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A new biomedical polyurethane with a high modulus based on 1,4-butanediisocyanate and ε-caprolactone

C. J. SPAANS, J. H. DE GROOT, V. W. BELGRAVER, A. J. PENNINGS*
Department of Polymer Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

A new approach to the synthesis of biomedical polyurethanes based on ε-caprolactone and 1,4-butanediisocyanate with a high modulus, has been developed. By chain extending an ε-caprolactone prepolymer with a long uniform-size diisocyanate block, a segmented polyurethane with uniform-size hard segments was obtained. It shows excellent mechanical properties; an extremely high modulus of 105 MPa and a tensile strength of 35 MPa. The polymer is soluble at high concentrations in various volatile solvents such as chloroform and 1,4-dioxane. By a combination of salt-leaching and freeze-drying, porous materials have been obtained in which macropores ranging in size from 150–300 μm are highly interconnected by micropores. The material shows a sufficiently high compression modulus of 200 kPa and appears to be suitable for biomedical applications such as meniscal prostheses.

1. Introduction

Polyurethanes are considered to be excellent biomedical materials having good mechanical properties and showing a satisfactory blood compatibility [1]. Porous polyurethanes have been used for numerous examples, such as regeneration of skin [2, 3], blood vessels [4, 5] and fibrocartilage [6–8]. Commercially available polyurethanes such as Estane, Biomer and Pellethane, exhibit good mechanical properties but, on degradation, the carcinogenic and mutagenic diphenylmethane diamine is formed and released [9, 10]. In previous papers [11, 12] we reported the development of new biomedical polyurethanes with good mechanical properties. The polymers consisted of ε-caprolactone or 50/50 *L*-lactide/ε-caprolactone soft segments and long 1,4-butanediisocyanate/1,4-butanediol hard segments. The long hard segments were found to be important for good mechanical properties such as a high tensile strength. On degradation, 1,4-butanediamine (putrescine), a growth factor essential for the cell division in mammals [13], is formed and released. However, as a result of transesterification reactions in the chain-extension step, a size distribution of the hard segments was still found. It is known that this affects the mechanical properties of the polymer in a negative way [14]. Of these properties, the modulus in particular has been recognized to be an important parameter for the ingrowth of fibrocartilage in porous polyurethanes [15]. In order to use porous polyurethanes as meniscal prostheses and to obtain 100% fibrocartilage formation, it has been found that the compression modulus should be at least 150 kPa [15] and the macropore size should be in the range of 150–300 μm [6].

In this paper, approach to the synthesis of polyurethanes based on ε-caprolactone with uniform hard segments and a high modulus, is presented. As a result of the good solubility of the polyurethane, interconnected porous materials with a high compression modulus could be obtained and the polymer seems to be very suitable to serve as meniscal prostheses. The mechanical properties have been evaluated and compared to the polyurethane described in the previous paper [11].

2. Experimental procedure

2.1. Materials

All reactions were carried out under an inert atmosphere of nitrogen in flame-dried glassware. Dimethylsulphoxide (DMSO, Acros Organics) and ε-caprolactone (CL, Acros Organics) were distilled from CaH_2 and 1,4-butanediol (BDO, Acros Organics) from 0.4 nm molecular sieves. 1,4-Butanediisocyanate (BDI) was synthesized according to literature procedures [16] and distilled under reduced pressure prior to use. The catalyst, stannous octoate (Sigma), was used as-received from the supplier.

*Author to whom all correspondence should be addressed.

2.2. Prepolymer synthesis

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

2.3. Synthesis of the BDO.BDI.BDO block [11]

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 h, 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 block was dissolved in hot chloroform (500 ml) and insoluble material was filtered off. Evaporation of the solvent afforded the BDO.BDI. BDO block (13.0 g, 40.6 mmol, 57%) as a white powder.

2.4. Synthesis of the BDI.BDO.BDI.BDO.BDI block

The BDO.BDI.BDO block (4.0 g, 12.5 mmol) was dissolved in DMSO (3.0 ml) and 1,4-butanediisocyanate (21.0 g, 150.0 mmol) was added. After reaction at 80 °C for 4 h the reaction mixture was allowed to cool to room temperature and a white powder was formed. Acetone (100 ml) was added and the product was isolated on a glass funnel. After washing with acetone and *n*-pentane, the product was dried under reduced pressure, yielding the BDI.BDO.BDI.BDO.BDI block (5.38 g, 9.45 mmol, 76%) as a white powder.

2.5. Synthesis of polyurethanes

2.5.1. Method 1

The BDI.BDO.BDI.BDO.BDI block (1.26 g, 2.1 mmol) was dissolved in DMSO (1.5 ml) at 80 °C and a solution of prepolymer (4.0 g, 2.0 mmol) in DMSO (2.0 ml) was added dropwise. After the addition was complete, the reaction mixture was stirred at 80 °C for an additional 8 h. In case of gelation of the polymer solution, small amounts of solvent were added in order to keep the system homogeneous. After dilution to a concentration of 1% (wt/wt) the polymer was precipitated in water and dried under reduced pressure at 40 °C.

2.5.2. Method 2 [11]

The prepolymer (10.0 g, 5.0 mmol) was dissolved in 1,4-butanediisocyanate and 1 drop of stannous octoate was added. After reaction at 80 °C for 4 h, the reaction mixture was transferred into dry Kugelrohr glassware and the excess of diisocyanate was distilled off at 80–90 °C under reduced pressure (0.005 bar). Subsequently, the macrodiisocyanate was chain extended with the BDO.BDI.BDO block at 80 °C at a concentration of 50% (wt/wt) in DMSO. After the addition was complete, the viscous reaction mixture was stirred at 80 °C for 10 h and diluted to a concentration of 1% (wt/wt). Precipitation in water followed by drying under reduced pressure afforded a white polyurethane.

2.6. Polymer films

The polyurethanes were dissolved (9 wt/wt%) by refluxing in 1,4-dioxane for 0.5 h and subsequently poured on to a Petri dish. The solvent was removed at 70 °C. The last traces of solvent were removed at 40 °C under reduced pressure.

2.7. Porous materials

The BDI.BDO.BDI.BDO.BDI-based polyurethane was dissolved in 1,4-dioxane at a concentration of 20 wt/wt% 5 ml solution was mixed with 0.5 g NaCl crystals of 150–300 μm and 0.30 g NaCl crystals of 50–90 μm. After addition of 4% water and mixing, the mixture was rapidly cooled to room temperature where gel formation occurred. 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.

2.8. Polymer characterization

Differential scanning calorimetry (DSC) was carried out with a Perkin–Elmer DSC-7 differential scanning calorimeter using sample weights of 5–10 mg with a heating rate of 10 °C min^{-1} over the temperature range of − 100 to 200 °C.

The intrinsic viscosity of the polymers was measured in chloroform at 25.0 °C using an Ubbelohde viscometer. Tensile testing was performed on rectangular-shaped specimens (40 mm × 1.0 mm × 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^{-1}.

For compression measurements, cylindrical specimens with a diameter on 10 mm and a length of about 8 mm were cut out of the foams under cooling with liquid nitrogen.

3. Results and discussion

3.1. Polymer synthesis

In method 1, the polyurethane was synthesized in such a way that long hard segments of uniform size were obtained. 1,4-Butanediisocyanate (BDI) was reacted with an excess of 1,4-butanediol (BDO). By using an excess of BDO, the formation of longer hard segments was avoided. The resulting BDO.BDI.BDO block was reacted with an excess of BDI, affording a BDI.BDO. BDI.BDO.BDI block of uniform size. By reacting this diisocyanate block with the prepolymer at 80 °C, a segmented polyurethane was obtained. Most importantly, transesterification reactions, which are known [12] to be severe at these temperatures, were avoided.

For reasons of comparison, the prepolymer was also end-capped with BDI followed by chain

extension with the BDO.BDI.BDO block. In principal, a polymer with the same hard segments should be obtained. However, as a result of the hydroxyl groups of the chain extender, the prepolymer might be susceptible to transesterification reactions resulting in a distribution of the hard segment size. The intrinsic viscosities of the resulting polymers are presented in Table I.

The lower viscosity of the first polymer can be explained by the lower reactivity of the BDI.BDO.BDI.BDO.BDI block compared to the BDO.BDI.BDO chain extender. Furthermore, a severe concentration effect was observed: higher concentrations resulted in higher molecular weights. For this reason, attempts were also made to polymerize the two components in the bulk. However, the phase-separated morphology of the polymer already implies the immiscibility of the sole components. Therefore, the polymerization was performed at maximum concentration in a solvent.

3.2. Thermal properties

The DSC thermograms of the polymers are presented in Fig. 1. For the BDI.BDO.BDI.BDO.BDI-based polyurethane, a glass transition, T_g, is observed at $-60.4\,^{\circ}C$. The melting endotherm corresponding to the soft segment is observed at $9.2\,^{\circ}C$ with a melting enthalpy of $13.9\,J\,g^{-1}$ and the melting endotherm corresponding to the hard segments at $128.3\,^{\circ}C$ with a melting enthalpy of $24.2\,J\,g^{-1}$. In the case where the polymer is synthesized with the BDO.BDI.BDO chain extender, a T_g is observed at $-54\,^{\circ}C$, indicating a more phase-mixed morphology. The melting endotherm corresponding to the soft segment is observed at $16.7\,^{\circ}C$ with a melting enthalpy of $11.0\,J\,g^{-1}$ and a melting endotherm corresponding to the hard segment at $130.4\,^{\circ}C$ with a melting enthalpy of $14.5\,J\,g^{-1}$. Furthermore, an additional melting endotherm is observed at $53\,^{\circ}C$ indicating transesterification reactions [12]. Owing to the transesterification reactions, a size distribution in hard segments is obtained.

TABLE I Intrinsic viscosities of the polyurethanes

Entry[a]	Intrinsic viscosity ($dl\,g^{-1}$)
1	1.02
2	2.00

[a]1. BDI.BDO.BDI.BDO.BDI-based polyurethane. 2. BDO.BDI.BDO-based polyurethane.

3.3. Mechanical properties

The transesterification reactions and thus the non-uniformity of the hard segments have a severe influence on the mechanical properties of the polymer [12]. The tensile properties of the polyurethanes are presented in Fig. 2. The polyurethane synthesized with the BDI.BDO.BDI.BDO.BDI block has a tensile strength of 35 MPa with a strain at break of 650% and a modulus of 105 MPa. The extremely high modulus is a result of the uniformity of the hard segments. Hard segments of uniform size pack better than non-uniform hard segments and are therefore more difficult to disrupt. When the polymer is synthesized with the BDO.BDI.BDO chain extender, the modulus decreases significantly to 70 MPa with tensile strength of 44.0 MPa and a strain at break of 560%. The higher tensile strength is a result of the higher molecular weight combined with the non-uniformity of the hard segments. As a result of the disruption of the hard segments, strain-induced crystallization of the poly(ε-caprolactone) soft segments can occur, resulting in a higher tensile strength.

3.4. Porous materials

The BDI.BDO.BDI.BDO.BDI-based polyurethane was made porous by a combination of salt-leaching and freeze drying [17]. First, the polymer was dissolved in 1,4-dioxane and mixed with NaCl crystals with sizes ranging from 150–300 μm and 50–90 μm. The smaller NaCl crystals were added in order to avoid sagging out of the salt crystals on cooling. Water was added in order to avoid skin formation in the freeze-drying process. After cooling and freeze

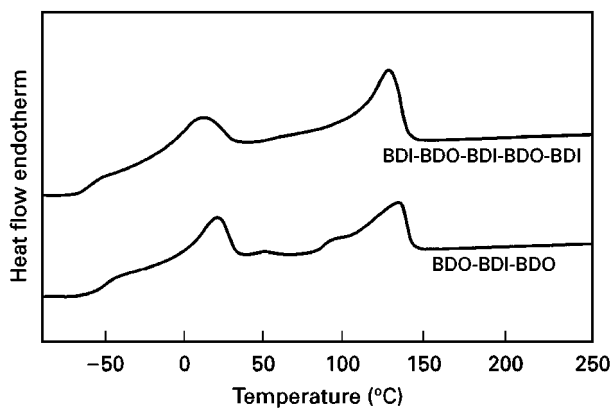

Figure 1 Differential scanning calorimeter thermograms of the polyurethanes.

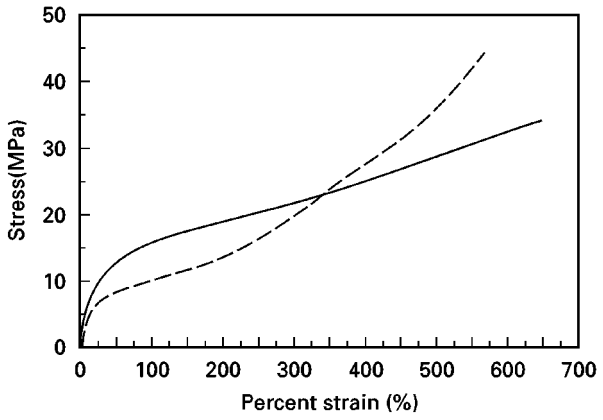

Figure 2 Stress–strain behavior of (——) the BDI.BDO.BDI.BDO.BDI-based polyurethane and (- - -) the BDO.BDI.BDO-based polyurethane.

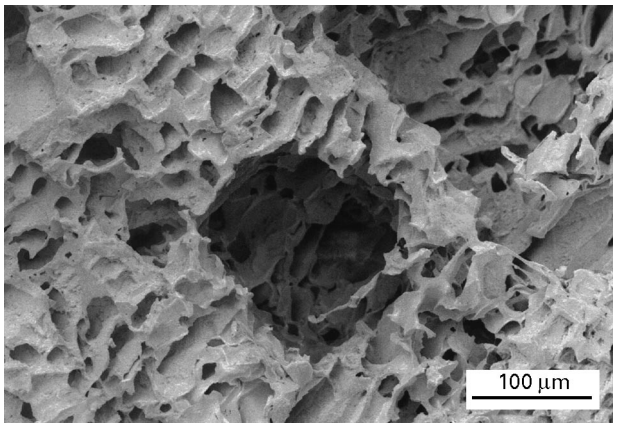

Figure 3 Scanning electron micrograph of the BDI.BDO.BDI.BDO.BDI-based porous polyurethane.

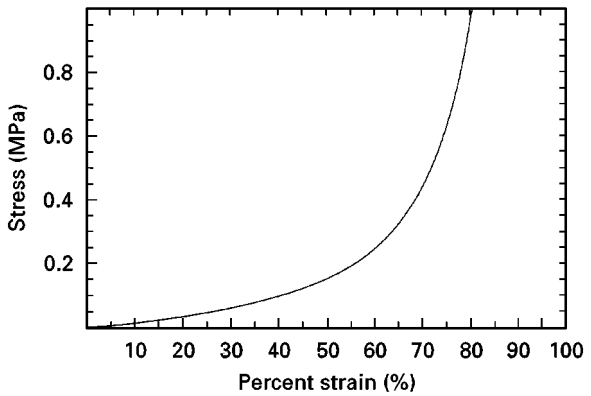

Figure 4 Stress–strain behavior of the BDI.BDO.BDI.BDO.BDI-based porous polyurethane.

drying, the salt was washed out with water, resulting in a porous polyurethane. A scanning electron micrograph is presented in Fig. 3. From Fig. 3, the macropores arising from the NaCl crystals are seen to be interconnected by micropores. Both large and small macropores are present.

3.5. Compression measurements

The polyurethane foam has been subjected to compression measurements. The stress–strain behavior is shown in Fig. 4. From this curve, the compression modulus was calculated to be 200 kPa which is sufficiently high for the regeneration of fibrocartilage [15].

4. Conclusion

A new approach to the synthesis of biomedical polyurethanes with uniform hard segments and a high modulus has been developed. By synthesizing a long diisocyanate block, followed by reaction with a diol prepolymer, transesterification reactions in the chain-extension step are avoided. The resulting polymer shows excellent mechanical properties such as a high modulus and a high tensile strength. The polymer is soluble at high concentrations in various volatile solvents such as chloroform and 1,4-dioxane. This enabled us to obtain a porous material in which the macropores are highly interconnected by micropores. The high compression modulus, the interconnected porous structure and the fact that the polymer will only release non-toxic products on degradation, makes it suitable for use as meniscal prostheses.

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