**MAGNETOACTIVE ELECTROSPUN
NANOFIBRES IN TISSUE ENGINEERING
APPLICATIONS**

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6.1. OVERVIEW OF THE ELECTROSPINNING PROCESS

After the first observation of electrospinning (electrostatic spinning) by L. Rayleigh in 1897, followed by its first patenting in 1902 by J.F. Cooley and W.J. Morton, in 1914 J. Neleny reported that a liquid jet could be emitted from a charged liquid droplet in the presence of an electrical field [1]. Twenty years later, when A. Formhals patented a process that allowed the spinning of synthetic fibres using electric charges [2,3], electrospinning became a valid technique to produce small-sized fibres. Following Formhals' pioneering work, researchers have focused on an in-depth understanding of the electrospinning process. In 1969, D.G. Taylor published on the jet formation process, examining the behaviour of the polymer solution droplet at the edge of a capillary under an electric field. From his studies he obtained the characteristic value of the elongated conical fluid structure known as the Taylor cone [4], generated at the tip of the needle due to the electrostatic forces being exerted at the fluid's surface. Since the early 1990s, the work of D.H. Reneker and co-workers focusing on the use of electrospinning for generating one-dimensional (1D) polymer nanostructures has attracted the attention of many researchers [5-7].

Although other methods can also be employed towards the fabrication of 1D nanomaterials, namely drawing [8], self-assembly [9,10], melt-blow [11], phase-separation [10], and template synthesis [12], electrospinning is considered to be the most popular and versatile fibre fabrication method [13]. It can be used to produce continuous synthetically and naturally-derived polymer nanofibres [6,14,15] with diameters ranging from micrometers down to a few nanometers [14]. Its simplicity, cost-effectiveness and applicability, not only to polymers [14,16] and ceramics [17,18] but also to composites, enable the development of polymer-based fibrous nanocomposites *via* the combination of polymers with inorganic nanofillers [19].

Although experimentally the electrospinning process is relatively simple and straightforward, the electrospinning mechanisms are rather complicated, including among others the Taylor cone theory [20], the bending instability [21] and the electrically forced jet-stability theory [22].

A simple electrospinning set-up consists of four major components: A high-voltage power supply, a syringe with a metallic needle, known as a spinneret, a syringe pump used for delivering the solution through the spinneret at a constant and controllable rate, and a grounded metallic (conductive) collector, on which the produced fibres accumulate (Figure 1).

Direct current (DC) power supplies are typically used in electrospinning, although the use of alternating current (AC) potential is also feasible. A high-voltage power supply is connected with both the needle and the collector. The positive electrode (anode) is connected to the needle and the negative electrode (cathode) is placed onto the collector, which is usually grounded. In a

typical fibre-generating process, a syringe is filled with a polymer solution and a high voltage (up to 30 kV) is applied between the syringe nozzle and the collector. The syringe may be placed perpendicularly, letting the polymer fluid drop with the help of gravity, or horizontally in respect to the grounded collector.

By applying a high voltage, the pendent drop of the polymer solution at the needle tip of the spinneret is highly electrified and the induced positive charges are evenly distributed over the droplet surface. The electrostatic repulsion forces developed between the surface charges and the electrostatic force exerted by the external electric field are the major electrostatic forces acting on the droplet. Under these electrostatic interactions the hemispherical surface of the fluid at the tip of the needle's syringe elongates, forming the Taylor cone. At a critical voltage, *i.e.*, once the strength of the electric field has surpassed a threshold value, the electrostatic repulsive forces overcome the surface tension of the solution and force a jet to erupt from the tip of the Taylor cone. The jet follows a direct path towards the grounded collector for a very short distance from its origin and reaches a bending instability point. After this point the jet undergoes a stretching and a rapid whipping process, as illustrated in Figure 1.

As the charged jet accelerates towards lower-potential regions, it dries in flight upon solvent evaporation, whereas the increase in the electrostatic repulsion forces generated between the charged polymer chains results in fibre elongation and consequently reduction in fibre diameters. With the combination of jet-bending instability and solvent evaporation, the jet eventually becomes solidified on the collector in the form of randomly oriented nanofibres.

Figure 1. Schematic presentation of a basic electrospinning set-up

As long as a polymer can be electrospun into nanofibres, ideally the diameters of the fibres should be consistent and controllable, the fibre surface defect-free or defect-controllable, and continuous single fibres should be collectable. However, research performed during the last 15 years on polymer processing *via* electrospinning has shown that the aforementioned are by no means easily achievable [14] and that the success of the whole process is governed by different parameters. The latter are classified in terms of: (a) Solution parameters, including viscosity / concentration [16,23-25], conductivity / solution charge density [15,26-29], surface tension [16,23,30-32], polymer molecular weight [23,33,34], dipole moment, and dielectric constant [14,23,35,36]; (b) Processing parameters, including electrical potential [36-38], solution flow rate [23,39], needle diameter [7,40,41], and distance between the syringe needle tip and the grounded collector [14,15,24,42,43]; (c) Ambient parameters, including solution temperature, humidity and air velocity in the chamber; and finally (d) Collector composition, geometry and motion [15,16,23,35]. Based on the above parameters, different results may be obtained using the same polymer system and electrospinning set-up. Thus, it is difficult to provide quantitative relationships that can be applied across a broad range of polymer / solvent systems. However, there are general trends which are useful when determining the optimum conditions for a certain system, which are summarized in Table 1 [44].

Table 1. Influencing parameters on the fibre morphology in the electrospinning process

Solution properties	
<u>Concentration / Polymer molecular weight / Viscosity</u> Low concentration / viscosity leads to beaded fibres and droplets. Fibres with fewer beads and free of droplets are obtained by increasing the concentration / viscosity. Low polymer molecular weight / viscosity (regardless of concentration) also generates beaded fibres, whereas polymers of extra high molecular weight are more difficult to spin. Fibres generated from viscous solutions appear to be relatively continuous and thicker compared to fibres generated from low viscosity solutions, which tend to be shorter and finer.	[14,26,45,46] [23,32-34] [25,36,47]
<u>Conductivity / Solution charge density</u> Thinner fibre diameters with fewer beads are obtained upon increasing conductivity whereas the tendency of droplet formation during the process is reduced. The increase of the net charge density can be realized <i>via</i> the addition of salts in the polymer solution.	[27-29] [16,35,39]
<u>Surface tension</u> By reducing the surface tension of the polymer solution, fibres can be	[5,14,46,48]

Solution properties	
obtained without beads.	[16]
Solutions with lower surface tension lead to the effective elimination of beads and the generation of fibres with larger diameters.	[14,36]
Different solvents may contribute differently to the surface tension.	
<u>Dipole moment and dielectric constant</u>	
Solvents with high dipole moment values result in the successful fabrication of continuous electrospun fibres.	[49]
Process parameters	
<u>Applied voltage</u>	
The increase of the applied field (related to the change in the instability mode – change in the shape of the jet initiating point) causes an increase in fibre length.	[7,28,36]
The jet diameters are also affected by applied voltage changes.	
Although initially they seem to decrease with increasing voltage, further increase results in thicker fibre diameters, due to a higher mass flow from the needle tip.	[7,24,37,50]
The increase of the voltage leads to the decrease of the beads, while further increase results in the formation of beaded fibres due to the decrease in the stability of the initiating jet.	[36,38]
<u>Polymer flow rate</u>	
At too high flow rates beaded defects can be observed.	[7,23,43]
Upon increasing the flow rates both diameters and pore size increase.	
<u>Needle tip-to-collector distance</u>	
The fibre diameter decreases by increasing the distance, whereas the formation of wet fibres and beaded structures is usually obtained by shortening the distance between the needle-tip and the collector.	[15,24,42,43]
<u>Collector composition and geometry</u>	
The more conductive collectors dissipate the charge of the fibres, whereas when this charge is not dissipated the fibres repel one another, resulting in the generation of a more porous structure.	[23,48]
Ambient parameters	
<u>Temperature</u>	
The increase in temperature results in the generation of fibres with smaller diameters due to the decrease of the polymer solution viscosity.	[7,23,28]
<u>Humidity</u>	
An increase in the humidity level results in the appearance of small circular pores on the surface of the fibres, while a further increase leads to pore coalescing, and the drying of the fibres is prevented.	[7,23,28]

6.2. ELECTROSPINNING TECHNOLOGY IN TISSUE ENGINEERING

Tissue engineering or regenerative medicine deals with the development and application of biological and therapeutic substitutes that restore, maintain, or improve tissue function by using matrix scaffolds derived from natural or synthetic polymers. These scaffolds need to be viable with human cell systems for the repair or regeneration of damaged or failed cells or tissues provoked by injury, disease, or congenital defects [51,52]. Significant considerations include the nanoscale dimensions and the three-dimensional (3-D) structure of these scaffolds, since many biologically functional molecules, extracellular matrix (ECM) components, and cells interact in the same range operating in 3-D, and mimic the properties of certain fibrous components of the native ECM in tissues [23,53].

General characteristics that are considered to be essential in scaffold design include the acceptable shelf-life and biocompatibility without eliciting undesirable responses such as inflammation and toxicity upon implantation in the body [51,54]. The degradation rate of the material should match the time required for the healing or regeneration process. The scaffold should be fully biodegradable and the degradation products should be non-toxic, and able to be metabolized and cleared from the body. Moreover, for maximum cell loading and cell-matrix interactions, high porosity and pore size are essential parameters for an appropriate scaffold destined for use in tissue engineering applications [51,54,55]. The mechanical properties, which depend mainly on the chemical structure and crosslinking density, play an important role in the adhesion and gene expression of the cells and their matching with the tissue at the implantation site [55].

Fibrous nanomaterials have been exploited in many biological applications, such as biosensing [56,57], drug delivery [58-60], bioseparation [61] and tissue engineering [62-64], thus opening new possibilities in the biomedical arena. As aforementioned, one of the most popular and versatile nanofibre fabrication techniques used for the production of synthetically or naturally-derived nanofibrous materials is electrospinning [38]. The materials derived from this technique exhibit a range of unique features and properties, including extremely long length, very small diameters resulting in high surface-to-volume ratios, highly porous structures, lightweight properties, and low cost [15,16,65,66]. Moreover, these materials are characterized by very good mechanical properties especially in the case of fibrous nanocomposites, derived from the incorporation of a variety of functional micro / nano particles within the fibres. More precisely, different nanoparticles or nanofiller types may be dispersed in polymer solutions, which are then electrospun to generate composites in the form of continuous nanofibres and nanofibrous assemblies [52,67].

These outstanding properties render electrospun polymer-based fibrous materials promising candidates for many applications, not only in the biomedical field, such as scaffolds in tissue engineering and drug delivery systems [38,68-70], but also in environmental applications including filtration and water remediation processes [71] and in catalysis [72] (Figure 2). Since the major challenges in the field of nanofibres is their utility as biomaterials and specifically in tissue engineering applications, many researchers have exploited the recent advances of this technology for producing a wide range of nanofibrous polymeric materials, both natural and synthetic, that have been used as scaffolds in tissue engineering [68].

In particular, electrospun nanofibres derived from biopolymers such as collagen [73,74], alginate [75,76], hyaluronic acid [77], chitosan (CS) [78], and starch [79], synthetic polymers such as polyurethanes, polymethacrylates, aliphatic polyesters such as poly(lactic acid) (PLLA) [80,81], polycaprolactone (PCL) [24,82] and poly(glycolic acid) (PGA) [83], poly(vinylpyrrolidone) (PVP), poly(acrylonitrile) (PAN), poly(vinyl alcohol) (PVA), poly(ethylene oxide) (PEO) [84], poly(ethylene terephthalate) (PET) [85] and their combinations have demonstrated great potential as scaffold platforms for musculoskeletal and connective tissue engineering (including bone, and skeletal muscles) [86], skin tissue engineering, vascular tissue engineering and neural tissue engineering, provided that they possess the correct design parameters as mentioned above [87-89].

6.3. ELECTROSPUN MAGNETOACTIVE NANOCOMPOSITES IN TISSUE ENGINEERING

One of the most exciting and developing classes of advanced materials are nanocomposites, which have gained considerable interest due to their potential applications in many technological and scientific fields [90]. These materials comprise two or more phases of different chemical constituents or structures, with at least one phase having nanometric dimensions [91]. The combination of functional inorganic / organic fillers at the nanometer scale with polymer-based fibres produced by electrospinning leads to novel and attractive nanocomposite systems which exhibit promising features for many applications including biomedicine [68,92,93], catalysis [72,94], in environmental [95], and in energy-related applications [27,91]. The combination of the properties of the different components and the enhanced materials' properties derived from the development of organic-inorganic interfacial interaction phenomena has led to an improved performance compared to pristine polymer fibres [26,35,91,96].

Figure 2. Schematic presentation of electrospun polymer-based fibrous materials employed in different applications

Among other inorganic nanoparticulates, magnetic nanoparticles (MNPs) offer attractive possibilities in biomedicine and are more beneficial compared to microparticles, since they exhibit controllable size ranging from a few nanometers up to tens of nanometers, and dimensions smaller than or comparable to those of cells (10–100 μm), viruses (20–450 nm), proteins (5–50 nm) or genes (2 nm wide and 10–100 nm long) [97,98], improving tissular diffusion [99,100]. Moreover, therapeutic NPs with diameters ranging from 10–100 nm can be distributed throughout the circulatory system and penetrate small capillaries [62]. Surface modification provides additional functions rendering them ideal candidates as contrast enhancement agents in magnetic resonance imaging (MRI), in biomolecular detection, cell tracking, and for targeted drug delivery in tumor therapy [100,101]. Additionally, MNP destined for use in drug delivery must retain sufficient hydrophilicity and must not exceed 100 nm in size (including the surface coating), so as not to be recognized by the reticuloendothelial system (RES). RES is a class of cells existing in different locations within the human body that are phagocytic, *i.e.*, they can engulf and destroy bacteria, viruses, and other foreign substances such as nanoparticles [102].

To date, numerous examples have appeared in the literature dealing with the fabrication of electrospun magnetoactive polymer-based fibrous nanocomposites that mainly focus on synthetic and characterization aspects [103]. In such materials different types of polymers including natural polymers, biopolymers and synthetic polymers, have been combined with magnetic nanoparticles (MNPs) including iron oxide (magnetite) (Fe_3O_4) [60,104-106], maghemite ($\gamma\text{-Fe}_2\text{O}_3$) [107-109], cobalt (Co) [110], nickel (Ni) [111], iron-platinum (FePt) [112,113] NPs *etc.* From all the above, iron oxide NPs have been the most widely studied due to their biocompatibility, non-toxicity, and stability and are, by far, the most commonly employed MNPs in biomedical applications [114].

MNP-loaded therapeutic systems have shown promising results in tissue engineering applications. More precisely, it has been demonstrated that magnetoactive tissue engineering scaffolds can be used in the treatment of bone diseases by promoting the proliferation and differentiation of osteoblasts, increasing osteointegration, and accelerating new bone formation [115]. According to previous reports, a possible mechanism explaining this effect might be that the presence of MNPs embedded within a tissue engineering scaffold may induce mechanical stresses on the bone tissue, which in turn results in an enhancement in cell growth, proliferation and differentiation. Moreover, it was suggested that the Fe^{2+} ions released from the Fe_3O_4 nanoparticles may also promote cell growth and differentiation. Osteoblasts have the ability to incorporate metal ions, where phagocytosis of metal oxide NPs with diameters smaller than 1000 nm by osteoblasts was also observed. Y. Wu and co-workers (2010) have reported that osteoblast-like cells of the series MG63 incorporated Fe_3O_4 magnetic NPs. The response of the metalloproteinases found within the ECM of the osteoblasts to the NPs resulted in the modulation of the ECM. Additionally, it was demonstrated that controlled bone growth may be realized by magnetically promoting osteoblast proliferation and differentiation in Fe_3O_4 -containing hydroxyapatite [116]. Furthermore, it has been reported that the Fe_3O_4 NPs stimulate mesenchymal stem cell growth owing to their ability to suppress intracellular H_2O_2 , thus leading to the acceleration of the cell cycle progression [117-119]. Based on previous literature reports, the applied static magnetic field promotes cell proliferation even in the absence of magnetic nanoparticles [119], thus stimulating bone tissue regeneration [120,121]. X. Ba *et al.* (2011) reported on the enhanced proliferation of osteoblasts under moderate static magnetic fields (SMFs) on magnetic-free scaffolds [122]. The authors stated that even in the presence of moderate SMF osteogenic differentiation an activity of the osteoblasts is promoted. The introduction of magnetic nanoparticles results in further enhancement in cell growth, proliferation and differentiation, thus demonstrating that the applied magnetic field in combination with the embedded magnetic nanoparticles acts in a synergistic manner [119].

Figure 3. Schematic presentation of different routes employed for the fabrication of magnetoactive electrospun nanofibres

Electrospun magnetoactive polymer-based nanofibres can be generated either by the direct mixing of MNPs (pristine or pre-stabilized by polymers or surfactants) with the polymer solution followed by electrospinning [108,123,124], through the electrospinning-electrospraying process [55,66,103,125] or *via* post-magnetization processes (Figure 3).

Examples include PAN / Fe_3O_4 [126], poly(ϵ -caprolactone)/FePt [112], PEO / PLLA / Fe_3O_4 [60], PVP / PLLA / Fe_3O_4 [127], poly(methyl methacrylate) (PMMA) / Fe_3O_4 [128,129], and polyurethane (PU) / Fe_2O_3 [123].

However, only a limited number of literature examples so far have dealt with the evaluation of electrospun magnetoactive polymer-based membranes as tissue engineering scaffolds, focusing more on bone regeneration processes.

Bone is a complex, highly organized living organ forming the structural framework of the body. It is composed of an inorganic mineral phase, namely hydroxyapatite, and an organic phase of mainly type I collagen. The treatment of bone injuries through tissue engineering depends, among others, on the mechanical properties of the bone tissue, the porosity, hardness and the overall 3-D architecture.

J. Meng *et al.* (2010) studied cell proliferation, differentiation and ECM secretion of osteoblast cells in the presence of magnetoactive electrospun nanofibrous composite mats under a static magnetic field, providing a system with promising application potential in bone tissue engineering and bone regeneration treatment [109]. More precisely, nanofibrous scaffolds composed

of $\gamma\text{-Fe}_2\text{O}_3$ nanoparticles coated with *meso*-2,3-dimercaptosuccinic acid (DMSA), poly(D,L-lactide) (PLA), and hydroxyapatite nanoparticles (nHA) were fabricated by electrospinning. Upon applying a static magnetic field (0.9–1.0 mT), a significantly higher proliferation rate and faster differentiation of osteoblast cells were displayed.

PCL-based magnetoactive electrospun nanofibrous scaffolds were fabricated by J.T. Kannarkat and co-workers (2010) for potential use in bone healing and regeneration [130]. From their studies they concluded that the MNPs do not alter the stability of the fibrous PCL scaffold. Moreover, they demonstrated that the MNPs did not prohibit cell growth; on the contrary, cell clustering was observed after 9 days of cell culture. Cell elongation was also observed, indicating cell differentiation. As stated by the authors, such cell elongation phenomena may be attributed to the high surface area of the electrospun fibrous scaffold, facilitating multiple site attachment.

Electrospun superparamagnetic aligned fibrous bundles were developed by W.Y. Lee *et al.* (2011) to be tested as biomaterial scaffolds. The development of aligned tissue engineering scaffolds is of paramount importance since the alignment of cells plays an important role in the skeletal muscle tissue characterized by a well-oriented architecture. This material consisted of highly oriented electrospun poly(L-lactide-*co*-glycolide) (PLGA) fibres with embedded superparamagnetic iron oxide NPs (SPION). Cell alignment and differentiation by using mouse C2C12 myoblasts (ATCC CRL-1772) demonstrated that C2C12 myoblasts proliferate along the direction of the aligned fibres, similarly to native skeletal muscle tissues [131]. In the presence of an externally applied magnetic field the generated cell rods self-assembled into highly ordered 3-D tissues. These results demonstrate the high potential of magnetoactive polymer-based fibrous bundles as a scaffold promoting cell growth and as a cargo for the magnetic field-induced generation of highly oriented 3-D cell-dense tissues.

Y. Wei *et al.* (2011) have reported on the fabrication of magnetic biodegradable fibrous mats by means of the electrospinning technique, with potential use in bone regeneration. More precisely, they have prepared a magnetoactive nanofibrous scaffold based on native polysaccharide CS, PVA, and Fe_3O_4 NPs. MG-63 cells were cultured on the Fe_3O_4 / CS / PVA nanofibrous membranes to evaluate the cell growth dynamics. The obtained results demonstrated that cell adhesion and proliferation increased in the presence of the MNPs [132].

The performance of magnetoresponsive fibrous mats on bone regeneration was also studied by K. Lai *et al.* (2012) who have reported on the fabrication of magnetic biocompatible fibrous scaffolds consisting of poly(lactic-*co*-glycolic acid) (PLGA) and superparamagnetic Fe_3O_4 NPs with variable nanoparticle loading. The authors studied their effect on different bone cells (Rps17/1.8 and MC3T3-E1) in the absence of an external magnetic field. The magnetite-containing nanocomposite scaffolds exhibited excellent biocompatibility,

enhanced osteoblast cell attachment and proliferation at an early culture time in comparison to the pristine PLGA fibrous analogues [133].

Aligned superparamagnetic nanofibres comprising poly(lactic-co-glycolide) (PLGA) and MNPs (Fe_3O_4) have been developed by H. Hu *et al.* (2013) by employing magnetic electrospinning. This electrospinning variation utilizes a magnetic field that causes the parallel stretching of magnetoactive polymer fibres. The effect of the fibre alignment on the cell performance was studied by using C2C12 myoblast cells. The magnetically aligned nanofibres exhibited superior cell attachment and proliferation in comparison to their randomly oriented analogues, offering guide cell growth along the longitudinal axis of the nanofibres [134].

J. Meng *et al.* (2013) reported on the fabrication of a novel nanofibrous composite scaffold by means of the electrospinning technique. The magnetoactive scaffold composed of superparamagnetic $\gamma\text{-Fe}_2\text{O}_3$ NPs, nHA NPs and PLA resulted in the acceleration and induction of a higher amount of osteocalcin positive cells *in situ*, under a static magnetic field [135].

A nanocomposite fibrous substrate for bone regeneration was also prepared by D. Shan *et al.* (2013). The magnetoresponsive matrix composed of PLLA and Fe_3O_4 NPs was prepared by using a modified chemical co-precipitation method. The dispersion of the MNPs within the fibrous mat showed a positive effect in cell attachment, while enhanced cell attachment was obtained when compared with the pristine PLLA nanofibres [136].

R.K. Singh *et al.* (2014) have reported on magnetic electrospun nanofibrous scaffolds, based on PCL and iron oxide MNPs, with mechanical and biological properties applicable for bone regeneration. Among others, the authors demonstrated that the presence of MNPs within the non-woven fibrous mats results in an enhancement of their mechanical performance. Moreover, it was shown that osteoblastic cells favoured the MNPs-incorporated nanofibres, providing excellent cellular interactions compared to the pristine PCL [137].

Since the presence of a magnetic field significantly influences the cell behaviour, in a last example L. Li *et al.* (2014) have studied the influence of a SMF of moderate intensity on osteoblast and 3T3 fibroblast cultures by using randomly oriented and aligned electrospun magnetic composite nanofibrous mats consisting of a biodegradable polyester, namely PLA and iron oxide MNPs [138].

6.4. CONCLUSIONS

The unique properties of magnetic nanoparticles, in combination with the special characteristics of electrospun polymer nanofibres have led to the development of novel, multifunctional fibrous nanocomposites with outstanding properties for tissue engineering applications, focusing more on bone regeneration processes. Recent studies in this field have demonstrated that the use of polymer-based magnetoactive electrospun fibres leads to an enhancement in cell growth, proliferation and differentiation in comparison to their pristine fibrous polymer analogues. The exact mechanism by which magnetic scaffolds promote cell proliferation is still under investigation [132,133,137] and the area of magnetically-triggered tissue engineering is wide open for further development in the near future.

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