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Polymer 46 (2005) 6746–6755
polymer
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Potential tissue implants from the networks based on 1,5-dioxepan-2-one and ε-caprolactone

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Received 8 April 2005; received in revised form 9 June 2005; accepted 13 June 2005
Available online 14 July 2005

Abstract

The synthesis and characterization of degradable polymeric networks for biomedical applications was performed. Cross-linked films of poly(ε-caprolactone) (PCL) and poly(1,5-dioxepan-2-one) (PDXO) having various mole fractions of monomers and different cross-link densities were successfully prepared using 2,2′-bis-(ε-caprolactone-4-yl) propane (BCP) as cross-linking agent. Reaction parameters were carefully examined to optimise the film-forming conditions. Networks obtained were elastomeric materials, easy to cast and remove from the mould. Effect of CL content and cross-link density on the final properties of the polymer network was evaluated. High CL content or degree of cross-linking led to increase in Young's modulus and decrease in elongation at break. An increase in crystalline domains in films having a higher CL content was observed by optical microscopy. A greater thermal stability was observed in films having a high CL content. The hydrophilicity of the materials could be tailored by changing the CL content. The surface of the films became rougher with higher CL content.

Keywords: 1,5-Dioxepan-2-one; ε-Caprolactone; 2,2′-Bis-(ε-caprolactone-4-yl) propane

1. Introduction

The need for polymers with strictly defined structures and properties aimed specifically for biomedical applications has necessitated the development of complex and advanced architectures during the last decade. Aliphatic polyesters are leading polymers in the biomedical and pharmaceutical industries because of their good mechanical properties, hydrolyzability, biocompatibility and controlled degradability [1,2]. Considerable research efforts have been made in the past to enhance the properties of these polymers and thus diversify their application areas. For example, the use of biodegradable aliphatic polyesters as a scaffold material providing a framework for the cells to attach, proliferate and form the extracellular matrix is an emerging research area in the field of tissue engineering [3]. These scaffolds may also serve as carriers for cells growth factors etc. Some of the essential requirements of biodegradable and biocompatible scaffolds are porosity, correct pore size (for candidate cells), permeability (for the proper diffusion of nutrient, transport of proteins and waste removal), and a surface conducive to cell attachment. Surface characteristics such as hydrophilicity, surface charge density, surface micro-morphology and specific chemical groups affect the cell adhesion and spreading and thus regulate a wide variety of biological functions. Polymers of lactic acid (PLLA), glycolic acid (PGA), ε-caprolactone (CL) and their copolymers have been widely used to create scaffolds for muscoskeletal tissue [4,5].

A number of ways to influence both the chemical and the physical properties of these polyesters have been reported, such as by varying the composition, polymerization and/or processing conditions. One of the approaches is the cross-linking of homo- and copolymers of linear systems to improve mechanical properties of these materials. This may offer several other advantages over linear systems, such as a more consistent loss of mass over time, which can avoid a sudden decrease in strength before the total loss of mass occurs [6]. A broader spectrum of mechanical properties

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doi:10.1016/j.polymer.2005.06.038

and degradation patterns can be achieved with cross-linked systems to meet the vast demand of biomedical applications. Polymeric networks can be synthesized by copolymerization of monomers with multi-functional cross-linking agent or reaction of a prepolymer with a cross-linking agent. Our group has developed degradable cross-linked films by copolymerization of 1,5-dioxepan-2-one (DXO) with a multifunctional cross-linking agent having reactivity similar to that of the monomer [7–9]. Cross-linked films could be formed with adipic anhydride using difunctional epoxide as a cross-linking agent [10]. Synthesis of polymeric networks based on six- and seven-member substituted lactones and ether-lactones, polycarbonates and polyesters following similar strategy have also been reported by other groups [11–14]. Recently the strategy of using a prepolymer to develop hydrogels was explored by our group where end-functionalized star shaped polymers, which can be photocross-linked, were synthesized using $Sn(Oct)_2$ as catalyst and pentaerythritol as branching agent [15]. Another approach used was synthesis of star-shaped and linear copolymers by spirocyclic and five-member cyclic tin initiators, which can further be used as sites for cross-linking using di- or tetra-functional acid chlorides [16]. Linear and three-armed structures of poly(caprolactone-*co*-valerolactone) and various copolymers of D,L-lactide, glycolide, ε-caprolactone (CL) and trimethylene carbonate were developed by other groups using hydroxyl or epoxide functionalities to cross-link [17–21].

As mentioned above, the networks of poly(1,5-dioxepan-2-one) (PDXO) have been formed using 2,2′-bis-(ε-caprolactone-4-yl) propane (BCP) as the cross-linking agent by our group [7,8]. The properties of such networks can be altered by incorporation of a co-monomer along with DXO. Linear PDXO is an ether-containing amorphous polyester and has a T_g of −39 °C [22]. Introduction of CL in the networks of DXO may improve its mechanical properties and dimensional stability. Cross-linked films of these co-monomers may give biodegradable material with a surface conducive for cell growth. It has been shown that the bulk polymerization of CL with DXO using $Sn(Oct)_2$ as initiator gave an ideal copolymer as a result of the similar reactivity ratios of the two co-monomers [23]. The advantage of incorporating CL into the network is that its molecular structure is similar to the cross-linking agent, which would not significantly alter the reactivity of the co-monomers and it would still be possible to sterilize these networks for biomedical applications [24]. Poly(ε-caprolactone) (PCL) is a tough, flexible biocompatible polymer with a melting point (T_m) around 60 °C and a (T_g) much below room temperature (−60 °C). It is permeable to low molecular weight species at body temperature. Both PDXO and PCL are hydrolytically degradable. Significant changes in T_g and crystallinity of copolymers of CL and DXO have been observed with changing feed composition [23,25–27]. Thus it is possible to tailor the properties of these copolymers to suit specific requirements.

Our objective was to develop easy to cast, strong and elastic cross-linked films which could be easily removed from the mould surface. DXO and CL were used as the co-monomers and were cross-linked with BCP as the cross-linking agent. This cross-linker was synthesized by a modification of the process reported before. The effect of reaction parameters, co-monomer composition and degree of cross-linking on physical and mechanical properties of networks of DXO and CL was evaluated.

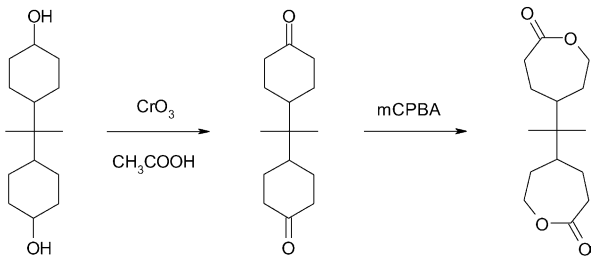
2. Experimental

2.1. Materials

ε-Caprolactone (Aldrich, Germany) was dried and distilled over CaH_2 at reduced pressure prior to use. Stannous octoate (Aldrich, Germany) was distilled under reduced pressure. Tetrahydro-4H-pyrane-4-one (Maybridge Chemical, UK), 2,2′-bis-(4-hydroxycyclohexyl) propane (Aldrich, Germany), acetic acid (Fluka, Sweden), chromium oxide (Aldrich, Germany), *m*-chloroperbenzoic acid (Acros, Belgium), isopropanol, toluene, dichloromethane, $MgSO_4$, $NaHSO_3$, $NaHCO_3$, diethyl ether and acetone (Labora, Sweden) were used as received. BCP and DXO were synthesized as described in the following sections.

2.2. Synthesis of 2,2′-bis-(ε-caprolactone-4-yl) propane (BCP)

BCP was synthesized according to Scheme 1 by a modified approach to the procedure given elsewhere [8]. An isomeric mixture of 2,2′-bis-(4-hydroxycyclohexyl) propane (30 g) was dissolved in 240 ml of acetic acid in a round-bottom flask which was cooled to 10 °C in a water-ice bath. 37.2 g of CrO_3 was dissolved in a mixture of 200 ml of acetic acid and 40 ml of water, and added drop-wise to the flask over a period of 1 h under continuous stirring. After 30 min, 400 ml of isopropanol was added to the mixture, which was stirred overnight. The mixture was subsequently concentrated under reduced pressure and the resulting thick solution was precipitated in water. The precipitated white powder was recrystallized from toluene and the di-ketone, 2,2′-bis-(4-cyclohexanone) propane, was obtained after



Scheme 1. Synthesis of BCP.

filtration and drying (yield = 76%). A Baeyer–Villiger oxidation was then performed on the di-ketone. 176.7 g of *m*-chloroperbenzoic acid (*m*-CPBA) was dissolved in 2000 ml of CH_2Cl_2 and, after removal of the aqueous phase, it was cooled to 10 °C in a water-ice bath. Twenty-two grams of di-ketone was dissolved in 333 ml of CH_2Cl_2 and added drop-wise over a period of 1 h to the *m*-CPBA solution with continuous stirring. The mixture was stirred overnight. The acid was neutralized by sodium bisulphate–sodium bicarbonate treatment and the resulting organic phase was concentrated to a white powder under reduced pressure. The white powder obtained was finally recrystallized from acetone and dried under vacuum (yield = 70%). ^{1}H NMR δ (ppm): 4.36 (*R*,*R*), 4.16 (*S*,*R*) (t, 2H, –*CH*$_2$OOC–), 2.74 (*R*,*R*), 2.58 (*S*,*R*) (t, 2H, –*CH*$_2$COO–), 1.95 (q, 2H, –*CH*$_2$–C–OOC–), 1.59 (q, 2H, –*CH*$_2$–CH$_2$–COO–) 1.39 (m, 1H, –CH$_2$–*CH*–CH$_2$–), 0.80 (3H, *CH*$_3$–).

2.3. Synthesis of 1,5-dioxepan-2-one (DXO)

DXO was synthesized from tetrahydro-4H-pyran-4-one through Bayer–Villiger oxidation according to the literature [22]. The DXO obtained was purified by recrystallization from diethyl ether and two subsequent distillations under reduced pressure. Finally the monomer was dried over CaH_2 overnight and distilled under reduced pressure. ^{1}H NMR δ (ppm): 4.25 (t, 2H, –*CH*$_2$–OOC–), 3.85 (t, 2H, –*CH*$_2$–O–CH$_2$–CH$_2$–COO–), 3.78 (t, 2H, –*CH*$_2$–O–CH$_2$–CH$_2$–OOC–), 2.85 (t, 2H, –*CH*$_2$–COO–).

2.4. Preparation of cross-linked poly(1,5-dioxepan-2-one), poly(ε-caprolactone) and poly(DXO-co-CL)

Networks were produced by ring-opening polymerization of DXO or CL or their mixture using BCP as cross-linking agent in the presence of stannous octoate ($Sn(Oct)_2$) as a catalyst (Scheme 2).

Monomer(s), BCP and $Sn(Oct)_2$ were weighed in a flask and the mixture was dissolved in a small amount of chloroform and spread over a pre-silanized Petri dish. The chloroform was evaporated under a nitrogen atmosphere and the resultant well-spread mixture was kept in an oven for cross-linking at 140 °C for an initial 1.5 h and finally at 180 °C for 30 min. Both homo- and copolymers containing different mole fractions of CL and DXO and cross-linking agent were prepared. The theoretical cross-linked density ρ (%) was calculated according to the Eq. (1):

$$\rho = \frac{2n}{2n+m} \times 100 \quad (1)$$

where n is the mole fraction of BCP and m is the mole fraction of monomer(s) in the formulation.

3. Characterization

3.1. Nuclear magnetic resonance (NMR)

Monomer conversion during the cross-linking of DXO and CL with BCP was monitored by ^{1}H NMR (400 MHz Bruker Avance) using $CDCl_3$ as solvent and tetramethyl silane as internal standard. Samples were withdrawn at regular intervals to determine the percentage conversion. All the samples were filtered through 0.45 μm disposable filters before ^{1}H NMR analysis.

3.2. Thermal analysis

The thermal characterization of the films was achieved by differential scanning calorimetry (DSC) using a Mettler-Toledo DSC 820 module under a nitrogen atmosphere (nitrogen flow rate 80 ml/min) with a sample mass of 5 ± 1 mg and a heating rate of 5 °C/min. The second heating scan was used for evaluation of the results.

Thermal stability was evaluated by thermo-gravimetric analysis (TGA) under a nitrogen atmosphere (nitrogen flow rate 50 ml/min) with a sample mass of 10 ± 1 mg and a heating rate of 10 °C/min.

3.3. Tensile testing

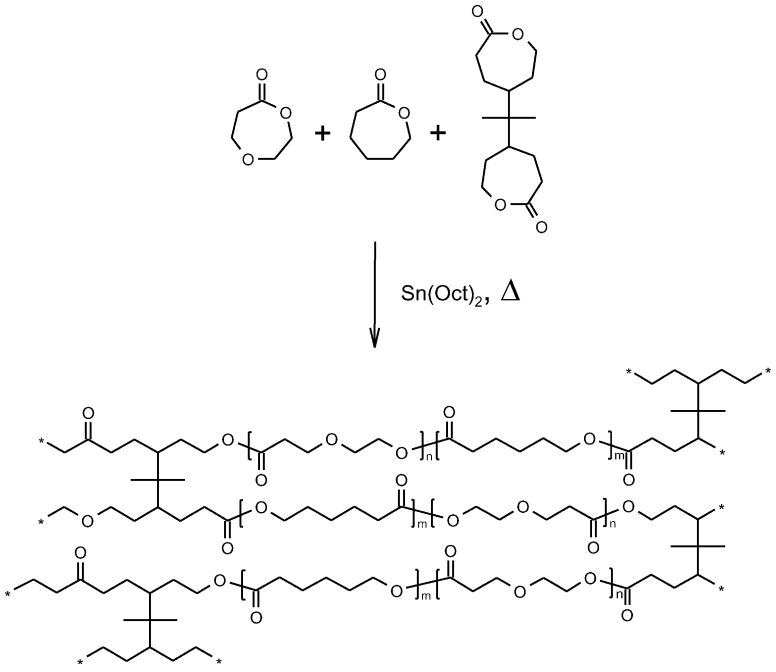
Tensile testing of the copolymers was performed on an Instron 5566 equipped with pneumatic grips and controlled by a Dell 466/ME personal computer. The tensile measurements were made with a crosshead speed of 50 mm/min and an initial grip separation of 32 mm. The samples had dimensions of 80×5 mm and a thickness of approximately 0.5 mm. The average thickness of each sample was calculated from five independent measurements with a Mitutoyo micrometer. The samples were preconditioned for 48 h at 50 ± 5% RH and 23 ± 1 °C. Five different samples from the same film were tested for each network. All tests were carried out in accordance with ASTM D882-95A.

3.4. Hydrophilicity evaluation

The static contact angles were measured on the air side of the films with a Ramé Hart goniometer using the sessil drop technique. Deionized water was used (Millipore, resistivity: 18.4 MΩ cm). The static contact angle was calculated from the mean value of at least eight contact angle measurements at four different positions on the surface.

3.5. Swelling

The degree of swelling of the network was determined gravimetrically. A piece of network film was weighed and kept in a sealed beaker containing chloroform. At regular intervals, the film was taken out; the excess solvent was



Scheme 2. Network formation of DXO and CL using BCP.

removed from the surface with the help of a tissue paper. The film was then weighed and returned to the medium. This procedure was continued until a constant weight was attained. The equilibrium degree of swelling (DS) was calculated according to Eq. (2).

$$\mathrm{DS} = \frac{(W - W_0)}{W_0} \times 100 \tag{2}$$

where W_0 is the initial weight of the dry sample and W is the final weight of the swollen sample.

3.6. Optical microscopy

A polarized optical microscope (Leitz Ortholux POL-BK II) was used to examine the morphology of the films.

3.7. Atomic force microscopy (AFM)

The surface topographies were further analyzed with an atomic force microscope (AFM), CSM Instruments Nano indentor with combined atomic force microscope. The analysis was performed in dynamic contact mode in air using a Pointprobe plus probe with a nominal spring constant of $\sim$46,5 N m^{-1} and a resonance frequency of 181–200 kHz. The length of the cantilever was 223 μm. Image analysis was performed in CSM Instruments ImagePlus v. 3.1.10.

4. Results and discussion

Biomedical applications such as tissue implants, artificial cartilages and skin require strong, elastic and tough polymers, which can withstand the specific requirement of these uses. Poly(1,5-dioxepan-2-one) (PDXO) is an amorphous, sticky material with low impact strength, while poly(ε-caprolactone) (PCL) is a semi-crystalline and tough polymer. When 1,5-dioxepan-2-one (DXO) and ε-caprolactone (CL) are cross-linked during their ring-opening polymerization using 2,2′-bis-(ε-caprolactone-4-yl) propane (BCP) as the cross-linking agent, a strong elastomeric polymer network is formed, where tetra-functional cross-links are incorporated into the growing polymer chains (Scheme 2).

The experimental procedure for such a cross-linking reaction was developed after thorough scouting runs on reaction conditions, particularly the cross-linking temperature and time. Cross-linking could be performed under relatively milder conditions than was previously observed with DXO and BCP alone, and this avoided the thermal oxidation of the material during cross-linking, which was indicated by the generation of colorless films. The molar ratio of co-monomers was varied from 0.2 to 1.0 with respect to CL. For the films having CL molar fraction at 0.2, the theoretical cross-link density was changed from 10 to 40%. The details of composition with the designations of the cross-linked films are given in Table 1. It was observed that BCP dissolves in caprolactone and this meant that it was not necessary to use chloroform as solvent. Cross-linking of PCL and PDXO with BCP under the described conditions led to the formation of smooth, homogeneous, colorless and elastic films which could easily be removed from the mould (Fig. 1). Introduction of CL gave more resilient films with improved tear properties. Films with a high DXO content

Table 1
Formulations of cross-linked films with different molar ratios of CL and DXO

Polymer designation	Theoretical X-link density (%)	Quantity of reagents (mole)			
		CL	DXO	BCP	$Sn(Oct)_2$
P1	10	56	222	17	1
P2	10	111	167	17	1
P3	10	166	111	17	1
P4	10	222	56	17	1
P5	10	279	0	17	1
P6	20	54	217	34	1
P7	30	54	218	58	1
P8	40	55	220	92	1

were transparent and flexible and they became slightly opaque and tough when the CL content was increased to 0.8-mole fraction.

4.1. ^1H NMR

The polymerization was monitored by ^1H NMR by following the disappearance of the resonance signals of oxymethylene protons of monomers (CL or DXO) as a function of time. The intensity of the peak at 4.16 ppm due to oxymethylene protons (–O–CH_2–) of CL monomer decreased with time and finally disappeared after 2 h, indicating that the monomer was completely polymerized (Fig. 2). On the other hand, the resonance signals due to the oxymethylene protons of polymer (PCL) appeared at 3.99 ppm and the intensity of these signals relative to the oxymethylene protons of the monomer increased with increasing polymerization time. Once the polymer was completely cross-linked (after 2 h), no proton resonance signals due to PCL could be observed.

A similar trend was observed with DXO, as shown in Fig. 3. The peaks due to DXO monomer disappeared with time indicating complete monomer conversion, while the relative intensity of the peaks due to PDXO increased with respect to that of the monomer protons. Proton resonance signals due to DXO monomer were observed at 4.25 ppm (t, 2H, –*CH_2*–OOC–), 3.85 ppm (t, 2H, –*CH_2*–O–CH_2–CH_2–COO–), 3.78 ppm (t, 2H, –*CH_2*–O–CH_2–CH_2–OOC–) and

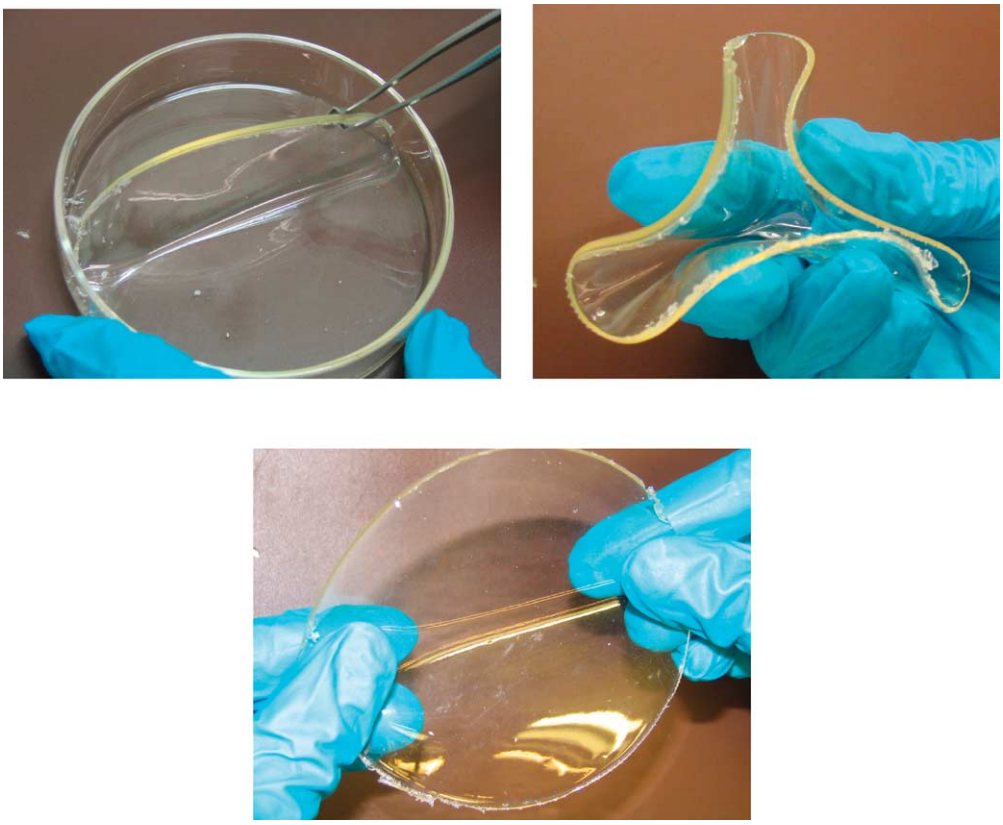


Fig. 1. Easy to remove, flexible, elastic and transparent film of cross-linked DXO-CL.

Proton	δ (ppm)
e	4.16
e'	3.99

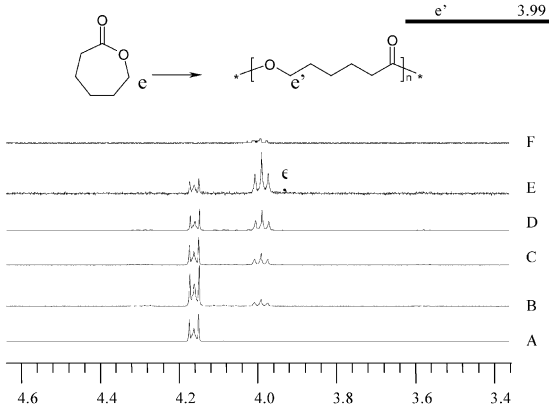


Fig. 2. ^{1}H NMR spectra of reaction mixture during cross-linking of CL with BCP: (A) 0 h; (B) 30 min; (C) 1 h; (D) 1.5 h; (E) 2 h; (F) 2.5 h.

2.85 ppm (t, 2H, $-CH_2$–COO–), which were shifted to 4.16 ppm (t, 2H, $-CH_2$–OOC–), 3.69 ppm (t, 2H, $-CH_2$–O–CH_2–CH_2–COO–), 3.59 ppm (t, 2H, $-CH_2$–O–CH_2–CH_2–OOC–) and 2.56 ppm (t, 2H, $-CH_2$–COO–) in the polymer (PDXO).

Fig. 4 shows the ^{1}H NMR results when CL and DXO were cross-linked together in a 20:80 molar ratio. A similar trend to that of the individual monomer cases was observed. Peaks due to both monomers disappeared with time and the

Proton	δ (ppm)
a	4.25
a'	4.16
b	3.85
c	3.78
b'	3.69
c'	3.59
d	2.85
d'	2.56

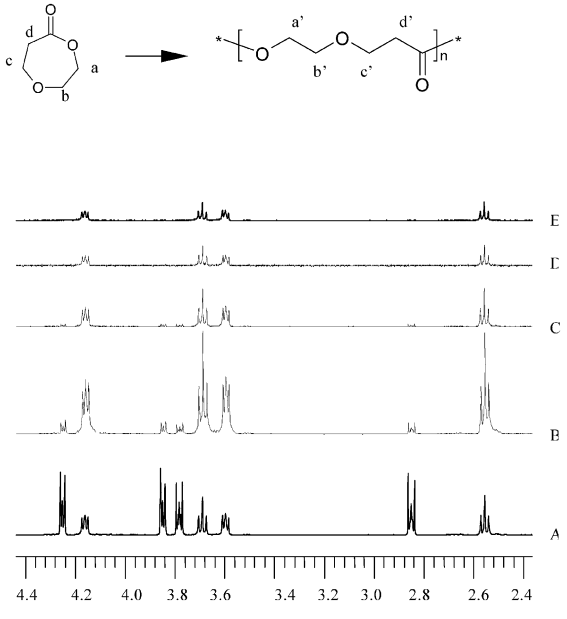
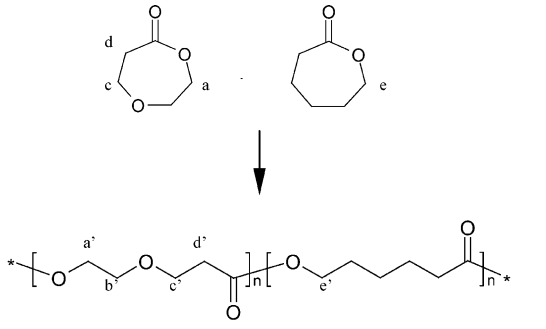


Fig. 3. ^{1}H NMR spectra of reaction mixture during cross-linking of DXO with BCP: (A) 30 min; (B) 1 h; (C) 1.5 h; (D) 2 h; (E) 2.5 h.

Proton	δ (ppm)
a	4.25
a'	4.16
e	4.16
e'	4.01
b	3.85
c	3.78
b'	3.69
c'	3.59
d	2.85
d'	2.56



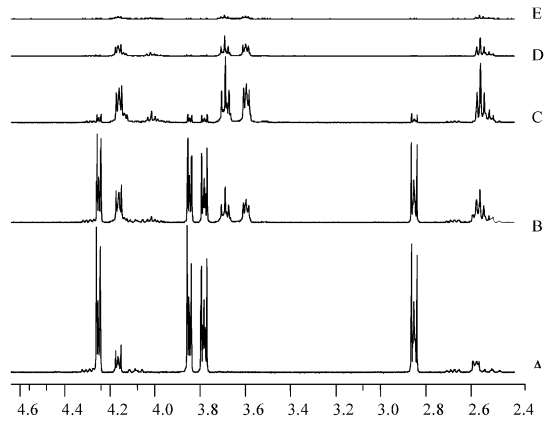


Fig. 4. ^{1}H NMR spectra of reaction mixture during cross-linking of CL:DXO with BCP (sample P1): (A) 30 min; (B) 1 h; (C) 1.5 h; (D) 2 h; (E) 2.5 h.

intensity of the peaks due to poly(ε-caprolactone-*co*-1,5-dioxepan-2-one) (poly(CL-*co*-DXO)) increased with respect to the signals of the monomers. The proton resonance signals appeared at the same positions as were observed for the monomers (CL and DXO) and cross-linked homopolymers (PCL and PDXO).

4.2. Thermal analysis

The DSC results showed a single glass transition temperature (T_g) for all the cross-linked copolymers, which was somewhere between the glass transition temperatures of the respective homopolymers of PDXO (−39 °C) and PCL (−60 °C), indicating the formation of relatively random copolymers. This is in agreement with the results obtained from the bulk polymerization of CL and DXO [23], which formed ideal copolymers due to the

similar reactivity ratios of the two co-monomers. The molecular architecture including molar mass, degree of cross-linking and chain branching also affects the T_g. Cross-links reduce the available free volume and the T_g is thus expected to increase with increasing cross-linking density, and an increase in T_g from −41.2 to −33.5 °C was observed when the cross-link density was increased from 10 to 40%. The approximate crystallinity of the copolymers was calculated according to Eq. (3):

$$w_c = \frac{\Delta H_f}{\Delta H_f^0} \tag{3}$$

where w_c is the crystallinity, ΔH_f is the heat of fusion of the sample, and ΔH_f^0 is the heat of fusion of 100% crystalline PCL. The value of ΔH_f^0 used for the calculations was 139.5 J/g [28]. DSC results and T_g values predicted by the FOX equation are summarized in Table 2.

A representative thermo-gravimetric analysis trace of cross-linked copolymers of CL and DXO is shown in Fig. 5. The characteristic decomposition temperatures and percentage weight losses depend on the backbone structure of the copolymers. As can be seen in Fig. 5, the largest weight loss occurred in the temperature range of 250–350 °C. Within this temperature range, the temperature of the maximum rate of weight loss T_{max} and the percentage weight loss at T_{max} were determined from the differential thermo-gravimetric (DTG) traces. They are plotted against CL content in poly(CL-*co*-DXO) copolymers cross-linked with 10% cross-link density in Fig. 6. A linear relationship between the T_{max} or the percentage weight loss and the CL content was observed, which can be utilized to determine the copolymer composition from thermo-gravimetric traces. A linear relationship was also observed when T_{max} and the percentage weight loss were plotted against cross-link density of the networks, as shown in Fig. 7. An increase in CL content led to more thermally stable polymers, as shown by the increase in T_{max} and decrease in percentage weight loss in Fig. 6. This can be due to the introduction of crystalline domains, which may account for the increased thermal stability of films with a high CL content.

4.3. Tensile properties

In the copolymers of CL and DXO cross-linked with BCP, the modulus increased gradually with increasing CL content. On the other hand, a decrease in elongation at break was observed (Fig. 8). These findings can be attributed to the semi-crystalline nature of the PCL segments present in the network. When only PCL cross-linked with BCP was tested, a modulus of 0.1 GPa and an elongation at break of 440% were obtained. As expected, an increase in cross-link density led to an increase in the modulus and a decrease in the elongation at break, as shown in Fig. 9.

Table 2
Thermal properties of cross-linked CL-DXO-BCP films

Polymer designation	T_g (°C)	w_c (%)	T_g (°C) (from FOX equation)
P1	−41.2	0.0	−39.2
P2	−46.8	0.0	−43.0
P3	−52.3	0.0	−47.6
P4	−56.9	1.0	−53.5
P5	−62.5	18.6	
P6	−39.6	0.0	
P7	−34.7	0.0	
P8	−33.5	0.0	

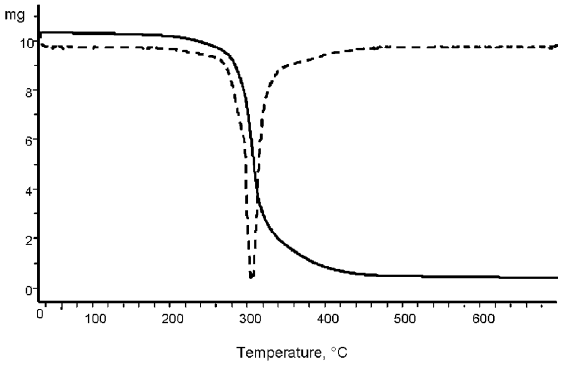


Fig. 5. Thermogravimetric trace of cross-linked CL:DXO with BCP (sample P2): TGA (—), DTG (- - -).

4.4. Hydrophilicity evaluation

It has been observed in previous study [27] that higher the CL content, the more hydrophobic the surface will be. As shown in Fig. 10, a linear increase in contact angle was observed when the CL content was increased from 20 to 100%. The hydrophilicity of the materials can thus be tailored by changing the CL content. An increase in the contact angle was observed with higher cross-link density (Fig. 10). This can be due to the presence of BCP, which increases the hydrophobicity of the network.

4.5. Swelling

With increase in CL content, a decrease in degree of swelling was observed, as shown in Fig. 11. This may be due to semi-crystalline nature of CL where the diffusivity of solvent molecules is less, leading to lower swelling values.

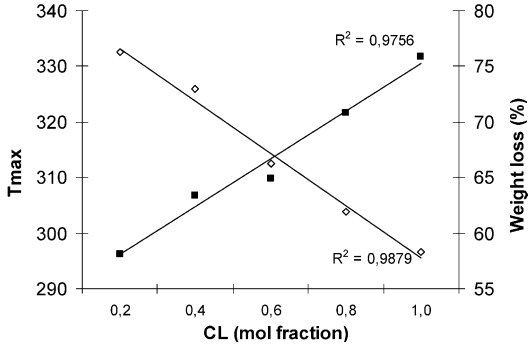


Fig. 6. Effect of CL content on decomposition temperature, T_{max} (■) and percentage weight loss (◇) of netwroks of CL and DXO having 10% theoretical cross-link density.

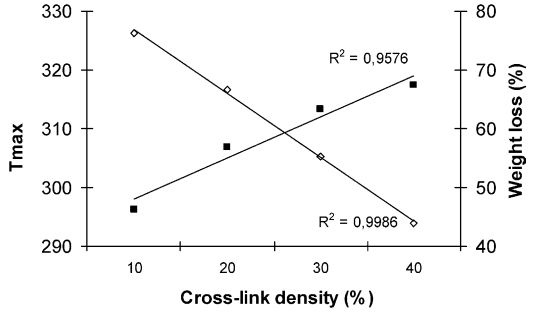


Fig. 7. Effect of cross-link density on decomposition temperature, T_{max} (■) and percentage weight (◇) loss of networks of CL and DXO (molar ratio 20:80).

The degree of swelling was expected to decrease with increasing cross-link density, since there was less space available for swelling of the network. As shown in Fig. 11, the expected trend was observed till the theoretical cross-link density was increased to 30%. Although a further increase in cross-link density led to an increase in the degree of swelling. This could be explained by the inhomogeneous cross-linking happened in this case due to very high amount of BCP. Since the amount of CL was very small in this film the solubility of BCP is greatly affected as it is more soluble in CL than DXO.

4.6. Morphology

PCL is a semi-crystalline polymer while PDXO is an ether-containing polyester which is totally amorphous. Results from thermal analysis showed a single glass transition temperature, indicating that the cross-linking of CL and DXO with BCP generates random copolymers. When the CL content was increased above a certain level, there was an expected tendency for PCL blocks to be formed that can crystallize in these cross-linked networks. Microcrystalline domains could be observed in photomicrographs of samples having a CL content of 80% or more. Below 80%, no significant features due to crystallinity could be seen. These crystalline domains were responsible for a gradual increase in the mechanical properties of networks with increase in CL content.

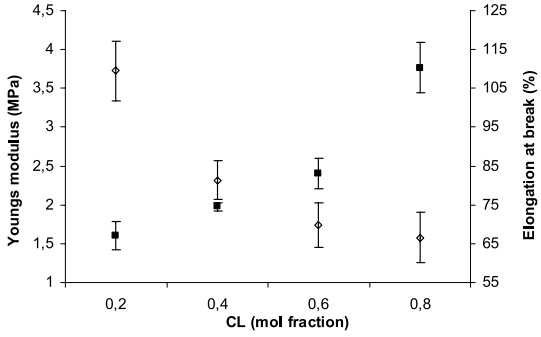


Fig. 8. Effect of CL content on tensile properties; Youngs modulus (■) and elongation at break (◇) in networks of CL-DXO having 10% theoretical cross-link density.

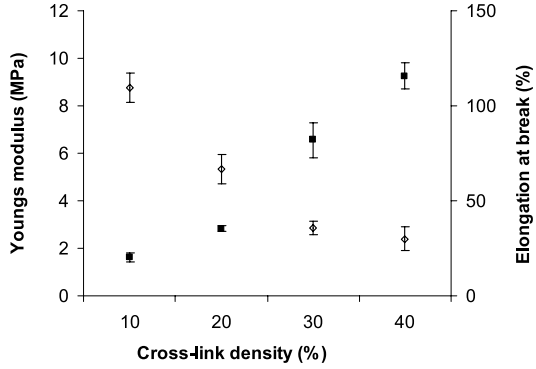


Fig. 9. Effect of cross-link density on tensile properties; Youngs modulus (■) and elongation at break (◇) in cross of CL and DXO (molar ratio 20:80).

4.7. Surface topography

These cross-linked copolymers were developed as scaffolds for tissue engineering applications and it was therefore necessary to evaluate the surface properties of the networks. Surface topography is a crucial aspect, which is required to be at an optimal level for cell growth and proliferation, since cells adhere differently to different surfaces depending upon the topography. In order to have a better understanding of height variations on surface of the cross-linked network, atomic force microscopy measurements were made on series of cross-linked copolymers having cross-link density of 10% (P1 to P5). It could be deduced from the surface analysis that roughness of the surface increased with higher CL content. This trend is shown in three-dimensional images of polymers P3, P4 and P5 in Fig. 12. Densely populated hills were observed in P5 and the surface became smoother from higher to lower CL content. On the other hand, the surface roughness was slightly increased in copolymer P1 as sparsely and unevenly distributed hills could be observed. This may be due to the localized presence of cross-link points from BCP, which was possible as BCP has lower solubility in DXO and therefore tend to remain in the CL rich areas.

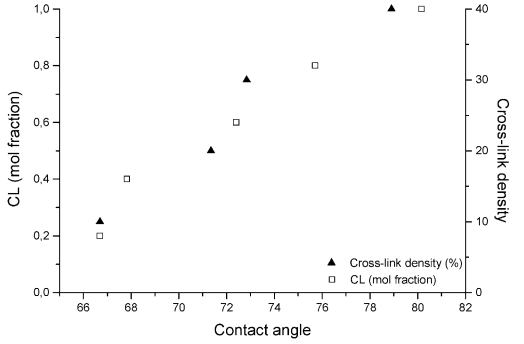


Fig. 10. Effect of CL content (with 10% cross-link density) and cross-link density (with CL and DXO molar ratio of 20:80) on contact angle in cross-linked films of CL-DXO.

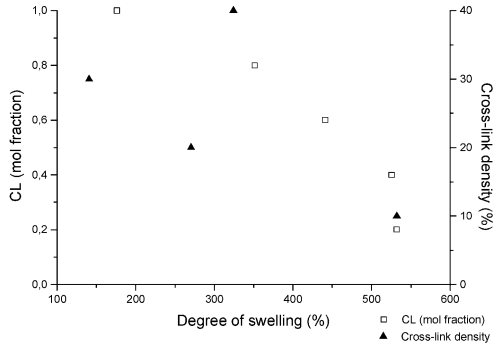


Fig. 11. Effect of CL content (with 10% cross-link density) and cross-link density (with CL and DXO molar ratio of 20:80) on the degree of swelling in cross-linked films of CL-DXO.

4.8. Cell response measurement

The cell growth has been tested on these CL–DXO–BCP-based network films by the groups of Prof U. Lindgren, Karolinska Institute at Huddinge University Hospital, Sweden and Prof G. Kratz, University Hospital of Lindköping, Sweden. The preliminary evaluation of cell growth has shown positive results on these films and it will be communicated in a separate article.

5. Conclusions

Easy to cast, smooth and elastic cross-linked films based on CL and DXO using 2,2′-bis-(ε-caprolactone-4-yl) propane (BCP) as the cross-linking agent were successfully obtained. The cross-linker could be synthesized by an improved method than reported before. Improvement in the tear properties of the films could be deduced as they could be easily removed from the mould surface. Homogeneous films were obtained under relatively mild cross-linking conditions. The absence of thermal oxidation of the material during cross-linking was inferred from the generation of colorless and transparent films. The ^{1}H NMR results indicated complete monomer conversion and the formation of cross-linked networks. Random copolymers were formed during cross-linking, as revealed by a single glass transition temperature in the DSC thermograms. Introduction of PCL crystalline domains gave high thermal stability to networks. A gradual increase in Young's modulus and a decrease in elongation at break was observed with higher CL content, which can again be attributed to the semi-crystalline nature of PCL segments present in the network. The resilient properties were improved with higher CL content. Increasing cross-link density led to a higher modulus and lower

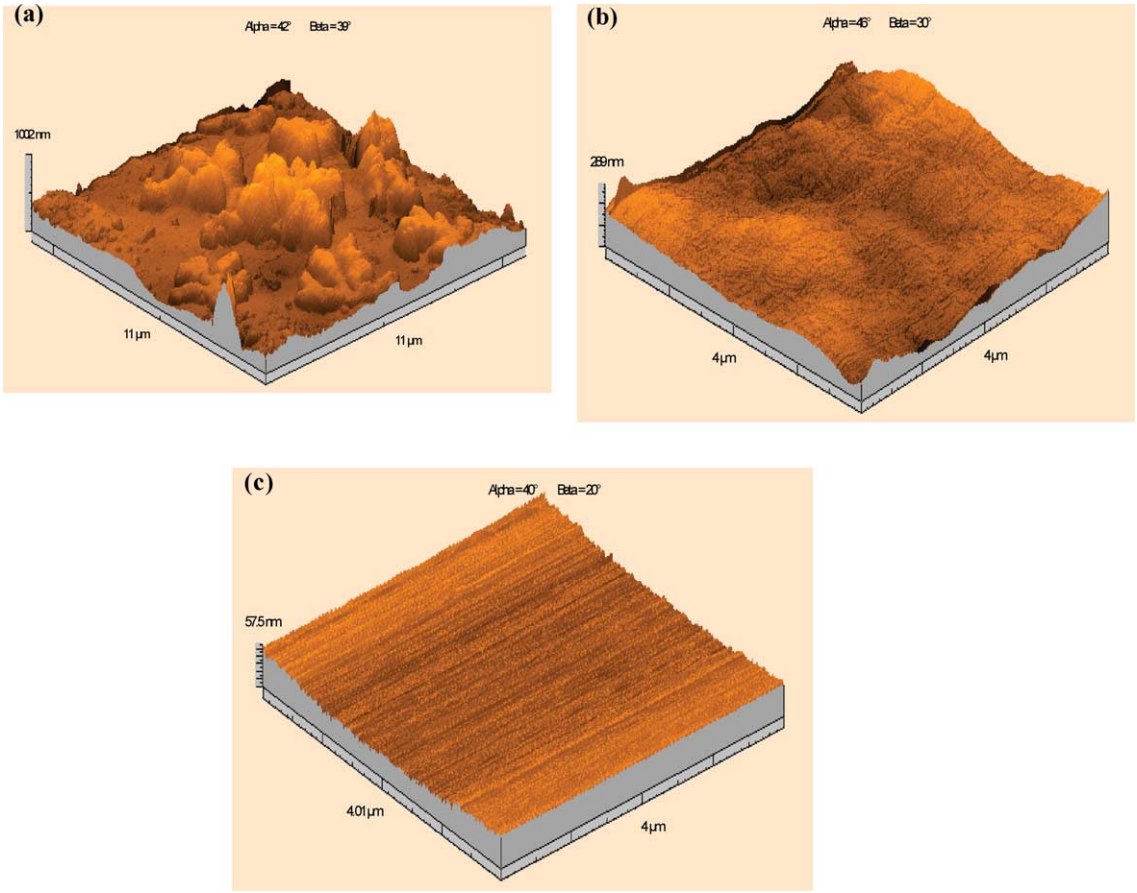


Fig. 12. AFM topographical three-dimensional image of networks of CL-DXO having 10% cross-link density: (a) CL content 1.0 mol fraction (P5) (b) CL content 0.8 mol fraction (P4) (c) CL content 0.6 mol fraction (P3).

elongation at break, as expected. Increasing CL content or increasing cross-link density decreased the hydrophilicity of the networks, as indicated by the contact angle measurements. The hydrophilic-hydrophobic balance of the networks surfaces could be tailored in this way. The roughness of the film surface increased with higher CL content. These cross-linked films have potential to be used in biomedical applications such as scaffolds for tissue engineering.

Acknowledgements

The authors thank Swedish Foundation for Strategic Research, Grant No A302:132, STINT (The Swedish Foundation for International Cooperation in Research and Higher Education) and The Royal Institute of Technology for financial support for this work.

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