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Contributions of Electrospinning Methods in Tissue Regeneration: Latest Applications and Novel Materials

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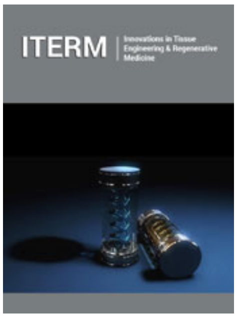

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Introduction

In the few last decades, tissue regeneration has gained considerable attention in clinical research, becoming one of the hotspots that holds great expectation as a possible remedy to tissues diseases by providing specific treatment for repairing damaged tissues or even to create organ components [1]. Among the different methods of investigations by academies and industries, electrospinning is definitely considered one of the most simple and promising tools for tissue repair and regeneration [2]. Several studies and industrial applications have been carried out and are currently available in the literature on the use of electrospinning method for tissue regeneration, mainly due to the peculiar ability of these processes for generating ultrathin fibers. However, in spite of the progress in this field, such techniques need to be further studied [3].

The magnetic and electrostatic phenomena, central to electrospinning, were well known from the late 16th century, when the first experiment on the electro spraying was recorded [4]. In 1969, Taylor SG [5] investigated the pillar of the mathematical model that governs the droplet shape, known as the “Taylor cone”, on which the theoretical understanding of the electrospinning method is funded [6]. Whereas it was in 1974 when the first electro spun fibers were used as wound dressing. The investigation on the electro spun fibers as implantable started just few years later. Nowadays, many applications of electrospinning have demonstrated the suitability of this technology to electro spun organic polymers into nanofibers and, as a result, an increasing number of studies on the driving mechanisms of the electrospinning process have been carried out [7,8].

In the medical field, electro spun fibers are not just used as medical textile materials, but electro spun scaffolds have been used for regenerating tissues by being penetrated by biological cells to treat damaged tissues, as well as for organ component replacement. Almost all human tissues and organs are characterized by a fibrous structure hierarchically organized, composed of nanometer fibers which make suitable the use of electrospinning methods [9]. However, the choice of the proper process parameters is essential to produce suitable polymer nanofibers with specific structural, mechanical, and functional properties. The electrospinning technique is based on the application of a high voltage between the spinneret and the ground collector, making possible to eject material from the syringe pumps to produce nanofibers. Currently, one of the main promising fields of application of this technology is the production of fibrous scaffolds with a high loading and encapsulation capacity [10,11]. The electrospinning has the advantages to produce continuous ultrafine fibers from polymers and composites with better uniformity, porosity large surface area and mechanical strength. Different studies have proved its potential application in tissue regeneration, in the fabrication of bio-chemical sensor and artificial muscles. Electrospinning methods can contribute to improve the use of conductive polymers as novel organic materials for biosensors, bio-actuators and meet the expected potential application in tissue engineering scaffolds [12].

Accordingly, Havlicek et al. [13] demonstrated how the use of different electrospinning methods clearly determine structural differences between the produced nanomaterials. Therefore, the effects of five different electrospinning methods have been analyzed, considering the application of direct current (DC) and alternating current (AC) voltages. Based on the evaluation of the scanning electron and confocal microscopy images, DC methods are more suitable for the preparation of more compact, less rough, and well-defined nanofiber structures. Furthermore, centrifugal DC methods appear to be the most appropriate procedures for medical and tissue engineering applications as they provide nanofibers in a narrow size range. On the other side, AC methods result more suitable in the sector of filtration and cosmetic product because they produce a finer structure and nanofiber coating substrates, which are more thread-like with higher surface roughness [13].

Previous studies demonstrate as the melt electrospinning method can overcome the concern relative to low solubility and the intrinsic brittleness of pure conductive polymers that are difficult in the use of direct electrospinning [14,15]. Currently, the melt electrospinning process enables the direct contact between the electros up nanofiber and the cells without affecting their survival rate [16]. Additionally, regular structure of 3D scaffolds with porosity higher than 85% can be produced [17-19]. For instance, emulsion electrospinning was demonstrated to be a potential method to build up biocompatible micron-fibers with suitable mechanical properties and osteo inductive capacity to osteoblasts for potential transplantable scaffolds to repair large-segment bone defects. In particular, Tao et al. [20] investigated the use of polycaprolactone/carboxymethyl chitosan/sodium alginate (PCL/CMCS/SA) micron-fibers prepared by emulsion electrospinning as micron-fibrous bionic periosteum for the bone tissue regeneration. Indeed, PCL/CMCS/SA micron-fibers produced by emulsion electrospinning were characterized by an average diameter of 2.381 ± 1.068μm with excellent tensile strength. Moreover, PCL/CMCS/SA composite scaffold shows no significant cytotoxicity [20]. Similarly, Liu et al. [21] demonstrated that electrospinning, considering its ability to produce fibers with a very high surface-to-volume ratio and modulated pore size, can be an effective method to synthesize biomimetic periosteum scaffolds by using organic and inorganic polymers [22,23]. Lastly, the use of biomimetic composite calcium-phosphate nanoparticles (CaPs) and gelatin-methacryloyl (GelMA) hybrid hydrogel electrospinning fibers could accelerate the bone regeneration [21].

The main advantage of electrospinning methods for scaffold applications in the tissue-engineering field is the possibility to manufacture biomimetic structures with the same scale and morphology as the native extracellular matrix (ECM). Tissue engineering scaffolds are not only required to be biomimetic with the ECM structure, but also, they should be characterized by the same signals contained within the ECM. Regarding that, the electrospinning technique allows to produce fibers of a suitable scale to induce adequate external signaling with nanofiber structures, improving thus the function of tissue engineering scaffolds of different human tissues (bone, cartilage, cardiovascular, nervous) and bladder regeneration [24]. Regarding the combination of such different methods as freeze-drying and 3D printing combined with electrospinning, further studies demonstrated that this fact enables the production of nanofibrous scaffolds with complex 3D features [25,26]. These methods have a large field of application in the regeneration of articular cartilages for the treatment of congenital defects. The reason is the unique morphology that characterizes the cartilage of the nose and ears, that can be reproduced by using 3D printable scaffolds [27].

In addition, the electrospinning has been used to coat the screws by Poly-Vinyl Alcohol (PVA) and Nano-Hydroxyapatite (nHA) nanofibers, with various concentrations of nHA. The study of Saniei et al. [28] analyses the MC3T3-E1 cells cultured on the 3D-printed Polylactic acid (PLA) and PVA-nHA nanofiber samples. The results opened a new gate of investigation in the biocompatible implants. The PVA-nHA nanofibers have demonstrated to improve the adhesion of the MC3T3-E1 cells as well as to enhance the growth of the cells.

In line with the use of the cellular electrospinning and 3D bioprinting, it has been demonstrated by Yeo et al. [29] that platforms for the cultivation of human umbilical vein endothelial cells (HUVEC) and C2C12 cells can be obtained. The produced cells are characterized by efficient growth, great cell viability (90%) and homogeneous distribution. Moreover, the scaffold, that includes myoblasts and HUVEC, can be used to restore the vascularization of an engineered skeletal muscle tissue and its physiological activities. Last, a study carried out by Kersani et al. [30] uses electrospinning technology for covering stents with nanofibers loaded with simvastatin (NF-SV), a drug commonly used for the prevention of restenosis. A different application of electrospinning has been the production of gelatin-base fibers for maxillofacial surgery. However, results were unsuccessful because the electro spun membranes lacked reproducibility due to their low diameters [31].

In the treatment of trauma and disease that causes bone defects [32], the incorporation of additive manufacturing to the rotational electrospinning have enabled the production of dual-scale scaffolds. The results show the influence of the electrospinning rotational velocity on the morphological, mechanical, and biological characteristics of the scaffolds. 3D scaffolds produce uniform, robust with well-defined geometries and the alignment of nanoscale electro spun fibers grows by increasing the electrospinning rotational velocity [32,33]. As main conclusion, it can be stated that a large variety of novel structured materials can be achieved by using electrospinning methods. Specifically, interesting in the biomedical field, this rising technique can contribute to the research of cancer therapy, cellular responses, engineering *in vitro* 3D tissue models and tissue regeneration [34]. The reviews presented in this work show the advantages of the combination of electrospinning with 3D printing technology, as well as the main goals achieved with a special focus on the tissue regeneration field. In spite of advances and promising results in tissue regeneration applications by electrospinning, specific mechanisms should be further studied, especially those related to novel materials for electro spun fibers fabrication in bone applications. Future research may be considered to better understand the driving mechanism of the nanofiber's compositions and to reach a fully reparative and tissue regeneration.

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