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

Heriberto Rodríguez-Tobías, Graciela Morales, Daniel Grande

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

3
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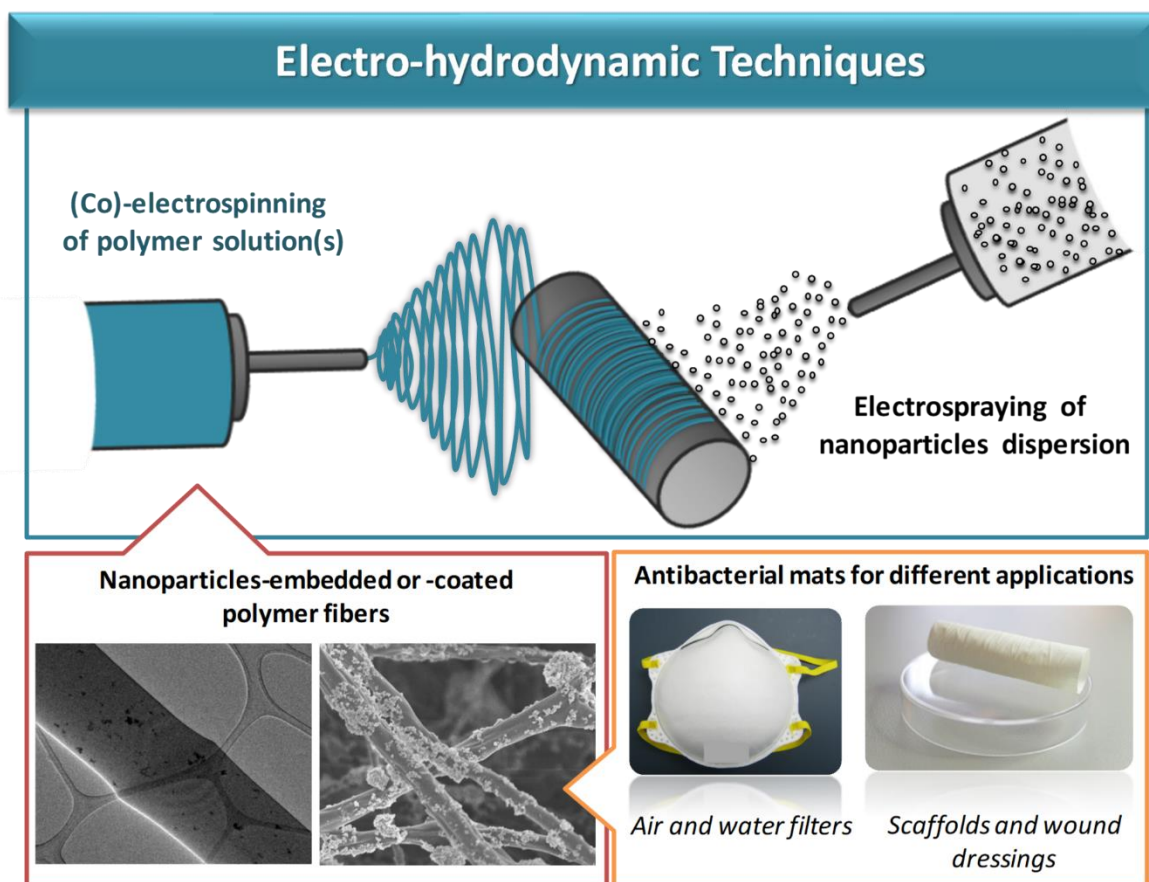
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1 **Graphical Abstract**

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12 **Abstract**

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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 electro spraying and electrospinning for the generation of nanoparticle-coated fibers, as well as coaxial electrospinning for obtaining fibers with nanoparticle-rich surface.

Keywords: electrospinning; electro spraying; coaxial electrospinning, antimicrobial particles; biopolymers; fibrous composites

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1 **1. Introduction**

2

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

14

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

24

1 Nanostructures with well-known antimicrobial properties have emerged as promising
2 compounds for developing fibrous mats with better antimicrobial performance than those
3 containing typical organic compounds, such as antibiotics and biocides. Likewise,
4 antimicrobial nanoparticles, including zinc oxide, titanium dioxide, silver, and gold
5 analogues, have demonstrated some advantages like their higher chemical and thermal
6 stability that may lead to a new generation of biomedical devices with improved
7 antibacterial activity as well as enhanced mechanical, thermal and other physical properties
8 [12].

9

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

17

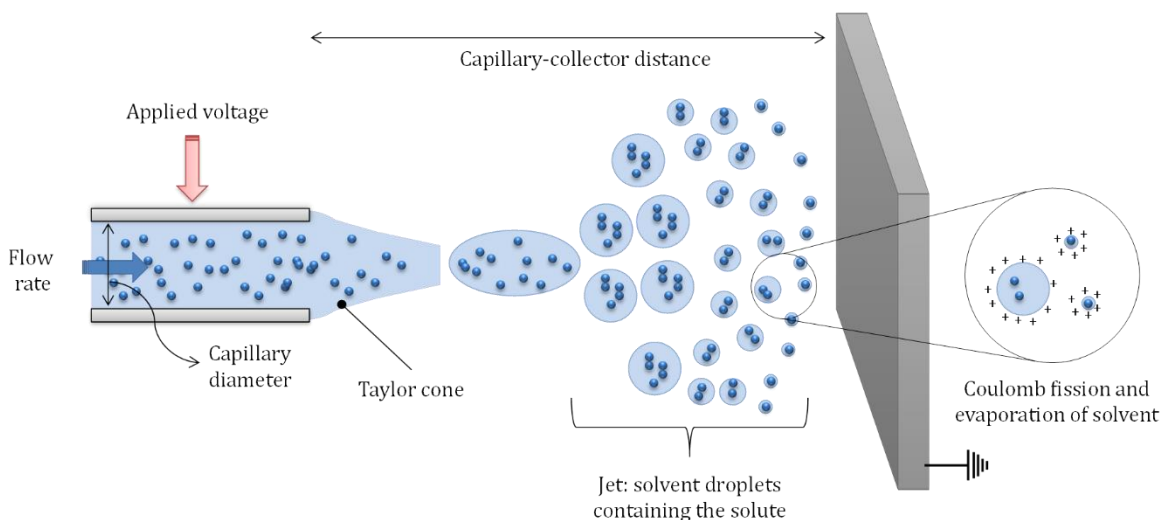
18 **2. Overview of electrospinning and related techniques**

19

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

24

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



12 **Figure 1.** Scheme of the electrospinning process, more specifically the section between
13 needle and collector, in which the formation of the Taylor cone, the Coulomb fission and
14 the solvent evaporation take place.

15

16 The versatility of the electrospinning technique is attributed to several advantageous
17 characteristics, including:

1

2 • Droplet size is smaller than that available from conventional mechanical atomizers, and
3 can be smaller than 1 μm . Therefore, the resulting particles can be in the nanoscopic
4 regime.

5 • The size distribution of the droplets is usually narrow, with small standard deviation
6 that allows for production of particles of nearly uniform size.

7 • Charged droplets are self-dispersing in space (due to their mutual repulsion), resulting
8 in the absence of droplet coagulation, and consequently lower agglomeration.

9 • The motion of charged droplets can be easily controlled (including deflection or
10 focusing) by varying electric fields.

11 • The deposition efficiency of a charged spray on an object is one order of magnitude
12 higher than that for uncharged droplets.

13

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

17

18 Electrical conductivity is a fundamental solution/dispersion property since it allows for the
19 charge transfer inside the liquid, so in turn, this property is governed by the nature of
20 solvent and solute. Generally, an increase in electrical conductivity results in a smaller
21 particle diameter due to a higher number of charges around the droplets, which promotes
22 their Coulomb fission (breakup). Solution/dispersion viscosity is another property that
23 strongly influences the electro spraying behavior and final morphology, and it is

1 proportional to solute concentration and molecular weight (especially for polymers). As a
2 rule, the solution/dispersion viscosity should be sufficiently low to allow for the formation
3 of droplets; moreover, a highly viscous solution requires higher voltage in order to
4 overcome the surface tension which is not practical [3, 13-15].

5

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

$$14 \quad d_p = \Phi^{1/3} d \sim G(\varepsilon) \left(\frac{Q \varepsilon \varepsilon_0}{\kappa} \right)^{1/3} \quad (1)$$

15

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

19

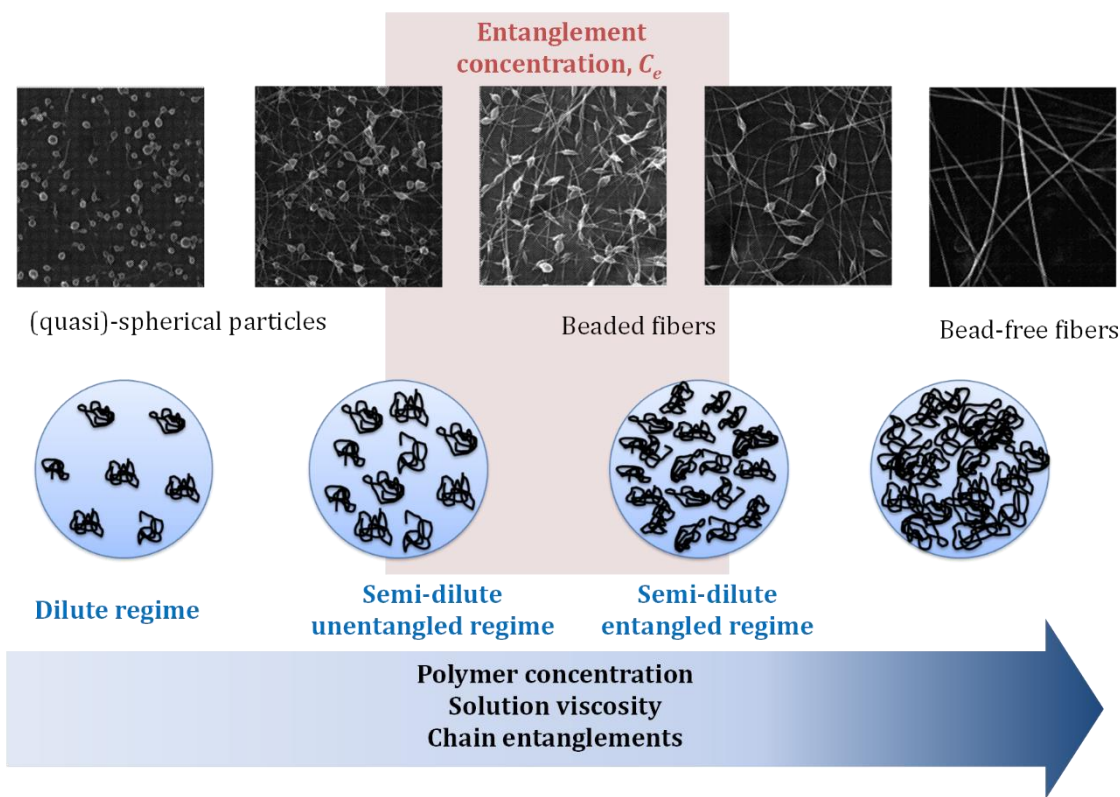
20 Other process parameters, more specifically those related to the electrospaying equipment,
21 are the capillary diameter and capillary-to-collector distance. The former determines the
22 size of the Taylor cone, which in turn influences the droplet and particle diameter.
23 Concerning the capillary-to-collector distance, it was demonstrated that a shorter distance is

1 beneficial for generating a higher electrical field strength, thus producing smaller particles
2 but also has the drawback of possible electric discharge and insufficient time for solvent
3 evaporation, which may lead to coalescence/agglomeration of wet particles on the collector.
4 Similarly, the applied voltage provokes a strong effect on particle morphology: the higher
5 the applied voltage, the lower the particle size, which can be explained in terms of higher
6 charge density in the solution/dispersion and breakup of ejected droplets [3, 13-15, 17].

7
8 Electrospinning is based on the same electro-hydrodynamic phenomena previously
9 discussed for the case of electrospraying. Therefore, the morphology of resulting materials
10 depends on similar parameters: electrical conductivity and viscosity of solution/dispersion,
11 flow rate, capillary diameter, capillary-to-collector distance and applied voltage. The main
12 difference between electrospinning and electrospraying is that the former technique
13 generates a continuous jet from the Taylor cone, thus collecting a mat consisting of
14 polymeric fibers [1, 18-20].

15
16 It is important to mention that fibers are typically engineered from a solution containing
17 high molar mass compounds, *i.e.* polymers, since the stability of the jet is a result of chain
18 entanglements. In this regard, a critical polymer concentration (*i.e.*, viscous polymeric
19 solution) is required for the occurrence of chain entanglements, thus producing fibers.
20 Below this critical polymer concentration (*i.e.*, dilute regime) only droplets are collected,
21 *i.e.* electrospraying takes place, since polymer chains are separated by the solvent. With an
22 intermediate concentration (*i.e.*, semi-dilute regime), the polymer chains overlap each
23 other, but this is not enough for significant entanglement formation, therefore, particle-like
24 morphology is still dominant. Fibers with high number of beads can be obtained up to the

1 entanglement concentration (C_e), *i.e.* the transition between semi-dilute unentangled and
 2 semi-dilute entangled regime. Above the entanglement concentration, fibers with well-
 3 defined morphology can be produced, which generally is 2-2.5 times C_e . The polymeric
 4 solution regimes and their repercussions on morphology of the obtained materials are
 5 illustrated in Figure 2. It is worth mentioning that the solution/dispersion and process
 6 parameter described in previous sections for the case of electrospinning process also affect
 7 the final morphological parameters of electrospun fibers, namely average fiber diameter,
 8 fiber diameter distribution and porosity ratio [21-23]. These solution and process factors as
 9 well as their corresponding effect on morphology are summarized in Table 1.



10

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

1 **Table 1.** Effect of different parameters on the morphology of polymeric fibers derived from
 2 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)

3 Source: Sill and von Recum 2008 [11].

4

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

7

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

15

16 **3.1. Approaches for designing fibrous composite materials by electrospinning** 17 **and related techniques**

18

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

24

1 Mere electrospinning is the most reported approach for obtaining composite fibers, and it
2 consists in preparing a polymeric solution containing the corresponding antimicrobial
3 nanoparticles or their precursory compounds, which eventually is subjected to
4 electrospinning process. The main advantage of this approach is its relatively
5 straightforwardness, thus producing polymeric fibers with nanoparticles mostly embedded
6 (some particles could however migrate to the fibers surface during the electrospinning
7 process). On the other hand, the main disadvantage is related to the low antimicrobial
8 efficiency due precisely to the embedding of nanoparticles, thus reducing the surface area
9 prone to interact with pathogen microorganisms [12,35-37].

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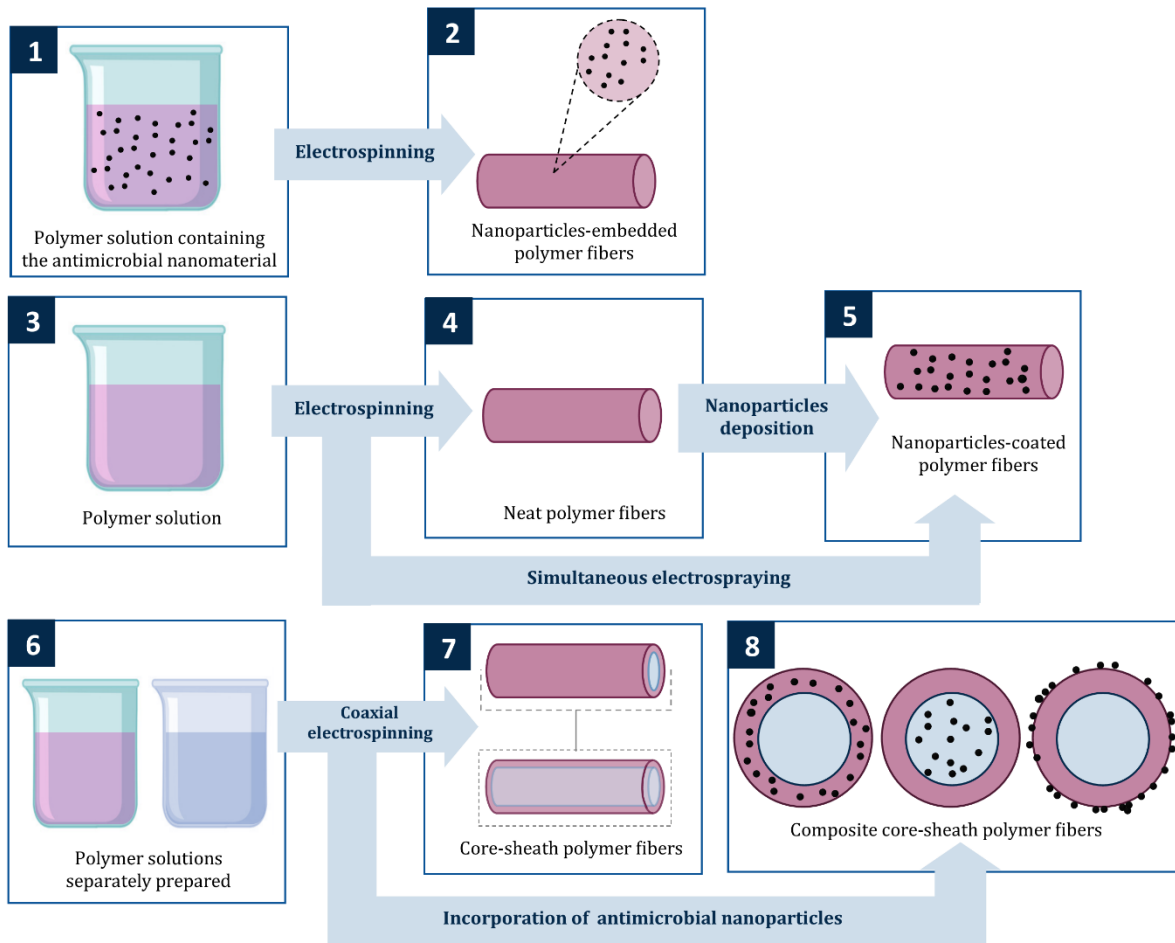
11 Nanoparticles-coated polymeric fibers can be engineered by two techniques. One of them
12 involves a two-step process, *i.e.* mere electrospinning to obtain neat polymeric fibers from
13 the corresponding solution, then followed by the deposition of the antimicrobial
14 nanoparticles by several well-known techniques, such as sputtering or impregnation. The
15 second technique is a tandem process denominated electrospinning/electrospraying, which
16 consists of a simultaneous electrospinning of a polymeric solution and the electrospraying
17 of the corresponding antimicrobial nanoparticles dispersion. Both techniques have been
18 utilized for enhancing the properties dependent on the nanoparticles surface area, such as
19 antimicrobial activity; however, an uninvestigated concern is related to the adhesion and
20 loss of nanoparticles. Comparing the techniques, electrospinning/electrospraying tandem
21 process has the advantage of producing nanoparticle-coated polymeric fibers in one-step.
22 Unfortunately, complementary equipment (*e. g.* electrospraying) is needed for carrying out
23 the fabrication of the composite fibers, thus increasing the initial technological investment
24 [38-46].

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

7

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

17



1

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

6

7 **3.2. Polymers used as fibrous matrices for tissue engineering**

8

9 An appropriate polymer for tissue engineering applications should be biocompatible,
 10 biodegradable, nontoxic, non-mutagenic, and non-immunogenic. Polymers are generally

1 classified into two types, namely synthetic polymers and natural polymers (*i.e.*
2 biopolymers) [52].

3
4 Natural polymers are produced by biological systems (*i.e.*, microorganisms, plants, and
5 animals) whose main advantages are their bioactivity, *i.e.* the ability to interact with the
6 surrounding host tissue and to induce cell deposition/proliferation. Moreover, this type of
7 polymers provokes low inflammatory effect, they can be degraded by enzymes, and their
8 degradation products can be consumed throughout the cellular metabolism. However,
9 natural polymers are highly temperature sensitive, and their complex structure makes them
10 difficult to be processed by electrospinning techniques. Another well-known disadvantage
11 of natural polymers is the highly divergent properties as a function of the bio-source or
12 batch. Two types of natural polymers are generally utilized for tissue engineering: (i)
13 polysaccharides, such as chitin, chitosan, and alginate; (ii) proteins, such as collagen and
14 gelatin.

15
16 Synthetic polymers on the other hand, are highly useful in tissue engineering as their
17 properties (*e.g.*, porosity, degradation time, and mechanical characteristics) can be easily
18 tailored for specific requirements of medical devices and host tissue. Furthermore, these
19 polymers are often less expensive compared with natural analogues, and they can be
20 produced in larger quantities. Since natural polymers exhibit certain difficulties for
21 processing them in electrospinning techniques (*i.e.*, mainly solubility), synthetic polymers
22 are typically blended with low amounts of natural polymers, which enhances their
23 solubility [48, 53-58]. Several reviews have hitherto been published in which the
24 mechanical and thermal properties as well as biocompatibility, solubility and

1 biodegradation of both natural and synthetic polymers are compiled and thoroughly
2 analyzed. Therefore, further information can be consulted for specific polymeric systems in
3 these feature publications [59-63].

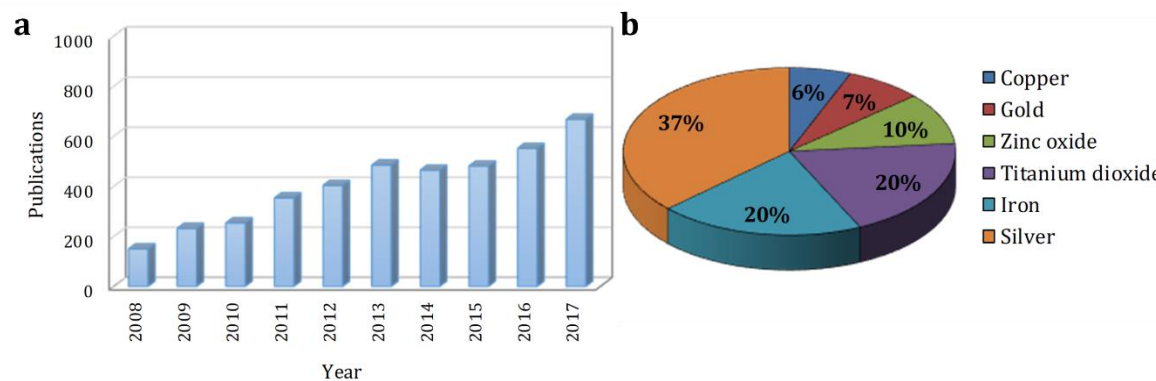
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5 **3.3. Antimicrobial nanomaterials and their incorporation into biopolymeric fibrous** 6 **materials**

7

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

19



1

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

6

7 **3.3.1. Metallic nanoparticles**

8

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

16

17 The (bio)polymer/nano-Ag composite fibers can be obtained from polymeric solutions
 18 containing the as-synthesized nanoparticles (Ag^0) or some silver salt. Silver-based
 19 compounds can enhance the spinability of the solution, leading to well-defined

1 (bio)polymeric fibers, which has been attributed to the increase in electrical conductivity by
2 the presence of Ag^+ ions released from Ag^0 or originated from the silver salt dissociation.
3 Currently there is a trend to add AgNO_3 as a precursor of nano-Ag since this salt is easily
4 solubilized in polar solvents typically used for electrospinning, thus increasing the electrical
5 conductivity. As expected, the presence of Ag^+ ions strongly affects the final morphology
6 of fibers: at low concentration ($< 8\%$) average fiber diameter is generally reduced, and on
7 the contrary, at high concentration ($> 8\%$) the agglomeration of Ag species promotes phase
8 segregation, thus increasing the average fiber diameter [65-68].

9

10 The use of AgNO_3 as precursory species for obtaining (bio)polymeric fibers with nano-Ag
11 involves a reduction step, which can be induced by heat [69], chemical reducing agents [36,
12 70] or photo-irradiation [32, 33, 69, 71, 72]. Recently, UV-induced photochemistry has
13 been taken advantage because of its simplicity, low cost, and sustainability. Interestingly,
14 several researchers have claimed about the fabrication of polymer/nano-Ag composite
15 fibers with controlled antimicrobial activity. This can be achieved by electrospinning the
16 corresponding solution containing AgNO_3 , followed by a photo-reduction. The size,
17 content, and dispersion/distribution of the embedded Ag nanoparticles are controlled by
18 AgNO_3 concentration and time of UV irradiation. Long irradiation time promotes the
19 migration of Ag^+ ions through the outer layer of the fibers as well as the production of Ag^0
20 and its increase in size, thus tailoring the antimicrobial performance reaching up to 99.9%
21 of growth inhibition at relatively low AgNO_3 concentration (from 0.1 to 1 wt-% in relation
22 to polymer) [32, 33, 69, 71, 72]. Thus, poly(vinyl alcohol) (PVA) [66, 69], cellulose
23 derivatives [32, 71-73], poly(lactic acid) [68], gelatin [33], chitosan, poly(ethylene oxide)
24 or polymer blend-based fibers [55, 57, 58, 74] have been engineered with high

1 antimicrobial *in vitro* performance against Gram-positive (mainly *Staphylococcus aureus*)
2 and Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas*
3 *aeruginosa*, *Proteus mirabilis*, *Bacillus cereus*), as well as fungal culture (*Candida*
4 *albicans*).

5
6 The ideal composite polymeric fibers must possess a nanoparticle-rich surface in order to
7 exhibit suitable antimicrobial activity for using in medical devices, which is very difficult
8 to achieve by mere electrospinning, since nanoparticles are buried in the inner part of the
9 fibers. However, a more accurate procedure is to create fibers with core-sheath
10 morphology, where the sheath contains Ag nanoparticles. These particular fibers can
11 exclusively be obtained by an alternative technique, the so-called coaxial electrospinning,
12 which is based on the same principles of simple electrospinning, but the system that ejects
13 the polymer solution consists of two coaxial capillaries with different diameters by which
14 two fluids converge forming a core of one polymer covered by the other polymeric system.
15 The second polymeric solution could contain specific nanoparticles in order to produce a
16 composite sheath with enhanced antimicrobial properties.

17
18 Coaxial electrospinning has scarcely been exploited for the design of polymer/nano-Ag
19 composite fibers, and the selected matrix has not been necessarily biocompatible or
20 biodegradable. Yu *et al.*[51] have deposited Ag nanoparticles preferentially on the surface
21 of polyacrylonitrile (PAN) fibers by coaxial electrospinning of the corresponding polymeric
22 solution (core) and N,N-dimethylacetamide/AgNO₃ solution (sheath). An additional device
23 for UV irradiation was adapted near to the capillary tip in order to reduce the Ag⁺ ions
24 during the ejection process. Interestingly, the authors found that the solution used for sheath

1 generation provoked the formation of thinner fibers than those derived from neat PAN
2 solution, which was attributed to the increase in electrical conductivity, *i.e.* more induced
3 charges over the polymer solution surface, thus reducing the average fiber diameter [49].
4 Moreover, it was demonstrated that the feed rate ratio of sheath/core precursory solutions
5 played a significant role for accomplishing good nanoparticle dispersion, since it regulated
6 the deposition of Ag⁺ ions on the core jet during the process of coaxial electrospinning. The
7 obtained composite fibers showed a high bacterial growth inhibition (>99.9%) against
8 *Escherichia coli* and *Bacillus subtilis* with only 4% Ag nanoparticles. Unfortunately, the
9 authors did not compare with fibers obtained by mere electrospinning to corroborate the
10 effect of the specific technique used.

11

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

19

20 There are some biocompatible and biodegradable polymers with good mechanical
21 performance for wound dressing materials and/or tissue engineering scaffolds, such as
22 PCL. Nevertheless, its hydrophobicity limits a suitable cell attachment and proliferation,
23 thus limiting its use in the aforementioned biomedical devices. Coaxial electrospinning
24 offers the possibility to adapt the surface properties by forming a polymeric sheath with

1 different chemical nature. In this regard, Kalwar *et al.* [48] designed co-electrospun fibers
2 based on PCL/chitosan (core/sheath) with average diameters ranging from 200 to 450 nm.
3 The presence of chitosan promoted an increase in the hydrophilicity of co-electrospun
4 fibers, and on the other hand, well-dispersed Ag nanoparticles into the sheath due to
5 interactions between nanoparticles and amino and hydroxyl groups of chitosan.
6 Furthermore, the obtained fibrous materials exhibited good inhibition growth of *E. coli* and
7 *S. aureus* when subjected to *in vitro* tests (disc diffusion method) and insignificant
8 difference was observed as a function of the bacterium type.

9

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

21

22 Even though polymer/nano-silver fibrous composites derived from electrospinning
23 techniques have showed promising antimicrobial properties, one of the most important
24 concerns is the potential toxicity of nanoparticles when exposed to tissue cells, which could

1 limit their massive production and application. Currently there are controversial results
2 associated with the viability of different tissue cells when exposed to polymeric mats
3 containing the aforementioned metallic nanoparticles. As a matter of example, Sumitha's
4 work evidenced that Ag-embedded PCL fibers (200-260 nm in diameter) could efficiently
5 kill *S. aureus* bacteria (disc diffusion tests) at concentration as low as ~0.002 wt-% without
6 compromising the adhesion of human mesenchymal stem cells (viability ~99%). On the
7 contrary, such PCL fibers with ~0.06 wt-% Ag exhibited 50% cell viability, implying that
8 nanoparticles induced toxicity to cells at very low concentration [76].

9

10 In 2014, Lin *et al.* evaluated the viability of the PA317 cell line (mouse fibroblasts with
11 herpes gene) in the presence of PVA/Ag composite mats derived from electrospinning and
12 subsequent chemical reduction (induced by the matrix, UV and heat). Some relevant
13 findings were reported, such as the effect of reduction methodology on the amount and size
14 of formed nano-Ag, and consequently on the antibacterial properties against *E. coli* and *S.*
15 *aureus* (all materials showed antibacterial activity >99%). The authors concluded that the
16 critical factor to avoid cell toxicity was to select an appropriate reduction process by which
17 no Ag⁺ ions remained into PVA fibers, since these ionic species hampered the proliferation
18 of PA317 cells. The Ag⁰ nanoparticles did not induce toxicity even at high concentration
19 (10 and 12 wt-%), thus increasing the potential of these mats as antibacterial wound
20 dressings and/or scaffolds [77].

21

22 Additional reports have corroborated the good biocompatibility of electrospun
23 biopolymeric fibers with embedded Ag nanoparticles [78-81]. In spite of these encouraging
24 results, most of the evaluation approaches have been carried out by *in vitro* tests, so that it

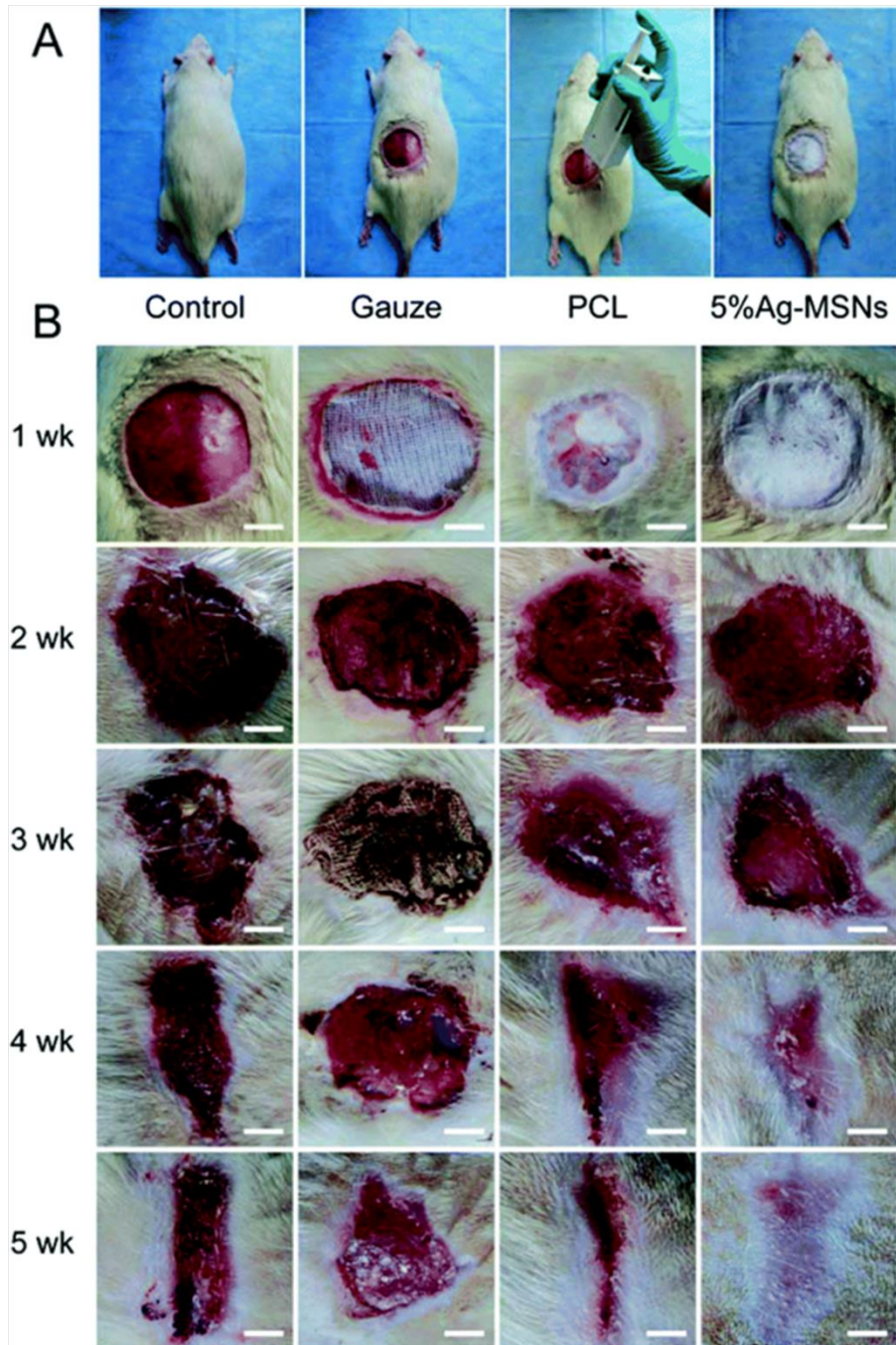
1 is necessary to perform more realistic studies, *i.e. in vivo* tests, which are limited. On this
2 topic, antibacterial electrospun fibers (130-190 nm in diameter) based on poly(vinyl
3 alcohol) and chitosan oligosaccharides (2:1 ratio) containing silver nanoparticles (15-22 nm
4 in diameter) or AgNO₃ (both silver species at 3 wt-% compared to polymer) were subjected
5 to *in vivo* tests with the aim of determine their biocompatibility. Initially, the obtained mats
6 were placed on dorsal skin of rabbits, and the irritation skin levels were monitored. It was
7 observed that mats caused no irritation to normal skin after 72 h, indicating the
8 acceptability of these fibrous materials for transdermal drug delivery. Furthermore, the
9 wound healing performance of PVA-based mats was inferred by wound healing and
10 histological examination in rat back during 14 days. It was observed that PVA-based
11 nanofibers containing Ag nanoparticles did not interfere with the healing process and the
12 wound closure was accomplished in the analyzed period. Moreover, PVA/chitosan/nano-
13 Ag mats showed histologically superior wound healing than commercial materials (wound
14 plast and gauze) and PVA/chitosan/AgNO₃ fibers since wounds with these mats displayed
15 ulcerated surfaces, formation of granulation tissue, and infiltration of inflammatory cells
16 after 7 days. On day 14, newly synthesized fibrous tissue and sparse inflammatory cells in
17 the dermis and subcutis were covered by completely re-epithelialized epidermis in each
18 group, thus confirming that the PVA/chitosan electrospun fibers with Ag nanoparticles
19 could provide a suitable scaffold for wound healing [53].

20

21 Dong *et al.* have also provided information about the *in vivo* biocompatibility of PCL fibers
22 containing silver-decorated mesoporous silica (Ag-MSN, 0.05 wt-% to polymer). As shown
23 in Figure 5, skin injuries were purposely made on the specimens (male Wistar rats). It was
24 found that the wounds healed better and faster after being treated with Ag-MSN/PCL

1 fibrous membranes than with other materials (gauze). On week 5, a rough and thin skin
2 layer was formed in the presence of PCL/Ag-MSN fibers and without signals of
3 inflammation by histological analysis. In contrast, the wounds without one such dressing,
4 with neat PCL or gauze, were still in the late phase of inflammation. These results
5 demonstrated that the Ag-MSN/PCL nanofibrous membranes could strongly help the
6 healing process [82].

7



1

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

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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*,

1 due to the presence of nano-Ag as well as good removal of toluene attributed to β -
2 cyclodextrin without affectation on air permeation and mechanical performance [84].
3 Similarly, soy protein has been used in conjunction with Ag to confer toxic gases removal
4 and antibacterial activity in fibrous materials based on polyamide 6 [85].

5
6 Gold nanoparticles have been also incorporated into electrospun biopolymeric fibers for
7 improving antimicrobial properties. Likewise, these metallic nanoparticles have attracted a
8 particular attention mainly due to their anti-proliferative activity on carcinogenic cells that
9 could lead to mats with anticancer properties. In this regard, Manjumeena *et al.* developed
10 PVA-based fibers containing a low content of gold nanoparticles (0.1 wt-%), which
11 resulted in a suitable environment for proliferation of Vero cells, thus leading to a viability
12 of ca. 90% after 72 h of incubation. The good cell proliferation was attributed to the
13 hydrophilicity of the mats as well as the electrostatic attraction between cell membrane and
14 PVA fibers, regardless of the presence of gold nanoparticles. More interestingly, the
15 presence of Au nanoparticles in the electrospun fibers provoked antiproliferative effects in
16 MCF-7 and HeLa cell lines, showing 8 and 9% proliferation, respectively. Additionally, the
17 obtained mats showed excellent antimicrobial performance against a wide range of
18 microorganisms, such as *B. subtilis*, *A. coli*, *K. pneumonia*, *M. luteus*, *P. aeruginosa*, *S.*
19 *aureus*, *C. albicans* and *C. krusei* [86].

20
21 Similarly, McKeon-Fischer *et al.* demonstrated that PLLA/Au nanoparticles could
22 successfully be engineered by the electrospinning technique. However, the resulting fibers
23 did not stimulate the proliferation of rat muscle cells, which was not caused by the presence
24 of gold nanoparticles since parallel studies corroborated the non-toxicity of isolated

1 nanoparticles at high concentrations (7-21 wt-%). The authors claimed that the cell seeding
2 on the obtained mats was insufficient to induce proliferation; however, no clear
3 experimental evidence was provided [87].

4

5 **3.3.2. Metal oxides**

6

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

17

18 Titanium dioxide (TiO₂) is a well-known multifunctional material with significant UV
19 absorption, antimicrobial, and catalytic properties; therefore, the nanoparticles derived from
20 this metal oxide have been applied in medicine and environment-related areas as UV-
21 blocking agents, sensors, photo-catalytic systems, etc. [93]. Currently, there is a trend to
22 produce TiO₂ nanostructures with controlled morphology by electrospinning a polymeric
23 solution containing a Ti-containing source (such as titanium isopropoxide), and
24 subsequently thermally degrade the polymeric matrix [94].

1
2 Regarding electrospinning for the fabrication of biopolymeric fibers, some researchers have
3 demonstrated the multi-functionality of the corresponding mats with nano-TiO₂ and have
4 also proved the antibacterial activity and potential application in tissue engineering by *in*
5 *vitro* approaches. In this sense, Lee *et al.* took advantage of the well-known
6 biocompatibility of poly(vinyl alcohol) for preparing PVA/nano-TiO₂ (2-3 wt-%)
7 composite fibers with excellent antibacterial activity against *S. aureus* and *K. pneumoniae*,
8 UV protection, and the ability to degrade formaldehyde, thus evidencing the possibility to
9 develop advanced textile materials [95]. Similarly, PVA-based composite mats with
10 enhanced antibacterial properties were obtained by incorporation of low amounts of
11 chitosan (3-15 wt-%), which is an inherent antibacterial natural polymer, and TiO₂
12 nanoparticles. When comparing fibers with embedded TiO₂ and Ag nanoparticles at the
13 same concentration, the latter nanoparticles exhibited superior antibacterial performance
14 (10% higher with 0.04 wt-% Ag nanoparticles), which could be explained in terms of
15 release feasibility [57].

16
17 Poly(3-hydroxybutyrate) (PHB) is another interesting natural polymer which strongly
18 draws attention for tissue engineering, due to its excellent biocompatibility in the presence
19 of a wide range of medically important cells [96, 97]. Nano-TiO₂ has been incorporated
20 into electrospun PHB fibers in order to prevent bacteria adhesion, specifically against *E.*
21 *coli*. Korina *et al.* studied PHB/TiO₂ fibrous materials obtained by mere electrospinning, its
22 combination with electrospaying or impregnation with TiO₂ nanoparticles, thus leading to
23 TiO₂-embedded mats for the mere electrospinning technique and TiO₂-coated mats for the
24 electrospinning/electrospaying or electrospinning/impregnation approaches. The

1 comparative study revealed that all composite fibers completely killed the bacterium, but
2 those with TiO_2 on the surface (electrospraying/electrospinning and
3 electrospinning/impregnation) achieved the maximum antibacterial effect in only 30 min,
4 while it took 60 min for fibers containing embedded TiO_2 . The main concern when
5 preparing PHB or other PHAs fibrous nanocomposites is the preservation of its inherent
6 cell adhesion and proliferation. In this regard, the presence of relatively high content of
7 TiO_2 nanoparticles (5-10%) did not interfere with the proliferation of different cell lines
8 [37, 98].

9
10 Poly(lactic acid) (PLA) and its copolymers with poly(glycolic acid) (PLGA) are
11 biodegradable polyesters with high potential as fibrous materials for medical applications,
12 due to their mechanical and thermal properties comparable with other commercially
13 available polyesters, and especially approval by the US Food and Drug Administration [38,
14 52, 99-102]. Concerning PLA-derived electrospun fibers with TiO_2 nanoparticles, it was
15 demonstrated that the combination of electrospinning of PLA and electrospaying of a Ti
16 precursor, followed by subsequent hydrothermal treatment, resulted in an excellent
17 approach to develop PLA-based mats with strong antibacterial activity against *E. coli* and
18 *S. aureus* at high TiO_2 content (*ca.* 35 wt-%) [103]. Further studies revealed that PLA/ TiO_2
19 fibers preserved their antibacterial efficiency against *S. aureus* at relatively low
20 nanoparticle content (1-5 wt-%) without evidence of *in vitro* cytotoxicity (24-168 h,
21 fibroblast cell line) [104].

22
23 Advanced biomedical devices consisting of two layers, the first one of chitosan/ TiO_2
24 electrospun fibers and the second one of adipose-derived extracellular matrix were recently

1 reported. These new materials exhibited low percentage of bacterial penetration (*E. coli* and
2 *S. aureus*), due to the synergistic effect of chitosan and TiO₂. Additionally, *in vivo* analysis
3 in conjunction with the corresponding histological and immunofluorescence staining
4 proved the ability of the obtained mats to heal wounds in only 21 days [105].

5
6 Variation and/or combination of electrospinning techniques have barely been used for
7 designing polymeric fibers with TiO₂, and the few reports are focused on non-medical
8 applications, with the exception of the previously cited works by Korina and Toniatto [45,
9 106]. For instance, in 2010 the production of chitosan fibers decorated with TiO₂ was
10 reported. The fibers were obtained by the coaxial electrospinning technique, and the
11 engineered mats were meant for self-cleaning textiles since TiO₂ assisted the degradation of
12 pigments [107]. The polymer/TiO₂ fibers derived from coaxial electrospinning have mainly
13 been used in applications associated to energy, photo-voltaic and photo-catalysis, in which
14 the polymeric matrices are typically non-biodegradable, and in most of the cases the
15 matrices are further sacrificed by thermal treatment [5, 108-111].

16
17 Another important inorganic nanomaterial with strong inhibitory and bactericidal effect is
18 zinc oxide, which has been utilized for decades. Furthermore, this metal oxide has
19 demonstrated a higher ability to kill various types of bacteria than TiO₂ nanoparticles [28,
20 112, 113]. For instance, methicillin-resistant *Staphylococcus aureus* is one of the major
21 nosocomial pathogens, whose proliferation has been inhibited by ZnO nanoparticles with
22 diameter size *ca.* 100 nm in a major extent than with TiO₂. This behavior resulted even
23 more interesting due to the fact that TiO₂ exhibited smaller size (*ca.* 50 nm), *i.e.* higher
24 surface area, which should potentially lead to higher antibacterial activity; however this

1 behavior was not observed [114]. Moreover, ZnO nanoparticles can open the possibility of
2 developing materials not only with antibacterial properties, but also with the power to exert
3 a toxic effect against cancer cells, which has recently been demonstrated by Akhtar *et*
4 *al.*[115].

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

17
18 PVA/ZnO fibers were fabricated by electrospinning of the corresponding PVA solution
19 containing zinc acetate as ZnO precursor (diameter ~ 240 nm), and they were evaluated as
20 antibacterial materials against both Gram-positive (Methicillin-resistant *Staphylococcus*
21 *aureus*) and Gram-negative (*Salmonella typhi*, *Proteus mirabilis* *Pseudomonas aeruginosa*
22 and *Klebsiella pneumonia*) bacteria. The *in vitro* results indicated good inhibition for *S.*
23 *aureus*, *S. typhi*, and *P. mirabilis*. However, no antibacterial activity was shown against *P.*
24 *aeruginosa* and *K. pneumonia*, which was justified in terms of affinity with the bacterium

1 cells and structure of cell wall. The ZnO nanoparticles were positively charged and
2 consequently could interact with the negatively charged cell wall surface of bacteria. Gram-
3 positive bacteria have a cytoplasmic membrane and a thick wall composed of a
4 peptidoglycan multilayer. On the other hand, Gram-negative bacteria have complex cell
5 wall structure with a layer of peptidoglycan between the outer membrane and cytoplasmic
6 membrane. The nanoparticles could then more easily attach to the Gram-positive bacteria
7 and cause higher damage compared to the Gram-negative bacteria [116].

8
9 Lubasova *et al.* also designed PVA/ZnO fibers by conventional incorporation of
10 nanoparticles into the corresponding polymeric solution and subsequent electrospinning.
11 Interestingly, the authors compared the antibacterial performance of ZnO with other metal
12 oxides, namely TiO₂, ZrO₂, and SiO₂. A high content of nanoparticles (10 wt-%) was
13 necessary in order to expose them on the PVA-based fiber surface, which was theoretically
14 a pre-requisite for good antibacterial activity. The results confirmed that the incorporation
15 of metal oxides conferred antibacterial properties to PVA fibers, and the growth inhibition
16 of the tested bacteria (*S. aureus* and *E. coli*) was increased when the nanoparticle content
17 was augmented for all metal oxide nanoparticles. Nonetheless, the antibacterial behavior of
18 PVA-based mats depended on the type of nanoparticles, and the ability to inhibit bacteria
19 growth was in the decreasing order as follows: ZnO > ZrO₂ > TiO₂ > SnO₂. It is important to
20 mention that ZnO inhibited the growth of *S. aureus* and *E. coli* in 90% and 100%,
21 respectively, while SnO₂ reduced exclusively the proliferation of *S. aureus* in 82% [117].
22 Similar studies were recently carried out by the same authors but using poly(vinyl butyral)
23 as a matrix, and the resulting fibers with ZnO showed superior antibacterial performance

1 than those containing other metal oxide-based nanoparticles (CuO, ZrO₂, TiO₂, SnO₂) and
2 even AgNO₃ [118].

3
4 PVA-based fibers have also been used as templates for the design of advanced mesoporous
5 materials with combined osteoconduction and antibacterial properties. These materials were
6 obtained by electrospinning of the corresponding polymeric solution with Ca(NO₃)₂·4H₂O
7 and a stoichiometric amount of NH₄H₂PO₄ as hydroxyapatite precursor. On the other hand,
8 zinc acetate was selected as ZnO precursor. After calcination of PVA fibers, novel
9 mesoporous materials based on hydroxyapatite/ZnO were obtained, and they inhibited
10 bacterial growth from 20 to 80%, which was directly proportional to the
11 ZnO/hydroxyapatite molar ratio (1/3, 1/5 and 1/10) and depended on the type of bacteria,
12 being *S. aureus* more susceptible to the presence of ZnO [119].

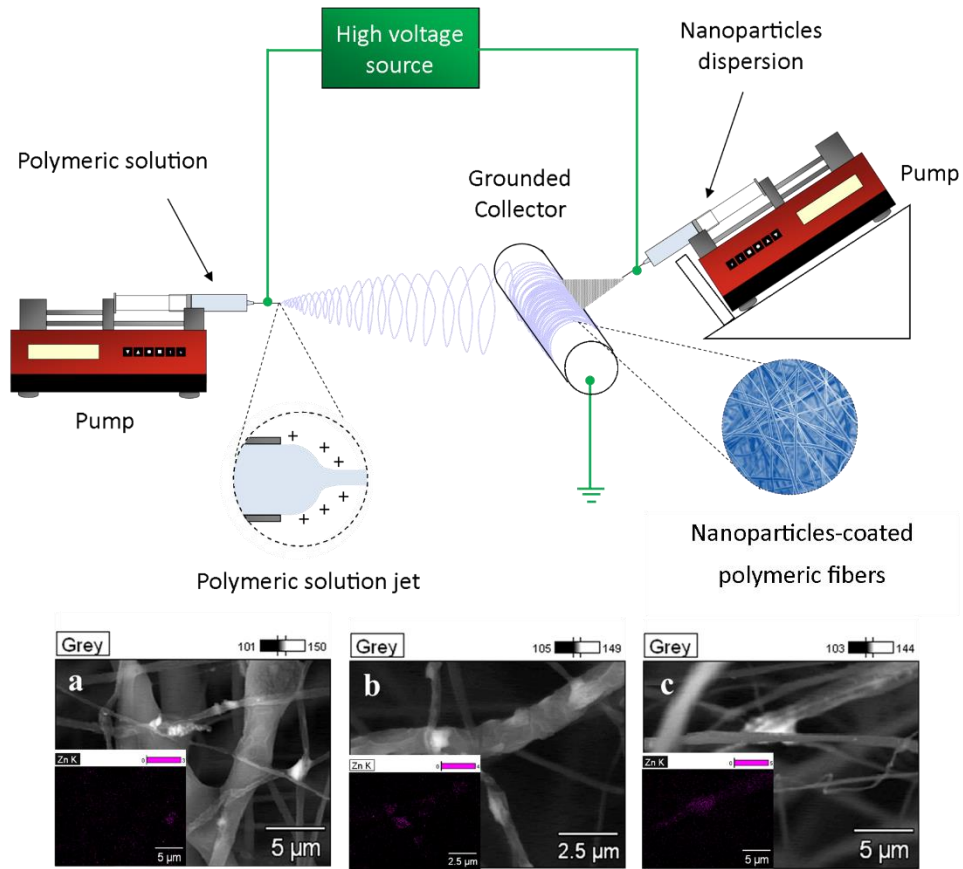
13
14 Natural polymers have also been exploited for developing electrospun fibers with potential
15 use as antibacterial wound dressings. Chitosan is a well-known polysaccharide which itself
16 provides bacteriostatic and fungistatic activities (*i.e.* momentarily stops the proliferation of
17 certain microorganisms). In this regard, Wang *et al.* demonstrated that the addition of ZnO
18 nanoparticles into chitosan-based fibers conducted to mats with synergistic antibacterial
19 effect against *E. coli* and *C. albicans*, since neat chitosan fibers exhibited a minimum
20 inhibitory concentration (MIC) of 130 and 190 µm/mL for *E. coli* and *C. albicans*,
21 respectively, while the composite fibers displayed lower values (110 and 160 µm/mL for *E.*
22 *coli* and *C. albicans*, respectively) [120]. Cellulose acetate was also used in the form of
23 sub-micrometric fibers with ZnO nanoparticles. The resulting mats were tested *in vitro*
24 against *S. aureus*, *E. coli*, *C. freundii* and *K. pneumonia*, and no antibacterial effect was

1 observed for the latter bacterium, which was attributed to differences in cell walls, as
2 mentioned above [121].

3
4 Regarding the biodegradable polyesters, PLA and PHB electrospun fibers with
5 incorporated ZnO nanoparticles have also showed moderate-to-good antibacterial
6 performance. Virovska *et al.* demonstrated the antibacterial activity of PLA fibers with high
7 content of surface-modified ZnO nanostructures (23 wt-%, rod-like with diameter 10-30 nm
8 and 100 nm in length) against *E. coli* and *S. aureus*. Moreover, the obtained PLA/ZnO mats
9 showed excellent photo-catalytic properties which were exploited for the degradation of
10 pollutant dyes (methylene blue and reactive red). Interestingly, the mats demonstrated high
11 degradation efficiency after several cycles, thus showing their reusability [41].

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

1



2

3 **Figure 6.** Scheme of the equipment used for the electrospinning/electrospraying technique.

4 The inserted micrographs are the obtained biopolyester fibers coated with (a) 1, (b) 3, and
5 (c) 5 wt-% of ZnO nanoparticles.

6

7 PCL is another important biodegradable polyester whose electrospun composite mats have
8 been exhaustively studied by Augustine *et al.* The authors evidenced that decreasing the
9 ZnO nanoparticle content (60 nm in size) in the polymeric solution up to 1 wt-% reduced
10 the diameter of the resulting PCL fibers (neat PCL fibers exhibited an average-diameter of
11 2.5 μm, meanwhile PCL/ZnO fibers was 1.3 μm). On the contrary, higher nanoparticle
12 contents induced the formation of thicker fibers, which was attributed to changes in

1 conductivity and viscosity. Regarding the antibacterial properties, the authors discovered
2 that significant antibacterial effect could be achieved only when ZnO concentration was
3 higher than 4 wt-%. Furthermore, PCL/ZnO fibers resulted more effective against *S. aureus*
4 than against *E. coli*, which was explained by cell wall differences, as discussed in previous
5 sections. Relevant insights into the cytocompatibility of PCL/ZnO fibers have also been
6 provided by Augustine *et al.* who proved that ZnO concentrations lower than or equal to 2
7 wt-% led to enhanced fibroblast proliferation compared with neat PCL fibers. The authors
8 carried out further analyses in order to elucidate the effect of PCL/ZnO fibers on the
9 healing of skin wounds. Interestingly, *in vivo* tests corroborated that PCL/ZnO fibrous mats
10 promoted the proliferation of cells, thus inducing faster healing process in Guinea pig
11 specimens within only 20 days. The reduction of biocompatibility of PCL fibers with
12 relatively high concentration of ZnO nanoparticles has been ascribed to higher production
13 of reactive oxygen species which could damage cells, thus inducing inflammation and
14 lowering wound healing index [122, 124].

15
16 Electrospun fibrous coatings consisting of PCL/ZnO (nanoparticles content equal to 1 and 3
17 wt-%) with enhanced biocompatibility for osteoblasts have recently been reported by Kim
18 *et al.* who deposited the mentioned composite fibers on magnesium alloy implants, which
19 showed corrosion resistance and antibacterial properties [125]. Contrasting results about
20 biocompatibility of PCL-based fibers with ZnO nanoparticles (irregular morphology with
21 size ranging from 20-150 nm) were reported in 2015 by Münchow *et al.*. The authors
22 demonstrated that relatively high contents of ZnO nanoparticles (5-30 wt-%) moderately
23 reduced the viability of human dental pulp stem cells, and the antibacterial properties

1 against important periodontal pathogens (*Porphyromonas gingivalis* and *Fusobacterium*
2 *nucleatum*) were preserved [126].

3

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

12

13 Last, copper is easily available and one of the most used metals for a wide range of
14 applications. Moreover, scientists have well documented the synthesis and properties of
15 CuO nanostructures. Nonetheless, up to date there are few reports related to the
16 incorporation of CuO nanostructures into polymeric fibers by means of electrospinning
17 techniques, and most of them have only addressed the effect of nanoparticles on the final
18 fiber morphology, while the ability to confer antimicrobial properties to electrospun
19 (bio)polymeric fibers has scarcely been considered. The limited use of CuO nanostructures
20 might be due to their propensity to oxidation reactions, thus changing their overall features
21 [35, 127-129].

22

23 Among the few research works related to the fabrication of antimicrobial polymer/CuO
24 fibers, that belonging to Haider *et al.* could be particularly mentioned. The authors

1 evidenced that the presence of a low amount of CuO nanoparticles (0.5 wt-%, 40-100 nm in
2 diameter) did not affect the average fiber diameter (*ca.* 550 nm) of poly(lactic acid-*co*-
3 glycolic acid) (PLGA) fibers. The relatively large size of CuO nanoparticles was enough
4 for their partial exposition on the polymeric fiber surface, thus facilitating the interactions
5 between the studied inorganic antimicrobial nanoparticles with the analyzed bacteria (*E.*
6 *coli* and *S. aureus* strains), and consequently inducing the growth inhibition (>60% for both
7 bacteria). The research work also demonstrated that the antibacterial mechanism was
8 governed by the release of Cu²⁺ ions. With regard to biocompatibility and cell viability,
9 various tests revealed that both PLGA/CuO and PLA/CuO fibers possess suitable
10 characteristics for adhesion and proliferation of fibroblastic cell lines, so that the obtained
11 electrospun mats could be envisioned as scaffolds and/or wound dressings with strong
12 antibacterial activity [35].

13

14 In another recent report, PLGA was once again preferred for obtaining electrospun
15 scaffolds with embedded CuO nanostructures combined with hydroxyapatite. Composite
16 PLGA ultrafine fibers were engineered via a two-step methodology. First, copper oxide
17 nanostructures were synthesized using a wet chemical method resulting in quasi-spherical
18 particles with average diameter of ~7 nm. Then, hydroxyapatite and the as-synthesized
19 CuO nanoparticles were incorporated by mixing with the PLGA solution, and the mixed
20 solution was subsequently electrospun. The resulting fibers showed an average diameter (1-
21 1.2 μm) larger than that for pristine PLGA, which was attributed to the high content of
22 hydroxyapatite (high solution viscosity). The added nanostructures were well-dispersed and
23 exposed on PLGA fiber surface since electron probe microanalysis showed CuO- and
24 hydroxyapatite-rich maps. A fact revealed for the first time by the authors was the

1 synergistic antibacterial effect (against *E. coli*) of hydroxyapatite and CuO nanostructures;
2 however, the governing mechanism was partially elucidated [128].
3 PHA-based multilayer materials have been extensively studied by Castro-Mayorga *et al.*
4 The authors have engineered PHBHV copolymer films with electrospun PHAs/CuO fibers
5 on their surface, which conferred exceptional antibacterial (*Salmonella enterica* and
6 *Listeria monocytogenes*) and antiviral (*Murine norovirus*) activity with only 0.05 wt-% of
7 CuO nanoparticles. It was further demonstrated that the obtained materials exhibited good
8 oxygen permeability, and mechanical performance. They were completely disintegrated
9 under composting after 27-30 days, thus making them as promising multilayer films for
10 food packaging [130].

11

12 Dimensional stability in conjunction with good elasticity performance are required features
13 for fibrous materials meant for tissue engineering scaffolds or similar applications, since
14 the receiving tissue could be subjected to constant stresses and/or movement. PVA is a
15 biodegradable and biocompatible polymer which can be mechanically stabilized by
16 crosslinking. For this reason, it was selected by Rezaee *et al.* for developing novel CuO-
17 coated PVA fibers by a three-step process consisting in electrospinning the PVA solution,
18 followed by a glutaraldehyde-catalyzed crosslinking reaction, and finally the
19 electrospinning of a colloidal CuO dispersion. The authors optimized the fabrication of
20 PVA fibers by varying some important parameters of the electrospinning process, namely
21 polymer molecular weight (viscosity) and flow rate. The effect of crosslinking degree on
22 final morphology of mats was also investigated, and it was revealed an optimal
23 concentration of glutaraldehyde in which the fibrous morphology was preserved. Even
24 though the antibacterial efficiency of isolated nanoparticles was excellent, the same

1 property was not determined for the PVA/CuO mats, thus limiting their potential
2 application as antibacterial scaffolds [129].

3 PVA has also been used as sacrificial matrix for electrospun multifunctional composite
4 filters based on CuO and ZnO nanostructures, whose elaboration was carried out by
5 electrospinning of a solution containing PVA/copper acetate monohydrate/zinc acetate
6 dehydrate, and a subsequent calcination step. The resulting inorganic CuO/ZnO mixed
7 fibers showed smaller diameter (*ca.* 180 nm) than those composed by PVA/CuO/ZnO (*ca.*
8 300 nm), which was attributed to PVA removal during the calcination step. Regarding the
9 antibacterial activity, it was demonstrated that *S. aureus* was more sensitive to CuO-ZnO
10 fibers than *E. coli*. Significant bactericidal effect was only achieved with 200 µg/mL of
11 composite fibers in the presence of *S. aureus*, while *E. coli* exhibited higher resistance since
12 bactericidal effect was observed when 350 µg/mL of composite fibers were used. On the
13 other hand, the composite fibers were highly effective for removal of Congo red dye, thus
14 validating the potential use as filters for water purification [131].

15

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

21

22 Iron oxide nanoparticles have mainly been utilized for conferring magnetic properties to
23 electrospun fibers. For instance, a contribution from Rashkov's group was related to the
24 design of PHB fibers embedded or coated with a combination of TiO₂ and Fe₂O₃

1 nanoparticles. The nanoparticle-embedded PHB fibers were derived from the
2 electrospinning of a solution consisting of dissolved PHB and dispersed nanoparticles (2.5
3 and 10 wt-% for Fe₂O₃ and TiO₂, respectively). The dispersion of the nanoparticles was
4 aided by a low amount of chitosan oligosaccharides (COS, 0.5 wt-%). On the other hand,
5 the nanoparticle-coated PHB fibers were designed by the combination of electrospinning of
6 PHB solution and electrospraying of TiO₂/Fe₂O₃/COS dispersion. Regarding the
7 morphology, the composite PHB fibers derived from electrospinning exhibited a significant
8 number of beads, while the materials produced by the combined techniques of
9 electrospinning/electrospraying showed aggregates on the surface. Furthermore, a smaller
10 amount of nanoparticles than initial feed was determined by X-ray photoelectron
11 spectroscopy (XPS), which was ascribed to the formation of a dense layer of the stabilizing
12 agent used (chitosan or oligomers). Since the antibacterial activity of identical materials
13 had already been explored [44], the new series of electrospun PHB fibrous mats were used
14 as membranes for the degradation of pollutants pigments. The degradation activity was
15 higher for the fibrous materials obtained by the conjunction of techniques, due to higher
16 nanoparticle surface area exposed to the solution containing the pigment [45].

17

18 Another report related to the design of polymeric fibers with iron oxide nano- and
19 microparticles was recently reported by Moon *et al.* From a solution containing
20 poly(ethylene oxide), sodium alginate and hydrated iron oxide, fibers were elaborated with
21 a diameter ranging from 160 to 475 nm. The authors carried out an exhaustive study of the
22 effect of hydrated iron oxide and sodium alginate on fiber diameter and morphology of the
23 obtained fibers, and the results were related to the increase of electrical conductivity. It was
24 demonstrated that increasing either the content of sodium alginate or iron-based

1 nanoparticles the fiber diameter was reduced and the fibers exhibited a smoother surface.
2 Furthermore, a blend consisted of sodium alginate with hydrated iron oxide showed
3 excellent ability to removal of *Vibrio vulnificus* (a strong human pathogen) and the authors
4 claimed the potential use as filters. However, the removal property of the engineered
5 fibrous materials was not determined, thus misleading the authors conclusions related to
6 final applications [132].

7

8 **3.4. Electrospun antimicrobial polymers combined with antimicrobial nanomaterials**

9

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

16

17 Regarding natural polymers, chitosan is well-known as an antimicrobial polymer able to
18 kill a broad spectrum of pathogen microorganisms; consequently, it is undoubtedly the
19 most studied. In the case of composite fibrous chitosan containing antimicrobial
20 nanomaterials, they have been generally fabricated by blending with other polymers since
21 chitosan possess poor solubility in common solvents. Thus, layered, core-sheath,
22 nanoparticles-decorated and nanoparticles-embedded chitosan-based fibrous materials have
23 been developed by combining techniques. Regarding the nanomaterials, the most
24 representative metallic (silver) and metal oxides (TiO₂, Fe₂O₃ and ZnO) have been used as

1 antimicrobial additives, whose combination with chitosan exhibited superior antimicrobial
2 performance against three microorganisms, *i.e. Escherichia coli*, *Staphylococcus aureus*,
3 and *Candida albicans* [10,48,53-55,57,58,74,98,105,120].

4
5 Other naturally occurring or bio-sourced polymers, such as cellulose derivatives, poly(L-
6 lysine), poly(hexamethylene guanidine), among others, have also been investigated as
7 antimicrobial materials, but only the last two have demonstrated inherent antimicrobial
8 activity and good biocompatibility. They have also been processed by electrospinning
9 techniques, however, the corresponding reports have been focused on the preparation of
10 fibrous materials based on blends of these polymers [136-139]. In the case of electrospun
11 cellulose derivatives, antimicrobial activity was conferred by the incorporation of silver or
12 zinc oxide nanoparticles, resulting in biocide materials for *Staphylococcus aureus*,
13 *Escherichia coli*, *Spectromyces arenus*, *Aspergillus flavus*, and *Citrobacter* [32,71-
14 73,121,140].

15
16 Electrospun materials based on antibacterial synthetic polymers have been more
17 investigated, which could be attributed to the wide range of raw materials for their
18 production, and the versatility in terms of chemical modifications. The main feature of this
19 type of polymers is the presence of ionic groups, by which a destructive interaction occurs
20 with the outer cell structure, thus conducting to the microbicidal effect. Quaternized poly[2-
21 (dimethylamino) ethyl methacrylate] (PDMAEMA) is a well-known antimicrobial polymer,
22 and it has been transformed into submicron fibers by the electrospinning technique.
23 PDMAEMA with a large variety of macromolecular structures (homo- or copolymers) or
24 compositions (blends) resulted suitable for killing *Escherichia coli*, *Staphylococcus aureus*,

1 and *Pseudomonas aeruginosa* [141-143]. Furthermore, nanoparticles-coated PDMAEMA
2 fibers showed higher antibacterial activity than that of neat fibers. It is noteworthy that the
3 coating process has been achieved by a two-step approach: mere electrospinning of
4 PDMAEMA followed by a sputtering process (ZnO and Ag nanoparticles were deposited
5 onto the fibers) [144] or immersion in a dispersion containing the nanoparticles (Ag
6 immobilized onto fibers surface by sodium citrate) [142]. The latter approach produced
7 mats with no cytotoxic effect, so that these fibrous materials are promising for tissue
8 engineering.

9

10 **4. Mechanical properties of antimicrobial fibrous composite materials derived from** 11 **electrospinning techniques**

12

13 Antimicrobial fibrous composite materials engineered by electrospinning techniques are
14 generally utilized as wound dressings and scaffolds in tissue engineering, and as filters for
15 water and/or air decontamination. These devices are subjected to deformation throughout
16 their life-time, so that the evaluation of mechanical properties is of paramount importance
17 [8,50,70,85,131]. In this regard, several authors have investigated the effect of
18 antimicrobial nanomaterial (nanoparticles) content and the electrospinning technique on
19 mechanical properties, mainly modulus and elongation.

20

21 Our research consortium has recently investigated the mechanical properties of ZnO-
22 embedded and ZnO-coated PLA fibers obtained by mere electrospinning and
23 electrospinning/electrospraying tandem process, respectively. The mechanical assessment
24 revealed an optimal ZnO nanoparticles concentration in which the higher mechanical

1 properties (tensile strength and Young's modulus) were achieved. This optimal value was
2 independent of the electrospinning technique; however, ZnO-coated PLA fibrous materials
3 exhibited the highest Young's modulus (38 MPa) and tensile strength (18 N). This
4 mechanical performance was attributed to hydrogen bonds between hydroxyl groups onto
5 de ZnO surface and the carbonyl groups of PLA fibers [43]. The effect of ZnO surface
6 modification (PLA grafts by ring-opening polymerization of D,L-lactide) on mechanical
7 performance of electrospun PLA fibers was further investigated, and it was evidenced that
8 the presence of PLA grafts significantly improved the dispersion and interaction with the
9 PLA-based fibers, thus improving not only the aforementioned mechanical properties but
10 also the antibacterial efficiency [42].

11

12 Mechanical properties enhancement has also been observed for other polymeric submicron
13 fibers, but containing silver nanoparticles. An *et al.* demonstrated that wet and dry
14 chitosan/poly(ethylene oxide)-based mats exhibited higher Young' modulus when Ag
15 nanoparticles were embedded in the fibers (49.2 MPa and 322 MPa for neat and composites
16 fibers, respectively). The main difference was observed in wet mats, which suffered more
17 elongation by the presence of water [55]. Other fibrous mats containing silver or its
18 precursory species, specifically PVA/chitosan with AgNO₃ or Ag nanoparticles, exhibited
19 tensile strength (9.9 and 15.2 MPa, respectively) suitable for handling related to wound
20 dressings [53]. This increase in mechanical properties was achieved with low silver
21 nanoparticles content, typically ≤ 5 wt-%.

22

23 In the case of composite fibrous antimicrobial materials derived from coaxial
24 electrospinning, their mechanical performance has scarcely been investigated. In tissue

1 engineering, coaxial electrospinning has been used only to create fibers with higher
2 mechanical stability, for example, a biocompatible sheath with a more mechanically stable
3 polymer. It was demonstrated that the main advantage of this techniques is the relatively
4 ease to control the morphology of the core-sheath fibers by adjusting the processing
5 parameters, thus tailoring their mechanical performance [145].

6

7 **5. Antimicrobial mechanism of electrospun fibers based on biopolymers and** 8 **nanoparticles**

9

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

19

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

23

- 1 *(i)* Initially, bacteria are transported near to the mat/fibers surface by long range
2 physical forces, such as gravitational and Brownian forces. In addition to this
3 passive transport, controlled-like motion is involved in the transport of bacteria
4 species having proteinic organelles called flagella.
- 5
- 6 *(ii)* Then, the attraction between microorganism and electrospun fibers surface takes
7 place by means of physico-chemical interactions, which can conduce to
8 reversible and irreversible adhesion, and they are influenced by the surface
9 chemistry and the fibers/mat morphology. Physico-chemical interactions are
10 basically electrostatic forces such as van der Waals and hydrogen bond
11 formation. The former leads to a reversible microbial adhesion and the latter
12 leads to irreversible microbial adhesion. Moreover, reaction between
13 microorganism surface and fiber surface might occur, thus provoking
14 irreversible adhesion.
- 15
- 16 *(iii)* After anchoring on the material surface (electrospun fibers), the microorganism
17 proliferate and synthesize the biofilm matrix (composed by exopolysaccharides,
18 proteins, lipids, among others compounds depending on the microorganism).
19 Proliferation is accomplished by cloning the cells which lead to formation of
20 colonies and eventually enhance the spreading of the surface.
- 21
- 22 *(iv)* Finally, biofilm maturation can be achieved and subsequent detachment occurs.
23 Mature biofilms are complex microorganism communities which possess a tri-
24 dimensional structure that allows the access to nutrients and oxygen also

1 protecting against hostile surroundings. It is noteworthy that despite common
2 characteristics, biofilms differ considerably between species and strains.

3
4 Considering the microbial adhesion mechanism explained above, either stage from I to IV
5 should be circumvented. The previously described metallic or metal oxide nanoparticles
6 can meet this aim, through a well-known mechanism based on the attack of microorganisms
7 by the metallic ions released from nanoparticles and/or the formation of reactive oxygen
8 species (ROS). Another mechanism based on the absorption of nanoparticles has also been
9 suggested, however, the experimental evidences have concluded that the ions released
10 and/or ROS formation are behind the biocide activity; therefore, this mechanism is
11 explained below.

12
13 Once the microorganism approximated to polymeric fiber surface, the presence of moisture
14 from different potential sources (environment, growth medium, adsorbed on polymer
15 and/or nanoparticle surfaces, etc.) promotes the corrosion and/or dissolution of
16 nanoparticles present in the fiber surface region, and eventually the production, release, and
17 diffusion of ions/ROS out of the polymeric matrix. Taking into account this stage of the
18 antimicrobial mechanism, the electrospinning techniques should be used for developing
19 polymeric nanofibers with nanoparticle-rich surface, since that is a critical concern in order
20 to enhance the production of the ionic or radical species. As largely illustrated in previous
21 sections, coaxial electrospinning or the combination of electrospinning and electrospraying
22 could be used to achieve this characteristic fiber morphology. It is important to consider
23 that the corrosion/dissolution process, ions/ROS release, and the attack to microorganism
24 can be changed by several factors, such as pH variation, radiation, porosity of fiber surface,

1 variation of the microorganism-polymer affinity, among others; for each specific polymer-
2 microorganism system, which is out of the scope of this review.

3

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

15

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

1 Fiber porosity is another factor with potential repercussions in the antimicrobial activity of
2 materials obtained by electrospinning techniques. It has been demonstrated that the more
3 heterogeneous the surface of polymeric substrates, the higher the surface area, thus
4 increasing the sites for cell attachments [154]. Therefore, it is important to control the
5 smoothness of fibers to avoid microorganism adhesion and proliferation, and it is well-
6 reported that this morphological feature can be minimized by the selection of solvents with
7 relatively low volatility [155,156]. In the case of composite fibrous materials meant for
8 antimicrobial devices, it is of paramount importance to achieve excellent distribution of
9 antimicrobial nanomaterials, since agglomeration of them could promote the formation of
10 fiber defects, which could be considered as sites of adhesion for microorganisms
11 [39,42,43].

12

13 **6. Conclusions and future prospects**

14

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

24

1 Researchers have focused their efforts on the investigation related to the variation or
2 combination of electrospinning-related techniques, which have yielded important findings
3 related to the influence of nanoparticle distribution/dispersion in electrospun
4 (bio)polymeric fibers. It was demonstrated that electrospinning/electrospraying and coaxial
5 electrospinning are suitable approaches for designing (bio)polymeric fibers with higher
6 antibacterial activity than that of mats fabricated with mere electrospinning, which is due to
7 higher surface area prone to interact with pathogenic microorganisms. However, in the case
8 of polymer/Ag composite fibers, mere electrospinning of the corresponding polymeric
9 solution containing AgNO₃ could also lead to fibers with Ag-rich surface, because of ion
10 migration, which can subsequently be reduced to Ag⁰.

11

12 Regarding the biocompatibility of the reported (bio)polymer/nanoparticles mats, *in vitro*
13 investigation has demonstrated that low contents (typically lower than 5 wt-%) of metallic
14 and metal oxide nanostructures, especially Ag, TiO₂, and ZnO, do not exhibit toxicity
15 against medically important cell strains, such as mesenchymal human cells, fibroblasts, and
16 osteoblasts. On the other hand, *in vivo* tests have been limited to skin healing, showing that
17 the fibrous materials can promote a faster wound healing in the same range of nanostructure
18 concentration than that for *in vitro* tests.

19

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

1 *in vivo* studies have to be carried out in order to provide more realistic findings and medical
2 prospections.

3

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

15

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

21

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3

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5

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