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Review Article

Biodegradable electrospun scaffolds for skin wound regeneration: a review

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ABSTRACT

Over the years, skin substitutes have been sought as an alternative for the treatment of different pathologies. In this article, we focus on describing the use of different biodegradable nanofibrillar polymers as skin substitutes in the treatment of acute and chronic wounds, obtained by the electrospinning technique. Electrospinning is a tissue engineering technique used to generate nanofibers of different polymers that are characterized by having a high surface area, low molecular weight, high resistance rates, and nanoporosity, which is why they are particularly interesting for biomedicine, with potential applicability. in the replacement of skin and tubular organs. In this context, the skin created by tissue engineering has high expectations of application in the study of treatment of skin wounds.

Keywords: Tissue engineering, Nanofibers, Skin, Electrospinning, Biodegradable polymers

INTRODUCTION

The skin constitutes the first defense barrier between the body and the environment, it is the largest organ in the human body and its main function is to act as a protective barrier against harmful stimuli such as microorganisms, radiation, chemical / physical agents in the environment. It also has other important functions such as maintaining the balance of body fluids and body temperature, synthesizing vitamin D, transmitting and detecting changes in the external environment, and regulating the immune response, therefore it is a great challenge to be able to mimic the functions of the skin in situations that require skin replacement, such as in burn patients, extensive resections of tumors, trauma.[1] Wound healing is a complex biological process mediated by the interaction of signal molecules and mesenchymal cells that may be altered in relation to different pathologies such as diabetes, which is why defective wound healing is becoming a growing health problem. world level.[2] In this context, the skin created by tissue engineering has high expectations of application in the study of wound treatment since conventional treatment generally focuses on a single factor or process of wound repair and frequently ignores the influence of the wound. pathological microenvironment of the wound on the final healing effect. Therefore, it is of great value for current medical practice to study, design and develop different therapeutic methods that can actively regulate the wound microenvironment and reduce the level of oxidative stress at the wound site to promote wound repair. of the skin. In recent years, several bioactive nanomaterials have shown great potential in tissue repair and regeneration due to their biodegradable and biocompatible properties, for this reason, in this article we focus on describing the current biomedical uses of different polymers developed with the electrospinning technique in relation to the application of biodegradable polymer nanofibers.[3]

TISSUE ENGINEERING

Over the years, skin substitutes have been sought as an alternative for the treatment of burn patients, where xenografts have been evaluated in controlled studies of dog, frog, fish, and pig skin. Cadaveric skin allografts have also been studied without conclusive results. However, to obtain approval for medical use in humans, these tissues must undergo very strict sanitary protocols, in order to verify their safety, efficacy and biocompatibility.[4-6] In Brazil, a phase III randomized controlled clinical trial compared the efficacy of silver sulfadiazine cream compared to the use of a Nile Tilapia (Oreochromis niloticus) skin-based dressing in the treatment of superficial partial-thickness burns. The results showed that patients treated with Tilapia skin-based dressings required fewer dressing changes, had a greater decrease in pain, a lower requirement for analgesic drugs, and the final average cost of treatment was reduced by one, 42.1% compared to patients treated with silver sulfadiazine. With respect to the days it takes for the skin to re-epithelialize, no statistically significant difference was demonstrated in both treatment groups.[7] The clinical interest in the skin of this fish arose from preclinical studies in which it was shown that the histological morphology of Tilapia skin presented similarities with human skin, highlighting that its skin contained a greater composition of type I collagen and greater tensile strength.[8] The use of Nile Tilapia skin is in the process of being approved as a medical graft by the Brazilian national health surveillance agency.[9] Currently, the most widely used skin substitute is cultured epidermal grafts, however, they have the disadvantage of being extremely delicate.[1011] Therefore, the treatment of extensive wounds is extremely complex and tissue engineering has made important leaps in the advancement of wound care, especially with the use and application of nanotechnology, nanofibers obtained by electrospinning and 3D bioprinting of components. cells in a prefabricated matrix and direct impression of the artificial skin into the wound.[11]

ELECTROSPINNING

Electrospinning is the technique used to generate ultrafine fibers of various materials, the most widely used are organic polymers and when the diameter of the fibers are less than approximately 500 nanometers they are called "nanofibers". The term electrospinning was first introduced in a study by William Gilbert in the year 1600, in which he observed the deformation of a drop of water into a cone shape in the presence of an electric field, however, until 1990 the scientists Darrell Reneker and Gregory Rutledge demonstrated the existence of different polymers that could be electrospun into nanofibers, this was the decisive fact that popularized the term "electrospinning".[12-14] Electrospinning is an electro hydrodynamic process, in which a high voltage power source, an injection pump, a needle and a collector plate are required (Figure 1). This process begins when the polymer solution is pushed through the injection pump towards the end of the capillary needle, and through the voltage difference that is created between the tip of the needle and the collector (flat or dynamic for the creation of tubular scaffolds) it is possible to overcome the surface tension force of the drop and forms a cone-shaped jet (Taylor cone), this jet is then expelled in the direction of the collector through very thin fibers (Figure 2).[16,17]

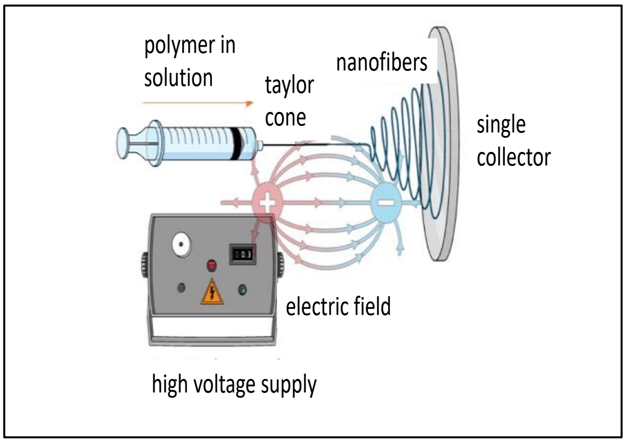

Figure 1: Electrospinning machine. Schematic diagram of the electrospinning process and the necessary equipment for the elaboration of nanofibers.

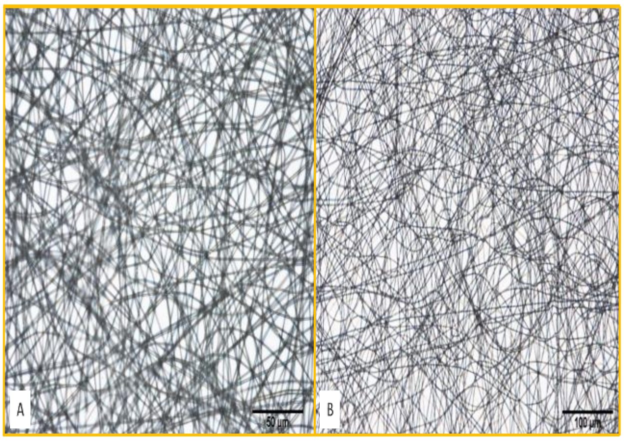

Figure 2 (A and B): Light microscopy of electrospun nanofibers. Optical microscopy of nanofibers with a 50 um scale, 100 um scale.

Nanofibers are characterized by having a high surface area, low molecular weight, high resistance rates, and nanoporosity, which is why they are particularly interesting for tissue engineering and biomedicine (Figure 3) because their manufacturing technique and configuration is Essentially simple, reproducible, versatile and effective, which is why it is usually accessible to most laboratories, in addition to its intrinsic physical and chemical characteristics that resemble/ mimic the extracellular matrix, which can favor tissue regeneration. Today, nanofibers are used as scaffolds for skin regeneration and rejuvenation and for the delivery of absorbable drugs, within their medical applications they function as excellent antimicrobial devices, protecting and coating the skin, complying with all standards of security.[18] In this article we focus on describing the biomedical application of biodegradable polymer nanofibers. For this reason, it is important to mention the meaning of this characteristic: biodegradability refers to a substance or material that can be decomposed by the action of living organisms and it must decompose without leaving toxic residues in the environment.[18] More than 100 different types of polymers have been successfully explored to produce nanofibers, there are a large number of biocompatible and biodegradable synthetic polymers such as polycaprolactone, polylactic-co-glycolic acid, polylactic-co-glycolic acid, polyvinyl alcohol, and polyethylene oxide, which are being studied as scaffolds for biomedical applications. Regarding the natural biopolymers, (Table 1) the most investigated by tissue engineering are: fibrinogens, dextran, chitin, chitosan, alginate, collagen and gelatin.[12,19] At present, despite the multiple investigations carried out, no dressing has proven to be superior to another in the management of donor site wounds after the excision of skin grafts with areas of 10 to 200 cm^2.[20,21] Non-adherent dressings are the most commonly used standard management, and of these, bismuth-impregnated Vaseline gauze for its low cost and benefits, however, wet dressings tend to be laborious for both patient and caregiver.[2223] For this reason, there are great expectations regarding the use of electrospun nanofibers, which have already been tested preclinically in wound healing using animal models where multiple favorable properties and excellent cost-benefit were demonstrated.[23]

In 2022, the first prospective randomized clinical trial published in which both dermal healing and the safety associated with the use of a matrix based on a electrospun nanofibrous polymer with a portable device compared to the current standard of care using non-adherent dressings. In the study, the results suggest that the nanofibrous dressing has similar properties to current treatment standards, however, there are additional advantages such as decreased pain.[2221] The use and application of different polymers is being studied (Table 2) in order to determine which could be the gold standard in the specific type of wound. In a study carried out by Koivuniemi et al it was observed that in the treatment of donor sites where cellulose nanofibrillar dressings were used, the viscoelasticity and elastic modulus of the skin improved significantly one month after surgery, compared to those wounds where polylactide-based copolymer dressings were used.[2425] There are multiple experimental studies that are trying to develop artificial skin with nanofibrous scaffolds built from layers of different cell lines and nanofibers.[25-28] Li et al he published an article evaluating the efficacy of a skin substitute created from polycaprolactone nanofibers, chitosan, mupirocin, and lidocaine hydrochloride. The study was carried out in vitro in human dermis fibroblasts and it was found that the scaffold showed hydrophilicity (favors cell adhesion), cytological compatibility, sustained drug release and antibacterial activity against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa* and did not show toxicity towards fibroblasts.[2829] A meta-analysis published in 2023 analyzed and searched for scientific evidence from the last 10 years on the application of chitosan nanofiber skin coverings in the healing process of burns and skin wounds in animals, shown to be safe, as no adverse effects were reported. in none of the studies, which indicates that these skin coverings have the potential to be used in humans in the future.[29] In a preclinical study in mice, an excisional skin defect was performed and the efficacy of nanofiber scaffolds created from chitosan and polycaprolactone compared to a commercial skin drape was evaluated. Wound size, measurement of defect recovery over time, and wound healing histology were evaluated. In the results, chitosan and polycaprolactone scaffolds showed an increased rate of wound healing and promoted more complete wound closure compared to commercial skin coverage, meaning that these scaffolds have the potential to be used as a substitute for skin or as a base for tissue engineering constructs.[2728] Another experimental study investigated the possibility of fabricating skin substitutes by assembling layers of human skin cells (fibroblasts and keratinocytes) and polycaprolactone and collagen nanofibers into 3D bioprinted constructs for the treatment of full-thickness wounds created in the back of mice after 14 days of culture, the constructs developed a structure similar to human skin and showed mechanical resistance. This skin substitute was compared with autografts and acellular dermal meshes. It was found that the skin substitute cultured for 14 days facilitated wound closure and had complete epithelialization similar to autografts.[26]

Table 1: The most frequent synthetic as well as the natural polymers used in the creation of the skin covers.

Biodegradable synthetics	Natural
Polylactic-co-glycolic acid	Chitosan, alginate, collagen
Polylactic acid or polylactic acid	Dextran, gelatin
Poly-caprolactone	Fibrinogens
polyvinyl alcohol	Chitin
polyethylene oxide	Hyaluronic acid

Table 2: Experimental tests for skin using nanofiber scaffolds manufactured by electrospinning technique.

Author	Material	Modelo experimental	Resultados
Koivuniemi et al, 2020	Cellulose nanofibers vs. polylactide copolymer.	24 human patients between 18 and 49 years.	-Same healing time, re-epithelialization, transepidermal water loss and decreased pain in both groups. -Greater epithelial elasticity of the donor site with nanofibrillar cellulose dressings one month after surgery.
Movahedi et al, 2020	Polyurethane nanofibers, starch and hyaluronic acid vs control group: sterilized cotton gauze.	18 rats	-Less wound closure time and less inflammation than the control group.
Mahjour et al, 2015	Polycaprolactone nanofibers, collagen, fibroblasts and keratinocytes vs. mouse skin autografts and acellular dermal meshes	40 rats	-21 days after treatment the skin substitute had rapid wound closure with complete epithelialization comparable to autografts. -Autografts produced the best healing result with minimal wound contraction (16±10%) and complete re-epithelialization. -Two-week skin substitute completely re-epithelialized with 31±7% wound contraction. - Wounds treated with acellular mesh did not completely re-epithelialize (7±4%) with a contraction of 45±11%.
Levengood et al, 2017	Chitosan and polycaprolactone nanofibers vs Tegaderm	20 rats	-Increased rate of wound healing and more completeness of the wound compared to Tegaderm.
Li et al, 2018	Polycaprolactone, chitosan, mupirocin and lidocaine hydrochloride nanofibers.	Fibroblastos dérmicos humanos *in vitro.*	-Excellent hydrophilicity, cytocompatibility, sustained drug release and antibacterial activity. -Highly effective antibacterial activity against Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa. - They did not cause toxicity in fibroblasts.

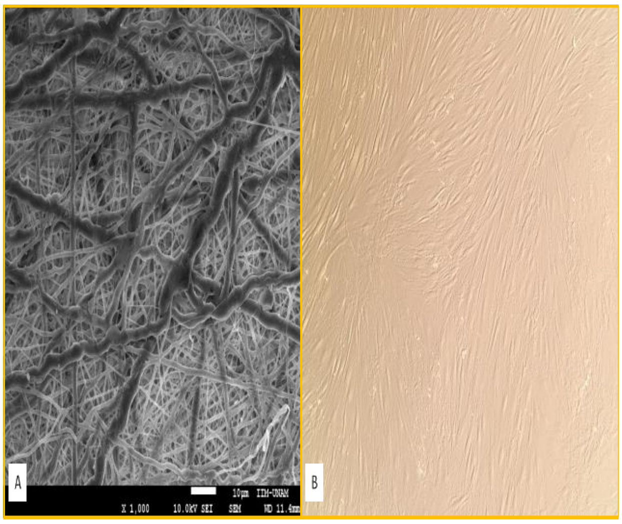

Figure 3 (A and B). Electron microscopy and cell culture. The heterogeneous morphology of a copolymer of nanofibers obtained by electrospinning is observed. Cell culture of fibroblast at 10 days on a scaffold of electrospun nanofibers.

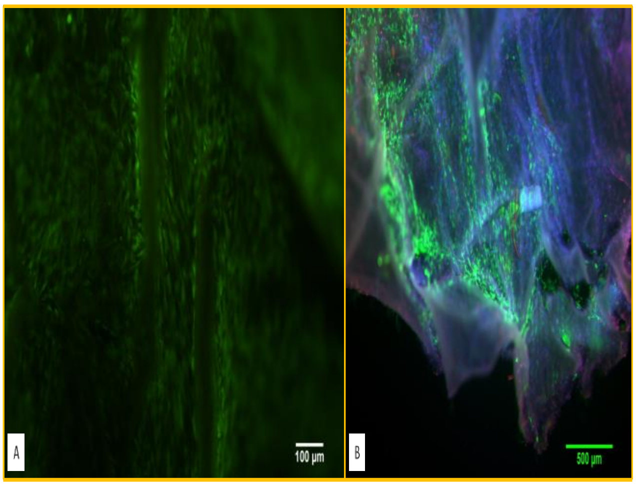

Figure 4 (A and B): Cell culture *in vitro*. Fibroblasts cultured on a scaffold of nanofibers obtained by electrospinning with fluorescence are observed, fluorescent cell viability with calcein at 100 um. Merge of calcein, ethidium homodimer and 4',6-diamidino-2-phenylindole (DAPI) at 500 um.

Figure 5 (A and B): Experimental biomedical applications of electrospinning. Group of researchers from the general hospital of Mexico-UNAM during the experimental study on replacement of tubular organs (blood vessels and extrahepatic bile duct).

DISCUSSION

Currently, tissue engineering by electrospinning has focused on the creation of scaffolds based on organic polymer nanofibers to create functional tissues or regenerate them. This technique has the advantage of being versatile, feasible and economical.[17] Scaffolds based on natural, synthetic and mixed organic polymer nanofibers manufactured by electrospinning have mechanical, physical and chemical properties that favor cell adhesion, provide greater mechanical resistance and stability between cells, as well as offer the necessary microenvironment for cell proliferation (Figure 4). *In vitro* and *in vivo* experimental studies carried out with scaffolds obtained by electrospinning, a shorter time for re-epithelialization and closure of the wound, a lower amount of proinflammatory cells without causing cytotoxicity have been shown, so they have the potential to be used. as patches created by tissue engineering in the treatment of skin wounds.[25] Multiple preclinical trials based on the electrospinning technique are being carried out to design the ideal skin substitute that promotes re-epithelialization, provides a moist environment, prevents the growth of microorganisms, absorbs exudate, is easy to apply, and is affordable for clinicians. patients. However, there is still a lack of clinical studies to support the safety and efficacy of these skin coverings.[24] These nanofibers can be composed of natural, synthetic and mixed polymers. Natural polymers are highly biocompatible, non-toxic, biodegradable and have the ability to cause skin contraction during the wound healing process, which is why they are used in wound treatment.[30] On the other hand, synthetic polymers can be modulated and modified during their preparation to meet specific requirements according to their application. Their chemical, physical, and mechanical properties can be controlled, allowing high reproducibility for these materials, including tubular organ replacement (Figure 5). There are also hybrid polymers, which represent the union of these characteristics, resulting in better performance for nanofibers and relative scaffolds with faster wound healing compared to other nanomaterials.[31]

CONCLUSION

Currently, chronic wounds have become a public and social health problem in the world, especially associated with the increase in metabolic diseases that delay the healing process and that lead to complications from infections, deformities and hemorrhages. In this context, the skin created by tissue engineering has high expectations of application in the study of treatment of skin wounds. Electrospinning is a feasible technique in tissue engineering due to its low cost, versatility, and accessibility in most laboratories. Clinical studies are still lacking to demonstrate the effectiveness and safety of the skin substitute and skin coverage techniques that are currently being developed, however, there are great expectations in this area.

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