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High molecular weight polyurethanes and a polyurethane urea based on 1,4-butanediisocyanate

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Summary
New biomedical polyurethanes and a polyurethane urea based on ε-caprolactone and 1,4-butanediisocyanate have been developed. On degradation, only non-toxic products are produced. The polyurethane urea with poly(ε-caprolactone) soft segments and butanediisocyanate/butanediamine hard segments shows a high tensile strength, a high modulus and a high resistance to tearing but as a result of the strong interactions between the solvent and the polymer processing is difficult. When butanediamine is replaced by butanediol in the chain extension step, a processible polyurethane is obtained but the polymer lacks the desired mechanical properties for biomedical applications. By chain extending with a longer urethane diol block, a processible polymer was obtained with mechanical properties comparable to the polyurethane urea. This polyurethane has been made porous and can be used as a meniscal prosthesis.

Introduction

Biomedical polyurethanes (PUs) have been used for a wide range of applications. Examples include nerve guides (1), meniscal reconstruction materials (2,3), artificial skin (4) and artificial veins (5-7).
For these applications, usually commercially available polyurethanes are used. These materials frequently exhibit good mechanical properties but an important disadvantage is that they contain aromatic diphenylmethane diisocyanate (MDI). MDI based polyurethanes are known to release carcinogenic and mutagenic products on degradation (8). Furthermore, they often show low resistances to tearing. A high resistance to tearing is important to prevent sutures from tearing out of a biomaterial. The development of new medical grade polyurethanes with good mechanical properties is therefore highly desirable. In this study, we wish to present new aliphatic polyurethanes and a polyurethane urea for biomedical applications. The polymers completely consist of aliphatic components and only release non-toxic products on degradation. Diphenylmethane diisocyanate (MDI) has been replaced by 1,4-butanediisocyanate (BDI) and on degradation 1,4-butanediamine (putrescine) is formed, a growth factor essential for the cell division in mammals.
First, a high molecular weight polyurethane urea was synthesized. This polymer consists of caprolactone soft segments and butanediisocyanate/butanediamine hard segments. It shows

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excellent mechanical properties like a high tensile strength, high modulus, high resistance to tearing and a low permanent deformation. However, as a result of the tight packing of the urea hard segments, the polymer is difficult to process. In order to improve the processibility, 1,4-butanediamine was replaced by 1,4-butanediol in the chain extension step and a caprolactone based polyurethane was obtained. Porous materials could be obtained but the mechanical properties significantly decreased. Finally, a polyurethane with longer hard segments was obtained by chain extending with a urethane diol block. The polymer shows good mechanical properties and is soluble in volatile solvents like chloroform and 1,4-dioxane. Porous materials have been obtained and the polymer can be used for biomedical applications.

Experimental

Materials

1,4-Butanediisocyanate (BDI, DSM) was distilled under reduced pressure prior to use. 1,4-Butanediamine (BDA) was distilled from KOH, 1,4-butanediol (BDO) from 4Å molecular sieves and 1-methyl-2-pyrrolidinone (NMP, Acros Organics), dimethylsulfoxide (DMSO, Acros Organics) and ε-caprolactone (CL, Acros Organics) from CaH_2. Stannous octoate was used as received.

Prepolymer synthesis

Prepolymer (M_n=2000) of ε-caprolactone was prepared under nitrogen atmosphere using 1,4-butanediol as an initator and stannous octoate as a catalyst. Reactions were carried out at 120 °C for 20 h. ^{1}H NMR showed complete conversion.

Synthesis of the BDO.BDI.BDO chain extender

1,4-Butanediisocyanate (9.0 mL, 70.8 mmol) was dissolved in 1,4-butanediol (100 mL, 1.13 mol) and 1 drop of stannous octoate was added. After reaction at 80 °C for 4 hours, the reaction mixture was allowed to cool to room temperature and a white powder was formed. Acetone (200 mL) was added and the product was isolated on a glass funnel and washed with acetone. After drying, the chain extender was dissolved in chloroform (500 mL) and unsoluble material was filtered off. Evaporation of the solvent afforded the BDO.BDI.BDO chain extender (13.0 g, 40.6 mmol, 57 %) as a white powder.

Polymer synthesis

Polymerizations were carried out in a two-step polymerization process under an inert atmosphere of nitrogen in flame dried glassware.

Poly(ε-caprolactone) 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 pressure (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.

In step two the macrodiisocyanate was dissolved in a solvent and chain extended. Chain extension with BDA and BDO was performed in NMP at respective concentrations of 6 and 25 w/w % and respective temperatures of 25 and 80 °C. Chain extension with the BDO.BDI.BDO chain extender was performed in DMSO at 80 °C at a concentration of 50 w/w %.

The chain extender in the respective solvent was added slowly under vigorous mechanical stirring. When the reaction mixture became viscous, more solvent was added to keep the system homogeneous. After the addition of chain extender was complete the reaction

mixture was stirred for 10 hours and subsequently diluted to a 1-2 w/w % solution. The polymer was precipitated in water and dried to constant mass at 40 °C under reduced pressure.

Polymer films
The PUU and PUs were dissolved (9 w/w %) by refluxing in DMF for 0.5 h. and subsequently poured onto a petrish dish. The solvent was removed at 70 °C. Last traces of solvent were removed at 40 °C under reduced pressure. Samples for phase-contrast microscopy were prepared by spincoating a 1 w/w % solution of the PUU in DMF on glass.

Polymer characterization
Differential scanning calorimetry (DSC) was carried out with a Perkin-Elmer DSC-7 differential scanning calorimeter using sample weigths of 5-10 mg with a heating rate of 10 °C/min. over the temperature range of -100 to 250 °C.
Intrinsic viscosity of polymers was measured in m-cresol at 25.0 °C using an Ubbelohde viscometer.
Tensile testing was performed on rectangular-shaped specimens (40 x 1.0 x 0.35 mm), cut from thin films at room temperature using an Instron (4301) tensile tester, equipped with a 100 N load cell and an extension rate of 10 mm/min. For determination of the permanent set, a 10 N load cell was used. Tearing properties were determined on an Instron 4301 tensile tester using trouser specimens of 3.75 cm long, 1.25 cm wide and a longitudinal slit of 2.5 cm. The force was applied normally to the plane, the extension rate being 250 mm/min.

Porous materials
The polymer was dissolved in 1,4-dioxane at a concentration of 17 w/w %. 5 mL of the solution was mixed with 0.77 g of NaCl crystals (150 µm - 300 µm). The mixture was rapidly cooled to room temperature where gel formation occured. After cooling to -15 °C the polymer was freeze dried at 0 °C under reduced pressure (0.05 mbar). NaCl crystals were removed by washing the polymer/crystal mixture with water.

Results and discussion
Synthesis of *macrodiisocyanates*
Synthesis of the caprolactone based macrodiisocyanate was performed in a 2-step process. First, the macrodiol was dissolved in a six-fold excess of diisocyanate. After reaction, the excess of diisocyanate was removed by distillation. It was confirmed by weight and by ^{1}H NMR that removal of unreacted diisocyanate was complete. By endcapping with an excess of diisocyanate formation of dimers and trimers is avoided (9, 10), resulting into hard segments of uniform size. Because the amount of removed diisocyanate matches the theoretical amount, it can be concluded that hardly no dimers or trimers have been formed. After end-capping, the macrodiisocyanate was chain extended.

Polyurethane urea
In a previous study (11), we found that polyurethane ureas show high resistances to tearing which is important to prevent sutures from tearing out of the biomaterial. These polymers however, lacked important properties like high tensile strengths and high moduli. By chain extending the macrodiisocyanate with 1,4-butanediamine in NMP at a

concentration of 6 w/w % at room temperature we succeeded in enhancing the intrinsic viscosity of the polymer from 1.04 to 3.55 dL/g, presented in table 1. Thin films were made from DMF solutions and the properties of the polymer were determined.
A DSC thermogram of the polyurethane urea is shown in figure 1. The polymer exhibits a Tg at -57 °C corresponding to the soft segment. The melting endotherm of the soft segment with a melting enthalpy of 28.0 J/g is observed at 19.7 °C. The melting endotherm corresponding to the BDA/BDI hard segments is observed at 189 °C with a melting enthalpy of 10.8 J/g.
The stress-strain behaviour of the polymer is presented in figure 2. Compared to our previous study (11), the tensile strength has been increased from 29.0 Mpa to 46.0 Mpa and the modulus from 52 MPa to 145 MPa with a strain at break of 835%. The high tensile strength and the high modulus are caused by the phase separated morphology and the high molecular weight of the polymer. As a result of the phase separation, the BDI/BDA hard segments are tightly packed (12). In order to vizualize the phase separated morphology, phase-contrast micrographs of a spin-coated film were made.
Figure 3 shows a phase-contrast micrograph of the polyurethane urea where the hard segments pack and are observed as small dark spheres in a matrix of soft segments. The size of the hard domains ranges from 2 to 5 µm.

The tearing energy is presented in table 1. The high value of 176 N/ram is a result of the tight packing of the BDI/BDA hard segments (12) and the high molecular weight. An additional effect might be the occurrance of strain induced crystallisation which increases the restance to tearing (13).

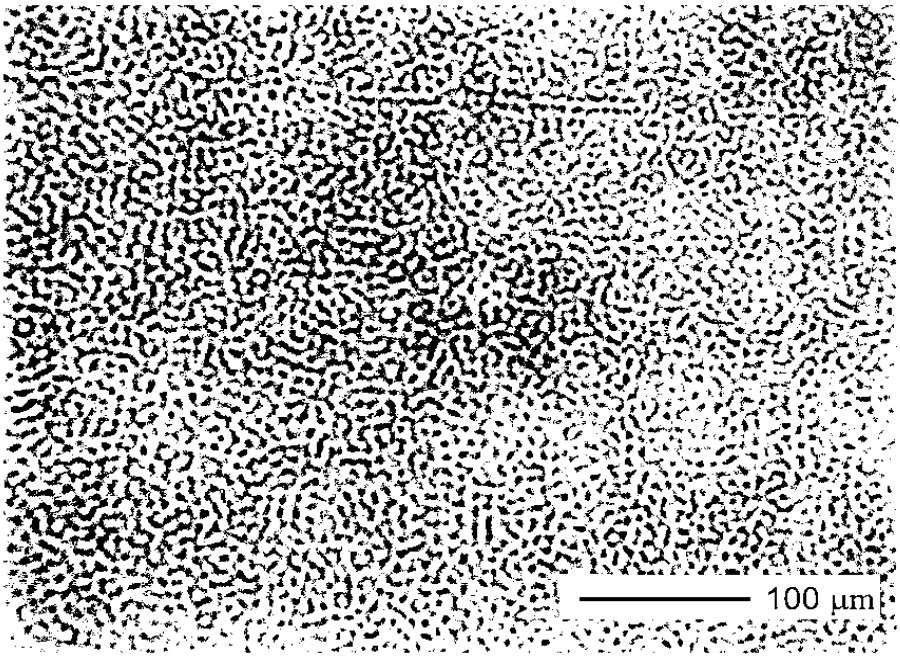

Figure 3. *Phase-contrast micrograph of the polyurethane urea consisting of caprolactone soft segments and BDI/BDA hard segments*

Entry	Intrinsic viscosity (dL/g)	Tearing energy (N/mm)	Tensile strength (MPa)	Modulus (MPa)	Permanent deformation (%)
1.	3.55	176	46.0	145.0	10.8
2.	3.04	79	23.1	23.2	15.0
3.	2.94	94	45.0	70.0	8.9

1. ε-caprolactone macrodiisocyanate chain extended with 1,4-butanediamine
2. ε-caprolactone macrodiisocyanate chain extended with 1,4-butanediol
3. ε-caprolactone macrodiisocyanate chain extended with BDO.BDI.BDO

Table 1. *Properties of the polyurethane urea and the polyurethanes*

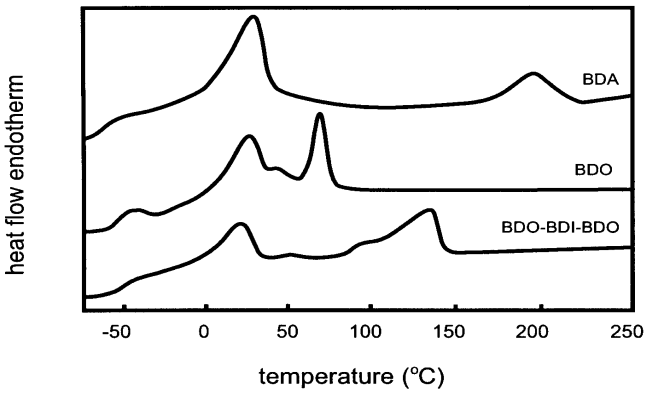

Figure 1. *DSC curves of a: BDA based PUU, b: BDO based PU and c: BDO.BDI.BDO based PU*

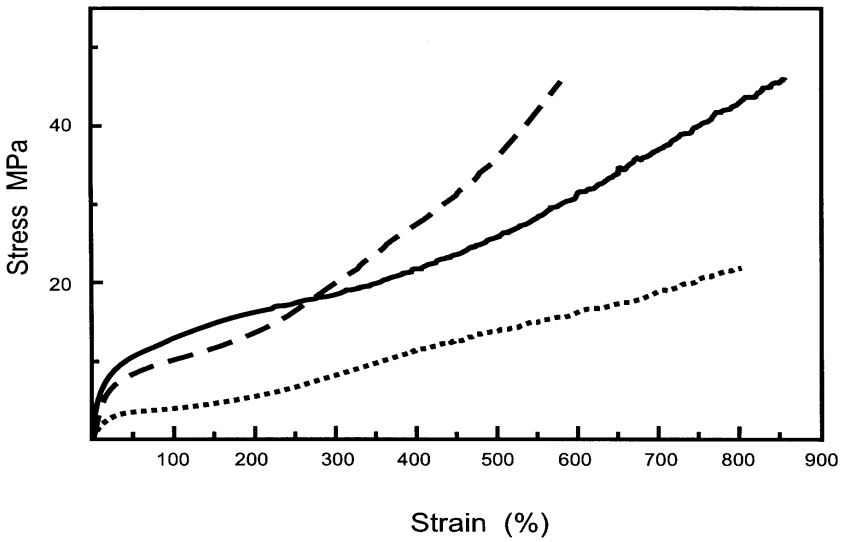

Figure 2. *Stress-strain behavior of a: BDA based PUU (_____), b: BDO based PU (.....) and c: BDO.BDI.BDO based PU (-------)*

As shown in table 1, the polymer shows a permanent deformation of 10.8% after 20 cyclic deformations up to 50% strain. This shows that the hard segments are only slightly disrupted on deformation.
Because the polyurethane urea shows excellent mechanical properties and will only release non-toxic products on degradation it might be suitable as a biomaterial. In a previous study (3) we reported the use of porous polyurethanes for meniscal prostheses. A combination of salt leaching and freeze drying afforded an interconnected porous structure but the polymers still contained the toxic MDI.
Following similar procedures we tried to obtain porous materials from the polyurethane urea. However, as a result of strong interactions between the solvent and the polymer only the solvent at the surface of the polymer could be removed with freeze-drying. Therefore, only very thin porous materials could be obtained.

Polyurethanes
Because of these problems, we decided to chain extend the macrodiisocyanate with 1,4-butanediol. In this case chain extension was performed in NMP at a concentration of 25 w/w % at 80 °C. The intrinsic viscosity of the resulting polyurethane is presented in table 1. Thin films were made from DMF solutions and the properties were determined.

A DSC thermogram of the polyurethane is shown in figure 1. The Tg corresponding to the soft segment has increased to -54 °C. The higher Tg compared to the polyurethane urea is an indication for a more phase mixed morphology. The melting endotherm corresponding to the soft segment is observed at 24.3 °C with a melting enthalpy of 9.3 J/g. The hard segments show a melting endotherm at 68.5 °C with a melting enthalpy of 11.2 J/g. The lower melting temperature of the hard segments compared to the polyurethane urea indicates a less tight packing of the hard segments.
The stress-strain behaviour of the polyurethane is presented in figure 2. The polymer shows a tensile strength of 23.1 MPa, a strain at break of 843% and a modulus of 23.2 MPa. Compared to the polyurethane urea, tensile strength and modulus have decreased dramatically. Furthermore, the tearing energy (table 1) has decreased to 79 N/mm. The permanent deformation is enhanced to 15.0%, indicating that the urethane hard segments are more easily disrupted than the urethane urea hard segments upon cyclic deformation. The polymer proved to be soluble in volatile solvents like chloroform and 1,4-dioxane and porous materials could be obtained. However, as a result of the low tensile strength, low modulus and low resistance to tearing it is not suitable for (biomedical) applications.

Polyurethane with uniform long hard segments
In order to enhance the mechanical properties of the material, a polyurethane with longer urethane segments was synthesized. This should result in a tighter packing of hard segments and thus better mechanical properties.

A new urethane-based diol chain extender of uniform size was synthesized by reacting butanediisocyanate with an excess of butanediol. The resulting macrodiol precipitated on cooling and the excess of butanediol was removed by washing with acetone. Unsoluble impurties were removed by dissolving the chain extender in chloroform followed by hot filtration and evaporation of the solvent. ^{1}H NMR showed that a uniform hard segment consisting of 1 equivalent of BDI and 2 equivalents of BDO had been formed.

Chain extension with the macrodiol was performed in DMSO at a concentration of 50 w/w % at 80 °C. The intrinsic viscosity of the polyurethane is presented in table 1. Thin films were made from DMF solutions and the properties were determined.

A DSC thermogram of the polyurethane is presented in figure 1. A Tg corresponding to the soft segment is observed at -54 °C and melting endotherm corresponding to the soft segment at 17.9 °C with a melting enthalpy of 9.1 J/g. Compared to the previous polyurethane, the melting temperature of the hard segment has increased from 68.5 to 130.4 °C with a melting enthalpy of 14.5 J/g, indicating a better packing of the hard segments.
The tensile properties are shown in figure 2. The polyurethane has a tensile strength of 45.0 MPa, a strain at break of 560% and a modulus of 70.0 MPa. Interestingly, the tensile strength has increased to a value comparable to the polyurethane urea. Also the modulus has increased significantly. The tearing energy (table 1) has increased to 94 N/mm. Compared to the polyurethane with BDO as chain extender, the permanent deformation has been lowered from 15 to 8.9%.
The polymer shows properties resembling the polyurethane urea and only releases non-toxic products on degradation. In order to use the material as a meniscal prosthesis we tried to obtain porous structures following procedures desribed before (3).

Porous materials
The polyurethane has been made porous by a combination of salt leaching and freeze-drying. By dispersing salt crystals (150 µm - 300 µm) in the polymer solution, followed by freeze-drying of the solvent and extraction of the salt with water, macropores of 150 µm - 300 µm were obtained, interconnected by micropores arising from the solvent crystals. In a previous study (3), we concluded that interconnection of macropores is essential for fast ingrowth of cells. A SEM micrograph of the porous structure is shown in figure 4.

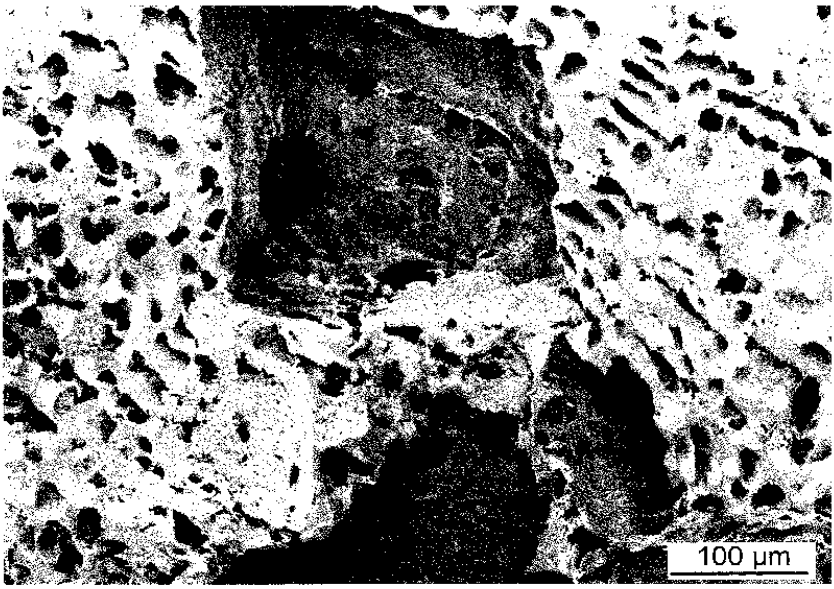

Figure 4. *SEM micrograph of porous polyurethane consisting of caprolactone soft segments and long BDI/BDO hard segments*

Conclusions

New aliphatic polyurethanes and a polyurethane urea for biomedical applications have been synthesized. All polymers completely consist of aliphatic components and only release non-toxic products on degradation. Furthermore, 1,4-butanediamine (putrescine), a growth factor essential for the cell division in mammals, will be formed.

The polyurethane urea shows excellent mechanical properties resulting from the high molecular weight and the phase separated morphology. As a result of the strong interactions between the solvent and the polymer it proved to be difficult to obtain porous materials. When the urethane urea hard segments are replaced by urethane hard segments porous structures can be obtained but the polymer lacks the desired mechanical properties for biomedical applications.

The excellent mechanical properties of polyurethane ureas have been combined with the processibility of polyurethanes by synthesizing a longer urethane-based diol chain extender of uniform size. The resulting polyurethane shows good mechanical properties and is soluble in high concentrations in volatile solvents like chloroform and 1,4-dioxane. Additionally, it only releases non-toxic products on degradation. By a combination of salt leaching and freeze-drying porous structures have been obtained and the material can be used as a meniscal prosthesis.

Acknowledgments

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