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Research Paper

Mechanically tissue-like elastomeric polymers and their potential as a vehicle to deliver functional cardiomyocytes

Bing Xu[a], *Yuan Li*[a], *Xiya Fang*[a], *George A. Thouas*[b], *Wayne D. Cook*[a], *Donald F. Newgreen*[c], *Qizhi Chen*[a,*]

[a]*Department of Materials Engineering and Monash Centre of Electron Microscope, Monash University, Clayton, Victoria 3800, Australia*

[b]*Department of Zoology, The University of Melbourne, Parkville, Victoria 3010, Australia*

[c]*Murdoch Childrens Research Institute, The Royal Children's hospital, Flemington Road, Parkville, Victoria 3052, Australia*

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ABSTRACT

One of the major challenges in the field of biomaterials engineering is the replication of the non-linear elasticity observed in soft tissues. In the present study, non-linearly elastic biomaterials were successfully fabricated from a chemically cross-linked elastomeric poly (glycerol sebacate) (PGS) and thermoplastic poly(L-lactic acid) (PLLA) using the core/shell electrospinning technique. The spun fibrous materials, containing a PGS core and PLLA shell, demonstrated J-shaped stress–strain curves, and having ultimate tensile strength, rupture elongation, and stiffness constants respectively comparable to muscle tissue properties. *In vitro* evaluations also showed that PGS/PLLA fibrous biomaterials possess excellent biocompatibility, capable of supporting human stem-cell-derived cardiomyocytes over several weeks in culture. Therefore, the core/shell electrospun elastomeric materials provide a new potential scaffold to support cells in the therapy of a wide range of soft tissues exposed to cyclic deformation, such as tendon, ligament, cardiac or smooth muscle and lung epithelium.

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1. Introduction

The stress–strain nature of biological tissues has been observed by several/many workers (Mirsky, 1976) to be quite unlike most materials. They undergo elastic (i.e, reversible) stretching to high levels of extensibility but they also exhibit non-linear deformation behaviour in which the stress rises at an increasing rate as the strain is raised. In contrast, thermoplastic polymers proposed for tissue replacement, such as polylactic acid (PLA), polyglycolic acid (PGA) and their copolymers, show a decreasing rate of rise in stress prior to plastic deformation (i.e. non-reversible deformation) at low strains. Therefore, one of the major problems encountered by biomaterials scientists in repairing the majority of soft tissue types is the need to replicate this innate and complex elasticity (Chen et al., 2008b). Despite some previous success (Seal et al., 2001), there are few synthetic tissue engineering products available for clinical use (Freed et al., 2009) in the

*Corresponding author. Tel.: +61 3 9905 3599; fax: +61 3 9905 4940.
E-mail addresses: qizhi.chen@monash.edu, qzchen202@gmail.com (Q. Chen).

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repair of soft, mechanically functional tissues, such as heart, lung and intestine. These mechanical dissimilarities between synthetic biomaterials and tissue for repair are believed to be the major cause of graft failure in experimental animal studies and preclinical trials (Freed et al., 2006).

Research activity focusing on the development and clinical application of synthetic biodegradable soft elastomers as transplantable biomaterials for tissue engineering has increased over the past decade (Chen et al., 2008b). For example, poly (polyol sebacate; PPS) is a new family of cross-linked, biodegradable elastomers that has recently been developed for soft tissue repair and regeneration applications (Bettinger et al., 2006; Wang et al., 2002). Chen et al., 2008a,b have reported that the Young's modulus of a PPS family member, poly(glycerol sebacate; PGS), ranges between 0.05 and 1.5 MPa, which is similar to the stiffness of muscle tissues (Chen et al., 2008a).

In an animal study using a rat model, PGS sheets were grafted as heart patches and performed the intended mechanical function in terms of inhibiting scar formation in infracted heart muscles (Stuckey et al., 2010). However, this study also revealed two critical drawbacks of using PGS patches. Firstly, the grafted patches were completely absorbed in 6 weeks. This time frame is too rapid for the recovery of a diseased heart, a process which takes approximately 6–12 months (Stuckey et al., 2010). Secondly, and perhaps more significantly, an arrhythmia (irregular heartbeat), attributable to the mechanical property mismatch between the PGS patch and the heart muscle, was observed. The stress–strain curves of synthetic elastomers are relatively *linear* at low strains, particularly at 15% which is the maximal strain of living tissues, but biological tissues, such as heart muscles, exhibit *non-linear* stress–strain curves (Chen et al., 2008b) which we call here "J-shaped" as discussed above. The primary reason for these different elastic behaviours may be that the polymer chains form random coils between the crosslink points within the synthetic elastomer network, while protein nanofibres tend to be straighter and aligned within muscle fibres. Therefore, the production of an aligned, or partially aligned, nanofibrous structure within a synthetic polymer may be ideal for matching the non-linear elasticity of biological tissues.

The production of nanofibres from cross-linked elastomers is technically challenging. The first challenge of producing synthetic core–shell nanofibres has been recently solved by electrospinning (Jiang et al., 2006; Sun et al., 2003; Zhang et al., 2004). A second problem is that a crosslinked elastomer cannot be dissolved in a solvent for the electrospinning process. While the literature reports studies on photopolymerization of monomers and oligomers during the electrospinning process (Anseth et al., 1999), such a technique is not possible with the PPS materials of interest here because they contain no photopolymerizable groups. If the material is not photopolymerized during electrospinning, it must be capable of forming a rigid, relatively non-adhesive fibre once the solvent has evaporated. However before thermal crosslinking of PPS it is a viscous polymer which could not retain a nanofibrous form after spinning. In fact the PPS oligomer needs to be thermally cured at elevated temperatures to form an elastomer. Fortunately, the recent development of a core/shell electrospinning technique could offer an opportunity to address these problems (Ou et al., 2011; Ravichandran et al., 2011; Yi and Lavan, 2008). Core/shell electro-spun fibres are formed when a pre-polymer that is not cross-linked is en-sheathed by a suitable thermoplastic in solution, with both materials being fed into the electrospinner simultaneously but via separate core and annulus flows. Following collection of the core–shell nano-fibre, thermal crosslinking process of the prepolymer can be undertaken in situ if the solid thermoplastic shell can maintain its tubular shape at the curing temperature. Yi and Lavan (2008) have reported the production of core–shell PGS/ poly-L-lactic acid (PLLA) nanofibres using this method. In addition, they claimed that they could remove the thermoplastic shell from the final product by dissolution in chloroform. However, we believe that, when used as a biomaterial scaffold, the addition of a thermoplastic shell would be beneficial in controlling the degradation rate of the final product. Therefore, the objective of the present study was to systematically explore the fabrication procedures of PGS/PLLA fibrous materials using the core/shell electrospinning technique, to investigate the mechanical behaviour of these mats, and evaluate their *in vitro* biocompatibility as biomaterial scaffolds.

2. Experimental procedures

2.1. Materials

Glycerol, sebacic acid, L(+)-lactic acid (LA) were purchased from Sigma-Aldrich (Castle Hill, NSW, AU). Chloroform, dimethylformamide (DMF) and tetrahydrofuran (THF) were purchased from Merck (Kilsyth, VIC, AU). The PLLA, also known as RESOMER® L 206S, was purchased from Sigma-Aldrich (Castle Hill, NSW, AU) and is reported to be ester-terminated with an inherent viscosity of 0.8–1.2 dl/g for a 0.1% solution in $CHCl_3$ at 25 °C, a glass transition temperature of 60–65° and a melting point of 180–185 °C [http://www.sigmaaldrich.com/materials-science/polymer-science/resomer.html]. This PLLA was chosen as the shell material because its melting point is sufficient to retain the nano-fibre shape during the cross-linking of PGS, at tem peratures which range from 120 to 150 °C (Chen et al., 2010d, 2011; Liang et al., 2010).

PLLA has been successfully spun from a mixture of dichloromethane and DMF at volume ratios of 9:1 by Ou et al. (2011) but we did not find this system to be successful due to the rapid evaporation of the dichloromethane. Substitution of dichloromethane by the higher boiling chloroform at differing solvent ratios revealed the 4:1 v/v of chloroform to DMF to be the most successful. So it was selected as the solvent for the PGS prepolymer. THF has been used as a solvent for the casting of PGS pre-polymers in our laboratory and so preliminary studies with PGS pre-polymer concentrations from 10% to 50% w/v in THF were used in core–shell electrospinning but solutions spun with 50% w/v were found to give the best results.

2.2. PGS/PLLA solution miscibility and preparation of PGS-PLLA blends

In the core/shell electrospinning process, the core (PGS) and shell (PLLA) solutions are extruded from two concentric syringe needles and are spun together, thus remaining in intimate contact during the process. An essential requirement for a

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