

New Biodegradable Elastic Polymers and Scaffold-Sheet Tissue Engineering Strategy

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Statement of Purpose: Biodegradable elastomers have been recognized as ideal scaffolding materials for soft and elastic tissues. For examples, crosslinked biodegradable polyesters, poly(diols citrates) [1-2] have been developed for cardiovascular tissue engineering. Although these polymers showed excellent biocompatibility, the relatively weak mechanical properties restricted them to be used for some mechanically strong elastic tissues such as ligament and tendon. In the present paper, we have developed a next generation of biodegradable elastomers, which were referred to as crosslinked urethane-containing polyesters (CUPEs). CUPEs incorporated the advantages from both crosslinked polyester which are soft and elastic (100% recovery from deformation without creep), and mechanically strong polyurethane. Based on CUPE, we proposed a new scaffold-sheet tissue engineering strategy for construct tissue grafts.

Methods: Synthesis: The synthesis route of CPEU is shown in Figure 1. Step 1: In the case of using 1,8-octanediol, citric acid and 1,8-octanediol with molar ratio 1/1.1 will be melted at 160 °C for 20 min, followed by heating at 140 °C for 1 hr to prepare the pre-POC with –OH at the both end of the prepolymer chains; The resulting pre-POC will be purified and reacted with 1,6-hexane diisocyanate (HDI) with a molar ratio of 1/0.9 to obtain the pre-CUPE. Pre-CUPE solution will then be purified by drop-wising into water under stirring. The resulting purified pre-CPEU will then be dried under vacuum at room temperature. Step 3, pre-CUPE will be postpolymerized by heating ranging from 60 °C to 120 °C for times ranging from 1 day to 2 weeks with or without vacuum in an oven to obtain the CUPE polymers. By varying the selection of diols, combination of diols (C4-C12 diol), diisocyanate (such as 1,4-butane diisocyanate (BDI)), and postpolymerization conditions, a new family of CUPE polymers were created.

Scaffold fabrication: CUPEs have also been fabricated into thin scaffold sheets (150 μm thick) via a thermally-induced phase separation method. Mouse 3T3 fibroblasts were seeded to evaluate the cell seeding efficiency on the CUPE scaffold-sheets. **Polymer characterization:** CUPEs was characterized by H-NMR (for pre-CUPE), FTIR, DSC, TGA, tensile mechanical test, and degradation studies. **Biocompatibility evaluation in vitro:** Mouse 3T3 fibroblasts were cultured on CUPE scaffold-sheets to study the cell compatibility of CUPEs. The host response to CUPEs was evaluated via subcutaneous implantation in a Sprague-Dawley rat model. The hemocompatibility of CUPEs was also evaluated with respect to platelet adhesion and activation, and leukocyte activation using human blood.

Results: Polymer characterization suggested that we have successfully synthesized a new generation of biocompatible, biodegradable, and elastic polymers,

CUPEs. Figure 1 showed that the mechanical strength of CUPEs could be up to 35 MPa and elongation at break could be 320% under the synthesis conditions studied. The CUPE films are much stronger than the reported poly(diols citrates) where tensile strength was not more than 13 MPa.[2] The mechanical data indicated our CUPE polymers have well combined the advantages of polyurethane and crosslinked polyesters. We were the first time to introduce urethane bonds into crosslinked polyester networks to generate the next generation of biodegradable elastomers, CUPEs.

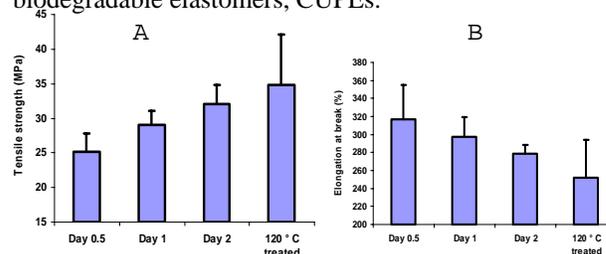


Figure 1. Tensile mechanical tests on CUPE films synthesized with various post-polymerization conditions. A) Tensile strength; B) Elongation at break.

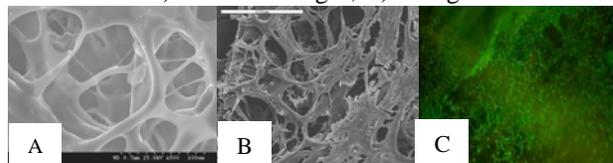


Figure 2. A) SEM of thin CUPE scaffold sheet (150 μm thick, scale bar: 100 μm); C) SEM of 3T3 fibroblasts seeded on CUPE scaffold sheets. D) Live-Dead assay for 3T3 fibroblasts on CUPE scaffold sheet for 7 d.

Two-dimensional (2-D) cell sheet tissue engineering has achieved some success such as easy tissue-assembling and even cell distribution. But cells may lose characteristics at 2-D culture environment. We proposed scaffold-sheet tissue engineering strategy. Thin scaffold sheets (<150 μm) would allow an even cell distribution by simply pipetting cells on the scaffold-sheets. Scaffold-sheets will provide a 3-D cell culture environment for cells grown on them. Soft and elastic scaffold sheets can be easily assembled into complex tissues just like cell sheets. Figure 3 B and C suggested an even distribution of cells on a thin 3-D CUPE scaffold sheet.

Conclusion: we have developed a biocompatible new family of biodegradable elastic polymers for tissue engineering. We proposed a new tissue engineering strategy, scaffold-sheet tissue engineering.

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References

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- 2 Jian Yang, etc. Biomaterials, 2006, 27: pp.1889-98.