(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 February 2003 (13.02.2003)

PCT

(10) International Publication Number
WO 03/011194 A1

(51) International Patent Classification[7]: A61F 2/16

(21) International Application Number: PCT/US02/23623

(22) International Filing Date: 26 July 2002 (26.07.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/308,374 27 July 2001 (27.07.2001) US

(71) Applicants *(for all designated States except US)*: **CALIFORNIA INSTITUTE OF TECHNOLOGY** [US/US]; 1200 E. California Boulevard, Pasadena, CA 91125 (US). **UNIVERSITY OF CALIFORNIA, SAN FRANCISCO** [US/US]; Suite 1, 1294 9th Avenue, San Francisco, CA 94143 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **JETHMALANI, Jagdish, M.** [IN/US]; 855 N. Madison Avenue, Apt. 48, Pasadena, CA 91101 (US). **MALONEY, Robert, K.** [US/US]; 640 Chatauqua, Pacific Palisades, CA 90272 (US). **GRUBBS, Robert, H.** [US/US]; 1700 Spruce Street, South Pasadena, CA 91030 (US). **KORNFIELD, Julia, A.** [US/US]; 1675 Oakdale, Pasadena, CA 91125 (US). **SANDSTEDT, Christian, A.** [US/US]; 680 Marengo Avenue, #10, Pasadena, CA 91106 (US). **SCHWARTZ, Daniel, M.** [US/US]; 42 Calhoun Terrace, San Francisco, CA 94133 (US).

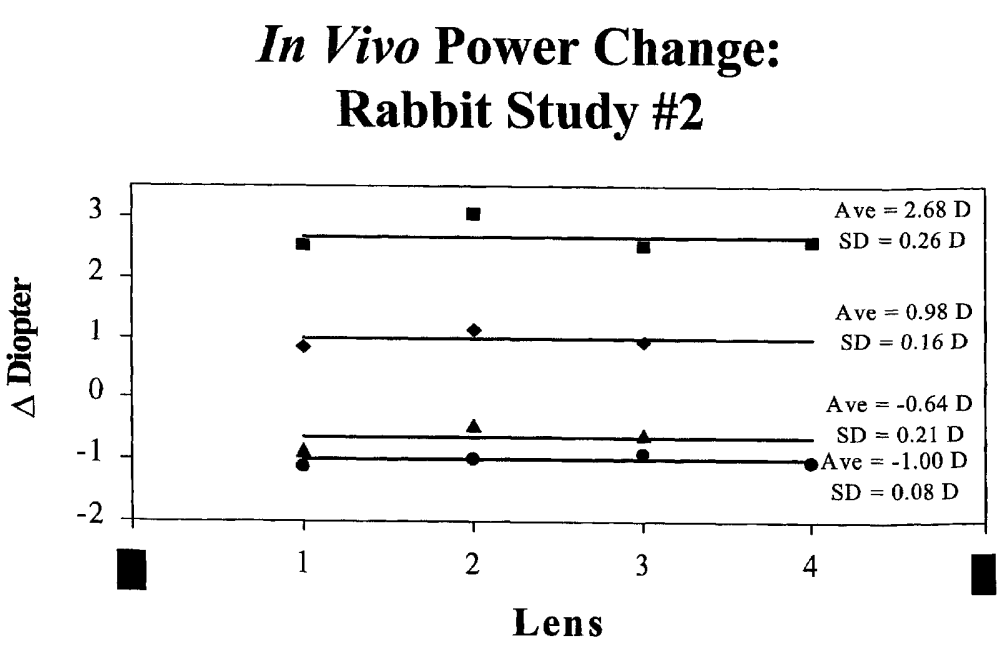
(74) Agent: **SCHNEIDER, John, E.**; Fulbright & Jaworski L.L.P., Suite 5100, 1301 McKinney, Houston, TX 77010-3095 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,

*[Continued on next page]*

(54) Title: INTRAOCCULAR LENSES WITH POWER ADJUSTABILITY IN VIVO




(57) Abstract: A method for evaluating the effectiveness of adjustable optical implants is provided. The implants are first inserted into a test subject. The implant is then exposed to an external stimulus, such as light, to induce a change in the properties of the implant. The implants are then evaluated to determine the nature and extent of the change in properties.

WO 03/011194 A1

TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

may itself either be a homopolymer or copolymer) which may be linked together to form a polymer containing repeating units of the same. If the FPMC monomer is a copolymer, it may be comprised of the same type of monomers (*e.g.*, two different siloxanes) or it may be comprised of different types of monomers (*e.g.*, a siloxane and an acrylic).

**[0025]** In one embodiment, the one or more monomers that form the first polymer matrix are polymerized and cross-linked in the presence of the macromer. In another embodiment, polymeric starting material that forms the first polymer matrix is cross-linked in the presence of the macromer. Under either scenario the macromer components must be compatible with and not appreciably interfere with the formation of the first polymer matrix. Similarly, the formation of the second polymer matrix should also be compatible with the existing first polymer matrix. Put another way, the first polymer matrix and the second polymer matrix should not phase separate and light transmission by the optical element should be unaffected.

**[0026]** As described previously, the macromer may be a single component or multiple components so long as (i) it is compatible with the formation of the first polymer matrix; (ii) it remains capable to stimulus-induced polymerization after the formation of the first polymer matrix; and (iii) it is freely diffusable within the first polymer matrix. In preferred embodiments, the stimulus-induced polymerization is photo-induced polymerization.

**[0027]** The inventive optical elements have numerous applications in the electronics and data storage industries. Another application for the present invention is as medical lenses, particularly as intraoccular lenses.

**[0028]** In general, there are two types of intraoccular lenses ("IOLs"). The first type of an intraoccular lens replaces the eye's natural lens. The most common reason for such a procedure is cataracts. The second type of intraoccular lens supplements the existing lens and functions as a permanent corrective lens. This type of lens (sometimes referred to as a phakic intraoccular lens) is implanted in the anterior or posterior chamber to correct any refractive errors of the eye. In theory, the power for either type of intraoccular lenses required for emmetropia (*i.e.*, perfect focus on the retina from light at infinity) can be precisely calculated. However, in practice, due to errors in measurement of corneal curvature, and/or variable lens positioning and wound healing, it is estimated that only about half of all patients undergoing IOL implantation will enjoy the best possible vision without the need for additional correction after surgery.

Because prior art IOLs are generally incapable of post-surgical power modification, the remaining patients must resort to other types of vision correction such as external lenses (*e.g.*, glasses or contact lenses) or cornea surgery. The need for these types of additional corrective measures is obviated with the use of the intraoccular lenses of the present invention.

**[0029]** The inventive intraoccular lens comprises a first polymer matrix and a macromer dispersed therein. The first polymer matrix and the macromer are as described above with the additional requirement that the resulting lens be biocompatible.

**[0030]** Illustrative example of a suitable first polymer matrix include: poly-acrylates such as poly-alkyl acrylates and poly-hydroxyalkyl acrylates; poly-methacrylates such as poly-methyl methaacrylate ("PMMA"), poly-hydroxyethyl methacrylate ("PHEMA"), and poly-hydroxypropyl methacrylate ("HPMA"); poly-vinyls such as poly-styrene and poly-vinylpyrrolidone ("PNVP"); poly-siloxanes such as poly-dimethylsiloxane; poly-phosphazenes,and copolymers of thereof. U.S. Patent No. 4,260,725 and patents and references cited therein (which we all incorporated herein by reference) provide more specific examples of suitable polymers that may be used to form the first polymer matrix.

**[0031]** In preferred embodiments, the first polymer matrix generally possesses a relatively low glass transition temperature ("$T_g$") such that the resulting IOL tends to exhibit fluid-like and/or elastomeric behavior, and is typically formed by crosslinking one or more polymeric starting materials wherein each polymeric starting material includes at least one crosslinkable group. Illustrative examples of suitable crosslinkable groups include but are not limited to hydride, acetoxy, alkoxy, amino, anhydride, aryloxy, carboxy, enoxy, epoxy, halide, isocyano, olefinic, and oxime. In more preferred embodiments, each polymeric starting material includes terminal monomers (also referred to as endcaps) that are either the same or different from the one or more monomers that comprise the polymeric starting material but include at least one crosslinkable group. In other words, the terminal monomers begin and end the polymeric starting material and include at least one crosslinkable group as part of its structure. Although it is not necessary for the practice of the present invention, the mechanism for crosslinking the polymeric starting material preferably is different than the mechanism for the stimulus-induced polymerization of the components that comprise the Macromer. For example, if the Macromer is polymerized by photo-induced polymerization, then it is preferred that the polymeric starting

materials have crosslinkable groups that are polymerized by any mechanism other than phot-induced polymerization.

**[0032]** An especially preferred class of polymeric starting materials for the formation of the first polymer matrix is poly-siloxanes (also known as "silicones") endcapped with a terminal monomer which includes a crosslinkable group selected from the group consisting of acetoxy, amino, alkoxy, halide, hydroxy, and mercapto. Because silicone IOLs tend to be flexible and foldable, generally smaller incisions may be used during the IOL implantation procedure. An example of an especially preferred polymeric starting material is bis(diacetoxymethylsilyl)-polydimethylsiloxane (which is poly-dimethylsiloxane that is endcapped with a diacetoxymethylsilyl erminal monomer).

**[0033]** The macromer that is used in fabricating IOLs is as described above except that it has the additional requirement of biocompatibility. The macromer is capable of stimulus-induced polymerization and may be a single component or multiple components so long as (i) it is compatible with the formation of the first polymer matrix; (ii) it remains capable of stimulus-induced polymerization after the formation of the first polymer matrix; and (iii) it is freely diffusable within the first polymer matrix. In general, the same type of monomers that is used to form the first polymer matrix may be used as a component of the macromer. However, because of the requirement that the macromer monomers must be diffusable within the first polymer matrix, the macromers generally tend to be smaller (*i.e.*, have lower molecular weights) than the monomers which form the first polymer matrix. In addition to the one or more monomers, Macromer may include other components such as initiators and sensitizers that facilitate the formation of the second polymer matrix.

**[0034]** In preferred embodiments, the stimulus-induced polymerization is photo-polymerization. In other words, the one or more monomers that comprise the macromers each preferably includes at least one group that is capable of photopolymerization. Illustrative examples of such photopolymerizable groups include but are not limited to acrylate, allyloxy, cinnamoyl, methacrylate, stibenyl, and vinyl. In more preferred embodiments, the macromer includes a photoinitiator (any compound used to generate free radicals) ether alone or in the presence of a sensitizer. Examples of suitable photinitiators include acetophenones (*e.g.*, -substituted haloacetophenones, and diethoxyacetophenone); 2,4-dichloromethyl-1,3,5-triazines; benzoin methyl ether; and o-benzoyl oximino ketone. Examples of suitable sensitizers include p-

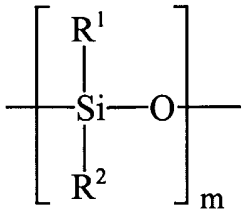
(dialkylamino)aryl aldehyde; N-alkylindolyidene Check sp; and bis[p-(dialkylamino)benzylidene] ketone.

**[0035]** Because of the preference for flexible and foldable IOLs, an especially preferred class of macromer monomers is poly-siloxanes endcapped with a termination siloxane moiety that includes a photopolymerizable group. An illustrative representation of such a monomer is

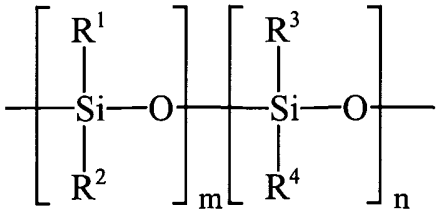
$$X\text{-}Y\text{-}X^1$$

**[0036]** As described more fully below, adjustable optical implants are those optical implants such as IOLs whose properties can be manipulated or adjusted post implantation by non-invasive measures. In the preferred embodiment, the adjustable implant's contain macromers which are capable of inducing change in the implant when the implant is exposed to an external stimulus.

**[0037]** Wherein Y is a siloxane which may be a monomer, a homopolymer or a copolymer formed from any number of siloxane units, and X and $X^1$ may be the same or different and are each independently a terminal siloxane moiety that includes a photopolymerizable group. An illustrative example of Y include

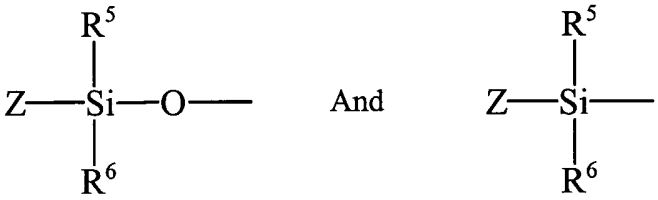


**[0038]** and



[0039] wherein m and n are independently each an integer and $R^1$, $R^2$, $R^3$, and $R^4$ are independently each hydrogen, alkyl (primary, secondary, tertiary, cyclo), aryl, or heteroaryl. In preferred embodiments, $R^1$, $R^2$, $R^3$, and $R^4$ is a $C^1$-$C^{10}$ alkyl or phenyl. Because Macromer monomers with a relatively high aryl content have been found to produce larger changes in the refractive index of the inventive lens, it is generally preferred that at least one $R^1$, $R^2$, $R^3$, and $R^4$ is an aryl, particularly phenyl. In more preferred embodiments, $R^1$, $R^2$, and $R^3$ are the same and are methyl, ethyl or propyl and $R^4$ is phenyl.

[0040] Illustrative examples of X and $X^1$ (or $X^1$ and X depending on how the Macromer polymer is depicted) are



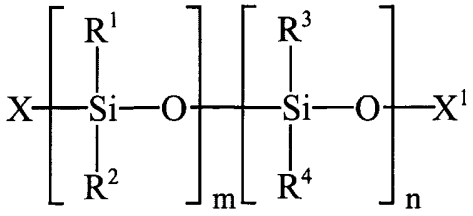
[0041] Respectively wherein:

[0042] $R^5$ and $R^6$ are independently each hydrogen, alkyl, aryl, or heteroaryl; and

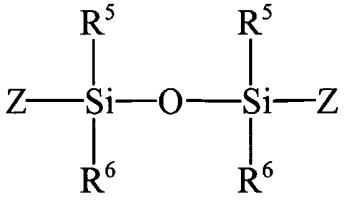
[0043] Z is a photopolymerizable group.

[0044] In preferred embodiments, $R^5$ and $R^6$ are independently each a $C_1$-$C^{10}$ or phenyl and Z is a photopolymerizable group that includes a moiety selected from the group consisting of acrylate, allyloxy, connamoyl, methaacrylate, stibenyl, and vinyl. In more preferred embodiments, $R^5$ and $R^6$ is methyl, ethyl, or propyl and Z is a photopolymerizable group that includes an acrylate or methacrylate moiety.

**[0045]** In especially preferred embodiments, an macromer monomer if of the following formula



**[0046]** Wherein X and $X^1$ are the same and $R^1$, $R^2$, $R^3$, and $R^4$ are as defined previously. Illustrative examples of such Macromer monomers include dimethylsiloxane-diphenylsiloxane copolymer endcapped with a vinyl dimethylsilane group; dimethylsiloxane-methylphenylsiloxane copolymer endcapped with a methacryloxypropyl dimethylsilane group; and dimethylsiloxane endcapped with a methacryloxypropyldimethylsilane group. Although any suitable method may be used, a ring-opening reaction of one or more cyclic siloxanes in the presence of triflic acid has been found to be a particularly efficient method of making one class of inventive macromers. Briefly, the method comprises contacting a cyclic siloxane with a compound of the formula



**[0047]** in the presence of triflic acid wherein $R^5$, $R^6$, and Z are as defined previously. The cyclic siloxane may be a cyclic siloxane monomer, homopolymer, or copolymer. Alternatively, more than one cyclic siloxane may be used. For example, a cyclic dimethylsiloxane tetramer and a cyclic methyl-phenylsiloxane trimer are contacted with bis-methacryloxypropyltetramethyldisiloxane in the presence of triflic acid to form a dimethyl-siloxane methyl-phenylsiloxane copolymer that is endcapped with a methacryloxypropyl-dimethylsilane group, an especially preferred macromer.

**[0048]** The adjustable IOLs may be fabricated with any suitable method that results in a first polymer matrix with one or more components which comprise the Macromer dispersed therein, and where the Macromer is capable of stimulus-induced polymerization to form a second polymer matrix. In general, the method for making an inventive IOL is the same as that for making an inventive optical element. In one embodiment, the method comprises

**[0049]** mixing a first polymer matrix composition with a Macromer to form a reaction mixture;

**[0050]** placing the reaction mixture into a mold;

**[0051]** polymerizing the first polymer matrix composition to form said optical element; and

**[0052]** removing the optical element from the mold.

**[0053]** The type of mold that is used will depend on the optical element being made. For example, if the optical element is a prism, then a mold in the shape of a prism is used. Similarly, if the optical element is an intraoccular lens, then an intraoccular lens mold is used and so forth. As described previously, the first polymer matrix composition comprises one or more monomers for forming the first polymer matrix and optionally includes any number of formulation auxiliaries that either modulate the polymerization reaction or improve any property (whether or not related to the optical characteristic) of the optical element. Similarly, the Macromer comprises one or more components that together are capable of stimulus-induced polymerization to form the second polymer matrix. Because flexible and foldable intraoccular lenses generally permit smaller incisions, it is preferred that both the first polymer matrix composition and the Macromer iniclude one or more silicone-based or low $T_g$ acrylic monomers when the inventive method is used to make IOLs.

**[0054]** Once the adjustable optical element has been formed, it is then implanted in a non-human test subject. Implantation entails removal of the existing lens by phaecoemulsification and extraction of the lens debries. This is followed by implantation of the element using standard surgical procedures.

**[0055]** After the eye has had sufficient time to heal, (1 to 2 weeks) the eye is then examined for evidence of inflammation. The same time, operability testing can also be conducted.

**[0056]** Operability testing involves attempting to manipulate the properties of the implant in vivo followed by an evaluation as to whether the desired changes have occurred.

**[0057]** In the preferred embodiment, this entails exposing at least a portion of the implant to an external stimulus so as to induce a change in the properties of the implant. In one embodiment, ultraviolet light is said to induce photopolymerization of macromers in at least a portion of an adjustable IOL polymerization of the macromers causes change in the shape of the IOL and/or the refractive index of the IOL. The extent of the changes is then evaluated to see if the desired optical properties have been achieved.

**[0058]** Determination of biocompatibility can be accomplished either in vivo or ex vivo or both. Physical examination of the eye can be used to determine the presence of inflammation and their biocompatibility. In some cases, however, it may be necessary to explant the lens and conduct histopathological studies of the eye tissue to determine biocompatibility.

**[0059]** The determination of operability requires that at least the adjustment phase be done in vivo followed by examination of the lens in vivo or ex vivo. In vivo examination of the lens can be done using an autoretractometer or a Scheimpflug imaging device to determine change in refraction and/or shape. Alternatively, the lens may be explanted after an ajustment lens has been attempted and the changes in the lens can be determined ex vivo.

## EXAMPLE 1

**[0060]** Sterilized, adjustable IOLs were implanted in albino rabbit eyes. After clinically following the eyes for one week, the rabbits were sacrificed. The extracted eyes were evaluated, placed in familiar and studied histopathologically. There was no evidence of corneal toxicity, anterior segment inflammation or other signs of lens toxicity.

## EXAMPLE 2

**[0061]** A series of adjustable IOLs were prepared for implantation. The IOLs comprised a silicon based polymer matrix with dimethylsiloxane macromer dispersed therein. The safety and operability of the lenses was evaluated in four rabbits. The rabbits were first anesthetized and the existing lens was removed using phaecoemulsification. The IOLs were then implanted into the rabbits.

**[0062]** The rabbit eyes were exposed to ultraviolet light for 60 to 120 seconds to induce localized polymerization of macromer in the center of the lens.

**[0063]** The next day, the rabbits were checked physically to determine if any infection develop or if there was any evidence that the lens was not biocompatible. No evidence of incompatibility or infection was noted.

**[0064]** The lenses were then examined to determine if the desired changes in optical properties had taken place. This was accomplished by explanting the lenses and then evaluating the change in lens power achieved. In this case the power of the lenses increased an average of 0.72 diopters.

## EXAMPLE 3

**[0065]** In this set of experiments, 16 adjustable lens were implanted into albino rabbit eyes. The lenses were adjusted in vivo to diopters of approximately –1.0, -0.5, +1.0 and 2.5 using ultraviolet light. The lenses were then evaluated for biocompatibility and operability by sacrificing the rabbits and explanting the lenses. As shown in Figure 1, four lenses showed a change in diopters of –1.00,D four had a change in diopter of –0.64D, three had a change in diopter of +0.98D and four had a change of +2.68D.

**[0066]** Histopathological studies of the eyes showed no inflammation. This indicated good biocompatibility for the lens.

**[0067]** Although the present invention and its advantages have been described in detail, it should be understood that various changes, substitutions and alterations can be made herein without departing from the spirit and scope of the invention as defined by the appended

claims. Moreover, the scope of the present application is not intended to be limited to the particular embodiments of the process, machine, manufacture, composition of matter, means, methods and steps described in the specification. As one of ordinary skill in the art will readily appreciate from the disclosure of the present invention, processes, machines, manufacture, compositions of matter, means, methods, or steps, presently existing or later to be developed that perform substantially the same function or achieve substantially the same result as the corresponding embodiments described herein may be utilized according to the present invention. Accordingly, the appended claims are intended to include within their scope such processes, machines, manufacture, compositions of matter, means, methods, or steps.

## Claims

1. A method for testing biocompatibility of an optical element containing a refraction modulating composition, comprising the steps of:

a) forming an optical element of a polymer with macromers dispersed therein, wherein the macromers is capable of stimulus-induced polymerization, such that a stimulus causes a desired change of refraction;

b) sterilizing the optical element;

c) implanting the optical element in an eye;

d) extracting the optical element from the eye after a period of time and testing for toxicity.

2. The method of claim 1, and further including the step of:

a) forming the optical element with a refraction modulating composition selected from the group consisting of an acrylate, methacrylate, vinyl, siloxane and phosphazene.

3. The method of claim 1, and further including the step of:

a) forming the optical element of polysiloxane matrix and a refraction modulating composition dispersed therein.

4. The method of claim 1, and further including the step of:

a) exposing at least a portion of the optical element to a stimulus after the step of implanting the optical element, whereby the stimulus induces the polymerization of the refraction modulating composition, such that the stimulus causes a desired change of refraction.

5. The method of claim 4, and further including the step of:

a) waiting an interval of time after the step of exposing, and

b) re-exposing the portion of the optical element to the stimulus to induce the further polymerization of the refraction modulation composition which the portion, such that the stimulus produces a desired change of refraction.

6. The method of claim 4, and further including the step of:

a) the step of exposing includes exposing at least a portion of the optical element to stimulus from a light source.

7. The method of claim 4, and further including the steps of:

a) implanting a plurality of optical elements in a like number of rabbit eyes;

b) exposing at least a portion of a number of the optical elements to a stimulus after the step of implanting the optical elements, whereby the stimulus induces the polymerization of the refraction modulating composition, such that the stimulus causes a desired change of refraction; and

c) explanting the optical elements from the rabbit eyes and testing for toxicity.

8. The method of claim 7, and further including the steps of:

a) maintaining at least some of the optical elements in the rabbit eyes without exposing the optical elements to a stimulus; and

b) explanting the optical elements from the rabbit eyes and testing for toxicity.

9. A method of evaluating an adjustable optical implant comprising:

a) Inserting an adjustable optical implant into a test subject.

b) Adjusting the optical properties of said implant in vivo; and

c) Evaluating the change in optical properties of the implant.

10. The method of claim 9 wherein the implant comprises macromers capable of inducing changes in the optical properties of the implant when the macromers are exposed to an external stimulus.

11. The method of claim 9 wherein the adjusting of the optical properties of the implant is accomplished by exposing at least a portion of said implant to an external stimulus.

12. The method of claim 10 wherein the external stimulus is light.

13. The method of claim 10 wherein the external stimulus is ultraviolet light.

14. The method of claim 10 wherein the implant is an intraoccular lens.

15. A method for evaluating an adjustable optical implant comprising

a) Inserting an adjustable optical implant in a test subject;

b) Adjusting the optical properties of the implant in vivo; and

c) Evaluating the changes in optical properties and the biocompatability of the implant.

16. The method of claim 15 wherein said optical implant comprises macromers which can induce changes in the optical properties of the implant upon exposure to an external stimulus.

17. The method of claim 15 wherein said adjusting step is accomplished by exposing at least a portion of said implant to an external stimulus.

18. The method of claim 17 wherein said external stimulus is light.

19. The method of claim 18 wherein said light is ultraviolet light.

20. The method of claim 15 further comprising the step of evaluating the biocompatibility of the implant.

21. The method of claim 15 wherein the implant is an intraoccular lens.

22. A method of evaluating an adjustable optical implant comprising:

a) Inserting an adjustable optical implant into a test subject.

b) Adjusting the optical properties of said implant in vivo; and

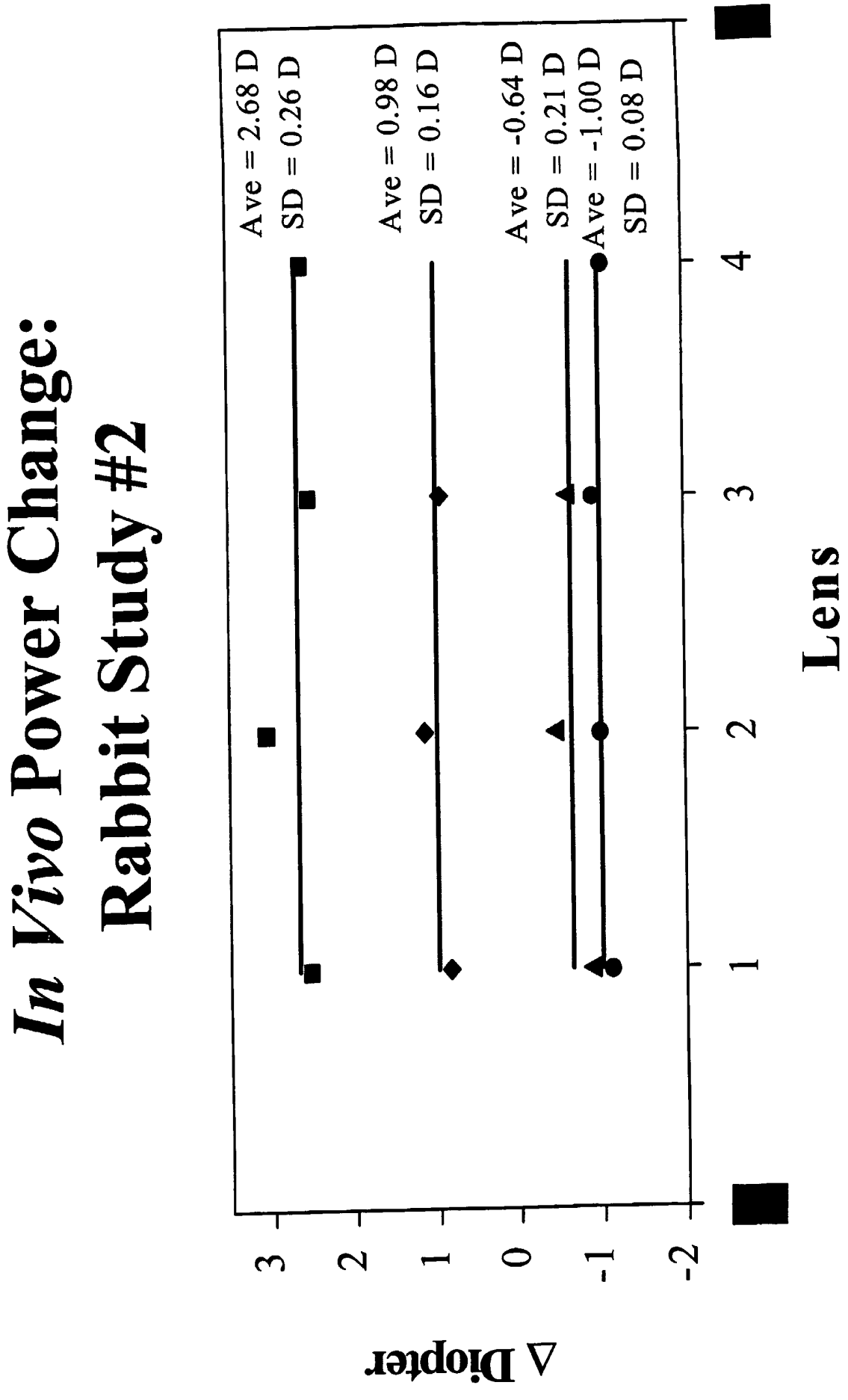
c) Evaluating the change in optical properties in the implant in vivo.

23. The method of claim 22 wherein the adjusting of the optical properties of the implant is accomplished by exposing at least a portion of said implant to an external stimulus.

24. The method of claim 23 wherein the external stimulus is light.

25. The method of claim 23 wherein the external stimulus is ultraviolet light.

26. The method of claim 22 wherein the implant is an intraoccular lens.


In Vivo Power Change:
Rabbit Study #2
Ave = 2.68 D
SD = 0.26 D
Ave = 0.98 D
SD = 0.16 D
Ave = -0.64 D
SD = 0.21 D
Ave = -1.00 D
SD = 0.08 D
3
2
1
0
-1
-2
Δ Diopter
1
2
3
4
Lens

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/23623

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A61F 2/16
US CL : 623/6.22, 912

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)
U.S. : 623/6.22, 912, 6.11-6.12, 6.56, 6.58-6.6

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 practicable, 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. |
|---|---|---|
| Y | WO 00/41650 A (JETHMALANI et al.) 20 July 2000 (10.07.2000): abstract; figures; page 12, lines 3-5 and 15-21; page 17, lines 20-30; page 18, lines 3-8; page 19, lines 25-32; page 21, lines 9-12; page 22, lines 8-10; etc. | 1-26 |
| Y | US 5,968,095 A (NORRBY) 19 October 1999 (19.10.1999): column 5, lines 23-27. | 9-14 and 22-26 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
20 September 2002 (20.09.2002)

Date of mailing of the international search report
24 DEC 2002

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703)305-3230

Authorized officer
Dave Willse
Telephone No. (703) 308-0858

Form PCT/ISA/210 (second sheet) (July 1998)

# INTERNATIONAL SEARCH REPORT

PCT/US02/23623

**Continuation of Item 4 of the first sheet:**
The title is too long under PCT Rule 4.3. The new title is:

INTRAOCULAR LENSES WITH POWER ADJUSTABILITY IN VIVO