

Summary

This thesis is concerned with the synthesis, physical properties and potential biomedical applications of some polyurethanes, especially cross-linked ones. Polyurethanes are a class of polymers having only in common the presence of urethane bonds somewhere in their chains. The name polyurethane given to a polymeric material does not tell anything about its chemical and physical characteristics. Polyurethanes may be lightly or highly cross-linked or uncross-linked and be highly crystalline, elastomeric or amorphous and glassy. In the biomedical field polyurethane usually stands for thermoplastic polyurethane elastomer. Thermoplastic polyurethanes, also named segmented polyurethanes, are linear blockcopolymers composed of chainextended diisocyanate hard segments dispersed in a soft segment polyol matrix. Due to their good mechanical properties (high tensile strength, good tear strength, high toughness, good flex life), reasonable bloodcompatibility and biocompatibility, elastomeric polyurethanes have been used in many medical applications, like total artificial heart, heart valves, vascular prostheses, wound dressings etc. By mixing segmented polyurethanes with (5-20 wt.%) high molecular weight poly(L-lactide) (PLLA), Gogolewski, Leenslag and Pennings in Groningen developed elastomeric, biodegradable mixtures with remarkable in vivo performance. Quenched physical polyurethane/PLLA mixtures, in porous form, were succesfully applied as a small-caliber vascular prosthesis, artificial skin, meniscus lesion repair material, nerve guide. Since these polyurethanes are not chemically cross-linked (formation of permanent cross-links), they show stress softening (stress hysteresis) when subjected to cyclic deformation. This problem can be overcome by chemically cross-linking the linear polyurethane chains, for instance, with peroxides (see chapter 5). Another drawback of commercial biomedical polyurethanes concerns their chemical composition. Nearly all these polyurethanes (Biomer, Estane, Pellethane, etc.) are composed of an aromatic diisocyanate MDI (4,4'-methylene diphenyl diisocyanate). Degradation (through hydrolysis) of the polymer may result in the formation of the toxic, carcinogenic, mutagenic MDA,

4,4'-methylenedianiline, the degradation product of the incorporated aromatic diisocyanate. Although it has not been shown unambiguously that MDI-based polyurethanes induce the formation of cancer, it would be more elegant and safer to seek for a replacement for this component in the polyurethane formulation. The use of cycloaliphatic diisocyanates, for instance, hydrogenated MDI in Tecoflex, also leads to segmented polyurethanes with good ultimate properties. Aliphatic diisocyanates, which are not particularly suited for the synthesis of thermoplastic polyurethane elastomers, may be used for the formation of chemically cross-linked polyurethanes. Especially aliphatic diisocyanates, producing non-toxic diamines (e.g., lysine, 1,4-diaminobutane) after eventual degradation, seem the ultimate choice for the synthesis of biomedical polyurethanes.

In chapter 2 such lysine diisocyanate-based elastomeric polyurethane networks are described. These polyurethane networks, designed to release only non-toxic degradation products, were prepared by cross-linking hexafunctional starshaped prepolymers with ethyl 2,6-diisocyanatohexanoate (i.e., lysine diisocyanate). The hydroxy terminated prepolymers were synthesized by the ring-opening copolymerization of L-lactide or glycolide and ϵ -caprolactone initiated by myo-inositol, a vitamin. The polyesterurethane networks, having T_g 's in the range 0-10 °C and gel contents of 90-95 %, showed rubber-like behaviour. It is noteworthy that the chloroform-extracted networks exhibited much better tensile properties (tensile strength ca. 30-40 MPa) than the unextracted networks (tensile strength ca. 10 MPa). Only the extracted networks exhibited pronounced strain-induced crystallization. The presence of plasticizer (sol fraction) suppressed the strain-induced crystallization.

In chapter 3 the polyurethane networks described in the previous chapter are evaluated as potential materials for the construction of a macroporous bottom-layer (dermal analogue) in a multi-layer artificial skin. An amorphous, elastomeric, porous lysine diisocyanate-based poly(glycolide-co- ϵ -caprolactone)urethane network degraded fast in vitro. In vivo the same material was degraded even faster. Subcutaneous implantation in guinea pigs showed that the porous polyurethane networks degraded almost completely between 4 and 8 weeks after implantation, allowed rapid cell

ingrowth and evoked no adverse tissue reaction. The lysine diisocyanate-based polyurethane networks can be considered biocompatible. Chapter 4 is concerned with the preparation and characteristics of a porous polyurethane wound covering. A very thin, porous membrane (15-20 μm) was prepared by means of a phase inversion process. This elastic film, made of a cycloaliphatic polyetherurethane (Tecoflex), contained micropores up to approximately 5 μm . The porous wound covering was impermeable to bacteria. The polyurethane membrane appeared to be very permeable to water vapour, whereas water in liquid form or wound exudate could not leak through the membrane. In guinea pigs epidermal wound healing of partial-thickness wounds under polyurethane wound coverings was accelerated as compared with uncovered controls and an occlusive wound covering (Op-Site). The high water vapour permeability of the polyurethane wound covering induced concentration of the wound exudate into a jellylike clot layer, which apparently accelerated reepithelialization. The main conclusion from a clinical study on 20 split-skin donor sites was that the use of the polyurethane covering reduces pain (as compared with the conventional treatment of tulle gras dressing), besides prevention of fluid retention and enhanced reepithelialization.

Chapter 5 describes a two-ply biodegradable artificial blood vessel made of polyurethane and poly(L-lactide). The microporous innerlayer of the small-caliber vascular prosthesis was constructed from a cycloaliphatic segmented polyurethane (Tecoflex) cross-linked with dicumylperoxide in the presence of linoleic acid. The reason for introducing chemical (permanent) cross-links into the polyurethanes is to eliminate the serious limitation of stress softening which occurs especially in cyclic loading. Cyclic creep-failure, resulting from the arterial pulsation of the blood, may lead to the formation of aneurysms (catastrophic dilation of blood vessels). Furthermore, carboxyl groups of the linoleic acid on the luminal side of the prosthesis contribute positively to the antithrombogenicity of the artificial blood vessel. It appeared that adding linoleic acid during the peroxide vulcanization led to a maintenance of the tensile strength of the prostheses. The outer ply was constructed by precipitating a (95/5) physical mixture of a polyesterurethane and poly(L-lactide) from solution in the presence of sugar crystals in the range 30-90 μm which were removed

by exposing the prosthesis to water. The two-ply vascular prostheses were tested in vivo by replacing 1 cm of the abdominal aorta of rats. All the prostheses remained patent at least up to one year and did not exhibit any aneurysmal formation, which has to be ascribed to the improved creep-resistance of the prosthesis as a result of the cross-linking. The inner layer of the prosthesis was covered with endothelial cells and several layers of smooth muscle cells. Essential components of a neo-artery were regenerated.

Chapter 6 deals with the synthesis, properties and potential ophtalmic applications (intraocular lenses, keratoprostheses) of highly cross-linked polyurethane networks. Such polyurethanes were prepared by the bulk stepreaction of various low molecular weight polyols and (cyclo)aliphatic diisocyanates. All these polyurethane networks were optically transparent, colourless, amorphous glassy thermosets. The properties of one particular glassy polyurethane, obtained from the bulk reaction of a tetrafunctional aminoalcohol tetrakis(2-hydroxypropyl)ethylenediamine (Quadrol) and hexamethylenediisocyanate (HDI) in stoichiometric proportions, were investigated in more detail. This glassy polyurethane, with an ultimate glass transition temperature of 85 °C, and a very low degree of swelling in chloroform (1,27), exhibited good ultimate mechanical properties (tensile strength 80-85 MPa, elongation at break ca. 15 %, modulus ca. 1,5 GPa). Infra-red spectra of these polyurethane networks revealed the absence of an isocyanate absorption, indicating that all isocyanates, apparently, had reacted during the cross-linking reaction.

These transparent cross-linked polyurethanes can be sterilized simply by autoclaving, in contrast to polymethylmethacrylate (PMMA) which has been used successfully as an intraocular lens material the last 15 years. The possibility of an autoclavable lens is especially interesting with respect to eye surgery in the developing world where the majority of the blind people live. These highly cross-linked Quadrol/HDI-based networks, after being autoclaved, were implanted in rabbit eyes, either in the form of small circular disks or in the form of a keratoprosthesis (artificial cornea). It was shown that the material was well tolerated by the rabbit eyes. A serious opacification of the cornea, indicating an adverse reaction to the implant, was never seen. One year after implantation of a

polyurethane keratoprosthesis the eye was still "quiet". These results show that the transparent highly cross-linked polyurethane network seems suited for use in ophthalmic applications.