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High Refractive Index Polysiloxane as Injectable, *In Situ* Curable Accommodating Intraocular Lens

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Abstract

Functionalised siloxane macromonomers, with properties designed for application as an injectable, *in situ* curable accommodating intraocular lens (A-IOL), were prepared via reequilibration of a phenyl group-containing polysiloxane of very high molecular weight with octamethylcyclotetrasiloxane (D₄) and 2,4,6,8-tetra(n-propyl-3-methacrylate)-2,4,6,8-tetramethylcyclotetrasiloxane (D₄^{AM}) in toluene using trifluoromethanesulfonic acid as a catalyst. Hexaethyldisiloxane was used as an end group to control the molecular weight of the polymer. The generated polymers had a consistency suitable for injection into the empty lens capsule. The polymers contained a low ratio of polymerisable groups so that, in the presence of a photo-initiator, they could be cured on demand *in situ* within 5 minutes under irradiation of blue light to form an intraocular lens within the lens capsule. All resulting polysiloxane soft gels had a low elastic modulus and thus should be able to restore accommodation. The pre-cure viscosity and post-cure modulus of the generated polysiloxanes were controlled by the end group and D₄^{AM} concentrations respectively in the re-equilibration reactions. The refractive index could be precisely controlled by adjusting the aromatic ratio in the polymer to suit such application as an artificial lens. Lens stretching experiments with both human and non-human primate cadaver lenses of different ages refilled with polysiloxane polymers provided a significant increase in amplitude of accommodation (up to 4 D more than that of the respective natural lens). Both *in vitro* cytotoxicity study using L929 cell lines and *in vivo* biocompatibility study in rabbit models demonstrated the non-cytotoxicity and ocular biocompatibility of the polymer.

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1. Introduction

Presbyopia, the loss of the eye's ability to change focus and provide clear vision for near objects (a function called “accommodation”), is the most common condition to affect the aged population.[1, 2] To visualise objects, the natural crystalline lens and the cornea function together to focus light on the retina. To change focus for different viewing distances, the natural lens changes shape upon action of the ciliary muscles. However, the natural lens becomes stiffer with age resulting in a reduction of accommodation.[3–5] While reading glasses can bring near objects into focus, they have a fixed focal length and thus can provide clear focus only at a single distance. An ideal solution to presbyopia would be to restore the eye's ability to change focus continuously and dynamically. This may be achieved by replacing the hardened natural lens with a soft gel.

Cataract is one of the main causes of blindness, where opacification occurs in the natural crystalline lens.[6, 7] The current standard procedure for the treatment of cataract involves removal of the natural lens contents, leaving an empty capsular bag.[8, 9] After removal of the opacified lens material, a ‘hard’ intraocular lens (IOL) is inserted in the empty capsular bag to restore the refractive used to fabricate IOLs are too stiff to alter shape upon action of the ciliary muscles, resulting in a power of the eye which is reduced by removal of the natural lens. However, conventional materials loss of useful accommodative function. Therefore, there is a demand for the development of an improved IOL material which would provide dynamic accommodation.[1, 10, 11]

The synthesis of materials used to replace the hardened natural lens, which are soft enough to restore the eye's ability to accommodate, has been the focus of many research groups around the world. To date a number of approaches have been used in an attempt to develop an accommodating intraocular lens (A-IOL). These include mechanical A-IOLs, membrane bound devices, and liquid or gel based A-IOLs.[11–14] ‘Mechanical’ A-IOLs produce mechanically-actuated accommodation by moving one or more lenses backwards or forwards on flexible haptics. Several A-IOLs based on this operation principle have been approved for human use or are in development.[11, 12, 15] However, to date, mechanical A-IOLs have not provided functionally sufficient accommodation for all individuals in human trials. Restoration of 3–4 D of true accommodation is generally considered to be sufficient to allow most presbyopes to read without reading glasses.[1, 16] Conceptually, the limitation to the mechanically-actuated A-IOLs is their limited range of axial lens movement (as the optical powers of their lens elements do not change). A system in which the lens power changes, e.g. by changing the lens surface curvatures, in a manner analogous to the natural lens, should offer superior accommodative performance.

Liquid-filled deformable membranes are a second type of A-IOL. Although these devices produce high accommodation amplitudes (by changing surface curvatures) they are complicated devices and pose a risk of leakage. A third approach involves replacing the hardened natural lens with soft gels and liquids.[17, 18] Both hydrophobic and hydrophilic materials have been tested for this application. To date, many attempts to refill the capsular bag with a liquid have failed due to leakage of the liquid. As a result, more recent efforts have concentrated on developing gel implants including various hydrogels[18–20] and siloxane polymers[21–23] that may be crosslinked to prevent leakage.

Polysiloxanes have several inherent properties which make them well suited as materials to replace the aged natural lens. These properties include transparency, elasticity, and a track record of application in various biomedical devices including ocular devices such as contact lenses, IOLs, and vitrectomy fluids to treat retinal detachments. Polysiloxane polymers of different refractive index (RI) have been evaluated for application as A-IOLs, e.g. 1.428[24]

and 1.405.[25] In our previous studies[21] a series of polysiloxane macromonomers containing no refractive index modifying groups and thus having a fixed and relatively low RI of 1.407 were used as injectable, *in situ* curable accommodating intraocular lens (A-IOL). It was observed that one of the polymers provided a refilled accommodation amplitude (AA) of 60% of the natural lens AA in lens stretching experiments when using non-human primate cadaver eyes.[21] The lens stretching results were consistent with *in vivo* trials in a primate model, which also showed a polymer refilled AA of 60% of natural lens AA.[26] While the primate study showed that low refractive index could maintain more than the target 3–4 D accommodation,[25] the polymer induced a hyperopic shift believed to be due to a refractive index mismatch. The RI of the polysiloxane polymers prepared in our previous study was 1.407, which appears to be too low for this application. Whilst the average RI for the human lens is reported at 1.41,[27] due to its gradient structure, the equivalent average RI of a 20 year old human lens is around 1.433.[28] Therefore, a material with a higher and modifiable RI was required.

This paper reports the development of soft polysiloxane gels with RI that can be varied in a controllable manner, designed for injectable, *in situ* curable A-IOLs. The macromonomers were prepared via a re-equilibration route, in which the phenyl groups were incorporated to increase the RI. The macromonomers contained a low ratio of polymerisable groups so that, under light irradiation, it may cure on demand in the presence of a photo-initiator within a clinically acceptable timeframe to form a soft gel *in situ*.

2. Experimental

2.1 Reagents, materials, and methods

Octamethylcyclotetrasiloxane (D_4), 2,4,6,8-tetramethylcyclotetrasiloxane (D_4^H), and hexaethyldisiloxane (HEDS) were used as supplied from Gelest Inc. Karstedt's catalyst (platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex, solution in xylene with ~2% of Pt) and trifluoromethanesulfonic acid (triflic acid) were purchased from Aldrich Chemical Company. Allyl methacrylate was purchased from Aldrich Chemical Company and purified by distillation. Anhydrous sodium carbonate, absolute ethanol, and toluene were purchased from Merck. Toluene was used as dried using a Glass Contour Solvent dispensing system (SG Water, New Hampshire, USA). Active black carbon was purchased from Calgon Carbon Corp. SiMePh (45–55 mol%)-SiPh₂ (45–55 mol%) siloxane copolymer was purchased from Petrarch Systems Inc. and used as supplied. Photo-initiator, Irgacure 819, was supplied by Ciba Specialty Chemicals and used as supplied. Light-scattering GPC, refractive index measurement, photo-rheometry, UV-Vis spectroscopy were all performed as already reported.[21] Chemical structures of synthesised monomers, number-average molecular weight, and composition of synthesised polymers were determined by ¹H and ²⁹Si NMR spectroscopy (Bruker, 400MHz and 500MHz). In all cases, the samples were prepared by dissolving in CDCl₃ at concentration of 0.1~0.15 g polymer mL⁻¹

2.2 Synthesis

2.2.1 Synthesis of D_4^{AM} — D_4^H (2.00 g, 8.32 mmol) was dissolved in 40 mL of dried toluene in a 250 mL round bottom flask equipped with a condenser, followed by addition of Karstedt's catalyst (10 drops). The flask was then covered with aluminum foil to exclude the light and heated to 60°C. Excess allyl methacrylate (4.30 g, 34.09 mmol) was added dropwise via the condenser over about one hour and the reaction mixture was maintained at 60°C for 18 hours. The catalyst was removed by addition of activated carbon (0.40 g) under stirring for 2 hours at room temperature. The activated carbon was filtered off through a Celite plug. The product was stored in toluene solution at 4°C and was used in subsequent reactions without further purification. The calculation from the ¹H NMR spectrum showed

that the content of attached allyl methacrylate was 75 mol%. The concentration of D₄^{AM} was determined by ¹H NMR at 3.46 wt%. ¹H NMR (CDCl₃, 400 MHz): 0.09 (m, SiCH₃), 0.58 (m, SiCH₂CH₂), 1.72 (m, SiCH₂CH₂), 1.95 (s, CH₂=CCH₃), 4.11 (t, *J* = 6.8 Hz, COOCH₂CH₂), 5.54 (m, C=CH₂), 6.10 (s, C=CH₂) ppm.

2.2.2 Synthesis of macromonomers via re-equilibration—The methylphenyl (45–55 mol%) diphenyl (45–55 mol%) siloxane copolymer (molecular weight (MW) >300k) (3.99 g) was dissolved in dry toluene (25 mL) and stirred overnight till a homogeneous solution was formed. D₄ (36.82 g), HEDS (0.22 g), and D₄^{AM} (0.14 g, in toluene stock solution with a concentration of 3.46 wt %) were weighed into the solution. The mixture was covered with aluminum foil to exclude the light and stirred to homogeneity with a stirrer bar. After purging the solution with nitrogen for about a minute, 60 μL of trifluoromethanesulfonic acid (triflic acid) was added under the continuous flow of nitrogen. The reaction was allowed at room temperature for 3 days while stirring. 8 g of anhydrous Na₂CO₃ was then added to neutralise the acidic catalyst and the solution was stirred at room temperature overnight. After the solution pH was around 7, the viscous solution was filtered through a glass filter under reduced pressure and the filtrate was concentrated and precipitated into 250 mL of ethanol. The precipitate was collected and dried to constant weight at 30°C under reduced pressure (< 15 mmHg) to afford the polymer as colourless oil (27.92g, 67.8% yield). Macromonomer/initiator mixture was then prepared and the mixture was sterilised by autoclaving following a standard procedure.[21] Other polymers with different compositions were prepared following a similar procedure using the ratios listed in table 1.

2.3 Ex Vivo Accommodation Simulator (EVAS): evaluation of accommodation restoration

Lens stretching was performed on fresh cadaver eyes obtained from Eye Banks in the United States (*n* = 4, Age 6 to 49 years), and on primate eyes obtained from the University of Miami Division of Veterinary Resources after euthanasia following institutional animal care guidelines and a protocol approved by the University of Miami (*n* = 5 Hamadryas Baboons, Age 4 to 21 years, and *n* = 3 Cynomolgus Monkeys, Age 7 to 9 years). The eyes were dissected according to a protocol described previously[29] to produce specimens that contain the lens maintained in its accommodating framework, including the zonules, ciliary body, and a segmented band of sclera. The specimens were mounted in a lens stretching system (EVAS) which simulates accommodation by stretching the outer sclera in 8 radial increments of 0.25 mm. The load, lens equatorial diameter, ciliary ring diameter, and power were measured at each step on the natural lens. Next, the lens contents were extracted and the empty capsule was refilled following the Phaco-Ersatz approach[30] and the aforementioned parameters were again measured. Then, in 3 of the eyes, the polymer was cured using a mercury arc source coupled to a custom designed hand-held optical probe which delivered only blue light to the lens. All parameters were plotted as a function of stretch and load, and the results were compared.

2.4 In vitro cytotoxicity

2.4.1 Sample preparation—About 0.5 g of the polymer and photo-initiator (0.16 w% in polymer) mixture was weighed into glass vials (6 replicates of each polymer). Uncured polymer was kept in the dark by wrapping with aluminum foil. The polymer was cured by blue light irradiation (400~500 nm) for 10 min using an intensity of 70 mW/cm². Commercial PDMS oil was used as a control.

2.4.2 Extraction—1 mL of sterile serum-free culture medium (SFM), composed of Gibco Minimum Essential Medium containing 1% non-essential amino acids from Gibco, Invitrogen Australia Pty Ltd, VIC, Australia, penicillin/streptomycin antibiotics at 60 μg/mL

and 200 µg/mL, respectively, both from CSL Ltd, VIC, Australia, and ITS™ Pre-mix from BD Biosciences, NJ, USA, was added to each of three replicate vials of the samples, re-sealed with screw caps and placed on a platform shaker for 66 hours at 37°C. After the extraction period the extract SFM was removed from each vial and transferred to a sterile vial ready for use in the cytotoxicity assay. The procedure was repeated on the second lot of three replicate vials and the result was obtained by taking average of all runs.

2.4.3 Cell cytotoxicity assay—L929 cells were seeded at 2×10^4 cells/well into individual wells of 96-well culture trays and allowed to attach and spread for 24 hours at 37°C in culture medium composed of SFM minus ITS™ Pre-mix supplemented with 10% (v/v) foetal bovine serum (FBS). After 24 hours incubation, the medium was removed and the cells washed twice with sterile SFM before the addition of test samples. The neat extracts (assigned a 100% value) from each sample were used as the starting concentration for the dilution series and the remainder of the replicate wells (4 per dilution point) were serially diluted with sterile SFM in doubling dilutions down to a lowest concentration of 0.4% (v/v) of the starting solution. SFM, 5% (v/v) phosphate buffered saline, pH 7.2, (PBS) in SFM, and 1% (v/v) dimethyl sulfoxide, Sigma Aldrich, NSW, Australia, (DMSO) in SFM were used as negative and positive controls, respectively, for all test samples. The cells were then incubated for a further 24 hours in the presence of the test samples and respective controls.

Cell viability was measured by incubating the cells with 3-(4, 5-dimethylthiazolyl)-2, 5-diphenyltetrazolium bromide (MTT, Sigma-Aldrich, NSW, Australia), 0.5 mg mL^{-1} , for the final 4 hours of the culture period. The resultant insoluble formazan product was solubilised with DMSO and the absorbance was measured at 595 nm. Cell viability was expressed as a percentage of that measured for cells exposed to SFM only. Components that reduced cell viability to less than 70% of that measured in the presence of the SFM control medium alone were deemed cytotoxic.

2.5 Biocompatibility and histology study

Six New Zealand White rabbits (Pasteurella free) were used for the polymer biocompatibility study. The surgical procedure followed a similar procedure described in literature.[21]

All animals underwent daily examination of the ocular surface and eyelids, body posture, activity, aspect of the fur, water and food intake and excretions. On postoperative day 1 and 3, the animals underwent a thorough slit-lamp examination under topical anesthesia and on postoperative days 7, 14, 21, 28 and monthly thereafter, all animals underwent a thorough examination under total anesthesia using an operation microscope (OMS 300, Topcon, Tokyo, Japan) equipped with a movable 35 degree slit-illuminator, fluorescence excitation and barrier filters as well as a digital recording system. High resolution still images (10Mp Nikon) and video recordings (SP-KR222 Panasonic and Sony DVD) of the different ocular structures were taken at each examination to monitor minute changes caused by the wound healing process and to document inflammation, infection, changes in the appearance of the polymer as well as anterior and posterior capsule opacification and lens re-growth.

For histology, after euthanasia, the eyes were enucleated, and immersed in 10% formalin solution for 5 days minimum to permit penetration into the vitreous and anterior chambers. Tissue was embedded in paraffin and sectioning was performed. For each eye, a series of slides were stained with hematoxylin and eosin (H&E), and when necessary, with Periodic acid-Schiff stain (PAS) and Masson Trichrome. Each slide was examined using a high power histology binocular microscope (Nikon Phase Contrast-2). Cornea, anterior chamber,

iris, lens capsule and content, ciliary body, vitreous, retina, choroid, retinal pigment epithelium (RPE), and the optic nerve were examined.

3. Results and Discussion

In our previous study,[21] polysiloxane macromonomers that could be injected and cured *in situ* to replace the hardened natural lens and restore accommodation were prepared. These polymers had a refractive index of 1.407 similar to the reported refractive index of the human natural lens (1.41).[27] The polymers showed very promising results for restoring accommodation in a variety of mammalian species. However, when one of these materials with a refractive index of 1.407 was used in lens refilling studies in a primate model, it had induced significant hyperopia.[26] We hypothesized that the induced hyperopia was due to RI mismatch.

The natural crystalline lens possesses a refractive index gradient both axially and circumferentially. That is, its refractive index varies spatially, three-dimensionally; being higher in its centre (the lens nucleus) and lower towards its periphery (the lens cortex). This RI gradient is known to contribute to a part of the lens' total optical power.[31] When a polymer gel of uniform RI is used to replace the natural lens, the optical contribution of the natural RI gradient is lost. In order to reproduce the same overall optical power of the lens, a uniform RI material would need to have a different RI than the numerical average RI of the natural lens to compensate for this loss. The single, uniform RI that produces the nearest optical power to the natural lens is called its “equivalent” RI.

Consequently, it was determined that not only the pre-cure viscosity and post-cure modulus of the polymer played important roles but also that the matching of the refractive index (RI) of the polymer to the equivalent RI of the natural lens was critical for the maintenance of the eye's refractive state and the restoration of accommodation.[26] As discussed in our previous publication,[21] the molecular weight and viscosity of the polymer could be controlled by end group concentration and the post-cure modulus could be tuned by both molecular weight and the ratio of polymerisable groups. These methodologies were also applied to prepare high RI polysiloxanes in this study.

While there are commercially available polysiloxanes with RI above 1.407 they are unsuitable for the A-IOL application for one or more of the following reasons: (1) their RI may not meet the target of 1.433 to 1.436, which is the human equivalent index of refraction at age 12 to 20;[28] (2) their viscosity may be too low or too high, and thus, may not have a consistency suitable for a controllable surgical injection; (3) they have no capacity to be crosslinked *in situ* (no crosslinkable groups). Therefore, a customised polymer specifically designed for this application needs to be developed.

3.1 Polymer synthesis and characterisation

The RI of a polymer can be changed by introducing such functional groups as phenyl, halogen, sulfur, etc into the polymer. In this study, the control of RI has been achieved by introduction of phenyl groups into the polymer backbone. There are a number of ways to incorporate phenyl groups into polysiloxanes including: (i) ring opening polymerisation (ROP) of methylphenyl or diphenyl cyclosiloxanes with D₄ (ii) re-equilibration of the phenyl group-containing siloxane copolymer with D₄ However, it can be difficult to obtain high molecular weight polymers with good molecular weight control via ring opening polymerisation of phenyl containing cyclosiloxanes such as methylphenyl or diphenyl cyclosiloxanes due to the hindrance of phenyl groups.[32] Instead, in this study, high RI siloxane macromonomers suitable for use as an injectable, *in situ* curable A-IOL were prepared by a re-equilibration route (Scheme 1) using a commercially available diphenyl

(45–55 mol%) methylphenyl (45–55 mol%) siloxane copolymer having a molecular weight of more than 300,000 and a refractive index of 1.582[33] (last entry in Table 2). This one-pot re-equilibration involved reduction of the molecular weight of the starting copolymer, the introduction of polymerisable groups, and the control of the RI by dilution with dimethylsiloxane units. A commercially available siloxane copolymer containing phenyl groups was re-equilibrated with cyclic monomers (D_4 and D^{AM}_4) and the end group HEDS using a strong acidic catalyst, triflic acid, to synthesise high RI polysiloxanes for the targeted application. Previously, re-equilibration has rarely been widely used to prepare or modify polysiloxanes. Chang *et al*[34] reported the formation of network structures by re-equilibration of octamethylcyclotetrasiloxane and an oligocyclosiloxane. There are no reports of re-equilibration being used in combination with the introduction of polymerisable groups.

The RI of the polymer was able to be precisely controlled by changing the ratio of phenyl group-containing copolymer in the re-equilibration. D_4 was used as a diluting agent to adjust the RI to a target value. The starting material (the commercial phenyl group-containing copolymer) and the resulting re-equilibration polymers with varied RI were characterised by NMR spectroscopy. The ratio of phenyl groups incorporated into the polymers was obtained by a combination of calculations from 1H NMR and ^{29}Si NMR spectra. Figure 1 shows a ^{29}Si NMR spectrum of the commercial phenyl group-containing copolymer (MW 336,000); peaks ranging from δ –26.35 to –35.86 ppm and from δ –40.75 to –48.94 ppm are assigned to the methyl phenyl siloxane unit ($SiMePh$) and di-phenyl siloxane unit ($SiPh_2$), respectively.[35] The ratios of $SiMePh$ and $SiPh_2$ in the copolymer are calculated at 57.7 and 42.3 mol%, respectively according to NMR analysis. Figure 2 shows a series of ^{29}Si NMR spectra of the re-equilibrated polymers with different RI (containing a different ratio of phenyl groups), in comparison with the starting material. The products from re-equilibration have a new peak ranging from δ –17.51 to –25.32 ppm, which is assigned to the dimethyl siloxane unit ($SiMe_2$). The starting material has a high ratio of phenyl group at 71.2 mol% ($57.7 \times 50\% + 42.3\%$) and thus a very high RI of 1.582. To be used as a replacement of the hardened natural lens, the RI of prepared polymers is required to be within the range of 1.43 to 1.44 to match that of the effective RI of a young natural lens.[28]

Figure 3 shows a linear correlation between polymer RI and the ratio of phenyl groups incorporated in the polymer as measured by NMR analysis. As expected, a temperature effect on RI was observed. RI measured at 37°C was slightly lower than those measured at room temperature presumably due to thermal expansion and consequent lower density.

The molecular weight of the polymer was controlled by the concentration of end group (EG), which was hexaethyldisiloxane (HEDS) in this work. The methyl group of HEDS appears distinctly in proton NMR spectrum at about δ 0.9 ppm, without overlapping with other resonances (Figure 4) and thus could be used to estimate the number average molecular weight (M_n) of the polymer by end group analysis. As described in our previous study,[21] molecular weight is a critical factor to achieve a balance of viscosity and elastic modulus for the desired application. In this study, the very high MW of the commercial copolymer was effectively reduced from more than 300 k to a usable consistency at about 20 k, as shown in Table 2. The molecular weights of the generated polymers were also determined by GPC. Due to the formation of cyclic polysiloxanes (i.e. without end groups) during ROP, M_n estimated by NMR is typically higher than that measured by GPC.

Zhou *et al*.[36] reported the synthesis of dichlorosilomethylate derivative. We chose a simpler route to prepare D^{AM}_4 by hydrosilylation of D^H_4 with an excess of allyl methacrylate to minimize the amount of residue silane groups (Scheme 2). However, calculations based on 1H NMR data showed that the content of attached allyl methacrylate was 75 mol%, which means that the prepared D^{AM}_4 contains 3 mol% of the residue silane groups.

arms rather than 4. Attempts to purify the D^{AM}_4 resulted in insoluble polymer gels. Due to the difficulty of purifying D^{AM}_4 , the reaction mixture was used without further purification. Despite this, as relatively small amount of D^{AM}_4 was used in the ROP and the impurities (mainly excess allyl methacrylate) from the D^{AM}_4 synthesis could be removed by precipitation of the resulting polymers, this approach still resulted in relatively pure macromonomers (Figure 4). The methacrylic double bonds can undergo crosslinking subject to light irradiation, in the presence of a photo-initiator. The ratio of polymerisable groups and the number average molecular weight were estimated from 1H NMR spectrum (Table 2). The resonances at δ 6.11 (double bond), 5.54 (double bond), 4.11 (CH_2O), 1.95 (Me), and 1.73 (CH_2) ppm were assigned to the propyl methacrylate side group. The resonances at δ 0.90 and 0.56 ppm were assigned to CH_3 and CH_2 of the end group (HEDS), respectively. The integration of these peaks was used to estimate the ratio of polymerisable groups and the M_n of the polymer (end group analysis). As D^{AM}_4 was essentially quantitatively incorporated into the final polymer, the ratio of the polymerisable groups could be controlled to a similar level for all high RI polysiloxanes prepared.

Functional cyclic monomer route has an advantage over the direct hydrosilylation route to siloxane macromonomers, as the products are expected to have a longer shelf life. In our previous study[21] low refractive index polysiloxanes were prepared via a two-step synthesis. Firstly, silane prepolymers were prepared via ring opening polymerisation of D_4 and D^H_4 . Then in a second step, polymerisable groups were introduced by hydrosilylation of silane groups with allyl methacrylate. However, it was difficult to reach full conversion of silane groups to methacrylates (less than 50% conversion in some cases, unpublished data). As a result, in some cases, the siloxane macromonomers prematurely cured without exposure to light. It was hypothesised that the incomplete hydrosilylation of the prepolymer led to the formation of silanol groups which can slowly crosslink (Scheme 3). In an attempt to improve the shelf life of the macromonomer used, in this study, the polymerisable groups were introduced via the methacrylate containing monomer (D^{AM}_4). This avoids incomplete hydrosilylation of the prepolymer, as hydrosilylation of D^H_4 can be pushed to a higher conversion (75%) than hydrosilylation of the silanes in the prepolymer.

3.2 Mechanical properties of high RI polysiloxanes

The high RI polysiloxane macromonomers prepared in this work were mixed with a photo-initiator, Irgacure 819, at a concentration of 0.16 wt% and were subjected to photo-rheological measurement to determine their cure rate and mechanical properties. The *in situ* cure profiles of macromonomers are shown in Figure 5. The data is also collected in Table 2. It was observed that the macromonomers reached plateau modulus (effectively cured) within 5 min upon exposure to blue light at an intensity of 70 mW/cm² to form soft gels. Since the ratio of polymerisable groups was controlled to a low level (around 0.16 mol% estimated by 1H NMR) the modulus of the prepared high RI polysiloxanes was below 350 Pa, which is similar to that of a young human natural lens.[4, 5, 37] The viscosity of the polymers was reduced to below 4.4 Pa.s from 96.5 Pa.s of the starting material copolymer. In order to refill the capsular bag with the macromonomer, it is essential that the macromonomer is amenable to injection through a 25ga thin wall cannula allowing injection of viscous siloxane polymers through a 1mm capsular opening closed with a mini flap valve. [38] With a viscosity below 4.4 Pa.s, the macromonomers prepared in this study meet this requirement. Therefore, the re-equilibration was proven as an efficient route to prepare polysiloxanes with desired viscosity and mechanical properties, which are critical for the successful application of injectable, *in situ* curable A-IOLs.

3.3 Optical clarity of high RI polysiloxanes

For the application of A-IOLs, to replace the hardened natural lens, the synthesised polysiloxanes must be optically transparent. The transmittance (T%) of a polysiloxane measured on a UV-Vis spectrophotometer is shown in Figure 6, in comparison with a commercial PDMS oil. The polymer mixed with the photo-initiator shows a comparable transmittance to the PDMS oil within the visible range of 450 to 700 nm wavelength, with T % over 95%. Due to a strong absorbance of the photo-initiator in the UV range, the transmittance of the polymer/initiator mixture declined to zero at 400 nm. However, after curing this cutoff wavelength was shifted to 310 nm, indicating the decomposition of the initiator following photolysis. Meanwhile, the transmittance of the cured polymer was comparable to PDMS oil and the uncured polymer. The cured polymer has in-built UV absorbency due to the residue initiator by-product which acts as a UV absorber in the range of 320–400 nm. The high RI polymers reported here have high optical transparency between 450 to 700 nm, which is suitable for A-IOLs.

3.4 *Ex vivo* evaluation of accommodation restoration

Selected high RI polysiloxane macromonomers were evaluated on an *Ex Vivo* Accommodation Simulator (EVAS) to assess their ability to restore accommodation. The EVAS instrument is designed to simulate accommodation by measuring changes in lens shape and lens optical power during stretching of cadaver eyes. By refilling the same eye (Phaco-Ersatz surgical procedure)[30] with macromonomer, comparisons can be made between the natural lens and the polymer refilled lens (both cured and uncured). A number of eyes from different species were used to evaluate the accommodation amplitude of polymer refilled lenses by comparison with their corresponding natural crystalline lenses. The EVAS studies are summarised in Table 3 & Figure 7, where in most of the cases, the polymer refilled eyes show a larger accommodation amplitude than their corresponding natural lens. For example, an *ex vivo* lens stretching study (EVAS) using a 6 year old human cadaver eye showed that the refilled eye with two siloxane polymers (RI = 1.4113 and 1.4512) achieved 5.7 and 9.3 D of accommodation amplitude, respectively, higher than the corresponding natural lens (about 4.6 D) (Figure 7 and Table 3). A plot of refilled amplitude of accommodation vs. natural amplitude of accommodation showed a significant correlation (Spearman's Ranked Correlation) between the refilled accommodation and the natural accommodation (Figure 8A). A Bland-Altman plot (Figure 8B) showed the difference in accommodation (refilled – natural), demonstrating an increase in the amplitude of accommodation upon refilling. Thus this material should enable the restoration of accommodation when implanted into presbyopic eyes. These results are comparable to both hydrogel[39] and polysiloxane[21, 24] materials previously tested in lens stretching experiments.

3.5 *In vitro* cytotoxicity study

Having a RI close to that of a young person's lens, polymer #3 (Table 2) with a RI of 1.4360 was selected to evaluate the cytotoxic effect of the high refractive index polysiloxanes using both *in vitro* cytotoxicity and *in vivo* biocompatibility assays. Extracts from polysiloxanes (both cured and uncured) were screened for the cytotoxic effect of leachables. Extracts from the PDMS oil control samples were found to be non-cytotoxic. In the neat extract of PDMS oil, cell viability was 97% of the SFM control value (Figure 9), well above the cytotoxicity cut-off value of 70%. The morphology of the cells exposed to all concentrations of the PDMS extracts was similar to that observed for L929 cells in the presence of the SFM control medium (Figure 10A). Extracts from the uncured polysiloxane samples were also not cytotoxic to L929 cells at all concentrations tested (Figure 9). Likewise, the morphology of the cells exposed to extracts from the uncured polysiloxane samples was equivalent to that observed in the SFM control (Figure 10C). However, the neat extracts from the cured

polysiloxane samples were cytotoxic to L929 cells with a measured viability of 57% of the SFM control value (Figure 9). The morphology of the cells exposed to neat extract was slightly elongated (Figure 10B) with cell density visibly reduced. However, by the first dilution point (50%), typical *in vitro* cell morphology had returned. Cell viability was also restored (to 85%) after the first doubling dilution point (50%) at a concentration level equivalent to the United States Pharmacopeia (4 g test sample: 20 mL extractant).[40] The introduction of phenylmethyl and diphenyl siloxane units into the polymer did not adversely affect the *in vitro* cellular response compared to the dimethyl polymers.[21] These results are consistent with previous studies which have shown that polysiloxanes are generally well tolerated *in vitro*. [41]

3.6 *In vivo* biocompatibility study

The effect of both cured and uncured polysiloxanes on ocular health was further investigated by an *in vivo* study involving both clinical and histological examinations. Two of the six surgeries were deemed failures due to an anterior capsule tear in one animal and failure of the microcapsulorhexis valve (MCV) to close in another animal. The surgery was complicated by the inherent stickiness of the polymer. However, four NZW rabbits were successfully implanted with the polymer having a RI of 1.4360 (entry 3 in table 2) and followed for 3 months. The ocular surface and eyelid remained normal at all time points and corneal edema was minimal and healed within a week. No iritis, uveitis, vitritis, retinal detachment, or corneal decompensation were observed, indicating that no clinical toxicity was encountered with crosslinked polysiloxane soft gels (Figure 11A–D). Under slit-lamp illumination, minute lens epithelium proliferation on the posterior capsule could be observed as early as 1 week (Figure 11A). The polymer slowly became cloudy with time preventing examination of the fundus from the one month time point and the iris synechiae formed with the MCV had deformed the iris border at the site of the capsulorhexis (Figure 11B). For comparison, a commercial PDMS oil (no initiator) was used as a control and did not develop cloudiness. Intraoperative fibrin created synechiae (tissue bridges) between iris/capsule and MCV (in rabbits, this can occur with FDA approved IOLs and is thus not implant material dependant). At 3 months, the peripheral regeneration of lens matter had pushed onto the polymer forcing a minute amount through the MCV into the anterior chamber (small bubbles). The 4 eyes operated remained quiet for the length of the 3 months follow-up. In lens capsule refilling, lens epithelial cells are in intimate contact with the polymer; their continuous growth demonstrates the lack of toxicity of the polymer (Figure 11A & C). *De novo* lens regeneration (normal in rabbits) grows in volume with time and pushes on the polymer which might escape in the anterior chamber (Figure 11D), and, with time, will push the iris forward and, might also close the angle causing glaucoma in the animal. No systemic toxicity was observed; rabbit weight increased normally and there were no cases of fur loss, abnormal excretions, etc. Histology done on all 4 eyes showed no sign of toxicity (e.g., giant cells, histiocytes). The polymers and FDA/EC approved IOLs induced the same biological behavior: they did not interfere with the lens epithelial cells (LEC) that were in contact with them. LEC had grown normally for their mission: to refill the lens capsule to capacity until endolenticular pressure becomes normal – this phenomenon will occur with all types of endolenticular implants, FDA/EC approved IOLs[42, 43] or injectable gels.[19, 22, 24]

As with the previous polymer we tested,[21] histology of all eyes followed to 3 months in this series was unremarkable. The introduction of phenylmethyl and diphenyl siloxane units into the polymer did not adversely affect the *in vivo* tissue response and is comparable to results obtained with the dimethyl polymers.[21]

Conclusions

Re-equilibration of polysiloxanes is a facile route to prepare functional polysiloxanes of lower molecular weight. High RI polysiloxane macromonomers prepared via re-equilibration have potential for use as an injectable, *in situ* curable accommodating intraocular lens to replace the hardened natural lens in the aged eye. Targeted properties of the macromonomers can be achieved by manipulating the molecular weight of the macromonomer (controlled by end-group concentration in the re-equilibration) and the crosslinking density (controlled by incorporation ratio of polymerisable groups, i.e. by concentration of D_4^{AM} in the re-equilibration reaction). Polymer RI is tunable and can be controlled by the incorporation ratio of phenyl groups (controlled by dilution of the starting polymer with D_4). The macromonomer prepared from re-equilibration can be rapidly cured by exposure to blue light with a suitable photo-initiator resulting in a soft transparent gel with over 95% transmittance within visible wavelengths. The polymer shows promise as an accommodating intraocular lens, typically restoring more than 100% of the accommodation amplitude of the corresponding natural lens in fresh cadaver eyes. The *in vitro* cytotoxicity study shows non-cytotoxicity of the polymer, both uncured and cured (except the neat extract). The *in vivo* biocompatibility study showed that, although the polymer lost some transparency with time, it demonstrated non-toxicity of the *in situ* cured polymer in rabbits.

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Scheme 1.

Synthetic route of high RI polysiloxane (entry 1 in Table 2)

Scheme 2.
Synthetic route of D_4^{AM}

Scheme 3.
Potential crosslinking reaction after incomplete hydrosilylation

Figure 1.
 ^{29}Si NMR spectrum of a commercial phenyl group-containing copolymer

Figure 2. ^{29}Si NMR spectra of prepared high RI siloxane polymers with aromatic ratio of 12.77% (b), 9.27% (c), 7.18% (d), 5.65% (e), and 1.42% (f), in comparison with commercial phenyl group-containing copolymer (a) (containing 71.15% aromatic group)

Figure 3. Correlation of RI measured at room temperature (dashed line) and 37°C (solid line) and incorporated aromatic ratio

Figure 4.
 ^1H NMR spectrum of a prepared high RI siloxane polymer

Figure 5. Photo-rheology profile of cure process for high RI polysiloxanes prepared via re-equilibration

Figure 6.
Transmittance of polymer #1 (uncured vs cured) compared with PDMS

Figure 7. Accommodation amplitude (ΔD) of a 6 year old cadaver human eye, determined by EVAS: natural lens vs refilled lens with Polymer #1 (RI = 1.4113 at 37°C) and Polymer #5 (RI = 1.4512 at 37°C)

Figure 8.
(left) Refilled amplitude of accommodation vs. natural amplitude of accommodation. (right)
Bland-Altman plot showing the difference in accommodation (refilled – natural)

Figure 9. Serial dilution cytotoxicity assay for high RI siloxane macromonomer (Polymer #3 from Table 2) and PDMS oil

Figure 10. Representative morphology of L929 cells exposed to extract from PDMS oil (A) and high RI siloxane macromonomer (Polymer #3 from Table 2) cured (B) and uncured (C) compared to controls SFM, PBS and 5% DMSO

Figure 11.
Images of NZW rabbits in biocompatibility study, implanted with a high RI polysiloxane (entry 3 in Table 1)

Table 1

Mass of components used in the synthesis of high RI polysiloxanes

Polymer #	(SiMePh)(SiPh ₂) copolymer (g)	D ₄ (g)	D ₄ ^{AM} (g)	HEDS (g)	Polymer (g)	Yield (%)
1	3.993	36.818	0.135	0.220	27.92	67.8
2	8.008	31.559	0.071	0.213	21.40	53.7
3	9.996	32.870	0.078	0.231	23.48	54.4
4	15.000	39.452	0.098	0.294	26.12	47.6
5	19.996	39.447	0.108	0.321	44.87	74.9

Table 2

Characterisation of high RI polysiloxanes prepared via re-equilibration

Polymer #	Ratio (mol%, NMR)						M _n (NMR)	LS GPC			Photo-rheology	
	EG	SiMe ₂	SiMePh	SiPh ₂	SiMeAM			M _n	M _w	PDI	Pre-cure viscosity (Pa-s)	Post-cure modulus (Pa)
1	0.19	97.52	1.42	0.71	0.16		40700	17160	23180	1.351	2.82	349.07
2	0.19	91.72	4.62	3.34	0.13		44020	13420	16670	1.242	3.20	191.57
3	0.20	89.41	6.12	4.12	0.16		42130	8290	14920	1.800	4.39	205.07
4	0.20	86.59	7.55	5.49	0.17		43420	16190	20160	1.245	4.37	167.70
5	0.22	81.60	10.48	7.53	0.16		40250	11670	14200	1.217	2.47	18.12
Starting Material copolymer			57.70	42.30							96.50	

EVAS evaluation of high RI polysiloxanes prepared via re-equilibration

Table 3

Species	Age (years)	Polymer + 0.16w% Irgacure 819	Natural Lens			Refilled Lens - Uncured			Refilled Lens - Cured		
			Unstretched Power (D)	Stretched Power (D)	Δ D	Unstretched Power (D)	Stretched Power (D)	Δ D	Unstretched Power (D)	Stretched Power (D)	Δ D
CYNO	7	3	53	35	17	54	35	19			
	9	1	41	36	5	37	29	8			
	8	3	52	34	17	53	41	12			
Human	31	5	27	24	3	40	32	8	36	31	5
	6	5	36	32	5	48	39	9			
	6	1	36	32	5	32	26	6			
	49	3	18	18	0	24	21	3	23	22	1
	37	5	23	21	3	32	29	3			
Baboon	21	3	29	21	8	41	17	24			
	14	3	36	26	10	42	30	12			
	10	3	44	34	10	44	37	8			
	9	3	44	29	15	48	41	8			
	4	5	48	36	12	70	46	24	44	31	14