Electrospun Nanomaterials Implementing Antibacterial Inorganic Nanophases

Nicoletta Ditaranto 1, Francesco Basoli 2, Marcella Trombetta 2, Nicola Cioffi 1,*, and Alberto Rainer 2,*

1 Dipartimento di Chimica, Università degli Studi di Bari “Aldo Moro”, via Orabona 4, 70125 Bari, Italy; nicoletta.ditaranto@uniba.it
2 Dipartimento di Ingegneria, Università Campus Bio-Medico di Roma, Via Álvaro del Portillo 21, 00128 Roma, Italy; f.basoli@unicampus.it (F.B.); m.trombetta@unicampus.it (M.T.)
* Correspondence: nicola.cioffi@uniba.it (N.C.); a.rainer@unicampus.it (A.R.); Tel.: +39-08-05-442020 (N.C.); +39-06-22-5419214 (A.R.)

Received: 2 August 2018; Accepted: 7 September 2018; Published: 13 September 2018

Abstract: Electrospinning is a versatile, simple, and low cost process for the controlled production of fibers. In recent years, its application to the development of multifunctional materials has encountered increasing success. In this paper, we briefly overview the general aspects of electrospinning and then we focus on the implementation of inorganic nanoantimicrobials, e.g., nanosized antimicrobial agents in electrospun fibers. The most relevant characteristics sought in nanoantimicrobials supported on (or dispersed into) polymeric materials are concisely discussed as well. The interesting literature issued in the last decade in the field of antimicrobial electrospun nanomaterials is critically described. A classification of the most relevant studies as a function of the different approaches chosen for incorporating nanoantimicrobials in the final material is also provided.

Keywords: Electrospinning; antimicrobial; metal nanoparticles; nanofibers

1. Electrospinning: Generalities

Electrospinning is an easy fabrication method in which electrostatic forces are used to produce fine fibers. For its versatility, simplicity, and low cost, electrospinning has attracted the interest of many researchers fascinated by the possibility to fabricate fibers with both micro and nano-sized structural features by finely tuning process parameters. For these reasons, electrospinning has been extensively reviewed with respect to its setup, applications, advantages, and prospective developments [1,2]. Even though the origin of electrospinning can be traced back to the first years of the twentieth century [1,3–7], the term “electrospinning” is rather recent. In fact, it was used for the first time in 1995 by R.H. Reneker and coworkers in two different scientific articles [8,9].

The electrospinning fabrication process can be briefly summarized as follows. A high voltage (generally in the order of a few tens of kilovolts) is applied between an extrusion system (i.e., a needle or spinneret) and a collector. A polymeric solution is fed at a set flow rate to the spinneret where, under the force exerted by the electric field, it starts elongating forming a characteristic cone-shaped tip (Taylor’s cone) [10,11]. When surface tension is overcome by electrostatic forces, a jet of liquid is ejected from the Taylor cone, and reaches the collector in the form of a solid nonwoven web, with solvent evaporating during flight [12]. Lateral instabilities in the charged travelling jet result in a whipping motion that further contributes to fiber elongation [13] (see Figure 1). A thorough analysis of the physical phenomena behind the electrospinning process and a detailed description of the main experimental setups can be found in Reference [14].
The electrospinning process is affected by three classes of parameters, including solution properties (e.g., concentration, viscosity, surface tension, conductivity, and solvent vapor pressure), process parameters (e.g., solution feed rate, applied voltage, nozzle-to-collector distance), and ambient parameters (e.g., humidity and temperature). Seyedmahmoud et al. have demonstrated the feasibility of applying statistical methods to gain a quantitative and systematic insight about the effects of process parameters on the resulting fiber properties [15,16].

Electrospinning has been the subject of many different setup modifications that have been implemented over the years to accommodate different application needs. In fact, besides the more conventional randomly oriented fiber mats, a variety of morphologies and structures can be achieved by purposely changing the electrospinning conditions and by modifying the setup (e.g., the spinneret and the collector, among others) [17].

Mat morphology (i.e., fiber alignment and pattern) can be influenced by the collector geometry. In order to produce a randomly oriented non-woven mat, a static planar target is the conventional choice, whereas to obtain aligned fibers, collection is performed around a rotating cylindrical target [18,19]. In different designs, a series of parallel electrodes have been used to generate aligned fibers [20,21]. For more specific applications, collectors have been designed with customized geometries to obtain specific orientations or patterns, such as a knife-edge rotating disk to collect highly aligned fibers [22], or the use of grid-shaped collectors to create patterned nanofibrous mats [23].

The spinneret was also the subject of various modifications targeting specific applications. One of the major advances in electrospinning is represented by the introduction of the coaxial configuration in 2003 [24], enabling the production of core-shell microarchitectures with compartmented properties. Further incremental improvements (i.e., triaxial spinneret) have led to the fabrication of multilayered fiber structures [25] with the possibility to independently tune thickness, degradation rate, and diffusion properties of each layer for advanced drug delivery applications.

In 2008, Liu et al. [26] demonstrated the possibility to fabricate electrospun nano-fibers by a needleless setup. Using an aerated polymer solution, they managed to produce continuous and uniform nanofibers. In fact, insufflation of gas inside a vessel containing the polymer solution led to the formation of bubbles on the solution surface, that could give rise to the extraction of nanofibers upon the application of a potential. The key advantages of this novel design, called bubble electrospinning, is represented by the easiness to overcome the surface tension of the small bubbles, and the scalability
of the process, which has the potential for the mass-production of nanofibers. Moreover, different from classical electrospinning, in which spinnability mainly depends on the solution properties, in bubble-electrospinning it mainly depends on the size of the bubbles [27].

Electrospun meshes are characterized by high surface-to-volume ratio, dimensions ranging from tens of nanometers to micrometers, high porosity, and variable pore size distribution, showing morphological similarities to the natural extracellular matrix (ECM). Hence, one of the main applications for electrospun fibers has been as scaffolds for tissue engineering.

Additionally, the possibility to modify fiber surface and the ease of incorporating molecules or nanoparticles of interest in the solution to be electrospun further enhanced their range of application, including drug delivery systems [28–30], water treatment [31,32], energy conversion and storage [33,34], biosensing devices [35], gas sensors [36,37], electronics [38], as sorbents in microextraction techniques [39], as chromatographic phases [40], as separators, concentrators, or mixers in microfluidic systems [41–43].

2. Nanoantimicrobials

In the last two decades, antimicrobial nanomaterials—concisely addressed as nanoantimicrobials (NAMs)—have risen a tremendous interest in both fundamental and application-oriented research [44]. The continuous search for new agents capable of preventing the growth of pathogens and other undesired microorganisms, urged by the increased worldwide concern about antimicrobial resistance [45], has stimulated a massive development of new materials and processes implementing NAMs [46–48]. This class of bioactive materials is being used in formulations, technological solutions, and commercial products, which are available for the consumer [49].

Among the different inorganic NAMs, nanomaterials composed of transition metals such as Ag, Cu, Zn, and their oxides are the most diffused, since they provide a wide-range biocidal activity, and on the other side, they are well tolerated by human beings at concentration levels that are effective already towards the growth of several microorganisms [48]. A comprehensive overview on real-life applications of NAMs is provided by References [44,50–57]. Silver-based NAMs are definitively the most investigated. This is due to the concurrence of different causes. Firstly, silver provides an efficient biocidal effect toward a broad range of microorganisms; and secondly, the general lack of solubility that silver salts and compounds show in several aqueous media (for instance chloride-containing fluids) intrinsically buffers the concentration of bioactive ionic species that can be released by Ag nanophases, thus prolonging their biocidal effects. Finally, the number of synthetic routes to coinage metal nanophases is enormous; this guarantees an easy access to nanosilver biocidal agents, and supports the production of an almost infinite number of goods implementing Ag-NAMs. Such a wide and indiscriminate diffusion of active nanomaterials is rising an increasing concern about their environmental toxicity, and particularly the risks related to the NAMs action towards non-target organisms [58]. In this respect, engineered nano-sized agents which are protected, encapsulated, or in any case, prevented from direct release into contact media are by far the most interesting NAMs. Since 2004 [59], we proposed the inclusion of copper nanoparticles into water insoluble polymers as one of the best routes to gain a controlled bioactivity from NAMs. In other words, NAMs should be better used as nano-reservoirs in a composite material, providing a tunable release of bioactive species (such as metal ions), rather than being just added (as entire nanophases) to the system where the biocidal effect is sought. The most important requisite for the resulting material is to protect the NAMs from being directly released into the contact solution, but on the other side, the inorganic nanophases has to retain part of its reactivity, in order to undergo the corrosion and ionic release processes, which support the final biocidal effects [60].

More recently, we have further explored this approach, combining microscopy and analytical spectroscopy techniques, demonstrating that a proper NAM adhesion or encapsulation in polymer coatings prevents the release of entire nanoparticles [61], paving the way to the development of efficient and safe NAMs [62].
With this in mind, we believe that the combination of NAMs with innovative polymer synthesis and/or processing technologies, such as the electrospinning technique, affording a high level of morphological and composition control over the resulting material, will represent a proper solution for a further step in the diffusion and exploitation of these agents.

3. Electrospun (Nano)Materials Implementing Antibacterial Properties

The advantage of using antimicrobial polymers to fight the increasing resistance against classical antibiotics arises from the possibility of synergistically combining these materials and applying them in different physical forms (e.g., coatings, films, emulsions and fibers). Polymer fibers produced via electrospinning are among the most efficient and cost effective systems for two main reasons: In the first place, because of their huge surface area-to-volume ratio; and secondly, the polymers can be implemented with antimicrobial functionalities before or after electrospinning. This provides the opportunity to design and modify the fibers in the smartest way to specifically target different types of microorganisms.

Antimicrobial polymers can be classified into two categories. The first one includes all those polymers with inherent antimicrobial or antiseptic properties, that can be directly applied or used in a variety of substrates, namely textiles, metal materials or plastics ones. The second category contains inert polymers incorporating additional antimicrobial phases/agents that are released over time.

The first class comprises natural and synthetic polymers, including polypeptides. Antimicrobial peptides are naturally associated to the defense system of microorganisms and humans [63], and are generally cationic species with an overall net positive charge. Based on those structures, synthetic amphiphilic polymers have been designed to mimic the antimicrobial peptides [64,65]. While many antimicrobial peptides have been described, their large-scale production is expensive, their in vivo stability is generally poor and relatively little investigated [66,67].

Electrospun nanofibrous membranes of natural polymers have recently drawn much attention as novel materials in biomedical applications, such as wound dressing, tissue engineering, and drug delivery. While the use of bio-based materials as precursors for electrospinning seemed to be an excellent solution to address all the raised concerns, many difficulties arose on the actual practical side. In fact, natural polymers are usually difficult to be electrospun, therefore the starting solution is frequently composed by a synthetic polymer in blend with the natural one. Another possible approach is to chemically modify the natural polymer, chitosan processing represents a classic example of this approach. Chitosan is an inherently antimicrobial natural polymer being highly active against both gram-positive and gram-negative bacteria. Thus, it would be an excellent candidate for the production of antimicrobial nanofibers [68]. Anyhow, pure chitosan cannot be merely electrospun into nanofibers, and this lead to the need of blending chitosan into the starting solution with other polymers (e.g., polyethylene oxide, polyvinyl alcohol, polycaprolactone) even though this dilution could lead to lowering the biocidal properties of the as made nanofibrous membranes. An interesting overview of different natural electrospun nanofibers for antibacterial uses, including a useful list of pure polymers and their blends successfully processed by electrospinning, is given by Vineis et al. and Bshena et al. [69,70].

The second class of antimicrobial nanofibers is by far the most investigated, since different active agents as well as different strategies have been explored. Most commonly, biocides (e.g., antibiotics, ammonium salts, cyclodextrins, chlorhexidine, metal, or metal oxide nanoparticles, etc.) are attached to or encapsulated into supporting fibers, by means of different preparation approaches. The most straightforward one consists in anchoring the active agent onto the surface of pre-synthesized fibers. This approach, however, provides little control over the release rate, that is usually characterized by a burst. Alternatively, the active material can be encapsulated inside the fiber either by blending the active agent in the polymer solution before electrospinning or by firstly encapsulating the active agent into nanostructures to be dispersed in the electrospinning solution. Additionally, precursor compounds can be blended in the solution to be electrospun, and conversion to their active form
can be performed as a post-electrospinning treatment. These approaches are effective in providing a sustained release of the active agent, regulated by its diffusion through the polymer matrix, by the degradation of the matrix, or by a combination thereof. More sophisticated approaches also foresee the use of a multi-axial electrospinning setup, in order to confine the active agent in the core of the obtained fibers, enhancing the control over the achievable release profiles (see Figure 2).

Many typologies of antibacterial nanofibers have been produced by the electrospinning technique, based on the incorporation of different biocides, as extensively reviewed in Reference [71], where a very comprehensive explanatory table is reported. As meaningful examples, we could focus on antibiotics incorporation (numerous hydrophilic and hydrophobic antibiotics have been used) [71] and cyclodextrines inclusion [72–75] into a polymeric solution. Attention has to be taken to the drug concentration, as an excess will probably lead to changes to polymer electrospinnability, and as a consequence, on fibers morphology, due to changes to solution properties as conductivity, viscosity, and surface tension.

**Figure 2.** Various methods of incorporating biocides into electrospun nanofibers. (1) blending/dispersion of the active agent in the polymer solution prior to electrospinning; (2) confinement of the active agent in the core of the fiber through co-axial electrospinning; (3) encapsulation/adsorption of the active agent in nanostructures before dispersion in the electrospinning solution; (4) conversion of a precursor to active agent in the nanofibers after electrospinning; and (5) attachment of the active agent onto the nanofibers after electrospinning. Reprinted from Reference [71], Copyright 2014, with permission from John Wiley and sons.

Another relevant drawback comes from the burst release associated to the loading of high drug amounts. Indeed, as soon as fibers are submerged into an aqueous solution, antibiotics will tend to leach out rapidly. This behavior provokes a reduced functionality of the nanofiber membrane against bacteria by releasing all the antibiotics in a very short time frame without guaranteeing a prolonged coverage period. To avoid burst release, different set-ups have been used: Coaxial electrospinning technique allows to create a polymer (e.g., polycaprolactone [76] poly(lactic-co-glycolic acid) [77], poly(lactic acid) [78], poly(methyl methacrylate)/nylon [79], and poly(l-lactide-co-caprolactone) [80]) sheath that encapsulate the antibiotic (e.g., gentamycin, ampicillin, tetracycline hydrochloride) component into the core section of the nanofibers. Another common approach for a sustained release of the antibiotics is to adsorb or encapsulate the drug in a nanostructure such as hydroxyapatite nanoparticles before dispersing it in the polymer solution [81–83]. This approach does not allow a high drug payload, but still provides a sufficient antibacterial activity. Among the others, potent antimicrobial materials
that have been investigated in conjunction with polymers are the quaternary ammonium salts (QACs) and N-substituted halamines [84]. The strategy of preparing antimicrobial polymers based on QACs is very attractive, because tertiary or/and secondary amino groups provide convenient reactive moieties to be properly modified.

One of the approaches is to permanently attach the active QAC agents by means of coupling agents, such as alkoxysilanes, to a variety of different substrates through covalent interactions [85–88]. Besides, other methods include the use of ammonium salts derivatives as monomers in a quaternization reaction or simply adding a mixture of them to different polymer solutions. A comprehensive review by Jaeger et al. [89] discussed the multiple synthetic routes of various charged polymer systems that have quaternary ammonium moieties.

Recently, some concerns have been raised over possible drawbacks in the use of nanoparticles/nanomaterials (including nanosized antimicrobial agents) and synthetic antibiotics. It has been pointed out that they could be of some hazard to the environment, could have collateral effects on human health, and/or could possibly create bacterial resistance issues. On the other hand, is strictly demanding an effective prevention of infections caused by biofilm-forming pathogens. To address those issues, many engineered nanofibrous membranes containing metal and/or metal oxides nanoparticles have been proposed, mainly based on the use of silver, copper, and zinc, thanks to their well-established disinfectant properties. It is generally accepted that the effect of metals in a nanoparticles form is due both to the release of metal ions and to the direct contact with the bacterial cell membranes; anyhow, metal nanoparticles present the advantage of acting as active reservoirs. In this context, the decreased amount of metal, combined with the encapsulation/stabilization into electrospun fibers, is expected to produce environmentally sustainable materials, nontoxic for human health, with reduced nanotoxicology issues [90].

Inclusion of Metal Nanophases as Biocides

Silver has long been known as an effective antibacterial agent and it has been used in various applications thanks to its chemical versatility. Copper and copper oxide, as well, possess antimicrobial properties that have been known for centuries on the macroscale [91]. With the progress of technological applications, the cost control remains a key factor when considering the scale up and the wide range of applications on a large scale. For this reason, cheaper metals (copper, zinc, iron, titanium) have increasingly become the selected metals to confer antimicrobial properties, in place of or in combination with silver. Among others, electrospun nanofiber materials have been produced incorporating metal nanostructures by different strategies and with various polymers, according to the final application.

One of the widespread methods consists of a salt solution mixed with a polymer one to obtain the final electrospinning mixture (blending). In this conditions the metal species are stabilized in the nanoparticle form by means of the polymer itself, acting both as reductant and as capping agent. Following this approach, Quiros at al [92] obtained Ag-, Zn- and Cu-poly(vinylpyrrolidone) (PVP) composite mats at different copper loadings, with good antibacterial performances against *E. coli* and *S. aureus*.

The same approach has been reported using poly(vinyl alcohol) (PVA), as one of the most used and desirable material for biomedical applications. Its highly favorable properties, such as biocompatibility, nontoxicity, and bioadhesive characteristics make it a good candidate to be modified with biocidal nanophases inclusion. As the incorporation of Ag salts into easily electrospinnable polymers matrices produces an even particles distribution, many papers have been published on the AgNPs/PVA system [93–95]. Typically, the polymer acts as stabilizer of the nanocomposite fibers and also has good reductant capabilities to yield Ag nanoparticles directly formed during the electrospinning process [96]. In some cases, *post-treatment* processes are required, like adding a second reductant [97] or a combination of UV irradiation and/or heat treatment/calcination [98,99]. This approach could be also beneficial from the application point of view. For instance, Celebioglu et al. [97] reported on the influence of AgNPs size and/or a second component on the antimicrobial effect (see Figure 3).
While Jin et al. [96] studied how different reducing conditions can affect the morphology of Ag-PVA nanofibers (Figure 4).

Figure 3. The photographs of antibacterial testing of nanofibrous mats that were performed against (a) E. coli and (b) S. aureus. Reprinted from [97], Copyright 2014, with permission from Elsevier.

Figure 4. On the (left): TEM of PVA nanofibers electrospun from 12 wt% PVA solutions containing 1 wt% of AgNO₃: (a) Not refluxed, (b) refluxed at 80 °C for 1 h, and (c) refluxed at 80 °C for 2 h. On the (right): TEM of PVA (polyvinyl alcohol) nanofibers electrospun from 12 wt% PVA solutions containing 1 wt% of AgNO₃ after being annealed at (a) 50 °C, (b) 80 °C, and (c) 110 °C for 14 h. Reprinted from [96], Copyright 2007, with permission from Elsevier.
Electrospun Cu-PVA fibers have been produced in conjunction with CuCl₂ [100] or copper acetate [101] to obtain PVA-protected copper nanoparticles. Additionally, mixed metal nanostructures have been produced, like CuO-ZnO, and have been included in PVA. The combination of two metals was demonstrated to be effective as enhanced adsorption and antimicrobial efficiency were obtained with these nanocomposite fibers [102]. Along with the antimicrobial results, the authors also proposed a mechanism responsible for the bactericidal action of those nanofibers (see Figure 5).

![Figure 5.](image)

**Figure 5.** (a) Comparative plot representing the antibacterial activity of CuO-ZnO (CZ) loaded nanofibers with different concentrations against GFP-E. coli (G−) and S. aureus (G+); (b) Proposed mechanism of bactericidal action CZ nanofibers; and (c) Fluorescence spectra depicting the ROS generation with different concentrations of CZ nanofibers. Reprinted from [102], Copyright 2017, with permission from Elsevier.

One of the major applications for electrospun fibers has long been in the filtration field and polyacrylonitrile (PAN) has been the most used, due to its high mechanical strength and chemical stability. One of the drawbacks in the filtration process is the rapid fouling by bacteria, negatively affecting the permeability and the throughput of the membrane. Moreover, PAN or composite cellulose/PAN fibers are widely employed in biomedical devices, where the bacterial control is an issue. In this respect, CuNPs and AgNPs may add a clear benefit when embedded in electrospun PAN and cellulose fibers. Additionally, in this case, the blending approach is the most investigated; silver and copper salts [103–105], or preformed ZnO-CuO-NPs [106], are included in the electrospinning solution. An interesting alternative is represented by the cellulose nanofibers, because the high number of –OH groups offers a location for fibers functionalization, thus regulating the nanophases upload and their release. Gouda et al. [107] published a comprehensive paper about carboxymethyl cellulose functionalized with copper, iron, and zinc NPs. They reported on the different morphology according to the different MeNPs (Figure 6), along with composite nanofibers release properties and their excellent antibacterial activity.
Then, the subsequent silver reduction step is a further independent parameter. Shi et al. [108] reported on Ag-PAN nanofibers obtained by soaking electrospun fibers into silver nitrate solution, and were subsequently performing a reduction reaction. In Figure 7 the SEM characterization of those fibers is reported, where it is evident that the influence of silver salt concentration and different parameters. Shi et al. [108] reported on Ag-PAN nanofibers obtained by soaking electrospun fibers into silver nitrate solution, and were subsequently performing a reduction reaction.

The attachment and core-sheath preparation methods are far less common and usually involve a two or three-step procedure. Nevertheless, they provide electrospun nanofibers with worthy performance as antimicrobial materials. In particular, when applications involve coatings [108] or barrier membranes [109], those methods offer good results. Moreover, the multi-step procedure offers the possibility to tune the materials properties and morphology, by acting on post-synthesis different parameters. Shi et al. [108] reported on Ag-PAN nanofibers obtained by soaking electrospun fibers into silver nitrate solution, and were subsequently performing a reduction reaction. In Figure 7 the SEM characterization of those fibers is reported, where it is evident that the influence of silver salt concentration and reaction time on the adsorption effect and crystallization ability of silver ions. Then, the subsequent silver reduction step is a further independent parameter.

Figure 6. On the (left): TEM images of CMC electrospun nanofiber (a) and CMC-MNPs electrospun nanofibers CuNPs (b), FeNPs (c) and ZnNPs (d). On the (right): SEM images of CMC electrospun nanofiber (a) and CMC-MNPs electrospun nanofibers CuNPs (b), FeNPs (c) and ZnNPs (d). Reprinted by permission from [107], Springer Nature, Copyright 2017.

Figure 7. SEM images of pretreating PAN (polyacrylonitrile) nanofibers in Ag NO₃ solution at different soaking times, different concentrations, and different reduction reaction time. Reprinted from [108], Copyright 2015, with permission from Elsevier.
An increased stabilization of the nanophases into the membranes is always beneficial and could be obtained by means of encapsulation approach, in order to avoid loosely attached nanoparticles to be dispersed in the environment. Few papers have been published so far following this method, which allows also a controlled release of metal species [110,111]. In particular, Quiròs et al. [110] reported how silver and copper NPs supported in sepiolite and silica act as reservoirs able to affect microorganism germination and growth, and to reduce fungal metabolic activity.

Table 1 reports a summary with some representative studies dealing with electrospun antimicrobial fibers embedding metal nanoparticles.

<table>
<thead>
<tr>
<th>Antibacterial Agent</th>
<th>Electrospun Polymer Composite</th>
<th>References</th>
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<tbody>
<tr>
<td>CuNPs, CuO NPs</td>
<td>Copper salt + PVP</td>
<td>[92]</td>
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<td></td>
<td>Commercial CuO + PHBV</td>
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<td></td>
<td>Supported copper salt + CA</td>
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<td>Cu/CuOx + PAN</td>
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<td></td>
<td>Copper salt + PVA</td>
<td>[100,101]</td>
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<tr>
<td></td>
<td>Copper salt + CMC</td>
<td>[107]</td>
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<td></td>
<td>Copper salt + PVDF</td>
<td>[112]</td>
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<td></td>
<td>Copper salt + PU</td>
<td>[113,114]</td>
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<tr>
<td>AgNPs</td>
<td>Silver salt + PVP</td>
<td>[92,93]</td>
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<td></td>
<td>Supported silver salt + CA</td>
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<td></td>
<td>Silver salt + PAN</td>
<td>[108]</td>
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<tr>
<td></td>
<td>Silver salt + PVA</td>
<td>[94–99]</td>
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<tr>
<td>Other Me/Me oxides NPs</td>
<td>Copper salt + zinc salt + PVA</td>
<td>[102]</td>
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<td></td>
<td>Zinc salt + CMC</td>
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<td>Iron salt + CMC</td>
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No matter the preparation method, all the above mentioned composite electrospun nanofibers have been proved to exert good antibacterial properties against many Gram-positive [70,92,97,99,102–108,113,114] and Gram-negative [70,92,97,99,102,103,105–108,113,114] species, as well as antifungal effect [70,108–110]. The detailed analysis on the antibacterial mechanisms involved and the overview on the different antimicrobial tests is beyond the aim of this review; nevertheless, the readers interested in the topic can refer to [115–120].

4. Conclusions

In the last decades, great advances have been achieved in the understanding of the electrospinning process, in terms of instrumental development and perspective applications. As a result, it is now possible to easily produce uniform nanofibers from most synthetic polymers and many natural polymers in the lab scale and also for industrial needs. Moreover, numerous biocides have been successfully incorporated into nanofibers to obtain electrospun mats potentially used as medical implants, scaffolds, wound dressings, textiles, or as filter media. Among others, different inorganic nanomaterials composed of transition metals were considered, thanks to their wide range of biocidal activity and because their ions are well tolerated by human beings at concentration levels that are effective towards several microorganisms.

Despite the significant advances, several issues still need to be further addressed in antibacterial nanofibers, mainly related to the controlled release of the antibacterial agents from the nanofibers.

With this in mind, we believe that the combination of metal nanoparticles with innovative polymer synthesis and/or processing technologies, such as the electrospinning technique, affording a high level of morphological and composition control over the resulting material, will represent a proper solution for a further step in the diffusion and exploitation of these agents.
In the last year, several engineering fields have benefited from the introduction of additive manufacturing technologies and, most recently, a growing tendency to the convergence of different processing techniques into a single, computer-aided manufacturing technology has been reported. It is an opinion of the Authors that this scenario could also affect the field of antimicrobial materials, enabling the large scale fabrication of complex-shaped structures with tailored properties.

**Author Contributions:** Each of the authors has equally contributed to the writing of the paper.

**Funding:** This research received no external funding

**Conflicts of Interest:** “The authors declare no conflict of interest.”

**References**

1. Huang, Z.M.; Zhang, Y.Z.; Kotaki, M.; Ramakrishna, S. A review on polymer nanofibers by electrospinning and their applications in nanocomposites. *Compos. Sci. Technol.* **2003**, *63*, 2223–2253. [CrossRef]


5. Frenot, A.; Chronakis, I.S. Polymer nanofibers assembled by electrospinning. *Curr. Opin. Colloid Interface Sci.* **2003**, *8*, 64–75. [CrossRef]


22. Theron, A.; Zussman, E.; Yarin, A.L. Electrostatic field-assisted alignment of electrospun nanofibres. *Nanotechnology* 2001, 12, 384. [CrossRef]


29. Zamani, M.; Prabhakaran, M.P.; Ramakrishna, S. Advances in drug delivery via electrospun and electrosprayed nanomaterials. *Int. J. Nanomed.* 2013, 8, 2997. [CrossRef]


36. Ding, B.; Wang, M.; Yu, J.; Sun, G. Gas sensors based on electrospun nanofibers. *Sensors* 2009, 9, 1609–1624. [CrossRef] [PubMed]


38. Luzio, A.; Canesi, E.V.; Bertarelli, C.; Caironi, M. Electrospun polymer fibers for electronic applications. *Materials* 2014, 7, 906–947. [CrossRef] [PubMed]


42. Wallin, P.; Zandén, C.; Carlberg, B.; Hellström Erkenstam, N.; Liu, J.; Gold, J. A method to integrate patterned electrospun fibers with microfluidic systems to generate complex microenvironments for cell culture applications. *Biomicrofluidics* 2012, 6, 024131. [CrossRef] [PubMed]

43. Giannitelli, S.M.; Costantini, M.; Basoli, F.; Trombetta, M.; Rainer, A. Electrospinning and microfluidics: An integrated approach for tissue engineering and cancer. In *Electrofluidodynamic Technologies (EFDTs) for Biomaterials and Medical Devices*; Woodhead Publishing: Sawston, UK, 2018; pp. 139–155. [CrossRef]


69. Vineis, C.; Varesano, A. Natural polymer-based electrospun fibers for antibacterial uses. In Electrofluidodynamic Technologies (EFDTs) for Biomaterials and Medical Devices; Woodhead Publishing: Sawston, UK, 2018; pp. 275–294. [CrossRef]


103. Xiao, Y.; Cao, Y.; Xin, B.; Liu, Y.; Chen, Z.; Lin, L.; Sun, Y. Fabrication and characterization of electrospun cellulose/polyacrylonitrile nanofibers with Cu (II) ions. *Cellulose* 2018, 25, 2955–2963. [CrossRef]


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