International Journal of Pharmaceutics 523 (2017) 441–453

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Current advances in electrospun gelatin-based scaffolds for tissue engineering applications

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ARTICLE INFO

Article history:
Received 11 July 2016
Received in revised form 2 September 2016
Accepted 13 September 2016
Available online 15 September 2016

Keywords:
Gelatin
Electrospun scaffolds
Tissue engineering
Biopolymers

ABSTRACT

The development of biomimetic highly-porous scaffolds is essential for successful tissue engineering. Electrospun nanofibers are highly versatile platforms for a broad range of applications in different research areas. In the biomedical field, micro/nanoscale fibrous structures have gained great interest for wound dressings, drug delivery systems, soft and hard-tissue engineering scaffolds, enzyme immobilization, among other healthcare applications. In this mini-review, electrospun gelatin-based scaffolds for a variety of tissue engineering applications, such as bone, cartilage, skin, nerve, and ocular and vascular tissue engineering, are reviewed and discussed. Gelatin blends with natural or synthetic polymers exhibit physicochemical, biomechanical, and biocompatibility properties very attractive for scaffolding. Current advances and challenges on this research field are presented.

1. Introduction

Electrospun nanofibers are highly versatile platforms for a broad range of applications in different areas such as catalysis, nanofluidics, sensors, medicine, energy, environmental engineering, biotechnology, defense and security, and healthcare (Agarwal et al., 2013). In the biomedical field, micro/nanoscale fibrous structures have gained much interest for wound dressings, drug delivery systems, soft and hard-tissue engineering scaffolds, enzyme immobilization, among other healthcare applications (Abrigo et al., 2014; Ravichandran et al., 2012). Tissue engineering approaches usually require fabrication of engineered scaffolds, which aid in the repair and regeneration processes of the damaged tissue. The extracellular matrix (ECM) is composed of proteins and polysaccharides, mainly collagen, hyaluronic acid, proteoglycans, glycosaminoglycans (GAGs), and elastin. This complex mixture provides mechanical and biochemical support to surrounding cells and directs and modulates their behavior. Thus, the creation of biomimetic and functionalized scaffolds as bioactive ECM analogues is essential to construct an *in vivo*-like microenvironment that mimics biological entities and triggers specific cell responses (Agarwal et al., 2009; Sell et al., 2010; Wang et al., 2013a,b; Pelipenko et al., 2015) Controllable fibrous structures with various compositions, fiber dimensions, and fiber architectures emulating the native ECM can be obtained by electrospinning technology. Mechanical, chemical, and biological properties of electrospun materials can also be tailored to replicate the many roles of native ECM (Sell et al., 2007).

Polymeric electrospun scaffolds provide a transitional three-dimensional support for cell adhesion, migration, proliferation, and differentiation. Moreover, the scaffolds should guide the maturation and tissue formation through a complex mechanical and biochemical signaling process. A number of natural and synthetic polymers have been considered to develop tissue engineered scaffolds (Ma, 2004). Nowadays, there is renewed interest in producing biodegradable scaffolds using biopolymers, including carbohydrate and protein-based biomaterials from both animal and plant origin (Sridhar et al., 2015). Biopolymers offer many advantages such as chemical cues, hydrophilicity, degradation properties, and biocompatibility making them key players in modulating cell behavior. Thus, some naturally occurring polymers, such as collagen, gelatin, elastin, fibrinogen, and laminin contain integrins with binding affinity for cell-surface receptors that initiate cell adhesion. Among the main disadvantages are the weak mechanical properties, rapid biodegradability, and processability issues. Composite nanofibrous scaffolds composed of polymer blends combine the highly favorable and desired biological characteristics of natural polymers and the mechanical performance (*i.e.*, strength and durability) of the synthetic ones. Thus, polymer mixtures can provide a straightforward pathway to design polymer-based scaffolds with different and superior bioactivities. The development of an ECM analogue is highly

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http://dx.doi.org/10.1016/j.ijpharm.2016.09.044
0378-5173/

challenging, and can be possible through the manipulation of natural polymers (Sell et al., 2010).

In this context, gelatin blends with natural or synthetic polymers exhibit physicochemical, biomechanical and biocompatibility properties which are very attractive for scaffolding. This mini-review is focused on electrospun gelatin-based matrices as tissue engineering scaffolds. First, a short description of the electrospinning process is included for those readers not acquainted with the technique. Then, gelatin properties are briefly described. Finally, the review deals with selected biomedical applications of electrospun gelatin-based scaffolds, such as bone, cartilage, skin, nerve, ocular and vascular tissue engineering. A vision of the future research on this topic is then presented.

2. Electrospinning process

Electrospinning or electrostatic spinning is a very attractive electrohydrodynamic technique for processing polymer solutions or melts in the form of micro/nanofibrous non-woven scaffolds. When a polymer solution or melt is subjected to a high-voltage, the surface of a pending drop held by its own surface tension forces is electrostatically charged. Once the electric field established between a spinneret tip and a grounded collector reaches a certain threshold value, the electrostatic forces overcome the surface tension of the solution and produce a microjet from the pendant drop. Before reaching the collector, the liquid jet undergoes stretching and whipping while the solvent evaporates during the process. The micro/nanofibers produced by electrospinning lead to the formation of non-woven mats of either randomly-oriented or aligned fibers (Bhardwaj and Kundu, 2010).

Although many authors refer to electrospinning as a simple technique, the process is complex, and it is governed by a number of parameters that greatly affect fiber formation, size, and morphology. The intrinsic solution properties (polymer structure, molecular weight, concentration, solvent/co-solvent type, viscosity, conductivity, and surface tension), the processing parameters (applied voltage, polymer solution flow rate, nozzle-to-collector distance, position, nozzle diameter and number, collector geometry and type, and collector polarity), and the ambient parameters (temperature, humidity, pressure and air velocity) strongly determine the quality and characteristics of the electrospun fibers and the resulting mats. Therefore, the electrospinning process is not as simple as it appears. In order to produce defect-free continuous fibers with reproducible fiber diameter distribution and orientation these parameters must be accurately controlled. Detailed explanations of each parameter and its influence on the electrospinning process can be found in the literature (Pham et al., 2006; Bhardwaj and Kundu, 2010).

A huge variety of biocompatible synthetic polymers, natural polymers, or blends of both can be electrospun, each one with different physical properties, mechanical performance, biodegradation rate, and cell-material interactions. Table 1 summarizes some of the polymers most commonly used in electrospinning for tissue engineering applications. Many other polymers were electrospun to satisfy different clinical requirements. Polyphosphazenes, polyethyleneimine, poly(propylene carbonate), polydioxanone, poly(glycerol-sebacate), and polyhydroxyalkanoates, are just some examples of the wide range of polymers investigated. Nanofibers can be functionalized through encapsulation, grafting, immobilization, coating, or blending of biologically active compounds such as proteins, enzymes, and growth factors (Zamani et al., 2013; He et al., 2014; Sridhar et al., 2015). Moreover, nanofibers can be assembled into a variety of arrays or architectures by manipulating their alignment, stacking, or folding (Li et al., 2014). In the last years, the production of advanced nanofibrous scaffolds includes multilayer mats, core/shell structures, compositional gradients, nanocomposite or drug-loaded nanofibers, structured with superior mechanical properties or with enlarged pores for regenerative engineering. All of these have attracted significant research interest and have demonstrated superiority over traditional nanofibrous scaffolds (Jiang et al., 2015).

Table 1
Synthetic and natural polymers and their properties for tissue engineering.

Polymers	Surface properties		Integrin binding	Biodegradability		Mechanical performance	
	Hydrophobic	Hydrophilic		Hydrolytic	Enzymatic	Good	Poor
Synthetic							
PGA	x			x		x	
PLLA	x			x		x	
PLGA	x			x		x	
PCL	x			x		x	
SPEU	x	x		x		x	
PVA		x		x			x
PEO		x		x			x
PVP		x		x			x
Natural							
Collagen		x	x		x		x
Gelatin		x	x	x	x	x	
Silk fibroin		x			x	x	
Fibrinogen		x	x		x	x	
Elastin		x	x		x		x
Laminin		x	x		x		x
Soy protein		x	x		x		x
Chitosan		x			x	x	
Alginate		x			x		x
Hyaluronic acid		x			x		x
Cellulose acetate		x		x		x	
Starch		x			x		x

PGA: poly(glycolide); PLLA: poly(lactic acid), PLGA: poly(lactide-*co*-glycolide); PEO: poly(ethylene oxide); PVA: poly(vinyl alcohol); PCL: poly(caprolactone); SPEU: segmented poly(esterurethane), PVP: poly(vinylpyrrolidone).