

Chapter 6

Autoclavable highly cross-linked polyurethane networks in ophthalmology

Summary

Highly cross-linked polyurethane networks have been 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 the glassy polyurethane, obtained from the bulk reaction of a tetrafunctional secondary aminoalcohol tetrakis(2-hydroxypropyl)ethylenediamine or Quadrol (containing an internal tertiary amino group, that can catalyze the urethane reaction) and hexamethylenediisocyanate (HDI) in stoichiometric proportions, have been 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 hydrophobic polyurethane networks (water uptake ca. 1 %) revealed the absence of an isocyanate absorption, indicating that all isocyanates, apparently, had reacted during the cross-linking reaction. Preliminary experiments and suggestions to increase the hydrophilicity of the networks have also been described.

In contrast to poly(methylmethacrylate) (PMMA), which has been used successfully as an intraocular lens material the last 15 years, these transparent cross-linked polyurethanes can be sterilized simply by autoclaving. The possibility of an autoclavable lens is especially interesting for use in 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, a direct result of an adverse reaction to the implant, was never seen. Even one year after implantation of a polyurethane keratoprosthesis the

eye was still "quiet" and these findings were comparable with the ones obtained from implantations of keratoprotheses made of PMMA or stainless steel/glass. These results show that the transparent highly cross-linked polyurethane network seems suited for use in opthalmic applications, like autoclavable intraocular lenses or keratoprotheses.

Introduction

It is estimated that cataract, i.e. an opacification of the crystalline lens of the eye and the main cause of blindness, is responsible for approximately 20 million blind people world-wide; most of them live in developing countries in Asia or Africa (1-4). It is now recognized that cataracts are not only another sad consequence of ageing. Other possible risk factors include malnutrition, sunlight exposure, smoking. This has led to the hypothesis that oxidative damage plays a major role in cataractogenesis (5,6). Surgical removal of the cataractous natural lens is the only medical treatment available for cataract patients. Spectacles or contact lenses used to be the conventional way of replacing the natural lens, but turned out to be far from ideal. However, implantation of an intraocular lens in the place of the removed cataractous lens is presently the best way to correct aphakia and to visually rehabilitate the cataract patient (7,8). Modern intraocular lens implantation, using artificial lenses made of poly(methylmethacrylate) (PMMA), had its start in 1949 after the Second World War during which Ridley, an English eye-surgeon who performed the first PMMA lens implantation, noticed that Perspex splinters of canopies of airplanes caused no irritations in the eyes of pilots. Since then many intraocular lens designs have been developed and implanted in cataract patients (8,9,12). The number of PMMA lens implantations has increased enormously during the last 15 years and nowadays lens implantation is considered a routine operation (7,10).

It is generally accepted that the artificial lens should be optically satisfactory, inert, non-toxic, biocompatible, lightweight (glass, for example, has always been considered as a possible, autoclavable lens material, but weight problems have limited its use (12)), structurally sound, durable, ultraviolet light absorbing, resistant to laser treatment (in case of secondary cataract formation), easily implanted and securely

fixated and of course be sterilized safely (8,11). PMMA meets almost all of the requirements listed, but does have some disadvantages as a lens implant material. Although non-toxic, PMMA is extremely damaging to the corneal endothelium if in contact during implantation surgery (13,18,19). Endothelial cells adhere to the hydrophobic PMMA and may be stripped off. Surgical skill is needed to minimize contact adhesion. Due to its rigidity PMMA may cause mechanical irritation of uveal tissue. Another serious problem with PMMA lenses has been with regard to sterilization. PMMA can not be sterilized simply by autoclaving due to its relatively low T_g (100 °C), and therefore has to be sterilized either with the toxic ethylene oxide or by sodium hydroxide sterilization. The last method has been prohibited in the United States by the FDA, but is still used in Europe (7,9). Both sterilization methods are, unlike autoclaving, not without a certain risk. According to eye-surgeon Worst there is a need for an autoclavable intraocular lens, especially for cataract surgery in developing countries (14). Research in this field has led to the development of other lens materials that are autoclavable. On the one hand amorphous, aromatic thermoplastics with a very high glass transition temperature, like polycarbonate, poly(ether)sulphone, polyimide, fulfil this requirement (7,11,15,16). On the other hand, polymeric networks can be used as autoclavable intraocular lens materials. Hydrophobic silicone elastomers and hydrogels (polyHEMA), which have been used in other medical applications, e.g. soft contact lenses (17), for a long time, are examples of polymeric networks which have been considered and evaluated as potential, clinical intraocular lens materials (11,18-23). Both materials are elastomeric and can be folded, which means that artificial lenses made of these materials can be inserted via a smaller incision into the eye than in the case of glassy polymers. Hydrogels are hydrophilic materials having a soft consistency and are known for their soft tissue biocompatibility (24). So, these materials are expected to be less damaging to the eye, especially to the corneal endothelium.

Besides opacification of the eye-lens, the cornea may become non-transparent, leading to so-called corneal blindness. Throughout the world about ten million people, mainly living in the developing world, suffer from corneal blindness, for example from trachoma (2). If a corneal

graft is not available, due to a lack of donor eyes, or not indicated, implantation of a keratoprosthesis is the only possibility to restore sight (25). A keratoprosthesis (an artificial cornea) is usually made of the same materials that are used for intraocular lenses. The requirements for an intraocular lens material and a keratoprosthesis material are virtually the same.

In this chapter we will describe the synthesis and properties of glassy, highly cross-linked polyurethanes and their potential application in ophthalmology as an autoclavable ocular implant material. Polyurethanes, which in general are relatively biocompatible and used in many medical applications (26), have never been considered as materials that might be used in ophthalmic applications. All this motivated us to synthesize a series of new, densely cross-linked polyurethane networks by stepgrowth polymerization of low molecular weight polyols and (cyclo)aliphatic diisocyanates.

Experimental

The polyols used in this study were:

tetrakis(2-hydroxypropyl)ethylenediamine (Quadrol),

triisopropanolamine (TIPA, mp.48-52 °C),

triethanolamine (TEA),

tetrakis(2-hydroxyethyl)ethylenediamine,

bis-N,N-(2-hydroxyethyl)isopropanolamine (BHEIPA),

tetrakis(2-hydroxyethyl)methylaminomethylmethane,

octakis(2-hydroxypropyl)pentaerythrityltetraamine ("octaol"),

trimethylolpropane (TMP, mp.60-62 °C),

pentaerythritol (mp.260 °C),

glycerol,

2,2-bis(hydroxymethyl)-2,2',2''-nitriloethanol (BIS-TRIS, mp.104 °C).

The chemical structures of these polyols are shown in figure 1. All polyols were liquids at room temperature, unless a melting point is mentioned in brackets, and were purified, if possible, by distillation under reduced pressure. Most polyols were commercially available. Two new polyols were synthesized as described below.

Tetrakis(2-hydroxyethyl)methylaminomethylmethane

A stirred mixture of 1 eq. pentaerythrityltetrachloride and 9 eqs. N-methyl-ethanolamine was refluxed for 8 days under a nitrogen atmosphere at ca. 165°C. Excess N-methylethanolamine then was distilled off and to the residue ethanol and 4 eqs. powdered potassium hydroxide were added. After stirring, ethanol was removed and the residue was extracted with chloroform. After removal of the solvent, fractional vacuum distillation yielded the product, a viscous, colourless liquid, bp. 148-155 °C/0,007 mbar. Analysis calculated for $C_{17}H_{40}N_4O_4$: C 56,04, H 10,99, N 15,38. Found: C 56,27, H 10,76, N 15,49.

Octakis(2-hydroxypropyl)pentaerythrityltetraamine was prepared in the same way as the previous compound from pentaerythrityltetrachloride and diisopropanolamine. The octafunctional polyol was isolated, in poor yield, as a yellowish, very viscous liquid, which could be decolorized by using activated carbon. Bp. 200 °C/0,005 mbar. Anal. calcd. for $C_{29}H_{64}N_4O_8$: C 58,39, H 10,74, N 9,39. Found: C 58,24, H 10,46, N 9,33.

The polyfunctional amines used were pentaerythrityltetraamine (also known as tetrakisaminomethylmethane), tetrakis(N-propylaminomethyl)methane, tris(2-aminoethyl)amine. In figure 1 the structural formulas are depicted. The syntheses of the two tetraamines are described below.

Pentaerythrityltetraamine was synthesized from pentaerythritol in 5 steps. In the first step pentaerythritol was converted to the tetrabenzenesulfonate according to a published method (27). Following a patented method (28), the tetrabenzenesulfonate was reacted with sodium-p-tosylamide in N-methylpyrrolidone solution at 200 °C for 20 hours to yield the tetratosyl-amide, a compound also described earlier by Litherland and Mann, who started from pentaerythrityltetrabromide (29,30). In the third step the tetratosylamide was hydrolyzed with 80% sulfuric acid resulting in the formation of pentaerythrityltetraamine disulphate. The next step was the continuous extraction of the disulphate with sodium hydroxide in benzene to give the tetrahydrate of pentaerythrityltetraamine. Both last steps were described in the literature (29,31). Finally, the tetrahydrate was converted to the pure, hygroscopic tetraamine by azeotropic distillation with benzene. The overall yield was ca. 60%. Anal. calcd. for $C_5H_{16}N_4$: C 45,40, H 12,19, N

42,37. Found: C 45,37, H 12,19, N 42,17.

Tetrakis(N-propylaminomethyl)methane

1 eq. pentaerythryltetrabenzenesulfonate and 8 eqs. N-propylamine were refluxed in N-methylpyrrolidone during 80 hours. The solvent was then removed and 8 eqs. powdered KOH and ethanol were added to the residue. After stirring for some time, the ethanol was distilled off and the crude product was extracted with diethylether, which was removed subsequently. The product, a colourless liquid with a strong odour, was obtained by fractional vacuum distillation, bp. 130°C/0,028 mbar. Anal. calcd. for $C_{17}H_{40}N_4$: C 68,0, H 13,33, N 18,66. Found: C 67,90, H 13,37, N 18,37.

The diisocyanates hexamethylenediisocyanate (HDI), isophoronediiisocyanate (IPDI), trans 1,4-cyclohexanediisocyanate (tCHDI) were commercially available, and ethyl 2,6-diisocyanatohexanoate (lysine diisocyanate, LDI) was synthesized according to a previously described procedure (32). In fig. 1 the structural formulas are shown. All diisocyanates were vacuum distilled prior to use.

Polyurethane network preparation

A polyol and a diisocyanate were thoroughly mixed in stoichiometric proportions ($[NCO]/[OH]=1$) at roomtemperature under a nitrogen atmosphere. The homogeneous, colourless mixture was degassed repeatedly and allowed to gelate at room temperature. Post-curing at a temperature above $T_{g\infty}$ (i.e. the glass transition temperature of the fully cured sample) yielded optically transparent, glassy thermosets. Cure of the polyurethane thermosets could also be achieved isothermally at a temperature above $T_{g\infty}$. Alternatively, polyurethane networks were formed very fast when the mixture was polymerized by means of microwave heating. Within minutes gelation was achieved. Microwave cure was conducted in an ordinary domestic microwave oven (microwaves with 2,45 GHz frequency).

All polyaminoalcohols, or poly(hydroxyalkyl)amines, from figure 1 were colourless, viscous liquids at room temperature, except TIPA which crystallized very slowly to a waxy solid after melting or distillation. Prior to mixing this triol had to be melted, just like TMP. The latter compound was mixed with diisocyanates at temperatures 80-110 °C, and also allowed to gelate at these temperatures. Gelation in these formulations

was rather fast (ca. 0,5 hr.). All diisocyanates from fig. 1 were colourless liquids at room temperature, except tCHDI, melting at 60 °C. This diisocyanate had to be mixed with polyols above its melting point. Gelation at these temperatures is very rapid. Triethanolamine was miscible with liquid diisocyanates only at temperatures higher than 40-50 °C.

Polyisocyanurate network formation

Hexamethylenediisocyanate, containing 0,25 wt.-% stannous octoate as a catalyst, was allowed to polytrimerize at 125 °C for some days. Gelation at this temperature took about three hours. The glassy, transparent solid was post-cured at 180 °C.

Characterization

Glass transition temperatures of the polyurethane networks were determined using a Perkin-Elmer DSC-7, calibrated with ICTA (International Confederation for Thermal Analysis) certified reference materials, and operated at a scan-speed of 10 °C/min.

Tensile testing was performed on rectangular-shaped specimens (ca. 50x6x2 mm), machined from glassy polyurethane samples, at room temperature using an Instron (4301) tensile tester, equipped with a 5 kN load-cell, at a cross-head speed of 10 mm/min. The gauge length was 25 mm. The reported tensile data are the mean values from at least six tests. Failure was nearly always initiated at the clamps as would be expected for rectangular shaped specimens.

Swelling measurements were carried out on polyurethane samples weighing less than ca. 0,5 g. that were immersed in chloroform at room temperature for 2 days. The volume degree of swelling was calculated from the weight increase, using the densities of chloroform ($\rho=1,48 \text{ g/cm}^3$) and the polyurethane networks. Both the Quadrol/HDI-based network and the TIPA/HDI-based network had a density of $1,135 \text{ g/cm}^3$, which were determined by weighing samples in air and by weighing them submersed in water.

Infra-red measurements were carried out on ultra thin (ca. 10 μm) polyurethane films with a Bruker IFS-88 FT-IR spectrometer.

UV/VIS transmission spectra of samples having 1 mm thickness were recorded on a Pye Unicam SP 8-200 UV/VIS spectrophotometer.

The refractive index of a Quadrol/HDI-based polyurethane network was measured on a thin film wetted with dichlorobenzene (having a higher refractive index than the polymeric material) with an Abbé refractometer (ATAGO).

Implantations

Circular disks with smooth edges having 6 mm diameter and 1 mm thickness, containing one big central hole and three smaller peripheral holes for fixation, were constructed from a fully cured Quadrol/HDI-based polyurethane network sample. After a cleaning procedure, the disks were sterilized by autoclaving at 120 °C for 20 minutes. Three disks were inserted into the anterior chamber of rabbit (Chinchilla) eyes through a corneal incision. Prior to implantation, the eyes had been made aphakic (lens less). The disks were hung up (fixated) in front of the pupil using two stainless steel 70 µm wires, led through the peripheral holes. The 70 µm wires were knotted together on the sclera.

One "mushroom"-shaped keratoprosthesis (artificial cornea) was cut on a lathe from a fully cured Quadrol/HDI-based polyurethane network sample (see figure 2). After polishing, cleaning, and autoclaving the keratoprosthesis for 20 minutes at 120 °C, it was implanted by Van Andel as a "porthole" in a cornea of an aphakic (Chinchilla) rabbit eye and fixed on the eye like a "champagne cork" on a bottle. The central "column" of the keratoprosthesis (the "leg" of the "mushroom") perforates the centre of the cornea through a 3 mm trephined hole. The "hat" of the "mushroom" (with a diameter of 6 mm) lies on the cornea and is "anchored" with two permanent 70 µm thin soft stainless steel (type: AINSI 316) wires around the whole eyeball, in two planes perpendicular to each other. The keratoprosthesis works now as a valve: the peribular fixation keeps the valve on the trephined hole and the internal pressure of the eye pushes the corneal rim around the trephined hole against the back of the "hat" of the "mushroom". The resulting pressure on the interface between keratoprosthesis and cornea prevents the leaking of aqueous humour, the melting away of corneal tissue, and the epithelial downgrowth (fistula-formation) (33).

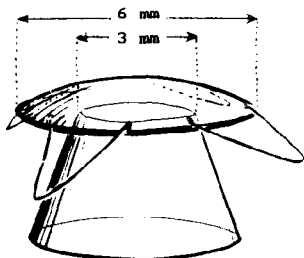


Figure 2. A "mushroom"-shaped keratoprosthesis.

Results and discussion

As outlined in the introduction, densely cross-linked polyurethanes might be interesting materials with potential opthalmic applications, like autoclavable intraocular lenses, and keratoprostheses.

First, it will be described how such polyurethane networks can be synthesized. From the literature numerous examples of elastomeric model polyurethane networks, formed by the endlinking of hydroxylterminated prepolymers with polyisocyanates, are known (34-40). In contrast to elastomeric polyurethane networks, densely cross-linked polyurethane networks are relatively unknown (41,42). These model networks are formed by stepreactions, which according to Boots is an intrinsically homogeneous process, unlike network formation by chain reactions (43,44). In this way polymer networks with a well-defined topology and a minimal number of dangling-end network imperfections can be obtained when the cross-linking reaction is carried out stoichiometrically and to very high conversion of the functional groups (45). Dušek and Stepto pointed out that the extent of cyclization in model networks prepared in the absence of a diluent is

rather small, but never negligible. Dilution may considerably increase intramolecular reactions, leading to elastically inactive loop structures and may cause the formation of inhomogeneities, or even phase separation (micro-, macrosyneresis) (39,46).

All this has led to the idea to prepare polyurethane networks from pure, low molecular weight polyols and diisocyanates in the bulk and to obtain highly cross-linked networks that are in principle homogeneous and contain a minimal concentration of network imperfections, which should result in materials with good (ultimate) mechanical and optical properties.

It is obvious that a first requirement for a network-forming reaction, in which more than one component participates, is that, in the absence of a solvent, the reactive components have to be miscible. Applying this to the polyurethane network formation this means that the polyol and the diisocyanate have to be miscible. It appeared that not all low molecular weight polyols from figure 1 were miscible with the (cyclo)aliphatic diisocyanates listed. For instance, pentaerythritol or glycerol were not miscible with any of the diisocyanates at any temperature. No sign of reaction could be observed. However, in the presence of a solvent (e.g., DMF) at room temperature, transparent swollen gels were obtained.

A second requirement is that in the case of a miscible formulation the reactivity of the components should be low, low enough to achieve complete miscibility before the polymerization reaction takes place in a controllable manner. It turned out that some polyols, tetrakis(2-hydroxyethyl)ethylenediamine, tetrakis(2-hydroxyethyl)methylaminomethylmethane, BIS-TRIS were too reactive. During mixing these polyols with diisocyanates noticeable polymerization (gelation) took already place, resulting in a very macroscopically heterogeneous network formation. It was also seen that low molecular weight polyfunctional amines, primary or secondary amines, tri- or tetrafunctional (see fig. 1), which are known to be highly reactive towards isocyanate groups (resulting in urea bonds instead of urethane bonds in the case of the reaction of an alcohol with an isocyanate), reacted instantaneously with diisocyanates, both in the absence and in the presence of a solvent (for instance, DMF, toluene). So, macroscopically homogeneous polyurea networks could not be obtained by the direct addition of polyfunctional amines and

diisocyanates, due to the fact that the very fast polymerization reaction interfered with the molecular mixing. Any attempt to slow down the reactivity of the amine group was unsuccessful.

The capping or blocking of isocyanates is a way to prevent premature reaction of the polyurethane (or polyurea) components. Isocyanate groups are reacted with compounds which form a thermally weak bond. The reactive isocyanate can be liberated at elevated temperatures (ca. 150 °C or higher). Examples of compounds used for the blocking of isocyanates are: phenols, caprolactam, oximes and β -dicarbonyl compounds (ethyl malonate) (47-49).

Fortunately, there were several low molecular weight polyols, having a relatively low reactivity, that were miscible with diisocyanates: tetrakis(2-hydroxypropyl)ethylenediamine (Quadrol), triisopropanolamine (TIPA), triethanolamine (TEA), octakis(2-hydroxyethyl)pentaerythrityl-tetraamine ("octaol"), bis(2-hydroxyethyl)isopropanolamine (BHEIPA), trimethylolpropane (TMP). At first sight it looks like these polyols have nothing in common, but this is an overstatement. First of all, one can see that the polyols containing only secondary alcohol groups (TIPA, Quadrol, octaol) are miscible with diisocyanates. All three compounds are so-called secondary polyaminoalcohols, or poly(hydroxyalkyl)amines which can be regarded as the reaction products of the corresponding amines and propylene oxide. It is noteworthy that triethanolamine can be mixed with diisocyanates whereas the analogous tetrakis(2-hydroxyethyl)-ethylenediamine was considered too reactive to be miscible with diisocyanates to form a homogeneous mixture that can be polymerized controllably. This may be explained by the fact that the gelation of the trifunctional primary polyol TEA/diisocyanate formulation is much slower than the gelation of the tetrafunctional primary polyol/diisocyanate mixture. The same was observed in the corresponding secondary polyol systems: TIPA/HDI gelates at room temperature in ca. two days, Quadrol/HDI gelates at room temperature in ca. 6-10 hours. So in the case of the triol the time available for mixing (before gelation sets in) is much longer than in the tetraol case. Due to the fact that primary alcohol groups are more reactive towards NCO groups than secondary alcohol groups, the gelation time becomes shorter when in the formulation TIPA/HDI TIPA is

replaced with TEA, or in the case Quadrol/HDI Quadrol is replaced with the analogous primary tetraol. In the latter case the polymerization (gelation) interferes with the mixing. The gel time is too short to permit sufficient mixing. The compound BHEIPA can be considered a polyol with properties lying between those of TEA and TIPA. Trimethylolpropane, finally, which also contains three primary OH groups, just like TEA, was also miscible with diisocyanates above its melting point (60°C) (From the literature aromatic, highly cross-linked polyurethane networks made from TMP and MDI are known (41)). In this context it is strange that glycerol, containing two primary and one secondary hydroxyl group, can not be mixed with any diisocyanate. From the above, it may be clear that it is rather unpredictable whether or not a certain pair of polyol/diisocyanate is miscible.

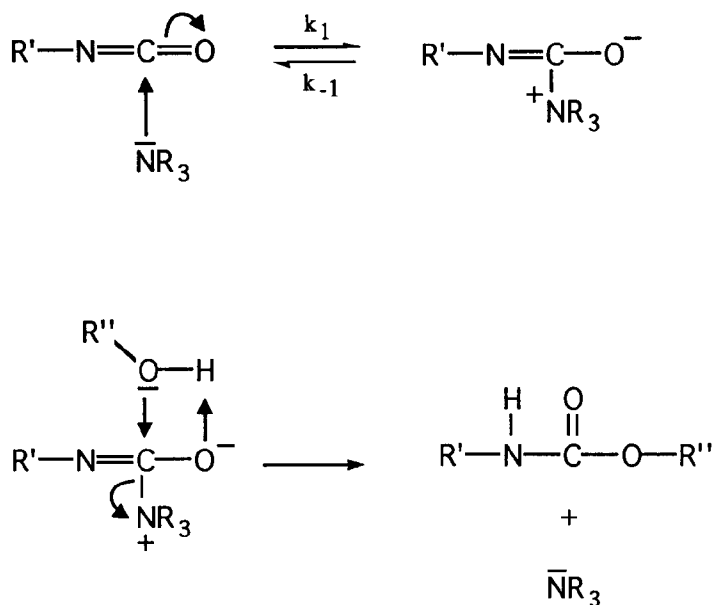


Figure 3. The mechanism of the tertiary amine catalyzed urethane reaction.

Another interesting thing that the above mentioned polyols have in common, except TMP, is the presence of tertiary amino groups in the molecular structure. Tertiary amines are known catalysts for the urethane reaction (26,47-49). The mechanism for tertiary amine catalysis involves the formation of an intermediate active complex of the isocyanate and the tertiary amine. After the OH group is added, the intermediate complex rapidly rearranges to the urethane linkage (figure 3). So, these polyaminoalcohols contain an internal, built-in catalyst (48). No external catalyst is needed for the polyurethane reaction, which is interesting with regard to the potential biomedical application of the polyurethane networks. Added catalysts, for instance toxic tin salts, may be responsible for complications after implantation.

The whole problem of miscibility can be avoided by using only one compound in the formation of a polymer network. An example is the polytrimerization of diisocyanates in the presence of a suitable catalyst (e.g. stannous octoate), resulting in polyisocyanurate networks. At temperatures higher than 120 °C HDI formed a glassy, transparent, densely cross-linked network with a high ultimate glass transition temperature of 150 °C. This high $T_{g\infty}$ is likely due to the presence of rigid 6-membered isocyanurate ring structures in the network.

Polyurethane networks were prepared by firstly mixing the polyol component and the diisocyanate under a nitrogen atmosphere, to avoid side reactions of the isocyanate group with water which gives rise to undesired bubble formation (or foaming). After mixing, the homogeneous, colourless viscous mixture was allowed to gelate (usually at temperatures below $T_{g\infty}$). Directly after gelation, the glass transition temperature of the network is equal to the gelation temperature. Due to vitrification the chemical reactions in principle are quenched. The mobility of the functional groups in the glassy network that have not reacted yet is very low, which means that the network formation takes place very slowly. After vitrification, the cross-linking reaction becomes diffusion-controlled (50). The samples were fully cured at temperatures above the ultimate glass transition temperature of the polyurethane networks $T_{g\infty}$. In order to reach a maximum conversion of the functional groups, the cure temperature has to be above the $T_{g\infty}$ of the system. The glass transition temperature is a sensitive

measure of the functional group conversion (51).

Instead of the conventional thermal curing of the samples, the polyurethane resins may be cured by means of electromagnetic waves in the microwave frequency range (2,45 GHz). In contrast to thermal heating, which involves heat conduction and thermal lag associated with it, microwaves can generate heat directly within the sample and thus offer the possibility of very fast, uniform curing which should result in improved physical/mechanical properties of the final material (52). Microwave heating has been used for the cure of epoxy resins and polyurethane foams (53).

All polyurethane networks were optically transparent, colourless, amorphous, glassy materials. The refractive index of a fully cured Quadrol/HDI-based polyurethane network is 1,50, slightly higher than the value (1,49) reported for PMMA (7,9,11,15,18). The networks were macroscopically homogeneous; apparently no phase separation had occurred during the process of network formation. In table 1 the ultimate T_g 's of the densely cross-linked networks, obtained from the bulk reaction of a polyol and a (cyclo)aliphatic diisocyanate in stoichiometric proportions, are collected.

Table 1. Ultimate glass transition temperatures (in °C) of polyurethane networks obtained from the bulk polymerization of a polyol and a diisocyanate in stoichiometric proportions

	TIPA	Quadrol	octaol	TEA	BHEIPA	TMP
HDI	75	85	106	33	45	83
LDI	-	72	-	34	-	-
IPDI	160	165	-	133	-	184
tCHDI	178	190	-	125	-	227

The ultimate glass transition temperature of a HDI-based polyurethane, as can be seen in table 1, increases when the functionality of the polyol increases (going from TIPA to Quadrol to the octaol), which is due to an increase in the cross-link density. The $T_{g\infty}$ is also markedly raised when an aliphatic diisocyanate (HDI, LDI) in a particular formulation is replaced with a cycloaliphatic one (t-CHDI, IPDI), which is a consequence of the higher rigidity in the case of a cycloaliphatic polyurethane network.

Since all these polyols, and all diisocyanates as well, are miscible, the $T_{g\infty}$ of a polyurethane network can be varied endlessly. The $T_{g\infty}$ of a multi-component system then lies between the $T_{g\infty}$'s of the networks resulting from the individual pair of reactants (two-component system). An interesting example is the polyurethane network made from a polyol mixture of TEA and TIPA in a 2:1 mole ratio, and HDI in stoichiometric proportions. This polyurethane had a $T_{g\infty}$ (44 °C) that was virtually equal to the one of the BHEIPA/HDI-based polyurethane, as could be expected, and inbetween the $T_{g\infty}$ values of the TEA/HDI-based and the TIPA/HDI-based polyurethane network.

Another way of influencing the $T_{g\infty}$ is to carry out the network-forming reaction using off-stoichiometric proportions of reactive groups. For example, when 1 eq. Quadrol is reacted with 1,5 eqs. HDI, instead of the stoichiometric 2 eqs, the $T_{g\infty}$ of the final network drops ca. 20 °C. In this case a considerable amount of unreacted alcohol groups (dangling ends) are present in the network, which are responsible for this lowering of the $T_{g\infty}$. One can also say that the cross-link density is much lower than in the case of a stoichiometric network formation. Another example is the drop in $T_{g\infty}$ when the octaol is reacted with 2 eqs. HDI instead of the stoichiometric 4 eqs.. The ultimate glass transition temperature of the network now drops from 106 °C to 54 °C.

From swelling measurements using chloroform, it could be established that the polyurethane networks were definitely highly cross-linked, i.e. having a low degree of swelling. The volume degrees of swelling for the Quadrol/HDI-based and the TIPA/HDI-based polyurethane network were 1,27 and 1,60, respectively. The higher degree of swelling of the trifunctional aliphatic polyurethane network compared to the corresponding

tetrafunctional network is ascribed to the lower cross-link density in the trifunctional network. It should be mentioned that in all cases it was found that the gel content was 100 % (The drying of the swollen networks to constant weight took about 3 weeks in a vacuum oven at 100 °C). No sol fraction could be detected in any cross-linked polyurethane network. It has been said before that by extraction of tight polymer networks, and subsequently drying, the gel content can not be determined accurately, since the actual sol fraction may not be able to diffuse out of the dense network.

Infra-red spectra of fully cured Quadrol/HDI-based or TIPA/HDI-based polyurethane networks, both spectra were virtually identical, revealed the absence of an isocyanate absorption at ca. 2250 cm^{-1} , indicating the completeness of the cross-linking reaction. Apparently, all isocyanate groups have reacted, either with the hydroxyl groups (urethane bond formation) or with urethane bonds to form allophanate linkages. The latter should not be excluded since the curing was carried out at ca. 100-110 °C, at temperatures where the allophanate formation becomes competitive with the urethane formation (54). The isocyanate absorption at 2260 cm^{-1} , however, was not absent in the infra-red spectrum of the HDI-based polyisocyanurate network. This indicates that in the case of a polytrimerization, where three NCO groups have to react simultaneously to form ring-like isocyanurate structures, residual isocyanate groups can be detected in the final network. Apparently, a complete conversion of the reactive groups can not be attained.

The Quadrol/HDI-based and TIPA/HDI-based polyurethane networks were subjected to tensile testing. Both glassy materials showed virtually identical stress-strain behaviour. Figure 4 shows a typical stress-strain curve of a Quadrol/HDI-based polyurethane network. The tensile strength of the two aliphatic polyurethane thermosets was in the range 80-85 MPa. Both formulations had comparable moduli (1,5 GPa) and comparable strains at break (ca. 15 %). The polyurethane glasses usually yielded prior to break, a phenomenon also displayed by other glassy cross-linked networks, for example epoxies (55-57), and by glassy thermoplastic polymers, like PMMA,

as well. The plastic deformation of glassy thermosets below T_g is similar to that of amorphous glassy thermoplastics (58). The mechanical properties of these densely cross-linked polyurethane networks will be discussed in more detail in a forthcoming paper (59), in which also results of dynamic mechanical measurements will be presented.

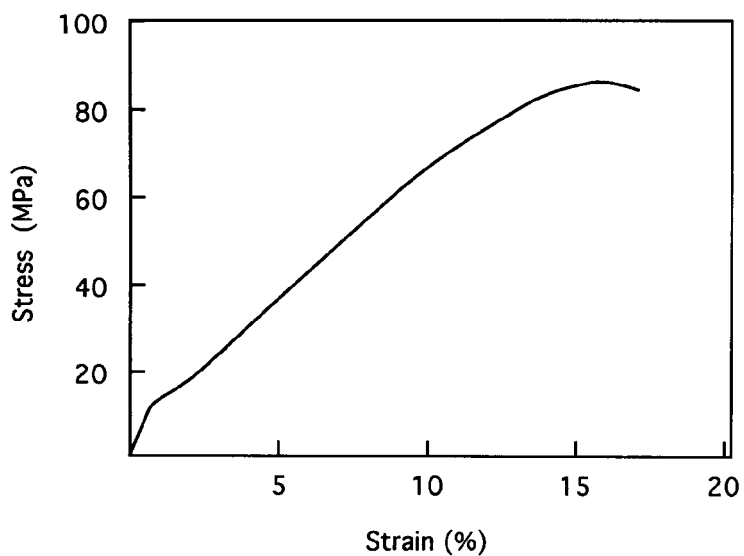


Figure 4. Stress-strain behaviour of a glassy polyurethane network obtained from the bulk polymerization of Quadrol and HDI in stoichiometric proportions.

Some densely cross-linked polyurethanes were immersed in water for about two months to measure their water uptake by weighing. The water uptake of Quadrol/HDI-based, octaol/HDI-based, TEA/HDI-based polyurethanes were 1,2 %, 1%, and 8 %, respectively. The water uptake of the Quadrol/HDI-based polyurethane was increased when the cross-linking reaction was carried out off-stoichiometrically. The residual, polar hydroxyl groups in the network, obtained from the polymerization of Quadrol with 1,5 eqs. HDI, were responsible for a higher water uptake (3,1 %) of this network. The same was observed for the octaol/HDI-based network. The water uptake was increased to ca. 8 % when the octaol was reacted with 2 eqs. HDI instead of the stoichiometric 4 eqs. In any case it was seen that the uptake of water dramatically lowered the T_g of the network, due to a plasticizing effect. The T_g of the stoichiometric Quadrol/HDI network dropped from 85 to 48 °C, and the T_g of the TEA/HDI network dropped from 33 to -20 °C (resulting in a rubberlike polymer). It is well-known that the presence of water in polymer networks positively contributes to their biocompatibility. Hydrogels, usually water swollen polymer networks, are said to be biocompatible due to a low interfacial tension which may be exhibited between the hydrogel surface and an aqueous solution (as in living tissue). An attempt to make the polyurethane networks more hydrophilic, so that the water uptake would increase, was the incorporation of low molecular weight polyols containing besides OH groups, carboxyl groups in their molecular structure: N,N-bis(2-hydroxyethyl)glycine (bicine), bis(hydroxymethyl)propanoic acid. These two compounds could be "dissolved" in the polyaminoalcohols from figure 1 only at high temperatures (ca. 100-150°C). The resulting clear polyol mixture was then reacted with the stoichiometric amount of HDI, but the water uptake of the resulting network was not noticeably higher than in the case of a normal polyurethane formulation. Apparently, the carboxyl groups had reacted during the course of the experiments, either with the hydroxyl groups (esterification) or with the NCO groups. Besides low molecular compounds, linear polymers may be incorporated into the polymer network. Thus, so-called semi-interpenetrating networks are formed. For example, poly(N-vinylpyrrolidone), a water-soluble polymer, can be dissolved in Quadrol (at elevated temperatures), and the resulting

polymer solution can be cross-linked with a diisocyanate to form a glassy thermoset.

PMMA intraocular lenses have been surface modified with covalently linked heparin to increase the biocompatibility (60,61). A (PMMA) lens surrounded by a solution of hydrophilic monomers can be γ -irradiated, resulting in a thin coating of grafted hydrophilic polymer (62). Another method used to modify the surface of a polymeric material is the glow-discharge technique (53,63). In this way surfaces can be made more hydrophilic, which might also work out nicely for the polyurethane networks described here.

Alternatively, the surface of the polyurethanes might be modified to increase the hydrophilicity by usual grafting techniques or by the two following methods. Since NCO groups can also react (slowly) with amide groups, the liquid polyol/diisocyanate mixture may be poured onto a dry polyacrylamide film, and subsequently cured at high temperatures (ca. 110°C). In this very straight-forward manner polyacrylamide may be grafted chemically to the polyurethane. Another possibility is the "surface etching" of the polyurethane network with a dicarboxylic acidchloride (e.g. succinyl chloride) for a short period of time, and then placing the whole sample in water in order to create carboxyl groups at the surface. This last method is in slight analogy with the sodium hydroxide sterilization technique used for the sterilization of PMMA, for instance (7,9). Local hydrolysis of the methyl ester at the surface through the action of sodium hydroxide results in the formation of carboxyl groups at the surface, making the surface more hydrophilic. Although not intended as a surface modification method, this sodium hydroxide sterilization might act this way in case of PMMA.

As a pilot experiment, three disks made of the Quadrol/HDI-based polyurethane network were implanted in rabbit eyes to see how the material was tolerated in the eye. All three implantations, basically, gave the same results. A serious opacification of the whole cornea, indicating an adverse reaction to the implant material, was never seen. The cornea was nearly completely clear two weeks after the surgical procedure. Only near the site of the corneal incision, the cornea was a little hazy, and starting from that site some vascular ingrowth, which was likely due to some surgical trauma, could be seen. Figure 5 shows a photo of a rabbit

eye containing a circular disk made of the highly cross-linked polyurethane two weeks after implantation. From these preliminary experiments it may be concluded that the highly cross-linked polyurethane material was rather well tolerated in the rabbit eye. The material did not turn out to be acute toxic and seems suited for use in opthalmic applications. These encouraging results have led to the additional implantation of a keratoprosthesis in a rabbit eye.

The preliminary experiment with one lathe-cut keratoprosthesis of the Quadrol/HDI-based polyurethane network implanted in one Chinchilla-rabbit eye also showed that the material was tolerated very well by the healthy rabbit eye. The cornea stayed clear, indicating that the endothelium, stroma and epithelium of the cornea and the anterior eyechamber did not

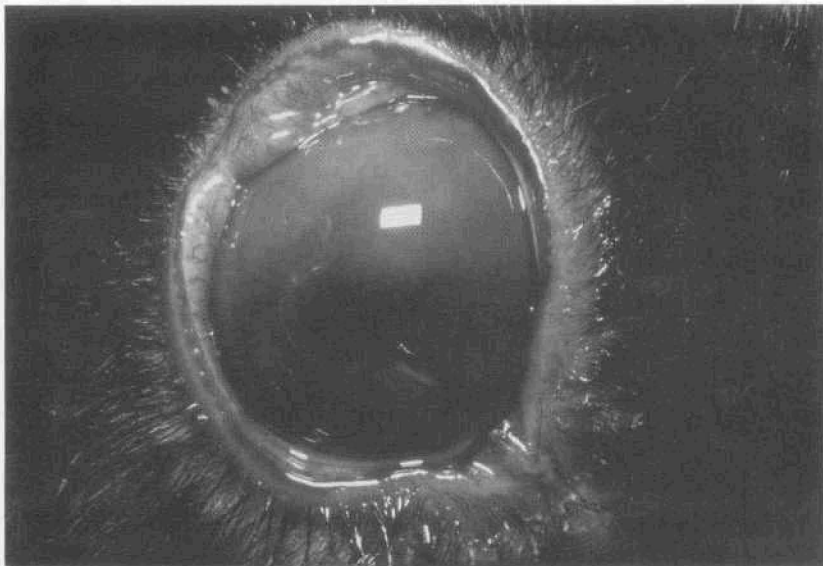


Figure 5. Photograph of a rabbit eye with a circular implant made of a highly cross-linked Quadrol/HDI-based polyurethane network two weeks after implantation.

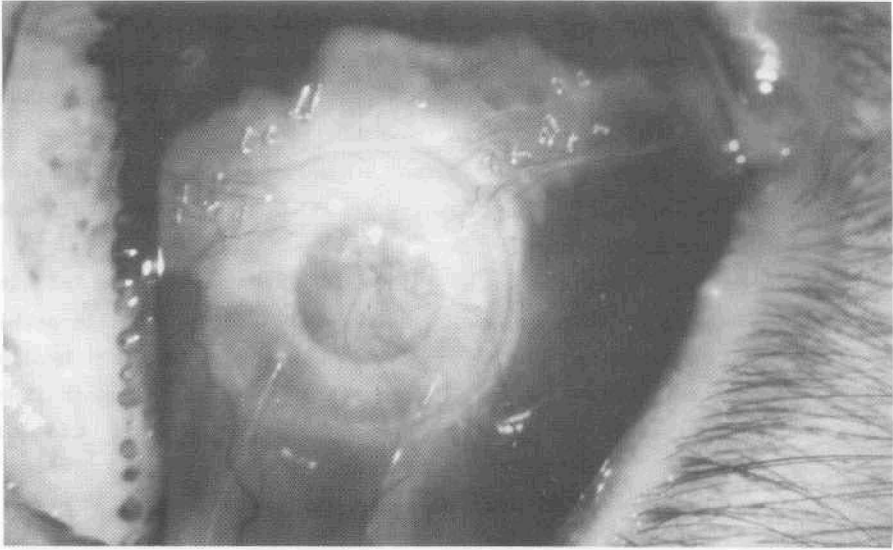


Figure 6. Photograph of a rabbit eye with a keratoprosthesis made of a highly cross-linked Quadrol/HDI-based polyurethane network one year after implantation.

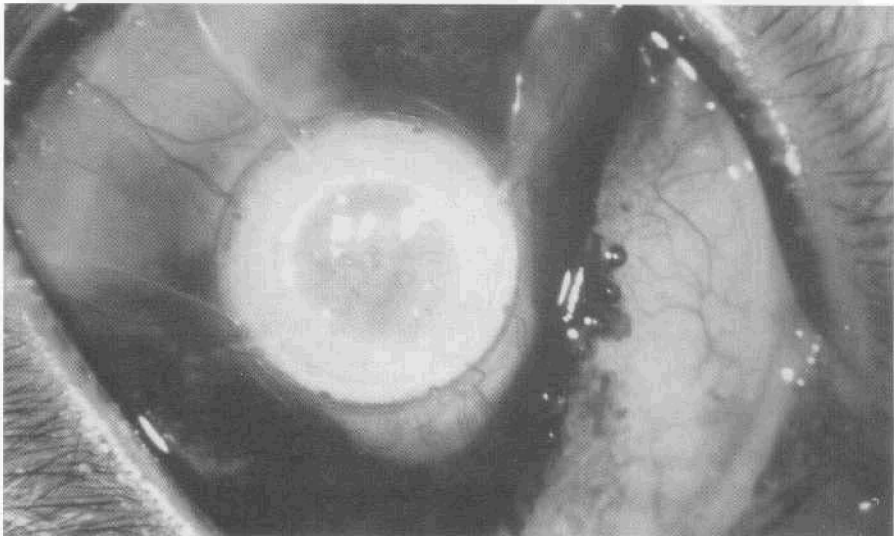


Figure 7. Rabbit eye with an implanted stainless steel/glass keratoprosthesis

react on the implant and/or its material. Even one year after implantation (see figure 6) the eye was still "clear" as it is called in the clinical terms. The opacification seen around the keratoprosthesis and the incision, made to extract the lens, are the result of "Kammerwasserausbruch": a reaction of the stromal tissue to the leakage of aqueous humour into the stroma of the sclera, unavoidably caused by the surgical trauma. The overgrowth of the keratoprosthesis by the stroma and epithelium of the sclera is not a reaction to the material as such. This also happens after implanting a keratoprosthesis made of inert PMMA CQ (clinical quality) or inert stainless steel/glass (see figure 7) (33,64,65). These results show that the transparent highly cross-linked polyurethane network is suited to make inert, autoclavable keratoprostheses.

The crystalline lens and cornea filter most of the solar ultraviolet radiation, having wavelengths from approximately 285 to 400 nm and which itself is damaging to the retina, to which the eye is exposed. Quanta with wavelengths below 300 nm are almost completely absorbed by the cornea. Ultraviolet radiation ranging from 300 to 400 nm is normally absorbed by chromophores in the crystalline lens. After cataract extraction, the posterior segment of the eye is therefore exposed to UV radiation not normally encountered in the phakic state. The ideal intraocular lens should be ultraviolet light absorbing, i.e. absorb UV light with wavelengths below 400 nm. Nowadays nearly all intraocular lenses contain a UV-absorbing chromophore, either in the form of a low molecular additive or polymer bound (66-68). It appeared that Coumarin 102 (see figure 8), a so-called laser dye, was soluble in the polyol component of the polyurethane formulation. This compound could withstand the curing process without losing its UV light absorbing activity, unlike the conventional hydroxyl containing UV absorbers, like hydroxybenzophenones or hydroxybenzotriazoles (69) (these compounds contain hydroxyl groups that can react with the diisocyanate used and consequently losing their UV-absorbing ability). In figure 8 UV/VIS transmission spectra are shown of a Quadrol/HDI-based polyurethane sample (1 mm thickness) with and without the additive Coumarin 102, in low concentration. As can be seen

the polyurethane thermoset without the additive transmits light with wavelengths above 275 nm (ca. 90 % transmission). A few promille Coumarin 102, which is a fluorescent compound with its absorption maximum at $\lambda=390$ nm and its fluorescence maximum at $\lambda=468$ nm, is enough to completely absorb the UV light with wavelengths below 450 nm.

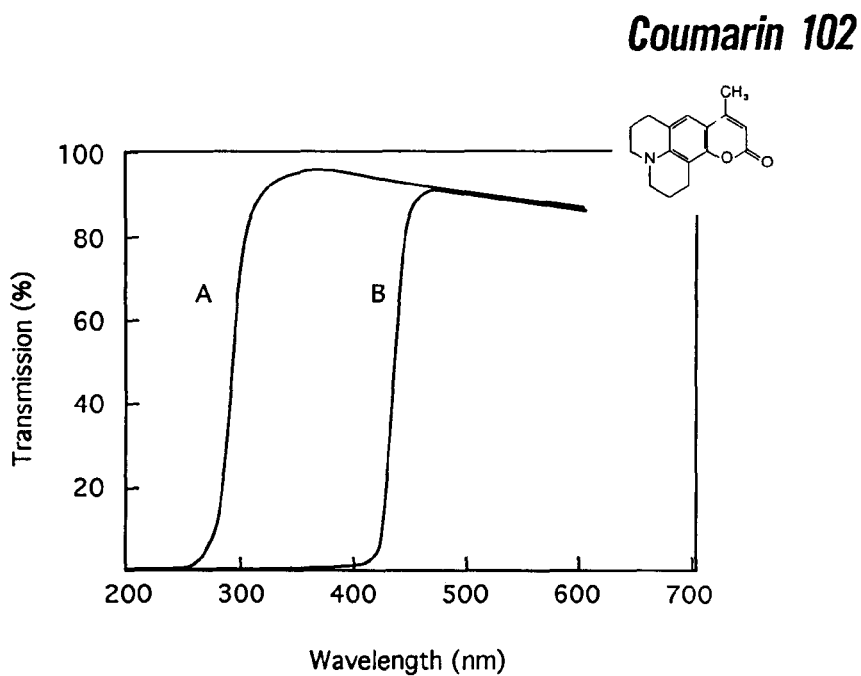


Figure 8. UV/VIS transmission spectra of the additive-free Quadrol/HDI-based polyurethane network (A), and of the same material containing 0,08% Coumarin 102 (B), a UV-absorbing chromophore (sample thickness 1 mm).

Finally, there may be some concern about the long-term stability of the highly cross-linked polyurethanes. As known from the literature (26,70), polyurethanes in general do (bio)degrade, although nearly all polyurethanes investigated are (uncross-linked) thermoplastic elastomers. In vivo degradation is usually hydrolytic, although tissue enzymes may also participate in the degradation process. Polyurethanes can be made deliberately degradable (see ref. 32), but also hydrolytically stable. Since the polyurethane networks described here are rather hydrophobic and very densely cross-linked, pronounced degradation is not to be expected. An indication for this is that the T_g of a Quadrol/HDI-based sample immersed in water for 20 months did not differ from the value of a sample of the same material immersed in water for 2 months ($T_g=48^\circ\text{C}$). Another noticeable feature is that the rabbit eye with the implanted polyurethane keratoprosthesis was quiet one year after the surgical procedure.

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