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The influence of cross-sectional morphology on the compressive resistance of polymeric nerve conduits

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ABSTRACT

Artificial nerve conduits are proposed as an alternative to repair peripheral nerves injuries; while mechanical properties are of great importance for successful clinical application of nerve conduits. In this work, the poly (D,L-lactide-*co*-glycolide) (PLGA) nerve conduits were fabricated by the dry-jet wet spinning, and the compressive resistance of nerve conduits was systematically measured. It was found that the compressive resistance of nerve conduits significantly increased with the PLGA concentration of dope fluids. A numerical model was developed to simulate the compression tests of nerve conduits; where the hyperelastic–plastic constitutive law and the morphological characters of the cross sections of nerve conduits were implemented. The numerical results indicated the layered morphology of the cross sections of nerve conduits played the most important role in determining the compressive resistance. In addition, the accuracy of the numerical model was well validated by good agreement of experimental and numerical results of nerve conduit compression tests. This study helps understanding how to characterize the compressive resistance of porous polymeric nerve conduits and how the morphology influences the compressive resistance, leading to better design of fabrication setup and material selection for nerve conduits.

1. Introduction

Peripheral nerves injuries caused by traumatic lesions, tumor extirpation or other mechanical/chemical reasons remain a challenging healthy problem all over the world. Using artificial nerve conduits is proposed as a potential approach to repair nerve injuries, showing the promising results compared to other clinical intervenes due to advantages as reducing neuroma and scar formation, reduction in collateral sprouting, facilitating the accumulation of neurotrophic factors [1], and minimizing the negative interaction between myofibroblasts and axon [2]. During nerve regeneration, nerve conduits serve as the initial three-dimensional (3D) physical support, i.e. hosting nerve cell populations, maintaining cell proliferation and differentiation, and transmitting mechanical stress; therefore, nerve conduits have to meet the requirements as adequate geometry, pore morphology, and mechanical properties, in order to temporarily perform the function of substitute extracellular matrix (ECM) components [3].

Currently, the mechanical properties of nerve conduits have drawn massive attention to scientists for how they influence the application of nerve conduits. First, the nerve conduits should be physically robust enough for clinical operation, such as sutures to proximal and distal nerve segments during in vivo implantation [4]; and stiff enough to resist in vivo physiological invasion and avoid channel collapse [5,6]. It even has been quantified that a minimum Young's modulus of 1200 kPa is required for the structural integrity of the nerve conduit to be maintained for in vivo clinical application [7]. However, the nerve conduits manufactured using polymers, i.e. poly (lactic-*co*-glycolic acid) (PLGA) [8] and

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polycaprolactone (PCL) [9], usually suffer from the lack of the physical robustness [4]. Thus, the precise regulation and characterization of the mechanical properties for polymeric nerve conduits is an essential step for their successful application. In addition, the polymeric nerve conduits are generally manufactured with porous wall [10–13] to facilitate nutrients, oxygen and metabolites transport and exchange with the surrounding environment. While, the experimental investigations have demonstrated the porosity significantly affects the mechanical properties of polymeric nerve conduits [14] and other polymeric hollow fiber membranes [15,16]. Therefore, the understanding of how the porosity and pore size influence the mechanical properties of nerve conduits and how to characterize the mechanical properties of porous polymeric nerve conduits is of great importance for the design of nerve conduit fabrication conditions and material selection.

The characterizations for the mechanical properties of nerve conduits in previous studies mainly include uniaxial stretching, three-point bending, and compression tests [5,14,17–19]. While according to the application conditions, the capability to resist compression is more crucial than other mechanical properties for the successful application of nerve conduits in the surgery. The nerve conduits not only have to be flexible enough to resist the deformation and kinking [14], but also need to maintain a certain strength level to protect the invasion by the surrounding tissues, since the chronic compression can result in damage to the nerve [20]. Therefore, the compressive resistance of nerve conduits has to be carefully measured, and the relation between porosity and compressive resistance of polymeric nerve conduits needs to be systematically interpreted.

Several finite element models have been established to investigate the mechanical behaviors of porous membranes [21–24]. Although, the models simulated the deformation of three dimensional (3D) planar membranes embedded with microspherical or microcylindrical pores, these models can neither be used to predict the influence of pore interaction, nor be applied to study the mechanical properties of hollow fiber membranes with asymmetric pore distribution. Thus, a sophisticated numerical model has to be established to describe the complex mechanical behavior of polymeric nerve conduits, such as compression.

In this work, the PLGA nerve conduits were fabricated using the dry-jet wet spinning method, and the compressive resistance of nerve conduits was measured. Then, a numerical model of porous polymeric nerve conduits was developed, which can take into account the morphological information of both macroscopic and microscopic structure of nerve conduits. The macroscopic structure of nerve conduit includes the inner/outer diameters; while the microscopic structure mainly is the porosity, pore size and distribution. The numerical study would help understanding the mechanism of how porous structure of nerve conduits controls their mechanical properties, and the goal of this study is to provide the characterization and prediction of compressive resistance of nerve conduits for further optimization of nerve conduit fabrication technology.

2. Nerve conduit fabrication and mechanical test

2.1. Fabrication of PLGA nerve conduits

Poly (D,L-lactide-*co*-glycolide) (PLGA) copolymer (50/50 D,L-lactide/glycolide, Mw = 60 kDa, and intrinsic viscosity = 0.57 dL/g; Shandong Institute of Medical Instruments. Jinan, Shandong, China) was used as the polymer material. Dimethyl sulfoxide (DMSO, purity ≥ 99.0%) purchased from Sinopharm Chemical Reagent Co. Ltd, was used as the solvent without further purification. The predetermined amount of PLGA were firstly dried under room temperature for 12 h and then dissolved in DMSO under room temperature for 24 h with continuous stirring to prepare the dope fluid. The PLGA dope fluid was kept standing for 4 h to remove the air bubble before spinning. Deionized water was used as bore fluid and external coagulant in the spinning process.

The PLGA nerve conduits were fabricated by dry-jet wet spinning method with an air gap of 2 cm as shown in Fig. 1. The flow rates of dope and bore fluids were controlled by two pumps (Harvard Apparatus, and Longer Pumps) with Hamilton Syringes (Hamilton, Switzerland). The nascent hollow fiber membranes were pumped into the coagulation bath without further drawing stretch (free fall). The spinning process was carried out under room temperature. After spinning process, the nascent hollow fiber membranes were kept in the water for 24 h to remove the residual DMSO. The detailed fabrication conditions are listed in Table 1.

2.2. SEM observation of morphology

The morphology of PLGA nerve conduits was observed and imaged by a scanning electron microscope (SEM, Hitachi SU-8010, Hitachi). In order to obtain the clean cross section of nerve conduits, the PLGA nerve conduits were fractured after freezing in the liquid nitrogen for 60 s to get a brittle fracture. Then, the samples were sputtered with gold vapor for 50 s. Finally, the morphology of the cross section of PLGA nerve conduits was observed under different magnification with an acceleration voltage of 3.0 kV.

2.3. Lateral compression test

All the lateral compression tests of PLGA nerve conduits were carried out under room temperature, and ElectroForce (TA Instruments, America) with parallel plates (25 mm in diameter, Fig. 2) was used in compression mode for the tests. As shown in Fig. 2, the force was applied perpendicular to the longitudinal axis of the tubular specimens, where the sample length was 10 mm and force loading speed was 1.0 mm/min. It should be pointed out that at least 10 samples were tested for each fabrication condition.

In order to analyze the compressive resistance of nerve conduits, the compressive strain of the cross section is defined as $\varepsilon = (d_0\text{-}d)/d_0$, where d_0 is the initial value of nerve conduit diameter, and d is the diameter after compression (Fig. 2). Also, the force per unit length is defined as $F = f/l_0$, where f is the compressive force applied on nerve conduit (Fig. 2), and l_0 is initial longitudinal length of the nerve conduit. Here, the compressive modulus is defined as

$$A_0 = \lim_{\varepsilon \to 0} \frac{F}{\varepsilon} \tag{1}$$

to characterize the mechanical properties of nerve conduits under compression. The A_0 value of each specimen is estimated from the initial slope of the F-ε curve.

3. Numerical model

3.1. Constitutive model

In this study, a finite element modeling is conducted to understand the influence of the porous morphology of nerve conduits on their compressive behavior. As previous numerical modeling of polymeric membranes [10,21], the bulk material of PLGA is assumed to be isotropic, homogeneous and nearly incompressible. In order to describe the nonlinear mechanical property of PLGA, a hyperelastic–plastic constitutive model is implemented in numerical modeling; where the deformation is assumed to be divided into an elastic part and a plastic part as [25]: