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Intraocular degradation behavior of crosslinked and linear poly(trimethylene carbonate) and poly(D,L-lactic acid)

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ABSTRACT

The intraocular degradation behavior of poly(trimethylene carbonate) (PTMC) networks and poly(-D,L-lactic acid) (PDLLA) networks and of linear high molecular weight PTMC and PDLLA was evaluated. PTMC is known to degrade by enzymatic surface erosion *in vivo*, whereas PDLLA degrades by hydrolytic bulk degradation. Rod shaped specimens were implanted in the vitreous of New Zealand white rabbits for 6 or 13 wk. All materials were well tolerated in the rabbit vitreous. The degradation of linear high molecular weight PTMC and PTMC networks was very slow and no significant mass loss was observed within 13 wk. Only some minor signs of macrophage mediated erosion were found. The fact that no significant enzymatic surface erosion occurs can be related to the avascularity of the vitreous and the limited number of cells it contains. PDLLA samples showed more evident signs of degradation. For linear PDLLA significant swelling and a large decrease in molecular weight in time was observed and PDLLA network implants started to lose mass within 13 wk. Of the tested materials, PDLLA networks seem to be most promising for long term degradation controlled intravitreal drug delivery since this material degrades without significant swelling. Furthermore the preparation method of these networks allows easy and efficient incorporation of drugs.

1. Introduction

Age-related macula degeneration (AMD) is the leading cause of blindness in the developed world [1]. Macula degeneration and other diseases of the posterior segment of the eye may require drug delivery to the posterior segment of the eye, which is challenging [2]. Topical ocular medications such as eyedrops hardly reach the posterior segment and the blood-retinal barriers prevent most systemically delivered drugs from achieving therapeutic levels in the posterior segment of the eye. Pharmacologically, the most efficient way to deliver drugs to the posterior segment is direct administration into the vitreous. Following injection, drugs are cleared from the vitreous within days or weeks, depending on the drug. The repeated injections that are often required can be stressful for patients and might lead to complications such as endophthalmitis.

Several controlled release systems have been developed to achieve sustained intraocular drug levels [3–5]. Degradable inserts overcome the need to remove the implant after the drug is released. Ozurdex (formerly Posurdex, Allergan Inc.) [6] is the only degradable device for drug delivery to the posterior segment of the eye currently on the market. The injectable rod-shaped PLGA (poly(lactic-co-glycolic acid)) implant releases dexamethasone and is applied for the treatment of diabetic macular edema. Several other degradable systems designed for drug delivery to the posterior segment of the eye are currently under investigation. Most often, the focus in these studies is primarily on drug release or therapeutic effect. Only very few studies

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Table 1
Characteristics of PDLLA and PTMC networks.

Material	Oligomer molecular weight (kg/mol)	Degree of methacrylatefunctionalization (%)	Gel content of photo-crosslinked network (%)	Network glass transitiontemperature (T_g, °C)
PTMC networks	2.9	91	97.1 ± 2.6	−7.9
PDLLA networks	3.2	93	95.5 ± 3.0	58

are available that provide details on the degradation behavior of the polymers which carry the drug in the eye. Most of the current literature on intraocular use of biodegradable polymers refers to poly(-lactic acid) (PLA) or copolymers with glycolic acid (PLGA). Moritera et al. [7] and Giordano et al. [8] evaluated the intravitreal degradation of PLGA and PLA microspheres with and without drugs incorporated. For a few other materials, initial studies regarding intravitreal behavior are available. Einmahl and Heller et al. [9–11] investigated the intravitreal degradation of two poly(ortho ester)s. Bruining et al. [12] studied the intravitreal behavior of poly(N-vinylpyrrolidone) networks designed for drug delivery applications. Hacker et al. [13] performed an initial two week intravitreal implantation study for their poly(propylene fumarate)/poly(N-vinylpyrrolidone) material. Silva-Cunha et al. [14] investigated the degradation of dexamethasone loaded ϵ-caprolactone intravitreal implants.

We set out to develop a system for controlled and sustained drug delivery to the posterior segment of the eye based on photo-crosslinked polymer networks. Polymer networks can be prepared by photo-polymerization of double-bond functionalized oligomers. The release profiles of these types of networks can be tuned by varying the crosslink density or by adjusting the network hydrophilicity [15–17]. Furthermore, networks can easily be loaded with drugs by dispersing or dissolving the drug in a liquid crosslinkable macromer or macromer solution prior to the crosslinking process. In this way, large amounts of drug can be loaded into a matrix efficiently. Samples with different shapes can simply be prepared using molds while crosslinked micro- and nanoparticles can be prepared by irradiating emulsions [18].

PTMC is a flexible, biocompatible polymer that has been shown to degrade by surface erosion *in vivo* [19,20]. This can be an advantage in drug delivery applications since release patterns of surface-eroding polymers are closely related to the polymer degradation rate and independent of the size of the drug molecule [21]. It has been suggested that enzymes and reactive oxygen species secreted by phagocytic cells play an important role in the *in vivo* degradation of PTMC [22,23]. It is not known whether this process also occurs in the vitreous as PTMC has never been applied in the vitreous before. The vitreous is a transparent gel that consists mostly of water (98–99%), some macromolecules, such as glycosaminoglycans and collagens, and only a small number of cells [24]. Another characteristic of PTMC is that it degrades without the formation of acidic compounds, which can be an advantage in protein delivery, since a drop in pH may lead to protein denaturation.

Poly(D,L-lactic acid) is a well known polymer that has been studied extensively for various biomedical applications [25] and has also been investigated for intravitreal delivery systems, mostly in the form of microspheres [26]. PDLLA degrades by bulk degradation into lactic acid.

In this study the intraocular degradation behavior of poly(trimethylene carbonate) (PTMC) networks was compared to that of poly(D,L-lactic acid) (PDLLA) networks. Besides the crosslinked polymers, also linear PTMC and PDLLA were investigated.

2. Materials and methods

2.1. Materials

Trimethylene carbonate (TMC) was purchased from Boehringer Ingelheim (Germany). D,L-lactide (DLLA) was purchased from Purac Biochem (The Netherlands). Tin 2-ethylhexanoate ($Sn(Oct_2)$), trimethylolpropane (TMP) and deuterated chloroform were obtained from Sigma Aldrich (U.S.A.). Methacryloyl chloride (MACl) was obtained from Alfa Aesar (Germany). Triethylamine (TEA) and toluidine blue were purchased from Fluka (Switzerland). Irgacure 2959 (2-hydrox-1-[4-(2-hydroxyethoxy)phenyl]-2-methyl-1-propanone) was obtained from Ciba Specialty Chemicals (Switzerland). Phosphate buffered saline (PBS, pH 7.4) was purchased from B. Braun (Germany). Analytical grade dichloromethane (DCM) was obtained from Biosolve (The Netherlands). DCM was dried over CaH_2 and distilled. Other solvents were of technical grade and were used as received (Biosolve, the Netherlands). Oxybuprocaine 0.4% eyedrops, phenylephrine 2.5% eyedrops and povidone iodine 0.3% eyedrops were obtained from the Hospital Pharmacy of the UMCG (the Netherlands). Ketamine was purchased from Alfasan (the Netherlands). Medetomidine was obtained from Janssen Pharmaceutica NV (Belgium). Tropicamide 2.5% eyedrops were obtained from Thea Pharma NV (Belgium). Chloramphenicol 1% ointment was purchased from Ratiopharm (the Netherlands). Buprenorphine was obtained from Scheringh Plough (U.S.A.). Paraformaldehyde was purchased from Polysciences Inc. (United Kingdom). Technovit 8100 was purchased from Heraeus Kulzer (Germany).

2.2. Implant preparation and characterization

2.2.1. Linear PTMC and PDLLA

High molecular weight poly(trimethylene carbonate) and poly(D,L-lactide) were synthesized in silanized glass ampoules. The ampoules were purged with argon and charged with trimethylene carbonate or D,L-lactide monomer (approximately 20 g) and stannous octoate as a catalyst. The system was switched to vacuum and dried for 15 min. Then the monomer mixture was molten (trimethylene carbonate at 55 °C, D,L-lactide at 130 °C) under argon and brought into Teflon tubes with an inner diameter of 0.8 mm using a syringe. The filled Teflon tubes were immersed in the monomer mixture. The system was cooled down and the ampoules were heat-sealed under vacuum. The polymerizations were conducted at 130 °C for 3 d. Then the ampoules were broken and the rod-shaped samples were taken out of the Teflon tubes and cut into pieces of approximately 5 mm.

The monomer conversion was determined from proton nuclear magnetic resonance (^{1}H NMR) spectra (Varian Inova 300 MHz NMR spectrometer). Deuterated chloroform was used as a solvent.

Gel permeation chromatography (GPC) was used to obtain number average molecular weights (M_n), weight average molecular weights (M_w), polydispersity indexes (PDI) and intrinsic viscosities (η) of the polymers. The polymers were dissolved in chloroform, and GPC measurements were conducted with a Viscotek GPCmax VE-2001 GPC solvent/sample module equipped with a series of ViscoGEL columns and a TDA 302 triple detector array (light scattering detector, differential refractive index detector, four-capillary differential viscometer).

The glass transition temperatures of the polymers were determined using a Perkin Elmer Pyris 1 differential scanning calorimeter. Samples were heated at a heating rate of 10 °C/min and quenched rapidly at 300 °C/min. After 5 min, a second heating scan was recorded. The glass transition temperature was taken as the midpoint of the heat capacity change in the second heating run.

2.2.2. PTMC and PDLLA networks

Three-armed poly(trimethylene carbonate) and poly(D,L-lactide) oligomers were synthesized by the ring opening polymerization of trimethylene carbonate and D,L-lactide respectively. The oligomer syntheses were carried out at a 20–60 g scale. Trimethylolpropane was used as a trifunctional initiator and stannous octoate was used as a catalyst. TMC or DLLA, TMP and stannous octoate (approximately 0.2 mmol/mol monomer) were reacted in the melt at 130 °C for 48 h under argon. The targeted molecular weight was 3100 g/mol for both oligomers, which corresponds to about 10 TMC units and about 7 DLLA units per arm. To achieve this, 30 mol TMC and 21 mol DLLA were added per mole of TMP.

Table 2
Diameters of the prepared implants.

Material	Rod diameter (mm)
High molecular weight PTMC	0.791 ± 0.009
PTMC networks	0.659 ± 0.006
High molecular weight PDLLA	0.779 ± 0.006
PDLLA networks	0.652 ± 0.014