A Blend of Poly(ε-caprolactone) and Poly[(ε-caprolactone)-*co*-glycolide] with Remarkable Mechanical Features and Wide Applicability as Biomaterial

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Summary: Hydrolytic degradation of poly(ε-caprolactone) [PCL] can be enhanced by introduction of 8 wt.% glycolide leading to poly[(ε-caprolactone)-*co*-glycolide] (PCG), which has a low elongation at break ε_B of 4%. PCG/PCL blends (50/50 w/w) combined the advantageous features of its individual components such as mechanical properties similar to pure PCL ($\varepsilon_{B,\ Blend}$: 900 ± 230%; $\varepsilon_{B,\ PCL}$: 730 ± 50 at 20 °C), water uptake rates during degradation similar to pure PCG, and linear mass loss during bulk degradation independent from sample dimensions. The outcome of cytotoxicity studies was depending on the cell type with promising results, e.g., for Tenon fibroblasts. Easy processing of the blend was demonstrated by melt compression, foaming with CO_2, and hot melt extrusion, suggesting a wide applicability as biomaterial, e.g., as drug carrier.

Keywords: biomaterials; blends; mechanical properties; poly(ε-caprolactone); poly[(ε-caprolactone)-*co*-glycolide]

Introduction

Degradable polymers have received substantial recognition as biomaterials due to the feasibility to tailor their properties and functions depending on, e.g., the selection of building blocks in polymer synthesis, the design of various polymer architectures, or the ratios of comonomers employed in copolymers.[1] This is important, since biomedical implants demand properties that are tailored to the specific application.[2] Hydrolytically degradable polymeric biomaterials remain an important focus of ongoing research, particularly when considering the need for implants that should stay only temporary in the body. In contrast, there is only a low number of materials so far being established for clinical applications that fulfil the requirement of hydrolytic degradability.

One widely accepted polyester biomaterial is PCL, which is used, e.g., in implants. PCL exhibits a slow hydrolytic degradation.[3] In order to enhance the rates of hydrolytic degradation, a common strategy in polymer synthesis involves the introduction of more easily hydrolyzable bonds

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('weak links') by means of copolymerization of ε-caprolactone with, e.g., diglycolide to PCG by ring opening polymerization.[4,5]

Importantly, in addition to the chemical composition, the sequence structure of the copolymer such as the distribution of glycolide units in PCG effects degradation rates.[6] It should be noted that the reaction conditions of the ring-opening polymerization is important, since blocky structures may be created for comonomers with different reactivities such as diglycolide and ε-caprolactone. Especially, the application of a catalyst can have a strong influence on the structure of the product. An example is the application of dibutyltin oxide as a transesterification catalyst, which results in a random distribution of glycolide and ε-caprolactone units in PCGs.

Another possibility to adjust polymer properties is blending, which is well suitable to alter, e.g., mechanical properties of materials.[7,8] Often, blending compromises the material properties depending on the mixing ratios. In this study, a blend of PCG and PCL is reported, which selectively combines the advantageous features of its constituents.

Experimental Part

Diglycolide (≥ 99%; Aldrich, Taufkirchen, Germany) was purified by recrystallization from ethyl acetate (> 99%; Acros, Geel, Belgium). It was copolymerized in the melt (130 °C, 4 weeks, nitrogen atmosphere) with ε-caprolactone (> 99%; Aldrich) as comonomer, 1,8-octanediol (>99%; Fluka, Taufkirchen, Germany) as starter molecule, and $(Bu)_2SnO$ (98%; Aldrich) as catalyst to yield PCG. A 50/50 (w/w) blend of PCG with commercial PCL (Capa® 6808, Perstorp, Cheshire, UK) was obtained by coextrusion at 100 °C (Prism Eurolab 16, L/D 25, Thermo Electron, Karlsruhe). Extrusion was performed using a rod die temperature of ~55 °C and an extruder speed of 50 rpm. The product was cooled in a water bath at ambient conditions.

Polymer samples were processed to 0.125 mm thick films by melt compression at 100 °C and 50 bars (P200E platen press, Collin, Ebersberg, Germany), to disks either by injection molding or by melt compression and punching (1 mm thick, ∅ 12 mm), and to foams by foaming with liquid CO_2 in a pressure chamber at 150 bar and temperatures ~5 °C below the melting temperature of the respective material. Images of samples were recorded by digital microscopy or scanning electron microscopy (SEM) with a Gemini Supra™ 40 VP SEM (Carl Zeiss NTS GmbH, Oberkochen, Germany).

The materials, either as prepared or after drying in the case of the degradation study in 5.8 mM phosphate buffer pH 7.4 at 37 °C, were comprehensively characterized. Tensile tests of dry samples were conducted at 20 °C and 37 °C with 0.4–0.7 mm thick polymer films cut into dumbbell-shaped test specimens using a Zwicki Z2.5 tensile tester (50 N load cell, pre-load 0.05 N; Zwick GmbH & Co. KG, Ulm, Germany). Differential scanning calorimetry (DSC) was performed in aluminium pans with pierced lids between −20 and +80 °C with heating and cooling rates of $4\,K \cdot min^{-1}$ on a Netzsch DSC 204. Thermogravimetry (TGA) was performed on a Netzsch TG 209 at $10\,K \cdot min^{-1}$. Gel permeation chromatography (GPC) in chloroform was performed on Jasco GPC systems with 300 mm x 8 mm linear M (10 μ) SDV-columns (Polymer Standard Service, Mainz, Germany). GPC samples were analyzed by universal calibration using data collected with a refractive index and a viscosity detector ($K = 0.0121$, $\alpha = 0.71$). The mass loss μ_{rel} and the water uptake H were determined from the dry-state or wet-state mass of samples in relation to their initial weights before degradation.

Polymer films were analyzed by Wide-angle X-ray scattering at a D8 Discovery (Bruker, Karlsruhe, Germany) at 40 kV and 40 mA with a two-dimensional detector (Hi-Star), a wavelength $\lambda = 0.154$ nm, a sample-to-detector distance of 150 mm, and an exposure time of 300 s. The crystal-

linity index X_c was determined from the area of crystalline peaks compared to the sum of peak areas of crystalline and amorphous phase. The average crystallite size l_c was calculated from the width of the peak at $2\theta \sim 21.8^\circ$ ($l_{c,110}$).

Cytotoxicity studies were performed with human primary cells (Tenon fibroblasts, keratocytes) and the murine fibroblast cell line L929 as described before.[9] Briefly, Tenon fibroblasts were obtained from conjunctival tissue biopsies and cultured in DMEM medium supplemented with 10% fetal calf serum (FCS) and 50 μg/ml gentamicin (all media from Sigma).[10] Keratocytes were harvested after 2 weeks as grown out from cornea biopsies cultured in Waymouth MB 752/1 Medium mixed with an equal volume of Ham's nutrient mixture F12 supplemented with 10% FCS and 50 μg/mL gentamicin. To stimulate cell proliferation epidermal growth factor (10 ng/mL) was added to the cell culture on day 3. L929 cells were cultured in DMEM containing 4.5 mg/mL glucose, 10% FCS, 100 U/mL penicillin G, 100 μg/mL streptomycin (PAA Laboratories GmbH, Cölbe, Germany), and 3.7 g/L $NaHCO_3$. Cells were harvested by trypsination (PAA Laboratories GmbH) and seeded into a 96-well microtiter plate (Greiner Bio-One GmbH, Frickenhausen, Germany). Polymer test specimens for cytotoxicity tests were sterilized by ethylene oxide and then extracted at 3 cm^2/ml extraction medium (no FCS) or used for direct contact tests.[11] Relative vitality after two days ($n = 4$), either compared to untreated controls (extracts, 2000 cells/well) or cells cultured on glass substrates (direct contact, 3000 cells/well), was determined by CellQuanti-Blue tests (BioAssay Systems, Hayward, CA, USA).

Results

Synthesis of PCG, Blending, and Material Properties

PCL is a slowly degrading material. PCL-based polymers were expected to have higher degradation rates, if glycolide units would be introduced in the copolyester backbone as more easily hydrolyzable links. During synthesis of PCG by ring opening polymerization, $(Bu)_2SnO$ was employed as a transesterification catalyst in order to obtain a homogeneous distribution of glycolide in the polyester chains. However, in order to preserve the capability of PCL segments to crystallize and show a thermal transition clearly above body temperature, the glycolide content should be low and was fixed to 8 wt.%.[5] In this study, PCG as well as a blend (50/50 w/w) of PCG and PCL being prepared by melt extrusion were characterized in order to explore blending as a strategy to combine advantageous material properties of the used components.

The average molecular weights of the employed polymers were characterized by multidetector GPC analysis. The shortcomings of the GPC standard (or 'conventional') calibrations with polystyrene standards and refractive index detection only became evident from the comparison given in Table 1. Standard calibration, which assumes matching retention times of (in this case) chemically different standards and samples, strongly overestimated the average molecular weights compared to universal calibration. This can be explained by differences in the hydrodynamic volume of the standard and the sample, which impedes the applicability of the polystyrene standard calibration for PCG. By universal calibration, a low number average mole-

Table 1.
Number average (M_n) and weight average (M_w) molecular weights and polydispersities PD of employed polymers.

Sample	GPC (universal calibration)			GPC (standard calibration)		
	M_n kDa	M_w kDa	PD –	M_n kDa	M_w kDa	PD –
PCL	66.8	109.3	1.6	140.4	226.6	1.6
PCG	16.5	23.1	1.4	29.2	46.3	1.6
PCG/PCL*	23.3	45.7	2.0	43.5	87.9	2.0

*Data correspond to samples after blending by coextrusion, which showed an asymmetric but monomodal distribution in GPC (compare Figure 1).

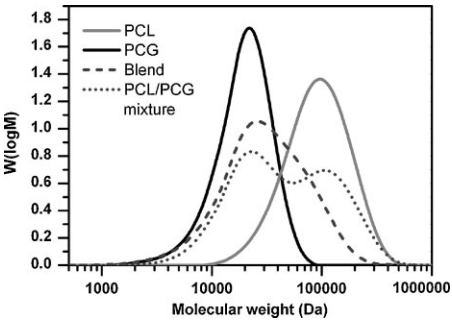

Figure 1.
GPC chromatograph showing alteration of material upon coextrusion.

cular weight M_n of 16.5 kDa was observed for PCG.

In this context, it should be noted, that the blending procedure by coextrusion affected the PCL homopolymer component of the blend. In theory, a bimodal molecular weight distribution of the blend was expected, which was also observed for a physical mixture of PCG and PCL without coextrusion. In contrast, after coextrusion a single broad asymmetric was detected for the PCG/PCL blend (Figure 1). In order to evaluate the probability of thermal degradation during coextrusion at 100 °C, TGA and DSC analysis were applied to characterize the thermal properties of the polymers. As summarized in Table 2, the processing condition was clearly above the melting transition temperature T_m of the PCL segments and below the onset of thermal decomposition. However, it cannot be excluded that the combination of temperature and pressure as present in the extruder may have caused thermal degradation of PCL or that mechanical stress may have resulted in rupture of long entangled PCL chains. Transesterification between PCG (M_n 16.5 kDa) and PCL (M_n 66.8 kDa) could be another potential mechanism, which could influence the molecular weight distribution curve of the blend. Transesterification should have affected the molecular weight distribution of PCG as well as PCL.

The glycolide units distributed in the PCG chain are expected to act as defects in terms of crystallization, since only the PCL-rich segments of PCG will be able to crystallize. Accordingly, smaller crystallites and a lower T_m are expected for PCG. Interestingly, PCG in some cases showed two melting peaks in the second DSC cycle. This could be confirmed in an additionally performed third DSC run. The observed two melting transitions indicate the presence of crystallites of different perfection from PCL-rich segments. After coextrusion, the melting transition of the PCL homopolymer at 56 °C was dominating the thermal properties of the blend, while the melting transition associated to PCL-rich segments of PCG (41 °C) only appeared as a shoulder of the main melting peak (Table 2).

The fact that after blending no shift of the T_m of the PCL homopolymer component occurred and that the corresponding ΔH_m was in the expected range indicated that incorporation of PCG may not have disturbed the crystallite formation in the material. Wide-angle scattering studies showed by trend a higher crystallinity and slightly smaller average crystallite size for the blend compared to pure PCL or PCG (Figure 2). Often, a higher crystallinity can be observed for a specific polymer if the molecular weight is decreased, which can

Table 2.
Characterization of the thermal properties of the blend and its components.

Sample	DSC		TGA				
	T_m	ΔH_m	Remaining mass (%) at temperature				
	°C	$J \cdot g^{-1}$	100 °C	200 °C	300 °C	350 °C	400 °C
PCL	57	64	100	99.8	99.2	98.5	76.7
PCG	34; 41	45; 28	99.9	99.7	98.4	94.3	16.7
PCG/PCL	41; 56	21; 46	100	99.9	99.0	96.8	68.8

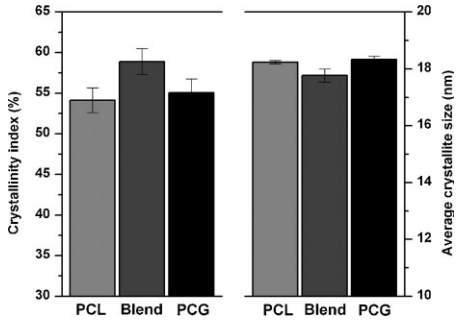

Figure 2.
Crystallinity index and average crystallite size as determined by WAXS (n = 3–9, mean, S.D.).

be explained by less entanglements and an improved sterical capability of shorter chains to properly orientate for crystallization. In the case of PCG with much lower molecular weight than the employed PCL, the effect of decreasing molecular weight may have been impeded by the presence of glycolide in the polymer chains, which disturb crystallisation. Thus, by chance, similar values may have resulted for PCL and PCG. Possibly, in the blend, PCL rich segments of the short chained PCG were able to diffuse into the entangled PCL homopolymer, thereby interacting with oriented PCL chains and enabling more crystallization (Figure 2).

Mechanical properties of materials for medical devices are highly relevant for their functionality, since implants often have to exhibit suitable strength for structural support of a tissue and at the same time suitable elastic properties, e.g., for cardiovascular applications.[2] Importantly, implants will always be subjected to mechanical stress after implantation and/or during insertion in the body. Therefore, the mechanical properties of the synthesized PCG were characterized by tensile tests. Surprisingly, compared to pure PCL, PCG exhibited very poor mechanical properties in terms of brittleness at room temperature and could not be handled in tensile tests at 37 °C (Table 3). The PCG material was brittle and, thus, hard to handle, which would impede its applicability as implant material.

Generally, blending is an often used approach in polymer engineering to adjust the mechanical properties of a material depending on the content of the added component(s). Therefore, when assuming additive contributions of both components, one may expect that blending of PCL with PCG resulted in compromised mechanical properties. Surprisingly, this was not the case as was most obvious from ε_B (Table 3), which was very low for PCG but had similar values for PCL and the PCG/PCL blend. In general, mechanical properties of linear polymers are strongly affected by their molecular weight and, as applicable for PCL spherolites, the presence of molecular superstructures. After blending, the entangled PCL homopolymer with the higher molecular weight (Table 1) dominated the mechanical properties. Importantly, in this way, the advantageous mechanical properties of PCL as desirable for implant materials were added to the features of the PCG/PCL blend.

Suitability of the Materials for Processing by Different Techniques

The obtained PCG could be processed by different techniques such as melt compression into films. However, in many cases, 3D structured polymeric devices such as scaf-

Table 3.
Mechanical properties of film samples as determined in tensile tests.

Sample	20 °C			37 °C		
	E MPa	σ_{max} MPa	ε_B %	E MPa	σ_{max} MPa	ε_B %
PCL	280 ± 10	30 ± 3	720 ± 65	200 ± 20	30 ± 5	920 ± 100
PCG	200 ± 10	6 ± 1	2.7 ± 0.4	n.d.*	n.d.*	n.d.*
PCG/PCL	200 ± 20	20 ± 3	900 ± 230	130 ± 16	12 ± 1	730 ± 60

*Could not be determined due to low T_m.

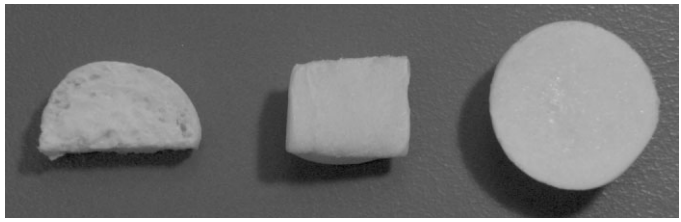

Figure 3.
PCG (cross section), PCG/PCL blend, and PCL samples (from left to right) as obtained by foaming with liquid CO_2.

folds are required for biomedical implants. Therefore, the general capability of the material for foaming with liquid CO_2 in a pressure chamber should be demonstrated. From these preliminary studies, foams were easily obtained with large internal pores but low porosity at the surface (Figure 3A).

In contrast, melt extrusion of PCG as a standard processing technique with high throughput and high industrial relevance was associated with challenges. When aiming to obtain polymer rods or catheters, the extruded product was very soft and did not solidify at ambient conditions nor could be easily transferred to a water bath for cooling. Additionally, due to their brittleness, extruded products could hardly be handled. In contrast, PCL showed excellent performance during processing by melt extrusion with different dies as well as during injection molding, which is why blending of PCG/PCL (50/50 w/w) was performed. This blending step enabled processing the material by melt extrusion, e.g, to rods. It may therefore be noted that the PCL component increased the number of suitable processing techniques for the blend.

Hydrolytic Degradation

The design of PCG with the introduction of few glycolide units as weak links into PCL during polymer synthesis was motivated by the aim to accelerate hydrolytic degradation. As mentioned above, in order to avoid disturbance of crystallization of PCL-rich segments of PCG, the glycolide content had to be kept low. Therefore, the suitability of only 8 wt.% glycolide to increase hydrolytic degradation was evaluated at 37 °C in phosphate buffer of pH 7.4.

For relatively hydrophobic PCL-based polyester materials that are known to undergo bulk degradation, the availability of water for inducing chain scission as measured by the water uptake H might be considered as a first indicator for possibly observed degradation rates. In hydrophobic semi-crystalline materials, polymer crystallites will not be permeated or easily dissolved by water, which is why water uptake into the matrix will preferentially occur through the amorphous polymer phase. The presence of glycolide as more hydrophilic units in these amorphous segments should incease water uptake. As illustrated in Figure 4A, H values remained very low for PCL during an extended, one-year degradation study. In contrast, H linearly increased for PCG during this time period from low initial values up to $> 15\%$.

Upon hydrolysis, oligomers are formed. At some stage, these degradation products gain water solubility, diffusivity, and finally are removed from the polymer bulk into the medium as analytically detected by the mass loss μ_{rel}. As illustrated in Figure 4B, PCL showed only a very minor mass loss, while a linear μ_{rel} of almost 35 wt.% was observed for PCG. This illustrates the capability of glycolide to be used as a tool to strongly alter degradation pattern even if introduced in copolyesters only at a low weight content.

Upon blending of PCG with PCL at a 50/50 weight ratio, the total number of weak links in the material was decreased. Still, water uptake was not impeded at all and

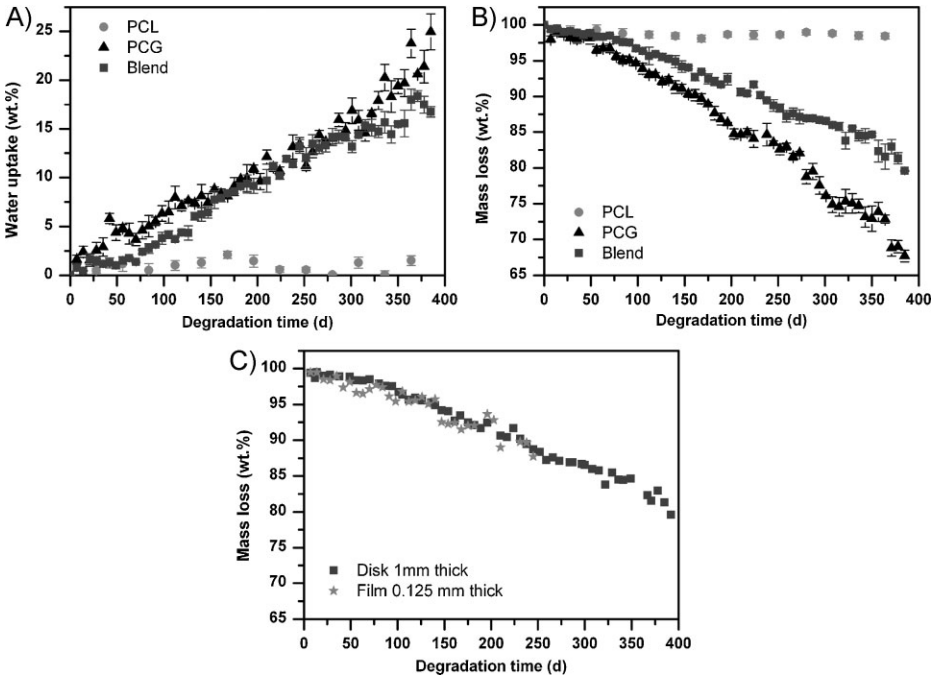

Figure 4.
Hydrolytic degradation of the blend and the pure components (n = 3, mean, S.D.). (A) Water uptake H of disk-shaped samples. (B) Mass loss μ_{rel} of disk-shaped samples. (C) Effect of sample thickness on mass loss of blend samples.

showed values similar to pure PCG (Figure 4A). Increasing water uptake due to the introduction of glycolide by copolymerization is generally expected, because of its more polar nature and thus a higher hydrophilicity of the resulting matrix.[12] Apparently, not only the overall weight content of glycolide units rules the water uptake. Possibly, the presence of glycolide units may have altered the preferred sterical arrangement of polymer chains in the amorphous segments and allowed for similar water uptake pattern in PCG and in the blend. Also, the entangled polymer chains may have hindered a theoretically higher H in pure PCG and the blend and limited it to a similar value. During subsequent scission of the entangled polymer chains, H was similarly increased for PCG and the blend. Mass loss, however, is ruled by the solubility of degradation products, which apparently was highest for PCG due to its highest content of more hydrophilic glycolide units (Figure 4B). During hydrolytic degradation, a shift in the blend composition can be expected towards higher PCL contents, since PCG will be preferentially hydrolyzed and removed.

Often, the sample geometry and size affects the degradation pattern of bulk degrading (co)polyester materials. Limited diffusivity and accumulation of degradation products in the core of the samples may accelerate degradation by acidic autocatalysis. In order to study the potential effects of autocatalysis, planar samples of different dimensions were tested, i.e., 125 μm thick films and 1 mm thick disks. This corresponds to an about tenfold increase of diffusion lengths from the sample core to the surface. These sample thicknesses are below and above the dimensions that were observed to be critical for autocatalytic acceleration of degradation as reported for poly(*D*,*L*-lactide).[13] Advantageously, no differences in mass loss were observed for

different sample geometries (Figure 4C). A linear rather than a sigmoid pattern of μ_{rel} as often observed for other linear copolyesters such as poly[(*rac*-lactide)-*co*-glycolide] was detected. This indicated that the structural arrangement of polymer chains in PCG and its blend with PCL may have enabled continuous removal of degradation products. Importantly, the PCG component was found to dominate and advantageously increase the hydrolytic degradation of the blend compared to pure PCL. Degradation of PCL may be additionally accelerated in the presence of certain enzymes.[14]

Testing of Cytotoxicity

For biomedical applications of polymer-based biomaterials such as for implants or drug delivery systems, the potential cytotoxicity of the materials has to be characterized. This analysis should be performed according to the regulations of the ISO 10993 series and typically bases on cell lines such as L929 murine fibroblasts. When adding both, extracts of PCL (Figure 5A) and the blend (Figure 5B) at serial dilutions to the cells, a clear dependency of extract dose and relative viability (compared to untreated cells) was observed for L929 fibroblasts (Figure 5). In direct contact tests, cells were cultivated on glass cover slips or on polystyrene as non-cytotoxic controls, on tin-substituted poly(vinyl chloride) [SnPVC] as highly cytotoxic control, and on films of PCL and the blend material. While PCL samples did not provide a good substrate for L929 cells, the blend samples were much more compatible with these cells (Figure 5C).

In addition to murine fibroblast cell lines, it is important also to consider the effect of new biomaterials on cells relevant for the application, i.e., primary cells of the specific target organism. As a model, the

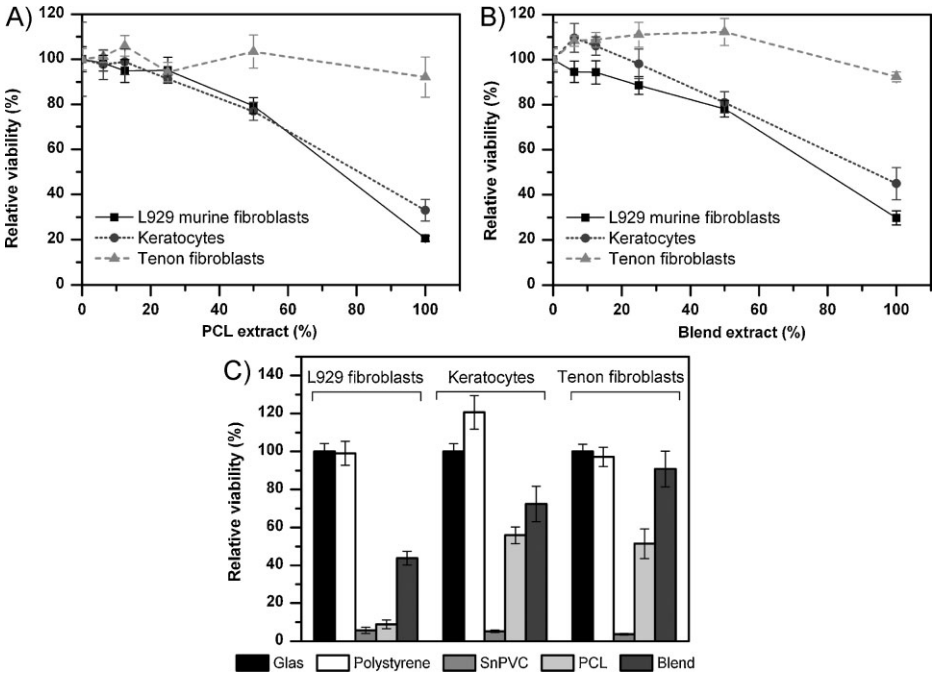

Figure 5.
Evaluation of cytotoxicity with the L929 murine fibroblast cell line as well as primary human keratocytes and Tenon fibroblasts. Relative viability of cells treated with PCL (A) and blend (B) extracts compared to untreated control. (C) Relative viability of cells cultured on different substrates in a direct contact test using glass as reference, polystyrene as non-cytotoxic controls, tin-substituted poly(vinyl chloride) as highly cytotoxic control (SnPVC).

materials were tested with some primary human cells found in the eye, i.e., Tenon fibroblasts and keratocytes. Polymer extracts had a similar effect on keratocytes as observed for mouse L929 fibroblasts. In contrast, Tenon fibroblasts were not affected at all (Figure 5). When primary cells were cultured in direct contact with the polymers, compatibility was acceptable particularly in the case of the blend with Tenon fibroblasts (Figure 5C). Since cytotoxic residuals from the synthesis may have been eluted from PCL and the blend (Figure 5A, 5B), it should be investigated on whether pre-incubation of the materials in water reduces material cytotoxicity. Importantly, the extracts should be analyzed to identify the potentially toxic substances. Furthermore, to transfer the blend material in a clinical application, each process step in the complex development chain will have to be checked to eliminate potential residues for establishing medical grade materials.[15]

Conclusion

A copolymer of ε-caprolactone with 8 wt.% diglycolide (PCG) was prepared, which showed an accelerated hydrolytic degradation compared to the very slowly degrading poly(ε-caprolactone), but exhibited only poor elastic properties. The elastic properties of PCG might be improved by higher molecular weights of the copolymer. Here, by blending poly[(ε-caprolactone)-*co*-glycolide] and poly(ε-caprolactone), the advantageous properties of both components could selectively be combined, resulting in a material showing i) elasticity rather than brittleness, ii) linear profiles of water uptake and hydrolytic mass loss rather than very slow or uncontrolled degradation, iii) independence of degradation from sample geometry in the tested micrometer to millimeter range, iv) suitability for various processing techniques, and v) promising results in selected first cytotoxicity tests. Therefore, the blend of poly[(ε-caprolactone)-*co*-glycolide] and poly(ε-caprolactone) may be useful as biomaterial, e.g., as matrix for implants or drug delivery systems.

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