Materials Science and Engineering C 45 (2014) 659–670

Contents lists available at ScienceDirect

Materials Science and Engineering C

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

Biodegradable polymers for electrospinning: Towards biomedical applications

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ARTICLE INFO

Article history:
Received 22 January 2014
Received in revised form 2 April 2014
Accepted 21 April 2014
Available online 28 April 2014

Keywords:
Electrospun nanofibers
Biodegradable polyesters
Tissue engineering
Drug delivery
Biosensors

ABSTRACT

Electrospinning has received much attention recently due to the growing interest in nano-technologies and the unique material properties. This review focuses on recent progress in applying electrospinning technique in production of biodegradable nanofibers to the emerging field of biomedical. It first introduces the basic theory and parameters of nanofibers fabrication, with focus on factors affecting the morphology and fiber diameter of biodegradable nanofibers. Next, commonly electrospun biodegradable nanofibers are discussed, and the comparison of the degradation rate of nanoscale materials with macroscale materials are highlighted. The article also assesses the recent advancement of biodegradable nanofibers in different biomedical applications, including tissue engineering, drug delivery, biosensor and immunoassay. Future perspectives of biodegradable nanofibers are discussed in the last section, which emphasizes on the innovation and development in electrospinning of hydrogels nanofibers, pore size control and scale-up productions.

1. Introduction

Electrospinning was first being introduced in early 1930s for fabrication of nanofibers as filter materials and textile yarns. Since 1990s, after Reneker et al. demonstrated the feasibility to produce electrospun nanofibers from many polymers, the number of publications about electrospinning has grown exponentially [1,2].

Electrospinning received much attention for biomedical applications mainly due to the growing interest in nano-technologies and the unique material properties. Electrospinning is an inexpensive and simple method to create nanoscale polymer fibers with diameter range from 3–5000 nm [3]. Nanofibers are suitable to mimic biological environment because they are in the same scale as biological molecules. In fact, nanomaterials like particles, fibrous morphologies or other complex forms, have shown improved interactions with cells, for example, selective endocytosis, adhesion and orientation [4–6]. In addition, large surface area to volume ratio (SVR) of these structures provides the nanofibrous mat high pore volumes with different pore sizes. These pores facilitate the loading of bioactive molecules and transportation of nutrients and waste. These outstanding properties enable the polymer nanofibers become an important class of biomaterial.

To date, over 100 types of natural and synthetic polymers were electrospun into nanofibers [7]. Popular materials includes: collagen, elastin, fibrinogen, alginates, polyesters, polyurethanes and their blends etc [8]. Nanofibers that are biodegradable and biocompatible have advantages in a few aspects: they metabolize into biocompatible degradation products in human body; therefore, second surgery for implant removal is unnecessary. Degradation profile of the nanofibers is tunable to match with the tissue regeneration time frame. Ideally nanofibers should degrade at the same pace as new tissue grows. Although degradation of polymers *in vitro* and *in vivo* is comprehensively studied, the degradation mechanisms of polymer nanofibers are still under-explored.

Based on relevant US patents filed in recent years, most of the applications nanofibers are in the field of biomedical prosthesis predominantly blood vessels and grafts. Specifically, biodegradable polymer nanofibers showed promising perspective in cosmetic, life science and tissue engineering scaffolds, in laboratory scale. More efforts are expected in future to scale-up these nanofibers into industrials scale.

In this review, we report brief theory and parameters of electrospinning process, types of biodegradable nanofibers and assess recent advancement of biodegradable nanofibers in different biomedical applications.

2. Fabrication of electrospun biodegradable nanofibers

2.1. Theory and parameters of electrospinning

Electrospinning is attractive thanks to the simplicity and inexpensive nature of setup. The basic setup for electrospinning is shown in

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http://dx.doi.org/10.1016/j.msec.2014.04.051
0928-4931/

Fig. 1(a) [9]. There are 3 elementary components to complete the process: a capillary tube as a reservoir for polymer solution, a high-voltage power supply, and a metallic collector. During the spinning process, high voltage (5–15 kV) is applied between a needle capillary end and a collector. The polymer solution is electrically charged. At the needle tip, the polymer solution deforms from a spherical pendant droplet to a conical shape, known as "Taylor cone". As the electric field is stronger than the surface tension of the polymer solution, the jet is ejected from the cone surface. As the jet travels, the solvent evaporates in the air, together with the stretching and acceleration of the polymer jet, leading to the extreme thin polymer fibers deposition on the collector [10]. Electrical bending instability occurs when the distance from the tip to collector is sufficiently long; in case of a short distance, the jet is typically straight. Fig. 1(b) shows the instability of polymer jet captured by high speed video [11]. Under the action of electric field, polymer jets experience the bending instability primarily due to mutual repulsion of the excess electric charges carried by electrospun jets.

The electrospinning process and the formation of polymer fibers are affected by many parameters. Spinnability, fiber diameters, fiber uniformity, fiber alignment, defects control (e.g. beads, junctions, and pores), and other properties are tunable by changing these parameters, (1) substrate-related parameters (polymer concentration, viscosity, molecular weight, surface tension); and (2) apparatus-related parameters (flow rate and electric field).

2.1.1. Substrate-related parameters

Most studies agreed that polymer viscosity the main determinants of fiber diameter and morphology. Increased viscosity due to high polymer molar mass or concentration can result in larger fiber diameters [2,12]. And also, beading is less likely to form, and more uniform fiber structures are observed [13,14].The relationship between polymer concentration and fiber diameter and morphology of biodegradable polymers including poly (DL-lactide-co-glycolide) (PLGA) (50:50), poly(DL-lactic acid) (PDLA), poly(L-lactide) (PLLA), gelatin, and dextran were reported in recent studies [9,13–17]. However, if the viscosity is too high, the flow of the polymer solution may be hindered and the droplet dries at the tip. On the other hand, if the viscosity is too low, fiber jet may break into droplets due to the lack of chain entanglement. For example, when the concentration of PLGA in (THF + DMF) was 0.10 g/mL or less, beads and droplets were obtained instead of nanofibers [9]. Ki et al. studied the gelatin nanofibers. In the range of polymer concentration of 8–12 wt. %, fiber diameter is exponentially increased with increasing polymer concentration. In other words, the change of fiber diameter vs. polymer concentration is nonliner. Uniform and beads-free gelatin fibers (76–169 nm) were obtained [16].

Polymer molar mass affects viscosity of polymer solution. Typically, low molar mass polymers lead to bead formation, while high molar mass polymers form fibers with larger diameters [10]. In addition, "electrospraying" happens instead of "electrospinning" when low molar mass polymers are used. Electrospraying results in small droplets due to instable jet formation. The spinnability of the polymer depends on the onset of chain entanglement between polymer chains, and it is varied for different polymers. For example, chitosan in acetic acid solution, with low molar mass of 30 kDa, it formed fragile fibers with many beads; with medium molar mass of 106 kDa, beads-free, uniform and continuous fibers (130 nm) were obtained [18].

The effect of surface tension of polymer solution on size or morphology of nanofibers is controversial. It depends on different polymer and solvent systems. Doshi and Reneker reported that by reducing surface tension of the polymer solution, beads-free fibers can be obtained. Zuo et al. reported the fiber morphologies of poly(hydroxybutyrate-co-valerate) (PHBV) in different solvent systems [19]. Smooth fibers were obtained when the surface tension of the solvent is lowered by adding alcohol. However, a lower surface tension is not always suitable for electrospinning. For example, acetone and dimethyacetamide (DMAc) have surface tension of 23.7 and 32.4 dyne/cm, respectively. Liu and Hsieh studied electrospinning of cellulose acetate and reported that using neither acetone nor DMAc alone can produce fiber free of beads. Only using a mixture of acetone and DMAc, beads-free fibers are obtained [20].

2.1.2. Apparatus-related parameters

Lower feeding rate (also known as flow rate of the polymer solution) leads to smaller diameter of the fibers [13]. On the other hand, high feeding rate results in more beads formation. Based on the results reported by Zuo et al., as the feeding rate increases, more solution is ejected from the needle tip [19]. The drying and evaporation of the solvent is less effective before the fiber reached the collector.

An increased in applied electric field typically resulted in reduced fiber diameter due to more stretching of the polymer solution. For PLGA, increase in voltage (from 0.375–1.0 kV/cm) resulted in significant reduction in fiber diameter, then the change of diameter was not significant when the voltage is further increased [9]. In addition, increasing applied voltage typically leads to more beads formation, for example in PDLA [14], chitosan [18] and gelatin [16]. However, for PHBV, higher voltage leads to formation of beads-free PHBV fibers [19].

2.2. Biodegradable polymers for electrospinning (synthetic/natural/blends)

The success of electrospun nanofibers that based on a wide range of biodegradable and biocompatible materials has been reported in recent reviews [21,22], including natural proteins such as collagen, gelatin, silk, chitosan and alginate; synthetic polymers such as polyglycolide (PGA), poly(ε-caprolactone) (PCL), PLA and their copolymers P(LLA-CL) and PLGA that have been approved by FDA for clinical use; and their blends [8]. Fig. 2 displays the biological, mechanical and physiochemical

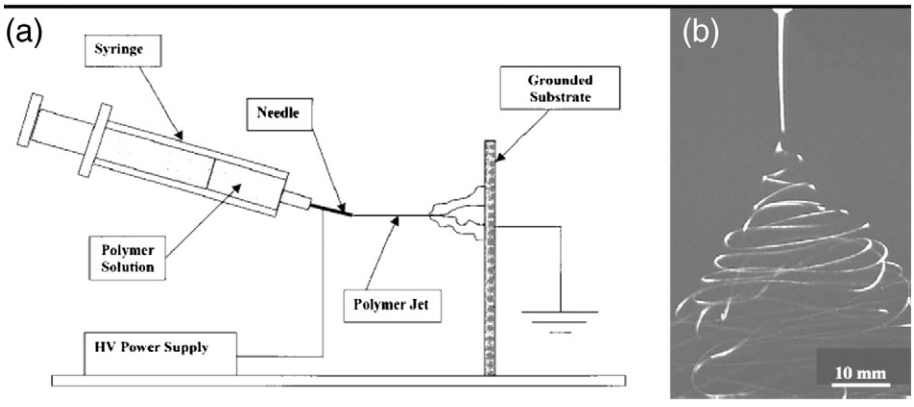

Fig. 1. (a) Schematic drawing of elementary setup for electrospinning. (Reprinted with permission from John Wiley and Sons [9]) (b) Typical bending instability of the jet during electrospinning captured by high speed video. (Reprinted with permission from Elsevier [11]).