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Polyester based nerve guidance conduit design

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ABSTRACT

Nerve conduits containing highly aligned architecture that mimics native tissues are essential for efficient regeneration of nerve injuries. In this study, a biodegradable nerve conduit was constructed by converting a porous micropatterned film (PHBV–P(L-D,L)LA–PLGA) into a tube wrapping aligned electrospun fibers (PHBV–PLGA). The polymers were chosen so that the protective tube would erode slower than the fibrous core to achieve complete healing before the tube eroded. The pattern dimensions and the porosity (58.95 (%) with a maximum pore size of 4–5 μm) demonstrated that the micropatterned film would enable the migration, alignment and survival of native cells for proper regeneration. This film had sufficiently high mechanical properties (ultimate tensile strength: 3.13 MPa, Young's Modulus: 0.08 MPa) to serve as a nerve guide. Electrospun fibers, the inner part of the tubular construct, were well aligned with a fiber diameter of ca. 1.5 μm. Fiber properties were especially influenced by polymer concentration. SEM showed that the fibers were aligned parallel to the groove axis of the micropatterned film within the tube as planned considering the nerve tissue architecture. This two component nerve conduit appears to have the right organization for testing in vitro and in vivo nerve tissue engineering studies.

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1. Introduction

Nerve damage could result from mechanical, thermal, chemical, or ischemic factors and could lead to the disruption of the communications between neurons and their supporting cells [1]. The annual incidence of spinal cord injury in the USA is approximately 12,000 [2] and five percent of all open wounds in the extremities caused by accidents are complicated by peripheral nerve trauma [3]. Self regeneration of nervous tissue is difficult in severe damages of peripheral nervous system (PNS) and almost impossible in central nervous system (CNS) [4,5]. In PNS injuries end-to-end anastomosis is a commonly used technique for small gaps to bridge the severed nerve ends via suturing [6]; however, it becomes difficult for long nerve gaps without applying any tension [7]. In such cases the most widely used technique is the use of autologous nerve grafts, grafting of a nerve segment removed from another part of the patient's body. Despite successful results these autologous grafts have inherent disadvantages, such as limited supply, permanent loss of the nerve function at the donor site and need for multiple surgeries [8,9].

Development of alternative treatments, especially for larger defects, is necessary to bridge the gap between the proximal and the distal nerve stumps. Biological or synthetic tubular nerve constructs with highly aligned architecture mimicking the native tissue could provide the bridge needed for nerve regeneration [10–13]. Directional axonal elongation is mainly based on the interactions between regenerating axons and the adjacent substratum [14]. Incorporation of some special micro and nano-architectures that allow structural support for axonal regrowth and affect cellular orientation is a promising strategy in nerve conduit design [15]. The performance of the nerve guides may be improved by the use of desired surface texture, longitudinally-oriented microchannels or polymer fibers [16]. The most common technique to produce patterned surfaces with controlled dimensions and specific shapes is microfabrication [17], by the use of photolithography which can be followed by micromachining, etching or deposition [18]. When the native neuron orientation and migration along the anisotropic direction is taken into account patterned substrates with channels appear to be more suitable for the control

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of neural cell orientation [19–22]. Fibrillar scaffolds, on the other hand, are generated by pressure-assisted microsyringe, self assembly, and electrospinning techniques. Use of uniaxially oriented, biodegradable electrospun fibrous mats is a promising approach to the restoration of the damaged nerve because it mimics the native architecture of the nerve tissue, and directional cell growth is a prerequisite for functional nerve regeneration.

Ideally, the nerve conduit should be porous to allow and control nutrient exchange and biodegradable to eliminate the need for its removal [23]. In this regard the choice of the construct material becomes an important point. Extensively used synthetic polymers, including polylactic acid (PLA) [24] and poly(D,L-lactide-co-glycolide) (PLGA) [25] are known for their ease of processing, low inflammatory response, and approval by the U.S. Food and Drug Administration. Naturally derived poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) is a degradable and biocompatible polymer of natural origin used in the design of implants. Its degradation products, 3-hydroxybutyric acid, which is a normal constituent of blood [26], and 3-hydroxyvaleric acid, are not known to lead to any long term tissue reaction at the implantation site.

In the present study, a polyester based, biodegradable, porous nerve guidance conduit was constructed. The conduit was designed for eventual use in the regeneration of nerves across long nerve gaps. The construct was composed of two parts; an aligned, electrospun mat of PHBV and PLGA serving as the inner component and a porous, micropatterned film of PHBV, poly(L-lactide-co-D,L-lactide) (P(L-D,L)LA) and PLGA as the tubular, outer part designed to wrap around the electrospun mat. The surface topography and macroscopic characteristics of the porous micropatterned films and the aligned electrospun mats were examined with scanning electron microscopy (SEM). The mechanical properties of the film showed that it is not rigid and could be sutured. The erosion rate of the fibrous mat and the micropatterned film was studied. In this study, the biodegradability of the polymers, the porosity of the film, and the channels for physical guidance satisfy the requirements for an ideal nerve conduit. In addition, the use of two different topographical cues, electrospun fibers and micropatterned films, in a single design is expected to maximize the influence of the guidance cues. Thus, the construct prepared in this study could be considered for use as a conduit in nerve regeneration and in the repair of gaps longer than a few centimeters by promoting the alignment of neurons and supporting cells.

2. Materials and methods

2.1. Preparation of polymeric films

Micropatterned (MP) silicon (Si) templates with perpendicular walls were produced by photolithography and subsequent reactive ion etching (kindly provided by Prof. A. Aydınlı and A. Kocabas, Bilkent University). A negative polydimethyl siloxane (PDMS) replica, obtained by using PDMS prepolymer–catalyst mixture (Sylgard 184 Elastomer Kit, Dow Corning, U.S.A), served as the template to prepare the micropatterned polymeric film via solvent casting. A PHBV (5% by mole of 3-hydroxyvalerate, Fw: 222.2 g/mol, Aldrich, UK), P(L-D,L)LA (70:30, Inherent Viscosity: 5.5–6.5 dL/g, AppliChem, Germany) and PLGA (50:50, Inherent Viscosity:

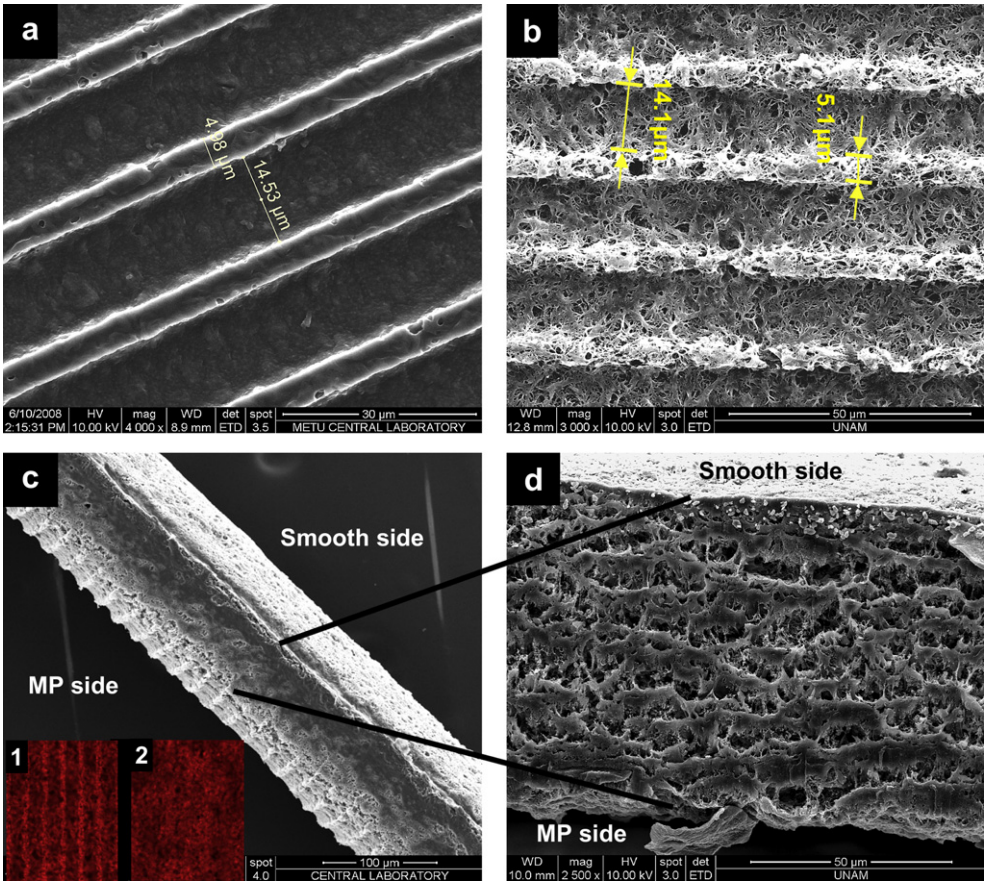

Fig. 1. Scanning electron micrographs of micropatterned polymeric films obtained from the PDMS replica of the Si template. (a) Nonporous micropatterned PHBV–P(L-D,L)LA (1:1, w/w) film, (b) porous micropatterned PHBV–P(L-D,L)LA–PLGA (2:2:1, w/w) film. (c–d) Cross-sections of porous micropatterned films ((d) at higher magnification). In (c) one side of the film (left) is micropatterned (MP) bottom, and the other side (right) is smooth top. Insets of (c) confocal micrographs of porous micropatterned film stained with Nile Red, inset 1 is the image of the surface, and inset 2 is the image of the bulk just beneath the surface (ca. 10 µm deep).

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