ISSN: 2476- 2334

Mini Review Article

International Journal of Nanotechnology & Nanomedicine

Evaluating the Therapeutic Effect of Nano Fibers on Diabetic Foot Ulcers – an Innovative Approach

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Submitted: 2023, Dec 30: **Accepted:** 2024, Jan 25: **Published:** 2024, Feb 10

Citation: Gokarneshan, N., Jothimanikandan, A., Periyasamy, P., Ponmaniselvan, M., Sridhar, K., et al. (2024). Evaluating the Therapeutic Effect of Nano Fibers on Diabetic Foot Ulcers – an Innovative Approach. *Int J Nanotechnol Nanomed, 9*(1), 01-05.

Abstract

Diabetes is one of the most prevalent diseases in the world with high-mortality and complex complications including diabetic foot ulcer (DFU). It has been reported that the difficulties in repairing the wound related to DFU has much relationship with the wound infection, change of inflammatory responses, lack of extracellular matrix (ECM), and the failure of angiogenesis. Following the development of medical materials and pharmaceutical technology, nanofibers has been developed by electrospinning with huge porosity, excellent humidity absorption, a better oxygen exchange rate, and some antibacterial activities. That is to say, as a potential material, nanofibers must be a wonderful candidate for the DFU treatment with so many benefits. Careful selection of polymers from natural resource and synthetic resource can widen the nano fibrous application. Popular methods applied for the nano fibrous fabrication consist of uniaxial electrospinning and coaxial electrospinning. Furthermore, nanofibers loading chemical, biochemical active pharmaceutical ingredient (API) or even stem cells can be wonderful dosage forms for the treatment of DFU. This review summarizes the present techniques applied in the fabrication of nano fibrous dressing (ND) that utilizes a variety of materials and active agents to offer a better health care for the patients suffering from DFU.

Keywords: Nanofibers, Nano Fibrous Dressing, Diabetic Foot Ulcer, Uniaxial Electrospinning, Coaxial Electrospinning.

1. Introduction

According to statistics, it is estimated that there were 366 million people worldwide with diabetes in 2013, and the number will be increased to almost 552 million by 2030 [1]. Diabetes is a kind of disease that relates to the dysfunction of glucose control, the destroyed management on the protein metabolism and lipid metabolism [2]. Following the deterioration of diabetes, a portion of diabetic patients will suffer from diabetic foot ulcer (DFU), one of the complications of diabetes, which possesses the characteristics of long term process of wound closure and has the tendency to hospitalization and even amputation in the future. Unfortunately, apart from the physical and mental impairment on diabetic patients, the cost for DFU treatment may be another heavy load. To solve this problem, we need to have a clear idea of the reason why it is so difficult to heal the wound and we need to figure out what has prolonged the healing process. Peripheral neuropathy, deformity, and macrovascular disease can be the main factors that cause the failure of DFU healing process [3]. Additionally, new findings can be the supplements to the factors [3], which including lacking resistance to infection, changing on microcirculation function, and damaging to growth factors (GF) expression and activity. Furthermore, another study is conducted to find out whether the peripheral arterial disease has a correlation with DFU, and the results indicate that there is some correlation between them, and DFU can be classified to two disease states according to whether there exists the peripheral arterial disease [4]. Other factors, which have significant contributions to DFU including low proliferative capacity of the fibroblasts, downregulation of receptors, and the absence of a suitable protein matrix in the dermis [5]. In brief, the mechanism of this issue is relatively complex, and there still has a big room for pharmaceutists to participate in DFU treatment. The methods of DFU treatment varies from individual symptoms and the disease stages. Several therapeutic approaches have been reported, glycemic regulation, such as adequate insulin administration, is essential. Debridement, skin graft and tissue replacement has relevantly high-efficiency of wound closure [3]. Other approaches such as vascular reconstruction, hyperbaric oxygen therapy, and granulocyte-colony stimulating factor are also

options to treat DFU. In most cases, the wound dressing is of use to create a beneficial environment for the open wound to achieve a better and faster wound closure [6]. Unfortunately, conventional wound dressings like gauze possess limited basic function for their defective material properties. What is more, different phases of the diabetic wound healing have different pathology features so that multifunctional wound dressing with specific material is under the urgency. Currently, advanced dressing technology like nanofibrous dressing (ND) that can employ specific materials to fit specific need for DFU treatment is harvesting large interests and attention. ND is the collection of nanofibers ranging from nanometers to micrometers, as shown in Fig. 1, ND is easy to be removed [7]. The technique of nanofibers fabrication has a long history, and it was firstly reported since 1900 [8]. Nanofibers as a promising matrix have lots of advantages such as small diameter, narrow diameter distribution, and high-specific surface area. Various polymers have been studied and developed into fabricate nanofibers for textiles, electrical and optical component, sensors, and filtration devices [9, 10]. The products manufactured through this technology are very soft and highly flexible, lacking of sharp corners and vulnerable to turn to sheets, tubes, and coatings [11]. ND employed by pharmaceutics shows great benefits and an increased prevalence in the drug delivery system. It utilizes the excipients or accessories to deliver the therapeutic agents to the site with high-efficiency, and low-adverse effects. For the DFU treatment, it is necessary to put emphasis upon the vascularization, collagen accumulation and normal physiological functions to control the deterioration process and even cure the wound [12]. Kinds of active pharmaceutical agents like molecules and cells play the key roles in this process; however, the matrix loaded them can also be a fundamental stage for their functional realization. Basically, it has crucial activities of the absorption of exudation and the exchange of oxygen, water, and nutrient [13]. Additionally, nanofibers with the similar diameter to the extracellular matrix (ECM) have been proven to accelerate the process of cell adhesion and proliferation. 1D–3D nanofibers production also has been investigated in biomaterials field [14].

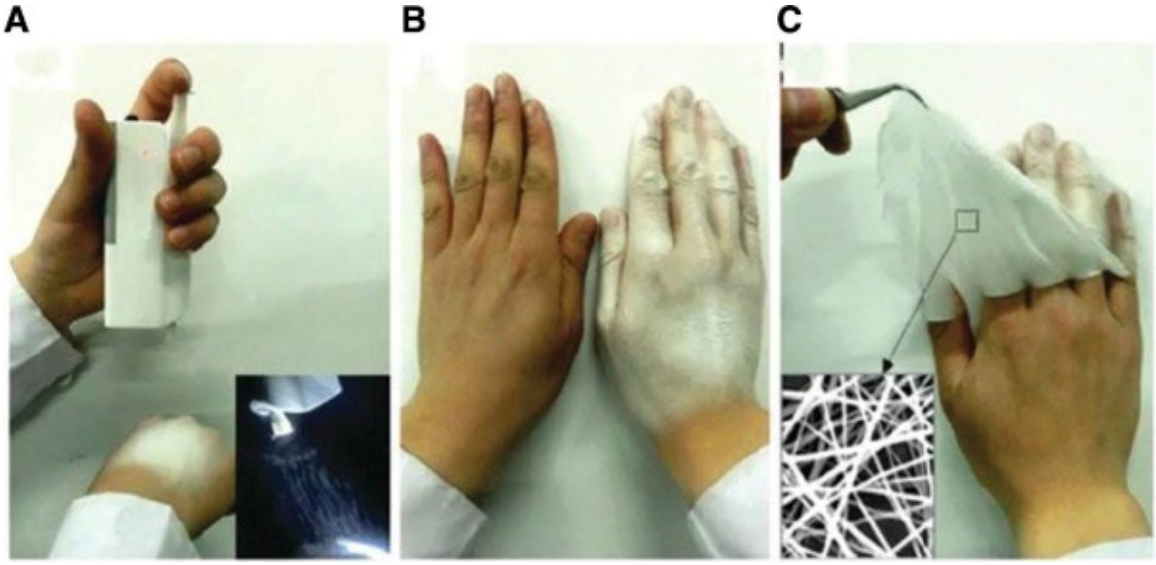

Figure 1: (A) Pla Fibers Electrospun by Portable Electrospinning Device on Hand; (B) The Final Appearance of a Homogenous Nd; (C) Removing the Nd with A Tweezer from Skin

1.1. Polymers For Nanofibers

There is no universal standard for the selection of the polymers applied for individual nanofibers, and the choice relies on the desirable function of the nanofibers. Different polymers with different molecules and sources will lead to notable differences on properties such as spinning solution viscosity, nanofibers morphology, mechanical strength, biocompatibility and physicochemical characteristics. A large number of polymers have been developed in the study of nanofibers utilized for DFU healing. They may be broadly classified into two categories: synthetic and natural polymers. In general, natural polymers have a better biocompatibility such as degradation and lower immune resistance, whereas the synthetic polymers possess an easier electrospinning with excellent mechanical strength such as flexibility and stiffness. To get the maximum benefits from those materials, taking the blending strategy is advisable. For example, chitosan and alginate with the addition of polyethylene oxide (PEO) or polyvinyl alcohol (PVA) has been fabricated into nanofibers [15].

Synthetic Polymers

The following synthetic polymers are found suitable:
Poly (lactic-co-glycolic acid) (PLGA), Poly (lactic acid) (PLA), Poly (ε-caprolactone) (PCL), Polyvinyl alcohol (PVA), Poly (ethylene oxide) (PEO) [16-41].

Natural Polymers

The natural polymers include the following:
Chitosan, Alginate, and Collagen [42-51].

2. Methods for Nanofiber Fabrication

Currently, the setup for nanofibers fabrication is relatively simple consisting of several components, such as micro pump, syringe, spinneret, voltage supply, electrode metal collector and polymer solution [52]. Two cartons representing the typical facilities used for the fabrication of nanofibers are shown as in the below, Fig. 2A exhibits the apparatus used for uniaxial electrospinning and Fig. 2B the coaxial electrospinning. The material attributes and process parameters, for example, the drug to polymer ratio, the solution viscosity, and the solution feed rate are crucial to the final function of the nanofibrous products. Each way of drug incorporation using respective polymers and nozzles needs individual material attributes and process parameters for a desired drug release profile including immediate release and controlled release [53, 54].

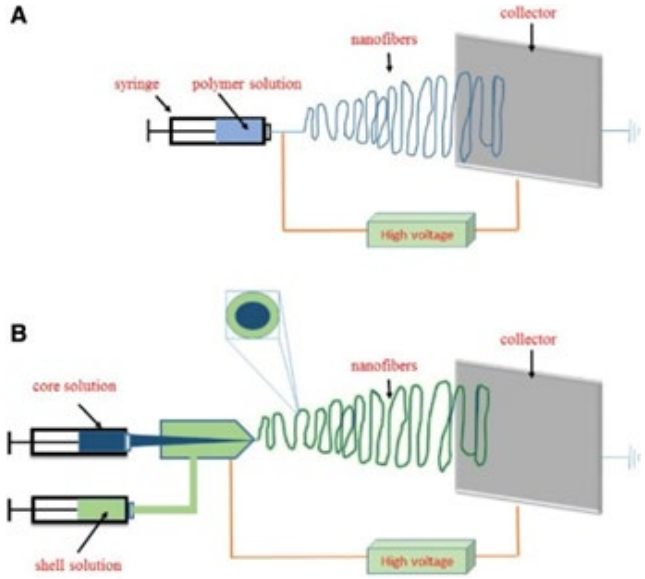

Figure 2: (A) Schematic Apparatus Used for the Uniaxial Electrospinning and (B) the Coaxial Electrospinning.

The following are the methods of spinning

- Uniaxial electrospinning
- Coaxial electrospinning

2.1. Further Perspectives

DFU imposes risks of amputation and economic lost on diabetic patients. Wound dressing is necessary in protecting and accelerating the wound closure. ND is an advanced technique with characters of thin diameters ranging from nanometers to micrometers, consequent capacities of oxygen penetration and ECM reconstruction are obtained. Furthermore, utilization of various polymers from natural and synthetic sources renders ND a better selection for diabetic wound closure compared with conventional dressing types. Additionally, bioactive small molecules, macromolecules, and cells can be loaded in the nanofibers to optimize the DFU recovery process. Proper selection of polymers and process parameters will fabricate desirable ND for DFU treatment. However, the rheological behavior that influences the physicochemical properties of nanofibers and the mathematical model for it in pharmaceutical cycle still has a big room for researchers to study and establish.

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