US 20070233240A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2007/0233240 A1

Frank et al. (43) Pub. Date: Oct. 4, 2007

(54) INTRAOCULAR LENS IMPLANT

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(21) Appl. No.: **11/725,190**

(22) Filed: **Mar. 16, 2007**

Related U.S. Application Data

(63) Continuation-in-part of application No. 11/243,952, filed on Oct. 4, 2005.
Continuation-in-part of application No. 11/409,218, filed on Apr. 20, 2006, and which is a continuation-in-part of application No. 11/243,952, filed on Oct. 4, 2005.
Continuation-in-part of application No. 11/636,114, filed on Dec. 7, 2006, and which is a continuation-in-part of application No. 11/243,952, filed on Oct. 4, 2005, and which is a continuation-in-part of application No. 11/409,218, filed on Apr. 20, 2006.
Continuation-in-part of application No. 11/639,049, filed on Dec. 13, 2006, and which is a continuation-in-part of application No. 11/243,952, filed on Oct. 4, 2005, and which is a continuation-in-part of application No. 11/409,218, filed on Apr. 20, 2006.

(60) Provisional application No. 60/783,601, filed on Mar. 17, 2006. Provisional application No. 60/616,262, filed on Oct. 5, 2004. Provisional application No. 60/673,172, filed on Apr. 20, 2005. Provisional application No. 60/673,600, filed on Apr. 21, 2005. Provisional application No. 60/843,942, filed on Sep. 11, 2006. Provisional application No. 60/783,307, filed on Mar. 17, 2006. Provisional application No. 60/843,942, filed on Sep. 11, 2006.

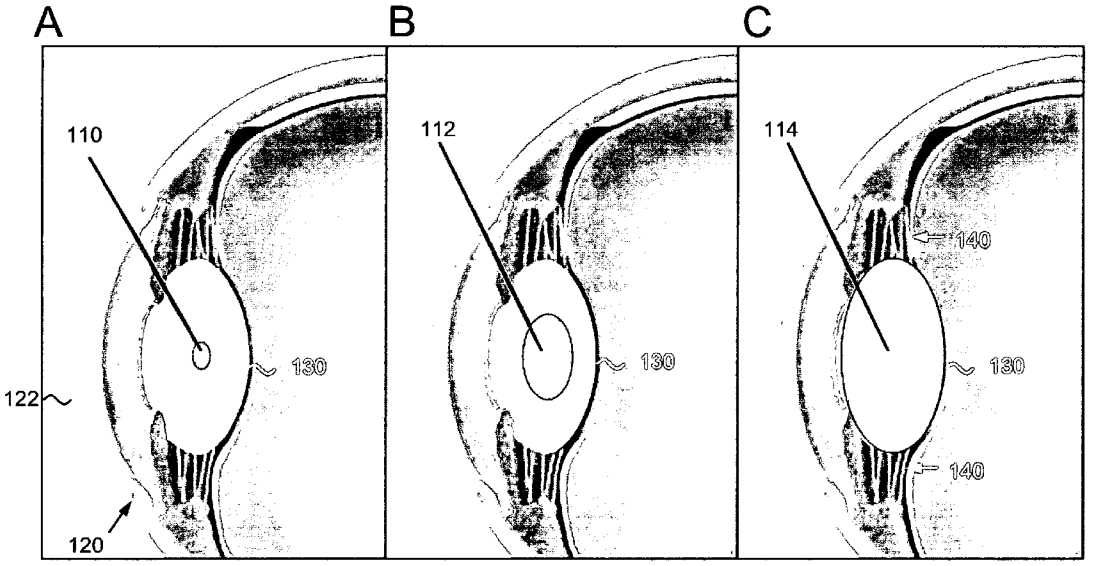
Publication Classification

(51) **Int. Cl.**
A61F 2/16 (2006.01)

(52) **U.S. Cl.** **623/6.59**

(57) ABSTRACT

The present invention provides a hydrogel-based intraocular lens (IOL) implant that can covalently attach to a lens capsule on implantation into an eye. The inventive IOL has a high refractive index, high elasticity, and is of a similar size to a naturally occurring lens. In addition, the IOL can be implanted in a smaller, dehydrated state, allowing the IOL to be placed in the lens capsule with a small incision (up to about 1/10 the volume of the IOL). Exposure to fluid can then initiate rapid swelling of the dried polymer to the shape and dimensions of a natural lens, with full occupation of the lens capsule. Upon equilibrium swelling, the IOL can then make contact with the inner aspect of the lens capsule and covalently bind to it. By this attachment process, the IOL may accommodate in a manner identical to that of the natural lens.



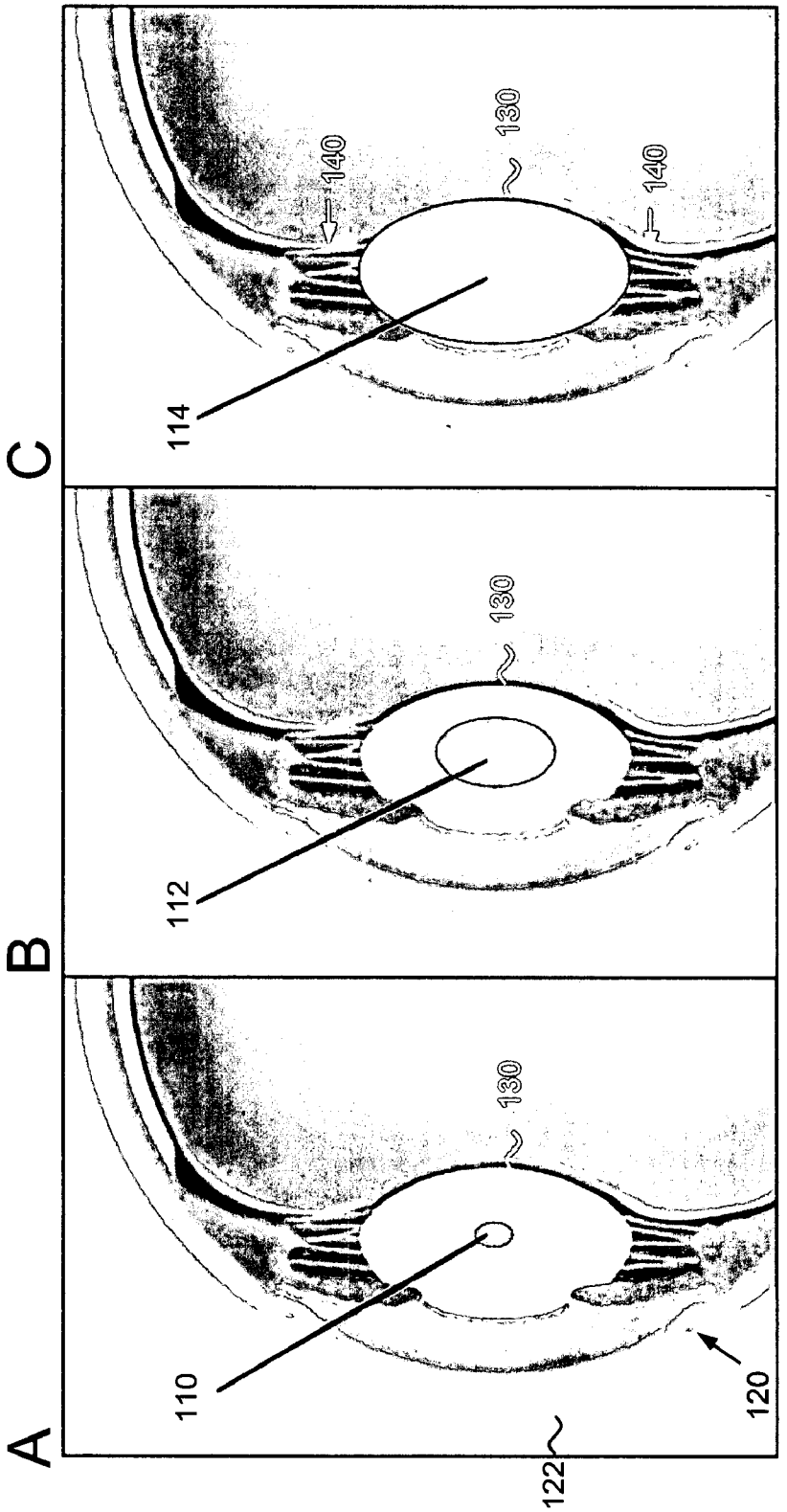


FIG. 1

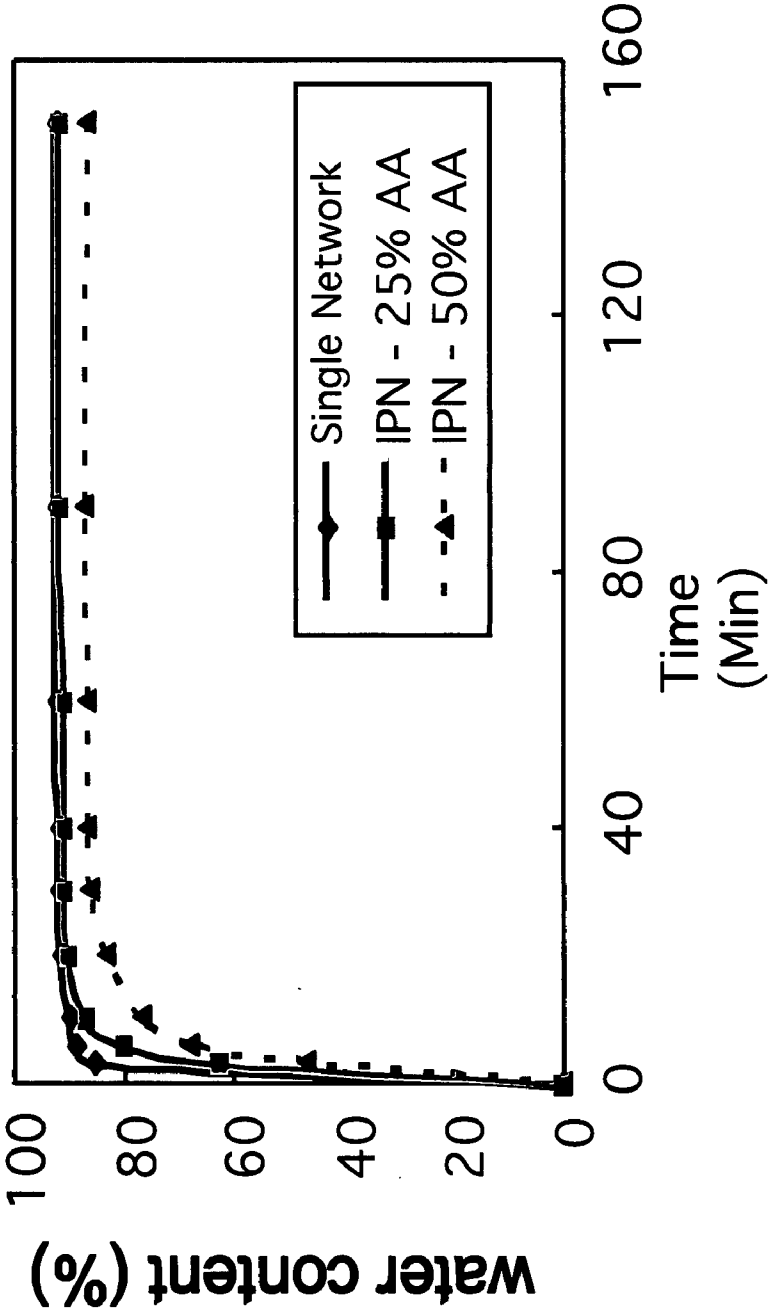

water content (%)
100
80
60
40
20
0
0
40
80
120
160
Time (Min)
Single Network
IPN - 25% AA
IPN - 50% AA

FIG. 2

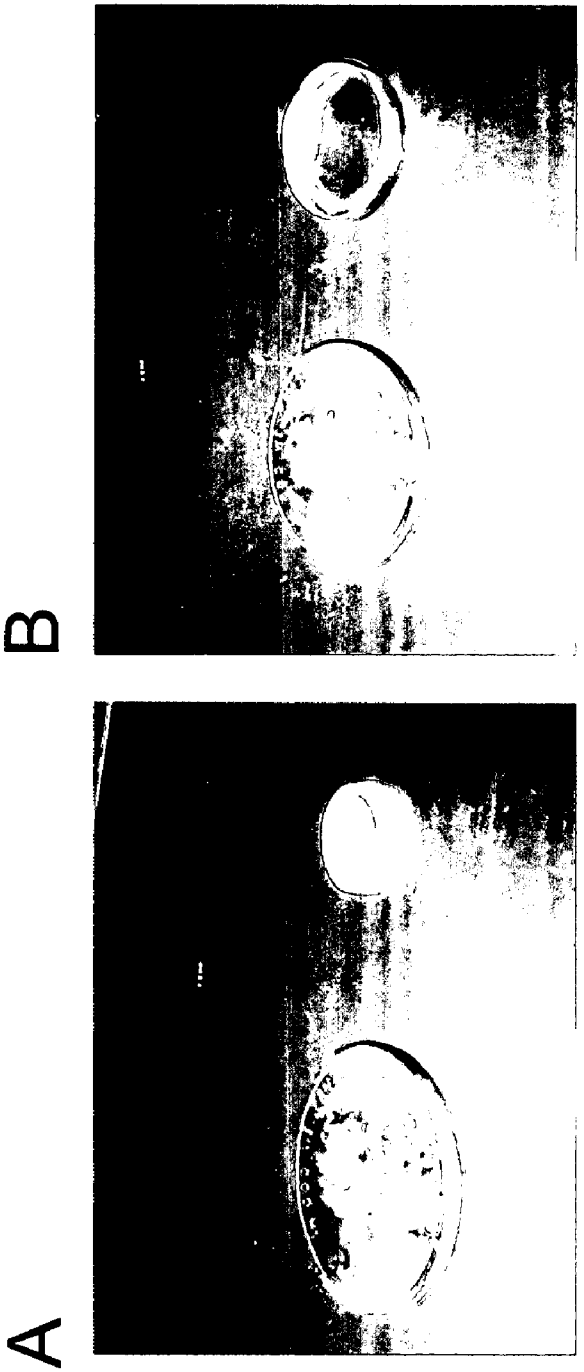


FIG. 3

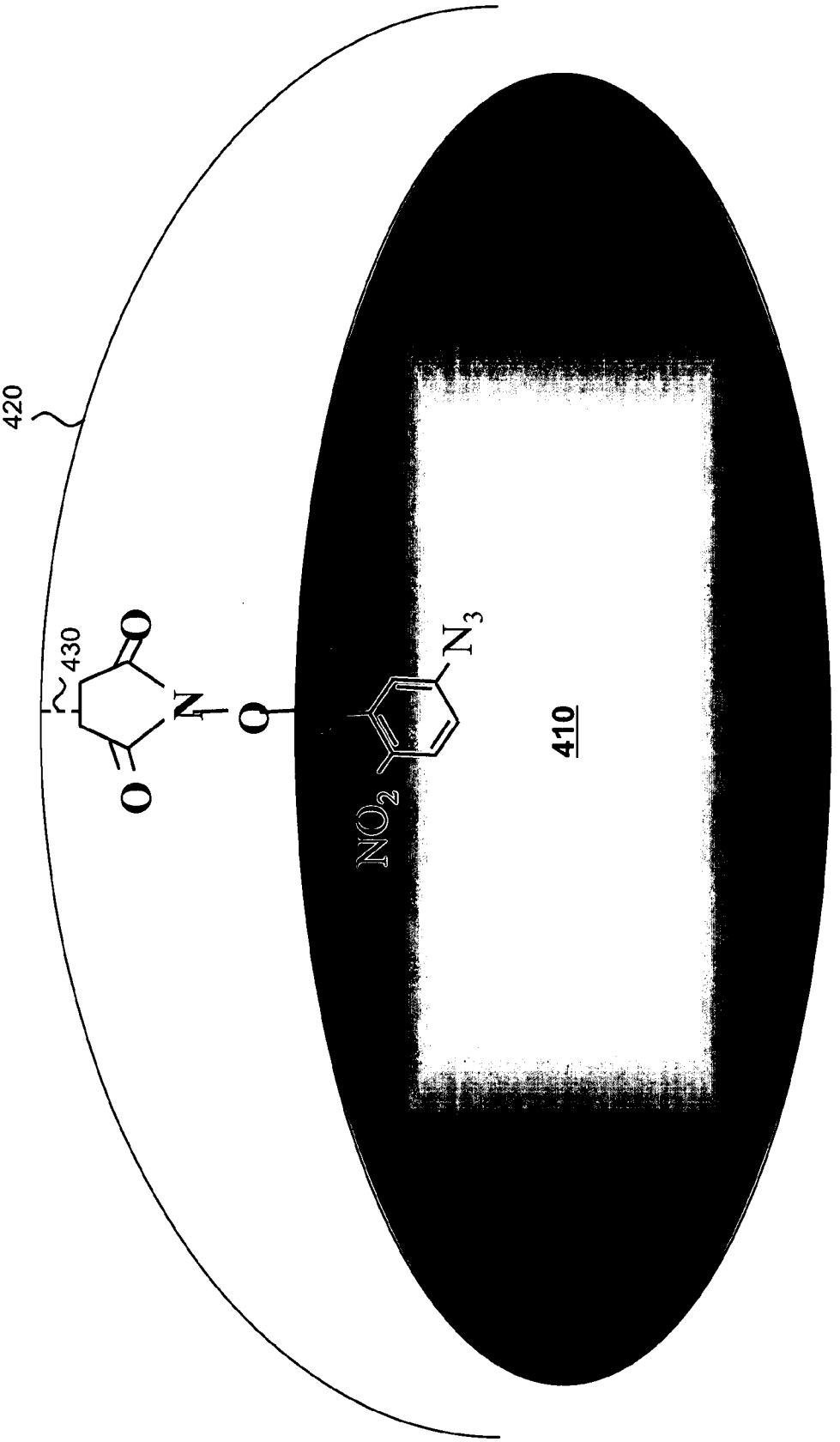


FIG. 4

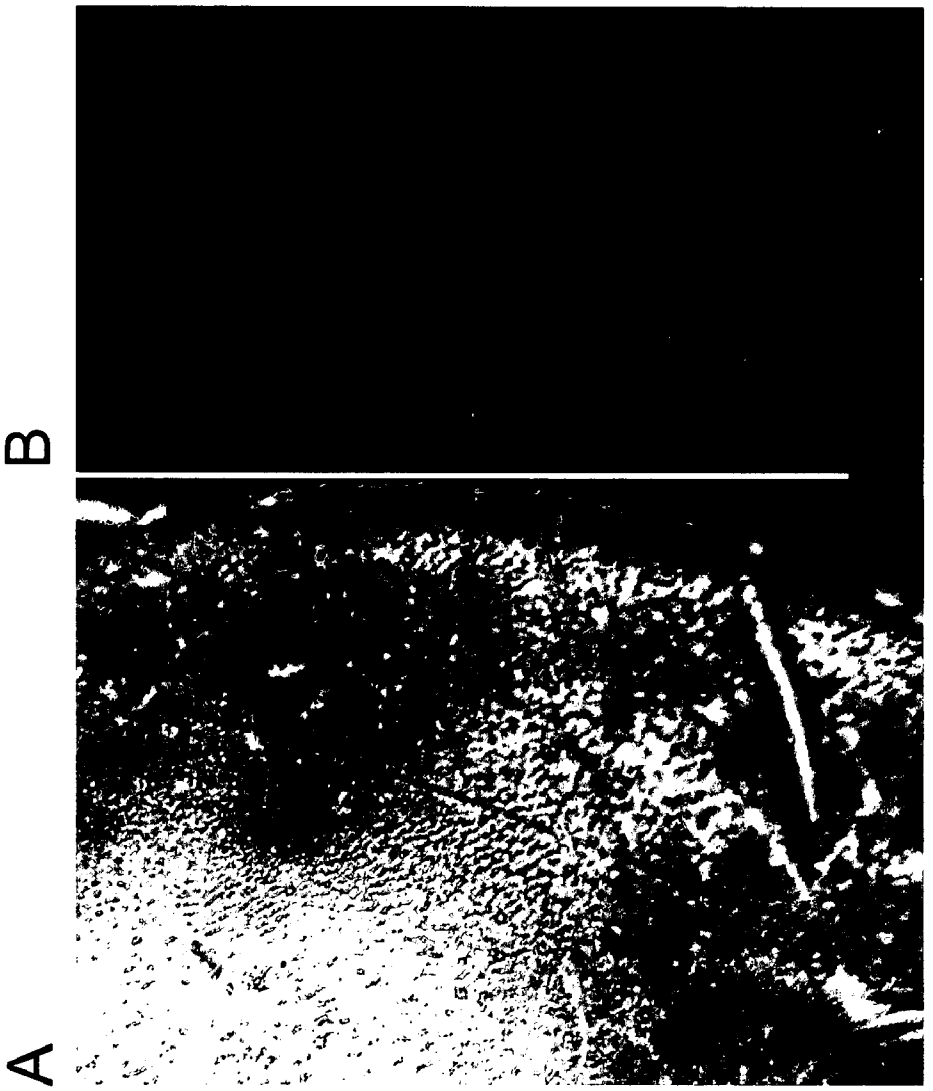


FIG. 5

INTRAOCULAR LENS IMPLANT

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority from U.S. Provisional Patent Application No. 60/783,601, filed Mar. 17, 2006, which is incorporated herein by reference.

[0002] This application is a continuation-in-part of U.S. patent application Ser. No. 11/243,952, filed Oct. 4, 2005, which claims priority from U.S. Provisional Patent Application No. 60/616,262, filed Oct. 5, 2004, and from U.S. Provisional Patent Application No. 60/673,172, filed Apr. 20, 2005, all of which are incorporated by reference herein.

[0003] This application is also a continuation-in-part of U.S. application Ser. No. 11/409,218, filed Apr. 20, 2006, which claims priority from U.S. Provisional Patent Application No. 60/673,600, filed Apr. 21, 2005, and which is a continuation-in-part of U.S. patent application Ser. No. 11/243,952, filed Oct. 4, 2005, all of which are incorporated by reference herein.

[0004] This application is also a continuation-in-part of U.S. patent application Ser. No. 11/636,114, filed Dec. 7, 2006, which claims priority from U.S. Provisional Application Nos. 60/843,942, filed on Sep. 11, 2006, and 60/783,307, filed Mar. 17, 2006, both of which are incorporated herein by reference. U.S. patent application Ser. No. 11/636,114 is a continuation-in part of U.S. patent application Ser. No. 11/243,952, filed Oct. 4, 2005, and of U.S. application Ser. No. 11/409,218, filed Apr. 20, 2006, both of which are incorporated by reference herein.

[0005] This application is also a continuation-in-part of U.S. application Ser. No. 11/639,049, filed Dec. 13, 2006, which claims priority from U.S. Provisional Patent Application No. 60/843,942, filed Sep. 11, 2006, both of which are incorporated herein by reference. U.S. application Ser. No. 11/639,049 is a continuation-in part of U.S. patent application Ser. No. 11/243,952, filed Oct. 4, 2005 and of U.S. application Ser. No. 11/409,218, filed Apr. 20, 2006

FIELD OF THE INVENTION

[0006] The present invention relates generally to intraocular lens implants. More particularly, the present invention relates to intraocular lens implants that can covalently bind to a lens capsule.

BACKGROUND

[0007] Cataract extraction is among the most commonly performed operations in the United States and the world. There are an estimated 20 million people worldwide who suffer from cataracts. In the United States alone, 1.5 million people have cataract surgery each year. Following removal of a cataractous lens, an intraocular lens (IOL) implant is typically implanted within the lens capsule in order to mimic the refractive function of healthy natural lens.

[0008] Current IOLs are made from hard and non-swellable materials such as poly(methyl methacrylate) (PMMA) and silicone, which do not accommodate when placed in the eye. They are typically secured within the lens capsule through two polymeric haptics, which extend radially from the device. The most recent innovation involves "foldable" IOLs that permit smaller incisions during their implantation. Some are able to facilitate accommodation, but not by the eye's natural mechanism. Another concern with current IOLs is their inability to prevent secondary opacification of the posterior capsule, thus requiring laser treatment. Accordingly, there is a need in the art to develop an IOL implant that can be implanted with a small incision, can prevent secondary opacification of the posterior capsule, and that can accommodate by the eye's natural mechanism.

SUMMARY OF THE INVENTION

[0009] The present invention provides a hydrogel-based intraocular lens (IOL) implant that can covalently attach to a lens capsule on implantation into an eye. The covalent binding of the IOL to the lens capsule is preferably mediated by active functional groups covalently linked to a surface of a hydrogel, for example through a photoreactive azide. The active functional groups are preferably N-hydroxysuccinimide functional groups tethered to the surface of the hydrogel. This tethering may be accomplished by use of a bifunctional chemical linker such as 5-azido-2-nitrobenzoic acid N-hydroxysuccinimide ester. Exposure to UV light converts the azide group of this linker to reactive nitrene groups that bind to the surface of hydrogels. This leaves the N-hydroxysuccinimide (NHS) groups free to form peptide linkages with proteins in the lens capsule via free amines on the lens capsule proteins. For example, the NHS groups may bind to collagen, such as collagen type I and collagen type III, which is naturally present in the lens capsule. The adhesion of the hydrogel to proteins by this esterification process occurs rapidly in aqueous solution at pH 7.4 if the materials are brought into close, sustained contact.

[0010] Preferably, the IOL has a high refractive index, high elasticity, and is of a similar size to a naturally occurring lens. Also preferably, the IOL can be implanted in a smaller, dehydrated state, allowing the IOL to be placed in the lens capsule with a small incision (up to about 1/10 the volume of the IOL). Exposure to fluid can then initiate rapid swelling of the dried polymer to the shape and dimensions of a natural lens, with full occupation of the lens capsule. Upon equilibrium swelling, the IOL can then make contact with the inner aspect of the lens capsule and covalently bind to it via the active-ester surface functionalization of the hydrogel. By this attachment process, the IOL will be in a position to accommodate in a manner identical to that of the natural lens.

BRIEF DESCRIPTION OF THE FIGURES

[0011] The present invention together with its objectives and advantages will be understood by reading the following description in conjunction with the drawings, in which:

[0012] FIG. **1** shows a schematic of swelling of an IOL according to the present invention on implantation into a lens capsule.

[0013] FIG. **2** shows time-dependence of the water content of a single network PEG hydrogels and PEG/PAA IPNs with different amounts of acrylic acid (AA). The hydrogels were placed in deionized water in the dry state at time=0 and then weighed at regular intervals.

[0014] FIG. **3** shows appearance of a PEG/PAA IPN based on PEG MW 4600 in the dried state (a) and after being immersed for 40 minutes in PBS, pH 7.4.

[0015] FIG. **4** shows a schematic of covalent binding of an IOL according to the present invention to a lens capsule.

[0016] FIG. **5** shows binding of collagen-fluorescein isothiocyanate (FITC) to an IOL according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0017] The present invention provides a hydrogel-based IOL capable of covalently binding to a lens capsule upon implantation into an eye. The hydrogel may be composed of any polymer capable of rapid swelling upon hydration. A schematic of swelling of an IOL on implantation into a lens capsule is shown in FIG. **1**. FIG. **1**A shows a dehydrated IOL **110** that has been implanted through incision **120** in cornea **122** into lens capsule **130**. In FIG. **1**B, dehydrated IOL becomes partially hydrated **112** on exposure to the aqueous environment of the lens capsule **130**. In FIG. **1**C, the IOL is fully swollen **114** within lens capsule **130**. Fully swollen IOL **114** can then be controlled by zonules **140** to accommodate the curvature of the lens to different distances.

[0018] Preferably, the hydrogel can swell from a dehydrated state to a rehydrated state within about 2 hours. Also preferably, the volume and weight ratios of dehydrated versus rehydrated hydrogel are between about 10:90 (dry:swollen) and about 40:60 (dry:swollen). The water content of a dehydrated hydrogel is preferably between about 0 and about 30%, whereas the rehydrated water content of the hydrogel is preferably between about 60 and about 90%. FIG. **2** shows time-dependence of the water content of a single network PEG hydrogels and PEG/PAA IPNs with different amounts of acrylic acid (AA). The hydrogels were placed in deionized water in the dry state at time=0 and then weighed at regular intervals. This graphs shows that both single network PEG hydrogels and PEG/PAA IPNs swell rapidly in deionized water. FIG. **3** shows that PEG/PAA IPNs also swell rapidly under physiological conditions. (FIG. **3**A shows the hydrogel in a dehydrated state. FIG. **3**B shows the hydrogel 40 minutes after hydration with PBS pH 7.4. A penny is shown in both parts of the figure for comparison of size).

[0019] The IOLs are preferably made of homopolymer, copolymer, or interpenetrating networks based on poly(ethylene glycol) (PEG) and/or poly(acrylic acid) (PAA). Due to their high degree of hydrophilicity, polymer networks of PEG and PAA rapidly swell upon exposure to water. Moreover, at physiologic pH (7.4 to 7.6), the carboxylic acid groups on PAA (pKa 4.7) ionize, causing the polymer chains to repel each other and the network to take up even more water. Both PEG and PAA are biocompatible. Other polymer components suitable for practicing the invention include PEG and PAA derivatives as well as poly(vinyl alcohol), poly(2-hydroxy ethylacrylate), poly(2-hydroxyethyl methacrylate), poly(methacrylic acid) and their derivatives.

[0020] The hydrogels can be polymerized in elliptical molds or reshaped after polymerization by lathing or by use of lasers such as a femtosecond laser. A typical hydrated lens is about 9.5 mm wide and 4.0-4.5 mm thick. Partially dehydrated lenses can be around 7.0 mm wide and 2.0 mm thick, and fully dehydrated lenses can be as small as 2.0 mm wide and less than 1.0 mm thick.

[0021] When PAA is polymerized in the presence of an existing PEG-diacrylate hydrogel network, an interpenetrating polymer network (IPN) structure is formed. These materials exhibit reversible, reproducible, swelling behavior with dehydration and hydration in aqueous solution. Details on PAA/PEG IPNs can be found in U.S. patent application Ser. No. 11/243952, which is incorporated by reference herein.

[0022] Like a human lens, hydrogels based on PEG and PAA have a low elastic modulus at physiologic pH, which allows IOLs made from these materials to accommodate by ciliary muscle-mediated circumferential tension on the lens capsule. High MW PEG macromers (≧8000) have low elastic moduli and are suitable for use in these devices. In addition, PAA polymers with low crosslinking density (≦mol 1%) and high water content (≧80%) have low elastic moduli. The preferred elastic modulus values are on the order of between about 1 kPa and about 250 kPa. Table 1 shows hydrogels of varying polymer composition and formulation. Depending on the type of polymer (PEG or PAA), its molecular weight (8000 kDa or 14000 kDa), or whether it is a homopolymer, copolymer, or an interpenetrating network, hydrogels of various rehydrated water content (84%-96%), tensile strength (σ_{max}) and elastic modulus (E_0) values (50 kPa-250 kPa) can be synthesized. The water content of a given hydrogel can be raised or lowered by changing the molecular weight or relative composition of the components of a hydrogel, or by simply changing the amount of polymer precursor (monomer) at the time of polymerization. The elastic modulus of the human lens is roughly 1 kPa.

TABLE 1

Properties of PEG and PAA-based hydrogels

specimen	WC (%)	σ_{max} (MPa)	E_o (MPa)
PAA	95.5 ± 1.7	0.068 ± 0.015	0.050 ± 0.001
PEG(8.0k)	90.5 ± 1.2	0.273 ± 0.036	0.199 ± 0.075
PEG(14.0k)	95.1 ± 1.2	0.073 ± 0.070	0.062 ± 0.005
PEG(14.0k)/PAA*	84.3 ± 1.7	0.247 ± 0.046	0.177 ± 0.013
PEG(8.0k)-co-PAA**	90.54 ± 0.08	0.275 ± 0.025	0.250 ± 0.013

*interpenetrating network
**copolymer network

[0023] Preferably, the hydrogels are engineered to match the refractive index of the human lens (1.42) by modulation of the relative content of PEG (1.46), PAA (1.52) and water (1.33). The refractive index of the hydrogel can be modulated in either of two ways: (1) by increasing the relative polymer content and/or (2) by the addition of high refractive index additives as either a filler material or as a co-polymeric element. By increasing the content of PEG and PAA relative to water, the refractive index of the material will be higher due to a greater proportion of materials (relative to water) with high refractive index. The range of preferred refractive index values are from about 1.33 to about 1.42. The swollen weight ratios of water to polymer in these combinations can range from about 1:1 to about 1:10.

[0024] To mediate covalent binding of the IOL to the lens capsule, an azide-active-ester chemical containing a photoreactive azide on one end and an N-hydroxysuccinimide (NHS) group (which can covalently bind to cell adhesion proteins and peptides) on the other end can be used. An

example of such a linker is 5-azido-2-nitrobenzoic acid N-hydroxysuccinimide ester. Another example of a bifunctional linker is 6-(4-azido-2-nitrophenylamino)hexanoic acid N-hydroxysuccinimide ester, which has a longer spacer arm between the reactive end groups. In addition, novel spacer arms that are both longer and more hydrophilic can be synthesized by conjugating 5-azido-2-nitrobenzoic acid N-hydroxysuccinimide ester with amine-terminated PEG macromers, which can then be further functionalized to possess NHS moieties that can bind to protein/peptides. In one example, 5 mg of 5-azido-2-nitrobenzoic acid N-hydroxysuccinimide ester is dissolved in 1 mL of N,N-dimethylformamide (DMF) (See Matsuda et al. (1990) in a paper entitled "*Development of micropatterning technology for cultured cells*" and published in "*ASAIO Transactions* 36(3):M559-562"). This solution is then evenly spread over the hydrogel surface and exposed to UV for 5 minutes after the hydrogel surface is air-dried. Upon UV irradiation, the phenyl azide group reacts to form covalent bonds with the hydrogel surface. The irradiated surfaces are then thoroughly rinsed with solvent to remove any unreacted chemicals from the surface. This results in hydrogels with exposed NHS end groups on the surface. These exposed NHS end groups can then covalently bind to a lens capsule upon implantation of the IOL into the lens capsule, as shown in FIG. **4**.

[0025] In FIG. **4**, swollen IOL 410, which has been functionalized with 5-azido-2-nitrobenzoyloxy-N-hydroxysuccinimide, makes sustained contact with lens capsule **420**. This in turn allows the functionalized IOL to covalently bind **430** to the lens capsule **420**. Preferably, the functionalized IOL covalently binds to the lens capsule through free amines on proteins present in the lens capsule.

[0026] Hydrogels that have been functionalized with 5-azido-2-nitrobenzoyloxy-N-hydroxysuccinimide can bind collagen, a protein normally found in the lens capsule, as shown in FIG. **5**. In FIG. **5**A, an IOL according to the present invention was incubated in a 0.1% collagen-FITC solution for 24 hours at 37 degrees C. In contrast to FIG. **5**B, which was not reacted with collagen-FITC, FIG. **5**A shows binding of collagen-FITC to the surface of the IOL. In this experiment, collagen type I was used.

[0027] IOLs according to the present invention may be used for any condition whereby the natural lens is damaged, missing, or defective. Examples include lens replacement for people suffering from cataracts and for people with age-related hardening of the lens (presbyopia).

[0028] In addition, IOLs according to the present invention preferably prevent secondary opacification of the posterior capsule. It does so by eliminating the potential space between the lens capsule and the lens element in which opacification typically occurs in vivo.

[0029] As one of ordinary skill in the art will appreciate, various changes, substitutions, and alterations could be made or otherwise implemented without departing from the principles of the present invention. Accordingly, the scope of the invention should be determined by the following claims and their legal equivalents.

What is claimed is:

1. An intraocular lens implant, comprising:

(a) a hydrogel; and

(b) active functional groups covalently linked to a surface of said hydrogel,

wherein said active functional groups mediate covalent binding of said intraocular lens implant to an eye's lens capsule upon implantation of said intraocular lens implant into said lens capsule.

2. The intraocular lens implant as set forth in claim 1, wherein said active functional groups comprise N-hydroxysuccinimide.

3. The intraocular lens implant as set forth in claim 1, wherein said active functional groups are covalently linked to said surface of said hydrogel through a photoreactive azide.

4. The intraocular lens implant as set forth in claim 3, wherein said photoreactive azide comprises 5-Azido-2-nitrobenzoic acid N-hydroxysuccinimide ester.

5. The intraocular lens implant as set forth in claim 1, wherein said active functional groups covalently bind to proteins in said lens capsule.

6. The intraocular lens implant as set forth in claim 5, wherein said proteins are at least one of collagen, collagen type I and collagen type III

7. The intraocular lens implant as set forth in claim 1, wherein said active functional groups covalently bind to said lens capsule via free amines on proteins present in said lens capsule.

8. The intraocular lens implant as set forth in claim 1, wherein said hydrogel can swell from a dehydrated state to a rehydrated state within about 2 hours.

9. The intraocular lens implant as set forth in claim 1, wherein the weight and volume ratios of said hydrogel in a dehydrated versus a hydrated state are between about 10:90 and about 40:60.

10. The intraocular lens implant as set forth in claim 1, wherein water content of said hydrogel in a dehydrated state is between about 0 and about 30%.

11. The intraocular lens implant as set forth in claim 1, wherein water content of said hydrogel in a rehydrated state is between about 60 and about 90%.

12. The intraocular lens implant as set forth in claim 1, wherein said hydrogel is a homopolymer, copolymer or interpenetrating network based on at least one of poly(ethylene glycol), poly(acrylic acid), poly(vinyl alcohol), poly(2-hydroxy ethylacrylate), poly(2-hydroxyethyl methacrylate), poly(methacrylic acid) and their derivatives.

13. The intraocular lens implant as set forth in claim 1, wherein said hydrogel has an elastic modulus of between about 1 kPa and about 250 kPa.

14. The intraocular lens implant as set forth in claim 1, wherein said hydrogel has a refractive index of between about 1.33 to about 1.42.

* * * * *