European Journal of Pharmaceutics and Biopharmaceutics 112 (2017) 1–17

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Review article

Recent advances in multiaxial electrospinning for drug delivery

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ARTICLE INFO

Article history:
Received 7 July 2016
Revised 6 September 2016
Accepted in revised form 1 November 2016
Available online 16 November 2016

Keywords:
Coaxial electrospinning
Multilayered fiber
Drug delivery
Scale up
Immune response
Modeling

ABSTRACT

Electrospun fibers have seen an insurgence in biomedical applications due to their unique characteristics. Coaxial and triaxial electrospinning techniques have added new impetus via fabrication of multilayered nano and micro-size fibers. These techniques offer the possibility of forming fibers with features such as blending, reinforced core, porous and hollow structure. The unique fabrication process can be used to tailor the mechanical properties, biological properties and release of various factors, which can potentially be useful in various controlled drug delivery applications. Harvesting these advantages, various polymers and their combinations have been explored in a number of drug delivery and tissue regeneration applications. New advances have shown the requirement of drug-polymer compatibility in addition to drug-solvent compatibility. We summarize recent findings using both hydrophilic and hydrophobic (or lipophilic) drugs in hydrophobic or hydrophilic polymers on release behavior. We also describe the fundamental forces involved during the electrospinning process providing insight to the factors to be considered to form fibers. Also, various modeling efforts on the drug release profiles are summarized. In addition new developments in the immune response to the electrospun fibers, and advances in scale-up issues needed for industrial size manufacturing.

Contents

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http://dx.doi.org/10.1016/j.ejpb.2016.11.010
0939-6411/

1. Introduction

Electrospinning is a fiber production method in which sub-micron fibers forming a matrix with interconnected pores are produced using a polymer jet with the use of electrical field [1]. Formals first patented electrospinning in the USA in 1934 [2]. The patent described the production of polymer filaments of cellulose acetate (CA) in ethylene glycol. In electrospinning, typical setup consists of a spinneret connected to a high electrical voltage (Fig. 1a), where the positively charged solution is pulled toward a collector plate by the effect of an electric field. An electric force is generated between two electrodes, with one connected to the nozzle ejecting the polymer solution, and the other connected to a conductive collector plate. Different types of collector plates such as rods and wheels are spun during the electrospinning process. The rotation speed of the collector plate determines the fiber alignment [3]. The charge build-up at the nozzle deforms the droplet into a conical structure referred to as a Taylor cone. The Taylor cone can be described as the shape of the drop of the polymer solution attached to an orifice by the effect of surface tension and viscoelastic stresses before the jet is issued [4]. Applied electrical force counteracts on the surface tension of the polymer solution, and the polymer jet ejects from the apex of the cone termed as the Taylor cone (Fig. 1b). Ejected polymer jet vacillates due to whipping from bending instabilities introduced by repulsive charges present along the jet length. Finally, the jet stretching stops when the solvent evaporates from the surface of the jet, resulting in the thinning of the fiber [5]. For successful electrospinning, formation of a stable Taylor cone is necessary, which will lead to the deformation of the jet into continuous uniform fibers with narrow distributions [6].

From 1934 to 1971, many patents were issued that were related to improving the setup for production of polymer filaments [5,7–9]. After few decades, the electrospinning has regained significant attention due to a surge of interest in nanofiber technology [10]. Electrospinning of biomaterials has given promise for generating fibers with characteristics mimicking various microenvironments in the body. Only electrospinning technique can produce fibers with diameters less than 100 nm fibers, unlike traditional fiber forming methods such as melt, dry, and wet spinning. Size and internal structure of fibers can be controlled by varying process and or system parameters [11], which have been extensively reviewed in literature [12]. Fibrous structures also offer a spatiotemporal configuration and sequestration of growth factors similar to *in vivo* conditions in addition to high surface to volume ratio. Cells attach to a substrate using specific sequence of amino acids and incorporating proteins possessing such domains into the fibers promotes cell attachment [13]. Effect of fiber characteristics on cellular interactions has been discussed in many reviews [14], and the readers could refer to those reviews.

The major advancement in electrospinning in 2003 was when coaxial electrospinning was introduced [15], where two concentric layers are formed with necessary features (Fig. 2) when fiber cross sections are analyzed. The unique advantage of coaxial electrospinning is the ability to sequester stimulants in various compartments and modulate the release kinetics by altering the fiber thickness and localization. For example, one could add only the needed therapeutic agents in the inner core. Also, one could modulate the mechanical and biological properties or add a third layer to form triaxial fibers. This new modification gained considerable attention in drug delivery applications and many biomedical applications [16]. Further, co-axial electrospinning technique resolves the limitations in the traditional drug delivery methods. This review discusses the recent advances on the characteristics and modeling of drug release from multiaxial electrospun fibers in drug delivery and tissue regeneration applications. For example, nanotopographies, fiber size, and fiber orientation influence the activation of the immune system, similar to stem cell differentiation. Our primary focus is drug delivery using coaxial fibers and modeling efforts.

2. Uses of electrospinning in biomedical applications

Encapsulating the drug in the fiber core provides protection and prolonged drug release [17]. Controlled drug delivery allows the release of therapeutic agent loaded electrospun fibers at a controlled rate and timely manner to avoid undesired side effects and high doses of the drug. In electrospinning, successful drug encapsulation is dependent on ensuring the distribution of the drug molecule into the electrospun fiber. Drug characteristics such as stability and solubility, as well as the morphology of the fibers, could significantly affect drug encapsulation efficiency [18]. Therefore, different electrospun fibers with differing types of structures have been investigated in controlled drug-delivery systems [19,20], and have been developed for generating fibers capable of encapsulating functional molecules or therapeutic compounds. These also offer protection to the therapeutic agent from the surrounding environment [21,22]. Drugs can be physically absorbed by fibers (surface immobilization), or directly loaded into polymer solution before electrospinning [23]. Another required feature of controlling drug delivery is to maintain the blood level of the drug between the toxic concentration and minimum threshold concentration for an extended period. This process helps in avoiding the toxicity that could occur at high blood drug level and preventing the drug from depleting in the blood in a short time [24]. Electrospun medicated fibers with the multilayered structure using a coaxial/triaxial fluid process (Fig. 2) provide altered release time profiles based on loading location and distribution of the drug in the fibers [25]. The idea of controlled drug delivery is to deliver a well-controlled amount of drug for an adequate period to a target site in the body [26].

Using these fibrous matrices as templates for regeneration has also been attractive, based on the concept of using biodegradable templates to develop functional substitutes that restore, improve or repair damaged tissues and/or organs [27]. The scaffold is formed into the shape of tissue that needs to be substituted, and substrate directly interacts with cells and stimulants presents in the surrounding medium to regenerate the tissue. Thus, one challenge is an ability to fabricate biodegradable and biocompatible polymeric materials that mimic the extracellular matrix with mechanical properties similar to the native tissue with appropriate degradation rate, so it degrades as the cells grow on the scaffold [28]. Coaxial or multiaxial fibers can be obtained using multiple polymers and/or blends of natural and synthetic polymers possessing appropriate chemical, biological and mechanical properties functional groups needed for the regeneration of specific target tissues with controlled dimension and arrangement [29–31]. The core-sheath structural scaffold has been developed to improve