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Synthesis, characterization and surface modification of low moduli poly(ether carbonate urethane)ureas for soft tissue engineering

Feng Wang [a], Zhenqing Li [a], John L. Lannutti [a], William R. Wagner [b], Jianjun Guan [a,*]

[a] Department of Materials Science and Engineering, The Ohio State University, 2041 College Road, Columbus, OH 43210, USA
[b] Departments of Surgery, Bioengineering & McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA 15219, USA

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Abstract

Flexible scaffolds are of great interest in engineering functional and mechano-active soft tissues as such scaffolds might allow mechanical stimuli to transfer effectively from the scaffolds to cells during tissue development. Towards this end, we have developed a family of flexible poly(ether carbonate urethane)ureas (PECUUs) with a triblock copolymer poly(trimethylene carbonate)–poly(ethylene oxide)–poly(trimethylene carbonate) (PTMC–PEO–PTMC) or pentablock copolymers PTMC–PEO–PPO–PEO–PTMC (PPO, polypropylene oxide) as soft segments, linked by 1,4-diisocyanatobutane and putrescine. All of the PECUUs had low glass transition temperatures (<−46 °C). The PTMC–PEO–PTMC-containing PECUUs had low tensile strength and breaking strain. Replacing PEO with the similar length PEO–PPO–PEO resulted in highly flexible and soft PECUUs possessing breaking strains of 362–711%, tensile strengths of 8–18 MPa and moduli of 5.5–7.4 MPa at room temperature in air. Under aqueous conditions at 37 °C, these polymers remained flexible while their moduli were decreased to 3.4–4.0 MPa. PECUUs based on PTMC–PEO–PPO–PEO–PTMC were thermosensitive as the water content at 37 °C was lower than that at 4 °C. PECUU using PTMC–PEO–PTMC as a soft segment showed 30% weight loss over 6 weeks in PBS at 37 °C, while that using PTMC–PEO–PPO–PEO–PTMC as a soft segment had weight loss <6%. Degradation products were found to lack cytotoxicity. The mechanical stresses and moduli of PECUUs based on PTMC–PEO–PPO–PEO–PTMC were unchanged during the degradation. To enhance cell adhesion, PECUUs were surface modified with Arg-Gly-Asp-Ser (RGDS). Smooth muscle cell adhesion was 114% of tissue culture polystyrene for unmodified PECUU and >180% for RGDS-modified PECUUs, with cell viability on both surfaces increasing during culture. These low moduli polyurethanes may find applications in engineering cardiovascular or other soft tissues.

Keywords: Poly(trimethylene carbonate); Poly(ether carbonate urethane)urea; Surface modification; Biodegradable

1. Introduction

With the increasing appreciation of the role of mechanics in tissue development and remodeling, designing scaffolds with mechanical properties approximating the target tissues is often considered in addition to scaffold degradation properties and the support of cell adhesion and growth [1–6]. It is believed that an appropriate combination of chemical, biological and mechanical properties within the scaffold is more likely to create an instructive microenvironment for cells to develop into functional soft tissues, either in vitro or in vivo. This is particularly true when engineering mechano-active soft tissues such as cardiac muscle and blood vessels, as such scaffolds would allow mechanical stimuli transfer effectively from the environment to the scaffold and from the scaffold to the cells to develop mechanically appropriate soft tissues [1–6].

As researchers have sought to explore mechanical effects in tissue engineering, the use of the relatively stiff, simple polyesters polylactide (PLA), polyglycolide (PGA) and their copolymers has been joined by new biodegradable polymers that are better suited for soft tissue applications. Flexible behavior for scaffolding materials has been of par-

* Corresponding author. Tel.: +1 614 292 9743.
E-mail address: guan.21@osu.edu (J. Guan).

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ticular interest to biomaterials scientists and engineers seeking to generate novel materials. Polyesters [7,8] and polyurethanes [9–11] have most commonly been used to create flexible scaffolds, with flexibility resulting from either chemical or physical crosslinking. One of the disadvantages of chemically crosslinked flexible polymers is the inability to process them into three-dimensional scaffolds with convenient solvent-related techniques such as solvent casting and salt leaching, phase separation and electrospinning. In contrast, physically crosslinked flexible polymers are attractive in that they are thermoplastic and can be processed either by solvent-based strategies or melt processing. In the past several years, we and others have developed a variety of families of physically crosslinked polyurethanes through the molecular design of soft and hard segments [12–16]. These polymers have been successfully fabricated into scaffolds for engineering soft tissues like blood vessels, cardiac patches and heart valves [17–19], but there is arguably a need to provide options for materials that have even lower stiffness (<17 MPa), while maintaining high flexibility. Furthermore, most of the flexible polymers rely on polyester linkages for hydrolytic liability and they undergo bulk degradation, limiting the period during which scaffold-based mechanical support can dominate [20].

The objective of this work was to generate biodegradable and low moduli flexible polymers that could be used to engineer low moduli soft tissues such as cardiac muscle (<0.5 MPa) [21] and blood vessel (~1.4 MPa) [17]. Inspired by the highly soft nature of poly(trimethylene carbonate) (PTMC), which has a modulus of ~2.9 MPa [22], PTMC was chosen as one of the components of the soft segment. Besides its low modulus, PTMC has been shown to undergo surface degradation, which may allow the synthesized polyurethanes to retain mechanical properties for prolonged periods as compared with polycaprolactone-based polyurethanes. Previous work demonstrated that the utilization of pure PTMC as a soft segment yielded hydrophobic polyurethanes with rather slow degradation rates and moderate to weak cell adhesive properties [23–26]. To overcome these limitations, PTMC has been copolymerized with other biodegradable polymers to increase hydrophilicity and degradation rate [23–26]. In this work, we sought to introduce variably hydrophilic segments into the polyurethane to vary polyurethane hydrophilicity and degradation properties. The moderately hydrophilic poly(ethylene oxide) (PEO)–polypropylene oxide (PPO)–PEO and the highly hydrophilic PEO were incorporated into the polymers. We found that the moderately hydrophilic PEO–PPO–PEO preserved the slower hydrolytic degradation characteristic of the PTMC, while the highly hydrophilic PEO allowed the polymer to undergo faster degradation. To enhance cell adhesion, polymers were surface modified with the cell adhesive peptide Arg-Gly-Asp-Ser (RGDS). Smooth muscle cells were cultured on the polymer surfaces to evaluate cytocompatibility of the synthesized polymers.

2. Materials and methods

2.1. Materials

Pluronic L31 (EO_2-PO_{16}-EO_2, mol. wt. ~1100, BASF), PEO (ol. wt. 1000, Sigma) and trimethylcarbonate (TMC; Boehringer Ingelheim) were vacuum dried overnight prior to use. Butanediisocyanate (BDI; Fluka) and putrescine (Aldrich) were vacuum distilled before synthesis. Stannous octoate (Sigma) and dimethyl sulfoxide (DMSO) were dried over 4 Å molecular sieves. RGDS (Sigma) was used as received.

2.2. Synthesis of block copolymer diols

The block copolymer diols $(TMC)_n$–PEO–PPO–PEO–$(TMC)_n$ and $(TMC)_n$–PEO–$(TMC)_n$ were synthesized by ring-opening polymerization of TMC using either PEO–PPO–PEO or PEO as an initiator and stannous octoate as a catalyst (Scheme 1) [5,27]. The polymerization was conducted at 110 °C for 18 h under a nitrogen atmosphere. The yielded copolymers were washed with ethyl ether and hexane, then dried in a vacuum oven at 50 °C for 24 h. Copolymers with variable TMC length were synthesized by utilizing different TMC/PEO or TMC/PEO–PPO–PEO ratios (Table 1).

2.3. Polyurethane synthesis and film preparation

The poly(ester carbonate urethane)ureas (PECUUs) were synthesized using a two-step solution polymerization method (Scheme 1) [5,27]. In brief, the synthesis was conducted in a 250 ml three-necked flask equipped with a nitrogen inlet and outlet. A 1 wt.% BDI (7.98 mmol) solution in DMSO was added into the flask followed by a 10 wt.% copolymer diol (3.99 mmol) solution in DMSO. Two drops of stannous octoate were then added and served as a catalyst [28]. The reaction was carried out at 80 °C for 3.5 h under continuously stirring. The solution was then cooled to room temperature, and a 1 wt.% putrescine solution (3.99 mmol) added. The reaction was continued for 12 h at room temperature. The polymer solution was precipitated in a saturated potassium chloride solution. The polymer was then immersed in deionized (DI) water for 24 h to leach out the salt, and dried under vacuum at 50 °C for 24 h. The synthesized polymers are abbreviated as PECUU–PPP*X* or PECUU–PEO*X*, where PPP and *X* represent PEO–PPO–PEO and number of TMC units, respectively.

2.4. Polyurethane film preparation

PECUU films were prepared by solution casting and solvent evaporation. The polymers were dissolved in dimethylformamide (DMF) to form a 3 wt.% solution. The solution was cast in a Teflon dish, and the solvent was evaporated in a vacuum oven at 50 °C. The formed film was further dried for 2 days before being used for characterization.

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