electron microscopy, and atomic force microscopy [7,63].

When collagen is exposed to thermal treatments above its denaturation temperature, its interactions are disrupted and lead to an irreversible destabilisation of its triple helix, generating gelatin. Fig. 4 shows a schematic representation of the processes followed by collagen denaturation, and how it affects not only the structure of the proteins, but also their solubility. For the denaturation to occur, collagen must be swollen in an acid or alkaline medium, depending on its degree of crosslinking; thus, the gelatin obtained can be type A (acidic) or B (alkaline), with different isoelectric points.

Regardless of the type, gelatin is formed by a mixture of polypeptides with α, β and γ chains, formed by single chains or by two or three α chains covalently crosslinked, respectively. Gelatin can also be classified according to the strength (Bloom) of the gel that it produces, which can be lower than 150 (low Bloom), between 150 and 220 (medium Bloom), or higher than 220 (high Bloom) [60,65].

Although gelatin does not have the same performance as collagen in biomedical applications, it is also a protein of interest for tissue engineering since it presents biodegradability and biocompatibility, in addition to great commercial availability and low cost. The main disadvantages of gelatin as a biomaterial are its high hydrophilicity and solubility in water, properties that affect its performance in most biological systems due to its rapid degradation and adsorption when in contact with aqueous media. However, like collagen, gelatin can be cross-linked through the use of various crosslinking agents to gain stability and resist the effects of temperature and application site composition, without losing its biodegradability [66,67]. The production of gelatin-based SBS fibers can be one way of increasing the hydrophobicity of this protein and making it suitable for application as a biomaterial.

In the next sections, the studies of the last 6 years involving the

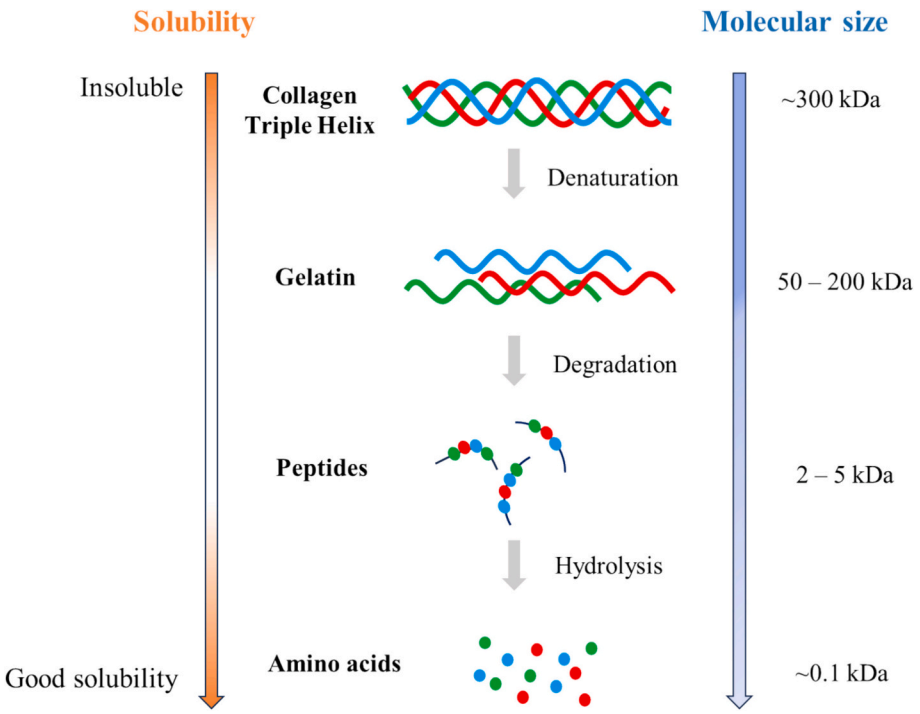

Fig. 4. Schematic representation of collagen structure and its influence in the protein solubility. Adapted from Kouguchi et al. [64].

preparation of ultrafine collagen and gelatin fibers by SBS will be presented, emphasising the main differences between the materials used in the production of the fibers, such as the sources of the polymers, their type, the solvents employed, as well as the experimental details of the spinning process.

3.1.1. *Collagen ultrathin fibers*

Due to the wide range of applications, collagen is a protein employed in many studies of distinct areas, such as food, pharmaceutical, and tissue engineering [17]. As collagen is the main component of the extracellular matrix in the animal kingdom, its use in producing materials for the regenerative field provides a highly biocompatible environment for cells [68]. Its ability to interact with receptors located on the surface of cells, such as α2β1, α1β1, α10β1, and α11β1, is closely related to its capacity to promote cell adhesion and proliferation [60].

The structure and properties of collagen are the key factors for its success as a raw material in producing ultrathin fibers. As a bio-based polymer, collagen displays an essential characteristic for such application due to its capacity to stimulate the formation of new tissues and promote regeneration [69,70].

Typically, collagen can be extracted from different sources, which impacts its structural organization. Tendons usually provide a highly anisotropic protein, while sources like skin are commonly related to low interconnected collagen. This structural arrangement is reflected in the performance of the extraction processes and the properties, like mechanical ones [61]. Additionally, different species are directly associated with producing distinct collagen, including in its primary structure [71]. For instance, collagen derived from fish skin exhibits a lower amount of hydroxyproline, an amino acid related to stabilising the protein triple helix. As previously observed, it reduces its thermal resistance [72,73].

Collagen synthesis occurs inside the ribosomes found in the fibroblasts, osteoblasts, and chondroblast structures, initially by producing the precursors of alpha sheets and pre-alpha chains. Its N-terminal domains, responsible for signing the amino acid sequence, are released into the endoplasmic reticulum, forming the pro-alpha chain. Amino acids like lysine and proline are hydrolyzed or glycosylated by the action of glucose and glycosyl-galactose compounds. The triple helix is formed by the junction of three of these formed chains by disulfide bonds at the C-terminus, resulting in the procollagen molecule. The tropocollagen is finally obtained when the C and N-terminal are cleaved outside the cell structure [61].

This protein structure is essential in tissues such as tendons, cartilage, bone, skin, and scales, contributing to their stability and performance [68]. Due to the growing tendency to use collagen in tissue engineering applications, its extraction process foments great interest and is currently discussed in the literature [74–77]. As mentioned, the extraction process and the collagen source are factors that affect the final characteristics of the protein.

Typically, collagen extraction is achieved by solubilization in aqueous solutions, like dilute acid associated or not with proteolytic enzymes ([78,79];). Acetic acid is the most common dilute acid used for collagen extraction, which better preserves the triple helix structure than citric acid or hydrochloric acid [80]. Adding enzymes like pepsin is advantageous in terms of environmental concerns, as it produces less waste in the extraction process. Nevertheless, its use is associated with being an expensive method [81].

As a general sequence, collagen extraction consists of cleaning the raw material, followed by an alkaline treatment, solubilization, and purification. Only some of the methods follow this strict order, as additional steps such as demineralization or defatting must be included depending on the source. Additionally, depending on the chosen method, different collagen structures can be obtained, as the acid treatment preserves the C and N-terminal telopeptide residues while the enzymatic treatment hydrolyses. When it happens, the molecule is denominated atelocollagen [82]. Although there are concerns about its immunogenicity, the incidence of adverse reactions of collagen derived from mammal sources is rare [83]. The idea of collagen immunogenicity was attributable to its terminal telopeptides, but in a study by Ruszczak [84] no evidence was found, suggesting that the removal of telopeptide had no beneficial effect.

Nevertheless, it opened a point of discussion about using collagen derived from mammalian sources, mainly associated with the outbreak of zoonotic infectious diseases [85] and on religious restrictions,

wherein certain mammalian-animal-isolated products are strictly prohibited [17]. Additionally, the necessity of several steps for collagen extraction from mammalians leads to low yields, and sources that demand mild conditions are considered suitable options [85].

Marine sources represent an alternative to the outcome of these limitations. They are valuable collagen sources, widely available, with reduced risk of disease transmission, and obtained as a sub-product of the food industry, as a discarded waste [86]. The resulting extractions are usually associated with an increase in the yield and a reduction in reagents [87], and its immunological safety was proved by different authors [88–90], confirming its safety as a biomaterial.

Electrospinning is the technique most employed and frequently used in diverse investigations focusing on the application of collagen to produce ultrathin fibers. Table 1 lists some studies that summarise the collagen source and the diameter of the produced fibers, among other information.

Even though investigations were conducted using the fibril-forming collagen types I, and II, type I is mainly used for producing fibers by the ES method. The main reason is its abundance in animal tissue [91]. Regarding the source, distinct ones are used to obtain collagen for ES, like calfskin, tendon, and bovine skin, as observed in Table 1. Ultrathin fibers fabricated from gelatin of tilapia skin demonstrate effective action, accelerating wound healing, and are associated with the proliferation and differentiation of keratinocytes during the re-epithelialization process [92].

The production of collagen fibers by ES is commonly related to the combination of the protein with a synthetic polymer, including PDO [93], PLA [94], PEO [62], PCL [95] and poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBV) ([96,97];) or natural, such as chitosan [98] and elastin [99]. As Chakrapani et al. [95] and Huang et al. [62] argued, this combination was essential for manufacturing fibers in a nanoscale since no fibers or irregular structures were formed without synthetic polymers. Different arrangements were also described, like coaxial ES, wherein the needles are concentrically positioned, producing fibers with a core composed of one polymer and the out portion of another [95,100].

The diameter of collagen fibers and their blends diverges depending on the concentration and ratio used for the fabrication. Values ranging from nanometric scale to micrometres had been reported by Matthews et al. [101] and Boland et al. [99], confirming a direct relation between the increase in the diameter by an increment in the concentration of the polymer solution. In addition, Zine and Sinha [97] described incorporating graphene oxide or graphene sheets to improve mechanical and antimicrobial properties. According to Chi and Wang [102], functionalized carbon nanotubes can be used to form biocomposite fibers with collagen, adding strength, electrical conductivity and with the potential application of the electrospun material to remedy the dysfunctional fibroblasts for therapeutic treatment of diseases.

Considering the solvents, the 1,1,1,3,3,3-hexafluoro-2-propanol (HFP) and 2,2,2-trifluoroethanol (TFE) are regularly applied in the ES of collagen fibers. However, they are commonly associated with potential toxicity, corrosion, and high cost [7,103]. Evidence of the disadvantages of using these solvents was reported by Zeugolis et al. [63], as electrospun type I collagen fibers were characterised by the absence of the D-period structure, low denaturation temperature, and high solubility in water. All these features indicate that these solvents inadequately preserve the collagen triple helix, resulting in a lack of its properties and being described as an expensive way to produce gelatin [104]. Although the spinning process is not expected to bring changes in the physical-chemical properties of collagen after spun, strong polar solvents like HFP and TFE interfere with the microfibrillar arrangement of collagen through the disruption of several intermolecular interactions and the secondary protein structure, as evidenced by Luo et al. [105]. However, Matthews et al. [106] reported preserving the collagen pattern in fibers produced by ES using type I and III collagen suspensions in HFP and crosslinked with glutaraldehyde.

Strategies related to collagen crosslinking are explored to raise its solubility limitations. As a crosslinking strategy, compounds such as glutaraldehyde vapor, genipin, or hydrochloride solutions of N-(3-dimethyl aminopropyl)-N′-ethyl carbodiimide with N-hydroxysulfosuccinimide (EDC/NHS) are extensively explored. It raises collagen's solubility limitation and enhances its structural stability for up to two months in aqueous media. Additionally, Luo et al. [105] confirmed the cellular proliferation of the MC3T3-E1 cell line (precursors of osteoblasts), although some changes in the diameter of the fibers depending on the crosslinking agent were observed. Arafat et al. [103] described using the wet spinning technique, obtaining stable fibers in an aqueous solution for at least one week with the preservation of collagen triple helix and fibers with diameters around 100 μm.

Replacing fluoroalcoholic solvents and exploring less toxic and safer materials are current concerns regarding environmental impacts and the costs involved in further purification steps for the final product. The risks regarding health issues are considered high in producing bio-based products for tissue engineering applications, as the damaged tissue to be

Table 1
Overview of the studies applying the electrospinning method to produce collagen fibers.

Type	Source	Blend	Solvent	Concentration	Diameter (nm)	Rate (mL h^{-1})	Reference
I	Tylapia skin	–	HFP	8 %	310 ± 117	1.0	[92]
I	Fish (Heliosorb ®)	–	HAc/DMSO (93/7)	10 %	200–1100	0.6	[7]
I	Rat tail	–	HFP/HAc (1/1)	9.1 %	363 ± 148	1.0	[105]
I	Calfskin	PLA	HFP	I/PLA (1:7) 8 %	1670 ± 410	0.5 to 1.5	[94]
I	Calfskin	PCL/PTHF copolymer	HFP	I/copolymer (1:9) 5 %	444 ± 67	1.0	[163]
I	Bovine skin	PCL (80 kDa)	HAc	I/PCL (3:1)	115 ± 39	0.7	[95]
				I/PCL (1:1)	130 ± 38		
				I/PCL (1:3)	148 ± 30		
I	Tendon from rat tail	PEO (900 kDa)	HCl	I/PEO 1 %	100–150	6.0	[62]
I	Calfskin	PHB/graphene oxide	TFE/chloroform (1/1)	16 %	400–500	1.0	[97]
I	Calfskin	PHBV	HFP	I/PHBV (3:7) 6 %	495 ± 92	1.0	[96]
I, III	Calfskin and human placenta	–	HFP	I (5.2 %)	100 ± 40	5.0	[106]
				III (2.5 %)	250 ± 150		
				I/III (3.75 %)	390 ± 290		
I, III	Calfskin and human placenta	Elastin (EL)	HFP	I (1.9 %)	100 ± 40	2.0–8.0	[99]
				I (6.2 %)	4600 ± 2100		
				III (5.2 %)	250 ± 150		
				I/III/EL (2:2:1) 5.2 %	490 ± 220		
I, III	Fetal calf dermis	PDO	HFP	(I/III)/PDO (1:9) (3.75 % / 6.25 %)	210 ± 110	8.0	[93]
				(I/III)/PDO (3:7) (3.75 % / 6.25 %)	340 ± 140		
II	Bovine neck ligament	–	HFP	3.75 %	180 ± 69	2.0	[164]
II	Chicken cartilage	–	HFP	2.5 %	110 ± 90	2.0	[101]
				6.25 %	1750 ± 900		

replaced is already under stress. Combined with this, lacking the collagen nature structure interferes with essential properties, mainly related to the regeneration process [104]. Preservation of the triple helix structure of the collagen during ES was successfully achieved by Elamparithi, Punnoose and Kuruvilla [7] using acetic acid/dimethyl sulfoxide (DMSO) as a solvent. Fibers with intact collagen D-period and capable of promoting the growth of cardiac cells were described as a material with possible application in cardiac tissue regeneration.

Aiming to replace the fluoroalcohols commonly employed in the production of protein fibers by ES, a solvent system composed of water, acetic acid (HAc), and ethyl acetate (AcEt) was described by Song, Kim and Kim [107] varying their ratio. A reduction in the superficial tension was observed when AcEt and HAc were added to the gelatin solution, followed by a gelification of the polymeric system at high ethyl acetate content. Additionally, the study reported that in the absence of AcEt, fibers without beads were formed only in the presence of at least 80 % HAc.

This study confirms another factor related to solvent characteristics involved in forming homogeneous fiber structures. Tenchurin et al. [108] investigated optimal rheological properties to efficiently ES highly concentrated collagen-based materials. Apparently, the pH of the solution displays an essential role in the spinning of collagen solutions and is one of the factors related to fabricating homogeneous fibers. It was suggested that solutions with pH lower than 3 exhibit a high availability of H^{+}, which permanently leads collagen chains to unwind into random-sized polypeptide chains. These conditions were confirmed by Qi et al. [104] by the observation that 57 % of native collagen chains were preserved by using a sodium acetate/acetic acid buffer solution at pH 3.0. Then, selecting the proper benign solvent is crucial to obtaining electrospun collagen ultrathin fibers with comparable architecture to that found in the native tissue [109].

Although ES is the most described method to fabricate fibers, SBS displays some advantages, as already described. An essential benefit of the use of no electrical field is that it allows the on-demand polymer fiber deposition directly in the damaged tissue. This adaptability and versatility of the technique meet the necessity of the future in clinical applications, as modulation of shapes and geometries can be personalised.

The method has been described as compatible with additives, such as an osteogenic zirconium-modified amorphous calcium phosphate, related by Hoffman et al. [110] using poly-D,L-lactic acid (P-DL-LA), polycaprolactone (PCL), and poly(methyl methacrylate) (PMMA) polymers. Additionally, as an electric field does not drive the fiber formation, there is no necessity to use highly toxic fluorinated solvents due to their electrical conductivity [32].

The ability to direct the deposition of the fibers is a considerable advantage in tissue engineering, expanding the investigation into bio-based polymers. Few investigations around collagen fibers produced by SBS are found in the literature, as its denatured form, gelatin, is usually employed as a bio-based source to produce ultrathin fibers. Zheng et al. [111] reported the production of a collagen blow-spinning nanofibrous membrane with enhanced specific surface area compared to the one produced by ES. Recently, the same group described the fabricating of collagen nanofibrous nerve guidance conduits [54], launching SBS as a promising technique for biomaterial scaffold fabrication with excellent biosafety and effectiveness.

3.2. Gelatin ultrathin fibers

When exposed to thermal treatments above its denaturation temperature, collagen undergoes the breaking of hydrogen and covalent bonds in such a number that the irreversible destabilisation of the triple helix occurs, resulting in gelatin. Prior to this thermal denaturation process, it is necessary to swell the protein source, and at this stage, acidic or alkaline solutions can be used, depending on the degree of crosslinking of the material. Less cross-linked sources are typically swollen with acidic solutions, resulting in a protein with an isoelectric point (pI) between 6.0 and 9.0 classified as type A; more crosslinked materials, in turn, are treated with basic solutions, resulting in type B gelatin, with a pI between 4.8 and 5.2. At the end of this process, a mixture of polypeptides of α, β, and γ chains is obtained, formed by single chains or by two or three covalently crosslinked α chains, respectively [60,61,65,112].

This protein is also a material of interest for the development of biomaterials. Although gelatin does not present the same performance as collagen in biomedical applications, it exhibits biodegradability and biocompatibility, and also higher commercial availability and low cost, having already demonstrated wound healing activity, assisting in tissue regeneration [172]. The main disadvantage of gelatin as a biomaterial is its water solubility, a property that affects its performance in biological systems, composed of aqueous media, resulting in rapid degradation and absorption. This property often compromises some functions of the device that the protein comprises. However, like collagen, gelatin can be crosslinked to gain chemical and thermal stability, and so to resist the degradation promoted by the composition of the deployment environment [60,61,113] without losing its biodegradability [66,67].

The gelatin market is concentrated in the food industry as a stabilising, gelling or clarifying agent, thickener, film former, among other applications. In pharmaceutical and biomedical industries, it is mainly used for the production of capsules, wound dressings, and supplements. This protein is also used, for example, for cosmetics in conditioners, shampoos, and lipsticks and in photography as a gelling agent for the suspension of silver salts [65]. In 2023 this market was globally estimated around 464 thousand tons, moving 7 billion dollars in 2024, with the growth expectation at a compound annual growth rate of 10.1 % from 2024 to 2030 [114,115].

Gelatin is also a protein widely used in the development of biomaterials. When used in the form of ultrafine fibers, the most employed technique for producing gelatin-based mats is ES, as for collagen. Reviews about gelatin ultrathin fibers produced exclusively by ES were written by El-Seedi [116] and by Li [48], with a focus in applications as dressing materials for wound healing. These nano, submicron or microfibers have been studied for applications in drug delivery [117–119], bone reconstruction [120], hemostatic materials [121,122], but also for food packaging [123,124] and air filtration [125], for example. These and other studies are listed in Table 2, highlighting the type and source of gelatin, the solvent used and the diameter of the produced fibers, among other information.

Both type A and type B gelatins are employed in ultrathin fiber production. While type A gelatins are generally more similar to collagen in terms of their amino acid composition and exhibit a wider distribution of molecular weight (10 to 200 kDa), type B gelatins are more strongly cross-linked and present a molecular weight around 100 kDa. This is because type B gelatin primarily utilises more cross-linked raw materials for extraction [126]. The authors employing SBS use equally type A and type B gelatin, however, when applying ES the most common is to spin type A gelatin. This may be, in part, due to the need for solutions with low viscosity and/or surface tension for ES, since type B gelatins are more cross-linked, what implies higher viscosity after solubilization or even lower solubility in some solvents.

The main source of gelatin applied for fibers production is porcine skin (type A), followed by bovine skin and also fish (skin, bones and scales). Although fish gelatin is less used for this purpose, there are several advantages for the use of this nonmammalian raw material, already mentioned in the previous section, ranging from cultural to safety aspects. Farias [127] electrospun gelatin from these three sources and reported that the thinner fibers were obtained from bovine and fish gelatin, with average diameters ranging from 47 to 110 nm for 20–30 % bovine gelatin solutions and from 68 to 109 nm for 25–35 % fish gelatin solutions, while porcine solutions (20 and 25 %) resulted in fibers with average diameter between 168 and 274 nm.

Liu and coworkers [37] tested the spinning of gelatins from two

Table 2
Overview of the studies applying the electrospinning and solution blow spinning methods to produce gelatin fibers.

Type	Source	Blend/Encapsulated substance	Solvent	Concentration	Flow rate (mL h^{-1})	Technique	Voltage (kV)	Pressure (MPa)	Average Diameter (nm)	Reference
n.i.	n.i.	–	90 % acetic acid	9, 12 and 15 %	10	*E*-SBS	0, 15 and 20	0.1, 0.2 and 0.3	94–250	Eticha et al. [125]
A B n.i.	porcine bovine cold-water fish skin	–	30 % acetic acid	20–35 %	1.2	ES	25	-	168 ± 60 (20 %) 274 ± 87 (25 %) 47 ± 14 (20 %) 89 ± 25 (25 %) 110 ± 24 (30 %) 68 ± 17 (25 %) 76 ± 22 (30 %) 109 ± 48 (35 %)	Farias et al. [127]
n.i.	n.i.	PLA/absorbable hemostatic particles	HFP	10 %	0.4	SBS	–	0.400	n.i.	Gao et al. [121]
B	n.i.	curcumin (CUR) and PCL	acetic acid	12.5 %	3	SBS	–	0.100	G: 960 G/CUR: 1258	Cai et al. [117]
A	porcine skin	PCL (80 kDa)	HFP	G/PCL 1:4, 5 % G/PCL 2:3, 5 % G-PCL core-shell 5 % PCL-G core-shell 5 %	1.0	ES	13–22	–	520 890 780 650	Longo et al. [131]
n.i.	n.i.	PLA/AgNP	acetic acid	24 %	6	SBS	–	0.05	743 (G) 773 (G/AgNP) 335 (G/PLA/AgNP)	Alinezhad Sardareh et al. [139]
B	n.i.	pullulan	acetic acid	12 %	3	SBS	–	0.1	211–414	Shen et al. [132]
A	pigskin	PLA	HFP	8 %*	n.i.	ES	10	–	584 ± 188	Chen et al. [133]
B	bovine skin	PCL; nHAp (different dipping time)	chloroform/methanol (3:1)	8 %	0.1	ES	22	–	444 ± 124 nm (0 min nHAp dipping) 505 ± 146 nm (10 min) 615 ± 269 nm (20 min) 477 ± 108 nm (30 min)	Gautam et al. [120]
A	n.i.	PCL and cellulose fibers (CNF) or acetylated CNF (ACNF)	formic acid/acetic acid (1:3)	10 %*	0.1 and 0.2	ES	11–14	–	300 (G) 95 ± 11 (PCL/G) 128 ± 2 (PCL/G/CNF) 154 ± 26 (PCL/G/ACNF)	Moazzami Goudarzi et al. [165]
A	n.i.	PCL/CuO NPs	TFE	4 %	1	ES	13	–	157 ± 16 (PCL/G) 135 ± 12 (PCL/G/NPs)	Karuppannan et al. [135]
A	porcine skin	glucose	10 mol/L aqueous acetic acid	20 %	n.i.	SBS	–	0.2	1520 ± 540	Klaas et al. [162]
n.i.	n.i.	PCL	TFE	10 %	0.05	ES	5	–	195 (100:0) GT/PCL 242 (70:30) 288 (50:50) 356 (30:70) 562 (0:100)	Lim et al. [166]
A	pork skin	ethanolic pomegranate peel extract (EPPE)	70 % acetic acid	15–35 %	0.1	ES	20	–	39 ± 6 (15 %) 143 ± 33 (20 %) 243 ± 34 (25 %) 367 ± 40 (30 %) 550 ± 82 (35 %) 80 ± 25 (20 % G + 25 % EPPE) 328 ± 81 (20 % G + 50 % EPPE)	Saadat, Emam-Djomeh and Askari [134]
B	n.i.	natamycin (NM) and zein (ZE)/PU	acetic acid solution	20 %*	3	SBS	–	0.1	4490 ± 2150 (G/ZE) 557–682 (G/ZE/NM)	Shen et al. [123]
n.i.	bovine	PDL-CL copolymer crosslinked with GA	HFP	8 %	1.5–2.0	ES	25	–	76.4 ± 21 (PDL-CL) 379 ± 67 PDL-CL/G (70:30) 470 ± 96 PDL-	Ulker Turan and Guvenilir [130]

(*continued on next page*)

Table 2 (*continued*)

Type	Source	Blend/Encapsulated substance	Solvent	Concentration	Flow rate (mL h^{-1})	Technique	Voltage (kV)	Pressure (MPa)	Average Diameter (nm)	Reference
									CL/G (60:40) 305 ± 46 PDL-CL/G (50:50)	
A	porcine skin	–	TFE	15 %	1.2	ES	8	–	780 ± 166 (membrane) 683 ± 147 nm (sponge)	Xie et al. [122]
n.i.	n.i.	nylon 66 (PA 66)	acetic acid	12 % G/PA (2:1, 1:1, 1:2)	3	SBS	–	0.06	1095 ± 36 (G) 172 ± 4 (G/PA 2:1) 199 ± 4 (G/PA 1:1) 322 ± 6 (G/PA 1:2)	Yang et al. [124]
n.i.	n.i.	PCL/PLA/oligo (L-lactide)/chitosan copolymer	chloroform	25 %*	n.i.	ES	13–17	–	7600 ± 5800	Demina et al. [167]
A	porcine skin	phenolic hydroxyl (Ph); horseradish peroxidase (HRP); PEO	n.i.	2, 4 and 8 %	0.3	ES	18	–	141 ± 27 (2 % G) 146 ± 31 (4 % G) 160 ± 37 (8 % G) 176 ± 38 (8 % G exposed to H_2O_2)	Furuno et al. [168]
B	bovine skin	cellulose acetate; berberine	HFP	6 %	0.2	ES	15	–	425 ± 79 (no berberine) 502 ± 150 nm (with berberine)	Samadian et al. [136]
n.i.	porcine skin	PCL	TFE:DMF (75:25)	10 %	1.5	ES	27	–	0.69 ± 0.19 (10 % PCL in TFE:DMF) 0.30 ± 0.07 (10 % PCL + GEL (1:1) in TFE)	Semitela et al. [169]
B	n.i.	PBAT and doxycycline	DMF/DCM (1:3)	50 %	0.5–0.8	ES	15–18	–	62–302 (G/PBAT) 75–529 (with doxycycline)	Varshosaz et al. [119]
A	porcine skin	PMETAC	formic/acetic acid (3:1)	n.i.	0.03–1.2	ES	15–25	–	distinct diameters, ranging from 201.16 ± 29.95 (100 % G, flow rate 1.2 and 25 kV) to 2410.12 ± 258.65 (20 % G/80 % PMETAC, flow rate 1.2 and 25 kV)	İnal and Mülazımoğlu [137]
A	porcine skin	sericin (S) and halloysite nanotubes (HN)	formic acid	8.5, 15 and 17 %	0.25	ES	8	–	183 ± 6 (G/S 1:1) 138 ± 6 (G/S 1:2) 274 ± 12 (G/S 2:1) 338 ± 5 to 1439 ± 15 (G/S/HN)	Massoumi et al. [138]
A	n.i.	PCL and *Gymnema sylvestre* extract (GS) or gymnemagenin (GY)	TFE	4 %	1	ES	13	–	234 ± 52 (PCL/G) 154 ± 21 to 176 ± 48 (PCL/G/GS) 202 ± 49 (PCL/G/GY)	Ramalingam et al. [118]
A	porcine	–	18 % acetic acid	10–45 %	0.120–120	SBS	–	0.05–0.35	110–1001 (20–35 %) 2000–3000 (40 %)	Singh et al. [128]
B	bovine skin	PLGA	HFP	10 %	0.3–1	ES	10	–	500 ± 200 (PLGA/G 9:1) 1700 ± 700 (PLGA/G 7:3) 1300 ± 500 (PLGA/G 5:5) 900 ± 200 (G)	Vázquez et al. [170]
n.i.	fish skins, bones and scales	–	80 % acetic acid	15 % 20 % 25 %	8.1	SBS	–	0.200	280 750 1195	Vilches et al. [129]

* Concentration of the blend; DCM: dichloromethane; DMF: dimethylformamide; ES: electrospinning; E-SBS: electrally-assisted SBS; GA: glutaraldehyde; HFP: hexafluoroisopropanol; nHAp: nano hydroxyapatite; n.i.: not informed; NPs: nanoparticles; PA: polyamide; PBAT: polybutylene adipate-co-terephthalate; PCL:

polycaprolactone; PDL-CL: poly(ω-pentadecalactone-*co*-ε-caprolactone); PEO: poly(ethylene oxide); PLA: polylactide; PLGA: poly (D-L lactide-*co*-glycolide); PMETAC: poly([2-(methacryloyloxy)ethyl] trimethylammonium chloride); PU: polyurethane; SBS: solution blow spinning; TFE: 2,2,2-trifluoroethanol.

sources, porcine and fish skin, by SBS. Gelatin from fish skin with high molecular weight allowed the production of ultrathin fibers, while porcine gelatins of different molecular weights (100, 150, and 225 Bloom) did not produce fibers under any of the tested concentrations and conditions. The authors attributed the milder treatment during fish gelatin extraction and consequently higher preservation of collagen fibers in this gelatin to its greater capacity for entanglement formation in its solutions, thus increasing its reliability. Later, however, other researchers [128] reported the production of gelatin fibers from porcine source (type A), using similar concentrations, solvents, and spinning parameters.

It is still possible to find recent studies [128,129] focused on better understanding how the properties of gelatin solutions and their processing conditions affect the characteristics of fibers produced by SBS. This is evidence of the more recent use of this technique for this purpose compared to ES, which is already widely used. Both studies indicate a direct relationship between the concentration of the solutions and the average fiber diameter, ranging from the submicrometer scale when using more diluted concentrations to the micrometer scale in samples above 25 or 35 % (using different concentrations of acetic acid as solvent). Additionally, Singh et al. [128] suggests that increasing the flow rate also increases the fiber diameter, while pressure seems to have a nonlinear relationship with the size of these fibers.

Blends of gelatin with synthetic polymers such as PCL and PDL-CL (poly ω-pentadecalactone-*co*-ε-caprolactone) were also electrospun to study the relationship between the characteristics of these fibers and the composition of the blends [130] or the mixing method - in solution or by coaxial spinning [131].

A gelatin blend was used to produce fibers by SBS mixing the protein with pullulan, a polysaccharide employed here to crosslink the polymer mats *via* Maillard reaction with controlled heating [132]. The authors observed that increases in reaction time led to higher crosslinking levels, which resulted in reduced water vapor permeability and increased hydrophobicity, as well as enhanced mechanical and thermal resistances, thereby improving the properties of interest for application as food packaging.

Gao et al. [121] produced fibers from a blend of gelatin/PLA by SBS with a simultaneous addition of absorbable hemostatic particles by spraying them out with a powder blower. The authors reported good water absorption rate and hemostatic performance (< 2 min), biocompatibility and degradability, with the advantage of being possible to be applied *in situ*. Xie et al. [122] produced tridimensional sponges of gelatin ultrathin fibers through the novel conjugation of two ES devices with opposite charges used to produce entangled fibers. The posterior thermal crosslinking resulted in water resistant materials with hemostatic capacity.

A method called electrically-assisted solution blow spinning (ESBS) was applied to produce gelatin nano and submicrometric fibers for air filtration. Eticha and Akgul [125] combined the principles of ES and SBS to overcome some drawbacks of these techniques, such as the tendency of SBS to produce fiber bundles rather than more oriented and separated fibers, and the low production rate typical of ES. The filters produced presented filtration efficiency above 90 %.

Aiming to combine the promising properties of gelatin fibers with the benefits of *in situ* application of these materials, a portable device was developed for wound healing applications. Chen et al. [133] created a device using 3D printing, which produced submicron fibers of PLA/gelatin and tested their performance in the repair of skin wounds in rats. In addition to the PLA/gelatin mats not exhibiting cytotoxicity, they preserved the cellular activity of fibroblasts cultured *in vitro*, increasing their proliferation. Finally, the authors reported complete recovery of skin wounds in the group treated with the ultrathin fibers mats, while the control group showed only partial recovery, reinforcing the applicability of this technology in skin wound healing.

An alternative to incorporate or enhance certain properties of ultrafine gelatin fibers produced by ES is the incorporation of active compounds, such as pomegranate peel extract [134], which is rich in compounds with antioxidant and antimicrobial activities, or other antibacterial agents like copper oxide nanoparticles [135], berberine [136], PMETAC, a quaternary ammonium polymer [137], halloysite nanotubes loaded with copper and zinc ions [138] or the herbal extract of *Gymnema sylvestre* [118].

As with electrospun fibers, it is common to incorporate active compounds into fibers produced by SBS to enhance or add certain properties. Silver nanoparticles were integrated by Alinezhad Sardareh et al. [139] to PLA/gelatin ultrathin fibers to produce antibacterial textiles. The material showed a very low level of cytotoxicity and higher antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus*. Curcumin was controlled released from multilayer films composed of spun gelatin/PCL fibers, resulting in *E. coli* and *S. aureus* inhibition [117]. Natamycin, an established food preservative, was incorporated to PU/gelatin/zein blends, resulting in fibers more hydrophobic and with antimicrobial activity against *Botrytis cinerea* and *Alternaria alternate*, two bacteria commonly found in food [123].

The most commonly used solvents to produce ultrafine gelatin fibers by SBS are aqueous acetic acid solutions, while for ES are fluoroalcohols like HFP and TFE. This difference may be related to the fact that SBS is less limited about solvents with lower volatility. Despite this advantage of using safer solvents, the solubility of gelatin makes it necessary for most of its applications to crosslink gelatin-based ultrathin fibers materials. So, various methods can be found to this end, including chemical methods using common crosslinking agents like glutaraldehyde, or safer options such as genipin, as well as crosslinking methods involving irradiation or thermal treatments [140–142].

3.3. Application of collagen and/or gelatin ultrafine fibers

SBS fibers, in general, have been widely used for different and several purposes, due to advantages such as their porous networks, high surface area, crystalline structures, and possibility of scaling production, among others [12]. Fig. 5(a) summarises some of the main applications for polymeric SBS fibers, with their possible ramifications. Fig. 5(b) shows the setup for the production of collagen type I fibrous scaffolds intended for meniscus tissue engineering [143]; the ultrathin fibers developed in Fig. 5(c), in turn, consisted of glycosylated gelatin/pullulan and were intended for food packaging purposes [132]. Finally, Fig. 5(d) shows the scanning electron microscopic images of solution-blown nanofibrous scaffolds (both mats and tubes) of polyurethane, polydopamine, and gelatin, intended for the rapid endothelialization of vascular scaffolds [144].

Biomedical applications stand out as one of the most explored areas of many biomaterials, including ultrathin fibers; despite the predominance of ES, SBS ultrafine fibers have been extensively used in the past decade for this purpose. Among the main biomedical applications, tissue engineering is the most studied due to the similarity of the fibers structure with the extracellular matrix, which facilitates cell adhesion [145]. Other popular applications in the field are the use of the SBS fibers for the controlled release of drugs, as well as antimicrobial materials [146,147].

After biomedical, environmental applications are the second most popular field for fibers produced by SBS; the fibers can be easily applied as membranes for air filtration or as adsorbents for water pollutants such as metal ions and CO_2 [148,149]. Regarding food applications, ultrafine fibers can be used as food packaging materials, acting as barriers against external agents (*e.g.*, microorganisms, water, heat, gas) that could cause spoilage and/or deterioration of food [150]. The fibers can also be

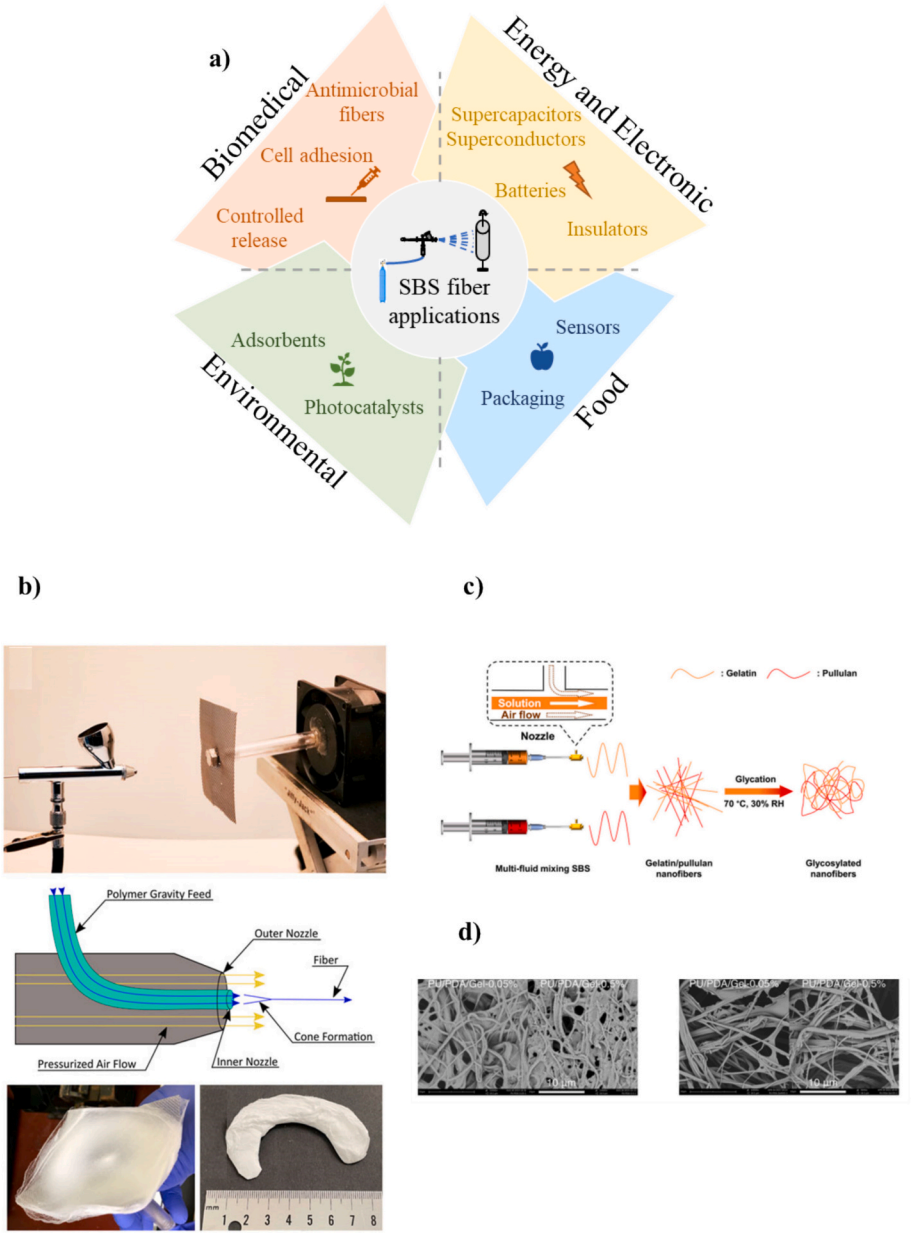

Fig. 5. In (a), the main areas of application of materials prepared by the SBS method; in (b), the pneumatospinning setup and the produced collagen type I fibrous scaffolds intended for meniscus tissue engineering ([143]; image reprinted under a CC BY license); in (c), the fabrication of glycosylated gelatin/pullulan ultrathin fibers by multi-fluid mixing solution blow spinning for food packaging applications ([132]; image reprinted with permission of Elsevier); in (d), the scanning electron microscopic images of solution-blown nanofibrous scaffolds of polyurethane, polydopamine, and gelatin, in the form of mats (left) and tubes (right), intended for the rapid endothelialization of vascular scaffolds ([144]; image reprinted under a CC BY license).

applied as smart sensors that change color when subjected to different conditions, such as the pH of the medium; according to the coloration of the fiber surrounding the food, the consumer could detect unfavourable consumption conditions [151].

Finally, SBS fibers can be used for energy and electronics-related applications, due to the increasing demand for storage devices of high-power and high-density energy; because of the versatility of their composition and their architecture, these materials can be used as supercapacitors, fuel cells, batteries, superconductors, among others [152,153].

Table 3 shows the articles from the last 6 years (2019–2024) that produced and characterised ultrafine collagen and gelatin fibers. Most of these studies were focused on tissue engineering as the main application of the developed materials. While some of them focused on the preparation and characterization of the fibers (as it will be discussed in the next section), others went further and also conducted *in vivo* studies with the developed materials.

Dorthé et al. [143], for example, assessed the *in vivo* potential of their pneumatospun collagen/glutaraldehyde scaffolds for the repair of meniscus tears; for that, they surgically created defects in the healthy bovine meniscus and in the osteoarthritic human meniscus and implanted the scaffolds seeded with mesenchymal stem cells. After 3 weeks of culture, the authors could observe neofibrocartilaginous tissue developed in both host tissues.

Gao et al. [121], in turn, developed a cardiac hemostatic plug of polylactic acid/ gelatin to block cardiac bleeding. For the *in vivo* study, the authors removed a portion of the heart tissue of pigs, creating 1 cm diameter penetrating wounds; the authors reported that the bleeding was effectively stopped by the ultrathin fibers plug, and that the entire hemostasis process took less than two minutes.

Table 3
Properties of the collagen/gelatin ultrafine fibers produced by SBS reported in the literature in the last 6 years.

Fibers	Water-related properties	Mechanical properties	Thermal properties	Release properties	Antimicrobial activity	Cytocompatibility	Application	Reference
Gelatin/ polycaprolactone/ curcumin	- The multilayer film was more hydrophobic than the gelatin films (with and without curcumin), with a water contact angle around 40° higher	- The tensile strength of the multilayer film was 9 times higher than the gelatin films (with and without curcumin)	- The melting temperature of the gelatin film increased with curcumin addition - The melting temperature was around 50 °C lower for the multilayer film	- The multilayer film released around 30 % less curcumin than the gelatin film	- Both the gelatin/ curcumin and the multilayer films had inhibitory effects against *Escherichia coli* and *Staphylococcus aureus*	–	Food packaging	Cai et al. [117]
Polycaprolactone/ poly(L-lactide)/ oligo(L-lactide)/ chitosan/gelatin	- The electro ionization-SBS (EA-SBS) fibers showed higher porosity, water retention capacity, and swelling capacity than the electrospinning (ES) fibers - The EA-SBS fibers were more hydrophobic (102°) than the ES fibers (89°)	- The fibers obtained with EA-SBS showed the same elongation at break values (around 18 %) as the ones obtained with ES, but lower tensile strength values (1.18 MPa)	–	–	–	- The EA-SBS fibers showed the highest viability and proliferative activity for the cultured cells	Tissue engineering	Demina et al. [157]
Collagen/ glutaraldehyde	–	- The pneumatospun scaffolds had their elastic modulus significantly reduced from 45 to 0.1 MPa after hydration - Larger interconnected porosities in the pneumatospun scaffolds (when compared to electrospun)	–	–	–	- Enhanced cell attachment and infiltration into the scaffold after crosslinking with glutaraldehyde - Viability of mesenchymal stem cells higher than 70 % in the pneumatospun scaffolds	Tissue engineering	Dorthé et al. [143]
Gelatin	- The crosslinking with glutaraldehyde decreased the hydrophilicity of the optimized gelatin fibers, decreasing water contact angle values	–	–	–	–	–	Air filtration	Eticha et al. (2024)
Polylactic acid/ gelatin	- Decrease in the hydrophobicity of the fibers with gelatin inclusion - Increase in the water absorption rate (around 700 %) of the fibers with gelatin inclusion	–	–	–	–	- Better cell ductility and more cells adhered in the fibers containing gelatin -Proven non-toxicity	Cardiac hemostasis	Gao et al. [121]
Gelatin/glucose	- In the hydrated state the material was considerably denser and the voids between the fibers were shrunk	–	–	–	–	- The materials were highly cytocompatible and facilitated the induction of hepatocyte gene expression in response to common medications	Tissue engineering	Klaas et al. [162]
Polyurethane/ polydopamine/ gelatin	- Porosity higher than 85 % for all the prepared materials (mats and tubes) - Inclusion of gelatin in both mats and tubes led to a significant decrease in the hydrophobicity of the polyurethane materials	- Coating with polydopamine and gelatin led to stiffer materials - Increase in the tensile strength and decrease in the elongation at the break of the mats	- Decrease in the mass loss and in the temperature of pyrolysis of the materials	–	–	- The number of human umbilical vein endothelial attached cells was significantly higher for the coated fibers	Tissue engineering	Kopeć et al. [144]

(*continued on next page*)

Table 3 (*continued*)

Fibers	Water-related properties	Mechanical properties	Thermal properties	Release properties	Antimicrobial activity	Cytocompatibility	Application	Reference
Poly-ε-caprolactone/ collagen	- Increase in the water contact angle of the films with collagen addition from 117° to ~125°	–	–	–	–	- Cell viability was higher than 90 % for all the films with collagen for 7 days - Cell proliferation between 300 and 400 % for all the films with collagen after 7 days	Tissue engineering	Lorente, Corral and González-Benito [156]
Polylactic acid/ gelatin/silver nanoparticles	–	–	–	- Gelatin inclusion increased the cumulative release of the nanoparticles from the films over time (around 0.1 mg after 24 h)	- The films containing gelatin and the nanoparticles were the only ones to show inhibition higher than 60 % for both *Escherichia coli* and *Staphylococcus aureus*	- The fibroblast cell viability was higher than 90 % for the films containing gelatin	Wound healing	Alinezhad Sardareh et al. [139]
Gelatin/zein/ polyurethane/ natamycin	- The hydrophobicity of the fibers increased with natamycin addition and the increase in its concentration (water contact angle ranging from 70 to 120°)	- The addition of polyurethane improved the elongation at the break of the fibers from 13.58 % to 531.38 %	- The thermal stability of the fibers was improved after natamycin encapsulation, with lower residual weight at 600 °C	- The fibers showed a continuous release of natamycin (between 50 and 60 %) for 240 h	- The inhibitory diameters of the fibers against *Botrytis cinerea* and *Alternaria alternate* were positively correlated with the weights of encapsulated natamycin	–	Food packaging	Shen et al. [123]
Glycosylated gelatin/ pullulan	- After 120 h of glycation, the water the contact angle of fibers increased from 0° to 79.1°, and the water vapor transmission rates decreased from 12.49 to 8.97 g mm/m^2 h kPa, indicating enhanced hydrophobicity and barrier properties	- The elongation at the break of the fibers significantly decreased from 10.19 % to 2.57 % after 120 h of glycation	- The thermal stability of the fibers was improved after the glycation, with lower degradation rates and higher residue weight	–	–	–	Food packaging	Shen et al. [132]
Gelatin/ glutaraldehyde	–	–	–	–	–	- Cell proliferation was higher in gelatin fibers scaffolds compared to the control sample - The natural morphology of cells on the materials confirmed that the airbrushed gelatin fibers mimic the structural microenvironment of the extracellular matrix	Tissue engineering/ wound healing	Singh et al. [128]
Gelatin	- Swelling ratio of 10, porosity around 67 %	- The stress of the gelatin sheets was 7.6 kPa at 30 % strain and 20.6 kPa at 50 % strain	–	–	–	- The number of cells that migrated into the gelatin sheet increased over time - The cells cultured in the sheets had higher collagen mRNA expression than those cultured on plastic dishes	Tissue engineering	Uemoto et al. [154]
Gelatin	–	–	- All fibrous mat gelatins (with concentrations ranging from 15 to 25 %) showed similar thermal profiles	–	–	–	Not specified	Vilches et al. [129]

(*continued on next page*)

Table 3 (*continued*)

Fibers	Water-related properties	Mechanical properties	Thermal properties	Release properties	Antimicrobial activity	Cytocompatibility	Application	Reference
			- The thermal stability was strongly influenced by the diameters of the fibers					
Gelatin/Nylon 66	- The water vapor barrier performance of the composite film was improved (permeability of 9.93 g mm/m^2 h kPa) - The hydrophilicity of the gelatin film was improved with Nylon 66 addition	- The elongation at the break of the composite film increased from 7.98 % to 30.36 %, and its tensile strength increased from 0.03 MPa to 1.42 MPa	- Decrease in the melting temperature of the gelatin films with Nylon 66 addition from 126.5 to 106.2 °C	–	–	–	Food packaging	Yang et al. [124]

Uemoto et al. [154] developed an artificial bile duct with gelatin fibers for biliary reconstruction. These fibers were implanted in the place of resected bile duct segments in rats, and after 2 weeks migrating cells could be already observed in the bile duct pores. After 6 weeks, the artificial bile duct was almost entirely degraded and replaced by collagen fibers. Finally, after 12 weeks most of the bile duct lumen had been covered by biliary epithelial cells, which confirms the successful bile duct regeneration in rats induced by the gelatin fibers due to the facilitated cell migration.

In addition to tissue engineering, the other application that appears in some of the studies of Table 3 is food packaging. Despite still being a recent area with little research, the number of articles that apply fibers obtained by SBS in food packaging has been growing in recent years. Because it is a technique that allows the rapid manufacture of fibers on a large scale, it has been gaining attention and prominence in a field where ES fibers still predominate [124,155]. All the studies presented in Table 3 that developed fibers for food packaging used gelatin as a matrix and, despite their extensive characterization of the prepared materials, they did not apply the fibers produced in any food model. Thus, much research is still needed in this area, to assess the properties of fibers when in contact with food and how they will contribute to extending their shelf life.

3.4. Properties of collagen and/or gelatin ultrafine fibers

The properties of SBS-developed fibers are directly related to their morphology and will directly affect their performance in the most diverse applications. As mentioned before in the description of the technique, factors such as the nature and concentration of the polymers, the gas flow rate, the injection rate, and the receiving distance are crucial for the morphology of the produced fibers, especially for their diameter. Therefore, morphological characterization is the first step to evaluate the feasibility of a new material produced by SBS for its targeted application.

In addition to morphological characterization, ultrafine fibers can also be characterised in terms of their wettability, their mechanical and thermal properties, as well as their activity against microorganisms, and their cytotoxicity and suitability for cell proliferation. All these tests are of extreme importance for the adequate choice of the fiber to be used and may dictate its application. In this section, the importance of these characterizations and the main observed effects by the studies in Table 3 will be explained.

3.4.1. Wettability

Regardless of the proposed application for the ultrafine fibers of collagen and gelatin, whether for tissue engineering or for food packaging, for instance, these materials will necessarily encounter a physiological medium, consisting mainly of water [156]. Thus, the wettability of the surface of these fibers must be evaluated, since it will dictate factors such as cell behaviour, antimicrobial agents loading, and bacteria biofilms development [124,156]. One of the most suitable characterizations for this purpose is to determine the water contact angle (WCA) of the fibers surface.

Demina et al. [157] compared the WCA of their polycaprolactone/poly(L-lactide)/ oligo(L-lactide)/chitosan/gelatin fibers obtained by ES and electro ionization-SBS (EA-SBS) and targeted for application in tissue engineering. Both fibers were hydrophobic, with WCA around or higher than 90°; the fibers obtained by EA-SBS, however, were more hydrophobic. The authors attributed this result to the higher surface roughness and unevenness of the EA-SBS fibers diameter, which could trap more air and cause a higher water repulsion. Lorente et al. [156], in turn, prepared poly-ε-caprolactone/collagen films by SBS and reported that collagen addition in different concentrations led to a slight increase in the WCA from 117 to 125°. The authors stated that the hydrophobicity of the prepared films would be useful for applications in which water adsorption is not desired and for the non-attachment of bacteria

and other pathogens.

Cai et al. [117] prepared multilayer films of gelatin/polycaprolactone/curcumin by SBS, aiming their application as food packaging materials. The authors reported that the multilayer film was more hydrophobic than the gelatin films (with and without curcumin), with a WCA around 40° higher. They attributed this result to the presence of polycaprolactone, which is useful to protect the inner layer composed of gelatin from water dissolution. Shen et al. [123] developed gelatin/zein/polyurethane/natamycin fibers by SBS, also for food packaging. In their case, the hydrophobicity of the ultrathin fibers increased with natamycin, with WCA ranging from 70 to 120°. The authors related this result to the hydrophobic nature of natamycin and to the interactions formed between it and the proteins in the fibers.

Besides wettability, other water-related properties can also be evaluated for ultrafine fibers, such as swelling and water vapor permeability (WVP). Uemoto et al. [154] prepared gelatin sheets by SBS and determined their swelling ratio by weighing the sheets dried and swollen, reaching a value of around 10. Yang et al. [124], in turn, developed gelatin fibers with Nylon 66 by SBS for food packaging applications and determined the WVP of these materials. The lower the WVP, the lower the exchange of water between the packaged food and the environment, which can be useful to extend the shelf life of the food and protect it from microbial contamination. The inclusion of Nylon 66 in the gelatin fibers at a 2:1 ratio improved their water barrier properties, decreasing the WVP from 16.99 to 9.93 g mm/m^2 h kPa.

3.4.2. Mechanical properties

The mechanical properties of collagen/gelatin ultrafine fibers are also of extreme importance to dictate their performance in the proposed applications. Despite their favorable biocompatibility, biodegradability, and nontoxicity, both gelatin and collagen produce ultrafine fibers with really poor mechanical characteristics [158]. In most of the articles presented in Table 3, these proteins are combined with crosslinking agents such as glutaraldehyde or synthetic polymers like poly(caprolactone) and Nylon 66, in order to improve their mechanical stability [124].

The inclusion of crosslinking agents will change the interactions between the polymer chains and the degree of molecular entanglements, leading to a lower mobility of the chains and, consequently, enhancing the elastic modulus and the tensile strength of the ultrafine fibers. The improvement in the tensile strength, in most cases, leads to a decrease in the elongation at the break of the materials [159]. Therefore, the elastic modulus, tensile strength, and elongation at break are the most common mechanical parameters determined for the characterization of collagen/gelatin fibers.

The gelatin films prepared by Yang et al. [124] had their mechanical properties improved with Nylon 66 inclusion; the gelatin film by itself had poor ductility and mechanical strength, but with Nylon 66 addition at a 1:1 ratio, its elongation at break increased substantially from 7.98 % to 30.36 %, while its tensile strength shifted from 0.03 MPa up to 1.42 MPa. Shen et al. [132] prepared glycosylated gelatin/pullulan nanofibrous films for food packaging applications, and reported that the glycation time had a significant influence on all the mechanical parameters of the materials, increasing the tensile strength from 0.025 to 0.094 MPa and decreasing the elongation at break from 10.19 to 2.57 % after 120 h.

Kopeć et al. [144] produced polyurethane mats and tubes coated with polydopamine and gelatin for endothelialization and tissue engineering; the authors reported that coating with polydopamine and gelatin led to stiffer materials for both mats and tubes. For the nanofibrous mats, the increased stiffness resulted in an increase in the tensile strength of samples, which means that the modified materials were able to sustain higher loads. Dorthé et al. [143] prepared collagen pneumatospun scaffolds crosslinked with glutaraldehyde for tissue engineering proposals and compared the mechanical properties of the scaffolds before and after hydration (*i.e.*, dry and wet). The elastic modulus of the collagen scaffolds decreased from 45 to 0.1 MPa after hydration, which emphasises that the mechanical properties of the materials produced can be directly influenced by their degree of hydration.

3.4.3. Thermal properties

In addition to water-related and mechanical properties, the thermal properties of collagen/gelatin ultrafine fibers are also important to evaluate their stability for the proposed application. The thermal stability and degradation of the materials can be analysed by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA). The DSC curves provide parameters like glass transition temperature, melting temperature, and melting enthalpy, which are directly related to the hydrogen bonds existent in the polymeric matrix [160]. TGA analysis, in turn, provides the phases of thermal degradation of the material, how fast they occur, and the residual weight that remains after a certain temperature, which can also be related to its thermal stability [123].

The gelatin films developed by Cai et al. [117] for food packaging had their melting temperature in the DSC curves increased from 108.52 to 114.35 °C with curcumin addition, which indicated the formation of new bonds between the protein and curcumin. Their multilayer film composed of polycaprolactone as the outer layer and gelatin/curcumin as the inner layer had a melting temperature of 57.69 °C, closer to the melting temperature of polycaprolactone.

Vilches et al. [129] prepared mats by SBS with different concentrations of gelatin (from 15 to 25 %) and related their thermal stability to the diameter of the obtained fibers. The authors detected three phases of mass loss in the TGA curves of the fibers: the first one, between 30 and 160 °C, was attributed to the adsorbed water evaporation; the second phase, between 160 and 260 °C, was related to the protein degradation, while the mass loss above 260 °C was attributed to the thermal decomposition of gelatin. The authors reported that the water content of the fibers decreased with increasing their diameter, which hindered the diffusion of water from the internal to the external region of the microfibers.

Shen et al. [123] prepared gelatin/zein/polyurethane/natamycin fibers for food packaging applications and also evaluated their thermal stability by TGA analysis. The authors found that the residual weight at 600 °C was increased from 4.92 % to 10.22 % by increasing the amount of natamycin from 0.01 g to 0.20 g in the ultrathin fibers, which proves that natamycin encapsulation improved the thermal stability of the ultrathin fibers.

3.4.4. Release properties

The SBS technique allows the incorporation of agents like nanoparticles, food additives, and antioxidant/antimicrobial extracts within the polymer, aiming to improve and/or provide some specific properties. Such incorporation can be achieved by chemical immobilization, like the covalent linking between the agent and the polymer, or by physical adsorption, like hydrogen bondings and hydrophobic effects; in the latter case, however, the interaction them is weaker [36].

Despite the encapsulation method, when developing ultrafine encapsulated fibers the release profile of these compounds by the fibers must be evaluated. Factors like the release rate and the maximum amount released can be related to the stability of the fibers when in contact with a physiological medium, which will allow the release process to occur. The preparation process of the fibers can also influence their performance as release media: as mentioned before, the high evaporation rate of solvent during the SBS process may lead to the appearance of the additives on the fibers' surface, which disturbs the release kinetics [32]. More specifically, both collagen and gelatin lead to hydrophilic materials, and their presence in the fibers can change their release profile, according to the material to which they are incorporated.

The gelatin/zein/polyurethane fibers developed by Shen et al. [123] containing natamycin as a food additive presented release percentages ranging from 47 to 55 % within the first 24 h; the authors attributed this result to the degradation and erosion of hydrophilic gelatin. However,

the ultrathin fibers continuously released the encapsulated natamycin for 240 h, which is a good result for the long-term protection that the food packaging material needs to provide.

Alinezhad Sardareh et al. [139] prepared polylactic acid/gelatin/silver nanoparticles fibers for wound healing purposes; when evaluating the release profile of the silver nanoparticles, the authors found that the gelatin inclusion to the polylactic acid fibers increased the cumulative release of the nanoparticles from the materials over time, releasing around 0.1 mg after 24 h. Cai et al. [117] also analysed the release profile of curcumin from their multilayer films of polycaprolactone and gelatin. The authors found that the sandwich structure was able to control the release of gelatin ultrathin fibers, since the gelatin film itself had a release rate 3 times higher than the one of the multilayer film, in 210 min. The multilayer film showed a slow release for a long time, which is a good result mainly attributed to the hydrophobicity of polycaprolactone.

3.4.5. Antimicrobial activity

Although gelatin and collagen do not show antimicrobial activity by themselves, the inclusion of compounds such as curcumin, silver nanoparticles and natamycin may confer this property to their ultrafine fibers. One of the most common methods of evaluating antimicrobial activity is the halo of inhibition test, which places the material in contact with colonies of test microorganisms and measures how far these microorganisms grow from the material. Shen et al. [123] performed this assay and concluded that the inhibitory diameters of the gelatin/zein/polyurethane ultrathin fibers against *Botrytis cinerea* and *Alternaria alternate* increased with the amount of encapsulated natamycin, reaching 63.46 and 69.98 mm of inhibition with 0.2 g of the additive, respectively.

Alinezhad Sardareh et al. [139] went further and not only proved that their fibers without silver nanoparticles had no inhibition against *Escherichia coli* and *Staphylococcus aureus*, as well as determined the quantitative antibacterial activity of the mats through the % inhibition when compared to the control. The polylactic acid mats containing both gelatin and the silver nanoparticles were the only ones to present an inhibition >60 % for both tested bacteria. Cai et al. [117] also tested these bacteria with their multilayer films containing curcumin, reaching 16.14 and 14.03 mm of inhibition for *E. coli* and *S. aureus*, respectively; the authors stated that the sandwich structure of their fibers did not alter the antimicrobial performance of curcumin.

3.4.6. Cytocompatibility

When the collagen/gelatin ultrafine fibers are developed for application in tissue engineering (*e.g.*, for bone repair, wound healing, hemostasis, among others), it is necessary to assess the safety of their application when in contact with cells. There are several methods to evaluate the cytotoxicity of biomaterials, based on different properties of the cells, such as their viability, proliferation, metabolic activity, and morphology [161].

Dorthé et al. [143] prepared pneumatosupun collagen scaffolds for tissue engineering purposes and crosslinked the protein with glutaraldehyde. The authors reported enhanced cell attachment and infiltration into the scaffold after crosslinking with glutaraldehyde; moreover, the viability of the mesenchymal stem cells was higher than 70 % in the pneumatospun scaffolds. Klaas et al. [162] studied the growth of primary human liver cells in gelatin/ glucose mats prepared by SBS; the hepatocytes retained their characteristic polygonal shape and their gene expression in response to common medications was facilitated.

Lorente et al. [156] prepared poly-ε-caprolactone/collagen films and measured both cell viability and proliferation according to the collagen concentration, for 7 days; all the films containing collagen showed cell viability higher than 90 % after 7 days, different from the film containing only poly-ε-caprolactone. Cell proliferation increased over time for all the films, but the ones with collagen showed the highest percentages of proliferation, between 300 and 400 %.

Singh et al. [128] analysed the proliferation and morphology of human bone marrow-derived mesenchymal stem cells cultured for up to 7 days in their airbrushed gelatin/glutaraldehyde fibers. Cell proliferation was higher in gelatin ultrathin fibers scaffolds compared to the control sample and the natural morphology of cells was maintained, which confirmed that the fibers mimic the microenvironment of the extracellular matrix.

4. Concluding remarks and outlook

The advances of collagen and gelatin ultrathin fibers are observed by the wide range of applications and the large number of recent studies, from biomedical to food packaging, using other polymers or other components to improve or include new properties. Since solution blow spinning overcomes some limitations of electrospinning, this technique is now also being largely explored to this end. Even with some intrinsic limitations, such as water solubility, gelatin fibers can be used in aqueous systems after crosslinking, which do not necessarily need to be done with toxic substances, although sometimes collagen also needs this treatment after processing by the spinning techniques. Typically, the mats obtained by these techniques are not cytotoxic, yet using toxic solvents as HFP and TFE, what indicates the complete volatilization of solvents during the processing or post-processing.

The most recent advances include the development of devices for *in situ* application of this technology, which has the potential to change the paradigm of polymeric materials usage in wound treatment and, possibly, even in more advanced procedures, such as surgeries and implants. Achieving these milestones involves critically analysing the latest discoveries to understand the true limitations and advantages of these techniques and materials, as well as the improvement of the know-how of researchers from various fields and attracting them to these investigation areas.

CRediT authorship contribution statement

Murilo Álison Vigilato Rodrigues: Writing – review & editing, Writing – original draft, Conceptualization. **Mirella Romanelli Vicente Bertolo:** Writing – review & editing, Writing – original draft, Conceptualization. **Marilia Marta Horn:** Writing – review & editing, Writing – original draft, Conceptualization. **Ademar Benévolo Lugão:** Writing – review & editing, Supervision, Funding acquisition. **Luiz Henrique Capparelli Mattoso:** Writing – review & editing, Supervision, Funding acquisition. **Ana Maria de Guzzi Plepis:** Writing – review & editing, Supervision, Funding acquisition.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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