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Review

Comprehensive review on electrospinning techniques as versatile approaches toward antimicrobial biopolymeric composite fibers

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ABSTRACT

Electrospun (bio)polymeric fibers have attracted widespread interest as functional materials with suitable morphology and properties for their use as tissue engineering scaffolds and/or wound dressings. The fibrous/porous morphology of this type of materials promotes the adhesion and proliferation of tissue cells, but on the other hand, pathogenic microorganisms unfortunately can also be attached to the fibers, thus leading to serious infections and consequently to the immediate removal of the scaffolds or wound dressings, which may imply greater tissue damage. In this context, this review addresses the more recent approaches based on electrospinning and related techniques for developing composite (bio)polymeric fibers with tailored antimicrobial properties either by using mere electrospinning for the incorporation of well-defined antimicrobial nanoparticles (silver, gold, titanium dioxide, zinc oxide, copper oxide, *etc.*) or by resorting to the combination of electrospraying and electrospinning for the generation of nanoparticle-coated fibers, as well as coaxial electrospinning for obtaining fibers with nanoparticle-rich surface.

1. Introduction

Polymeric fibers derived from electrospinning and related techniques have recently been exploited for obtaining new materials with potential application in medicine, energy, and environmental issues [1–7]. The most attractive features of these materials are those related to the morphology, such as fiber diameter in the sub-micrometric regime, high porosity with interconnected voids, large surface area-to-volume ratio, *etc.* In this context, the ability of fibrous polymeric materials to mimic the extracellular matrix is particularly important for their use in tissue engineering, as scaffolds and/or wound dressings, since it promotes good adhesion and proliferation of tissue cells [1,8]. Nevertheless, the fibrous morphology is prone not only to tissue cell ingrowth but also to pathogenic microorganisms; therefore, it is necessary to develop polymeric fibers with biocide properties but without cytotoxic effects on the receiving tissue.

In this regard, a vast diversity of organic compounds with recognized antimicrobial activity have been incorporated into polymers and subsequently subjected to electrospinning techniques in order to develop antimicrobial fibers. The reported organic compounds exhibit a relevant drawback related to their thermal and chemical instability, which could lead to difficulties throughout the electrospinning process and also produce fibrous mats with limited antimicrobial activity due to partial decomposition of the antimicrobial agent. Moreover, the massive use of antibiotics has provoked that a wide range of microorganisms developed a strong resistance against the majority of drugs; therefore, there is a need to explore novel antimicrobial agents [9–11].

Nanostructures with well-known antimicrobial properties have emerged as promising compounds for developing fibrous mats with better antimicrobial performance than those containing typical organic compounds, such as antibiotics and biocides. Likewise, antimicrobial nanoparticles, including zinc oxide, titanium dioxide, silver, and gold analogues, have demonstrated some advantages like their higher chemical and thermal stability that may lead to a new generation of biomedical devices with improved antibacterial activity as well as enhanced mechanical, thermal and other physical properties [12].

In this context, the most recent reports related to approaches for obtaining antimicrobial polymeric fibers by means of electrospinning and related techniques are addressed in the subsequent sections of this review. Some significant concepts of electro-hydrodynamic techniques (*i.e.*, electrospraying and electrospinning) and typical polymers meant for the design of biomedical devices are also discussed. Lastly, the main mechanism of microbial adhesion to the (bio)polymeric fibers as well as that related to the antimicrobial activity associated with nanoparticle-containing composite fibers are detailed.

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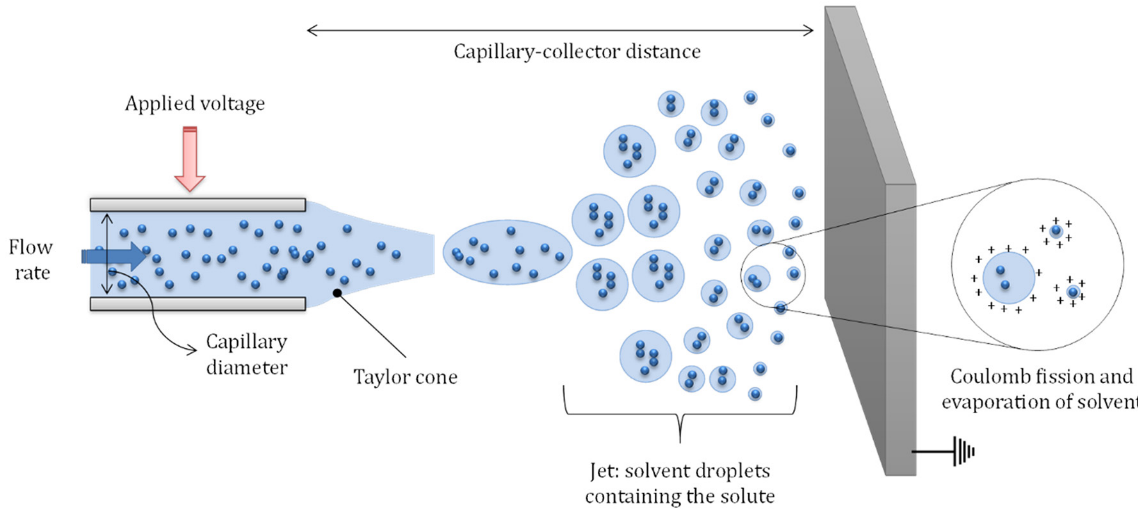

Fig. 1. Scheme of the electrospraying process, more specifically the section between needle and collector, in which the formation of the Taylor cone, the Coulomb fission and the solvent evaporation take place.

2. Overview of electrospinning and related techniques

In this section, basic principles of electrospraying and electrospinning are addressed as well as the most important process and solution parameters that influence fiber morphology. Furthermore, some recent approaches based on these techniques for producing composite fibrous materials are analyzed.

Electrospraying is basically the atomization of a liquid (passing through a capillary) by means of the application of a high voltage (typically 1–30 kV). This electro-hydrodynamic technique can be used for obtaining either inorganic or polymeric nano- or micro-particles derived from the corresponding solution/dispersion, as depicted in Fig. 1. The process begins at the tip of the capillary, where a droplet of the solution/dispersion is subjected to high voltage, whose electric charges generate an electrostatic force inside the droplet, which is eventually deformed into a cone (known as Taylor cone) from which smaller droplets will be ejected as soon as the surface tension is overcome. These generated droplets are accelerated toward the grounded collector, and the solvent is simultaneously evaporated throughout that occurrence [3,13–15].

The versatility of the electrospraying technique is attributed to several advantageous characteristics, including:

- Droplet size is smaller than that available from conventional mechanical atomizers, and can be smaller than 1 μm. Therefore, the resulting particles can be in the nanoscopic regime.
- The size distribution of the droplets is usually narrow, with small standard deviation that allows for production of particles of nearly uniform size.
- Charged droplets are self-dispersing in space (due to their mutual repulsion), resulting in the absence of droplet coagulation, and consequently lower agglomeration.
- The motion of charged droplets can be easily controlled (including deflection or focusing) by varying electric fields.
- The deposition efficiency of a charged spray on an object is one order of magnitude higher than that for uncharged droplets.

The morphological characteristics of the particles derived from the electrospraying technique are affected by different parameters related to both the solution/dispersion properties and process conditions, which will be described below.

Electrical conductivity is a fundamental solution/dispersion property since it allows for the charge transfer inside the liquid, so in turn, this property is governed by the nature of solvent and solute. Generally, an increase in electrical conductivity results in a smaller particle diameter due to a higher number of charges around the droplets, which promotes their Coulomb fission (breakup). Solution/dispersion viscosity is another property that strongly influences the electrospraying behavior and final morphology, and it is proportional to solute concentration and molecular weight (especially for polymers). As a rule, the solution/dispersion viscosity should be sufficiently low to allow for the formation of droplets; moreover, a highly viscous solution requires higher voltage in order to overcome the surface tension which is not practical [3,13–15].

Regarding the process conditions, solution/dispersion flow rate is a crucial parameter for controlling the final morphology of electrosprayed nano- or micro-particles along with the previously discussed solution parameters. The flow rate should be in a sufficiently low range so that complete solvent evaporation might occur, which is not possible when a higher flow rate is used. In case of incomplete solvent evaporation, a distorted morphology is commonly obtained due to fusion of wet and partially solvated particles after deposition on the collector. The relationship between the flow rate, solution/dispersion properties and particle diameter is established by Eq. (1) [16].

$$d_p = \Phi^{1/3} d \sim G(\varepsilon)\left(\frac{Q\varepsilon\varepsilon_0}{\kappa}\right)^{1/3} \tag{1}$$

where d_p and d are the particle and droplet diameter, respectively, Φ is the solute volume fraction, Q is the flow rate, ε and ε_0 are the permittivity of solution/dispersion and vacuum, respectively, and κ is the solution/dispersion conductivity.

Other process parameters, more specifically those related to the electrospraying equipment, are the capillary diameter and capillary-to-collector distance. The former determines the size of the Taylor cone, which in turn influences the droplet and particle diameter. Concerning the capillary-to-collector distance, it was demonstrated that a shorter distance is beneficial for generating a higher electrical field strength, thus producing smaller particles but also has the drawback of possible electric discharge and insufficient time for solvent evaporation, which may lead to coalescence/agglomeration of wet particles on the collector. Similarly, the applied voltage provokes a strong effect on particle morphology: the higher the applied voltage, the lower the particle size, which can be explained in terms of higher charge density in the solution/dispersion and breakup of ejected droplets [3,13–15,17].

Electrospinning is based on the same electro-hydrodynamic phenomena previously discussed for the case of electrospraying. Therefore, the morphology of resulting materials depends on similar parameters: electrical conductivity and viscosity of solution/dispersion, flow rate, capillary diameter, capillary-to-collector distance and applied voltage. The main difference between electrospinning and electrospraying is that the former technique generates a continuous jet from the Taylor cone, thus collecting a mat consisting of polymeric fibers [1,18–20].

It is important to mention that fibers are typically engineered from a solution containing high molar mass compounds, *i.e.* polymers, since the stability of the jet is a result of chain entanglements. In this regard, a critical polymer concentration (*i.e.*, viscous polymeric solution) is required for the occurrence of chain entanglements, thus producing fibers. Below this critical polymer concentration (*i.e.*, dilute regime) only droplets are collected, *i.e.* electrospraying takes place, since polymer chains are separated by the solvent. With an intermediate concentration (*i.e.*, semi-dilute regime), the polymer chains overlap each other, but this is not enough for significant entanglement formation, therefore, particle-like morphology is still dominant. Fibers with high number of beads can be obtained up to the entanglement concentration (C_e), *i.e.* the transition between semi-dilute unentangled and semi-dilute entangled regime. Above the entanglement concentration, fibers with well-defined morphology can be produced, which generally is 2–2.5 times C_e. The polymeric solution regimes and their repercussions on morphology of the obtained materials are illustrated in Fig. 2. It is worth mentioning that the solution/dispersion and process parameter described in previous sections for the case of electrospraying process also affect the final morphological parameters of electrospun fibers, namely average fiber diameter, fiber diameter distribution and porosity ratio [21–23]. These solution and process factors as well as their corresponding effect on morphology are summarized in Table 1.

3. Design of antimicrobial composite fibers based on electrospun polymers and inorganic nanoparticles

As previously mentioned in the Introduction, polymeric fibers derived from electrospinning techniques are suitable for applications related to tissue engineering (scaffolds and/or wound healing materials) due to the sub-micrometric fibrous structure with interconnected pores that could mimic the extracellular matrix, thus promoting the adhesion and proliferation of distinct tissue cells. Nonetheless, that particular morphology is also prone to adhesion of pathogenic microorganisms, which can originate a protecting assembly known as biofilm (composed of extracellular DNA, proteins and polysaccharides). For this reason, there is a trend to develop new electrospun composite materials with antimicrobial properties. Although there are several organic compounds with antimicrobial activity, nanoparticles have recently been preferred since they could confer new properties and/or enhance others. Hence, the subsequent sections will firstly focus on the design of composites fibers by electrospinning and related techniques and, secondly, on the most studied antimicrobial nanoparticles and their effect on the generation and final properties of (bio)polymeric fibers [24–34].

3.1. Approaches for designing fibrous composite materials by electrospinning and related techniques

Several approaches for fabricating composite materials with tailored morphology have been studied, whose basic methodology and some advantages/disadvantages will be revised in this section. To get a better understanding of the electrospinning and related techniques, Fig. 3 shows a scheme of the different steps for obtaining composite fibrous materials and the resulting morphology.

Mere electrospinning is the most reported approach for obtaining composite fibers, and it consists in preparing a polymeric solution containing the corresponding antimicrobial nanoparticles or their

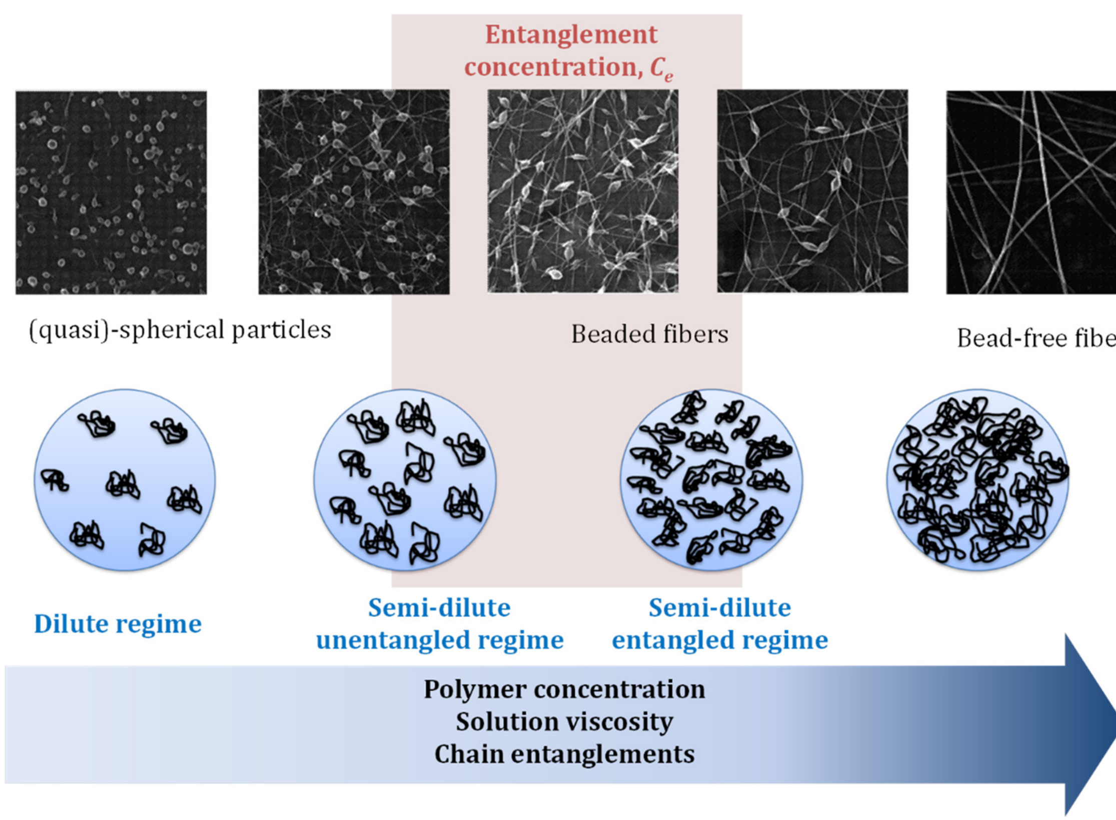

Fig. 2. Influence of the concentration of the polymeric solution on chain entanglements, formation of fibers and their final morphology derived from the electrospinning process.

Table 1
Effect of different parameters on the morphology of polymeric fibers derived from the electrospinning process.

Parameter	Effect on fiber morphology
Increase in applied voltage	Fiber diameter initially decreases, then increases (not monotonic)
Increase in flow rate	Fiber diameter increases (beaded morphologies occur if the flow rate is too high)
Increase in needle-to-collector distance	Fiber diameter decreases, (beaded morphologies occur if the needle-to-collector distance is too short)
Increase in polymer concentration (viscosity)	Fiber diameter increases (within optimal range)
Increase in solution conductivity	Fiber diameter decreases (broad diameter distribution)
Increase in solvent volatility	Fibers exhibit surface microtexture (pores/rugosity on their surfaces, which may increase surface area)

Source: Sill and von Recum 2008 [11].

precursory compounds, which eventually is subjected to electrospinning process. The main advantage of this approach is its relatively straightforwardness, thus producing polymeric fibers with nanoparticles mostly embedded (some particles could however migrate to the fibers surface during the electrospinning process). On the other hand, the main disadvantage is related to the low antimicrobial efficiency due precisely to the embedding of nanoparticles, thus reducing the surface area prone to interact with pathogen microorganisms [12,35–37].

Nanoparticles-coated polymeric fibers can be engineered by two techniques. One of them involves a two-step process, *i.e.* mere electrospinning to obtain neat polymeric fibers from the corresponding solution, then followed by the deposition of the antimicrobial nanoparticles by several well-known techniques, such as sputtering or impregnation. The second technique is a tandem process denominated electrospinning/electrospraying, which consists of a simultaneous electrospinning of a polymeric solution and the electrospraying of the corresponding antimicrobial nanoparticles dispersion. Both techniques have been utilized for enhancing the properties dependent on the nanoparticles surface area, such as antimicrobial activity; however, an uninvestigated concern is related to the adhesion and loss of nanoparticles. Comparing the techniques, electrospinning/electrospraying tandem process has the advantage of producing nanoparticle-coated polymeric fibers in one-step. Unfortunately, complementary equipment (*e. g.* electrospraying) is needed for carrying out the fabrication of the composite fibers, thus increasing the initial technological investment [38–46].

Another outstanding technique is coaxial electrospinning, which can be performed in a similar apparatus than that used for conventional electrospinning, but the ejection device is formed by concentric needles, thus when solutions are ejected from them, core-sheath fibers are collected. Combination with other electrospinning-related techniques could be used for generating a variety of morphologies with potential applications as antimicrobial devices for medical and environmental concerns (see Fig. 3) [4,47–51].

The wide range of electrospinning and related techniques for

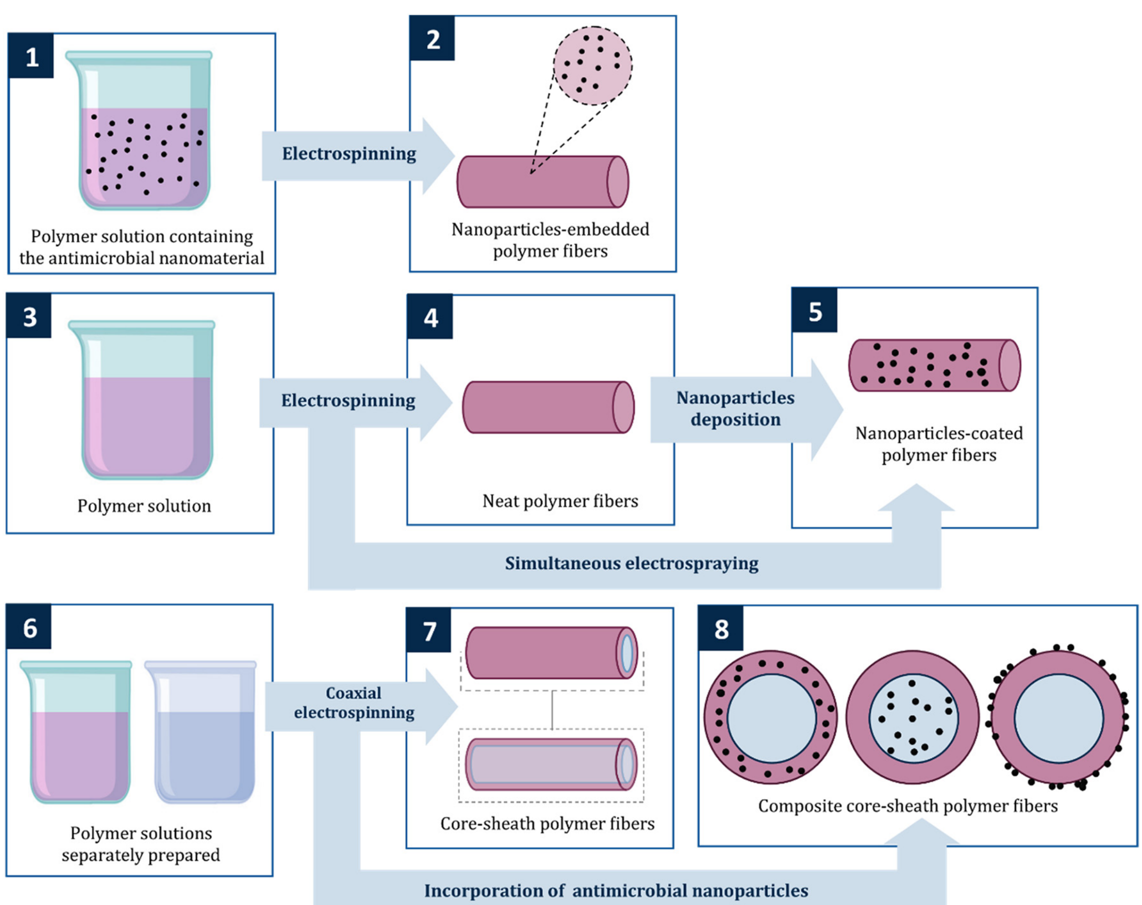

Fig. 3. Scheme of the approaches for designing composite fibrous materials engineered by electrospinning and related techniques and the corresponding outer and inner morphologies: (1,2) mere electrospinning, (3–5) electrospinning/electrospraying and (6–8) coaxial electrospinning.

designing composite fibrous materials has permitted to tune the antimicrobial activity. As a matter of example, mere electrospinning could produce antimicrobial activity based on migration of ionic species form the fibers, thus producing wound dressings or scaffolds for controlled release during long time. In contrast, the use of electrospinning/electrospraying tandem process could produce antimicrobial materials for rapid antimicrobial activity when needed. Further insights related to the effect of electrospinning techniques, type of antimicrobial nanoparticles and others relevant factors on composite fibrous materials properties, especially antimicrobial activity, will be discussed in subsequent sections.

3.2. Polymers used as fibrous matrices for tissue engineering

An appropriate polymer for tissue engineering applications should be biocompatible, biodegradable, nontoxic, non-mutagenic, and non-immunogenic. Polymers are generally classified into two types, namely synthetic polymers and natural polymers (*i.e.* biopolymers) [52].

Natural polymers are produced by biological systems (*i.e.*, microorganisms, plants, and animals) whose main advantages are their bioactivity, *i.e.* the ability to interact with the surrounding host tissue and to induce cell deposition/proliferation. Moreover, this type of polymers provokes low inflammatory effect, they can be degraded by enzymes, and their degradation products can be consumed throughout the cellular metabolism. However, natural polymers are highly temperature sensitive, and their complex structure makes them difficult to be processed by electrospinning techniques. Another well-known disadvantage of natural polymers is the highly divergent properties as a function of the bio-source or batch. Two types of natural polymers are generally utilized for tissue engineering: (i) polysaccharides, such as chitin, chitosan, and alginate; (ii) proteins, such as collagen and gelatin.

Synthetic polymers on the other hand, are highly useful in tissue engineering as their properties (*e.g.*, porosity, degradation time, and mechanical characteristics) can be easily tailored for specific requirements of medical devices and host tissue. Furthermore, these polymers are often less expensive compared with natural analogues, and they can be produced in larger quantities. Since natural polymers exhibit certain difficulties for processing them in electrospinning techniques (*i.e.*, mainly solubility), synthetic polymers are typically blended with low amounts of natural polymers, which enhances their solubility [48,53–58]. Several reviews have hitherto been published in which the mechanical and thermal properties as well as biocompatibility, solubility and biodegradation of both natural and synthetic polymers are compiled and thoroughly analyzed. Therefore, further information can be consulted for specific polymeric systems in these feature publications [59–63].

3.3. Antimicrobial nanomaterials and their incorporation into biopolymeric fibrous materials

Several inorganic nanostructures have been incorporated into polymeric fibers by using electrospinning and related techniques. The inspection of recognized scientific data bases generates interesting statistical results (see Fig. 4). Approximately 4000 reports related to nanofibrous composites have been published over the last decade. About 30% of these publications have focused on the use of well-known antimicrobial metallic (silver and gold) and metal oxide (mainly those based on zinc, titanium, copper and iron) nanoparticles. Researchers have mainly focused on the analysis of process and solution properties associated with electrospinning techniques, and on final fiber morphology and properties, such as optical, mechanical, photo-catalytic, among others. Nevertheless, it is noteworthy that only one third out of the resulting materials has been used for antimicrobial applications, whose more relevant results are discussed below.

3.3.1. Metallic nanoparticles

Silver nanoparticles (nano-Ag) have been extensively studied as antimicrobial agents in (bio)polymeric fibers derived from electrospinning and related techniques, due to their exceptional ability to kill a wide range of pathogenic microorganisms. Regarding the polymeric matrices used, several aliphatic polyesters, such as polylactide (PLA) or its *co*-polymers, poly(ε-caprolactone) (PCL), and poly(3-hydroxyalkanoate)s (PHAs), have been preferred, due to their well-known biodegradation behavior and good mechanical properties for tissue engineering applications [29,64].

The (bio)polymer/nano-Ag composite fibers can be obtained from polymeric solutions containing the as-synthesized nanoparticles (Ag^0) or some silver salt. Silver-based compounds can enhance the spinability of the solution, leading to well-defined (bio)polymeric fibers, which has been attributed to the increase in electrical conductivity by the presence of Ag^+ ions released from Ag^0 or originated from the silver salt dissociation. Currently there is a trend to add $AgNO_3$ as a precursor of nano-Ag since this salt is easily solubilized in polar solvents typically used for electrospinning, thus increasing the electrical conductivity. As expected, the presence of Ag^+ ions strongly affects the final morphology of fibers: at low concentration ($<$ 8%) average fiber diameter is generally reduced, and on the contrary, at high concentration ($>$ 8%) the agglomeration of Ag species promotes phase segregation, thus increasing the average fiber diameter [65–68].

The use of $AgNO_3$ as precursory species for obtaining (bio)polymeric fibers with nano-Ag involves a reduction step, which can be induced by heat [69], chemical reducing agents [36,70] or photo-irradiation [32,33,69,71,72]. Recently, UV-induced photochemistry has been taken advantage because of its simplicity, low cost, and sustainability. Interestingly, several researchers have claimed about the fabrication of polymer/nano-Ag composite fibers with controlled antimicrobial activity. This can be achieved by electrospinning the corresponding solution containing $AgNO_3$, followed by a photo-reduction. The size, content, and dispersion/distribution of the embedded Ag nanoparticles are controlled by $AgNO_3$ concentration and time of UV irradiation. Long irradiation time promotes the migration of Ag^+ ions through the outer layer of the fibers as well as the production of Ag^0 and its increase in size, thus tailoring the antimicrobial performance reaching up to 99.9% of growth inhibition at relatively low $AgNO_3$ concentration (from 0.1 to 1 wt-% in relation to polymer) [32,33,69,71,72]. Thus, poly(vinyl alcohol) (PVA) [66,69], cellulose derivatives [32,71–73], poly(lactic acid) [68], gelatin [33], chitosan, poly(ethylene oxide) or polymer blend-based fibers [55,57,58,74] have been engineered with high antimicrobial *in vitro* performance against Gram-positive (mainly *Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Proteus mirabilis, Bacillus cereus*), as well as fungal culture (*Candida albicans).*

The ideal composite polymeric fibers must possess a nanoparticle-rich surface in order to exhibit suitable antimicrobial activity for using in medical devices, which is very difficult to achieve by mere electrospinning, since nanoparticles are buried in the inner part of the fibers. However, a more accurate procedure is to create fibers with core-sheath morphology, where the sheath contains Ag nanoparticles. These particular fibers can exclusively be obtained by an alternative technique, the so-called coaxial electrospinning, which is based on the same principles of simple electrospinning, but the system that ejects the polymer solution consists of two coaxial capillaries with different diameters by which two fluids converge forming a core of one polymer covered by the other polymeric system. The second polymeric solution could contain specific nanoparticles in order to produce a composite sheath with enhanced antimicrobial properties.

Coaxial electrospinning has scarcely been exploited for the design of polymer/nano-Ag composite fibers, and the selected matrix has not been necessarily biocompatible or biodegradable. Yu et al. *[51]* have deposited Ag nanoparticles preferentially on the surface of

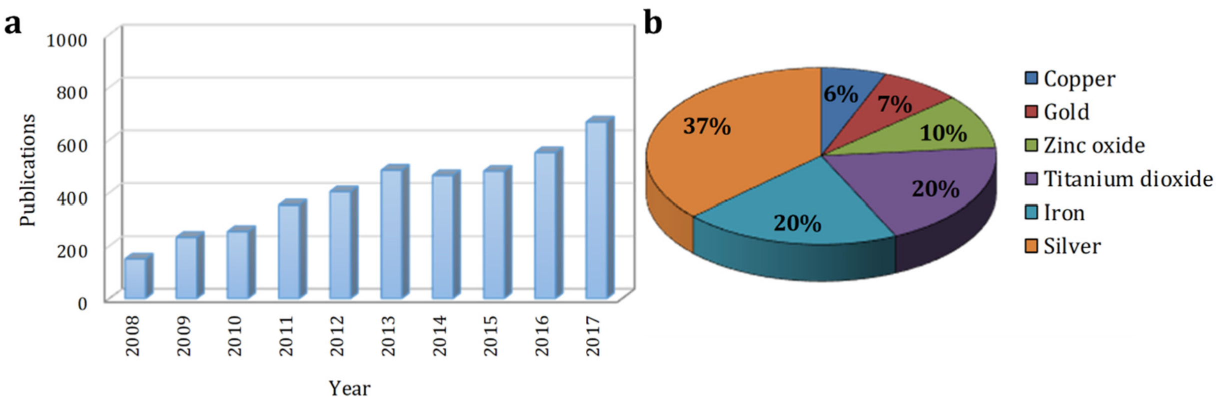

Fig. 4. (a) Comparison of the number of publications per year related to electrospinning and related techniques used for developing composite polymeric fibers. (b) Percentage of publications which are focused on antimicrobial electrospun fibers with different nanoparticles. Source: ISI Web of Knowledge, May 2018.

polyacrylonitrile (PAN) fibers by coaxial electrospinning of the corresponding polymeric solution (core) and *N*,*N*-dimethylacetamide/ $AgNO_3$ solution (sheath). An additional device for UV irradiation was adapted near to the capillary tip in order to reduce the Ag^+ ions during the ejection process. Interestingly, the authors found that the solution used for sheath generation provoked the formation of thinner fibers than those derived from neat PAN solution, which was attributed to the increase in electrical conductivity, *i.e.* more induced charges over the polymer solution surface, thus reducing the average fiber diameter [49]. Moreover, it was demonstrated that the feed rate ratio of sheath/ core precursory solutions played a significant role for accomplishing good nanoparticle dispersion, since it regulated the deposition of Ag^+ ions on the core jet during the process of coaxial electrospinning. The obtained composite fibers showed a high bacterial growth inhibition (> 99.9%) against *Escherichia coli* and *Bacillus subtilis* with only 4% Ag nanoparticles. Unfortunately, the authors did not compare with fibers obtained by mere electrospinning to corroborate the effect of the specific technique used.

Castro-Mayorga et al. have recently reported an electrospinning-based approach to develop antibacterial multilayer materials consisting of a poly(3-hydroxybutyrate-*co*-3-hydroxyvalerate) (PHBHV) film coated with submicron fibers of PHAs and Ag nanoparticles. The obtained films exhibited high toxicity against *Listeria monocytogenes* and *Salmonella enterica*. More interestingly, the antimicrobial activity was achieved with only 0.002 wt-%, while preserving thermal, mechanical and optical performances for their use as food packaging [75].

There are some biocompatible and biodegradable polymers with good mechanical performance for wound dressing materials and/or tissue engineering scaffolds, such as PCL. Nevertheless, its hydrophobicity limits a suitable cell attachment and proliferation, thus limiting its use in the aforementioned biomedical devices. Coaxial electrospinning offers the possibility to adapt the surface properties by forming a polymeric sheath with different chemical nature. In this regard, Kalwar et al. *[48]* designed co-electrospun fibers based on PCL/ chitosan (core/sheath) with average diameters ranging from 200 to 450 nm. The presence of chitosan promoted an increase in the hydrophilicity of co-electrospun fibers, and on the other hand, well-dispersed Ag nanoparticles into the sheath due to interactions between nanoparticles and amino and hydroxyl groups of chitosan. Furthermore, the obtained fibrous materials exhibited good inhibition growth of *E. coli* and *S. aureus* when subjected to *in vitro* tests (disc diffusion method) and insignificant difference was observed as a function of the bacterium type.

Further studies related to the use of co-electrospun fibrous materials as wound dressings and tissue engineering scaffolds have been published by Duan and Wei [47,50]. The authors described the production of co-electrospun fibers based on multi-components: PCL core containing vitamin A and collagen sheath with embedded Ag nanoparticles. The obtained materials showed good swelling ratio (190%) and antibacterial activity against *S. aureus* (*in vitro*). On the other hand, the fibers exhibited a persistent release of vitamin A within 72 h, in conjunction with good cell attachment (L929 cells), thus indicating that these fibrous mats could be used as biocompatible dressings with dual function, namely antibacterial and wound healing ability. Nonetheless, the authors did not give any information about final Ag nanoparticles content, which could be useful for determine the minimal amount at which nanoparticles do not cause cytotoxicity.

Even though polymer/nano-silver fibrous composites derived from electrospinning techniques have showed promising antimicrobial properties, one of the most important concerns is the potential toxicity of nanoparticles when exposed to tissue cells, which could limit their massive production and application. Currently there are controversial results associated with the viability of different tissue cells when exposed to polymeric mats containing the aforementioned metallic nanoparticles. As a matter of example, Sumitha's work evidenced that Ag-embedded PCL fibers (200–260 nm in diameter) could efficiently kill *S. aureus* bacteria (disc diffusion tests) at concentration as low as ~0.002 wt-% without compromising the adhesion of human mesenchymal stem cells (viability ~99%). On the contrary, such PCL fibers with ~0.06 wt-% Ag exhibited 50% cell viability, implying that nanoparticles induced toxicity to cells at very low concentration [76].

In 2014, Lin et al. evaluated the viability of the PA317 cell line (mouse fibroblasts with herpes gene) in the presence of PVA/Ag composite mats derived from electrospinning and subsequent chemical reduction (induced by the matrix, UV and heat). Some relevant findings were reported, such as the effect of reduction methodology on the amount and size of formed nano-Ag, and consequently on the antibacterial properties against *E. coli* and *S. aureus* (all materials showed antibacterial activity > 99%). The authors concluded that the critical factor to avoid cell toxicity was to select an appropriate reduction process by which no Ag^+ ions remained into PVA fibers, since these ionic species hampered the proliferation of PA317 cells. The Ag^0 nanoparticles did not induce toxicity even at high concentration (10 and 12 wt-%), thus increasing the potential of these mats as antibacterial wound dressings and/or scaffolds [77].

Additional reports have corroborated the good biocompatibility of electrospun biopolymeric fibers with embedded Ag nanoparticles [78–81].In spite of these encouraging results, most of the evaluation approaches have been carried out by *in vitro* tests, so that it is necessary to perform more realistic studies, *i.e. in vivo* tests, which are limited. On this topic, antibacterial electrospun fibers (130–190 nm in diameter) based on poly(vinyl alcohol) and chitosan oligosaccharides (2:1 ratio) containing silver nanoparticles (15–22 nm in diameter) or $AgNO_3$ (both silver species at 3 wt-% compared to polymer) were subjected to *in vivo* tests with the aim of determine their biocompatibility. Initially, the obtained mats were placed on dorsal skin of rabbits, and the irritation skin levels were monitored. It was observed that mats caused no irritation to normal skin after 72 h, indicating the acceptability of these fibrous materials for transdermal drug delivery. Furthermore, the wound healing performance of PVA-based mats was inferred by wound healing and histological examination in rat back during 14 days. It was observed that PVA-based nanofibers containing Ag nanoparticles did not interfere with the healing process and the wound closure was accomplished in the analyzed period. Moreover, PVA/chitosan/nano-Ag mats showed histologically superior wound healing than commercial materials (wound plast and gauze) and PVA/chitosan/$AgNO_3$ fibers since wounds with these mats displayed ulcerated surfaces, formation of granulation tissue, and infiltration of inflammatory cells after 7 days. On day 14, newly synthesized fibrous tissue and sparse inflammatory cells in the dermis and subcutis were covered by completely re-epithelialized epidermis in each group, thus confirming that the PVA/chitosan electrospun fibers with Ag nanoparticles could provide a suitable scaffold for wound healing [53].

Dong et al. have also provided information about the *in vivo* biocompatibility of PCL fibers containing silver-decorated mesoporous silica (Ag-MSN, 0.05 wt-% to polymer). As shown in Fig. 5, skin injuries were purposely made on the specimens (male Wistar rats). It was found that the wounds healed better and faster after being treated with Ag-MSN/PCL fibrous membranes than with other materials (gauze). On week 5, a rough and thin skin layer was formed in the presence of PCL/Ag-MSN fibers and without signals of inflammation by histological analysis. In contrast, the wounds without one such dressing, with neat PCL or gauze, were still in the late phase of inflammation. These results demonstrated that the Ag-MSN/PCL nanofibrous membranes could strongly help the healing process [82].

Other researchers have exploited collagen as the matrix for electrospinning, as this natural polymer is the most abundant protein in the human body, a key element of the extracellular matrix and imparts structural integrity and tensile strength to tissues. Tissue disruption following injury requires collagen for the repair and restoration of structure and function. Rath et al. designed cross-linked collagen/silver nanoparticles through electrospinning. The obtained mats inhibited the proliferation of *S. aureus* and *P. aeruginosa* (minimum inhibitory concentration of 5.8 ± 0.3 mg/mL and 7.4 ± 0.2 mg/mL, respectively). It was also demonstrated an increase of wound healing by wound examination, histological study, and hydroxyproline determination. Complementary studies, such as swelling index and quantification of silver ions released helped to suggest that the presence of collagen formed hydrophilic gels that maintained a moist environment, thus promoting faster re-epithelization and wound contraction. Besides, anti-inflammatory property of nano-Ag also promoted wound healing by reducing the level of pro-inflammatory cytokine or decreasing mast cell infiltration. Finally, controlled release profile of silver nanoparticles supported the wound-healing process by maintaining the drug concentration in the therapeutic range over an extended period of time [83].

Recently, the addition of natural additives has emerged as a sustainable trend and for imparting multifunctionality to polymer fibers containing Ag nanoparticles. As a matter of example, rice flour-based fibers containing Ag and PVA/β-cyclodextrin as binders have been studied as sustainable filters. The authors demonstrated the multifunctionality of the obtained mats through antibacterial tests, air permeability and adsorption of volatile organic compounds. Fibrous materials exhibited high inhibition growth of *E. coli* and *S. aureus,* due to the presence of nano-Ag as well as good removal of toluene attributed to β-cyclodextrin without affectation on air permeation and mechanical performance [84]. Similarly, soy protein has been used in conjunction with Ag to confer toxic gases removal and antibacterial activity in fibrous materials based on polyamide 6 [85].

Gold nanoparticles have been also incorporated into electrospun biopolymeric fibers for improving antimicrobial properties. Likewise, these metallic nanoparticles have attracted a particular attention mainly due to their anti-proliferative activity on carcinogenic cells that could lead to mats with anticancer properties. In this regard, Manjumeena et al. developed PVA-based fibers containing a low content of gold nanoparticles (0.1 wt-%), which resulted in a suitable environment for proliferation of Vero cells, thus leading to a viability of *ca.* 90% after 72 h of incubation. The good cell proliferation was attributed to the hydrophilicity of the mats as well as the electrostatic attraction between cell membrane and PVA fibers, regardless of the presence of gold nanoparticles. More interestingly, the presence of Au nanoparticles in the electrospun fibers provoked antiproliferative effects in MCF-7 and HeLa cell lines, showing 8 and 9% proliferation, respectively. Additionally, the obtained mats showed excellent antimicrobial performance against a wide range of microorganisms, such as *B. subtilis*, *A. coli*, *K. pneumonia*, *M. luteus*, *P. aeruginosa*, *S. aureus*, *C. albicans* and *C. krusei [86].*

Similarly, McKeon-Fischer et al. demonstrated that PLLA/Au nanoparticles could successfully be engineered by the electrospinning technique. However, the resulting fibers did not stimulate the proliferation of rat muscle cells, which was not caused by the presence of gold nanoparticles since parallel studies corroborated the non-toxicity of isolated nanoparticles at high concentrations (7–21 wt-%). The authors claimed that the cell seeding on the obtained mats was insufficient to induce proliferation; however, no clear experimental evidence was provided [87].

3.3.2. Metal oxides

Nanostructures based on metal oxides are other extensively utilized antimicrobial compounds. The increasing interest in metal oxide nanoparticles mainly arises from their simple and inexpensive synthesis, which is commonly carried out by solution-phase methods (sol-gel, co-precipitation, hydrothermal, *etc.*), affording excellent control over particle morphology. Besides, such nanoparticles are relatively environmentally friendly. Regarding the applications, several optical, electrical, magnetic and catalytic properties of metal oxides can be exploited for designing sensors, catalytic systems, (opto)-electronic materials, among others [88–92]. Furthermore, metal oxides have been studied as antimicrobial species when incorporated into (bio)polymeric fibers, especially those based on zinc, iron, titanium, and copper.

Titanium dioxide (TiO_2) is a well-known multifunctional material with significant UV absorption, antimicrobial, and catalytic properties; therefore, the nanoparticles derived from this metal oxide have been applied in medicine and environment-related areas as UV-blocking agents, sensors, photo-catalytic systems, *etc.* [93]. Currently, there is a trend to produce TiO_2 nanostructures with controlled morphology by electrospinning a polymeric solution containing a Ti-containing source (such as titanium isopropoxide), and subsequently thermally degrade the polymeric matrix [94].

Regarding electrospinning for the fabrication of biopolymeric fibers, some researchers have demonstrated the multi-functionality of the corresponding mats with nano-TiO_2 and have also proved the antibacterial activity and potential application in tissue engineering by *in vitro* approaches. In this sense, Lee et al. took advantage of the well-known biocompatibility of poly(vinyl alcohol) for preparing PVA/nano-TiO_2 (2–3 wt-%) composite fibers with excellent antibacterial activity against *S. aureus* and *K. pneumoniae*, UV protection, and the ability to degrade formaldehyde, thus evidencing the possibility to develop advanced textile materials [95].Similarly, PVA-based composite mats with enhanced antibacterial properties were obtained by incorporation of low amounts of chitosan (3–15 wt-%), which is an inherent antibacterial natural polymer, and TiO_2 nanoparticles. When comparing fibers with embedded TiO_2 and Ag nanoparticles at the same concentration, the latter nanoparticles exhibited superior antibacterial performance (10% higher with 0.04 wt-% Ag nanoparticles), which could be explained in terms of release feasibility [57].

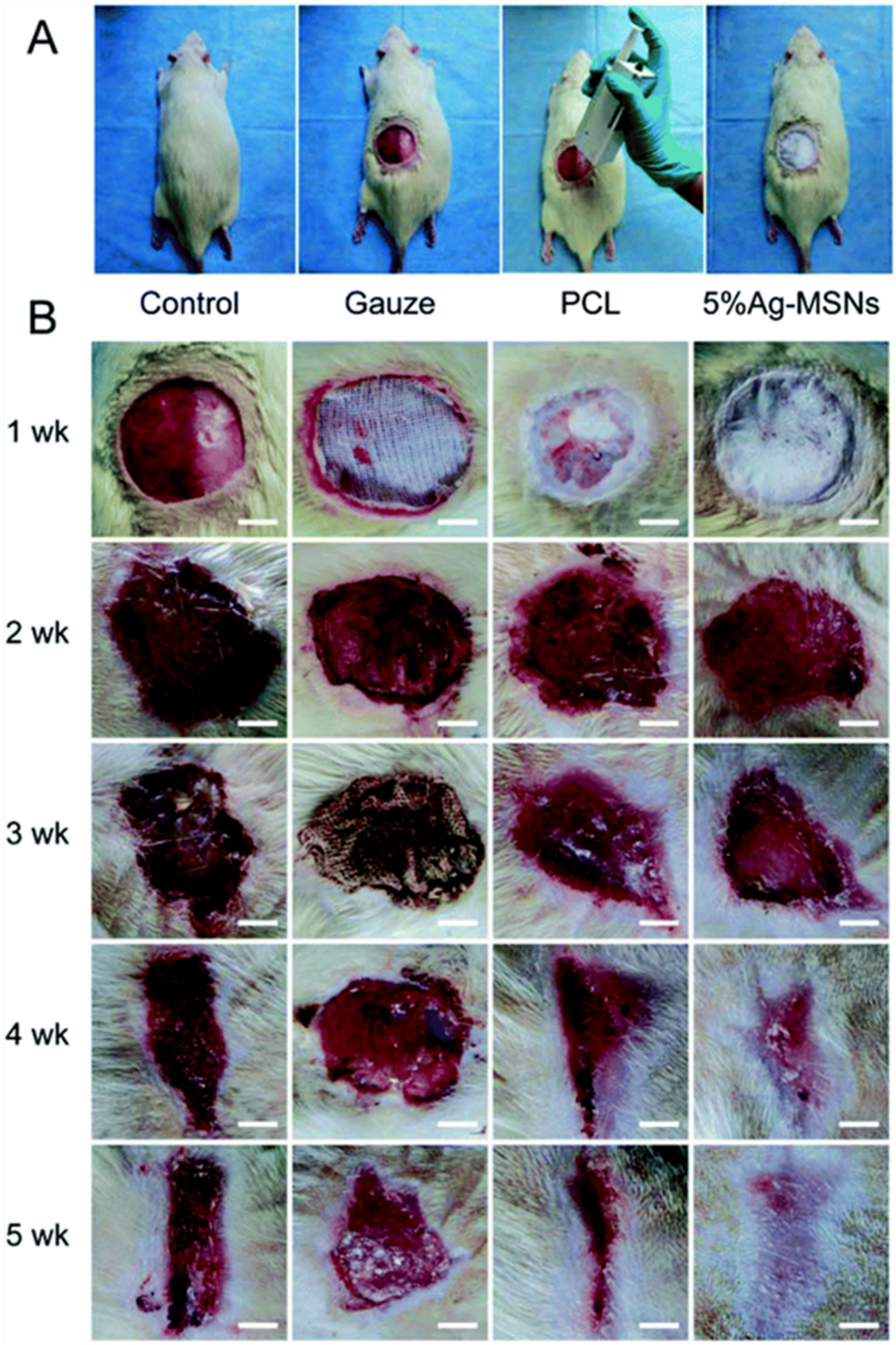

Fig. 5. Skin wound healing accelerated by Ag-MSN/PCL nanofibrous membranes. (A) Exhibition of the entire skin injury model and treatment process in a Wistar rat. (B) Gross observation of skin wounds treated with gauze, virgin PCL, Ag-MSN/PCL respectively at 1, 2, 3, 4, and 5 weeks after injury. Untreated wound was considered as the control. Bars represent 10 mm [82].

Poly(3-hydroxybutyrate) (PHB) is another interesting natural polymer which strongly draws attention for tissue engineering, due to its excellent biocompatibility in the presence of a wide range of medically important cells [96,97]. Nano-TiO_2 has been incorporated into electrospun PHB fibers in order to prevent bacteria adhesion, specifically against *E. coli*. Korina et al. studied PHB/TiO_2 fibrous materials obtained by mere electrospinning, its combination with electrospraying or impregnation with TiO_2 nanoparticles, thus leading to TiO_2-embedded mats for the mere electrospinning technique and TiO_2-coated mats for the electrospinning/electrospraying or electrospinning/impregnation approaches. The comparative study revealed that all composite fibers completely killed the bacterium, but those with TiO_2 on the surface (electrospraying/electrospinning and electrospinning/impregnation) achieved the maximum antibacterial effect in only 30 min, while it took 60 min for fibers containing embedded TiO_2. The main concern when preparing PHB or other PHAs fibrous nanocomposites is the preservation of its inherent cell adhesion and proliferation. In this regard, the presence of relatively high content of TiO_2 nanoparticles (5–10%) did not interfere with the proliferation of different cell lines [37,98].

Poly(lactic acid) (PLA) and its copolymers with poly(glycolic acid) (PLGA) are biodegradable polyesters with high potential as fibrous materials for medical applications, due to their mechanical and thermal properties comparable with other commercially available polyesters, and especially approval by the US Food and Drug Administration [38,52,99–102]. Concerning PLA-derived electrospun fibers with TiO_2 nanoparticles, it was demonstrated that the combination of electrospinning of PLA and electrospraying of a Ti precursor, followed by subsequent hydrothermal treatment, resulted in an excellent approach to develop PLA-based mats with strong antibacterial activity against *E. coli* and *S. aureus* at high TiO_2 content (*ca.* 35 wt-%) [103]. Further studies revealed that PLA/TiO_2 fibers preserved their antibacterial efficiency against *S. aureus* at relatively low nanoparticle content (1–5 wt-%) without evidence of *in vitro* cytotoxicity (24–168 h, fibroblast cell line) [104].

Advanced biomedical devices consisting of two layers, the first one of chitosan/TiO_2 electrospun fibers and the second one of adipose-derived extracellular matrix were recently reported. These new materials exhibited low percentage of bacterial penetration (*E. coli* and *S. aureus*), due to the synergistic effect of chitosan and TiO_2. Additionally*, in vivo* analysis in conjunction with the corresponding histological and immunofluorescence staining proved the ability of the obtained mats to heal wounds in only 21 days [105].

Variation and/or combination of electrospinning techniques have barely been used for designing polymeric fibers with TiO_2, and the few reports are focused on non-medical applications, with the exception of the previously cited works by Korina and Toniatto [45,106]. For instance, in 2010 the production of chitosan fibers decorated with TiO_2 was reported. The fibers were obtained by the coaxial electrospinning technique, and the engineered mats were meant for self-cleaning textiles since TiO_2 assisted the degradation of pigments [107]. The polymer/TiO_2 fibers derived from coaxial electrospinning have mainly been used in applications associated to energy, photo-voltaic and photo-catalysis, in which the polymeric matrices are typically non-biodegradable, and in most of the cases the matrices are further sacrificed by thermal treatment [5,108–111].

Another important inorganic nanomaterial with strong inhibitory and bactericidal effect is zinc oxide, which has been utilized for decades. Furthermore, this metal oxide has demonstrated a higher ability to kill various types of bacteria than TiO_2 nanoparticles [28,112,113]. For instance, methicillin-resistant *Staphylococcus aureus* is one of the major nosocomial pathogens, whose proliferation has been inhibited by ZnO nanoparticles with diameter size *ca.* 100 nm in a major extent than with TiO_2. This behavior resulted even more interesting due to the fact that TiO_2 exhibited smaller size (*ca.* 50 nm), *i.e.* higher surface area, which should potentially lead to higher antibacterial activity; however this behavior was not observed [114]. Moreover, ZnO nanoparticles can open the possibility of developing materials not only with antibacterial properties, but also with the power to exert a toxic effect against cancer cells, which has recently been demonstrated by Akhtar et al. *[115]*.

ZnO nanoparticles have also been incorporated as antimicrobial agents for textiles with fiber diameters ranging from 5 to 10 μm [31,112]; however, the interest in developing sub-micrometric fibers has increased significantly, due to the peculiar features of these fibers, as mentioned in previous sections. With respect to the incorporation of ZnO nanoparticles into biopolymeric fibers for obtaining antibacterial mats, several papers have been published, in which mere electrospinning or combined techniques were implemented, thus leading to new insights into the effect of nanoparticles dispersion/distribution on final properties, especially bactericidal activity. Concerning the ZnO-incorporated mats derived from mere electrospinning, the matrices have mainly been limited to poly(vinyl alcohol), some natural polymers, namely chitosan, cellulose or gelatin, and aliphatic (bio)polyesters, such as PLA, PCL, and PHAs.

PVA/ZnO fibers were fabricated by electrospinning of the corresponding PVA solution containing zinc acetate as ZnO precursor (diameter ~240 nm), and they were evaluated as antibacterial materials against both Gram-positive (Methicillin-resistant *Staphylococcus aureus*) and Gram-negative (*Salmonella typhi, Proteus mirabilis Pseudomonas aeruginosa* and *Klebsiella pneumonia*) bacteria. The *in vitro* results indicated good inhibition for *S. aureus*, *S. typhi,* and *P. mirabilis*. However, no antibacterial activity was shown against *P. aeruginosa* and *K. pneumonia*, which was justified in terms of affinity with the bacterium cells and structure of cell wall. The ZnO nanoparticles were positively charged and consequently could interact with the negatively charged cell wall surface of bacteria. Gram-positive bacteria have a cytoplasmic membrane and a thick wall composed of a peptidoglycan multilayer. On the other hand, Gram-negative bacteria have complex cell wall structure with a layer of peptidoglycan between the outer membrane and cytoplasmic membrane. The nanoparticles could then more easily attach to the Gram-positive bacteria and cause higher damage compared to the Gram-negative bacteria [116].

Lubasova et al. also designed PVA/ZnO fibers by conventional incorporation of nanoparticles into the corresponding polymeric solution and subsequent electrospinning. Interestingly, the authors compared the antibacterial performance of ZnO with other metal oxides, namely TiO_2, ZrO_2, and SiO_2. A high content of nanoparticles (10 wt-%) was necessary in order to expose them on the PVA-based fiber surface, which was theoretically a pre-requisite for good antibacterial activity. The results confirmed that the incorporation of metal oxides conferred antibacterial properties to PVA fibers, and the growth inhibition of the tested bacteria (*S. aureus* and *E. coli*) was increased when the nanoparticle content was augmented for all metal oxide nanoparticles. Nonetheless, the antibacterial behavior of PVA-based mats depended on the type of nanoparticles, and the ability to inhibit bacteria growth was in the decreasing order as follows: ZnO > ZrO_2 > TiO_2 > SnO_2. It is important to mention that ZnO inhibited the growth of *S. aureus* and *E. coli* in 90% and 100%, respectively, while SnO_2 reduced exclusively the proliferation of *S. aureus* in 82% [117]. Similar studies were recently carried out by the same authors but using poly(vinyl butyral) as a matrix, and the resulting fibers with ZnO showed superior antibacterial performance than those containing other metal oxide-based nanoparticles (CuO, ZrO_2, TiO_2, SnO_2) and even $AgNO_3$ [118].

PVA-based fibers have also been used as templates for the design of advanced mesoporous materials with combined osteoconduction and antibacterial properties. These materials were obtained by electrospinning of the corresponding polymeric solution with $Ca(NO_3)_2{\cdot}4H_2O$ and a stoichiometric amount of $NH_4H_2PO_4$ as hydroxyapatite precursor. On the other hand, zinc acetate was selected as ZnO precursor. After calcination of PVA fibers, novel mesoporous materials based on hydroxyapatite/ZnO were obtained, and they inhibited bacterial growth from 20 to 80%, which was directly proportional to the ZnO/hydroxyapatite molar ratio (1/3, 1/5 and 1/10) and depended on the type of bacteria, being *S. aureus* more susceptible to the presence of ZnO [119].

Natural polymers have also been exploited for developing electrospun fibers with potential use as antibacterial wound dressings. Chitosan is a well-known polysaccharide which itself provides bacteriostatic and fungistatic activities (*i.e.* momentarily stops the proliferation of certain microorganisms). In this regard, Wang et al. demonstrated that the addition of ZnO nanoparticles into chitosan-based fibers conducted to mats with synergistic antibacterial effect against *E. coli* and *C. albicans*, since neat chitosan fibers exhibited a minimum inhibitory concentration (MIC) of 130 and 190 μm/mL for *E. coli* and *C. albicans*, respectively, while the composite fibers displayed lower values (110 and 160 μm/mL for *E. coli* and *C. albicans*, respectively) [120]. Cellulose acetate was also used in the form of sub-micrometric fibers with ZnO nanoparticles. The resulting mats were tested *in vitro* against *S. aureus*, *E. coli*, *C. freundii* and *K. pneumonia*, and no antibacterial effect was observed for the latter bacterium, which was attributed to differences in cell walls, as mentioned above [121].

Regarding the biodegradable polyesters, PLA and PHB electrospun fibers with incorporated ZnO nanoparticles have also showed moderate-to-good antibacterial performance. Virovska et al. demonstrated the antibacterial activity of PLA fibers with high content of surface-modified ZnO nanostructures (23 wt-%, rod-like with diameter 10–30 nm and 100 nm in length) against *E. coli* and *S. aureus*. Moreover,

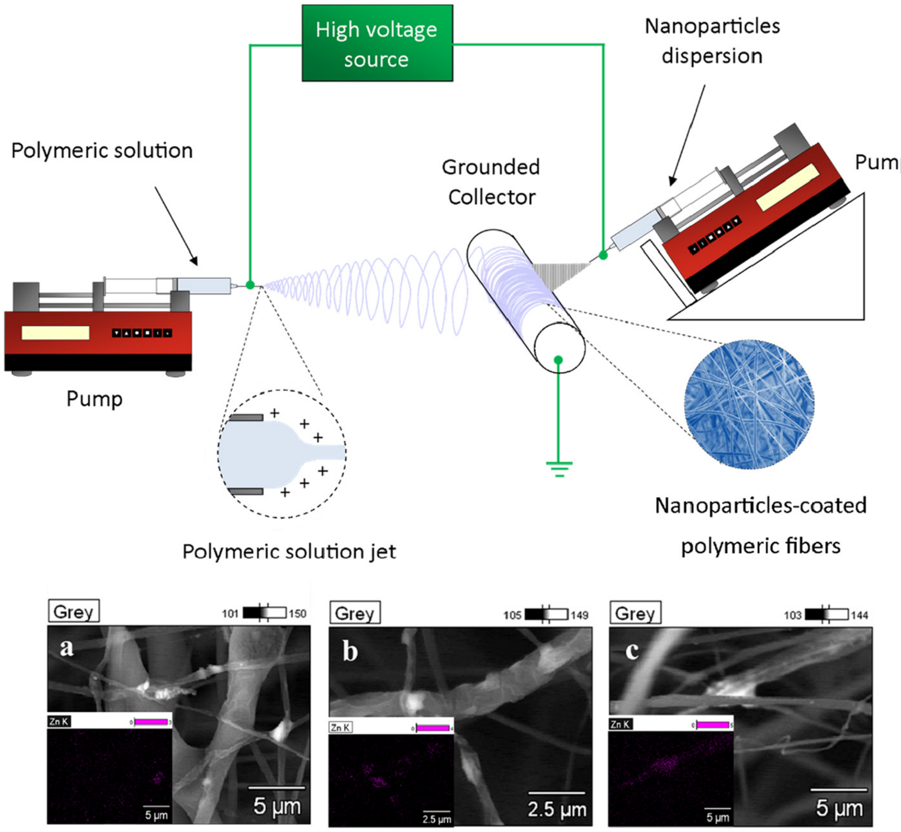

Fig. 6. Scheme of the equipment used for the electrospinning/electrospraying technique. The inserted micrographs are the obtained biopolyester fibers coated with (a) 1, (b) 3, and (c) 5 wt-% of ZnO nanoparticles.

the obtained PLA/ZnO mats showed excellent photo-catalytic properties which were exploited for the degradation of pollutant dyes (methylene blue and reactive red). Interestingly, the mats demonstrated high degradation efficiency after several cycles, thus showing their reusability [41].

A parallel study carried out by Rodríguez-Tobías et al. evidenced that electrospun polymeric fibers based on PLA or PHB with low content of smaller ZnO nanoparticles (1–5 wt-%, 12 nm in diameter) successfully inhibited the proliferation of the same bacterium strains as those examined by Virovska [39,42,43,122]. The incorporation of low ZnO content is an advantageous feature, since it ensures the biocompatibility of this type of materials as reported by other authors [123,124]. Additionally, these research groups have corroborated that the combination of electrospinning and electrospraying techniques enhance the antibacterial properties of the resulting mats (the tandem system and the obtained materials are depicted in Fig. 6), which was explained by the fact that a larger ZnO surface area was directly exposed to bacteria. Such ZnO nanoparticles deposited on polymeric nanofibers were then more prone to act as efficient antibacterial agents, thus potentiating the use of ZnO-coated mats as antibacterial wound dressings.

PCL is another important biodegradable polyester whose electrospun composite mats have been exhaustively studied by Augustine et al. The authors evidenced that decreasing the ZnO nanoparticle content (60 nm in size) in the polymeric solution up to 1 wt-% reduced the diameter of the resulting PCL fibers (neat PCL fibers exhibited an average-diameter of 2.5 µm, meanwhile PCL/ZnO fibers was 1.3 µm). On the contrary, higher nanoparticle contents induced the formation of thicker fibers, which was attributed to changes in conductivity and viscosity. Regarding the antibacterial properties, the authors discovered that significant antibacterial effect could be achieved only when ZnO concentration was higher than 4 wt-%. Furthermore, PCL/ZnO fibers resulted more effective against *S. aureus* than against *E. coli*, which was explained by cell wall differences, as discussed in previous sections. Relevant insights into the cytocompatibility of PCL/ZnO fibers have also been provided by Augustine et al. who proved that ZnO concentrations lower than or equal to 2 wt-% led to enhanced fibroblast proliferation compared with neat PCL fibers. The authors carried out further analyses in order to elucidate the effect of PCL/ZnO fibers on the healing of skin wounds. Interestingly, *in vivo* tests corroborated that PCL/ZnO fibrous mats promoted the proliferation of cells, thus inducing faster healing process in Guinea pig specimens within only 20 days. The reduction of biocompatibility of PCL fibers with relatively high concentration of ZnO nanoparticles has been ascribed to higher production of reactive oxygen species which could damage cells, thus inducing inflammation and lowering wound healing index [122,124].

Electrospun fibrous coatings consisting of PCL/ZnO (nanoparticles content equal to 1 and 3 wt-%) with enhanced biocompatibility for osteoblasts have recently been reported by Kim et al. who deposited the mentioned composite fibers on magnesium alloy implants, which showed corrosion resistance and antibacterial properties [125]. Contrasting results about biocompatibility of PCL-based fibers with ZnO nanoparticles (irregular morphology with size ranging from 20 to 150 nm) were reported in 2015 by Münchow et al.. The authors demonstrated that relatively high contents of ZnO nanoparticles (5–30 wt-%) moderately reduced the viability of human dental pulp stem cells, and the antibacterial properties against important periodontal pathogens (*Porphyromonas gingivalis* and *Fusobacterium nucleatum*) were preserved [126].

It is thus noteworthy that the use of electrospinning in combination with electrospraying for developing antimicrobial (bio)polymeric fibers with ZnO has only been explored in two series of works. Rodríguez-Tobías et al. and Virovska et al. have implemented the combination of electrospinning of a polyester solution with simultaneous electrospraying of ZnO suspensions. The former authors have additionally provided relevant information about the influence of ZnO concentration, surface modification, nanoparticle distribution/dispersion on mechanical, phase transitions, thermal stability, and photodegradation of the resulting composite polyester mats [39–43,46].

Last, copper is easily available and one of the most used metals for a wide range of applications. Moreover, scientists have well documented the synthesis and properties of CuO nanostructures. Nonetheless, up to date there are few reports related to the incorporation of CuO nanostructures into polymeric fibers by means of electrospinning techniques, and most of them have only addressed the effect of nanoparticles on the final fiber morphology, while the ability to confer antimicrobial properties to electrospun (bio)polymeric fibers has scarcely been considered. The limited use of CuO nanostructures might be due to their propensity to oxidation reactions, thus changing their overall features [35,127–129].

Among the few research works related to the fabrication of antimicrobial polymer/CuO fibers, that belonging to Haider et al. could be particularly mentioned. The authors evidenced that the presence of a low amount of CuO nanoparticles (0.5 wt-%, 40–100 nm in diameter) did not affect the average fiber diameter (*ca.* 550 nm) of poly(lactic acid-*co*-glycolic acid) (PLGA) fibers. The relatively large size of CuO nanoparticles was enough for their partial exposition on the polymeric fiber surface, thus facilitating the interactions between the studied inorganic antimicrobial nanoparticles with the analyzed bacteria (*E. coli* and *S. aureus* strains), and consequently inducing the growth inhibition (> 60% for both bacteria). The research work also demonstrated that the antibacterial mechanism was governed by the release of Cu^{2+} ions. With regard to biocompatibility and cell viability, various tests revealed that both PLGA/CuO and PLA/CuO fibers possess suitable characteristics for adhesion and proliferation of fibroblastic cell lines, so that the obtained electrospun mats could be envisioned as scaffolds and/or wound dressings with strong antibacterial activity [35].

In another recent report, PLGA was once again preferred for obtaining electrospun scaffolds with embedded CuO nanostructures combined with hydroxyapatite. Composite PLGA ultrafine fibers were engineered *via* a two-step methodology. First, copper oxide nanostructures were synthesized using a wet chemical method resulting in quasi-spherical particles with average diameter of ~7 nm. Then, hydroxyapatite and the as-synthesized CuO nanoparticles were incorporated by mixing with the PLGA solution, and the mixed solution was subsequently electrospun. The resulting fibers showed an average diameter (1–1.2 μm) larger than that for pristine PLGA, which was attributed to the high content of hydroxyapatite (high solution viscosity). The added nanostructures were well-dispersed and exposed on PLGA fiber surface since electron probe microanalysis showed CuO- and hydroxyapatite-rich maps. A fact revealed for the first time by the authors was the synergistic antibacterial effect (against *E. coli*) of hydroxyapatite and CuO nanostructures; however, the governing mechanism was partially elucidated [128].

PHA-based multilayer materials have been extensively studied by Castro-Mayorga et al. The authors have engineered PHBHV copolymer films with electrospun PHAs/CuO fibers on their surface, which conferred exceptional antibacterial (*Salmonella enterica* and *Listeria monocytogenes*) and antiviral (*Murine norovirus*) activity with only 0.05 wt-% of CuO nanoparticles. It was further demonstrated that the obtained materials exhibited good oxygen permeability, and mechanical performance. They were completely disintegrated under composting after 27–30 days, thus making them as promising multilayer films for food packaging [130].

Dimensional stability in conjunction with good elasticity performance are required features for fibrous materials meant for tissue engineering scaffolds or similar applications, since the receiving tissue could be subjected to constant stresses and/or movement. PVA is a biodegradable and biocompatible polymer which can be mechanically stabilized by crosslinking. For this reason, it was selected by Rezaee et al. for developing novel CuO-coated PVA fibers by a three-step process consisting in electrospinning the PVA solution, followed by a glutaraldehyde-catalyzed crosslinking reaction, and finally the electrospraying of a colloidal CuO dispersion. The authors optimized the fabrication of PVA fibers by varying some important parameters of the electrospinning process, namely polymer molecular weight (viscosity) and flow rate. The effect of crosslinking degree on final morphology of mats was also investigated, and it was revealed an optimal concentration of glutaraldehyde in which the fibrous morphology was preserved. Even though the antibacterial efficiency of isolated nanoparticles was excellent, the same property was not determined for the PVA/CuO mats, thus limiting their potential application as antibacterial scaffolds [129].

PVA has also been used as sacrificial matrix for electrospun multifunctional composite filters based on CuO and ZnO nanostructures, whose elaboration was carried out by electrospinning of a solution containing PVA/copper acetate monohydrate/zinc acetate dehydrate, and a subsequent calcination step. The resulting inorganic CuO/ZnO mixed fibers showed smaller diameter (*ca.* 180 nm) than those composed by PVA/CuO/ZnO (*ca.* 300 nm), which was attributed to PVA removal during the calcination step. Regarding the antibacterial activity, it was demonstrated that *S. aureus* was more sensitive to CuO-ZnO fibers than *E. coli*. Significant bactericidal effect was only achieved with 200 μg/mL of composite fibers in the presence of *S. aureus*, while *E. coli* exhibited higher resistance since bactericidal effect was observed when 350 μg/mL of composite fibers were used. On the other hand, the composite fibers were highly effective for removal of Congo red dye, thus validating the potential use as filters for water purification [131].

At this stage, taking into consideration the previous information, it could be inferred that metal oxides based on titanium, zinc, and copper are the main nanoparticles used as antimicrobial agents. However, there is a great interest in employing naturally available metal oxides, and iron oxides are among these types of materials, however their antimicrobial activity is the property least investigated.

Iron oxide nanoparticles have mainly been utilized for conferring magnetic properties to electrospun fibers. For instance, a contribution from Rashkov's group was related to the design of PHB fibers embedded or coated with a combination of TiO_2 and Fe_2O_3 nanoparticles. The nanoparticle-embedded PHB fibers were derived from the electrospinning of a solution consisting of dissolved PHB and dispersed nanoparticles (2.5 and 10 wt-% for Fe_2O_3 and TiO_2, respectively). The dispersion of the nanoparticles was aided by a low amount of chitosan oligosaccharides (COS, 0.5 wt-%). On the other hand, the nanoparticle-coated PHB fibers were designed by the combination of electrospinning of PHB solution and electrospraying of TiO_2/Fe_2O_3/COS dispersion. Regarding the morphology, the composite PHB fibers derived from electrospinning exhibited a significant number of beads, while the materials produced by the combined techniques of electrospinning/electrospraying showed aggregates on the surface. Furthermore, a smaller amount of nanoparticles than initial feed was determined by X-ray photoelectron spectroscopy (XPS), which was ascribed to the formation of a dense layer of the stabilizing agent used (chitosan or oligomers). Since the antibacterial activity of identical materials had already been explored [44], the new series of electrospun PHB fibrous mats were used as membranes for the degradation of pollutants pigments. The degradation activity was higher for the fibrous materials obtained by the conjunction of techniques, due to higher nanoparticle surface area exposed to the solution containing the pigment [45].

Another report related to the design of polymeric fibers with iron oxide nano- and microparticles was recently reported by Moon et al. From a solution containing poly(ethylene oxide), sodium alginate and hydrated iron oxide, fibers were elaborated with a diameter ranging from 160 to 475 nm. The authors carried out an exhaustive study of the effect of hydrated iron oxide and sodium alginate on fiber diameter and morphology of the obtained fibers, and the results were related to the increase of electrical conductivity. It was demonstrated that increasing either the content of sodium alginate or iron-based nanoparticles the fiber diameter was reduced and the fibers exhibited a smother surface. Furthermore, a blend consisted of sodium alginate with hydrated iron oxide showed excellent ability to removal of *Vibrio vulnificus* (a strong human pathogen) and the authors claimed the potential use as filters. However, the removal property of the engineered fibrous materials was not determined, thus misleading the authors conclusions related to final applications [132].

3.4. Electrospun antimicrobial polymers combined with antimicrobial nanomaterials

A vast number of researchers have taken advantage of inherently antimicrobial activity of natural or synthetic polymers to develop new materials with stronger biocide effect than the typical polymers used in packaging, filters, medical devices, *etc.* [133–135]. Nevertheless, the use of electrospinning techniques to generate fibrous materials based on antimicrobial polymers is limited, and the fabrication of the corresponding nanoparticle-containing materials is even more so, therefore, the more relevant reports will be addressed below.

Regarding natural polymers, chitosan is well-known as an antimicrobial polymer able to kill a broad spectrum of pathogen microorganisms; consequently, it is undoubtedly the most studied. In the case of composite fibrous chitosan containing antimicrobial nanomaterials, they have been generally fabricated by blending with other polymers since chitosan possess poor solubility in common solvents. Thus, layered, core-sheath, nanoparticles-decorated and nanoparticles-embedded chitosan-based fibrous materials have been developed by combining techniques. Regarding the nanomaterials, the most representative metallic (silver) and metal oxides (TiO_2, Fe_2O_3 and ZnO) have been used as antimicrobial additives, whose combination with chitosan exhibited superior antimicrobial performance against three microorganisms, *i.e. Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans* [10,48,53–55,57,58,74,98,105,120].

Other naturally occurring or bio-sourced polymers, such as cellulose derivatives, poly(L-lysine), poly(hexamethylene guanidine), among others, have also been investigated as antimicrobial materials, but only the last two have demonstrated inherent antimicrobial activity and good biocompatibility. They have also been processed by electrospinning techniques, however, the corresponding reports have been focused on the preparation of fibrous materials based on blends of these polymers [136–139]. In the case of electrospun cellulose derivatives, antimicrobial activity was conferred by the incorporation of silver or zinc oxide nanoparticles, resulting in biocide materials for *Staphylococcus aureus*, *Escherichia coli*, *Spectromyces arenus*, *Aspergillus flavus,* and *Citrobacter* [32,71–73,121,140].

Electrospun materials based on antibacterial synthetic polymers have been more investigated, which could be attributed to the wide range of raw materials for their production, and the versatility in terms of chemical modifications. The main feature of this type of polymers is the presence of ionic groups, by which a destructive interaction occurs with the outer cell structure, thus conducing to the microbicidal effect. Quaternized poly[2-(dimethylamino) ethyl methacrylate] (PDMAEMA) is a well-known antimicrobial polymer, and it has been transformed into submicron fibers by the electrospinning technique. PDMAEMA with a large variety of macromolecular structures (homo- or copolymers) or compositions (blends) resulted suitable for killing *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* [141–143]. Furthermore, nanoparticles-coated PDMAEMA fibers showed higher antibacterial activity than that of neat fibers. It is noteworthy that the coating process has been achieved by a two-step approach: mere electrospinning of PDMAEMA followed by a sputtering process (ZnO and Ag nanoparticles were deposited onto the fibers) [144] or immersion in a dispersion containing the nanoparticles (Ag immobilized onto fibers surface by sodium citrate) [142]. The latter approach produced mats with no cytotoxic effect, so that these fibrous materials are promising for tissue engineering.

4. Mechanical properties of antimicrobial fibrous composite materials derived from electrospinning techniques

Antimicrobial fibrous composite materials engineered by electrospinning techniques are generally utilized as wound dressings and scaffolds in tissue engineering, and as filters for water and/or air decontamination. These devices are subjected to deformation throughout their life-time, so that the evaluation of mechanical properties is of paramount importance [8,50,70,85,131]. In this regard, several authors have investigated the effect of antimicrobial nanomaterial (nanoparticles) content and the electrospinning technique on mechanical properties, mainly modulus and elongation.

Our research consortium has recently investigated the mechanical properties of ZnO-embedded and ZnO-coated PLA fibers obtained by mere electrospinning and electrospinning/electrospraying tandem process, respectively. The mechanical assessment revealed an optimal ZnO nanoparticles concentration in which the higher mechanical properties (tensile strength and Young's modulus) were achieved. This optimal value was independent of the electrospinning technique; however, ZnO-coated PLA fibrous materials exhibited the highest Young's modulus (38 MPa) and tensile strength (18 N). This mechanical performance was attributed to hydrogen bonds between hydroxyl groups onto de ZnO surface and the carbonyl groups of PLA fibers [43]. The effect of ZnO surface modification (PLA grafts by ring-opening polymerization of D,L-lactide) on mechanical performance of electrospun PLA fibers was further investigated, and it was evidenced that the presence of PLA grafts significantly improved the dispersion and interaction with the PLA-based fibers, thus improving not only the aforementioned mechanical properties but also the antibacterial efficiency [42].

Mechanical properties enhancement has also been observed for other polymeric submicron fibers, but containing silver nanoparticles. An et al. demonstrated that wet and dry chitosan/poly(ethylene oxide)-based mats exhibited higher Young' modulus when Ag nanoparticles were embedded in the fibers (49.2 MPa and 322 MPa for neat and composites fibers, respectively). The main difference was observed in wet mats, which suffered more elongation by the presence of water [55]. Other fibrous mats containing silver or its precursory species, specifically PVA/chitosan with $AgNO_3$ or Ag nanoparticles, exhibited tensile strength (9.9 and 15.2 MPa, respectively) suitable for handling related to wound dressings [53]. This increase in mechanical properties was achieved with low silver nanoparticles content, typically ≤ 5 wt-%.

In the case of composite fibrous antimicrobial materials derived from coaxial electrospinning, their mechanical performance has scarcely been investigated. In tissue engineering, coaxial electrospinning has been used only to create fibers with higher mechanical stability, for example, a biocompatible sheath with a more mechanically stable polymer. It was demonstrated that the main advantage of this techniques is the relatively ease to control the morphology of the core-sheath fibers by adjusting the processing parameters, thus tailoring their mechanical performance [145].

5. Antimicrobial mechanism of electrospun fibers based on biopolymers and nanoparticles

The majority of current polymeric medical devices are prone to microorganism colonization, and in the case of electrospun materials, this propensity could be increased due to larger surface area available to interact with microorganisms. Adhesion of microorganisms is a multi-stage process which eventually leads to biofilm formation, and this is the predominant mode of microbial life (both in Nature and in disease), due its inherent resistance to antimicrobials. Therefore, when developing antimicrobial electrospun fibers, it is crucial to understand how the cells initially interact with fibrous mats, and more importantly, how this interaction could be avoided, being the incorporation of antimicrobial nanoparticles one of the most developed approaches.

Currently, there are few studies related to the microbial adhesion on electrospun fibers. However, from the existing reports, it can be established that the mechanism occurs by several stages [146–150], which are summarized below:

(i) Initially, bacteria are transported near to the mat/fibers surface by long range physical forces, such as gravitational and Brownian forces. In addition to this passive transport, controlled-like motion is involved in the transport of bacteria species having proteinic organelles called flagella.
(ii) Then, the attraction between microorganism and electrospun fibers surface takes place by means of physico-chemical interactions, which can conduce to reversible and irreversible adhesion, and they are influenced by the surface chemistry and the fibers/mat morphology. Physico-chemical interactions are basically electrostatic forces such as van der Waals and hydrogen bond formation. The former leads to a reversible microbial adhesion and the latter leads to irreversible microbial adhesion. Moreover, reaction between microorganism surface and fiber surface might occur, thus provoking irreversible adhesion.

(iii) After anchoring on the material surface (electrospun fibers), the microorganism proliferate and synthesize the biofilm matrix (composed by exopolysaccharides, proteins, lipids, among others compounds depending on the microorganism). Proliferation is accomplished by cloning the cells which lead to formation of colonies and eventually enhance the spreading of the surface.

(iv) Finally, biofilm maturation can be achieved and subsequent detachment occurs. Mature biofilms are complex microorganism communities which possess a tri-dimensional structure that allows the access to nutrients and oxygen also protecting against hostile surroundings. It is noteworthy that despite common characteristics, biofilms differ considerably between species and strains.

Considering the microbial adhesion mechanism explained above, either stage from I to IV should be circumvented. The previously described metallic or metal oxide nanoparticles can meet this aim, through a well-known mechanism based on the attack of microorganisms by the metallic ions released from nanoparticles and/or the formation of reactive oxygen species (ROS). Another mechanism based on the absorption of nanoparticles has also been suggested, however, the experimental evidences have concluded that the ions released and/or ROS formation are behind the biocide activity; therefore, this mechanism is explained below.

Once the microorganism approximated to polymeric fiber surface, the presence of moisture from different potential sources (environment, growth medium, adsorbed on polymer and/or nanoparticle surfaces, *etc.*) promotes the corrosion and/or dissolution of nanoparticles present in the fiber surface region, and eventually the production, release, and diffusion of ions/ROS out of the polymeric matrix. Taking into account this stage of the antimicrobial mechanism, the electrospinning techniques should be used for developing polymeric nanofibers with nanoparticle-rich surface, since that is a critical concern in order to enhance the production of the ionic or radical species. As largely illustrated in previous sections, coaxial electrospinning or the combination of electrospinning and electrospraying could be used to achieve this characteristic fiber morphology. It is important to consider that the corrosion/dissolution process, ions/ROS release, and the attack to microorganism can be changed by several factors, such as pH variation, radiation, porosity of fiber surface, variation of the microorganism-polymer affinity, among others; for each specific polymer-microorganism system, which is out of the scope of this review.

Another important factor that potentially influences the antimicrobial properties of fibers derived from electrospinning techniques is their morphology, mainly the fiber average diameter and the mat porosity. Abrigo et al. have reported a comprehensive study to evaluate the growth behavior of *E. coli*, *P. aeruginosa*, and *S. aureus* on polystyrene micro- and nano-fibers [151]. It was demonstrated that the bacteria adhered to fibers regardless the average fiber diameter, but they preferentially adhered to fibers with diameter similar to bacteria size. Furthermore, the bacteria shape also influenced the adhesion to electrospun fibers, since round bacterium (*S. aureus*) evidenced higher adhesion and growth that rod-like bacteria (*E. coli* and *P. aeruginosa*) [151]. These findings could be exploited to increase the antibacterial activity of neat or composite fibrous materials and control the adhesion and proliferation of tissue cells [152].

Regarding the porous morphology typically exhibited in materials engineered by electrospinning techniques, it has been evidenced that fibrous wound dressings with porosity higher than 60% were suitable for wound healing, since they allowed for permeation and diffusion of oxygen from air to skin [1]. Additionally, one such porous morphology acted as a barrier to some microorganisms as long as the interfiber average size was smaller than the dimensions of the microorganism involved, this antimicrobial mechanism being well-recognized as sieve effect. It is noteworthy that sieve effect by itself is not highly effective, while the incorporation of nanoparticles has proven to be a coadjutant approach [153].

Fiber porosity is another factor with potential repercussions in the antimicrobial activity of materials obtained by electrospinning techniques. It has been demonstrated that the more heterogeneous the surface of polymeric substrates, the higher the surface area, thus increasing the sites for cell attachments [154]. Therefore, it is important to control the smoothness of fibers to avoid microorganism adhesion and proliferation, and it is well-reported that this morphological feature can be minimized by the selection of solvents with relatively low volatility [155,156]. In the case of composite fibrous materials meant for antimicrobial devices, it is of paramount importance to achieve excellent distribution of antimicrobial nanomaterials, since agglomeration of them could promote the formation of fiber defects, which could be considered as sites of adhesion for microorganisms [39,42,43].

6. Conclusions and future prospects

Electrospinning and related techniques, namely tandem electrospinning/electrospraying or coaxial electrospinning, have demonstrated versatility for developing polymeric fibrous materials with strong antimicrobial properties conferred by means of the presence of inorganic nanostructures. The incorporation of metallic silver and gold nanoparticles as well as metal oxides based on titanium, zinc, copper and iron, is the most developed approach. These inorganic compounds in the nano-metric regime have demonstrated strong antimicrobial properties, and additionally, other relevant properties can be modified or conferred, such as mechanical, magnetic, catalytic, and optical properties, thus increasing the possibility to develop multi-functional fibrous materials with wider application areas.

Researchers have focused their efforts on the investigation related to the variation or combination of electrospinning-related techniques, which have yielded important findings related to the influence of nanoparticle distribution/dispersion in electrospun (bio)polymeric fibers. It was demonstrated that electrospinning/electrospraying and coaxial electrospinning are suitable approaches for designing (bio)polymeric fibers with higher antibacterial activity than that of mats fabricated with mere electrospinning, which is due to higher surface area prone to interact with pathogenic microorganisms. However, in the case of polymer/Ag composite fibers, mere electrospinning of the corresponding polymeric solution containing $AgNO_3$ could also lead to fibers with Ag-rich surface, because of ion migration, which can subsequently be reduced to Ag^0.

Regarding the biocompatibility of the reported (bio)polymer/

nanoparticles mats, *in vitro* investigation has demonstrated that low contents (typically lower than 5 wt-%) of metallic and metal oxide nanostructures, especially Ag, TiO_2, and ZnO, do not exhibit toxicity against medically important cell strains, such as mesenchymal human cells, fibroblasts, and osteoblasts. On the other hand, *in vivo* tests have been limited to skin healing, showing that the fibrous materials can promote a faster wound healing in the same range of nanostructure concentration than that for *in vitro* tests.

Despite the major findings about antimicrobial electrospun composite fibers, there is currently a need to evaluate the toxicity against more microorganisms, since most of the analyses have been restricted to two model bacteria, *i.e. Escherichia coli* and *Staphylococcus aureus*. In sharp contrast, few or no information related to fungi, viruses and other dangerous bacteria has been published. It could also be inferred that further *in vivo* studies have to be carried out in order to provide more realistic findings and medical prospections.

Another challenging issue is to carry out further studies related to the use of coaxial electrospinning and the combination electrospinning/electrospraying techniques for the fabrication of a large variety of antimicrobial composite polymeric fibers. It is also necessary to develop novel or adapted equipment that enable the fabrication of electrospun sub-micrometric fibers in a larger scale in order to achieve cheaper, sustainable, and massive commercialization of obtained mats. In this regard, alternative techniques also based on electro-hydrodynamic principles have been developed, such as needle-less electrospinning [157,158], multi-jet electrospinning [159,160] and portable electrospinning [161]. In addition, sub-micrometric polymeric fibers have also been obtained by an interesting process denominated Force-spinning®, which uses centrifugal force for promoting the flow of the polymeric solution or melted polymer [162–164].

The aforementioned contributions about the incorporation of antimicrobial nanomaterials, their dispersion, the control of fiber morphology, the evaluation of antimicrobial performance, *in vitro* and *in vivo* studies, and so on, could foster faster development and application of composite (bio)polymeric electrospun fibers as tissue engineering scaffolds and wound dressings.

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