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Creep-resistant elastomeric networks prepared by photocrosslinking fumaric acid monoethyl ester-functionalized poly(trimethylene carbonate) oligomers

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Abstract

Biodegradable elastomeric networks were prepared from ethyl fumarate-functionalized poly(trimethylene carbonate) oligomers. Photocrosslinkable macromers were synthesized by reacting three-armed, hydroxyl group-terminated poly(trimethylene carbonate) oligomers with fumaric acid monoethyl ester at room temperature using *N*,*N*-dicyclohexylcarbodiimide as a coupling agent and 4-dimethylamino pyridine as a catalyst. Poly(trimethylene carbonate) macromers with molecular weights ranging between 4500 and 13,900 were prepared and crosslinked by ultraviolet-initiated radical polymerization. The gel contents of the resulting transparent networks varied between 74% and 80%. All obtained networks had low glass transition temperatures, which varied between −18 and −13 °C. They showed rubber-like behavior and excellent mechanical properties, with tensile strengths and elongations at break of up to 17.5 MPa and 750%, respectively. Moreover, static- and dynamic creep experiments showed that these amorphous networks were highly elastic and resistant to creep. In cyclic tensile testing to 50% strain, the permanent deformation after 20 cycles was 0%, while static creep tests at 35% of the yield stress did not indicate creep or permanent deformation after removal of the load. Porous structures were prepared by photopolymerizing the macromers in the presence of salt particles, and subsequent leaching of the salt. Such networks, built up of non-toxic compounds and designed to release benign degradation products, may find application as tissue engineering scaffolds for dynamic cell culture.

Keywords: Creep-resistant networks; Biodegradable elastomers; Poly(trimethylene carbonate) macromers

1. Introduction

Mechanical stimulation plays an important role in the biosynthetic activity of cells in tissue engineering scaffolds by promoting cell differentiation and proliferation, extracellular matrix synthesis, and tissue formation and organization [1–3]. The application of a cyclic mechanical stress may also facilitate the release of growth factors from scaffolds and subsequently accelerate tissue repair [4]. In particular, long-term application of cyclic strain could facilitate the organization of the regenerating tissues by up-regulating elastin and collagen gene expression [5]. Therefore, in a dynamic cell culture, specific mechanical stimuli have been utilized in the regeneration of various tissues [2,6–8]. However, biodegradable polymers commonly used in the preparation of tissue engineering scaffolds, like poly(lactide), poly(glycolide) and their copolymers, are

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quite rigid and undergo plastic deformation and (premature) failure under long-term cyclic loading conditions [6,9].

Poly(1,3-trimethylene carbonate) (PTMC) is a flexible material, supporting adhesion and growth of many different cells [10,11]. It is an amorphous polymer with a low glass transition temperature (T_g) (−19 to −14 °C) and a low Young's modulus (6 MPa), allowing direct mechanical stimulation of the cells. In addition, it degrades in vivo to non-acidic products by a surface erosion process. However, the low creep compliance of the linear polymer limits its application in (long-term) dynamic cell culture. Attempts have been made to improve the creep-resistance of PTMC by γ-irradiation crosslinking [12], and by the formation of physical network structures through stereocomplexation [13,14].

To improve the creep-resistance of PTMC further, we set out to prepare covalent networks from PTMC macromers by radical initiated crosslinking reactions, as was shown to be effective for polysaccharides and for D,L-lactide and ε-caprolactone copolymers [15,16]. The formation of chemical networks by photocrosslinking reactions is of special interest. The advantages of photocrosslinking over other crosslinking techniques include [17,18]: high curing rates at room temperature, spatial control of polymerization, and solidification of the networks in vivo with minimal heat production. Especially from the clinical point of view, photoinitiated crosslinking is very attractive, as it minimizes patient discomfort, risk of infection, scar formation, and cost of treatment. The method has therefore often been used in the preparation of tissue engineering matrices [19–21]. Photocurable macromers containing acrylate- or methacrylate functional groups have been used the most often, but macromers containing styryl-, coumarin- and phenylazide functional groups have been employed as well [22,23].

If the networks are formed in situ, or if the networks are not to be extracted prior to their application, the toxicity of the compounds involved in the crosslinking is an important issue. Fumarate-containing macromers such as oligo(poly(ethylene glycol) fumarate) and poly(propylene fumarate), are attractive since these compounds and the degradation products of the resultant networks can be expected to be non-toxic and biocompatible [24,25]. We have previously reported the preparation of well-defined networks by photopolymerization of oligomeric precursors end-functionalized with fumaric acid monoethyl ester (FAME) [26].

Here, we describe the preparation of biodegradable elastomeric networks by ultraviolet (UV) photopolymerization of three-armed poly(trimethylene carbonate) oligomers functionalized with FAME. The network properties, thermal properties and mechanical behavior of crosslinked structures, prepared from PTMC macromers varying in molecular weight, were determined. The resistance to creep of the networks was evaluated by cyclic deformation experiments, as well as by static creep tests. Their behavior was compared with that of linear, non-crosslinked, high-molecular-weight PTMC.

2. Experimental

2.1. Materials

High-purity 1,3-trimethylene carbonate (1,3-dioxan-2-one, TMC) was obtained from Boehringer Ingelheim, Germany and used as received. Stannous octoate ($SnOct_2$) was obtained from Sigma, USA. Glycerol (spectrophotometric grade), FAME and 4-dimethylamino pyridine (DMAP) were purchased from Aldrich, USA, and used without further purification. *N*,*N*-Dicyclohexylcarbodiimide (DCC) was purchased from Fluka, Switzerland, 2,2-dimethoxy-2-phenylacetophenone (DMPA) (Aldrich, USA) was used as photoinitiator. Dichloromethane (Biosolve, The Netherlands) was dried over CaH_2 and distilled. Chloroform (p.a. quality) (Biosolve, The Netherlands) and petroleum ether (b.p. 40–60 °C) (Merck, Germany) were used as received.

Linear, high-molecular-weight PTMC ($\overline{M}w = 530{,}000$, $\overline{M}n = 300{,}000$, $T_g = -13.9$ °C), prepared by ring-opening polymerization and compression molded to specimens of 500 μm thickness, were used as a comparison in the tensile testing and creep experiments.

2.2. Synthesis of FAME-functionalized PTMC oligomers

Star-shaped functionalized PTMC macromers were prepared by esterification of the PTMC oligomeric triols with FAME at room temperature using DMAP as a catalyst and DCC as a coupling agent.

Star-shaped hydroxyl-terminated PTMC precursors (3-OH precursors) were synthesized by ring-opening polymerization (oligomerization) of TMC in the presence of glycerol and $SnOct_2$.

Polymerizations were carried out on a 5–20 g scale. Trimethylene carbonate, glycerol and 0.2 mmol of $SnOct_2$ per mol of monomer were polymerized under an argon atmosphere at 130 °C for 40 h in a three-necked flask. The molecular weights of the oligomers could readily be controlled by adjusting the TMC monomer to glycerol ratio. The reaction mixture was cooled to room temperature, dissolved in dichloromethane and precipitated in an excess of petroleum ether to remove unreacted monomer. The purified star-shaped hydroxyl-terminated oligomers were then dried in a vacuum oven for 2 days at room temperature.

The PTMC oligomers were functionalized with FAME at room temperature, using DCC as a coupling agent and DMAP as a catalyst [27]. An amount of these three-armed hydroxyl-terminated PTMC precursors (1 mmol) was charged into a three-necked flask equipped with a magnetic stirrer and dried by heating to 110 °C under vacuum for 6 h. After cooling to room temperature under an argon atmosphere, the contents were dissolved in 60 ml of dried dichloromethane, and 3.6 mmol of FAME was added to the solution. After 30 min, a chloroform solution contain-

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