Chapter 2
Design and synthesis of biodegradable poly(ester-urethane) elastomer networks composed of non-toxic building blocks

Summary
Biodegradable poly(ester-urethane) networks, designed to release only non-toxic degradation products, were prepared from hydroxy terminated star-shaped prepolymeres, synthesized by ring-opening copolymerization of L-lactide or glycolide and ε-caprolactone initiated by myo-inositol, and ethyl 2,6-diisocyanatohexanoate. The poly(ester-urethane) networks, having $T_g$s in the range 0-10 $^\circ$C and gel contents up to 95 %, showed rubber-like behaviour and after extraction relatively high tensile strength (30-40 MPa).

Introduction
Polyurethanes are considered "excellent" biomedical materials possessing good mechanical and physical properties and showing relatively good bio- and bloodcompatibility (1). For these reasons segmented polyurethane elastomers have been used in biodegradable polyurethane/poly(L-lactide) (PLLA) mixtures for application as vascular prosthesis (2,6), meniscus prosthesis (3), artificial skin (4) and nerve guide (5), which have been developed in our laboratory.

The in vivo rate of degradation, after initially observed fragmentation, of the polyurethane/poly(L-lactide) mixtures appeared to be very low (6). A further complication was the observation of creep failure upon dynamical (cyclic) loading as a consequence of stress softening, always associated with thermoplastic elastomers, which led to aneurysms of the artificial blood vessels (6).

However, the major drawback of so called biomedical grade polyurethane elastomers, like Blomer or Estane, used for biodegradable applications, is their chemical composition. These polyurethanes contain the aromatic diisocyanate 4,4'-methylenediphenyl diisocyanate (MDI), which is converted to the toxic, mutagenic, carcinogenic diamine 4,4'-methyleneedianiline (MDA) after degradation (7,8). This problem has been overcome by using
Stashaped polyester prepolymer

(cyclo)aliphatic diisocyanates like hydrogenated MDI, 4,4'-methylenedicyclosohexyl diisocyanate H_{12}MDI in Tecoflex (7) or hexamethylene diisocyanate (HDI) (9), but the corresponding diamines are still more or less toxic.

Therefore, it is more elegant to use L-lysine based di-(or tri)isocyanates for the synthesis of biodegradable polyurethanes. In scheme 1 two approaches to the design of such degradable poly(ester-urethane) elastomer networks, which are designed to release only non-toxic degradation products, are depicted.

Schindler et al. have already reported on the alcohol initiated ring-opening polymerization of ε-caprolactone. In this manner starshaped polycaproalactone polymers were obtained by using sugar alcohols, like sorbitol, xylitol or ribitol (10). Lately, Pitt et al. have reported on the synthesis of biodegradable polyurethanes composed of trihydroxy
terminated prepolymer, made by glycerol initiated ring-opening copolymerization of a 1:1 mixture of \( \delta \)-valerolactone and \( \varepsilon \)-caprolactone, cross-linked with HDI (11). Lipatova et al. have investigated the (enzymatic) hydrolysis of poly(ester-urethane) networks, containing 20 wt% sugar as a filler (12). From the literature, degradable copolyesters of \( L \)-lactide or glycolide and \( \varepsilon \)-caprolactone are well known (13, 14).

The polyurethane networks in scheme 1 (A) are built up from hexafunctional hydroxy terminated starshaped polyester prepolymer, synthesized by ring-opening copolymerization of \( L \)-lactide or glycolide and \( \varepsilon \)-caprolactone initiated by myo-inositol, which can be cross-linked with ethyl 2,6-diisocyanatohexanoate (i.e. lysine diisocyanate). The degradation products, myo-inositol, a vitamin widely distributed in the human body (15), \( L \)-lactic acid or glycolic acid, 6-hydroxyhexanoic acid, \( L \)-lysine and ethanol, which are set free upon biodegradation of this polyurethane network, are all non-toxic which is very essential for the use as a degradable biomedical material. This chapter reports in more detail on these networks. The other polyurethane network (scheme 1 (B)) consists of linear polyester prepolymer, dihydroxy terminated copolyesters of \( L \)-lactide or glycolide and \( \varepsilon \)-caprolactone, using 2-isocyanatoethyl 2,6-diisocyanatohexanoate as a cross-linking agent (16).

**Experimental part**

**Prepolymer synthesis**

\( L \)-lactide (C.C.A. Gorinchem, The Netherlands; recrystallized from dry toluene) or glycolide (DuPont) and \( \varepsilon \)-caprolactone (Janssen Chemical, Belgium; distilled) and myo-inositol (Merck) were dissolved in dry DMF at 140°C. Stannous octoate (Sigma Chem. Corp. USA; 0.5 wt%) was added and polymerization was carried out for 20 h at 120-130°C under nitrogen atmosphere. After removal of the solvent i. vac. a tacky, yellowish prepolymer resulted, which could be precipitated in ethanol (-70°C) from chloroform solution and subsequently dried i. vac. at ambient temperature.

**Ethyl 2,6-diisocyanatohexanoate (17)**

\( L \)-lysine monohydrochloride (Janssen Chemical, Belgium) was first converted to \( L \)-lysine ethyl ester dihydrochloride by refluxing in ethanol while
passing HCl gas through the solution. The dihydrochloride was phosgenated in o-dichlorobenzene or dioxane at 100-110 °C for ca. 8 h. The crude diisocyanate was purified by vacuum distillation (bp. 125 °C/0.1 mmHg).

Network formation
Prepolymers poly(L-lactide-co-c-caprolactone)s were cross-linked by treatment with ethyl 2,6-diisocyanatohexanoate ([OH]/[NCO] = 1) in toluene, and poly(glycolide-co-c-caprolactone) prepolymers in CH2Cl2. Thin films were obtained by reaction in a Petri-dish at room temperature under nitrogen for one day and post-curing at 100-110 °C for 3 h. The elastic, transparent films were dried at 50 °C i. vac. Porous materials were synthesized by curing a viscous slurry of the prepolymer, diisocyanate, solvent and an amount of dried NaCl powder of variable particle size by the method described previously. Afterwards the salt was removed by washing the NaCl/polymer mixture with water.

Characterization
Gel contents (in wt%) were determined by extraction of the networks with chloroform. The extracted networks were first carefully air-dried and then dried i. vac. at 50 °C to constant weight. Swelling measurements were carried out on extracted networks in chloroform at room temperature. The degree of swelling was calculated from the weight increase after swelling using the densities of chloroform (ρ=1.48 g/cm³) and the dry extracted networks (ρ=0.90-0.95 g/cm³). Thermal analysis of the networks was performed by means of a Perkin-Elmer DSC-7, calibrated with I. C. T. A. (International Confederation of Thermal Analysis) certified reference materials and operated at a scan speed of 10 °C/min.
Mechanical properties were determined at room temperature using an Instron (4301) tensile tester equipped with a 10 N load-cell, at a cross-head speed of 12 mm/min. Specimens (15 x ca. 0.75 x ca. 0.25 mm) were cut from (un)extracted thin films. An I. S. I.-DS 130 scanning electron microscope was used to study the microstructure of the porous materials.
Results and discussion
Poly(ester-urethane) networks were formed by treatment of hexahydroxy terminated starshaped prepolymers with ethyl 2,6-diisocyanatohexanoate. Prepolymers were synthesized by ring-opening copolymerization of L-lactide or glycolide with ε-caprolactone in a 1:1 mole ratio, initiated by myo-inositol (hexahydroxycyclohexane) using stannous octoate as a catalyst.

A rather unique aspect of these polyurethane networks is the use of ethyl 2,6-diisocyanatohexanoate, which has not been reported that often in the literature (21-23). Besides the fact that L-lysine is the degradation product of the incorporated diisocyanate, hydrolysis first of the ethyl ester results in the introduction of a carboxylic group into the network. The choice of prepolymers poly(L-lactide(or glycolide)-co-ε-caprolactone)s was based on the idea to obtain elastomeric polyurethanes exhibiting a high rate of degradation (see next chapter). Polyurethane networks composed of prepolymers poly(L-lactide (or glycolide)-co-myoinositol)s have glass transition temperatures above room temperature. Therefore, copolyester prepolymers containing L-lactide (or glycolide) and ε-caprolactone in a 1:1 mole ratio were used in order to obtain poly(ester-urethane) elastomer networks, having $T_g$ values far below room temperature. The other extreme, polyurethane networks composed of only poly(ε-caprolactone) prepolymers are expected to degrade more slowly than the co-poly(ester-urethane) networks. For some applications, however, a low rate of biodegradation seems desirable (3).

In table 1 some relevant data of the poly(ester-urethane) networks are collected. The $T_g$ values of the networks were in the range of 0-10 °C, depending on the branch length. The $T_g$ can be lowered by increasing the branch length of the copolyester prepolymers. The $T_g$ of a network was raised after extraction with chloroform. Remnants of unreacted monomers (and oligomers), which were removed by the extraction procedure had a plasticization effect on the networks. These remnants also had to be held partially responsible for the observed gel content. Polyurethane networks with the highest gel contents (95%) were obtained by using precipitated prepolymers. Even higher gel contents can be expected by using a slight excess of isocyanate groups ([OH]/[NCO] < 1). Besides urethane bond
formation excess cross-linking can take place through formation of allopahate groups (18).

Table 1. Poly(ester-urethane) network data

<table>
<thead>
<tr>
<th>poly-urethane network&lt;sup&gt;a)&lt;/sup&gt;</th>
<th>prepolymer branch length&lt;sup&gt;b)&lt;/sup&gt;</th>
<th>&lt;sup&gt;T&lt;sub&gt;g&lt;/sub&gt;&lt;/sup&gt; (°C)</th>
<th>gel content (%)</th>
<th>elongation at break (%)</th>
<th>tensile strength (MPa)</th>
<th>degree of swelling&lt;sup&gt;c)&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6,3</td>
<td>2,1</td>
<td>91</td>
<td>300</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6,3</td>
<td>8,2</td>
<td>400</td>
<td>30-36</td>
<td>2,70</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6,3</td>
<td>7,7</td>
<td>95</td>
<td>300</td>
<td>11-12</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6,3</td>
<td>8,3</td>
<td>425</td>
<td>28-34</td>
<td>3,05</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>9,5</td>
<td>-</td>
<td>94,2</td>
<td>350</td>
<td>16-20</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>9,5</td>
<td>2,3</td>
<td>500</td>
<td>40</td>
<td>4,75</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>#1=Prepolymer poly(myo-inositol-co-glycolide-co-ε-caprolactone) + ethyl 2,6-diisocyanatohexanoate; #2=extracted network 1; #3=precipitated prepolymer poly(myo-inositol-co-glycolide-co-ε-caprolactone) + ethyl 2,6-diisocyanatohexanoate; #4=extracted network 3; #5=prepolymer poly(myo-inositol-co-L-lactide-co-ε-caprolactone) + ethyl 2,6-diisocyanatohexanoate; #6=extracted network 5.

<sup>b</sup>Branch length: number of lactone molecules (L-lactide, glycolide, ε-caprolactone) per OH group of myo-inositol, calculated from the initial proportions of starting materials employed.

<sup>c</sup>In chloroform at 20 °C.
Fig. 1. Stress-strain curves of poly(glycolide-co-ε-caprolactone)-urethane networks before (----) and after (-----) extraction with chloroform (respectively networks 3 and 4 in table 1).

Fig. 2. Scanning electron micrograph of a porous poly(ester-urethane) matrix.
The networks were also characterized by their degree of swelling in chloroform, which ranged from ca. 3.0 for the glycolide based networks to 4.75 for the L-lactide based networks.

Fig. 1 shows typical stress-strain curves of poly(glycolide-co-e-caprolactone) networks before and after extraction with chloroform. All the polyurethane networks showed rubber-like behaviour, but from Table 1 and Fig. 1 it is clear that the extracted polyurethane networks exhibit better tensile properties, increased elongation at break and higher tensile strength (30-40 MPa). Only the extracted networks exhibit pronounced strain-induced crystallization. Crystallites thus formed have a reinforcing effect within the network, and thus increase its ultimate strength and maximum extensibility. The presence of diluent (plasticizer) suppresses the strain-induced crystallization and thus diminishes the ultimate properties (20).

Fig. 2 shows a scanning electron micrograph of a porous poly(ester-urethane) matrix, which was obtained by curing of prepolymer poly(L-lactide-co-e-caprolactone) with ethyl 2,6-diisocyanatohexanoate in the presence of an amount of salt (pore volume ca. 85%). In a very straightforward way (salt casting method) porous materials of these polyurethane networks for degradable biomedical applications can be constructed. Preliminary experiments in guinea pigs have shown that the poly(ester-urethane) networks biodegrade when implanted subcutaneously (19). Concluding, we state that degradable poly(ester-urethane) networks, designed to produce only non-toxic degradation products, as described here, are very promising biodegradable materials. Further work and especially in vitro and in vivo degradation studies are in progress (19).
References

23. S.J. Huang, K.-W. Leong, ACS Polymer Preprints, 20 (2), 552 (1979)