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On the role of aminolysis and transesterification in the synthesis of ε-caprolactone and L-lactide based polyurethanes

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Summary

Polyurethanes based on a 50/50 copoly(L-lactide/ε-caprolactone) prepolymer and butanediisocyanate were made. Chain extending a diisocyanate terminated prepolymer with butanediamine was not possible due to the susceptibility of the lactide bond to aminolysis. Chain extension with butanediol resulted in a polymer with poor mechanical properties due to transesterification. When the copolymer prepolymer was chain-extended with an isocyanate terminated block, transesterification with the chain-extender was avoided and the mechanical properties were increased. When the length of the hard segments was increased the mechanical properties increased further. A L-lactide/ε-caprolactone based polyurethane with a tensile strength and modulus of respectively 45 MPa and 60 MPa was made. The polymer contained no poly(L-lactide) crystals and was easy to process. Compared to the high molecular weight 50/50 copoly(L-lactide/ε-caprolactone) the polyurethane showed better mechanical properties, is expected to have the same adhesive properties and is expected to have a slower degradation rate. These factors makes this polymer excessively useful for in-vivo tissue engineering in for instance meniscal reconstruction material, nerve guide and artificial skin.

Introduction

Porous 50/50 copoly(ε-caprolactone/L-lactide) materials were used for the reconstruction of meniscal lesions [1]. They showed a very good adhesion to the meniscal tissue and, therefore, a good healing of the meniscal lesion. The mechanical properties of this copolymer are comparable to the mechanical properties of polyurethanes due to the high molecular weight and the presence of crystallizable L-lactide sequences [2]. The polymer had, however, certain drawbacks. Firstly, the degradation rate was somewhat too high. New meniscal tissue, the so-called fibrocartilage, is formed after a certain induction time of 10 to 20 weeks. Secondly, due to the very high molecular weight of the polymer maximal concentration of 5% could be reached. This resulted in very low compression moduli of porous materials. For the ingrowth of fibrocartilage higher moduli were needed. Finally, the poly(L-lactide) crystals, which are still present after 8 years of in-vitro degradation, may induce an inflammatory reaction since cells cannot digest them unlike poly(ε-caprolactone) and polyglycolide crystals [3-5].

To avoid lactide crystallinity, an amorphous 50/50 copoly(ε-caprolactone/85,15 L,D-lactide) was used for the production of nerve guides [6]. Due to the absence of crystals, however, this polymer showed swelling upon degradation. Therefore, in this study we focus on the synthesis of an ε-caprolactone and L-lactide based polyurethanes. The

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urethane hard segments crystals are likely to be small and susceptible to enzymatic degradation [7]. In addition, by making an ε-caprolactone and L-lactide based PU the biocompatibility may be improved [8,9].

A polyurethane of this copolymer was made by chain extending a copolymer prepolymer with a diisocyanate [10]. However, the mechanical properties of this polymer are very poor due to the absence of a phase separated morphology [10]. Phase separated morphologies can be reached when the conventional method of polyurethane synthesis is used; An isocyanate terminated polyol is chain-extended with a diamine or diol resulting in a polyurethane urea and polyurethane respectively. However, the L-lactide and ε-caprolactone based prepolymer showed a deviant behavior with respect to chain extension using a diamine and diol. It appeared that the prepolymer was susceptible to aminolysis and transesterification. This paper reports on the role of aminolysis and transesterification in the synthesis of ε-caprolactone and L-lactide based polyurethanes.

Experimental

Materials

L-lactide, poly(L-lactide) and poly(ε-caprolactone) was obtained from Hycail bv. (Noordhorn, The Netherlands) and used without purification. ε-Caprolactone (Jansen Chimica, Belgium) was dried with CaH_2 and distilled under reduced nitrogen pressure prior to use. The catalysts, stannous octoate ($SnOCt_2$) was obtained from Sigma Corp. USA and were used directly from the supplier. 1,4-Butane diisocyanate (DSM, Geleen, The Netherlands) was distilled under reduced nitrogen pressure. 1,4-Butanediamine (BDA, Acros Organics) was distilled under reduced nitrogen pressure from KOH, 1,4-butanediol (BDO, Acros Organics) from 4Å molecular sieves, N,N-dimethylformamide (DMF, Acros Organics), dimethyl sulfoxide (DMSO, Acros Organics) and 1-methyl-2-pyrrolidinone (NMP, Acros Organics) from CaH_2.

Prepolymer synthesis

A prepolymer with a molecular weight of 2000 was made. A typical example is given. The 50/50 L-lactide and ε-caprolactone, 20 gram of L-lactide (0.14 mol) was mixed with 16 gram ε-caprolactone (0.14 mol) under nitrogen atmosphere. 0.84 gram butanediol (9.3 mmol) and 40 mg stannous octoate were added as initiator and catalyst respectively. The mixture was polymerized for 24 hours at 130°C. ^{1}H-NMR showed complete conversion.

Isocyanate terminated prepolymer (macrodiisocyanate)

The prepolymer was dissolved in a six-fold excess of BDI. After stirring the reaction mixture at 80°C for four hours, the excess of diisocyanate was removed under reduced presuure (0.005 mm Hg) at 80-90 °C using a Kugelrohr apparatus. It was confirmed by weight and by ^{1}H NMR that the removal of unreacted diisocyanate was complete.

Block synthesis

The isocyanate terminated urea block (BDI/BDA/BDI) was prepared by mixing butanediamine with a six-fold excess of butanediisocyanate in ethanol at -90°C. The temperature was increased to -10°C for reaction. The excess diisocyanate was removed by washing with cold ethanol (-90°C).

The isocyanate terminated urethane block (BDI/BDO/BDI) was prepared by reaction of butanediol with a six-fold excess of butanediisocyanate at 80°C without catalyst for 5 hours. The excess diisocyanate was removed by washing with dry hexane.

The hydroxyl terminated urethane block (BDO/BDI/BDO) was prepared by mixing butanediisocyanate with a six-fold butanediol excess of at 80°C without catalyst. The excess butanediol was removed by washing with dry acetone.

Polymerization

Polymerizations were carried out under an inert atmosphere of nitrogen in flame dried glassware. The copolymer prepolymer was chain extended with the BDI/BDO/BDI block in DMSO at 80°C and at a concentration of 30 w/w%. The macrodiisocyanate was chain extended with BDA, BDO and the BDO/BDI/BDO block in DMSO at respective temperatures of 25, 80 and 80°C and respective concentrations of 5, 30 and 50 w/w%.

Characterization

Intrinsic viscosities were measured in DMSO, NMP and DMF at a concentration of 0.5 g/dl using an Ubbelohde viscometer. The concentration of the chain extender (butanediol and butanediamine) was 3% with respect to the polymer.

Calorimeter studies were carried out with a Perkin Elmer DSC 7 calorimeter. The scanning rate was 10°C per minute.

^{1}H-NMR (200 MHz) was used to characterize the blocks.

Tear strength and hysteresis was determined as described before [11].

Results and discussion

In a previous paper we reported on the synthesis and mechanical properties of a biodegradable ε-caprolactone, butanediisocyanate and butanediamine based polyurethane urea [11]. Upon degradation the diisocyanate in the polymer will be converted in butanediamine. This is also known as putrescine and is present in cells of mammals in which it plays an important role in the cell division [12]. The polymer was made by end-capping a poly(ε-caprolactone) diol prepolymer with a six-fold excess of butanediisocyanate. After removal of the excess, the isocyanate-terminated prepolymer (macrodiisocyanate) was chain extended with butanediamine. By using an excess diisocyanate the formation of soft segment dimers, trimers etc. can be avoided resulting in well-defined and uniform hard segments. The uniformity of the hard segments is known to be extremely important for phase separation and, therefore, for the mechanical properties [13]. With this technique polyurethane ureas with excellent mechanical properties and high molecular weight could be made.

For the synthesis of a polyurethane urea based upon 50/50 ε-caprolactone and L-lactide the same technique was used. ε-Caprolactone and L-lactide where copolymerized and end-capped with butanediisocyanate. It appeared, however, that in the chain extension step with butanediamine, no polymer was formed. First an increase of the viscosity was observed followed by a decrease of the viscosity. It seems that the polyurethane degraded as a result of aminolysis due to the presence of butanediamine.

Aminolysis was demonstrated by viscosity experiments. The intrinsic viscosities of PLLA and PCL in different solvents in presence of butanediamine or butanediol and catalyst, as a function of time were determined. The results are presented in figure 1. PCL does not degrade in the presence of butanediamine whereas the intrinsic viscosity of PLLA decreases very rapidly in the presence of butanediamine. PLLA degrades much slower in the presents of butanediol. The reason for the susceptibility of the lactide bond could be the high density of ester bonds in the chain. In that case glycolide should show the same degradation. It, however, appeared that an isocyanate terminated 75/25 copoly(glycolide/trimethylenecarbonate did not show degradation in the presence of butanediamine but instead a polymer was formed [14]. In the presence of butanediol the PLLA degrades slowly. Therefore, although some transesterification may occur, chain extension with butanediol should be possible.

When the butanediisocyanate-terminated prepolymer was chain extended with butanediol (table la), a polymer with an intrinsic viscosity of 1.8 dl/g could be made. The DSC thermogram of the polymer is shown in figure 2a. The relatively high Tg of -9°C and low melting temperature of 53°C of the polymer is an indication of a phase mixed morphology, probably due to transesterification. The mechanical properties are presented in table 2a.

Transesterification of the prepolymer with the chain extender could be overcome by chain-extending the prepolymer with a diisocyanate instead of a diol. Seppäla et al. chain-extended the prepolymer with hexanediisocyanate [10] but this resulted in a polymer with very poor mechanical properties due to the absence of hard segments of significant length. The polymer had a phase mixed morphology. Normally the hard segments of polyurethanes are formed in the chain-extending step and contain two diisocyanates and one low molecular weight diamine or diol. By forming the hard block BDI/BDO/BDI before chain-extension it is possible to form the polymer by chain-extending the copolymer prepolymer with a diisocyanate block instead of a diol.

Table 1

	Prepolymer	chain-extender
a	Macrodiisocyanate*	BDO
b	Copolymer*	BDI/BDO/BDI
c	Macrodiisocyanate*	BDO/BDI/BDO

* isocyanate terminated copolymer

** 50/50 L-lactide/ε-caprolactone copolymer 2000

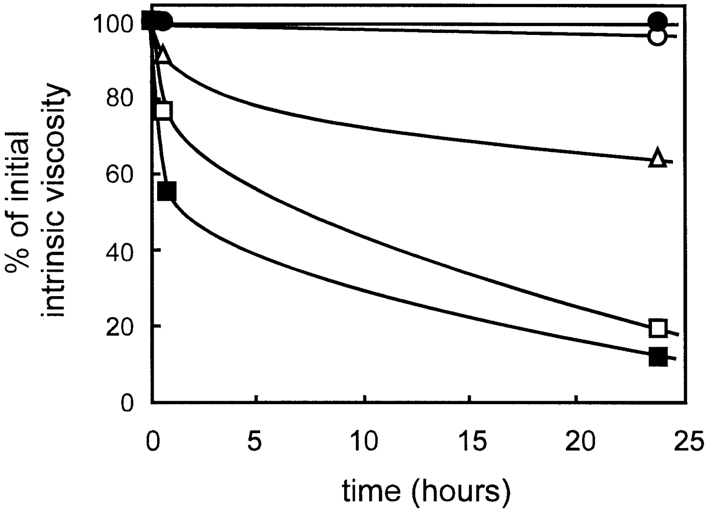

***Figure 1**. Percentage of initial intrinsic viscosity of ● PCL and 1,4-butanediamine in DMSO (30^{o}C); O PLLA and 1,4-butanediol in DMSO (80^{o}C); Δ PLLA and butanediamine in DMF (30^{o}C); □ PLLA and butanediamine in NMP (37^{o}C); ■ PLLA and butanediamine in DMSO (30^{o}C). Polymer concentration was 0.5 g/dl, butanediamine or butanediol concentration was 3 wt.-% relatively to polymer.*

Table 2

	[η] (dl/g)	Modulus (MPa)	Tensile Strength (MPa)	Strain at break (%)	Tm (°C)	ΔH (J/g)	Tg (°C)	Permanent Deformation (%)
a	1.8	12	12	750	53	5.5	-9	13.5
b	1.0	60	23	640	50, 92	8.6, 4.6	-21	13.5
c	2.0	62	44	560	49,112	2.3, 16	-5	10.0

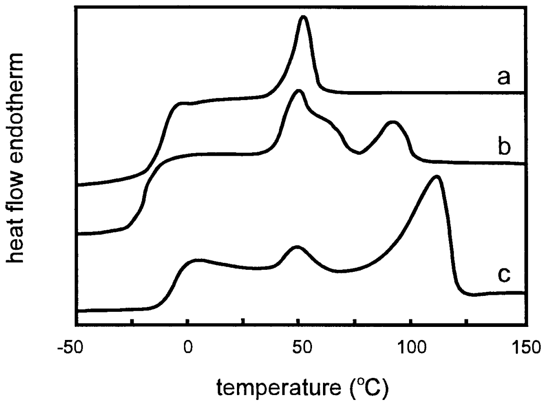

Figure 2. *DSC thermogram of different ε-caprolactone and L-lactide based polyurethanes listed in table 1. a: Macodiisocyanate, chain-extended with butanediol. b: Copolymer chain-extended BDI/BDO/BDI block. c: Macrodiisocyanate, chain-extended with BDO/BDI/BDO block.*

The isocyanate terminated urethane block (BDI/BDO/BDI) was prepared by reaction of butanediol with a six-fold excess. The number of isocyanate groups of the block were determined with H^1-NMR by measuring the ratio of the protons next to isocyanate group and protons next to the urethane bond. The ratio was between 0.7 and 0.8, which means that the blocks were somewhat longer than expected. The lower ratio can also be a result of allophanate and trimerization reactions. The block has two melting temperatures at 62°C and 114°C with energies of 46 and 5 J/g respectively. It shows liquid crystalline behavior when observed with a light microscope. The prepolymer was chain extended with the urethane block (table 1b) and the properties of this polymer are presented in table 2b. Although the chemical contents is the same as the butanediol chain extended isocyanate terminated prepolymer (table 1a), preventing transesterification increased the modulus and the tensile strength from respectively 12 and 12 MPa to respectively 60 and 23 MPa. In figure 1b the thermal behavior of the polymer is presented. Compared to the butanediol chain-extended polyurethane the Tg decreased from -9 to -21°C and the crystallinity increased. This is an indication for a more phase separated morphology and is also confirmed by the better mechanical properties of the polymer.

The method of avoiding transesterification can also be used to avoid aminolysis. Therefore, an isocyanate terminated urea block (BDI/BDA/BDI) was prepared by mixing butanediamine with a six-fold excess of butanediisocyanate at -90°C. The temperature was increased to -10°C for reaction. However, the block had a melting point above 250°C and was not soluble in any suitable solvent. Therefore, a polyurethane urea based upon ε-caprolactone and L-lactide could not be made.

Compared to the high molecular weight 50/50 copolymer of L-lactide and ε-caprolactone, which has a modulus and tensile strength of respectively 12 and 34 MPa, the polyurethane made by chain-extending the copolymer prepolymer with the BDI/BDO/BDI block has poorer mechanical properties. Therefore, the length of the hard segments was increased. This was done by chain-extending the isocyanate terminated copolymer prepolymer with a BDO/BDI/BDO block (table 1c). The hydroxyl terminated urethane block (BDO/BDI/BDO) was prepared by mixing butanediisocyanate with a six-fold butanediol excess [15]. The number of OH groups of the block were determined by H^1-NMR by measuring the ratio of the protons next to the OH group and the protons next to the urethane bond. The ratio was 1.0, which means that the block was as long as was expected. Due to the good solubility of the hydroxyl terminated block, the chain extension was carried at a concentration of 50 w/w%, which resulted in a intrinsic viscosity of 2.00 dl/g. The DSC thermogram of the polymer is presented in figure 2c. The relatively large endotherm at 112°C is due to the larger hard segments. The relatively high Tg of -5°C is an indication of a phase mixed system, probably due to a certain degree of transesterification. The properties of the polymer are presented in table 2. Although the morphology is partially phase mixed, lengthening of the hard segments has a tremendous effect upon the tensile strength; it increases from 23 MPa to 44 MPa.

The permanent deformation after cyclic deformation decreased from 13.5% to 10%. The mechanical properties are comparable to the mechanical properties of the polyurethane ureas described before [15]. The advantage of this polymer compared to the polyurethane ureas is the processability. The polymer has a relatively low melting temperature and is soluble in for instance chloroform and 1,4-dioxane, which makes it possible to make porous materials out of the polymer [16].

Compared to the high molecular weight 50/50 copolymer of L-lactide and ε-caprolactone, the mechanical properties are increased. The tensile strength and the modulus increased from respectively 34 MPa and 12 MPa to 45 MPa and 60 Mpa. Poly(L-lactide) crystallinity could be avoided. The degradation rate is expected to be lowered due to the incorporation of urethane bonds and the phase separated morphology. Finally the polyurethane is expected to have the same adhesive properties as the high molecular weight 50/50 copoly(L-lactide/ε-caprolactone) because it is known that in polyurethanes the soft flexible segments, in this case the copolymer, are more abundant to the surface and the crystalline hard segments to the bulk [17].

Conclusions

Due to susceptibility of the poly(L-lactide) bond to aminolysis, an butanediisocyanate terminated 50/50 copoly(L-lactide/ε-caprolactone) prepolymer could not be chain extended with butanediamine. The butanediisocyanate terminated prepolymer could be chain extended with butanediol. However, due to transesterification the polymer possessed poor mechanical properties. When the prepolymer was chain extended with a butanediisocyanate terminated urethane block, transesterification with the chain extender could be avoided. This resulted in a more phase separated morphology and better mechanical properties. An isocyanate terminated urea block was not soluble in a suitable solvent and therefore, an ε-caprolactone and L-lactide base polyurethane urea could not be made. When the length of the urethane hard segments was increased by chain extending an isocyanate-terminated copolymer prepolymer with a hydroxyl terminated block, the mechanical properties increased further. The polyurethane had better mechanical properties than the high molecular weight 50/50 copoly(L-lactide/ε-caprolactone) and had comparable mechanical properties of the polyurethane ureas made before.

The combination of, good mechanical properties, releasing non-toxic degradation products, processability, the absence of L-lactide crystals, an expected lowered degradation rate, expected good adhesion properties makes this polyurethane excessively useful for in vivo tissue engineering in for instance meniscal reconstruction material, nerve guide and artificial skin.

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