Poly(propylene fumarate)-*co*-Poly(ε-caprolactone) Tube for Guided Nerve Regeneration

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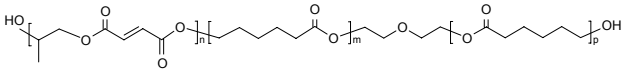
Introduction: Currently, an autologous nerve graft still is the clinic gold standard for repair of a nerve defect in peripheral nerve injuries. Disadvantages of the use of an autograft however are the need for an extra incision, loss of donor nerve function and limited availability of donor nerve. Biodegradable nerve tubes made from different materials have therefore been developed as potential/possible alternative for repair with an autologous nerve graft. One novel copolymer poly(propylene fumarate-*co*-caprolactone) (PPF-*co*-PCL) has been invented (Scheme 1) to obtain controllable physical properties to satisfy various needs, particularly, bone and nerve regenerations.[1] The physical properties have been extensively investigated and the glass transition temperature decreases progressively with increasing the PCL composition in the copolymer. The biodegradation rate and mechanical properties can therefore be well modulated by the different molecular structure, copolymer composition, and crosslinking density.



Scheme 1

Methods: One particular PPF-*co*-PCL copolymer with a high PCL composition of 90% was used for the fabrication of single lumen and multi-channel nerve tubes. Photocrosslinking were initiated with UV (λ=315-380 nm) using a photoinitiator bisacylphosphine oxide (BAPO, Ciba Geigy). BAPO solution in CH_2Cl_2 was added into PPF-*co*-PCL solution in CH_2Cl_2 and put in an incubator to mix thoroughly. The homogenous mixture was injected from a syringe to a mold formed by a glass tube, wires, and end-caps. The mold was rotated under UV light to facilitate crosslinking. After crosslinking, the polymer tubes were soaked in acetone to wash away the solvent and then dried in a vacuum oven. The polymer tubes were sterilized in 80% ethanol for 30 min prior to implantation. The thermal and mechanical properties of the final products were determined by DSC, TGA, and DMA. After the PC12 cells (15-25K/cm^2) were seeded, add the transwell with the polymer disks at the bottom of the transwell to the 24, 48, and 72 hr conditions. MTS assay was used to determine the cell viability of the sterilized disks. 100 μL of cells in culture medium was placed on the polymer disks and allowed to incubate for 1 day to check cell attachment. For *in vivo* analysis polymer tubes were implanted in a 1 cm gap of the rat sciatic nerve model. After 4 and 12 weeks of implantation tubes were removed and imbedded. Sections were taken from the mid-part of the tubes, stained with toluidine blue, and evaluated for the presence of myelinated axons, macrophages, and fibroblasts.

Results/Discussion: The new fabrication method using UV photo-crosslinking proves to be efficient for making tubes without defects (Fig. 1). Because the melting point is lower than 37 ^oC, nerve tubes are transparent during *in vivo* implantation. Little swelling was found in PBS solution. The mechanical and thermal properties of the crosslinked PPF-*co*-PCL can be regulated by the amount of crosslinking initiator. By controlling the degree of crosslinking and impeded crystallization structure, the final copolymer network is strong, which is important for the ability of the nerve to hold the suture, but flexible, which is important in moving body parts.

The cell viability of the copolymer disks were found to be close to 100% compared to the tissue culture plate. Furthermore, cells are liable to attach onto the polymer disks (Fig. 2a). Results for i*n vivo* implantation showed that the nerve tubes are biocompatible with only a small layer of fibroblast tissue around the tube. Myelinated axons were present in the mid-part of the channels of the tube 4 weeks after implantation (Fig. 2b). The structure of tube was thereby still intact.

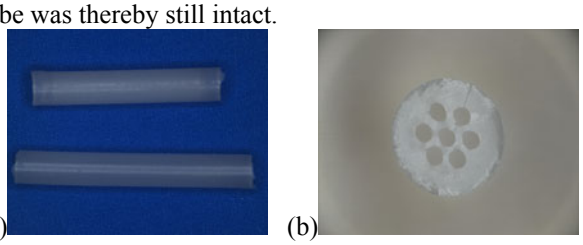


Fig. 1: (a) PPF-*co*-PCL tubes; (b) cross section of a multi-channel tube.

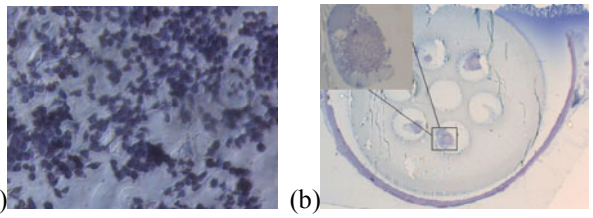


Fig.2: (a) PC12 cell attachment on copolymer disk after 24 hr (hematoxylin stain); (b) Section taken through the mid-part of a multi-channel nerve tube 4 weeks after implantation (toluidine blue stain).

Conclusions: A novel copolymer P(PF-*co*-CL) has been used to make nerve guide conduits using an UV crosslinking fabrication method. As well *in vitro* as *in vivo* results showed the new materials have promising characteristics for use in peripheral nerve repair.

References

1. Wang SF. Macromolecules 2005;38:7358.

Acknowledgments

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