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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 ($D_4$) and 2,4,6,8-tetramethylcyclotetrasiloxane ($D_4^H$) 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 $D_4^H$ concentrations, respectively, in the ROP. The macromonomers were fully cured within 5 min under light irradiation, as shown by the rapid change in modulus monitored by photo-rheology. *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 had good biocompatibility 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.



## 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

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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]. Such IOLs require a capsulorhexis of 5–6 mm 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[1] [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 1960s [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 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 leachables, 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 minimise 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.

[1] 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.