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Functionalised Polysiloxanes as Injectable, *In Situ* Curable Accommodating Intraocular Lenses

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Abstract

The aged eye's ability to change focus (accommodation) may be restored by replacing the hardened natural lens with a soft gel. Functionalised polysiloxane macromonomers, designed for application as an injectable, *in situ* curable accommodating intraocular lens (A-IOL), were prepared via a two-step synthesis. Prepolymers were synthesised via ring opening polymerisation (ROP) of octamethylcyclotetrasiloxane (D₄) and 2,4,6,8-tetramethylcyclotetrasiloxane (D₄^H) in toluene using trifluoromethanesulfonic acid (TfOH) as catalyst. Hexaethyldisiloxane (HEDS) was used as the end group to control the molecular weight of the prepolymers, which were then converted to macromonomers by hydrosilylation of the SiH groups with allyl methacrylate (AM) to introduce polymerisable groups. The resulting macromonomers had an injectable consistency and thus, were able to be injected into and refill the empty lens capsular bag. The macromonomers also contained a low ratio of polymerisable groups so that they may be cured on demand, *in situ*, under irradiation of blue light, in the presence of a photo-initiator, to form a soft polysiloxane gel (an intraocular lens) in the eye. The pre-cure viscosity and post-cure modulus of the polysiloxanes, which are crucial factors for an injectable, *in situ* curable A-IOL application, were controlled by adjusting the end group and D₄^H concentrations, respectively, in the ROP. The macromonomers were fully cured within 5 minutes under light irradiation, as shown by the rapid change in modulus monitored by photorheology. *Ex vivo* primate lens stretching experiments on an *Ex Vivo* Accommodation Simulator (EVAS) showed that the polysiloxane gel refilled lenses achieved over 60% of the accommodation amplitude of the natural lens. An *in vivo* biocompatibility study in rabbits using the lens refilling (Phaco-Ersatz) procedure demonstrated that the soft gels were biocompatible with the ocular tissue. The polysiloxane macromonomers meet the targeted optical and mechanical properties of a young natural crystalline lens and show promise as candidate materials for use as injectable, *in situ* curable A-IOLs for lens refilling procedures.

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1. Introduction

Presbyopia, a condition where the eye loses its ability to accommodate or focus on near objects, mainly due to hardening of the natural crystalline lens [1–4] inevitably affects every human as we age. For many years, spectacles have been the conventional treatment for presbyopic vision correction. Contact lenses and various IOLs (in bifocal or multifocal designs, or used in monovision modes) have become popular alternatives. However, all these approaches only provide a static correction due to their fixed focal length in contrast with the true dynamic power change of the natural crystalline lens, which has continuously variable focal length during natural accommodation. [5] Furthermore, the increasing public demand for a cosmetically pleasing solution and the drive to pursue a better solution for the treatment of presbyopia by restoring the eye's ability to change ocular power has encouraged the development of an accommodating intraocular lens (A-IOL).

Cataract formation, which results in a loss of lens transparency, is the most common eye disease related to the natural lens. The opacification in a cataractous lens may be caused by trauma, systemic chemical effects (e.g. use of quinine in the tropics), aging or UV exposure. [6] Conventionally, a cataract is treated with a surgical procedure that involves removal of the cataractous lens material, followed by replacement with an IOL through a central opening (capsulorhexis) in the anterior capsule surface. However, conventional IOL materials such as poly(methyl methacrylate) are very rigid materials and therefore their implantation requires a large corneal incision. [7] All above IOLs require a capsulorhexis of 5 to 6mm in diameter to maintain a clear vision postoperatively. In addition, conventional IOLs do not provide accommodation due to their stiffness. The development of foldable IOLs (silicone, hydrogel, and acrylic soft lenses) allowed the implantation of the IOL through a smaller incision (3–4 mm or less). [7,8] As a young person's natural crystalline lens is very soft with a shear storage modulus (G') close to 200 Pa, [9–11] even 'soft' foldable IOLs are too stiff to allow effective accommodation.

Restoring 3–4 dioptres (D) of true (dynamic) accommodation would satisfy most presbyopes [1] and 5 D and above would allow presbyopes a comfortable and prolonged reading of small print. Currently, there are two types of accommodating intraocular lens (A-IOL), namely a mechanical A-IOL and an injectable* [or 'gel-like'] A-IOL. Typically, mechanical A-IOLs have a rigid optical lens or lenses which move within the capsular bag by deformation of the soft supporting arms (haptics) by the ciliary body. Mechanical A-IOLs have recently become available (e.g., Crystalens from Bausch & Lomb; Synchrony from Visiogen-AMO) and can provide a low degree of accommodation (about 1 D) by small relative movement of the optics in the eye. [12–17]

Since the concept was first proposed by Kessler in the 1960's, [18] researchers have been attempting to restore accommodation by replacing the hardened natural lens with a liquid-like material, an injectable A-IOL. Unlike mechanical A-IOLs which are relatively rigid and have a preformed shape, injectable A-IOLs are significantly softer and require the capsular bag of the crystalline lens to form the shape of the lens. These devices include the liquid-filled lenses bounded by flexible membranes which can change shape to vary the power, [19] and liquid crystal designs in which the power change is achieved by a change in refractive index induced by an appropriate electric field. [20–22] Problems associated with the liquid-filled lenses include liquid leakage and damage to the flexible membranes. To overcome these drawbacks, a pre-cured viscous silicone material was used to refill the capsular bag, from which the lens core (cortex and nucleus) had been removed, to achieve dynamic accommodation. [23–29] It

*It should be noted that conventional IOLs are often described as 'injectable' as they are often rolled up when they are inserted into capsular bag with the use of an injector. However, for the purpose of this paper, 'injectable' IOLs refers to liquid or gel-like materials.

is known that the change in lens shape underlies geometric and optical accommodation. [30–34] Further, it is believed that the ciliary muscle, which is the active component of the accommodative system that effects lens shape change, retains its function for many years beyond the onset of presbyopia. [35] Indeed, crosslinked polysiloxanes, engineered to have a modulus similar to that of a young natural crystalline lens and a suitable injecting consistency, achieved an increase in accommodation in refilled *ex vivo* lenses of a range of ages in stretching experiments compared to the natural lens. [36] Although success has been achieved in restoring accommodation *ex vivo*, to a certain extent, this material experienced problems related to inflammation caused by implantation [37,38] and severe capsular opacification occurring post-implantation. [24,39] It is possible that the low molecular weight silicone components migrated into adjacent tissues or stimulated other cellular and immunological responses. [40,41]

One potential solution to the problem of leakage from the capsular bag, and also to reduce the level of polymer extractables, is to crosslink the polysiloxane *in situ*. In addition, crosslinked polysiloxane can be expected to have a faster accommodative response. [24] However, the cure mechanism of the two component silicone system discussed in the literature is a relatively slow process via hydrosilylation, usually taking a few hours. [24] The prolonged surgery time resulting from the slow cure rate may increase the risk of the polymer escaping from the capsular bag and seeping into the anterior chamber, endangering the corneal endothelium. The development of a material that can be cured *in situ* on demand within a few minutes to minimize surgery time would be highly beneficial.

Although it is attractive that intraocular lenses can be formed *in situ* after crosslinking an injected viscous liquid into the lens capsular bag by allowing even smaller incisions (less than 1.5 mm), [7,25,36,37,42] there are several challenges with this approach. Chemical reactions are required to cure the injectable material in the eye and these reactions must be safe for the patient. In addition, the chemical crosslinking reaction needs to take place over a relatively short time under mild reaction conditions to facilitate surgery. Most importantly, no by-products or residues that may have an adverse biological effect on the surrounding tissue can be produced during crosslinking. Therefore, pH, temperature, and cytotoxicity of by-products need to be strictly controlled.

This paper reports the development of a soft polysiloxane gel for use as an injectable, *in situ* curable, accommodating intraocular lens. These materials are designed to mimic the optical properties such as transparency and refractive index (1.41, [43,44]) as well as the mechanical properties of a young person's natural lens.

2. Materials and Methods

2.1 Reagents and materials

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), hexachloroplatinic acid (used as a 0.02 M solution in 2-propanol (Speier's catalyst)), 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 systems (SG Water, New Hampshire, USA). Active black carbon was purchased from Calgon Carbon Corp. Photo-initiator Irgacure® 819 was supplied by Ciba Specialty Chemicals.

2.2 Instrumental analysis

2.2.1 Light scattering GPC—Dried polymers were dissolved in toluene with an accurate concentration (about 30 mg of polymer in 1 mL of toluene) and filtered through a 0.22 μm filter. Light scattering gel permeation chromatography (LS-GPC) data were collected from a system consisting of a Shimadzu DGU-20A5 Degasser, a Shimadzu LC-10 AT Pump, a Shimadzu SIL-10 AD auto-injector, a Shimadzu SCL-10A System Controller, Waters Styragel columns in a Shimadzu CTO-10A Column Oven, and Wyatt Technology Dual Detector of OptiLab DSP Interferometric Refractometer and DAWN EOS Light Scattering Detector. Toluene was used as the mobile phase at a flow rate of 1.0 mL/min. Measurements were conducted at a temperature of 40°C with an injection volume of 50 μL .

2.2.2 Refractive index measurement—The refractive index of polysiloxanes was measured by taking the average of 5 readings at 37°C on an RFM81 Multi Scale Refractometer (supplied by Selby Anax).

2.2.3 Viscosity measurement—The instantaneous viscosity of the dried polymers (viscous liquids) was measured against shear stress in spinning mode at 23°C using a Bohlin rheometer (CSR-10). About 1 g of polymer was loaded between two parallel plates (25 mm in diameter) within a 1 mm gap.

2.2.4 NMR—Chemical structures of synthesised monomers, number-average molecular weight and composition of synthesised polymers were determined by ^1H NMR spectroscopy (Bruker, 400MHz). In all cases, the samples were prepared by dissolving in CDCl_3 at a concentration of about 0.1 g polymer/mL.

2.2.5 *In situ* FTIR—*In situ* FTIR was utilized for monitoring the progress of hydrosilylation on ReactIR 4000 (Mettler Toledo). Typically, a mixture of 2.00 g of prepolymer containing 1 mol% SiH functional groups, 15 mL toluene and 80 mg allyl methacrylate was added and stirred in a 2-neck round bottom flask, one neck equipped with an air condenser and drying tube and another neck connected to the FTIR probe which was in direct contact with the reaction mixture. The mixture was scanned against a toluene background to obtain a baseline before adding Karstedt's catalyst. After the catalyst was added, the reaction mixture was heated at 60°C for 6 hours, with data collection every 5 minutes. The change of silane group adsorption at 2152 cm^{-1} was monitored by FTIR to follow the progress of the reaction.

2.2.6 Photo-rheometry—Dynamic viscoelastic measurement was carried out on an ARES photo-rheometer (TA Instruments, USA) connected to an EXFO Acticure 4000 light source via a liquid light-guide. A Peltier temperature controller was also connected to the rheometer to maintain the cure temperature at 37°C. The sample was loaded in the centre of two parallel plates of 20 mm in diameter. The gap between the two plates was set at 0.3 mm. The *in situ* cure kinetics was studied at a constant temperature of 37°C for 10 minutes. For the first 60 seconds, the light source (400–500 nm) was controlled in off-mode to get a baseline and automatically converted to on-mode with an intensity of 70 mW/cm^2 for 9 minutes. Parameters such as storage shear modulus (G'), the loss shear modulus (G''), and viscosity (η^*) etc were measured as a function of time at a constant frequency of 100 rad/s and a strain of 1.0% at a data acquisition rate of 2 measurements per second.

2.2.7 UV-Vis spectroscopy—Transmittance of siloxane polymers was measured on a Cary 5E UV-Vis-NIR Spectrophotometer (Varian) against a background of water in a plastic cuvette (Eppendorf UVette, 220–1600 nm). Uncured polymer was covered by aluminum foil before measurement to exclude light that might cause the polymer to pre-cure. After measurement the

uncured polymer was irradiated by blue light (400~500 nm) at an intensity of 70 mW/cm² for 10 minutes to ensure that the polymer was fully cured before re-measurement.

2.3 Synthesis

2.3.1 Synthesis of prepolymers via ring opening polymerisation (ROP)—

Typically, 0.30 g of D₄^H stock solution (7.26 w/w% in D₄) (0.091 mmol D₄^H), 1.02 g of hexaethyldisiloxane (HEDS) stock solution (4.28 w/w% in D₄) (0.177 mmol HEDS) and 8.69 g of D₄ (9.94 g/33.55 mmol in total) were weighed into a 50 mL round bottom flask and then 10 mL of dry toluene was added. The mixture was stirred with a mechanical stirrer. After purging the flask with nitrogen, 15 μ L of trifluoromethanesulfonic acid (triflic acid) was added under a continuous flow of nitrogen. The reaction was stirred at room temperature overnight, then 2.00 g of anhydrous Na₂CO₃ was added to neutralise the acid catalyst and the solution was stirred for a further 2 hours. The viscous solution was filtered through a glass filter under reduced pressure and the filtrate was concentrated and precipitated in 40 mL of ethanol. The precipitate was collected and dried to constant weight at 30°C under reduced pressure (< 15 mmHg) to afford the prepolymer as colourless oil (5.34 g, 53 % yield).

2.3.2 Synthesis of macromonomer via hydrosilylation—Typically, 2.00 g of prepolymer prepared in 2.3.1 was weighed into a 50 mL round bottom flask. Toluene (15 mL) was added to fully dissolve the prepolymer using a mechanical stirrer for 1 hour. The round bottom flask was protected from light and equipped with a drying condenser. After purging the flask with nitrogen, 0.01 g (0.079 mmol) of allyl methacrylate and 0.1 mL of Karstedt's catalyst were added under a continuous flow of nitrogen and the reaction allowed to proceed at 60°C overnight. At the end of reaction 0.10 g of activated black carbon was added and the solution was stirred for another 2 hours. The viscous solution was filtered through a glass filter paper. The filtrate was concentrated and precipitated into 50 mL of ethanol. The precipitate was collected and dried to constant weight at 30 °C under reduced pressure (< 15 mmHg) to afford the macromonomer as a colourless oil (1.76 g, 88 % yield).

2.3.3 Macromonomer/initiator mixture preparation—An accurately weighed sample of the dried macromonomer (about 2g) was dissolved in chloroform (5 mL) in a 25 mL round bottom flask which was covered with aluminum foil to protect from light exposure. A pre-determined amount of Irgacure[®] 819 stock solution (~0.22 w/w% in CHCl₃) was added to the polymer solution to make up a final concentration of 0.16 w/w% (initiator/polymer). The mixture of macromonomer and initiator was stirred while protected from light until homogeneous. The solvent was then completely removed while protected from light using a rotary evaporator and then on a Kugelrohr at 30°C/1.5 mmHg until solvent-free, affording a pale yellow mixture of Irgacure[®] 819 in macromonomer.

2.4 Autoclaving macromonomer/initiator mixture

Macromonomer/initiator mixtures were transferred into syringes, covered with aluminum foil to exclude light, packaged in a Medipack[®] self-sealing sterilisation pouch, then sealed into a second Medipack[®] self-sealing sterilisation pouch to which a sterilisation marker was attached. The whole package was then steam autoclaved at 120°C for 20 minutes.

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

Lens stretching was performed on post-mortem tissues obtained from non-human primates' eyes from the University of Miami, Division of Veterinary Research under an Institutional Animal Care and Use Committee (IACUC) approved protocol. The eyes were dissected according to a protocol described previously [45,46] to produce specimens that contain the lens maintained in its accommodating framework, including the zonules, ciliary body, choroid

and a band of sclera that was dissected in 8 equal segments. The specimens were mounted in a lens stretching system (EVAS I), where accommodation may be simulated. [47,48] The load and optical power were measured on both natural and polymer refilled lenses (both uncured and cured).

2.6 Biocompatibility study

Twelve healthy New Zealand white rabbits were used for the *in vivo* polymer biocompatibility study. The animals were housed and treated in accordance with the Association for Research in Vision and Ophthalmology Statement for Use of Animals in Ophthalmic and Vision Research. In accordance with an authorized IACUC protocol, one eye of each rabbit underwent the Phaco-Ersatz procedure; [23,25,49,50] while the contralateral eye was used as a control. Ophthalmic slit-lamp examinations were performed at 1, 2 and 3 days post-operation (POD) and complete ophthalmic examinations were performed under anesthesia at 7, 14, 21, 28 POD and monthly thereafter for up to 3 months. The eyes were examined for the presence of ocular surface and intraocular inflammatory response, lens transparency, and retinal integrity. A FDA approved medical grade high molecular weight sodium hyaluronate (Healon, AMO Inc, USA) was implanted in the capsule of one rabbit as control.

3. Results and discussion

In order to be able to restore accommodation, the polymer gel must be soft enough to allow a change in optical power of the refilled lens by changing shape upon action of the ciliary body. In order to optimise the properties of the material to closely mimic those of a young person's natural crystalline lens (around 20 years old), which has a storage shear modulus (G') close to 200 Pa, [9–11] it is necessary to manipulate the mechanical properties of the siloxane polymers using efficient chemical approaches.

In our one-part system, there are a few key characteristics of a macromonomer which are critical for its successful application as an injectable, *in situ* curable accommodating intraocular lens. The post-cure elastic modulus of the intraocular lens, the polymer cure kinetics, the polymer optical properties and the viscosity of the uncured macromonomer (which relates to the ease of injectability) are considered to be critical factors. The introduction of polymerisable groups into the polymer backbone is an important process as these groups enable cure on demand to be possible by crosslinking the macromonomer upon exposure to light. The ratio of polymerisable groups is one of the important factors to control the mechanical properties of the gel as it affects the post-cure modulus as well as the cure rate. In addition, the molecular weight of the polymer plays an important dual role in determining the viscosity of the polymer which in turn controls the ease of injectability as well as influencing elastic modulus of the crosslinked gel. Therefore, the effects of the molecular weight of macromonomer and the ratio of polymerisable groups (crosslink density) on properties of the polymer is discussed in detail in the following sections (3.2 and 3.3).

3.1 Prepolymer and macromonomer synthesis

Siloxane polymers have a long history of application as biomedical implants due to their unique properties and biocompatibility with body tissues. [51] Polysiloxanes are typically prepared via two routes: (1) ring opening polymerisation (ROP) of cyclic siloxane monomers and (2) condensation of linear siloxane monomers. The preferred synthetic route to polysiloxanes has been the ROP of cyclic siloxane monomers as it offers a greater control over the conformation and molecular weight of the resulting polymer. [52–54] In this paper, the functionalised siloxane macromonomers were synthesised via two steps: (1) through ROP of D_4 and D_4^H to generate a functionalised prepolymer; followed by (2) hydrosilylation of the SiH functional groups along the backbone with allyl methacrylate (AM) to introduce polymerisable groups

(Scheme 1). An acidic catalyst, triflic acid, was used to initiate ROP for preparation of the prepolymer containing SiH functional groups. The cationic polymerisation of cyclic siloxane monomers is often a preferred method for the synthesis of polysiloxanes containing base-sensitive substituents such as SiH groups. [55] The molecular weight of the prepolymer was controlled by the concentration of end group (EG), which in this case is hexaethyldisiloxane (HEDS). HEDS was chosen as its methyl group appears distinctly in proton NMR spectroscopy at about δ 0.9 ppm without overlapping with other resonances and thus can be used to determine number average molecular weight (M_n) of the prepolymer (end group analysis). A linear correlation between molecular weight and inverse EG concentration was obtained, as shown in Figure 1.

An injectable A-IOL capable of restoring accommodation requires the pre-cure viscosity of the polymer to be at a level at which a surgeon can inject the polymer into the capsular bag through a narrow cannula in a controllable manner. However, to reduce the possibility of the polymer leaking from the capsular bag before curing the viscosity should not be too low. The viscosity of the siloxane polymer can be tailored by adjusting the molecular weight via variation of the end group concentration during the ROP as seen in Figure 2. This correlation can be used to predict the viscosity of the prepolymer, which is dramatically influenced by molecular weight.

In the second step of macromonomer synthesis, polymerisable groups from the methacrylic moiety were introduced into the prepolymer as side groups via a hydrosilylation reaction. This methodology has been already used to introduce functional groups into polysiloxane backbones including the methacrylate group. [56–60] However, these methacrylate containing polysiloxanes reported in the literature are not suitable for A-IOL application as they have a far too high methacrylate content resulting in materials too stiff to allow accommodation. The silane groups in the prepolymer react with the double bond of allyl methacrylate in the presence of Karstedt's catalyst to form a linkage between the methacrylic group and the backbone of the polymer. A three carbon atom spacer ($-\text{CH}_2\text{CH}_2\text{CH}_2-$) was introduced by using allyl methacrylate, which potentially allows the reaction to proceed to completion in a relatively short period. The spacer between the polymerisable group and the backbone allows more flexibility in the network, resulting in a higher conversion and a more flexible polymer gel compared to a shorter spacer. The completion of hydrosilylation was confirmed by proton NMR spectroscopy, which showed the disappearance of the silane group (resonance at about δ 4.7 ppm) and appearance of methacrylic moiety (resonances: double bond at δ 6.1 and 5.5 ppm; OCH_2 group at δ 4.1 ppm; methyl group at δ 1.9 ppm, respectively), as shown in Figure 3.

In situ FTIR was used to monitor the dynamic progress of the hydrosilylation reaction by following the change of silane group adsorption at 2152 cm^{-1} (Figure 4). Figure 5 shows the reaction profile of a hydrosilylation reaction of a prepolymer containing 30 mol% of silane groups with allyl methacrylate in which the change of silane group adsorption at 2152 cm^{-1} was plotted against reaction time. It is worth noting that a prepolymer containing a high concentration of silane groups was easily gelled while subjected to hydrosilylation. Therefore, the reaction conditions, such as temperature, reagent concentration, moisture level, and the loading rate of reagent need to be strictly controlled. The cause of the gelling is not fully understood but it may be a result of hydrolysis of the silane groups into silanol groups ($-\text{SiOH}$), which further undergo condensation to form a network structure. [55,61] In contrast, prepolymers containing a lower concentration of silane groups did not gel during hydrosilylation and the reaction went to completion faster as a result. Figure 6 shows an *in situ* FTIR profile curve of the hydrosilylation of a prepolymer containing 1 mol% of silane groups using two different catalysts, namely, Karstedt's and Speier's catalyst. It shows that the reaction was completed in about 80 min, regardless of the type of catalyst used. However,

the hydrosilylation using Speier's catalyst did not proceed to 100% conversion although the *in situ* FTIR curve shows that the reaction stopped after 80 min. The incomplete reaction was confirmed by ^1H NMR, in which the resonance of residual silane groups was visible in the hydrosilylated product (data not shown). In contrast, the product prepared using Karstedt's catalyst showed the absence of residual silane groups, indicating that the hydrosilylation went to completion and was therefore a better choice of catalyst. It was also found that the molecular weight increased slightly after hydrosilylation, as shown by LS-GPC chromatography curves in Figure 7. The molecular weight (M_w) determined by LS-GPC was 49,840 and 59,460 for a prepolymer and its corresponding macromonomer, respectively. The LS-GPC determined M_w was comparable to the theoretical MW of the prepolymer (55,000), which was calculated according to the feed ratio. The GPC results were consistent with NMR data, in which the number average molecular weight (M_n) was determined to be 45,300 and 46,100 for a prepolymer and its corresponding macromonomer, respectively.

3.2 Manipulating mechanical properties of polysiloxane gels by molecular weight

Photorheology is a rapid and useful method of measuring the pre-cure viscosity, rate of cure and post-cure modulus of photocurable formulations.[62,63] In this study, the macromonomers were crosslinked by exposing a mixture of the macromonomer and photo-initiator (Irgacure[®] 819) to blue light (wavelength 400–500nm) at an intensity of 70 mW/cm². The cure process was followed by photo-rheometry, which shows the dynamic change of storage modulus (G'), loss modulus (G''), and viscosity (η^*) with cure time. The initial exposure of the mixture to light was intentionally delayed for one minute to obtain a baseline for the measurement of the rheological properties. No change in modulus and viscosity was observed before the mixture was exposed to blue light. Upon exposure to blue light a dramatic increase of moduli and viscosity of the polymer was observed, indicating that the macromonomer was rapidly crosslinked (Figure 8).

As outlined above, molecular weight of the macromonomer is an important parameter in tuning the mechanical properties of the crosslinked gel. A crosslinked gel used to replace the natural lens must have a low storage modulus similar to that of a young person's natural lens in order to enable accommodation. The low modulus allows the capsular bag to change the shape of the gel upon the influence of forces from the ciliary muscles via the zonules and hence enables the eye to change focus. The modulus of the crosslinked polymer can be adjusted by changing the molecular weight of the macromonomer. At a fixed ratio of polymerisable groups, the mechanical properties of a crosslinked polymer gel are controlled by the molecular weight of the macromonomer. A comparison of post-cure G' between macromonomers having a similar ratio of polymerisable groups but different molecular weight is shown in Figure 9. A summary of the experimental data is also tabulated in Tables 1 and 2 for prepolymer and macromonomer, respectively. An unexpected variation in the molar ratios of SiH and AM was observed between the prepolymers and the macromonomers, which could be caused by experimental error from NMR measurements due to the relatively very low levels of these components in the polymers. The correlation between molecular weight and post-cure modulus (G') as measured by photo-rheometry is shown in Figure 10. The molecular weight of macromonomer also affects the cure rate (Figure 11). At a fixed ratio of crosslinkable groups, macromonomer of a higher molecular weight contains more crosslinkable groups and thus cures faster.

3.3 Manipulating mechanical properties of polysiloxane gel by crosslink density

In addition to molecular weight, the crosslink density is another critical factor affecting the mechanical properties of the polysiloxane gel. The crosslink density is directly related to the ratio of polymerisable groups. As expected and as shown by photorheological measurements, at fixed molecular weights, macromonomers containing a higher ratio of polymerisable groups gave higher post-cure modulus due to a higher crosslinking density (Figure 12). It is observed

that the ratio of polymerisable groups dramatically affects post-cure G' of crosslinked polymer in an exponential manner (Figure 13). In order to form a very soft gel the ratio of polymerisable groups has to remain at a very low level so that the gel is able to restore and maintain accommodation. A summary of this experimental data is tabulated in Tables 3 and 4 for the prepolymer and macromonomer, respectively. Again, it was found that the molecular weight of the generated macromonomer was higher than its corresponding prepolymer, indicating that extra crosslinking of silanol groups may have occurred from hydrolysis of silane groups during hydrosilylation. As expected, the ratio of crosslinkable groups (crosslink density) also affects the cure rate as shown in Figure 14. Macromonomers with a higher crosslink density cure faster than those with a lower crosslink density.

3.4 Optical clarity of polysiloxanes

For use as an A-IOL to replace a hardening natural lens in the eye, the synthesized polysiloxane is required to be optically transparent. The transmittance of cured and uncured macromonomer and a commercially available PDMS oil, as a control, were measured on a UV-Vis spectrophotometer (Figure 15). The uncured macromonomer mixed with photoinitiator showed a comparable transmittance (90 to 94%) to the PDMS oil within the visible wavelength range of 450 to 700 nm. Compared to PDMS oil, the transmittance of the macromonomer/initiator mixture before curing dropped to zero at 400 nm due to the strong absorbance of the photo-initiator within the UV range. However, after curing, this cutoff wavelength shifted to 310 nm, indicating the formation of the initiator by-product after photolysis. The transmittance of the cured polymer is above 95% within the visible range, which was essentially identical to that of the PDMS oil and uncured polymer and it has the added advantage of built-in UV protection.

3.5 *Ex vivo* evaluation of accommodation restoration of polysiloxane gel

Optimisation of ROP and hydrosilylation conditions for targeted molecular weight and post-cure modulus becomes practical when facilitated by the use of a photo-rheometer. With a suitable and fixed viscosity (thus a suitable injectability), the ratio of polymerisable groups in a polymer can control the post-cure G' of the crosslinked gel to a level at which the gel closely mimics the mechanical properties of a young person's natural crystalline lens. Based on these balancing considerations, a polymer with targeted properties identified for use as an A-IOL was developed for *ex vivo* evaluation and *in vivo* trials, using an *Ex Vivo* Accommodation Simulator (EVAS) and in rabbit models, respectively. The results are discussed in this section and the following section 3.6.

The macromonomer developed was firstly evaluated on EVAS to test its ability to restore accommodation using cadaver eye tissues. The EVAS is designed to simulate accommodation by stretching of the ciliary body and lens via the zonules with a known force. [47] The optical power of the natural lens and refilled lens was measured at different increments of stretch. When stretched with the same load, lens stretching experiments showed that the uncured and cured polymer refilled lenses ($n = 12$) gave $10.36 \text{ D} \pm 3.56 \text{ D}$ and $8.37 \text{ D} \pm 2.33 \text{ D}$ accommodation, respectively, compared to $14.04 \text{ D} \pm 3.88 \text{ D}$ accommodation for the natural lens (cynomolgus monkey species). Compared to the natural lens, the polymer refilled lenses ($n = 12$) maintained, on average 73.9% and 61.9% of the accommodation amplitude of the natural lens using uncured and cured polymer, respectively. The results obtained in our study showed a comparable level of accommodation amplitude to reported data using other polymer systems measured in pig and human cadaver lens stretching studies. [36,64] This is a very promising result as we aim for a functional accommodation above 5 D, which is believed to be sufficient for comfortable, prolonged near vision such as required for the reading of small print. While the dioptric power of accommodation required for near vision is typically around

2.5 D, it is known that approximately double the accommodation amplitude is required to support reading over a longer duration without visual fatigue. [65]

3.6 Biocompatibility study

The *in vivo* ocular biocompatibility of the cured macromonomer was assessed by clinical and histological examination following implantation into rabbits. The surgical implantation of the gel occurred without event. All implanted rabbits remained healthy throughout the 3 month follow-up period. No iritis, uveitis, retinal detachment, or corneal decompensation were observed, indicating the lack of clinical toxicity of the crosslinked polysiloxane soft gel (Figure 16).

However, as with all intraocular lens implants (IOLs and A-IOLs) and the control animal that received sodium hyaluronate, capsular opacification started at POD 7 in all rabbits and the capsule leafs became more opaque with time preventing examination of the fundus after about 4 weeks of follow-up and strong lens regeneration occurred at about 6 weeks. [49,66] Histologically, all tissues, including the cornea, ciliary body and lens capsule, retina, and the optic nerve were normal in all animals (Figure 17). Overall the developed polysiloxane gel was well tolerated by the surrounding ocular tissues and there appeared to be no adverse responses to it.

4. Conclusions

Polysiloxane soft gels are promising candidates for use as an injectable, *in situ* curable accommodating intraocular lens to replace the hardened natural lens in the eye. The targeted mechanical properties of the soft gels can be achieved by manipulating the molecular weight and crosslinking density of the macromonomer. Likewise, the pre-cure viscosity was also tailored by manipulating the molecular weight of macromonomer. The molecular weight of the macromonomer was controlled by the end-group concentration in ROP. The crosslink density was controlled by the ratio of incorporated polymerisable groups in the macromonomer (i.e. degree of functionalisation). The macromonomer 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 the visible wavelength range. The initiator by-product acts as a UV absorbent below 400 nm. Cadaver lens stretching studies have shown that the refilled lens (non-presbyopic) maintains on average 10.36 D (uncured polymer) and 8.37 D (cured polymer) accommodation compared to 14.04 D of the young natural primate lens when stretched with the same load. That is, the refilled lens maintains on average over 60% of the accommodation amplitude of the natural young primate lens. When used to replace the natural lens (Phaco-Ersatz surgery), clinical and histological examination of the implanted polymer was found to be well tolerated by ocular tissue in the rabbit model over 3 months. There were no adverse responses and the eyes remained quiet over the follow up period, demonstrating good biocompatibility of the polymer. Overall, the polysiloxane macromonomers reported here show great potential for use as injectable, *in situ* curable accommodating intraocular lenses and have potential to restore accommodation in the aged eye.

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Figure 1.
Correlation between molecular weight (M_n determined by NMR) of prepolymer and inverse end group (EG) concentration of hexaethyldisiloxane (HEDS)

Figure 2.
Correlation between viscosity (logarithmic) and molecular weight (M_n determined by LS-GPC) of prepolymers

Figure 3.
 ^1H NMR spectra of the prepolymer (above) and macromonomer (below)

Figure 4.

In situ real time monitoring of hydrosilylation by FTIR analysis: 3D FTIR spectra showing decrease of SiH absorption at about 2152 cm^{-1} with increasing reaction time

Figure 5.
In situ FTIR reaction profile curve of hydrosilylation of a prepolymer containing 30 mol% silane group with allyl methacrylate, using Karstedt's catalyst at 60°C in toluene

Figure 6.
In situ FTIR reaction profile curve of hydrosilylation of a prepolymer containing 1 mol% silane group with allyl methacrylate, using Karstedt's catalyst (solid dots) and hexachloroplatinic acid hydrate catalyst (circles) at 60°C in toluene

Figure 7.
Light scattering GPC chromatograph of a prepolymer (solid black line) (MW = 55k, SiH = 0.25 mol%) and the corresponding macromonomer (dashed red line)

Figure 8. Photo-rheology profile of cure process for a macromonomer having M_W of 59460 (determined by LS-GPC) and 0.22 mol% of polymerisable groups

Figure 9. Photo-rheology profile of cure process for macromonomers having different MW and same ratio of polymerisable group at 0.22 mol%

Figure 10.

Calibration curve for prediction of post-cure G' given a targeted MW (ratio of polymerisable group fixed at 0.22 mol%)

Figure 11.
Effect of molecular weight of macromonomer on cure rate

Figure 12. Photo-rheology profile of cure process for macromonomers having different incorporation ratio of polymerisable groups and the same MW (27500)

Figure 13. Correlation between post-cure G' and the ratio of polymerisable groups (allyl methacrylate mol %), for macromonomers with a fixed molecular weight (27500)

Figure 14.
Effect of crosslink density on cure rate of macromonomer

Figure 15.
Transmittance of polysiloxane (uncured vs cured) compared with PDMS

(A) Slit lamp view of implant at POD 8

(B) Eye quiet at POD 42

Figure 16.

Slit lamp images of NZW rabbits eyes implanted with a polymer (MW around 55000, viscosity around 12.5 Pa.s, and post-cure G' around 1300 Pa) at post operation day (POD) 8 (A), and POD 42 (B)

Figure 17.
Histopathological image of the cornea (lens capsule refilled with crosslinked siloxane polymer)

Scheme 1.
Synthetic route of prepolymer and macromonomer

Table 1

Properties of the prepolymers (used for macromonomer synthesis). SiH ratio was constant and the molecular weight was varied

Entry	SiH mol% calc. ^a	MW/calc. ^b	Mn/ NMR ^c	Light-scattering GPC (in toluene)			SiH mol% NMR	Viscosity η (Pa.s) ^d
				M _n	M _w	PDI		
1.1	0.27	28124	23800	12630	27530	2.18	0.26	1.27
1.2	0.27	37566	32300	26840	37170	1.385	0.26	2.50
1.3	0.27	56429	45300	34000	49840	1.466	0.24	6.13
1.4	0.27	77039	60800	55230	70290	1.273	0.24	17.00
1.5	0.27	113366	90800	68960	88170	1.279	0.25	41.92

^aThe molar ratio of SiH groups was calculated from feed ratio.

^bMolecular weight was calculated according to the relative ratio of end group to monomer.

^cMolecular weight was determined by ¹H NMR based on end group analysis.

^dViscosity was measured on a rheometer (spinning mode).

Table 2
Properties of the macromonomers generated from hydrosilylation of the prepolymers (listed in Table 1) with allyl methacrylate

Entry	M _n /NMR ^a	Light-scattering GPC (in toluene)			Methacrylate content mol% NMR	Photo-rheology Data ^d		Catalyst
		M _n	M _w	PDI		Pre-cure viscosity (Pa.s) ^b	Post-cure G' (Pa) ^c	
2.1	26300	27350	36420	1.331	0.22	1.95	27.87	Karstedt's
2.2	34000	27490	44390	1.615	0.22	4.77	497.59	Karstedt's
2.3	46100	41110	59460	1.446	0.17	11.23	2917.82	Karstedt's
2.4	62000	66250	87700	1.324	0.22	28.28	9385.08	Karstedt's
2.5	85500	98330	128400	1.306	0.36	67.70	25147.92	Karstedt's

^a Molecular weight was determined by ¹H NMR based on end group analysis.
^b Viscosity was measured on a rheometer (oscillating mode), average was taken from values before curing started.
^c Average post-cure modulus (G') was taken from values after full curing of the polymer.
^d Photo-rheology measurements were conducted on the mixture of macromonomer and photo-initiator, Irgacure 819 (0.16 w/w%).

Table 3

Properties of the prepolymers (used for macromonomer synthesis). Molecular weight was constant and SiH ratio was varied

Entry	SiH mol% calc. ^a	MW/ calc. ^b	M _w / NMR ^c	Light-scattering GPC (in toluene)			SiH mol% NMR	Viscosity ^d η (Pa.s)
				M _n	M _w	PDI		
3.1	0.27	28124	23600	26170	31160	1.191	0.24	1.55
3.2	0.54	28124	24200	22440	29450	1.312	0.45	1.49
3.3	0.81	28124	24200	20870	31400	1.505	0.72	1.85
3.4	1.08	28124	24300	23070	30950	1.342	0.96	1.34

^aThe molar ratio of SiH groups was calculated from feed ratio.

^bMolecular weight was calculated according to the relative ratio of end group to monomer.

^cMolecular weight was determined by ¹H NMR based on end group analysis.

^dViscosity was measured on a rheometer (spinning mode).

Table 4

Properties of the macromonomers generated from hydrosilylation of the prepolymers (listed in Table 3) with allyl methacrylate

Entry	M _n /NMR ^a	Light-scattering GPC (in toluene)			Methacrylate content mol% NMR	Photo-rheology Data ^e		Catalyst
		M _n	M _w	PDI		Precure viscosity (Pa.s) ^b	Postcure G' (Pa) ^c	
4.1	26100	27450	33800	1.231	0.19	1.95	27.87	Karstedt's
4.2	26200	30930	39600	1.280	0.36	2.21	3319.54	Karstedt's
4.3	27500	21130	40830	1.933	0.47	3.42	10259.44	Karstedt's
4.4 ^d	28300	38240	64070	1.675	0.72	5.31	37901.84	Karstedt's
4.5 ^d	28700	24900	34480	1.385	0.67	2.52	23873.15	HfCl ₆

^a Molecular weight was determined by ¹H NMR based on end group analysis.

^b Viscosity was measured on a rheometer (oscillating mode), average was taken from values before curing started.

^c Average post-cure modulus (G') was taken from values after full curing of the polymer.

^d Prepolymer used for entries 4 and 5 is the entry 4 polymer in Table 3, containing 0.96 mol% SiH.

^e Photo-rheology measurements were conducted on the mixture of macromonomer and photo-initiator, Irgacure 819 (0.16 w/w%).