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(54) Title: OPHTHALMIC AND OTORHINOLARYNGOLOGICAL DEVICE MATERIALS CONTAINING AN ALKYL ETHOXYLATE

(57) Abstract: Disclosed are soft, high refractive index, acrylic device materials. The materials contain a functionalized alkyl ethoxylate to reduce glistenings.

OPHTHALMIC AND OTORHINOLARYNGOLOGICAL DEVICE MATERIALS CONTAINING AN ALKYL ETHOXYLATE

Field of the Invention

This invention is directed to improved ophthalmic and otorhinolaryngological device materials. In particular, this invention relates to soft, high refractive index acrylic device materials that have improved glistening resistance.

Background of the Invention

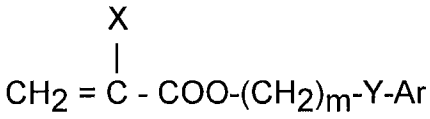
With the recent advances in small-incision cataract surgery, increased emphasis has been placed on developing soft, foldable materials suitable for use in artificial lenses. In general, these materials fall into one of three categories: hydrogels, silicones, and acrylics.

In general, hydrogel materials have a relatively low refractive index, making them less desirable than other materials because of the thicker lens optic necessary to achieve a given refractive power. Conventional silicone materials generally have a higher refractive index than hydrogels, but tend to unfold explosively after being placed in the eye in a folded position. Explosive unfolding can potentially damage the corneal endothelium and/or rupture the natural lens capsule. Acrylic materials are desirable because they typically have a high refractive index and unfold more slowly or controllably than conventional silicone materials.

U.S. Patent No. 5,290,892 discloses high refractive index, acrylic materials suitable for use as an intraocular lens ("IOL") material. These acrylic materials contain, as principal components, two aryl acrylic monomers. The IOLs made of these acrylic materials can be rolled or folded for insertion through small incisions.

U.S. Patent No. 5,331,073 also discloses soft acrylic IOL materials. These materials contain as principal components, two acrylic monomers which are defined by the properties of their respective homopolymers. The first monomer is defined as one in which its homopolymer has a refractive index of at least about 1.50. The second monomer is defined as one in which its homopolymer has a glass transition temperature less than about 22 °C. These IOL materials also contain a cross-linking component. Additionally, these materials may optionally contain a fourth constituent, different from the first three constituents, which is derived from a hydrophilic monomer. These materials preferably have a total of less than about 15% by weight of a hydrophilic component.

U.S. Patent No. 5,693,095 discloses foldable, high refractive index ophthalmic lens materials containing at least about 90 wt.% of only two principal components: one aryl acrylic hydrophobic monomer and one hydrophilic monomer. The aryl acrylic hydrophobic monomer has the formula



wherein: X is H or CH_3 ;
m is 0-6;
Y is nothing, O, S, or NR, wherein R is H, CH_3, C_nH_{2n+1} (n=1-10), iso-OC_3H_7, C_6H_5, or $CH_2C_6H_5$; and
Ar is any aromatic ring which can be unsubstituted or substituted with CH_3, C_2H_5, n-C_3H_7, iso-C_3H_7, OCH_3, C_6H_{11}, Cl, Br, C_6H_5, or $CH_2C_6H_5$.

The lens materials described in the '095 Patent preferably have a glass-transition temperature ("T_g") between about –20 and +25 °C.

Flexible intraocular lenses may be folded and inserted through a small incision. In general, a softer material may be deformed to a greater extent so that it can be inserted through an increasingly smaller incision. Soft acrylic or methacrylic materials typically do not have an appropriate combination of

strength, flexibility and non-tacky surface properties to permit IOLs to be inserted through an incision as small as that required for silicone IOLs.

Polyethylene glycol (PEG) dimethacrylates are known to improve glistening resistance of hydrophobic acrylic formulations. See, for example, U.S. Patent Nos. 5,693,095; 6,528,602; 6,653,422; and 6,353,069. Both the concentration and molecular weight of PEG dimethacrylates have an impact on glistening performance. Generally, use of higher molecular weight PEG dimethacrylates (1000 MW) yield copolymers with improved glistening performance at low PEG concentrations (10 – 15 wt%), as compared to lower molecular weight PEG dimethacrylates (<1000 MW). However, low PEG dimethacrylate concentrations are desirable to maintain a high refractive index copolymer. Addition of PEG dimethacrylates also tends to decrease the modulus and tensile strength of the resulting copolymer. Also, higher molecular weight PEG dimethacrylates are generally not miscible with hydrophobic acrylic monomers.

Summary of the Invention

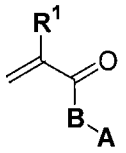
Improved soft, foldable acrylic device materials which are particularly suited for use as IOLs, but which are also useful as other ophthalmic or otorhinolaryngological devices, such as contact lenses, keratoprostheses, corneal rings or inlays, otological ventilation tubes and nasal implants, have been discovered. These polymeric materials comprise a functionalized alkyl ethoxylate.

Among other factors, the present invention is based on the finding that use of alkyl ethoxylate monomers in acrylic intraocular lens formulations reduces or eliminates temperature-induced glistening formation in hydrophobic acrylic copolymers. The subject monomers allow synthesis of glistening resistant, low equilibrium water content, high refractive index IOLs.

Detailed Description of the Invention

Unless indicated otherwise, all component amounts are presented on a % (w/w) basis ("wt.%").

The device materials of the present invention are copolymers comprising a) a monofunctional acrylate or methacrylate monomer [1], b) a difunctional acrylate or methacrylate cross-linker [2], and c) a functinoalized alkyl ethoxylate [3]. The device materials may contain more than one monomer [1], more than one monomer [2], and more than one monomer [3]. Unless indicated otherwise, references to each ingredient are intended to encompass multiple monomers of the same formula and references to amounts are intended to refer to the total amount of all monomers of each formula.



[1]

wherein

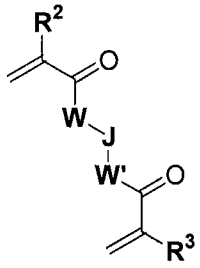
B = $O(CH_2)_n$, $NH(CH_2)_n$, or $NCH_3(CH_2)_n$;

R^1 = H, CH_3, CH_2CH_3, or CH_2OH;

n = 0 - 12;

A = C_6H_5 or $O(CH_2)_mC_6H_5$, where the C_6H_5 group is optionally substituted with $-(CH_2)_nH$, $-O(CH_2)_nH$, $-CH(CH_3)_2$, $-C_6H_5$, $-OC_6H_5$, $-CH_2C_6H_5$, F, Cl, Br, or I; and

m = 0 – 22;



[2]

wherein

R^2, R^3 independently = H, CH_3, CH_2CH_3, or CH_2OH;

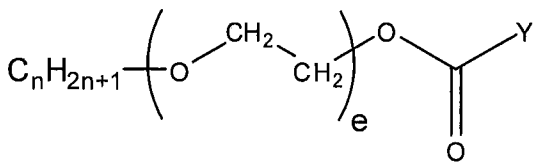
W, W' independently = $O(CH_2)_d$, $NH(CH_2)_d$, $NCH_3(CH_2)_d$, $O(CH_2)_dC_6H_4$, $O(CH_2CH_2O)_dCH_2$, $O(CH_2CH_2CH_2O)_dCH_2$, $O(CH_2CH_2CH_2CH_2O)_dCH_2$, or nothing;

J = $(CH_2)_a$, $O(CH_2CH_2O)_b$, O, or nothing, provided that if W and W' = nothing, then J ≠ nothing;

d = 0 - 12;

a = 1 – 12;

b = 1 – 24;

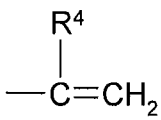
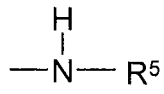


[3]

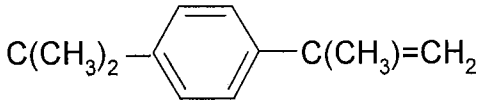
wherein:

n = 12, 13, or 14;

e = 1 – 100;

Y =  or  ;

R^4 = H, CH_3, CH_2CH_3, CH_2OH; and

$R^5 =$ $CH_2CH_2OC(=O)C(CH_3)=CH_2$ or .

Preferred monomers of formula [1] are those wherein:

B = $O(CH_2)_n$;

R^1 = H or CH_3;

n = 1 - 4; and

A = C_6H_5.

Preferred monomers of formula [2] are those wherein:

R^2, R^3 independently = H or CH_3;

W, W' independently = $O(CH_2)_d$, $O(CH_2)_dC_6H_4$, or nothing;

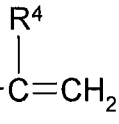
J = $O(CH_2CH_2O)_b$ or nothing, provided that if W and W' = nothing, then J ≠ nothing;

d = 0 - 6; and

b = 1 – 10.

Preferred monomers of formula [3] are those wherein:

e = 8 – 50;

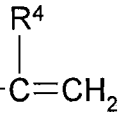
Y =  ; and

R^4 = H or CH_3.

Most preferred monomers of formulas [3] are those wherein

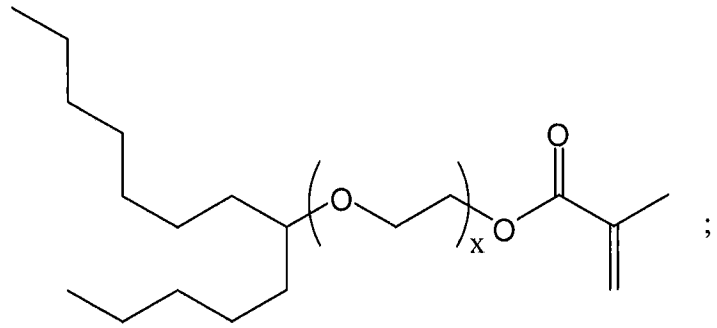
n = 13;

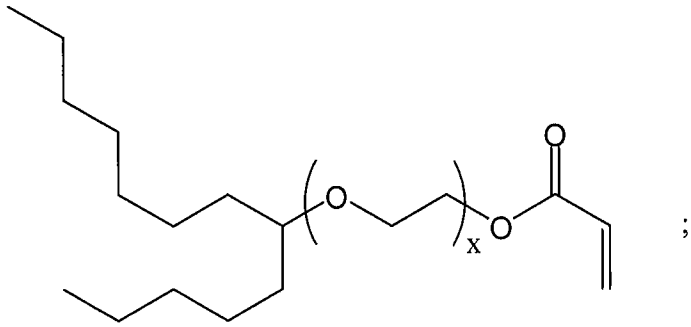
e = 15 – 40;

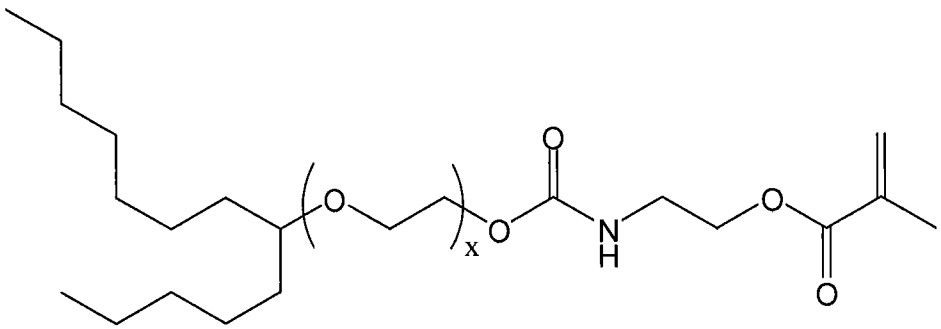
Y =  ; and

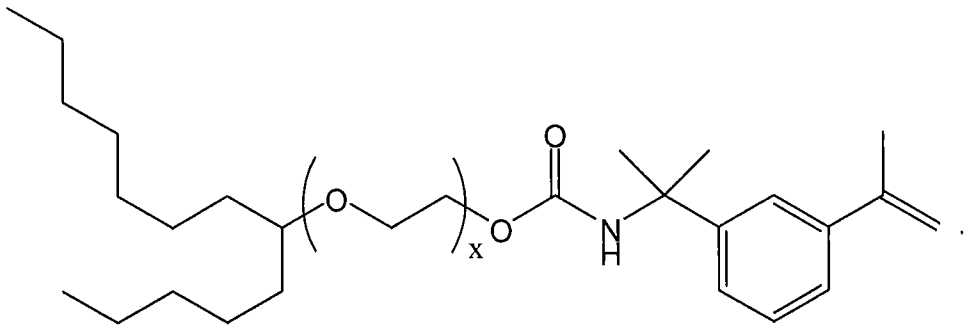
R^4 = H or CH_3.

Representative monomers of formula [3] include:


;


;


; and


.

Monomers of formula [1] are known and can be made by known methods. See, for example, U.S. Patent Nos. 5,331,073 and 5,290,892. Many monomers of formula [1] are commercially available from a variety of sources. Preferred monomers of formula [1] include benzyl methacrylate; 2-phenylethyl methacrylate; 3-phenylpropyl methacrylate; 4-phenylbutyl

methacrylate; 5-phenylpentyl methacrylate; 2-phenoxyethyl methacrylate; 2-(2-phenoxyethoxy)ethyl methacrylate; 2-benzyloxyethyl methacrylate; 2-(2-(benzyloxy)ethoxy)ethyl methacrylate; and 3-benzyloxypropyl methacrylate; and their corresponding acrylates.

Monomers of formula [2] are known and can be made by known methods, and are commercially available. Preferred monomers of formula [2] include ethylene glycol dimethacrylate ("EGDMA"); diethylene glycol dimethacrylate; triethylene glycol dimethacrylate; 1,6-hexanediol dimethacrylate; 1,4-butanediol dimethacrylate; 1,4-benzenedimethanol dimethacrylate; and their corresponding acrylates. Most preferred is 1,4-butanediol diacrylate.

Monomers of formula [3] can be made by known methods. For example, such monomers may be made by esterification reactions involving, for example, the alkyl ethoxylate alcohol and suitable carboxylic acids, acyl halides, or carboxylic acid anhydrides. For example, the alkyl ethoxylate can be heated with a carboxylic acid or carboxylic acid alkyl ester in the presence of a catalyst to form the desired ester, with water or low boiling alcohol as a byproduct which can be removed to drive the reaction to completion. The alkyl ethoxylate can also be treated with an acyl halide in the presence of a base such as triethylamine which serves as a hydrohalide acceptor. The alkyl ethoxylate can also be treated with a carboxylic acid anhydride in the presence of a base such as triethylamine or pyridine which catalyzes the reaction and neutralizes the acid formed.

The copolymeric materials of the present invention contain a total amount of monomer [1] from 75 to 97 %, preferably from 80 to 95 %, and most preferably from 80 – 93 %. The difunctional cross-linker [2] concentration is generally present in an amount from 0.5 – 3 %, and preferably 1 – 2 %.

The materials of the present invention have at least one monomer [3]. The total amount of monomer [3] depends on the desired physical properties for the device materials. The copolymeric materials of the present invention contain a total of at least 1 % and can contain as much as 20 % of monomer [3]. Preferably, the copolymeric device materials will contain from 1 to 15 % of monomer [3]. Most preferably, the device materials will contain from 1 to 10 % of monomer [3].

The copolymeric device material of the present invention optionally contains one or more ingredients selected from the group consisting of a polymerizable UV absorber and a polymerizable colorant. Preferably, the device material of the present invention contains no other ingredients besides the monomers of formulas [1] and [2], the monomer [3], and the optional polymerizable UV absorbers and colorants.

The device material of the present invention optionally contains reactive UV absorbers or reactive colorants. Many reactive UV absorbers are known. A preferred reactive UV absorber is 2-(2'-hydroxy-3'-methallyl-5'-methylphenyl)benzotriazole, commercially available as o-Methallyl Tinuvin P ("oMTP") from Polysciences, Inc., Warrington, Pennsylvania. UV absorbers are typically present in an amount from about 0.1 - 5 %. Suitable reactive blue-light absorbing compounds include those described in U.S. Patent No. 5,470,932. Blue-light absorbers are typically present in an amount from about 0.01 - 0.5 %. When used to make IOLs, the device materials of the present invention preferably contain both a reactive UV absorber and a reactive colorant.

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Blue-light absorbers are typically present in an amount from about 0.01 - 0.5 %. When used to make IOLs, the device materials of the present invention preferably contain both a reactive UV absorber and a reactive colorant.

In order to form the device material of the present invention, the chosen ingredients [1], [2], and [3], along with any of the optional ingredients, are combined and polymerized using a radical initiator to initiate polymerization by the action of either heat or radiation. The device material is preferably polymerized in de-gassed polypropylene molds under nitrogen or in glass molds.

Suitable polymerization initiators include thermal initiators and photoinitiators. Preferred thermal initiators include peroxy free-radical initiators, such as t-butyl (peroxy-2-ethyl)hexanoate and di-(tert-butylcyclohexyl) peroxydicarbonate (commercially available as Perkadox® 16 from Akzo Chemicals Inc., Chicago, Illinois). Particularly in cases where the materials of the present invention do not contain a blue-light absorbing chromophore, preferred photoinitiators include benzoylphosphine oxide initiators, such as 2,4,6-trimethyl-benzoyldiphenyl-phosphine oxide, commercially available as Lucirin® TPO from BASF Corporation (Charlotte, North Carolina). Initiators are typically present in an amount equal to about 5 % or less of the total formulation weight, and more preferably less than 2 % of the total formulation. As is customary for purposes of calculating component amounts, the initiator weight is not included in the formulation weight % calculation.

The particular combination of the ingredients described above and the identity and amount of any additional components are determined by the desired properties of the finished device material. In a preferred embodiment, the device materials of the present invention are used to make IOLs having an optic diameter of 5.5 or 6 mm that are designed to be compressed or stretched and inserted through surgical incision sizes of 2 mm or less. For example, the monomer [3] is combined with at least one mono-functional acrylate or methacrylate monomer [1] and a multifunctional acrylate or methacrylate

cross-linker [2] and copolymerized using a radical initiator in a suitable lens mold.

The device material preferably has a refractive index in the hydrated state of at least about 1.50, and more preferably at least about 1.53, as measured by an Abbe' refractometer at 589 nm (Na light source) and 25 °C. Optics made from materials having a refractive index lower than 1.50 are necessarily thicker than optics of the same power which are made from materials having a higher refractive index. As such, IOL optics made from materials with comparable mechanical properties and a refractive index lower than about 1.50 generally require relatively larger incisions for IOL implantation.

The proportions of the monomers to be included in the copolymers of the present invention should be chosen so that the copolymer has a glass transition temperature (T_g) not greater than about 37 °C, which is normal human body temperature. Copolymers having glass transition temperatures higher than 37 °C are not suitable for use in foldable IOLs; such lenses could only be rolled or folded at temperatures above 37 °C and would not unroll or unfold at normal body temperature. It is preferred to use copolymers having a glass transition temperature somewhat below normal body temperature and no greater than normal room temperature, e.g., about 20 - 25 °C, in order that IOLs made of such copolymers can be rolled or folded conveniently at room temperature. T_g is measured by differential scanning calorimetry at 10 °C/min., and is determined at the midpoint of the transition of the heat flux curve.

For IOLs and other applications, the materials of the present invention must exhibit sufficient strength to allow devices made of them to be folded or manipulated without fracturing. Thus the copolymers of the present invention will have an elongation of at least 80%, preferably at least 100%, and most preferably between 110 and 200%. This property indicates that lenses made of such materials generally will not crack, tear or split when folded. Elongation of polymer samples is determined on dumbbell shaped tension test specimens

with a 20 mm total length, length in the grip area of 4.88 mm, overall width of 2.49 mm, 0.833 mm width of the narrow section, a fillet radius of 8.83 mm, and a thickness of 0.9 mm. Testing is performed on samples at ambient conditions using an Instron Material Tester (Model No. 4442 or equivalent) with a 50 Newton load cell. The grip distance is set at 14 mm and a crosshead speed is set at 500 mm/minute and the sample is pulled until failure. The elongation (strain) is reported as a fraction of the displacement at failure to the original grip distance. Since the materials to be tested are essentially soft elastomers, loading them into the Instron machine tends to make them buckle. To remove the slack in the material sample a pre-load is placed upon the sample. This helps to reduce the slack and provide a more consistent reading. Once the sample is pre-loaded to a desired value (typically 0.03 to 0.05 N) the strain is set to zero and the test begun. The modulus is calculated as the instantaneous slope of the stress-strain curve at 0% strain ("Young's modulus"), 25% strain ("25% modulus") and 100 % strain ("100% modulus).

IOLs made of the ophthalmic device materials of the present invention are more resistant to glistenings than other materials. Glistenings are measured according to the following test. The presence of glistenings is measured by placement of a lens or disk sample into a vial or sealed glass chamber and adding deionized water or a balanced salt solution. The vial or glass chamber is then placed into a water bath preheated to 45 °C. Samples are to be maintained in the bath for a minimum of 16 hours and preferably 24 ± 2 hours. The vial or glass chamber is then cooled to ambient temperature for a minimum of 60 minutes and preferably 90 ± 30 minutes. The sample is inspected visually in various on angle or off angle lighting to evaluate clarity. Visualization of glistenings is carried out at ambient temperature with a light microscope using a magnification of 50 to 200x. A sample is judged to have many glistenings if, at 50 – 200x magnification, there are approximately 50 to 100 % as many glistenings as observed in control samples based on 65 weight % PEA, 30 weight % PEMA, 3.2 weight % BDDA, and 1.8 weight % OMTP. Similarly, a sample is judged to have few glistenings if there are

approximately 10 % or more glistenings relative to the quantity observed in control samples. A sample is judged to have very few glistenings if there are approximately 1 % or more glistenings relative to a control sample. A sample is judged to be free of glistenings if the number of glistenings detected in the eyepiece is zero. A sample is judged to be substantially free of glistenings if, at 50 - 200x magnification, the number of glistenings detected in the eyepiece is less than about $2/mm^3$. It is often very difficult to detect glistenings, especially at surfaces and edges where more defects and debris have formed, so the sample is rastered throughout the entire volume of the lens, varying the magnification levels (50 - 200x), the aperture iris diaphragm, and the field conditions (using both bright field and dark field conditions) in an attempt to detect the presence of glistenings.

The copolymers of the present invention preferably have an equilibrium water content (EWC) of 0.5 to 3 weight %. EWC is measured by placing one rectangular 0.9 x 10 x 20 mm slab in a 20 ml scintillation vial filled with deionized water and subsequently heating in a 35 °C water bath for a minimum of 20 hours and preferably 48 ± 8 hours. The slab is blotted dry with lens paper and the % water content is calculated as follows:

$$\% \text{ water content} = \frac{(\text{wet weight} - \text{dry weight})}{\text{wet weight}} \times 100$$

IOLs constructed of the device materials of the present invention can be of any design capable of being stretched or compressed into a small cross section that can fit through a 2-mm incision. For example, the IOLs can be of what is known as a one-piece or multi-piece design, and comprise optic and haptic components. The optic is that portion which serves as the lens and the haptics are attached to the optic and are like arms that hold the optic in its proper place in the eye. The optic and haptic(s) can be of the same or different material. A multi-piece lens is so called because the optic and the haptic(s) are made separately and then the haptics are attached to the optic. In a single piece lens, the optic and the haptics are formed out of one piece of material.

Depending on the material, the haptics are then cut, or lathed, out of the material to produce the IOL.

In addition to IOLs, the materials of the present invention are also suitable for use as other ophthalmic or otorhinolaryngological devices such as contact lenses, keratoprostheses, corneal inlays or rings, otological ventilation tubes and nasal implants.

The invention will be further illustrated by the following examples, which are intended to be illustrative, but not limiting.

The following abbreviations are used throughout the Examples and have the following meanings.

PEA	2-phenylethyl acrylate
PEMA	2-phenylethyl methacrylate
BzA	benzyl acrylate
BzMA	benzyl methacrylate
BDDA	1,4-butanediol diacrylate
AIBN	azobisisobutyronitrile
THF	tetrahydrofuran
AIBN	azobisisobutyronitrile
OMTP	2-(2H-benzo[d][1,2,3]triazol-2-yl)-4-methyl-6-(2-methylallyl)phenol
TMI	3-isopropenyl-alpha,alpha-dimethylbenzyl isocyanate
MEHQ	methyl hydroquinone or 4-methoxyphenol
Terg15S3-MA	Reacted adduct of Tergitol™ 15-S-3 alkyl ethoxylate and methacrylic anhydride
Terg15S7-MA	Reacted adduct of Tergitol™ 15-S-7 alkyl ethoxylate and methacrylic anhydride
Terg15S30-MA	Reacted adduct of Tergitol™ 15-S-30 alkyl ethoxylate and methacrylic anhydride
Terg15S40-MA	Reacted adduct of Tergitol™ 15-S-40 alkyl ethoxylate and methacrylic anhydride
Terg15S3-TMI	Reacted adduct of Tergitol™ 15-S-3 alkyl ethoxylate and TMI
Terg15S7-TMI	Reacted adduct of Tergitol™ 15-S-7 alkyl ethoxylate and TMI
Terg15S15-TMI	Reacted adduct of Tergitol™ 15-S-15 alkyl ethoxylate and TMI

EXAMPLE 1

Terg15S30-MA. 50.1 g (34.0 mmol based on OH# = 38.0 mg KOH/g) of Tergitol 15-S-30 surfactant (Dow/Union Carbide), 15.7 g (102 mmol) methacrylic anhydride (Aldrich, 94%), and 20 mg MEHQ (Sigma-Aldrich) were dissolved in 120 g anhydrous pyridine (Burdick & Jackson) in a 500 ml round bottom flask equipped with magnetic stirrer and nitrogen inlet. The reaction mixture was heated at 50 °C for 20 hours, poured into 3000 ml diethyl ether, and subsequently cooled to -20 °C. The solvent was decanted and the solid was recovered by centrifugation. The solid was redissolved in ether and the product was recovered as previously described to give 43.8 g (80 %) of a white waxy solid.

EXAMPLE 2

Terg15S40-MA. 105.0 g (54.7 mmol based on OH# = 29.2 mg KOH/g) of Tergitol 15-S-40 (Dow/Union Carbide) was dissolved in 300 ml anhydrous pyridine. 20 mg MEHQ and 50 mg dibutyltin dilaurate (Aldrich, Milwaukee, WI) were added followed by 17.6 g methacrylic anhydride (Alfa Aesar, 94%). The reaction mixture was heated at 60 °C for 15 hours and the solid isolated by precipitation in diethyl ether 3 times as described in Ex. 1 to give 90 g (82 %).

EXAMPLE 3

Lens Materials

The reaction components listed in Tables 1 - 4, except for AIBN, were mixed together with stirring or shaking for at least 30 minutes at 23 °C, until all components were dissolved. The AIBN was subsequently added and the reaction mixture was stirred for an additional 5 minutes or longer, until the initiator was dissolved. The reactive components are reported in weight %.

The reactive components were purged for approximately 15 minutes using N_2 and placed inside a low humidity N_2 purged glove box.

The reactive components were syringed or pipetted onto clean polypropylene mold halves containing 1 x 10 x 20 mm rectangular wells and covered with the complementary flat polypropylene mold halves. The mold halves were compressed using binder clips and the mixtures were heat ramped from ambient temperature to 70 °C in 15 minutes, and then cured at 70 °C for 1 hour and 110 °C for 2 hours using a Yamato DKN400 constant temperature oven. The molds were allowed to cool to room temperature. The top mold halves were removed and the rectangular polymer slabs were removed from the wells with tweezers and placed individually in 38 x 8 mm Histo Plas tissue processing capsules (Bio Plas Inc., San Rafael, CA). The slabs were extracted in acetone for a minimum of 8 hours and then air dried at ambient temperature for 20 hours, followed by high vacuum (~0.1 mm Hg) at ambient temperature for 20 hours, and high vacuum at 70 °C for 20 hours.

TABLE 1

	Example					
	% (w/w)					
Component	3A	3B	3C	3D	3E	3F
Ex 1	5.0	5.1	5.1	5.0	5.0	6.0
BzA	87.0	82.0	81.2	79.8	90.0	92.0
BzMA	6.0	11.4	12.2	13.6	3.0	0
BDDA	2.0	1.6	1.5	1.6	2.0	2.0
AIBN	0.52	0.50	0.53	0.56	0.50	0.52

TABLE 2

	Example					
	% (w/w)					
Component	3G	3H	3I	3J	3K	3L
Ex 1	5.0	5.0	5.0	5.0	5.0	6.1
PEA	50.0	54.1	58.0	51.3	49.9	48.4
PEMA	43.6	39.5	35.5	42.2	44.0	43.7
BDDA	1.5	1.4	1.6	1.5	1.1	1.8
AIBN	0.50	0.52	0.48	0.50	0.49	0.55

TABLE 3

	Example					
	% (w/w)					
Component	3M	3N	3O	3P	3Q	3R
Ex 1	5.0	8.1	5.0	6.1	6.1	5.9
PEA	63.6	61.5	63.9	62.7	63.1	63.2
PEMA	9.0	28.6	14.8	7.4	7.1	11.7
BzMA	20.5	0	14.6	21.9	21.9	17.4
BDDA	1.9	1.8	1.8	2.0	1.8	1.7
AIBN	0.48	0.48	0.56	0.52	0.51	0.57

TABLE 4

	Example					
	% (w/w)					
Component	3S	3T	3U	3V	3W	3X
Ex 1	0	5.0	5.0	0	0	6.1
Ex 2	6.1	0	0	6.1	6.1	0
PEA	62.9	52.0	0	48.0	33.4	62.9
PEMA	7.3	41.4	13.7	43.9	58.5	7.3
BzA	0	0	79.8	0	0	0
BzMA	21.8	0	0	0	0	21.8
BDDA	1.8	1.5	1.5	2.0	2.0	2.0
AIBN	0.49	0.52	0.50	0.53	0.55	0.51

The % extractables were calculated as follows:

$$\% \text{ extractables} = \frac{(\text{non-extracted weight} - \text{extracted weight})}{\text{non-extracted weight}} \times 100$$

The equilibrium water content (EWC) was measured by placing a slab in 20 ml deionized water in a scintillation vial and heating in a 35 °C water bath for a minimum of 20 hours. The slab was blotted dry with lens paper and the % water content was calculated as follows:

$$\% \text{ water content} = \frac{(\text{wet weight} - \text{dry weight})}{\text{wet weight}} \times 100$$

Refractive index values of the hydrated samples were measured using a Bausch & Lomb refractometer (catalog # 33.46.10) at 35 °C.

The extent of glistening formation was evaluated by equilibrating samples in water at 45 °C followed by cooling to 23 °C and subsequent examination using a light microscope. Samples were first placed in 20 ml scintillation vials containing deionized water and heated at 45 °C for a minimum of 20 hours. The entire cross section (~200 mm^2) of samples was examined for glistening formation approximately 1 to 2 hours after cooling to ambient temperature using an Olympus BX60 microscope equipped with 10X and 20X objectives. The samples were also visually inspected for haze after the ΔT test and all samples remained clear.

The refractive index (R.I.), % extractables, equilibrium water content (EWC), and glistening results are shown in Table 5.

TABLE 5

Ex. #	R.I.	% Extractables	EWC	Relative Glistening Concentration
3A	1.554	2.2	----	Very few
3B	1.558	2.6	0.8	0
3C	1.556	2.5	0.8	0
3D	1.559	3.1	0.8	0
3E	1.553	2.8	0.5	0
3F	1.553	3.8	1.0	Very few
3G	1.547	1.6	0.6	Very few
3H	1.547	1.7	0.9	0
3I	1.547	1.8	0.6	0
3J	1.547	1.8	0.9	0
3K	1.547	1.9	0.8	0
3L	1.546	1.6	1.0	0
3M	1.547	0.8	0.7	0
3N	1.542	2.3	2.0	0
3O	1.547	1.8	1.0	Very few
3P	1.548	2.5	1.1	Very few
3Q	1.547	2.6	1.1	Very few
3R	1.546	1.8	1.0	Very few
3S	1.545	1.7	1.9	Very few
3T	1.550	1.9	0.6	Very few
3U	1.553	2.2	0.8	0
3V	1.547	1.5	1.9	Very few
3W	1.549	1.4	1.5	Very few
3X	1.550	1.9	1.2	Very few

The results of Examples 3A through 3X show that the reaction mixture components and their amounts may be varied. All materials were clear and showed low haze.

The refractive index (R.I.) values of Examples 3A through 3F and 3U which contain BzA were higher than 1.55, whereas R.I. values of Examples 3G through 3X, excluding 3U, which contain PEA were slightly lower and between 1.54 and 1.55.

The equilibrium water contents (EWCs) were generally 1 % or less when 5 weight percent of the functionalized hydrophilic component was added. The EWC was as high as 2 % in Example 3N which contained 8 weight percent of the functionalized hydrophilic component.

In all examples, zero to very few glistenings could be observed per entire slab using 10X or 20X magnification objectives (such that the overall magnification was 50 – 200X). Glistening sightings were rare and observed mainly along edges.

The materials from Examples 3A through 3X were analyzed to determine their tensile properties. The results are shown in Table 6, below.

TABLE 6

Ex. #	Stress at Break (MPa)	Strain at Break (%)	Young's Modulus (MPa)	25% Secant Modulus (MPa)	100% Secant Modulus (MPa)
3A	9.2	163	37.8	6.6	3.6
3B	9.8	211	55.1	8.9	3.5
3C	10.4	216	61.5	9.4	3.6
3D	10.4	151	119	15.2	6.4
3E	9.0	168	27.5	5.3	3.2
3F	8.1	163	17.8	3.8	2.5
3G	7.7	156	59.5	9.9	4.3
3H	7.2	170	34.6	6.3	3.1
3I	6.3	153	24.2	5.0	2.9
3J	6.1	147	27.0	5.3	2.9
3K	7.6	200	53.8	9.1	3.4
3L	9.2	145	48.1	9.2	4.8
3M	7.4	140	27.3	5.5	3.5
3N	4.4	140	7.4	2.4	1.9
3O	8.2	160	20.1	4.5	2.8
3P	6.6	136	24.9	5.3	3.5
3Q	7.3	151	22.3	4.9	3.0
3R	7.1	153	19.6	4.3	2.7
3S	6.7	152	16.2	3.9	2.6
3T	7.1	145	20.0	4.6	3.1
3U	8.7	140	46.5	9.3	4.8
3V	8.3	137	37.2	7.6	4.5
3W	9.5	91	113	24.4	----
3X	6.3	137	19.8	4.5	3.2

EXAMPLE 4

Terg15S3-MA. 10.0 g (28.3 mmol based on OH# = 158.6 mg KOH/g) of Tergitol 15-S-3 (Dow/Union Carbide) was dissolved in 100 ml anhydrous pyridine. 20 mg MEHQ and 50 µl of 0.3 M dibutyltin dilaurate (Aldrich, Milwaukee, WI) in toluene were added followed by 8.7 g (56.4 mmol) methacrylic anhydride (Alfa Aesar, 94%). The reaction mixture was heated at 50 °C for 20 hours and the resultant liquid was dissolved in 500 ml methylene chloride and washed with 0.2 N HCl (3 x 500 ml), 0.2 M $NaHCO_3$ (3 x 500 ml), brine, and water. The organic layer was dried with anhydrous Na_2SO_4 and the product was isolated as a slightly yellow liquid (8 g, 67% yield).

EXAMPLE 5

Terg15S7-MA. 10.0 g (18.55 mmol based on OH# = 104.1 mg KOH/g) of Tergitol 15-S-3 (Dow/Union Carbide) was dissolved in 100 ml anhydrous pyridine. 20 mg MEHQ and 50 µl of 0.3 M dibutyltin dilaurate (Aldrich, Milwaukee, WI) in toluene were added followed by 7.2 g (47 mmol) methacrylic anhydride (Alfa Aesar, 94%). The reaction mixture was heated at 50 °C for 20 hours and the resultant liquid was dissolved in 500 ml methylene chloride and washed with 0.2 N HCl (3 x 500 ml), 0.2 M NaHCO3 (3 x 500 ml), brine, and water. The organic layer was dried with anhydrous Na2SO4 and the product was isolated as a slightly yellow liquid (5 g, 44% yield).

EXAMPLE 6

Terg15S3-TMI. 4.97 g (14.0 mmol based on OH# = 158.6 mg KOH/g) of Tergitol 15-S-3 (Dow/Union Carbide) was dissolved in 30 ml chloroform. 20 mg MEHQ and 20 mg dibutyltin dilaurate (Aldrich, Milwaukee, WI) were added followed by 2.96 g (14.7 mmol) 3-isopropenyl-alpha,alpha-dimethylbenzyl isocyanate (Aldrich). The reaction mixture was heated at 60 °C for 16 hours and the resultant liquid was dissolved in 300 ml methylene chloride and washed with 0.2 N HCl (3 x 500 ml), 0.2 M $NaHCO_3$ (3 x 300 ml), brine, and water. The organic layer was dried with anhydrous Na_2SO_4 and the solvent removed by rotary evaporation to yield a slightly yellow liquid (5 g, 64%). Data on 13117-27

EXAMPLE 7

Terg15S7-TMI. 4.97 g (9.22 mmol based on OH# = 104.1 mg KOH/g) of Tergitol 15-S-7 (Dow/Union Carbide) was dissolved in 30 ml chloroform. 20 mg MEHQ and 20 mg dibutyltin dilaurate (Aldrich, Milwaukee, WI) were added followed by 2.06 g (10.2 mmol) 3-isopropenyl-alpha,alpha-dimethylbenzyl isocyanate (Aldrich). The reaction mixture was heated at 60 °C for 16 hours and the resultant liquid was dissolved in 300 ml methylene chloride and washed with 0.2 N HCl (3 x 500 ml), 0.2 M $NaHCO_3$ (3 x 300 ml), brine, and water. The organic layer was dried with anhydrous Na_2SO_4 and

the solvent removed by rotary evaporation to yield a slightly yellow liquid (3.5 g, 51%). Data on 13117-28

EXAMPLE 8

Terg15S15-TMI. 5.0 g (5.7 mmol based on OH# = 64.4 mg KOH/g) of Tergitol 15-S-15 (Dow/Union Carbide) was dissolved in THF (100 ml). 20 mg MEHQ and 20 mg dibutyltin dilaurate (Aldrich, Milwaukee, WI) were added followed by 1.13 g (5.61 mmol) 3-isopropenyl-alpha,alpha-dimethylbenzyl isocyanate (Aldrich). The reaction mixture was heated at 60 °C for 16 hours and the solvent removed by rotary evaporation to yield a slightly yellow liquid. Data on 13117-29

EXAMPLE 9

Lens Materials Using Lower Molecular Weight Alkyl Ethoxylates

The reaction components listed in Table 7 were mixed together and cured as previously described. Higher concentrations of alkyl ethoxylate were used as compared to Tables 1 through 4 due to the relatively lower molecular weight and lower PEG contents of alkyl ethoxylates in Examples 4 through 8. This enables the incorporation of greater amounts of the functionalized alkyl ethoxylates while still maintaining equilibrium water contents of approximately 1.5 % or less as shown in Table 8.

The results of Examples 9C through 9G which contain between 3 to 12 weight % of Terg15S15-TMI, as shown in Table 7, show that decreasing the alkyl ethoxylate content below approximately 8 weight % results in the appearance of glistenings and noticeable haze. The results of Examples 9A show that a relatively high incorporation of approximately 15 weight % Terg15S3-TMI, the lowest molecular weight alkyl ethoxylate, results in clear samples but does not eliminate glistening formation.

TABLE 7

	Example (% w/w)						
Component	9A	9B	9C	9D	9E	9F	9G
Ex 6	14.7	0	0	0	0	0	0
Ex 7	0	13.2	0	0	0	0	0
Ex 8	0	0	11.8	9.9	7.8	5.7	3.2
PEA	55.3	56.3	57.1	58.5	59.9	61.3	63.0
PEMA	25.5	26.0	26.4	27.0	27.7	28.3	29.1
BDDA	3.0	3.0	3.1	2.9	3.0	3.0	3.1
OMTP	1.5	1.6	1.6	1.6	1.7	1.7	1.7
AIBN	0.43	0.47	0.44	0.45	0.47	0.48	0.51

TABLE 8

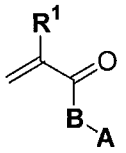
Ex. #	R.I.	% Extractables	EWC	Sample Appearance Post Glistening Test	Relative glistening concentration
9A	1.542	2.7	0.5	clear	many
9B	1.543	2.8	0.7	clear	few
9C	1.546	6.1	0.9	clear	0
9D	1.545	5.4	0.8	clear	0
9E	1.550	4.0	0.6	slightly hazy	----
9F	1.549	4.1	0.6	slightly hazy	many
9G	1.551	2.5	0.9	slightly hazy	many

This invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its special or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

What is claimed is:

1. A polymeric ophthalmic or otorhinolaryngological device material comprising

a) 75 to 97 % (w/w) of a monofunctional acrylate or methacrylate monomer of formula [1]:



[1]

wherein

B = $O(CH_2)_n$, $NH(CH_2)_n$, or $NCH_3(CH_2)_n$;

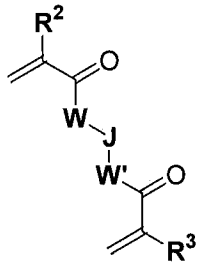
R^1 = H, CH_3, CH_2CH_3, or CH_2OH;

n = 0 - 12;

A = C_6H_5 or $O(CH_2)_mC_6H_5$, where the C_6H_5 group is optionally substituted with $-(CH_2)_nH$, $-O(CH_2)_nH$, $-CH(CH_3)_2$, $-C_6H_5$, $-OC_6H_5$, $-CH_2C_6H_5$, F, Cl, Br, or I; and

m = 0 – 22;

b) a difunctional acrylate or methacrylate cross-linking monomer of formula [2]:



[2]

wherein

R^2, R^3 independently = H, CH_3, CH_2CH_3, or CH_2OH;

W, W' independently = $O(CH_2)_d$, $NH(CH_2)_d$, $NCH_3(CH_2)_d$, $O(CH_2)_dC_6H_4$, $O(CH_2CH_2O)_dCH_2$, $O(CH_2CH_2CH_2O)_dCH_2$, $O(CH_2CH_2CH_2CH_2O)_dCH_2$, or nothing;

J = $(CH_2)_a$, $O(CH_2CH_2O)_b$, O, or nothing, provided that if W and W' = nothing, then J ≠ nothing;

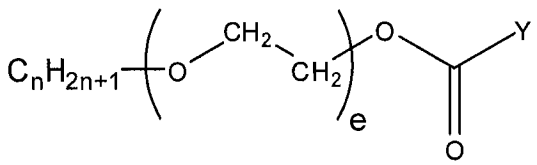
d = 0 - 12;

a = 1 – 12; and

b = 1 – 24;

and

c) 1 to 20 % (w/w) of an alkyl ethoxylate monomer of formula [3]:

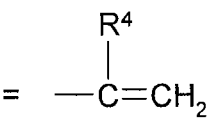
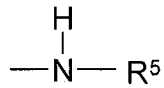


[3]

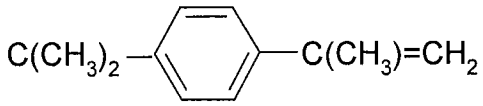
wherein:

n = 12, 13, or 14;

e = 1 – 100;

Y =  or  ;

R^4 = H, CH_3, CH_2CH_3, CH_2OH; and

R^5 = $CH_2CH_2OC(=O)C(CH_3)=CH_2$ or 

2. The polymeric device material of Claim 1 wherein

$B = O(CH_2)_n$;

R^1 = H or CH_3;

n = 1 - 4; and

$A = C_6H_5$.

3. The polymeric device material of Claim 1 wherein

R^2, R^3 independently = H or CH_3;

W, W' independently = $O(CH_2)_d$, $O(CH_2)_dC_6H_4$, or nothing;

$J = O(CH_2CH_2O)_b$ or nothing, provided that if W and W' = nothing, then J ≠ nothing;

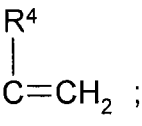
d = 0 - 6; and

b = 1 – 10.

4. The polymeric device material of Claim 1 wherein:

n = 12, 13, or 14;

e = 8 – 50;

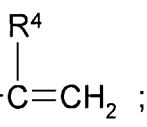
Y =  ; and

R^4 = H or CH_3.

5. The polymeric device material of Claim 4 wherein:

n = 13;

e = 15 – 40;

Y =  ; and

R^4 = H or CH_3.

6. The polymeric device material of Claim 1 wherein the monomer of formula [1] is selected from the group consisting of benzyl methacrylate; 2-phenylethyl methacrylate; 3-phenylpropyl methacrylate; 4-phenylbutyl methacrylate; 5-phenylpentyl methacrylate; 2-phenoxyethyl methacrylate; 2-(2-phenoxyethoxy)ethyl methacrylate; 2-benzyloxyethyl methacrylate; 2-(2-(benzyloxy)ethoxy)ethyl methacrylate; 3-benzyloxypropyl methacrylate; benzyl acrylate; 2-phenylethyl acrylate; 3-phenylpropyl acrylate; 4-phenylbutyl acrylate; 5-phenylpentyl acrylate; 2-phenoxyethyl acrylate; 2-(2-phenoxyethoxy)ethyl acrylate; 2-benzyloxyethyl acrylate; 2-(2-(benzyloxy)ethoxy)ethyl acrylate; and 3-benzyloxypropyl acrylate.

7. The polymeric device material of Claim 1 wherein the monomer of formula [2] is selected from the group consisting of ethylene glycol dimethacrylate; diethylene glycol dimethacrylate; triethylene glycol dimethacrylate; 1,6-hexanediol dimethacrylate; 1,4-butanediol dimethacrylate; 1,4-benzenedimethanol dimethacrylate; ethylene glycol diacrylate; diethylene glycol diacrylate; triethylene glycol diacrylate; 1,6-hexanediol diacrylate; 1,4-butanediol diacrylate; and 1,4-benzenedimethanol diacrylate.

8. The polymeric device material of Claim 1 wherein the amount of monomer [1] is 80 to 95 % (w/w).

9. The polymeric device material of Claim 1 wherein the amount of monomer [2] is 0.5 to 3 % (w/w).

10. The polymeric device material of Claim 1 wherein the amount of monomer [3] is 1 to 15 % (w/w).

11. The polymeric device material of Claim 10 wherein the amount of monomer [3] is 1 to 10 % (w/w).

12. The polymeric device material of Claim 1 further comprising an ingredient selected from the group consisting of a polymerizable UV absorbers and a polymerizable colorants.

13. The polymeric device material of Claim 12 comprising 0.1 – 5 % (w/w) of a polymerizable UV absorber and 0.01 - 0.5 % (w/w) of a polymerizable colorant.

14. An ophthalmic or otorhinolaryngological device comprising the device material of Claim 1 wherein the ophthalmic or otorhinolaryngological device is selected from the group consisting of intraocular lenses; contact lenses; keratoprostheses; corneal inlays or rings; otological ventilation tubes; and nasal implants.

15. The ophthalmic or otorhinolaryngological device of Claim 14 wherein the ophthalmic or otorhinolaryngological device is an intraocular lens.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/078362

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61L27/16 A61L27/50 A61F2/16 G02B1/04

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)
A61L A61F G02B C08F

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)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/138213 A (ALCON INC [CH]; SCHLUETER DOUGLAS C [US]; KARAKELLE MUTLU [US]) 28 December 2006 (2006-12-28) page 4, line 4 - line 16 page 5, line 1 - page 7, line 30 examples 1-12 claims 1-20	1-15
Y	US 2004/131849 A1 (WIRES DUANE L [US]) 8 July 2004 (2004-07-08) page 1, paragraph 16 - paragraph 18 page 2, paragraph 25 - paragraph 28 page 3, paragraph 44 - page 4, paragraph 46 examples 1-6 claims 1-34	1-15

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

[X] 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 document but 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

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Date of the actual completion of the international search	Date of mailing of the international search report
13 November 2008	19/11/2008

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/078362

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/138188 A (ALCON INC [CH]; SCHLUETER DOUGLAS C [US]) 28 December 2006 (2006-12-28) page 4, line 4 - page 6, line 13 examples 1-11 claims 1-19	1-15
Y	US 5 331 073 A (WEINSCHENK III JOSEPH I [US] ET AL) 19 July 1994 (1994-07-19) cited in the application column 2, line 19 - line 57 column 4, line 39 - column 5, line 7 examples 1-5 claims 1-22	1-15
A	WO 2006/019404 A (ALCON INC [CH]; SCHLUETER DOUGLAS C [US]) 23 February 2006 (2006-02-23) the whole document	1-15
A	WO 2004/007579 A (ALCON INC [CH]; SCHLUETER DOUGLAS C [US]; LEBOEUF ALBERT R [US]; KARAK) 22 January 2004 (2004-01-22) the whole document	1-15

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/078362

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006138213 A	28-12-2006	AU 2006259605 A1	28-12-2006
		CA 2609866 A1	28-12-2006
		CN 101193929 A	04-06-2008
		EP 1891127 A1	27-02-2008
		KR 20080026564 A	25-03-2008
US 2004131849 A1	08-07-2004	NONE	
WO 2006138188 A	28-12-2006	AU 2006259671 A1	28-12-2006
		CA 2609857 A1	28-12-2006
		CN 101198887 A	11-06-2008
		EP 1891466 A1	27-02-2008
		KR 20080039350 A	07-05-2008
US 5331073 A	19-07-1994	AT 213338 T	15-02-2002
		AU 5549794 A	08-06-1994
		DE 69331583 D1	21-03-2002
		DE 69331583 T2	02-10-2002
		EP 0667966 A1	23-08-1995
		ES 2172526 T3	01-10-2002
		JP 8503506 T	16-04-1996
		WO 9411764 A2	26-05-1994
		US 5359021 A	25-10-1994
WO 2006019404 A	23-02-2006	AU 2005273035 A1	23-02-2006
		CA 2572935 A1	23-02-2006
		EP 1769271 A1	04-04-2007
		JP 2008506453 T	06-03-2008
WO 2004007579 A	22-01-2004	AT 393175 T	15-05-2008
		AU 2003249203 A1	02-02-2004
		CA 2491319 A1	22-01-2004
		DK 1521786 T3	28-07-2008
		EP 1521786 A1	13-04-2005
		ES 2301830 T3	01-07-2008
		JP 2005533153 T	04-11-2005
		SI 1521786 T1	31-08-2008