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(54) Title: INJECTABLE INTRAOCULAR LENS

(57) Abstract

The present invention relates to polysiloxanes suitable for the preparation of intraocular lenses by a cross-linking reaction, having a specific gravity of greater than about 1.0, a refractive index suitable for restoring the refractive power of the natural crystalline lens and a viscosity suitable for injection through a standard cannula. The present invention includes an injectable intraocular lens material based on said polysiloxanes and methods of preparing intraocular lenses by direct injection into the capsular bag of the eye.

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INJECTABLE INTRAOCULAR LENS

FIELD OF INVENTION

The present invention relates to an intraocular lens and to materials useful in making intraocular lenses (IOLs), specifically, injectable IOLs and methods for their preparation. More particularly, the invention relates to high specific gravity silicone materials suitable for making accommodative IOLs, which can be injected into the capsular bag with greater convenience than previously suggested materials.

BACKGROUND OF THE INVENTION

The human eye is a highly evolved and complex sensory organ. It is composed of a cornea, or clear outer tissue which refracts light rays enroute to the pupil, an iris which controls the size of the pupil thus regulating the amount of light entering the eye, and a lens which focuses the incoming light through the vitreous fluid to the retina. The retina converts the incoming light into electrical energy that is transmitted through the brain stem to the occipital cortex resulting in a visual image. In the perfect eye the light path from the cornea, through the lens and vitreous fluid to the retina is unobstructed. Any obstruction or loss in clarity within these structures causes scattering or absorption of light rays resulting in diminished visual acuity. For example, the cornea can become damaged resulting in oedema, scarring or abrasions, the lens is susceptible to oxidative damage, trauma and infection, and the vitreous can become cloudy due to hemorrhage or inflammation.

As the body ages, the effects of oxidative damage caused by environmental exposure and endogenous free radical production accumulate resulting in a loss of lens flexibility and denatured proteins that slowly coagulate reducing lens transparency. The natural flexibility of the lens is essential for focusing light onto the retina by a process referred to as accommodation. Accommodation allows the eye to automatically adjust the field of vision for objects at different distances. A common condition known as presbyopia results when the cumulative effects of oxidative damage diminish this flexibility reducing near vision acuity. Presbyopia usually

begins to occur in adults during their mid-forties; mild forms are treated with glasses or contact lenses.

Lenticular cataract is a lens disorder resulting from the further development of coagulated protein and calcification. There are four common types of cataracts: senile cataracts associated with aging and oxidative stress, traumatic cataracts which develop after a foreign body enters the lens capsule or following intense exposure to ionizing radiation or infrared rays, complicated cataracts which are secondary to diseases such as diabetes mellitus or eye disorders such as detached retinas, glaucoma and retinitis pigmentosa, and toxic cataracts resulting from medicinal or chemical toxicity. Regardless of the cause, the disease results in impaired vision and may lead to blindness.

Treatment of severe lens disease requires the surgical removal of the lens involving phakoemulsification followed by irrigation and aspiration. However, without a lens the eye is unable to focus the incoming light on the retina. Consequently, an artificial lens is used to restore vision. Three types of prosthetic lenses are available: cataract glasses, external contact lenses and IOLs. Cataract glasses have thick lenses, are uncomfortably heavy and cause vision artifacts such as central image magnification and side vision distortion. Contact lenses resolve many of the problems associated with glasses, but require frequent cleaning, are difficult to handle (especially for elderly patients with symptoms of arthritis), and are not suited for persons who have restricted tear production. Intraocular lenses are used in the majority of cases to overcome the aforementioned difficulties associated with cataract glasses and contact lenses.

IOLs mentioned in the prior art literature usually belong to one the following categories: non-deformable, foldable, expansible hydrogels and injectable. The earliest IOLs coming into surgical practice are non-deformable implants having rigid structures composed of acrylates and methacrylates. This type of lenses requires a large surgical incision in the capsular bag and is not accommodative. The large incision results in protracted recovery times and the likelihood of introducing astigmatism. In an effort to reduce recovery time and patient discomfort numerous small incision techniques and lenses have been developed.

Present IOLs designed for small incision implantation have elastomeric characteristics and are made of silicone materials. This type of lenses can be rolled or folded, inserted into the capsular sac then unfolded once inside. Occasionally, the folding of the lens before insertion

results in permanent deformation adversely effecting the implant's optical qualities. Foldable lenses meet the requirement of reducing the large surgical incision non-deformable lenses required, but are not accommodative. Moreover, both non-deformable and foldable IOLs are susceptible to mechanical dislocation resulting in damage to the corneal endothelium.

It has further been suggested to use an elastomeric polymer that becomes pliable when heated to body temperature or slightly above in small incision IOL implantation. Once pliable, such a lens would be deformed along at least one axis reducing its size sufficient for easy insertion through a small incision. The lens is then cooled to retain the modified shape until re-heated. The cooled lens is inserted into the capsular sac and the natural body temperature warms the lens and it returns to its original shape. The primary drawback to the thermoplastic lens is the limited number of polymers that meet the exacting needs of this approach. Most polymers are composed of polymethylacrylate which have solid-liquid transition temperatures above 100°C. To reduce these transition temperatures modifications of the polymer substrate with the use of plasticizers is required which eventually may leach into the eye.

Dehydrated hydrogels have also been suggested for small incisions techniques. Hydrogel lenses are dehydrated before insertion and naturally rehydrated once inside the capsular sac. However, once fully rehydrated the polymer structure is notoriously weak due to the large amount of water absorbed. The typical dehydrated hydrogel's diameter will expand from 3 mm to 6 mm resulting in a lens that contains about 85% water. At this water concentration the refractive index drops to approximately 1.36 which is unacceptable for an IOL. To achieve a refractive index equal or greater than that of the natural lens (>1.40) a significantly thicker lens is required; this is even further exacerbated when lens diameters exceed 6 mm.

To further develop IOLs and reduce surgical incisions to below 1.5 mm, techniques with injectable IOLs have been suggested, wherein the low viscosity lens material is directly injected into the empty capsular bag and cured *in situ* as a part of the surgical procedure. In this process the capsular bag is to be used as a mold to form the shape of the lens and thereby contribute control its refraction. There have been several attempts to develop materials suitable for use as injectable IOLs. For example, Gerace et al. describe a fast curing mixture of vinyl-containing polyorganosiloxane, organosilicone comprising hydride groups and a platinum group metal catalyst used to form an IOL in their 5,278,258, 5,391,590 ('590) and 5,411,553 patents. The

resulting polymers demonstrate a reduced tendency of discoloration compared to other platinum catalyzed silicone polymers. The '590 patent also discloses a substantially non-functional polymer component of the mixture that has a viscosity at least 50 times greater than the functional polymers. The non-functional component is mixed with the functional components to adjust viscosity to a pre-determined specification. Kelman discloses an injectable collagen IOL in US patent number 5,476,515. This lens is clear, resistant to epithelialation and is capable of accommodation. It is made from a transparent collagen compound that has a refractive index range from 1.2 to 1.6 that can be used in either its original viscous state, or polymerized into a soft gel. The collagen compound is injected directly into the capsular sac following natural lens removal.

Apart from problems with obtaining control over the crosslinking process and finding clinically acceptable conditions, there have been a struggle to perfect the polyorganosiloxane compositions, since they need to have a suitable viscosity for injection, a suitably high refractive index as well as suitable mechanical characteristics after crosslinking, i.e. a suitable modulus. Polydimethylsiloxane (PDMS) has been employed as a material in foldable IOLs and has refractive index similar to that of the natural crystalline lens. This material is also exemplified as a part of the injection mixture in the above mentioned patents to Gerace et al. PDMS has also been found to have a relatively low viscosity and thereby a tendency to leak out of out of the desired injection site (i.e. the capsular bag). This is considered in the mentioned US Patent 5,391,590, wherein an additional high viscosity polysiloxane is added to the injection mixture. However, high viscosity silicones have the drawback in that they can entrap air bubbles, which can impair the optical quality of the resulting product. In addition, it has been found that polyorganosiloxanes having a high fraction of dimethylsiloxane units may have an unacceptable low specific gravity with the undesired result that the injected lens material will float on an aqueous layer in the capsular bag. In such a case, it will be difficult to fill the capsular sac completely and requires the surgeon to manually express water in order to maintain the correct lens shape during the curing process. Therefore, it is desirable to formulate an injectable lens forming material from polysiloxanes which can overcome the problems with floating and leakage, while still having a suitably high refractive index and the desirable mechanical and optical qualities so as to constitute an optimal replacement for the natural lens. These features are

accomplished by the presently invented injectable lens material with a specific gravity greater that 1.0 which maintains a sufficiently high refractive index at least similar to that of natural lenses and provides for an optically smooth surface of the resulting lens.

OBJECTS AND SUMMARY OF THE INVENTION

The objects of the present invention are to provide injectable materials useful in making IOLs, specifically, injectable IOLs, and methods for their preparation and use. In particular it is an object of the present invention to provide intraocular lenses having the advantage of a specific gravity greater than 1.0 that greatly simplifies injection of the lens forming silicone material and helps to assure proper positioning and conformation once cured *in situ,* while yet being able to provide a controllable refractive index within the physiological range the recipient requires for proper vision and suitably low modulus of the cured product, so as to better replicate the accommodative characteristics of the implanted lens. A further object is to provide materials and methods that lead to a fully cured injectable IOL with an optically smooth surface. These and other objects not specifically enumerated are addressed by identifying high specific gravity silicone materials suitable for making accommodative IOLs that can be injected with greater convenience than current materials.

In its most general form the present invention relates to polysiloxanes suitable for the preparation of intraocular lenses by a crosslinking reaction, having a specific gravity of greater than about 1.0, a refractive index suitable for restoring the refractive power of the natural crystalline lens and a viscosity suitable for injection through a standard cannula. It is to be understood that the polysiloxanes comprise a certain amount of functional unsaturated groups suitable for reaction with silicone bonded hydride (Si-H) groups in the presence of a catalyst. The skilled person knows of a large number of different alkenyl moieties and routes of how to synthesize vinyl functional polysiloxanes. A suitable and commonly employed route is to introduce end-blocking groups of vinyldimethyl siloxane wherein the olefinic vinyl group will enable curing by crosslinking. The polysiloxanes according to the invention can have refractive index ranges between 1.382 and up to about 1.60, preferably between from about 1.38 to 1.46 and more preferably index ranges from about 1.38 to 1.43, in order to be suitable as a material for

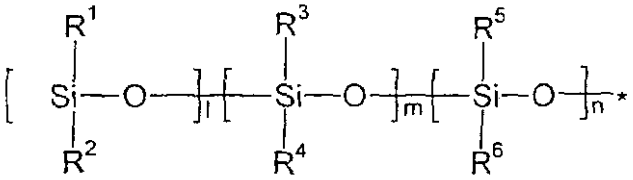
the production of intraocular lenses. Most preferably, the inventive polysiloxanes have a specific gravity within the range of about 1.03 to about 1.20. The polysiloxanes should also have a suitable viscosity to be readily injectable through conventional cannula having an 18 Gauge needle dimension or finer dimensions. Preferably, the polysiloxanes should be able to pass through a 21 Gauge needle. To comply with these criteria of injectability, polysiloxanes according to the present invention should have a viscosity less than about 60 000 cSt. More preferably, the viscosity should be less than about 8000 cSt. The skilled person will be able to relate these requirements to suitable degrees of polymerization.

The polysiloxanes typically consist essentially of different siloxane monomer units having the general formula $-R_aR_bSiO-$, wherein R_a and R_b are the same or different substituted or unsubstituted alkyl or aryl groups bound to the silicone atom. In accordance with the present invention at least one of the siloxane monomers included in the polysiloxanes has specific gravity greater than about 1.0. According to one aspect of the invention the polysiloxanes has at least one monomer, wherein R_a and R_b are the same or different alkyl or aryl groups of which at least one of said groups is substituted with one or several fluorine atoms. Preferably, the polysiloxanes comprises monomer units, wherein R_a is fluoroalkyl and R_b is alkyl and most preferably the polysiloxanes comprise 3,3,3-trifluoropropylmethylsiloxane monomers. In order to provide the polysiloxanes with the typically high specific gravity, it is preferred that the fluoroalkyl containing monomers exceed about 4 mol%. Further, it is also preferable that one of the siloxane monomers is an arylsiloxane and especially preferred arylsiloxanes are diphenylsiloxane and phenylalkylsiloxane.

According to an aspect of the invention, the polysiloxanes essentially are terpolymers derived from three different siloxane monomers of the general formula $(R_1R_2SiO)_l$ $(R_3R_4SiO)_m$ (R_5R_6SiO), wherein one of the three monomers has a specific gravity greater than about 1.0 and said terpolymer has a refractive index of about 1.41. In order to accomplish polysiloxanes with the mentioned requirements which the inventors have found to be advantageous for obtaining a material suitable for being injected into the capsular bag of the eye, it has been found suitable that R_1 and R_2 are the same or different lower substituted or unsubstituted alkyl and most preferable both are methyl. R_3 and R_4 shall be selected among the same or different substituted or unsubstituted aryl and alkyl groups, preferably R_3 is phenyl and R_4 is phenyl or methyl. R_5 and R_6

shall be selected among fluoroalkyl and alkyl groups and preferably R_5 is trifluoropropyl and R_6 is methyl. Alternatively, the inventive polysiloxanes can be higher polymers than terpolymers including but not limited to tetracopolymers with the same monomer types as mentioned.

According to preferred aspect of the invention, polysiloxanes essentially are vinyl-terminated terpolymers having the formula:



wherein R^1 and R^2 are independently C_1–C_6 alkyl; R^3 is phenyl; R^4 is phenyl or C_1–C_6 alkyl; R^5 is $CF_3(CH_2)_X$ wherein x is 1–5; R^6 is C_1–C_6 alkyl or fluoroalkyl; l is in the molar fraction range of 0 to 0.95; m is in the molar fraction range of 0 to 0.7; and n is in the molar fraction range of 0 to 0.65. It is preferred that R^1 is methyl, that R^2 is methyl, R^4 is phenyl, that x is 2, either independently, or in combination. Preferably according to these alternatives R^6 is methyl. According to one embodiment, the polysiloxane is a copolymer of diphenyl or phenylalkyl siloxane and dialkyl siloxane. According to further embodiments, the polysiloxane is a copolymer of diphenyl or phenylalkyl siloxane and trifluoroalkyl(alkyl)siloxane, or a terpolymer or higher order polymer of diphenyl and/or phenylalkyl siloxane, dialkyl siloxane and trifluoroalkyl alkyl siloxane. According to a specific preferred embodiment, polysiloxane is a terpolymer of dimethyl siloxane, diphenyl siloxane or phenylmethyl siloxane and 3,3,3-trifluoropropylmethyl siloxane. Preferably, said polysiloxanes comprise at least about 4 mol% of trifluoropropylmethyl siloxane and 1 to 50 mol% of diphenylsiloxane and/or phenylmethylsiloxane. More preferably said polysiloxanes comprise about 4 to 65 mol% 3,3,3 trifluoropropylmethyl siloxane, 1 to 50 mol% of diphenylsiloxane and dimethylsiloxane monomer units. One suitable polysiloxane composition for being a part of a composition for injection into the capsular bag of the human eye for the formation of IOL comprises about 28

mol% trifluoropropylmethyl siloxane, about 4 mol% diphenyl siloxane and dimethyl siloxane monomer units.

An important part of the present invention is the provision of an injectable lens material, comprising polysiloxanes having a specific gravity that is greater than about 1.0 and a refractive index of a natural lens which are defined as above, a crosslinking agent having a suitable amount of unreacted Si-H groups and a catalyst. It is to be understood by the skilled person that such a material is prepared by mixing the a formulation of the polysiloxane and catalyst with a formulation of the crosslinking agent, just prior to its use. It is also to be understood that these formulations can comprise further conventional constituents, such as agents for affecting the crosslinking and agents commonly associated with the production of IOLs from silicone materials, e.g. UV light absorbers.

The catalysts can be found among platinum group metal containing catalysts commonly employed for catalyzing the formation of bonds between Si-H groups and vinyl groups as referred to in US patent No. 5,278,258.

The crosslinking agents are of the siloxane or polysiloxane (i.e. a multifunctional organohydrogenpolysiloxane) type carrying at least two, preferably at least three Si-H groups, as disclosed in US Patents No. 5,278,258 and 5,444,106 which documents are incorporated as references for the crosslinking process. Other suitable crosslinkers are the branched siloxanes mentioned in US Patent No. 2,877,255. An example of a particularly suitable crosslinking agent for the present invention is tetrakis(dimethylsiloxy)silane.

The amounts of the components of the injectable material can be varied in accordance to the specific conditions. For example it is desirable to have reasonable fast curing process at ambient body temperature so final curing is accomplished within about 2 to 6 hours and that the injected composition is gelled into a stable polymeric network within a suitable working time for the surgeon. The skilled person will be able find suitable variation of the amount of the components and selecting suitable catalysts and crosslinking agents to obtain a suitable crosslinking density and so the resulting lens quality not will be compromised from any optical deficiency, such as discoloration from excessive catalyst levels. Examples of preferred routes to produce IOLs of the inventive lens material bases on specific polysiloxanes are given below.

The high specific gravity polysiloxanes preferably are prepared from a mixture of siloxane compounds including, either trimers, tetramers, or higher order cyclic siloxanes. The monomers used in the preferred embodiments of the present invention include, but are not limited to, methyl and substituted methyl siloxanes, phenyl siloxanes and trifluoropropyl methylsiloxanes having individual specific gravities ranging between about 0.97 and 1.28.

A crosslinkable terpolymeric silicone fluid, suitable for IOL can be prepared by copolymerizing three or more siloxane monomers in a predetermined ratio. Once formed the polymer has a specific gravity greater than 1.0 and can be injected into the patient's previously prepared capsular bag in a mixture with a crosslinker, the necessary catalyst and inhibitor formulation and cured *in situ*. During the early, i.e. gelation, phase of the curing process intraocular pressure is maintained to assure proper lens positioning and conformation within the capsular sac. The resulting IOL will have a refractive index within the physiologic range previously determined optimum for the given application and an optically smooth surface.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

The types of siloxane monomers useful in preparing the IOLs of this preferred embodiment include, but are not limited to, methyl and substituted methyl siloxanes, phenyl siloxanes and trifluoropropyl methyl siloxanes with individual specific gravities ranging between 0.97 and 1.28. The high specific gravity silicone co-polymers of the present invention are prepared by mixing a plurality of these compounds in a predetermined ratio to achieve a desired specific gravity and refractive index.

According to one embodiment, three siloxane monomers are mixed together with a suitable end blocker and dried in a reduced atmosphere under controlled thermal conditions. The reaction mixture is then catalyzed to induce co-polymerization in an inert atmosphere. The reaction is allowed to continue for a predetermined time in a precise thermal environment then terminated. Next, the reaction product is washed, precipitated and dried. The specific gravity, refractive index and mean molecular weight are determined.

In another embodiment of the present invention three siloxane monomers are mixed together with a suitable end blocker and dried in a reduced atmosphere under controlled thermal

conditions as before. The reaction mixture is then catalyzed to induce co-polymerization in an inert atmosphere. The reaction is allowed to continue for a predetermined time in a precise thermal environment then terminated. Next, the reaction product is washed, precipitated and dried. The resulting precipitate is then re-dissolved in a suitable solvent and filtered to enhance clarity. The specific gravity, refractive index and mean molecular weight are determined. Changes in the reactants, their relative concentrations and reaction conditions will result in a variety of end products with different specific gravities and refractive indices. The benefits of these differences will become apparent to one skilled in the art from the specific examples below.

According to the methods of the present invention, the ratio of siloxane monomer reactants necessary to achieve a desired refractive index and specific gravity can be approximated mathematically. If N is the desired IOL's refractive index and P is the specific gravity of the lens' copolymer and where n_{1-3} are the refractive indices and p_{1-3} are the specific gravities of the monomer reactants then the following mathematical relationship can be used:

$$N = x_1n_1 + x_2n_2 + x_3n_3$$

$$P = x_1p_1 + x_2p_2 + x_3p_3$$

Where x_{1-3} represent the ratio of the individual siloxane monomer reactants required to achieve an IOL with the desired optical and physical properties and $x_1 + x_2 + x_3 = 1$.

Having an injectable silicone lens with a specific gravity greater than 1.0 will greatly simplify the injection process and represents a significant improvement over previously suggested materials for injectable lens materials. Prosthetic lenses made by the process described herein are compliant and retain the refractive index of the natural lens making them ideal as corrective lenses as well as replacements for damaged and cataractous lenses.

The present invention improves considerably on previously suggested polysiloxane based materials for injectable IOLs due to its increased specific gravity to above 1.0, so displace residual water after its injection into the capsular sac's aqueous environment. This characteristic will reduce post-injection manipulation of the surgeon and will assure that the lens will assume a natural position and configuration. In accordance with the methods of the present invention an injectable IOL material is formed that greatly simplifies the injection, positioning and curing process. By the mentioned selection of siloxane monomers a high density injectable material can be provided with a controlled suitable refractive index comparable to that of the natural lens

without compromising the other important requirements including a viscosity suitable for injection. This will greatly contribute to that is possible to adjust the refractive outcome of the injected lens formed with the capsular bag as a mold by having suitable fractions of siloxane units contributing to a high refractive index and siloxane units contributing to a high density. Another advantage of this invention is that extremely compliant nature fully cured lenses can be obtained. If a conventional foldable silicone lens is considered to have a stiffness of 100, a cured injectable lens made from the material of the present invention could be designed to have a stiffness ranging from zero to five. Therefore, lenses made from the material described herein can be accommodative and respond naturally to the changes in the eyes' shape as focal length is adjusted. The accommodative nature of lenses fabricated from materials of the present invention would make them particularly suitable for corrective purposes besides replacements for diseased natural lenses and is considered within the scope of this invention. An unexpected, and beneficial, advantage of the present invention is the optically smooth surface formed after the lens has cured *in situ*.

The following examples are offered as being illustrative of the principles of the present invention and not by way of limitation.

Example 1

Preparation of poly(dimethyl-co-methylphenyl-co-trifluoropropylmethyl)siloxane.

To a dry 50ml flask were added siloxane monomers: hexamethylcyclotrisiloxane, 6.0g, 3,3,3-trifluoropropylmethylcylclotrisiloxane, 7.3g, 1,3,5-trimethyl-1,3,5-triphenylcyclotrisiloxane, 1.7g (1.55ml), and an end-blocker, 1,3-divinyltetramethyldisiloxane, 0.14g (0.17ml). The mixture was dried under vacuum at 80 °C for 30 minutes, then purged with argon. The temperature was raised to 140 °C and potassium silanolate catalyst, 7 mg, was added to initiate polymerization. The reaction proceeded quickly as indicated by an increase in viscosity. After about 30 minutes the mixture clarified. After about 3 hours the temperature was

raised to 160°C and the reaction continued for a further 3 hours, after which the reaction was cooled to room temperature. The polymer was cleaned using a procedure of dilution with tetrahydrofuran and precipitation in methanol, then dried. The dried silicone product was glass clear, with refractive index: 1.4070 (calculated: 1.410), specific gravity: 1.116 (calculated: 1.104), and molecular weight by GPC 25,000. Crosslinking of the polymer produced a clear silicone gel.

Example 2

Preparation of poly(dimethyl-co-methylphenyl-co-trifluoropropylmethyl)siloxane

A reaction mixture was prepared according to Example 1 except that the siloxane monomers were hexamethylcyclotrisiloxane, 9.0g, 3,3,3-trifluoropropylmethylcylclotrisiloxane, 4.65g, 1,3,5-trimethyl-1,3,5-triphenylcyclotrisiloxane, 1.35g (1.23ml). The resulting silicone polymer product was glass clear, the refractive index was 1.4082 (calculated: 1.410), specific gravity was 1.066 (calculated: 1.056) and the molecular weight by GPC was 26,000 .

Example 3

Preparation of poly(dimethyl-co-diphenyl-co-trifluoropropylmethyl)siloxane

To a dry 50ml flask were added siloxane monomers: hexamethylcyclotrisiloxane, 7.5g, 3,3,3-trifluoropropylmethylcylclotrisiloxane, 6.66g, hexaphenylcyclotrisiloxane,1.68g, and an end-blocker, 1,3-divinyltetramethyldisiloxane, 0.28g (0.34ml). The mixture was dried under vacuum at 80°C for 30 minutes, then purged with argon. The temperature was raised to 140°C and potassium silanolate catalyst, circa 7mg, was added to initiate polymerization. The reaction proceeded quickly as indicated by an increase in viscosity. After about 30 minutes the solution was almost clear with some residue at the bottom of the reaction vessel. The viscosity of the reaction mixture was decreasing. After about 2 hours the temperature was raised to 160°C and the reaction continued for a further 3 hours, after which the reaction was cooled to room

temperature. The polymer was washed with tetrahydrofuran and precipitated in methanol, then dried. The dried silicone product was slightly hazy. The material was dissolved in tetrahydrofuran, filtered through a 0.45 micrometer filter, and again dried, yielding a glass clear silicone polymer. The refractive index was 1.4095 (calculated: 1.424), specific gravity was 1.10 (calculated: 1.094) and the molecular weight by GPC was 18,000 . Crosslinking of this material yielded a clear silicone gel.

Example 4

Preparation of poly(dimethyl-co-diphenyl-co-trifluoropropylmethyl)siloxane

To a dry 1000ml flask were weighed in order: octaphenylcyclotetrasiloxane, 90.61g, 3,3,3-trifluoropropylmethylcylclotrisiloxane, 101.88g, octamethylcyclotetrasiloxane, 368.27g, and an α,ω-divinyl dimethylsiloxane oligomer end-blocker (Mn 1287 by NMR analysis), 40.93g. The flask was equipped for reflux and the reagents dried under vacuum on a bath at 80°C for 30 minutes. The system was purged with nitrogen, and potassium silanolate (Mn 395), 267mg, added. The bath temperature was increased to 160°C and the mixture heated and stirred for 20 hours, yielding a clear colourless polymer mixture. After cooling, the product was diluted with 420ml dichloromethane, and washed four times with 420ml portions of water, the first portion being acidified with 3.0ml of 0.1N HCl and the second portion with 0.6ml 0.1N HCl (the third and fourth portions were not acidified). The polymer was then washed twice with 420ml portions methanol, diluted with 180ml tetrahydrofuran, and washed twice more with methanol, as before. The solvent was then removed under vacuum over a few hours, with heating on a bath at 100°C, to a pressure of below 1mbar. The polysiloxane product was clear and colourless, with refractive index 1.428 (calculated: 1.432) and density 1.04 (calculated: 1.043). Viscosity at 25°C was 1802 cP. H-NMR, 500MHz, gave unit mole ratios: dimethyl / diphenyl / trifluoropropyl / divinyltetramethyl of 0.819 / 0.071 / 0.105 / 0.00494 (monomer ratios were: 0.827 / 0.070 / 0.099 / 0.00483), implying Mn 18,600 . GPC gave Mn 18,500 and Mw 36,600 .

Example 5

Preparation of poly(dimethyl-co-diphenyl-co-trifluoropropylmethyl)siloxane.

The polymerization method of Example 3 was repeated on a 125g reagents scale, employing octaphenylcyclotetrasiloxane, 34.88g, 3,3,3-trifluoropropylmethylcyclotrisiloxane, 25.25g, octamethylcyclotetrasiloxane, 56.4g, and an α,ω-divinyl dimethylsiloxane oligomer end-blocker (Mn 1287), 8.50g, and potassium silanolate, 55mg. The work-up differed from Example 3, using chloroform, 57ml, to dilute the polymer, followed by three washes with water and two with methanol, all 88ml portions, then dilution with 44ml tetrahydrofuran, followed by two more washes with 88ml portions methanol, then vacuum stripping to <1mbar on a bath at 100°C. The clear colourless product had refractive index 1.455 (calculated: 1.460) and density 1.08 (calculated: 1.080). Viscosity at 25°C was 3324 cP. H-NMR, 500MHz, gave unit mole ratios: dimethyl / diphenyl / trifluoropropyl / divinyltetramethyl of 0.697 / 0.158 / 0.140 / 0.00570 (monomer ratios were: 0.713 / 0.146 / 0.135 / 0.00549), implying Mn 18,600 . GPC gave Mn 16,900 and Mw 33,400 .

Example 6

Curing of prepolymers

The silicone polymers were prepared for curing by formulating two parts, a Part A containing platinum catalyst in the form of the 1,3-divinyltetramethyldisiloxane complex, and a Part B containing crosslinker and siloxane inhibitor. The preferred crosslinker was tetrakisdimethylsiloxysilane, TKDMSS, but a polymeric silicon hydride (Gelest/ABCR HMS-151, a copolymer of methylhydrosiloxane and dimethylsiloxane having nominal Mn 1900-2000 and 15-18mol% MeHSiO units) is here also reported for comparison. Optimum ratios of catalyst, crosslinker, and inhibitor were determined by studying the curing profiles of silicone mixtures using a rheometer (Rheometrics RDA 2, with determination of the moduli of the cured materials. Mixtures were formulated to give gel times circa 15-20 minutes at 20°C. Tests were performed

at 35°C using 25mm diameter plates with 1mm spacing. Frequency and strain sweeps were regularly performed on the materials. Mixtures for testing were prepared by accurately weighing portions of Parts A and B, mixing for 2 minutes, and degassing under reduced pressure before transferring the mixture to the plates. The disks obtained from the mixtures were clear and colourless. The results obtained are illustrated by the following examples:

Example 6(a).

Prepolymer prepared in Example 4 was formulated as Part A, containing circa 8ppm platinum, and Part B containing 18.2mg TKDMSS /g Part B, plus siloxane inhibitor. The mixture was analysed on the rheometer in different weight ratios of B/A at 35°C, determining shear moduli, G', after 3000 seconds, at which time the mixutures were fully cured. The results for ratios B/A were: ratio: 0.86, G' 199.2 kPa; ratio: 1.00: G' 217.2 kPa; ratio: 1.15, G' 214.5 kPa.

Example 6(b).

Prepolymer prepared as per Example 4 was formulated as Part A, containing circa 12ppm platinum, and Part B containing 8.23%ww polymeric silicon hydride, Gelest/ABCR HMS-151, plus siloxane inhibitor. The mixture was analysed on the rheometer at 35°C as above. Shear moduli, G', after 3000 seconds for ratios B/A were: ratio: 0.821, G' 100.7 kPa; ratio: 1.00: G' 167.9 kPa; ratio: 1.22, G' 193.2 kPa; ratio: 1.52, G' 184.0 kPa.

Example 7

Implantation of silicone material into pig cadaver eyes

A fresh pig cadaver eye was prepared, with small aperture incision into the capsular bag and removal of the crystalline lens. The silicone composition was prepared from the prepolymer of Example 4, having refractive index 1.428, with Part A containing ca.12 ppm platinum as a divinyltetramethyldisiloxane complex, and Part B containing tetrakisdimethylsiloxysilane crosslinker, 18.9mg/g mixture, with siloxane inhibitor. Gel time was circa16 minutes at 20°C. Silicone for injection was prepared by mixing equal weights of Parts A and B in a Teflon pot, taking up in a syringe, vacuum degassing, and then injecting into the capsular bag via a 21 gauge

cannula, so as to refill the bag and give appropriate curvature. After curing (ca. 45 minutes from the start of mixing) the lens was removed from the eye. The transparent tack-free lens had anterior radius 10.1±0.4mm, posterior radius 5±0.1mm, thickness 5.33±0.03mm, diameter 9.2±0.1mm. Its power in air was 115±2diopter, and focal length 8.7±0.1mm (in water, lens power was 29.1±0.5 diopters, and focal length 45.7±0.8mm). The natural crystalline lens of the pig has higher RI than that of the human lens. From the measured dimensions of 11 pig lenses it was calculated that an RI of circa 1.51 is required to restore natural refractive power in a refilled pig lens.

Example 8

Implantation of silicone material into a human cadaver eye

A human cadaver eye was prepared, with small aperture incision into the capsular bag and removal of the crystalline lens. The silicone composition was prepared and a lens made as per Example 7. The transparent tack-free lens had anterior radius 8.7±0.5mm, posterior radius 6.2±0.1mm, thickness 4.11±0.06mm, diameter 8.2±0.1mm. Its calculated focal length, 49.08mm gave a power in water of 27.1±0.7 diopters. The power in water of the average human lens is 21.8 diopters, and to have obtained this power in the lens refilled herein would have required filling material of RI 1.41 .

CLAIMS

1. Polysiloxanes suitable for the preparation of intraocular lenses by a crosslinking reaction, having a specific gravity of greater than about 1.0, a refractive index suitable for restoring the refractive power of the natural crystalline lens and a viscosity suitable for injection through a standard cannula.

2. Polysiloxanes according to claim 1, wherein the refractive index ranges between 1.382 up to about 1.60

3. Polysiloxanes according to claim 2 comprising at least one siloxane monomer with a specific gravity greater than about 1.0.

4. Polysiloxanes according to claim 3 comprising at least one siloxane monomer $-R_aR_bSiO-$, wherein R_a and R_b are the same or different alkyl or phenyl groups of which at least one is substituted with one or several fluorine atoms.

5. Polysiloxanes according to claim 4 comprising fluoroalkyl(alkyl)siloxane monomers.

6. Polysiloxanes according claim 5 comprising trifluoropropylmethylsiloxane monomers.

7. Polysiloxanes according to any of claims 1 to 6 being terpolymer or higher polymer of three or more siloxane monomers units.

8. Polysiloxanes according to any of claims 3 to 7 comprising arylsiloxane monomers.

9. Polysiloxanes according to claim 8 comprising methyl and substituted methylsiloxanes, phenylsiloxanes and trifluoropropylsiloxanes.

10. Polysiloxanes according to claim 9 being essentially a terpolymer of

a) dimethylsiloxane,

b) methylphenylsiloxane or diphenylsiloxane;

c) and trifluoropropylmethylsiloxane monomers.

11. Polysiloxanes according to claim according to claim 6 comprising at least about 4 mol % trifluoropropylmethylsiloxane.

12. Polysiloxanes according to any of claims 2 to 11 having a specific gravity of within the range of about 1.03 to 1.20 and refractive index from above about 1.38.

13. An injectable lens material, comprising polysiloxanes having a specific gravity that is greater than about 1.0 and a refractive index comparable to that of a natural lens according to any of claims 1 to 12, a crosslinking agent having a suitable amount of unreacted Si-H groups and a catalyst.

14. A reaction mixture for making polysiloxanes of an injectable lens material comprising a plurality of siloxane monomers having a specific gravity ranging from 0.97 to 1.28, wherein the siloxane monomers comprise one or more trimer or tetramer or higher order cyclic siloxane monomers forming a silicone lens material with a specific gravity greater than 1.0.

15. The reaction mixture of claim 14, wherein the plurality of siloxane monomers is copolymerized to make a terpolymer with a refractive index of about 1.41 and a specific gravity of about 1.1.

16. The reaction mixture of claim 15 wherein at least one of the monomers has a specific gravity that is greater than 1.0.

17. The reaction mixture of claim 15, wherein the plurality of siloxane monomers are selected from a group consisting of methyl and substituted methyl siloxanes, phenyl siloxanes and trifluoropropyl methyl siloxane.

18. The reaction mixture of claim 15, wherein the plurality of siloxane monomers consists essentially of cyclic dimethylsiloxane monomer, cyclic diphenylsiloxane monomer and 3,3,3-trifluoropropylmethyl cyclotrisiloxane..

19. The reaction mixture of claim 15, wherein the plurality of siloxane monomers consists essentially of cyclic dimethylsiloxane monomer, triphenyltrimethyl cyclosiloxane monomer and 3,3,3-trifluoropropylmethyl cyclotrisiloxane.

20. A method of preparing an intraocular lens, comprising:
providing a reaction mixture according to any of claims 14 to 19;
polymerizing the siloxane monomers to form a polysiloxane having a specific gravity greater than 1.0; transferring the polymerized siloxane monomers in a mixture together with a crosslinking agent and a catalyst to the capsular sac; and curing the mixture to the final lens.

21. A method of preparing an intraocular lens including the provision of a mixture comprising the polysiloxanes according to any of claims 1 to 12, a crosslinker and a catalyst, injecting the said mixture into a mold and curing said mixture at curing temperature optionally under forming pressure for a time sufficient to prepare said lens.

22. A method according to claim 21, wherein the mixture is injected into the capsular bag of a human eye and cured at an ambient temperature.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/EP 99/07780

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G02B1/04 A61L27/00 C08G77/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 23476 A (ALLERGAN INC) 25 November 1993 (1993-11-25) cited in the application claims 1-5,17-19 page 6, line 31 -page 8, line 5	1,2,4-6, 13
X	US 5 391 590 A (GERACE JOHN D ET AL) 21 February 1995 (1995-02-21) cited in the application claims 1,10,12 column 4, line 31 - line 60 column 7, line 54 -column 8, line 12 column 11; example 2	1,2,4-6, 13
A	US 5 116 369 A (NOSE NORIYUKI ET AL) 26 May 1992 (1992-05-26) claims 1-11	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

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PCT/EP 99/07780

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

Inte ional Application No
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权利要求书3页 说明书14页 附图页数0页

[54]发明名称 可注射的眼内镜片

[57]摘要

本发明涉及适用于通过交联反应制备眼内镜片的聚硅氧烷,其比 重大于约1.0,屈光指数适合于恢复天然晶状体的折光力,粘度适于通 过标准套管进行注射。本发明包括基于所述聚硅氧烷的可注射的眼内镜 片材料以及通过直接注射进眼囊袋中制备眼内镜片的方法。

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权 利 要 求 书

1. 适用于通过交联反应制备眼内镜片的聚硅氧烷，其比重大于约1.0，屈光指数适合于恢复天然晶状体的折光力，粘度适于通过标准套管进行注射。

2. 根据权利要求1的聚硅氧烷，其中，屈光指数在1.382至高达约1.60的范围内。

3. 根据权利要求2的聚硅氧烷，其至少包含一种比重大于约1.0的硅氧烷单体。

4. 根据权利要求3的聚硅氧烷，其至少包含一种硅氧烷单体$-R_aR_bSiO-$，其中，R_a和R_b为相同或不同的烷基或苯基，其中至少一个基团被一个或几个氟原子取代。

5. 根据权利要求4的聚硅氧烷，其包含氟代烷基(烷基)硅氧烷单体。

6. 根据权利要求5的聚硅氧烷，其包含三氟丙基甲基硅氧烷单体。

7. 根据权利要求1-6任一项的聚硅氧烷，其为三种或更多种硅氧烷单体单元的三元共聚物或更高级聚合物。

8. 根据权利要求3-7任一项的聚硅氧烷，其包含芳基硅氧烷单体。

9. 根据权利要求8的聚硅氧烷，其包含甲基和取代的甲基硅氧烷、苯基硅氧烷和三氟丙基硅氧烷。

10. 根据权利要求 9 的聚硅氧烷，其基本上为下述单体成分的三元共聚物：

a) 二甲基硅氧烷，

b) 甲基苯基硅氧烷或二苯基硅氧烷；

c) 三氟丙基甲基硅氧烷。

11. 根据权利要求 6 的聚硅氧烷，其包含至少约 4mol%的三氟丙基甲基硅氧烷。

12. 根据权利要求 2-11 任一项的聚硅氧烷，其比重在约 1.03-1.20 范围内，屈光指数大于约 1.38。

13. 一种可注射的镜片材料，其包含比重大于约 1.0 且屈光指数与天然晶状体可相比的权利要求 1-12 任一项的聚硅氧烷，具有适宜量未反应的 Si-H 基团的交联剂和催化剂。

14. 一种用于制备可注射镜片材料的聚硅氧烷的反应混合物，其包含比重在 0.97-1.28 范围内的多种硅氧烷单体，其中，所述硅氧烷单体包含一种或多种形成比重大于 1.0 的硅氧烷镜片材料的三聚物或四聚物或更高级的环状硅氧烷单体。

15. 根据权利要求 14 的反应混合物，其中，所述多种硅氧烷单体共聚制成具有屈光指数约 1.41 和比重约 1.1 的三元共聚物。

16. 根据权利要求 15 的反应混合物，其中，至少一种单体的比重大于 1.0。

17. 根据权利要求 15 的反应混合物，其中，所述多种硅氧烷单体选自甲基和取代的甲基硅氧烷、苯基硅氧烷和三氟丙基甲基硅氧烷。

18. 根据权利要求 15 的反应混合物，其中，所述多种硅氧烷单体基本上由环状二甲基硅氧烷单体、环状二苯基硅氧烷单体和 3,3,3-三氟丙基甲基环三硅氧烷组成。

19. 根据权利要求 15 的反应混合物，其中，所述多种硅氧烷单体基本上由环状二甲基硅氧烷单体、三苯基三甲基环硅氧烷单体和 3,3,3-三氟丙基甲基环三硅氧烷组成。

20. 一种制备眼内镜片的方法，包括：

提供一种权利要求 14-19 任一项的反应混合物；

将硅氧烷单体聚合以形成比重大于 1.0 的聚硅氧烷；将聚合的硅氧烷单体以与交联剂及催化剂的混合物形式转移至囊袋中；将混合物固化成最后的镜片。

21. 一种制备眼内镜片的方法，包括：

提供包含权利要求 1-12 任一项的聚硅氧烷、交联剂和催化剂的混合物，将所述混合物注射入模具中，任选地在形成压力下，在固化温度下将所述混合物固化足够的时间以制备所述的镜片。

22. 根据权利要求 21 的方法，其中，将混合物注射入人眼的囊袋中并在环境温度下固化。

说　明　书

可注射的眼内镜片

发明领域

本发明涉及一种眼内镜片和用于制备眼内镜片(intraocular lenses, IOL)的材料，具体而言，本发明涉及可注射的眼内镜片及其制备方法。更具体地说，本发明涉及适用于制备适应性眼内镜片的高比重硅氧烷材料，该材料可比目前给出的材料更方便地注射进入囊袋中。

发明背景

人眼是一种高度进化且非常复杂的感觉器官。它是由角膜或澄清的外部组织(其折射光线进入瞳孔)、虹膜(其控制瞳孔的尺寸从而调节进入眼睛的光线量)和晶状体(其聚焦进来的光线通过玻璃体液体进入视网膜)组成。视网膜将进来的光线转化成电能，其通过脑干传送至枕骨皮层，形成视觉上的图像。在完好的眼睛中，通过角膜、穿过晶状体和玻璃体液体进入视网膜的光路是无障碍的。这些结构内任何障碍或澄明度方面的损失均会引起光线的散射或吸收，导致视敏度减弱。例如，角膜损伤会导致水肿、瘢痕形成或擦伤，晶状体有可能会受到氧化性损伤、外伤或感染，由于出血或发炎，玻璃体可能会变得到混浊。

随着年龄增加，由于环境照射而造成的氧化性损伤的作用及内源性游离基产生的积聚会导致晶状体屈曲性丧失，以及会缓慢地凝固使晶状体透明性降低的变性蛋白。晶状体的天然屈曲性对于通过被称为眼调节的过程来将光线聚焦于视网膜上是必要的。眼调节使眼睛自动调节在不同距离中目标的视觉领域。当氧化性损伤的累积效应减少这种屈曲性时，会导致通常被称为老视的公知状态，降低了近视敏度。老视通常是在成人于其四十岁左右开始的；温和方式是配戴眼镜或隐形眼镜(contact lenses)。

晶状体白内障是一种晶状体病症，是由凝固蛋白和钙化进一步发

展而引起的。白内障有四种常规类型：与年龄和氧化性应力有关的老年性白内障；创伤性白内障，其是因外物进入晶状体囊后引起或遭受强离子辐射或红外线照射形成的；并发性白内障，其是诸如糖尿病或眼疾病如视网膜分离、青光眼和色素性视网膜炎等疾病引起的并发症；和中毒性白内障，它是由于药物或化学毒性引起的。不论成因为何种，该疾病均会导致视力减弱并可导致失明。

严重的晶状体疾病的治疗需要外科手术通过冲洗法和吸引术以除去涉及晶状体乳化作用的晶状体。但是，如果没有晶状体，眼睛就不能聚焦视网膜上进来的光线。结果，使用人工晶状体以恢复视力。已有三种类型的人工晶状体供应：白内障眼镜、外置式隐形眼镜和眼内镜片。白内障眼镜具有非常厚的镜片，由于很重，戴起来很不舒服，并会造成视觉假象如中心图像放大而侧视变形。隐形眼镜解决了许多与一般眼镜相关的问题，但其需要经常清洁，并难于处置(特别是对有关节炎疾病的年老患者)，还不适用于限制流泪的人群。眼内镜片用于大多数情形下以克服上述白内障眼镜和隐形眼镜相关的问题。

在现有技术中提到的眼内镜片通常属于下述类别之一：不会变形的、可折叠的、能扩张的水凝胶和可注射的。最早投入外科手术实践的眼内镜片为不会变形的植入物，其具有刚性结构，由丙烯酸酯和甲基丙烯酸酯组成。这种类型的镜片需要在囊袋中很大的外科切口且是非调节性的。大的切口导致恢复时间延长，并有可能引起散光眼。为缩短恢复时间和患者的不适感，已研究了很多种小切口技术和镜片。

目前对小切口植入法所设计的眼内镜片均具有弹性体特性，是由硅氧烷材料制成的。这种类型的镜片可卷曲或折叠，插入囊袋中然后再内部展开。有时候，在插入之前镜片会展开，导致永久性变形，损坏了植入物的光学性质。可折叠的镜片可满足不可变形镜片所需的减小大外科切口的要求。此外，不可变形的和可折叠的眼内镜片均可能会机械脱位，造成对角膜内皮的损伤。

还有人建议使用一种弹性体聚合物，当将这种弹性体聚合物加热至体温时或稍高于体温时，其会在小切口眼内镜片植入法中变得柔软。

在软化后，这种镜片可沿着至少一个轴变形，使得其尺寸足以易于通过小切口插入。然后，将这种镜片冷却以保持改变后的形状直至再次加热。将冷却后的镜片插入囊袋中，自然体温将其温热，其又恢复其原始形状。这种热塑性镜片的主要缺点是，只有很少的一些聚合物能够满足该研究的具体要求。大多数聚合物是由固液转变温度大于100℃的聚甲基丙烯酸酯组成的。为了降低所述转变温度，就要求采用增塑剂对聚合物底物进行改性，使其最终可过滤进入眼睛中。

脱水的水凝胶也被建议用于小切口技术。水凝胶镜片在插入前脱水，在插入囊袋中后自然再水化。但是，在完全再水化后，由于吸收了大量的水，聚合物结构公知将会变弱。通常脱水后水凝胶的直径将从 3mm 扩展至 6mm，导致镜片包含约 85%的水。在这种水浓度下，屈光指数（refractive index）将降至大约 1.36，这对于眼内镜片来说是不可接受的。为使屈光指数等于或大于天然晶状体(>1.40)，需要显著增稠的镜片；而当镜片直径超过6mm时，上述情形又进一步加剧。

为了进一步开发眼内镜片并减小外科切口至低于1.5mm，已建议采用可注射的眼内镜片，其中，低粘度的镜片材料直接注射进入空的囊袋中并作为外科手术过程的一部分原位固化。在该方法中，囊袋被用作模具以形成镜片形状，从而有助于控制其折射。已提出各种方案以开发出适用于作为可注射眼内镜片的材料。例如，在其 5,278,258, 5,391,590('590)和 5,411,553 专利文献中，Gerace 等描述了一种用于形成眼内镜片的快速固化混合物，该混合物包括含乙烯基的聚有机硅氧烷、含氢化物基团的有机硅氧烷和铂系金属催化剂。与其它铂催化的硅氧烷聚合物相比，所形成的聚合物显示出减少变色的可能。'590 专利也描述了一种基本上无官能团聚合物组分的混合物，所述混合物的粘度至少比官能团聚合物大 50 倍。将无官能团组分与官能团组分混合以调节粘度至预定规格。在US专利5,476,515中，Kelman描述了一种可注射的胶原眼内镜片。这种镜片是澄清的，能够耐受上皮形成并能够适应性调节。它是由一种屈光指数为 1.2-1.6 的透明的胶原化合物制成的，可以其原始粘稠态使用，或者聚合成软凝胶使用。这种胶原

化合物可在除去天然晶状体后直接注射入囊袋。

除了获得对交联过程的控制并找到临床可接受的条件等问题外，为完善聚有机硅氧烷组合物还需做出艰苦的努力，因为它们需要具有适于注射的粘度、适宜的高屈光指数以及交联后的适宜机械特性，即适宜的模量。聚二甲基硅氧烷(PDMS)已被用作可折叠眼内镜片的材料，其屈光指数与天然晶状体类似。这种材料也在上述 Gerace 等的专利中作为注射混合物的一部分举例。PDMS 也已发现具有相对较低的粘度，因而有可能从所要求的注射部位(即囊袋中)泄漏出来。这一点在所述 US 专利 5,391,590 中有所考虑，其中，向注射混合物中加入附加的高粘度聚硅氧烷。但是，高粘度硅氧烷的缺点在于，它们会产生空气泡，这会损害形成的产品的光学性质。此外，还发现，具有高比率二甲基硅氧烷单元的聚有机硅氧烷具有不能令人接受的低比重，导致不希望出现的结果，即注射的镜片材料将浮在囊袋中水层的上面。在此情形下，将很难完全填充囊袋，需要外科医生手工急送水以保持在固化过程中合适的镜片形状。因此，还需要由聚硅氧烷配制一种可注射的镜片形成材料，这种材料应能克服浮动和泄漏问题，同时仍具有适宜的高屈光指数和理想的机械与光学性质，从而构造对天然晶状体的最佳代用品。这些特性可通过本发明比重大于 1.0 的可注射镜片材料来实现，所述材料保持至少与天然晶状体类似的足够高的屈光指数，并能使所形成的镜片具有光学上平滑的表面。

发明目的和概述

本发明的目的是提供用于制备眼内镜片，特别是可注射的眼内镜片的可注射材料，和其制备方法及用途。具体而言，本发明的一个目的是提供具有比重大于 1.0 这一优点的眼内镜片，其可大大简化形成镜片的硅氧烷材料的注射过程，并有助于确保适当的定位和一旦原位固化后的构造，同时，能够提供接受者适当视觉所需的生理范围之内的可控制屈光指数以及适当低的固化制品模量，从而更好地复制植入式镜片的适应性特征。本发明的另一个目的是提供产生具有光学上平滑表面

的完全固化的可注射眼内镜片的材料和方法。这些目的和其它不能明确地列举出的目的通过确认高比重硅氧烷材料实现，所述材料适用于制备比目前的材料具有更大便利性的可注射的适应性眼内镜片。

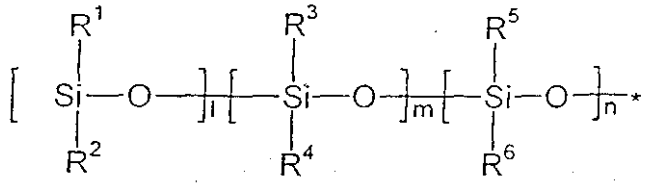
以其最常规的形式，本发明涉及适用于通过交联反应制备眼内镜片的聚硅氧烷，其比重约大于1.0，其屈光指数适合于恢复天然晶状体的折光力，并且其粘度适于通过标准套管注射。可以理解，聚硅氧烷包含一定量的适于在催化剂存在下与硅氧烷键合的氢化物(Si-H)基团反应的功能性不饱和基团。本领域的技术人员熟知大量的不同的链烯基部分和如何合成乙烯基功能化聚硅氧烷。一种适宜的也是常规采用的路线是引入乙烯基二甲基硅氧烷的末端嵌段基团，其中，烯属乙烯基基团能够通过交联固化。为适宜作为生产眼内镜片的材料，本发明的聚硅氧烷的屈光指数范围为1.382至高达约1.60，优选约1.38-1.46，更优选约 1.38-1.43。最优选的是，本发明的聚硅氧烷的比重为约1.03-1.20。聚硅氧烷也应具有适宜的粘度以易于通过常规具有 18 Gauge 针头尺寸或较细尺寸的套管注射。优选地，聚硅氧烷应能够通过21 Gauge 针头。为遵守这些注射性标准，本发明聚硅氧烷的粘度应低于约 60 000 cSt，更优选低于约 8000 cSt。本领域的技术人员将能够使这些要求对应适宜的聚合度。

聚硅氧烷通常基本上由具有通式$-R_aR_bSiO-$的不同硅氧烷单体单元组成，其中，R_a和 R_b为相同或不同的与硅原子相连的取代或未取代的烷基或芳基。根据本发明，包含于硅氧烷中的至少一种硅氧烷单体其比重应大于约1.0。按照本发明的一个方面，聚硅氧烷具有至少一种单体，其中，R_a和 R_b为相同或不同的烷基或芳基，所述基团的至少一个被一个或多个氟原子取代。优选地，聚硅氧烷包含这样的单体单元，其中，R_a为氟代烷基，R_b为烷基，最优选的聚硅氧烷包含 3,3,3-三氟丙基甲基硅氧烷单体。为了提供具有典型的高比重的聚硅氧烷，优选含氟代烷基的单体超过约 4mol%。进而，同样优选硅氧烷单体之一为芳基硅氧烷，特别优选的芳基硅氧烷为二苯基硅氧烷和苯基烷基硅氧烷。

按照本发明的一个方面，聚硅氧烷基本上是一种由三种不同的硅

氧烷单体得到的通式为$(R_1R_2SiO)_l(R_3R_4SiO)_m(R_5R_6SiO)$的三元共聚物，其中，三种单体之一的比重大于约 1.0，所述的三元共聚物的屈光指数约为 1.41。为了使聚硅氧烷达到本发明人发现可有利地获得适用于被注入眼睛囊袋中的材料所述的要求，已发现，适宜地，R_1和 R_2为相同或不同的低级取代或未取代的烷基，首选它们均为甲基。R_3和 R_4将选自于相同或不同的取代或未取代的芳基和烷基，优选 R_3为苯基和 R_4为苯基或甲基。R_5和 R_6将选自氟代烷基和烷基，优选 R_5为三氟丙基和 R_6为甲基。或者，本发明的聚硅氧烷可为比三元共聚物更高的聚合物，包括但不限于四元共聚物，其具有如上所述相同的单体类型。

按照本发明的优选方面，聚硅氧烷基本上为具有下式的终端为乙烯基的三元共聚物：



其中，R^1和 R^2彼此独立地为 C_1-C_6烷基；R^3为苯基；R^4为苯基或 C_1-C_6烷基；R^5为 $CF_3(CH_2)x$，其中，x 为 1-5；R^6为 C_1-C_6烷基或氟代烷基；l 为 0-0.95 的摩尔分数；m 为 0-0.7 的摩尔分数；n 为 0-0.65 的摩尔分数。优选 R^1为甲基，优选 R^2为甲基，优选 R^4为苯基，优选 x 为 2，或者优选其中之一，或者优选全部。按照这些选择方式，优选 R^6为甲基。根据一种实施方案，聚硅氧烷为二苯基或苯基烷基硅氧烷与二烷基硅氧烷的共聚物。根据另一种实施方案，聚硅氧烷是二苯基或苯基烷基硅氧烷和三氟烷基(烷基)硅氧烷的共聚物，或者是二苯基和/或苯基烷基硅氧烷、二烷基硅氧烷和三氟烷基烷基硅氧烷的三元共聚物或更高级聚合物。按照特别优选的实施方案，聚硅氧烷为二甲基硅氧烷、二苯基硅氧烷或苯基甲基硅氧烷与 3,3,3-三氟丙基甲基硅氧烷的三元共聚物。优选地，所述聚硅氧烷包含至少约 4mol%的三氟丙基甲基硅氧烷和 1-50mol%的二苯基硅氧烷和/或苯基甲基硅氧烷。更优选地，所述的聚硅氧烷包含约 4-65mol%的 3,3,3-三氟丙基甲基硅氧烷，

1-50mol%的二苯基硅氧烷和二甲基硅氧烷单体单元。一种适宜的聚硅氧烷组合物(为注入人眼睛的囊袋中形成眼内镜片的组合物的一部分)包含约 28mol%的三氟丙基甲基硅氧烷，约 4mol%的二苯基硅氧烷和二甲基硅氧烷单体单元。

本发明的重要部分是提供一种可注射的镜片材料，其包含具有比重大于约 1.0 及如上所定义天然晶状体屈光指数的聚硅氧烷，具有适宜量未反应 Si-H 基团的交联剂和催化剂。本领域的技术人员可以理解，这种材料可在使用前使聚硅氧烷和催化剂的制剂与交联剂的制剂混合制成。同样可以理解，这些制剂还可包含常规成分，如用于影响交联作用的试剂和通常与由硅氧烷材料生产眼内镜片相关的试剂，如紫外光吸收剂。

催化剂可为常规用于催化在 Si-H 基团与乙烯基基团间形成键的含铂系金属的催化剂，如 US 专利 5,278,258 所述。

交联剂为硅氧烷或聚硅氧烷(即多官能的有机氢聚硅氧烷)类型，其带有至少两个，优选至少三个 Si-H 基团，如 US 专利 5,278,258 和 5,444,106 所述，这两篇文献均引入本文作为交联方法的参考。其它适宜的交联剂为支化的硅氧烷，如 US 专利 2,877,255 所述。特别适用于本发明的一种交联剂为四(二甲基甲硅烷氧基)硅烷。

可注射材料中各组分的量可根据具体条件而改变。例如，比较理想的是在环境体温下具有合理的快速固化过程从而最后的固化在约 2-6 小时内完成，并且，注射的组合物在适宜的外科医生工作时间内胶凝成稳定的聚合网络。本领域的技术人员将能够找到各组分的适宜用量变化范围，并选择适宜的催化剂和交联剂以获得适宜的交联密度，从而使形成的镜片质量不会产生任何光学缺陷的危害，如因过量催化剂水平导致的变色。以下给出生产本发明基于特定聚硅氧烷镜片材料的眼内镜片的优选路线实例。

高比重聚硅氧烷优选由一种包括三聚物、四聚物或更高级环状硅氧烷的硅氧烷化合物的混合物制备。用于本发明优选实施方案中的单体包括但不限于：甲基和取代的甲基硅氧烷、苯基硅氧烷和三氟丙基甲基硅

氧烷，各自比重范围为约 0.97-1.28。

适用于眼内镜片的可交联三元共聚硅氧烷液体可通过使三种或更多种硅氧烷单体以预定比率进行共聚来制备。在形成后，聚合物具有大于 1.0 的比重，并可以与交联剂、必要的催化剂和抑制剂制剂的混合物形式注入患者预先制备的囊袋中并原位固化。在早期，即固化过程的胶凝阶段，保持眼内压力以确保适宜的镜片定位和在囊袋内的构造。形成的眼内镜片其屈光指数将在对给定应用来说先前确定的最佳值生理范围之内，并且其具有光学上平滑的表面。

实施方案的详细描述

可用于制备该优选实施方案中的眼内镜片的硅氧烷单体的类型包括但不限于甲基和取代的甲基硅氧烷、苯基硅氧烷和三氟丙基甲基硅氧烷，各自比重范围为约 0.97-1.28。本发明的这种高比重硅氧烷共聚物是通过使这些化合物按预定的比例混合以达到所需比重和屈光指数而制备的。

按照一种实施方案，这些硅氧烷单体与适宜的封端剂一起混合，并在控制加热的条件下进行减压干燥。然后，将反应混合物在惰性气氛下催化以进行共聚反应。使反应在精确的加热环境下进行预定的时间，然后终止。接着将反应产物洗涤、沉淀和干燥。测量比重、屈光指数和平均分子量。

在本发明的另一个实施方案中，将三种硅氧烷单体与适宜的封端剂混合，并如前在控制加热的条件下进行减压干燥。然后，将反应混合物在惰性气氛下催化以进行共聚反应。使反应在精确的加热环境下进行预定的时间，然后终止。接着将反应产物洗涤、沉淀和干燥。将形成的沉淀再溶解于适宜的溶剂中，过滤以增强澄清度。测量比重、屈光指数和平均分子量。改变反应物、它们的相对浓度和反应条件将导致具有不同比重和屈光指数的各种最终产品。对于本领域的技术人员来说，由下述具体的实施例将很清楚这些差异的有益效果。

按照本发明的方法，可从数学上粗略估计达到所需屈光指数和比重所必需的各硅氧烷单体反应物的比例。如果 N 为所希望的眼内镜片的屈光指数，P 为镜片共聚物的比重，并且，其中 n_{1-3} 为单体反应物的屈光指数，P_{1-3} 为单体反应物的比重，则可使用下述数学关系：

$$N = x_1n_1 + x_2n_2 + x_3n_3$$

$$P = x_1p_1 + x_2p_2 + x_3p_3$$

其中，x_{1-3} 表示获得具有所需光学性质和物理性质的眼内镜片的单个硅氧烷单体反应物的比例，并且，$x_1 + x_2 + x_3 = 1$。

比重大于 1.0 的可注射硅氧烷镜片将大大简化注射过程，并对目前用于可注射镜片材料的推荐材料有显著的改善。由本文所述方法制得的人工晶状体适应性强并保留了天然晶状体的屈光指数，使其与矫正镜片一样完美，并可置换损伤和白内障性晶状体。

本发明对目前已提出的基于聚硅氧烷的可注射眼内镜片材料有显著改善，由于将比重增加至大于 1.0，从而在将其注射入囊袋的含水环境中后能够置换残余的水。这一特性将减少外科医生的后期注射操作，并将确保镜片将呈现天然位置和构造。按照本发明的方法形成的可注射的 IOL 材料将大大简化注射、定位和固化过程。通过所提及的对硅氧烷单体的选择，可提供一种高密度的可注射材料，其具有与天然晶状体可比的适宜的屈光指数，并且不会损害其它重要的要求，包括适用于注射的粘度。这将具有极大的好处，使得可通过调整有助于高屈光指数的硅氧烷单元与有助于高密度的硅氧烷单元的适宜比率，而调整在作为模具的囊袋内形成的注射镜片的折光性。本发明的另一个优点是可获得极具适用性能的全固化镜片。如果常规的可折叠硅氧烷镜片其刚度视为是 100，则由本发明的材料制成的固化后的可注射镜片可设计成刚度范围为 0-5。因此，由本文所述的材料制成的镜片可自然适应和响应眼睛形

状中的变化，就像调节焦距一样。除置换害病的天然晶状体外，由本发明的材料构造的镜片的可调节性能使其特别适用于校正目的，这也属于本发明的保护范围。本发明的一个出人意料的有益优点是在镜片原位固化后会形成光学上平滑的表面。

下述实施例用于说明本发明的原理，并非对本发明的限制。

实施例 1

制备聚(二甲基-共-甲基苯基-共-三氟丙基甲基)硅氧烷

向 50ml 的干烧瓶中加入硅氧烷单体：六甲基环三硅氧烷，6.0g，3,3,3-三氟丙基甲基环三硅氧烷，7.3g，1,3,5-三甲基- 1,3,5-三苯基环三硅氧烷，1.7g (1.55ml)和一种封端剂，1,3-二乙烯基四甲基二硅氧烷，0.14g (0.17ml)。将混合物在 80℃真空下干燥 30 分钟，然后用氩气吹扫。将温度升至 140℃，再加入硅烷醇酸钾（potassium silanolate）催化剂，7mg，以引发聚合反应。由粘度增加表明反应快速进行。在约 30 分钟后，混合物澄清。在约 3 小时后，将温度升至 160℃，继续反应 3 小时，此后，将反应物冷却至室温。采用用四氢呋喃稀释、甲醇中沉淀的过程使聚合物澄清，然后干燥。干燥后的硅氧烷产物为玻璃澄清状的，屈光指数为 1.4070 (计算值：1.410)，比重：1.116 (计算值：1.104)，经 GPC 测得的分子量为 25,000。聚合物进行交联产生了澄清的硅氧烷凝胶。

实施例 2

制备聚(二甲基-共-甲基苯基-共-三氟丙基甲基)硅氧烷

按照实施例 1 制备反应混合物，只是硅氧烷单体为：六甲基环三硅氧烷，9.0g，3,3,3 -三氟丙基甲基环三硅氧烷，4 .65g，1,3,5-三甲基- 1,3,5-三苯基环三硅氧烷，1.35g (1.23ml)。形成的硅氧烷聚合物为玻璃澄清状，屈光指数为 1.4082 (计算值：1.410)，比重为 1.066 (计算值：1.056)，经 GPC 测得的分子量为 26,000。

实施例 3

制备聚(二甲基-共-二苯基-共-三氟丙基甲基)硅氧烷

向50ml的干燥烧瓶中加入硅氧烷单体：六甲基环三硅氧烷，7.5g，3,3,3-三氟丙基甲基环三硅氧烷，6.66g，六苯基环三硅氧烷，1.68g和一种封端剂，1,3-二乙烯基四甲基二硅氧烷，0.28g (0.34ml)。将混合物在 80℃及真空下干燥 30 分钟，然后用氩气吹扫。将温度升至140℃，再加入硅烷醇酸钾催化剂，大约 7mg，以引发聚合反应。由粘度增加表明反应快速进行。在约 30 分钟后，溶液几乎澄清，在反应容器的底部有少量的残余物。该反应混合物的粘度降低。在约 2 小时后，将温度升至 160℃，继续反应 3 小时，此后，将反应物冷却至室温。聚合物用四氢呋喃洗涤，在甲醇中沉淀，然后干燥。干燥后的硅氧烷产物有轻微混浊。将物料溶解于四氢呋喃中，用 0.45μm 的滤器过滤，再干燥，得到玻璃澄清状的硅氧烷聚合物。其屈光指数为 1.4095 (计算值：1.424)，比重为 1.10 (计算值：1.094)和经 GPC 测得的分子量为18,000。该物料的交联得到一种澄清的硅氧烷凝胶。

实施例 4

制备聚(二甲基-共-二苯基-共-三氟丙基甲基)硅氧烷

向干燥的 1000ml 烧瓶中以下述次序加入：八苯基环四硅氧烷，90.61g，3,3,3-三氟丙基甲基环三硅氧烷，101.88g，八甲基环四硅氧烷，368.27g 和α,ω-二乙烯基二甲基硅氧烷低聚物封端剂(由 NMR 分析得到的 Mn 为 1287)，40.93g。烧瓶备有回流装置，并将试剂在80℃的浴中于真空下干燥 30 分钟。将体系用氮气吹扫，加入硅烷醇酸钾(Mn 395)，267mg。将浴温升至 160℃，加热并搅拌混合物 20 小时，得到一种澄清的无色聚合物混合物。在冷却后，将产物用 420ml 的二氯甲烷稀释，各用 420ml 水洗涤四次，第一次的水用 3.0ml 的 0.1N HCl 酸化，第二次的水用 0.6ml 0.1N HCl 酸化(第三次和第四次水不酸化)。然后，将聚合物各用 420ml 的甲醇洗涤两次，再用 180ml 的四氢呋喃

稀释，再如前所述用甲醇洗涤两次。然后，在几个小时内，在浴温加热至100℃并同时减压至低于1mbar下真空除去溶剂。聚硅氧烷产物为澄清和无色的，屈光指数为1.428(计算值：1.432)和密度为1.04(计算值：1.043)。在25℃时的粘度为1802 cP。H-NMR，500MHz，给出单元摩尔比率：二甲基/二苯基/三氟丙基/二乙烯基四甲基为0.819/0.071/ 0.105/0.00494 (单体比例为：0.827/0.070/0.099/0.00483)，暗示Mn 18,600。由GPC得到Mn 18,500和Mw 36,600。

实施例5

制备聚(二甲基-共-二苯基-共-三氟丙基甲基)硅氧烷

在125g的试剂规模上重复实施例3的聚合过程，采用八苯基环四硅氧烷，34.88g，3,3,3-三氟丙基甲基环三硅氧烷，25.25g，八甲基环四硅氧烷，56.4g 和α,ω-二乙烯基二甲基硅氧烷低聚物封端剂(Mn 1287)，8.50g，和硅烷醇酸钾，55mg。与实施例3不同的是，采用氯仿，57ml，稀释聚合物，再用水洗涤三次，用甲醇洗涤两次，每将均用88ml，然后用44ml的四氢呋喃稀释，再用88ml的甲醇洗涤两次，然后在<1 mbar下于100℃浴温下进行真空汽提。澄清的无色产物其屈光指数为1.455 (计算值：1.460)，密度为1.08 (计算值：1.080)。25°C时的粘度为3324 cP。H-NMR，500MHz，给出单元摩尔比：二甲基/二苯基/三氟丙基/二乙烯基四甲基为0.697/0.158/0.140/0.00570 (单体比例为：0.713/0.146/0.135/0.00549)，暗示Mn 18,600。由GPC给出Mn 16,900和Mw 33,400。

实施例6

预聚物固化

制备用于固化的硅氧烷聚合物，配制两部分，A部分包含铂催化剂，为1,3-二乙烯基四甲基二硅氧烷配合物形式，B部分包含交联剂和硅

氧烷抑制剂。优选的交联剂为四（二甲基甲硅烷氧基）硅烷，TKDMSS，作为比较此处也报导采用聚合硅烷(Gelest/ABCR HMS-151，甲基氢化硅氧烷和二甲基硅氧烷的共聚物，标称 Mn 为 1900-2000，具有 15-18mol%的 MeHSiO 单元)。通过采用流变仪(Rheometrics RDA 2)，测量固化后材料的模量，研究硅氧烷混合物的固化曲线，测定催化剂、交联剂和抑制剂的最佳比率。配制混合物以便在 20℃下的胶凝时间大约为 15-20 分钟。实验在 35℃下进行，采用间隔 1mm 的 25mm 直径的板。对物料有规则地进行频率和应变扫描。实验用混合物这样制备：准确地称量 A 部分和 B 部分，混合 2 分钟，在将混合物转移至板上之前减压下脱气。由混合物获得的盘澄清且无色。获得的结果通过下述实例说明：

实施例 6(a)

将在实施例 4 中制备的预聚物配制成 A 部分，其包含大约 8ppm 的铂，B 部分，其包含 18.2mg 的 TKDMSS/g B 部分，加上硅氧烷抑制剂。在 B/A 不同重量比下于 35℃下用流变仪分析混合物，测量在 3000 秒后的剪切模量 G'，在此时间混合物完全固化。对下述 B/A 比例的结果为：比例 0.86，G' 199.2 kPa；比例：1.00：G' 217.2 kPa；比例：1.15，G' 214.5 kPa。

实施例 6(b)

将在实施例 4 中制备的预聚物配制成 A 部分，其包含大约 12ppm 的铂，B 部分，其包含 8.23%w/w 的聚合硅烷，Gelest/ABCR HMS-151，加上硅氧烷抑制剂。如上所述于 35℃下用流变仪分析混合物。测量在 3000 秒后的剪切模量 G'，对比例 B/A 的结果为：比例：0.821，G' 100.7 kPa；比例：1.00：G' 167.9 kpa；比例：1.22，G' 193.2 kPa；比例：1.52，G' 184.0 kPa。

实施例 7

将硅氧烷材料植入猪尸体眼中

制备一份新鲜的猪尸体眼睛，在囊袋中切一小孔切口并除去晶状体。由实施例 4 的预聚物制备硅氧烷组合物，其屈光指数为 1.428，A 部分包含大约 12ppm 的铂，作为二乙烯基四甲基二硅氧烷复合物，B 部分包含四（二甲基甲硅烷氧基）硅烷交联剂，18.9mg/g 混合物，和硅氧烷抑制剂。在 20℃时的胶凝时间大约为 16 分钟。用于注射的硅氧烷这样制备：将等重量的 A 部分与 B 部分在特氟隆罐中混合，放入注射器中，真空脱气，然后经 21 gauge 的套管注射入囊袋中，从而再填充囊袋，并得到适宜的曲度。在固化后(从混合开始约 45 分钟)，从眼睛中取出镜片。透明的不粘镜片前半径为 10.1±0.4mm，后半径 5±0.1mm，厚度 5.33±0.03mm，直径 9.2±0.1mm。其在空气中的折光力为 115±2 屈光度，焦距为 8.7±0.1mm(在水中，镜片折光力为 29.1±0.5 屈光度，焦距为 45.7±0.8mm)。猪的天然晶状体比人晶状体具有更高的 RI 值。从 11 只猪晶状体的测量尺寸可计算出，需要大约 1.51 的 RI 值以恢复在再填充的猪晶状体中的天然折光力。

实施例 8

在人尸体眼睛中植入硅氧烷材料

制备一份人尸体眼睛，其在囊袋中具有小的孔切口并除去了晶状体。制备硅氧烷组合物并如实施例 7 制备镜片。透明的不粘镜片具有前半径 8.7±0.5mm，后半径 6.2±0.1mm，厚度 4.11±0.06mm，直径 8.2±0.1mm。其计算的焦距 49.08mm，在水中折光力为 27.1±0.7 屈光度。平均人晶状体在水中的折光力为 21.8 屈光度，为在本发明中再填充的晶状体中获得该折光力，需要填充材料 RI 值为 1.41。

Title: INJECTABLE INTRAOCULAR LENS

Abstract

The present invention relates to polysiloxanes suitable for the preparation of intraocular lenses by a cross-linking reaction, having a specific gravity of greater than about 1.0, a refractive index suitable for restoring the refractive power of the natural crystalline lens and a viscosity suitable for injection through a standard cannula. The present invention includes an injectable intraocular lens material based on said polysiloxanes and methods of preparing intraocular lenses by direct injection into the capsular bag of the eye.