Synthesis of High Molecular Weight and Strength Polyisobutylene-Based Polyurethane and Its Use for the Development of a Synthetic Heart Valve

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Under optimized synthesis conditions we prepared, for the first time, polyisobutylene-based polyurethane (PIB-PU) with 70% PIB soft segment (i.e., a bioinert and calcification resistant PU) with Mn >100,000 Da, 32 MPa ultimate strength and 630 % elongation. The key parameters for this achievement were (a) the precise stoichiometry of the polyurethane forming reaction, specifically the use of highly purified diisocyanate (MDI), and (b) the increased the solid content of the synthesis solution to the limit beyond which increased viscosity prevents stirring. The shape of the stress-strain trace of PIB-PU indicates two-step failure starting with a reversible elastic (Hookean) region up to ~50 % yield, followed by a slower linearly increasing high modulus deformation region suggesting the strengthening of PIB soft segments by entanglement/catenation, and the hard segments by progressively ordering urethane domains. This PIB-PUs is a candidate for a fully synthetic bioprosthetic heart valve since preliminary studies show that PIB-PU has impressive fatigue life.

1. Introduction

Polyisobutylene-based polyurethanes (PIB-PUs) PIB containing 70% PIB are bioinert (biocompatible and biostable) calcification resistant thermoplastic elastomers for long-term implantable medical devices for a modest cost.[1-3] These TPEs exhibit exceptional combinations of hydrolytic, oxidative, and enzymatic resistance, together with exceptional softness, barrier properties, low creep, and low cell adhesion.[4-8] Importantly, the inert continuous -CH_2-$C(CH_3)_2$- soft segments shield the environmentally vulnerable urethane (-NHCOO-) hard segments and lead to desirable combinations of properties.

On the downside, however, the inert PIB soft segment lacks H bond accepting sites, so that the strength of these PIB-PUs is inherently lower than those of conventional PUs whose soft segments contain nucleophilic (i.e., O or N) sites. To overcome this shortcoming, we carried out systematic investigations, however, we could not increase the tensile strength and elongation above ~26 MPa and ~500 %, respectively. [7, 9-11]

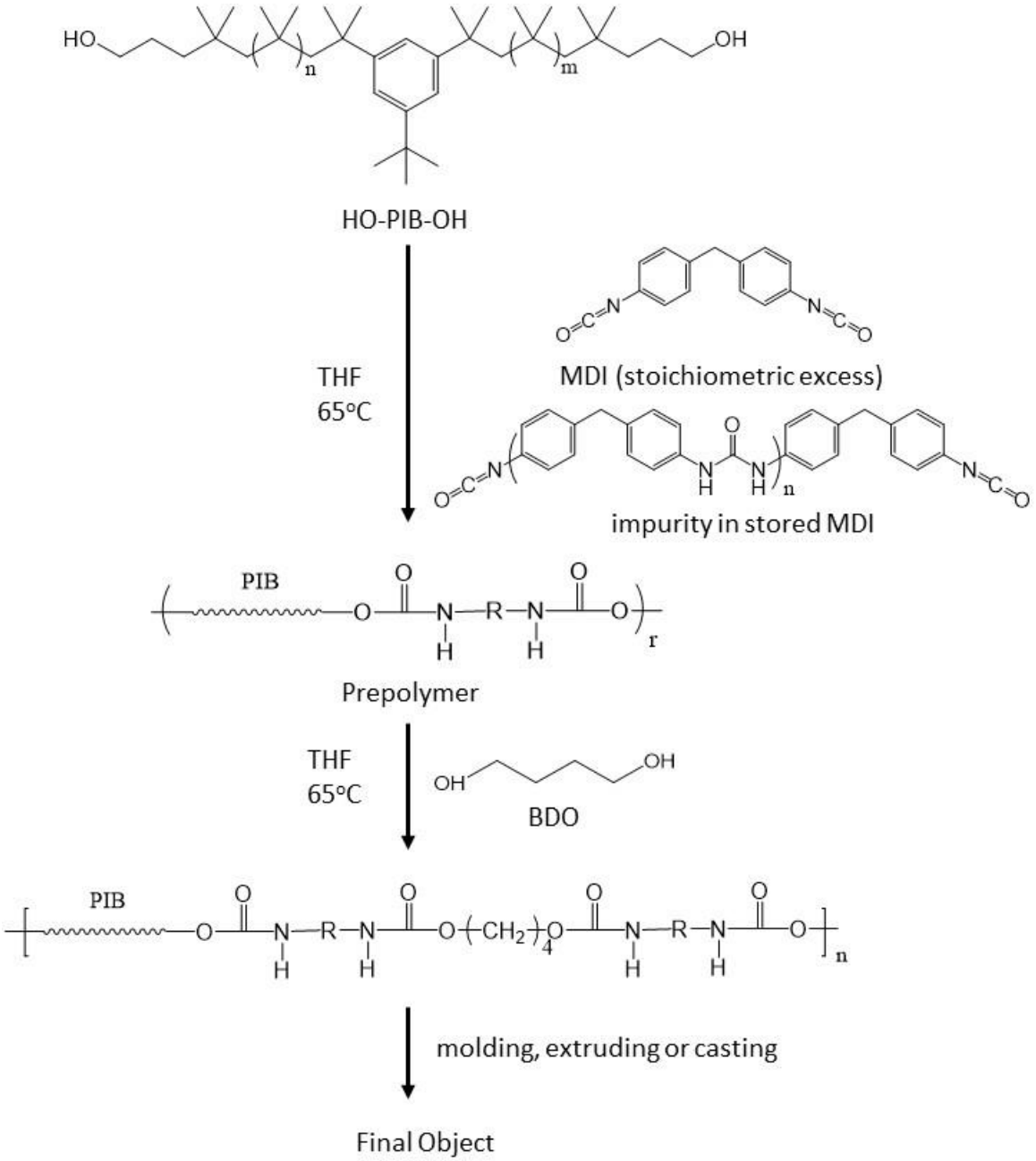
An aim of this communication is to report recent research to enhance key mechanical properties of PIB-PU. By optimizing synthetic conditions, we were able to significantly increase the MW of PIB-PU and hence its tensile strength and elongation. We obtained PUs that are likely bioinert, calcification resistant and whose protein adsorption is less than that of silicone rubber-based Pus. [3, 8] These PIB-PUs are designed for biomaterial applications and can be used where earlier PIB-PUs could not be employed, for example, for a fully synthetic heart valve.

Over 500,000 prosthetic heart valves are implanted per year. Clinically available prosthetic valves are life-saving but imperfect: mechanical valves require lifelong anti-coagulation medication and carry associated bleeding and thrombosis risks; while bioprosthetic valves show structural deterioration ultimately requiring reoperation. Polymeric heart valves have the potential to achieve long durability without the need for anticoagulation medication. For this reason, there has been interest since the 1970s in producing a viable polymeric valve; but none has achieved regulatory approval for clinical application. With improvements in materials, manufacturing techniques and modelling, there has been a resurgence of research into polymeric valves in the past decade or so, with several promising prototypes emerging, the most advanced being the Foldax Tria polyurethane valve, which started first in human trials in July 2019. Much attention has focused on thermoplastic polyurethanes because of their good physico-chemical properties and ease of processing; and recent formulations (such as the Foldax material) have shown improved biocompatibility and stability. Nonetheless, to date, polyurethanes have suffered from calcification and/or gradual oxidation/degradation *in vivo*, resulting in mechanical failure and/or thrombosis. [12,13] A polyurethane combining excellent mechanical properties with outstanding long-term resistance to oxidation and calcification *in vivo* therefore remains a holy grail of material development for heart valve, and other medical, applications.

2. Results and Discussion

2.1 Synthesis conditions

We reexamined data collected over several years relative to the effect of experimental conditions on molecular weights and mechanical properties of PIB-PUs. Typical synthetic route for PIB-PU is given in Scheme 1.



Scheme 1 Synthesis of PIB-PU

Our analysis suggested that the purity (pretreatment) of 4,4′-Methylenebis (phenyl isocyanate) (MDI), and the concentration (solid content) of the synthesis solutions strongly influenced PIB-PU properties. Consequently, we investigated the effects of MDI pretreatment and shelf life, and PIB diol concentration on MW and mechanical properties of PIB-PUs. Table 1 summarizes pertinent data.

Table 1 Effects of MDI pretreatment and shelf-life, and HO-PIB-OH concentration on PIB-PU molecular weight and key mechanical properties

Expt. #	MDI Pretreat-ment [a)]	MDI Storage time [week]	MDI Storage temp. [^{o}C]	HO-PIB-OH conc. [wt.%]	MW/ MWD [kDa/-]	Stress at break [MPa]	Strain at break [%]	Energy to break [J]	Appearance of colorless films
1	as-received	-	-	21.4	21/1.8	9	110	0.07	very hazy
2	Distilled, stored	6	-12	21.4	24/1.8	12	141	0.20	hazy
3	Distilled, stored	3	-12	21.4	29/1.8	14	190	0.50	hazy
4	Freshly distilled	-	-	21.4	56/1.9	22	480	1.90	optically clear
5	Freshly distilled	-	-	28.5	101/3.1	32	630	4.07	optically clear

[a)] (distilled at $2x10^{-2}$ mmHg and 115 ^{o}C)

2.1.1. The Effect of MDI Purity

The mechanical properties of PUs are strongly affected by the purity of the diisocyanate and other reagents. Isocyanates, because of their very high reactivity, are particularly prone to react with impurities (moisture, etc.) and, particularly after lengthy storage times (weeks), contain slowly forming impurities, i.e., dimers, oligomers, polyureas. [14] Thus, the shelf life of MDI will affect its purity. [15,16]. Impurities reduce the concentration of the isocyanate function and obviate the precise stoichiometry needed for highest quality PUs. Slowly forming isocyanate oligomers and polyureas are particularly onerous as they can enter the hard segments, disrupt their morphology, and thus compromise mechanical and optical properties (see Figure 1). These impurities may also function as stress concentrators and reduce strength, elongation, and toughness. [17]

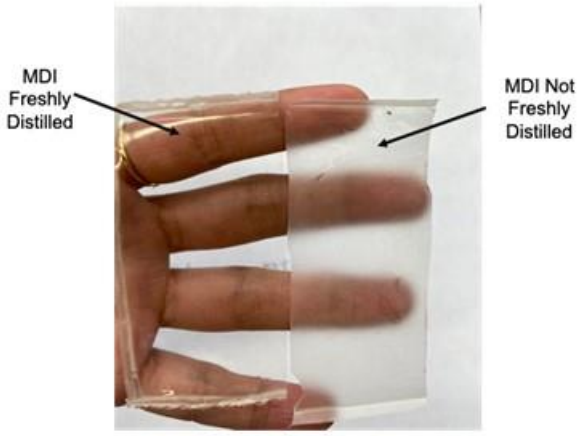


Figure 1. Optical clarity of PIB-PU films. Left: prepared with freshly distilled MDI (Expt. 4), Right: prepared with MDI distilled-and-stored for 6 weeks (Expt. 2).

Thus, the synthesis of highest quality PIB-PU requires purest MDI.

We carried out experiments to explore the effect of MDI pretreatment (i.e., as-received, distilled and stored for 3 and 6 weeks at -12 ^{o}C, freshly distilled) on MWs and key mechanical properties of PIB-PUs.

Inspection of the results of Expts. 1 - 4 in Table 1 shows that the use of freshly distilled MDI in place of as-received MDI more than doubled MWs (from 21 to 56 kDa), significantly increased stress and elongation (from 9 MPa to 22 MPa, and from 110 % to 480 %, respectively), and close to tripled toughness (from 0.07 to 1.9 J).

As mentioned, the shelf life of MDI is also an important purity issue. We observed that after vacuum distillation of as-received MDI a white insoluble residue remained in the distillation flask. Similarly, a white precipitate appeared after a few days of MDI stored at -12 ^{o}C, and the amount increased with time.

The impurities in MDI were identified by ^{1}H NMR spectroscopy. Figure 2 shows the spectrum of freshly distilled MDI and shows the methylene protons at 3.90 ppm and aromatic protons at 6.99-7.14 ppm. The formulae in the figure show the structure of MDI and that of an isocyanate dimer with urea groups. The resonances of aromatic protons (a, b) ortho and meta to the urea group appear at 7.42-7.52 ppm[14].

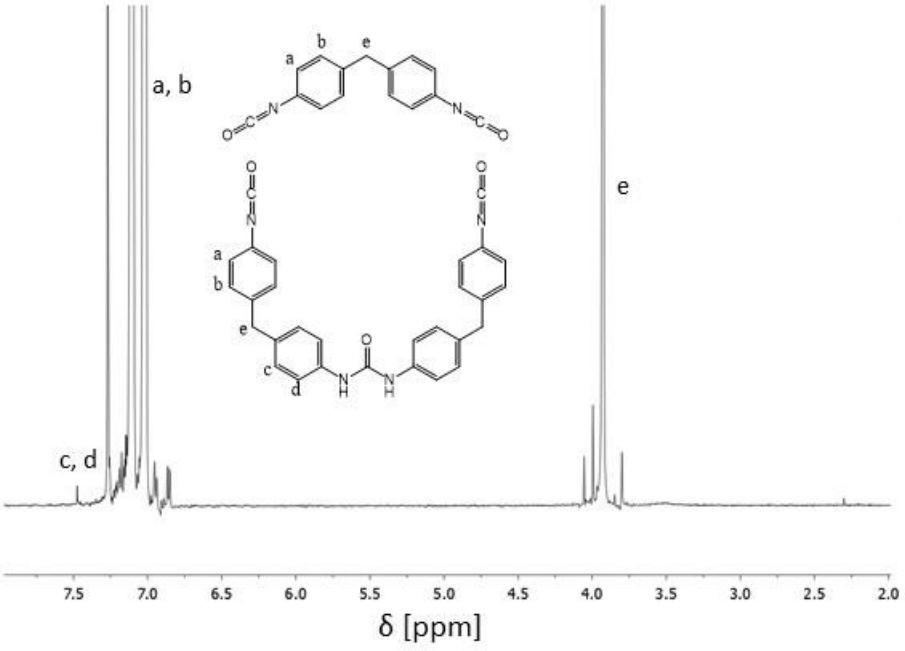


Figure 2. ^{1}H NMR spectrum of freshly distilled MDI

The set of NMR spectra in Figure 3 clearly shows that polyurea impurities in MDI that arise during extended storage (see resonances in the 7.42-7.52 ppm region) can be almost eliminated by routine distillation.

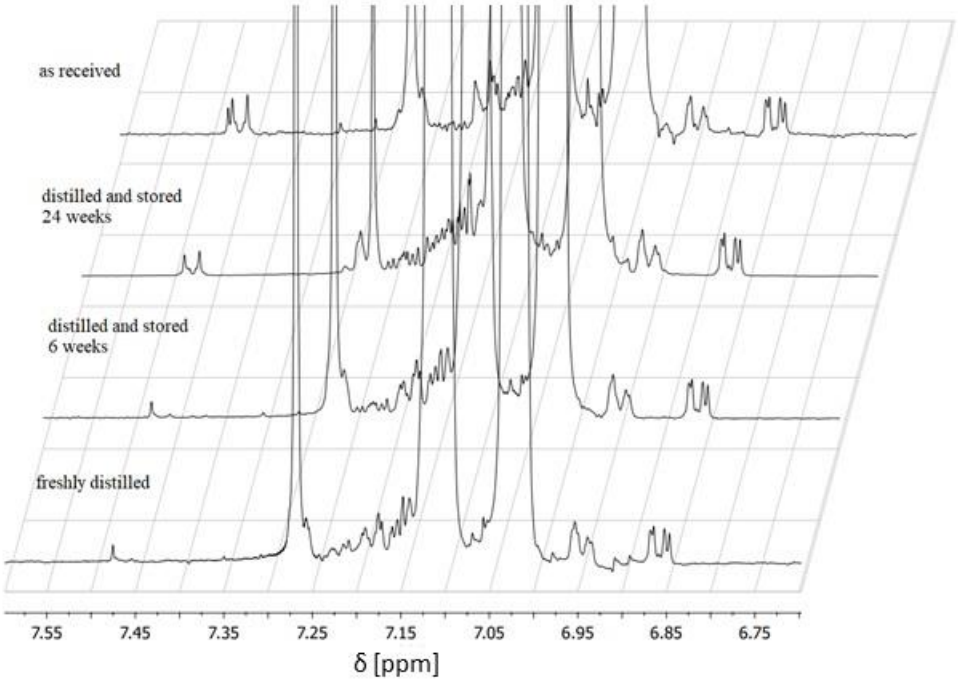


Figure 3. The 6.7-7.5 ppm region of ^{1}H NMR spectra of MDI (from top to bottom: as-received, distilled and stored 24 weeks, distilled and stored 6 weeks, freshly distilled).

According to the data in Table 1 (compare results of Expts. 2 or 3 with 4) the MW and strength properties of PIB-PU more than doubled using freshly distilled MDI.

2.1.2. The Effect of HO-PIB-OH Concentration

Experiments were carried out to explore the effect of HO-PIB-OH concentration on key mechanical properties of PIB-PU. Thus, the PIB diol concentration was increased from 21.4 to 28.5 wt. % in THF. In Expts. 1-4, with 21.4 wt. % PIB diol, the polymerizing systems became increasingly viscous but stirring remained satisfactory. In contrast, in Expt. 5, the system became extremely viscous and stirring became impossible ~20 mins after chain extender addition. Stirring for up to 3 hrs could be resumed by diluting with 2-3 mL THF.

As shown by the data in Table 1 (see Expts. 4 and 5), key mechanical properties increased significantly by increasing the PIB diol concentration from 21.4 to 28.5 wt. %. Stress at break increased from ~22 to ~32 MPa, elongation increased from 480 to 630 %, and toughness doubled. Films made at the higher PIB-diol concentration were colorless and optically clear, similarly to those made with freshly distilled MDI.

Evidently, higher synthesis solution concentration increased the rate and extent of the reaction, leading to higher PIB-PU molecular weights and superior mechanical properties. Similar observations have been reported. [18,19]

Figure 4 shows GPC traces of HO-PIB-OH and PIB-PU. The very high MW of the PIB-PU obtained in Expt. 5 suggests essentially complete stoichiometric chain extension.

High MWs produce significantly enhanced levels of entanglement and catenation, and lead to the observed high elastic moduli.

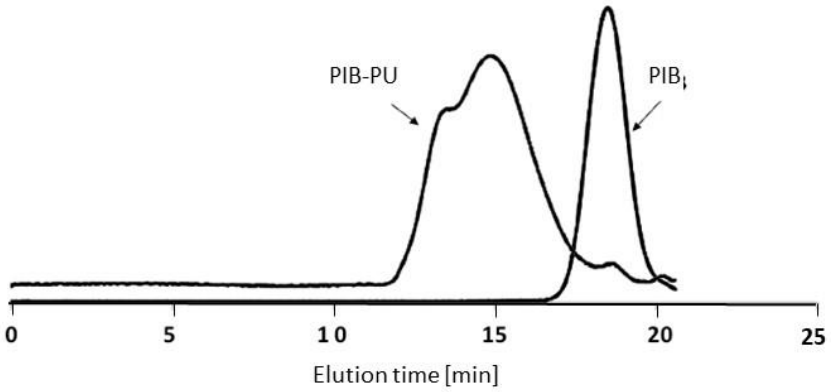


Figure 4. GPC traces of HO-PIB-OH (Mn=3000 g/mol; Mw/Mn = **1.1**) and PIB-PU obtained in Expt. 5, Table 1 (Mn= 101,400 Da; Mw/Mn: 3.1)

In sum, using purified MDI and increasing the PIB diol concentration we obtained PIB-PUs with heretofore-unseen levels of ultimate strength elongation and toughness. These key properties lead to new fatigue resistant PIB-PUs, suitable for synthetic heart leaflets, that could not be made using earlier PIB-PUs.

2.2. Stress-strain behavior of PIB-PU

Figure 5 shows stress vs. strain traces of PIB-PU obtained in this work (Expt. 4, Table 1), together with the highest quality PIB-PU reported to date [7] and for comparison a commercial silicon rubber-based PU (Elast-Eon).

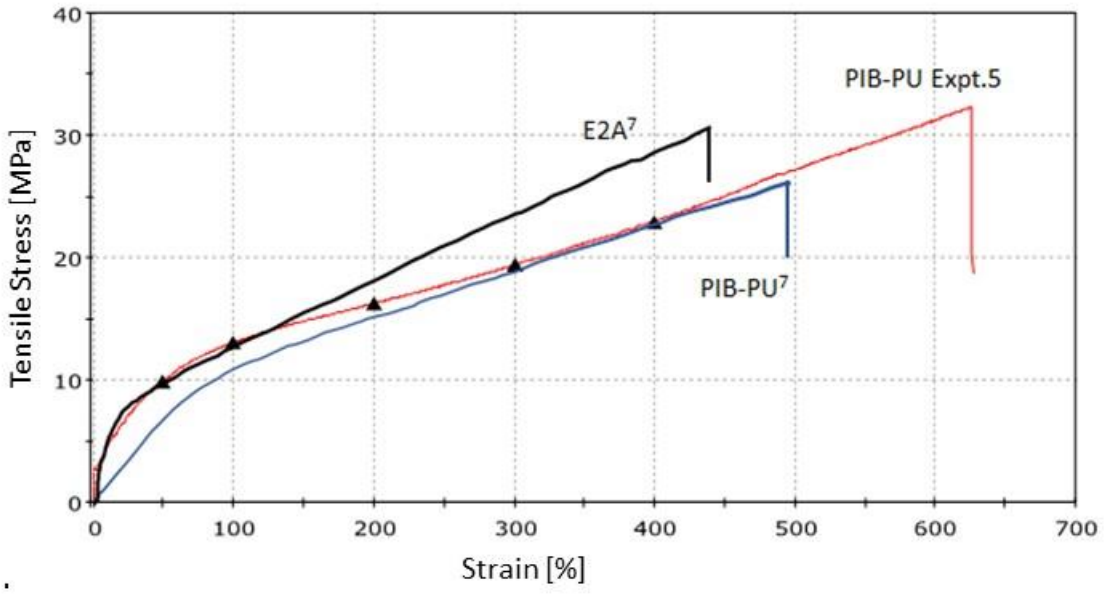


Figure 5. Stress-strain traces of PIB-PU prepared (Expt. 5, Table 1), the best previously synthesized PIB-PU (ref. 7) and Elast-Eon (E2A). Adapted with permission.[7] 2015, John Wiley &Sons.

The stress /strain trace of PIB-PUs starts with a reversible elastic (Hookean) region up to ~50 % yield, followed by high modulus deformation region suggesting the strengthening of hard segments by alignment and ordering, until failure. High modulus and continuously increasing Young moduli are characteristic of highly elastic though materials. In respect to mechanical behavior, the new PIB-PU, although it contains only 30 wt. % hard segments, is superior to polysiloxane-based PU (Elast-Eon) with 52% hard segments. In comparison to earlier PIB-PUs (with 30 wt. % hard segment), the new PIB-PU, due to its higher MW and therefore higher extents of entanglements and/or catenation, exhibits superior strength, elongation, and toughness.

2.3. Fatigue behavior of PIB-PU

A key aspect of a polymer's properties for an application such as a prosthetic heart valve is fatigue lifetime, particularly over very many cycles at low strain. Typical maximum strain experienced by a polymer in a heart valve leaflet is around 10% (with maximum strain energy density of 0.05 MPa or less) and the lifetime must be 25 years or more (1 billion cycles +). It is desirable to test the polymer at a similar frequency to that experienced in practice (around 1 Hz). Clearly it is impractical to test fatigue to failure at realistic strain, and so there is a compromise required between the strain used for testing and the time taken to complete the experiment; typically strains of 50-100% are therefore used. Loading PIB-PU samples under cyclic fatigue leads to stress softening and therefore, elongation, which is partially recovered upon unloading. Samples were tested until excessive elongation prevented further cycling at close to the desired strain, and the displacement was then re-set to return the sample to the nominal strain required (50% or 100%) and the test continued. As a result, a range of strains was achieved over the course of the experiment (particularly at 100% nominal strain), as the sample crept and was then re-set. Interestingly, this creep was, at least largely, reversible after completion of the test. The results are detailed in Table 2 and the corresponding cyclic stress-strain curves for the tests conducted at 50% and 100% strain are presented in Figures 6 and 7, respectively. In both cases it is apparent that fatigue testing under displacement control results in a small and gradual reduction in the stress and strain in the material with increasing cycles. Figure 6 highlights the effect of resetting the sample to retain the 100% strain loading condition. The strain energy density (SED) determined by the integrated area under the stress-strain curve is given as a range for the reason just described. It is notable that creep was much more pronounced at 100% strain than at 50%, which accords with the two stress/strain regimes already described and gives reason to be optimistic that creep is unlikely to be a major problem at the low strains required of a polymeric heart valve leaflet.

Table 2 Fatigue test results

Strain [%]	Cycles	Elongation [%]	Force [N]	SED range [MPa]
50	910,633	11	6.5-8.5	1.15-1.18
100	590,185	91	12-14	2.02-3.51

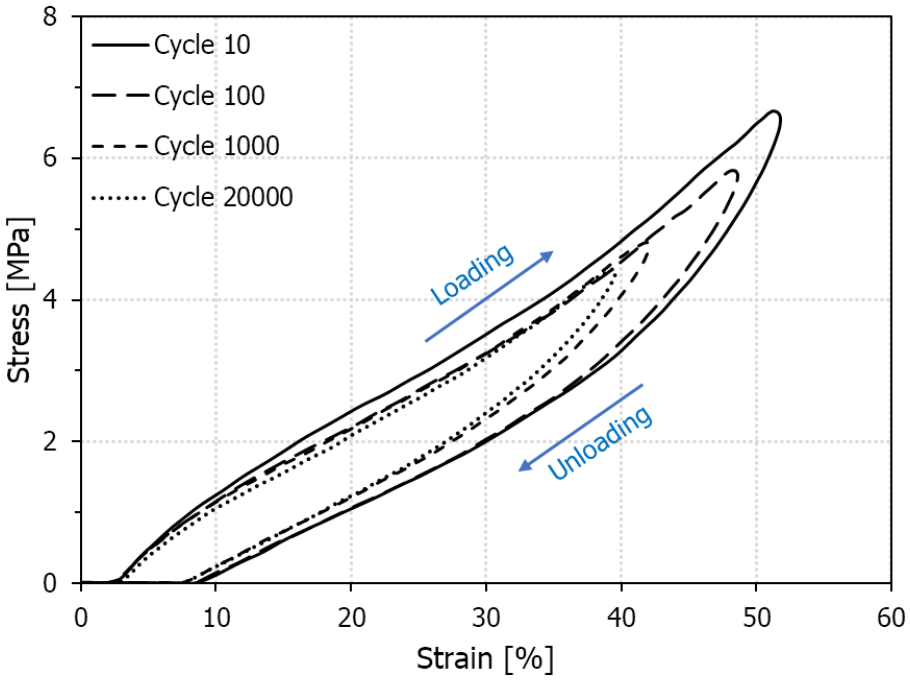


Figure 6. Cyclic stress-strain behaviour across fatigue testing on dog-bone sample at 50 % strain shows there is a gradual reduction in the loading stress and strain due to stress softening of the PIB-PU.

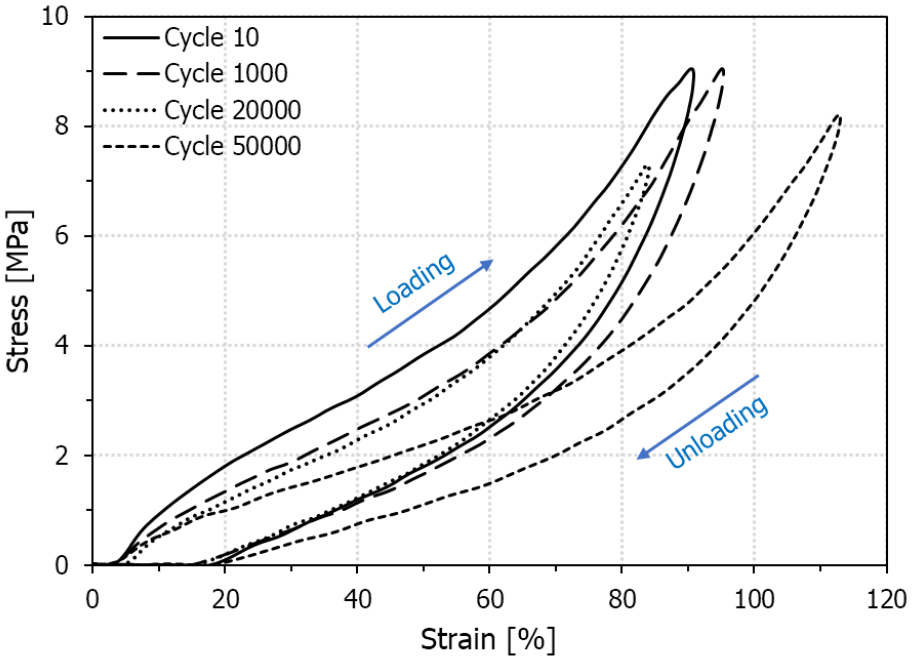


Figure 7. Cyclic stress-strain behaviour across fatigue testing on dog-bone sample at 100 % similarly exhibits the reduction in stress and strain with increasing cycles, where above 20,000 cycles, resetting the sample ensures high strain conditions are maintained.

Fatigue life is usually expressed as the number of cycles to failure at a given strain. In this study, we were unable to achieve failure of PIB-PU, even at relatively high strain; at 50 % strain, which is very far beyond that experienced by a polymeric heart leaflet (max 10 %) [20]

the approximate number of cycle without failure is about 10^6. Because we were unable to achieve failure at 50% strain within a reasonable timeframe, the nominal strain was increased to 100% and again failure was not achieved, after almost 600,000 cycles. Higher strains were not attempted because the increasing creep with higher strains make the experiments impractical. To date, we have therefore not managed to achieve fatigue failure in PIB-PU. One can, of course, deduce that at smaller strains (max 10 %) very many more cycles will be reached before fatigue failure. This extremely high number of cycles without failure in PIB-PU as compared, for example, to SIBS or SEBS (< 100 000 cycles at SED around 1 MPa, 50% strain)[21] suggests that a PIB-PU based material can be expected to have excellent fatigue life and is a very promising candidate for a synthetic hearth leaflet. Further fatigue life studies are in progress.

Currently available heart valve prostheses are of two types: mechanical and bioprosthetic. Mechanical valves are made of hard materials, usually metal, and operate by one or two flat plates opening and closing via a hinge. This gives unparalleled mechanical stability and these valves will reliably last a lifetime without failure. However, the highly non-physiological flow pattern of blood through the valves, particularly at closure, results in thrombosis; hence, lifelong anticoagulation therapy (usually Warfarin) is required, which brings with it significant compromises in patient quality of life, as well as significant risks of thrombo-embolic or haemorrhagic events. Bioprosthetic valves are made from three leaflets dead and glutaraldehyde fixed animal tissue (bovine pericardium or porcine valve) painstakingly hand stitched onto a metal supporting framework. These are functionally similar to the natural valve, thus avoiding the problem of thrombosis; and so long term anti-coagulation therapy is not necessary. Bioprosthetic valves show good durability in vitro, probably in excess of one billion cycles (25+ years equivalent). However, in vivo they calcify rapidly, which leads to stiffening of the tissue, ultimately resulting in structural failure, usually within 10-15 years. Moreover calcification is faster in younger patients, and so bioprosthetic valves are unsuitable for this patient cohort. Generally, mechanical valves are recommended for younger patients, perhaps below 65 years; whilst bioprosthetic valves are suitable for older patients.

The “holy grail” of prosthetic valve design is a valve which could achieve the durability of a mechanical valve, with the performance of a bioprosthetic valve, whilst not being subject to the problem of in vivo calcification, nor prone to long term oxidation or hydrolysis in vivo. As yet there is no clinically available such valve, largely due to the challenge of finding a polymer combining the required mechanical properties with oxidation/hydrolysis resistance and resistance to calcification. The most advanced polymeric valve under development is the Foldax Tria valve, which is undergoing an Early Feasibility first in human study at present. This valve is made from a polymer closely related to Elast-Eon, a polyurethane developed for the Aortech valve, which showed encouraging in vitro results, but did not progress beyond the stage of animal testing. PIB-PU has already been shown to have excellent stability to oxidation and hydrolysis, and resistance to calcification; superior to other polymer candidates for prosthetic valves, such as Elast-Eon and SIBS [3,7].

Here we present preliminary durability data, suggesting that PIB-PU also has the mechanical properties required for a prosthetic valve which could last 25 years or more in vivo. We have shown that at high strain (around 50% or greater), PIB-PU shows at least an order of magnitude greater durability than SEBS. Valves made from SEBS have been shown to be capable of achieving durability of 1.4 billion cycles (35 years equivalent) in accelerated wear testing [22]. Typical maximum strain in a well designed polymeric heart valve is around 10%, so the strain regime used in these tests is not representative of that experience in an

operating valve, required to last decades in vivo; however it is necessary to use these higher strains to make the experiments tractable over a practical timescale. Whilst extrapolation of durability from high to low strain is not direct, the order of magnitude superiority over a material itself capable of achieving outstanding durability in a polymer valve is most encouraging. Future work will involve detailed modelling to allow accurate extrapolation of the high strain durability to the low strain regime found in heart valves, and so prediction of the valve lifetime which could be expected using PIB-PU.

3. Conclusion

The maximum MW, tensile strength and elongation of PIB-PU containing 70 wt.% PIB soft segment reported in the literature are ~70 kDa, ~26 MPa and ~500 %, respectively. By optimizing synthesis conditions, specifically, using freshly distilled MDI and increasing the PIB diol concentration in the synthesis solution, we prepared superior PIB-PUs with increased MW of >100 kDa, tensile strength of ~32 MPa, elongation of ~630 % and toughness of >4.0 J. Preliminary studies show that PIB-PU has impressive fatigue life: > 1 million cycles around 1 MPa SED, > half million at 2-3 MPa SED. Whereas silicone rubber-based PU (Elast-Eon) shows extensive calcification, protein adsorption and cell attachment, PIB-PU containing 70 % PIB, i.e., a polyurethane whose surface is covered with PIB, exhibits no calcification, less protein adsorption and cell attachment. The recently synthesized PIB-PUs with 70 wt.% PIB are implantable biomaterials and are candidates for the preparation of a fully synthetic bioprosthetic heart valve.

4. Experimental

4.1. Materials

The source and purity of materials used for the synthesis of PIB-PUs have been described. [7] Elast-Eon was provided by the manufacturer. 4,4′-Methylenebis (phenyl isocyanate) (MDI, Sigma-Aldrich) was distilled at $2x10^{-2}$ mmHg and 115 ^{o}C and stored at -12 ^{o}C under N_2. For comparison, MDI was used as-received, distilled and stored for various times before use, and freshly distilled before use.

4.2. Syntheses

Syntheses of HO-PIB-OH (3000 MW, f_n = ~2) and PIB-PUs containing 70 wt. % PIB have been described. [7] A representative experiment, for example, with 21.4 % HO-PIB-OH, was carried out as follows: A flame dried 40 mL glass vial equipped with a mechanical stirrer was charged with well dried HO-PIB-OH (0.5 mmol, 1.5 g), MDI (2.025 mmol, 506 mg), and 4 mL distilled THF under a blanket of N_2. The system was stirred, heated to 65^{o} C, DBTDL catalyst (0.24 mL of 25 mg/5 mL stock solution in THF) was added and stirred for one hour. For chain extension, butane diol (1,525 mmol, 137.4 mg dissolved in 3 mL THF) was added, the system stirred for 3 hrs. at 65 ^{o}C, diluted with THF, and poured into a glass mold while still warm. The product was slowly dried at room temperature for 24 hrs., and further dried in vacuum for 2 days at 75^{o} C. Resulting films were colorless and optically clear. Reaction stoichiometry was kept constant in all experiments.

4.3 Characterization

MWs and MWDs were determined by gel permeation chromatography and structures were analyzed by ^{1}H NMR spectroscopy. Details of these techniques have been described. [7]

Stress-Strain traces were obtained by Instron, Model 5543, Universal Tester, controlled by Blue Hill software. Dumbbell shaped samples (25 mm long, 3.1 mm width at the neck) were used. The extension rate was 100 mm/min. Averages of 3 determinations are shown.

To study PIB-PU fatigue performance, crack nucleation experiments were conducted using ISO 37-2 dog-bone samples prepared from 30 x 70 mm sheets of solvent cast films. Instron ElectroPuls E10000 was used to cycle samples under displacement control at 1 Hz frequency at 50 % and 100 % strain.

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