$CaCl_2$, sodium acetate, potassium acetate, ammonium acetate, sodium citrate, potassium citrate, ammonium citrate, sodium sulphate, potassium sulphate, ammonium sulphate, calcium acetate or mixtures thereof. Additional organic salts include alkylammonium salts such as ethylammonium nitrate, sodium citrate, sodium formate, sodium ascorbate, magnesium gluconate, sodium gluconate, trimethamine hydrochloride, sodium succinate, and combinations thereof. Without being held to theory, it is believed that the identity of the ion, e.g., Li+, Na+ and K+, can affect the ability of the γ-crystallin charge masking agent to prevent γ-crystallin aggregation.

[0043] It was unexpectedly shown herein that salt, e.g. KCl, concentrations of less than 300 nM did not provide a reduction in the size of γ-crystallin aggregates. However, at KCl concentrations to 400 to 1000 mM, aggregate formation was effectively inhibited.

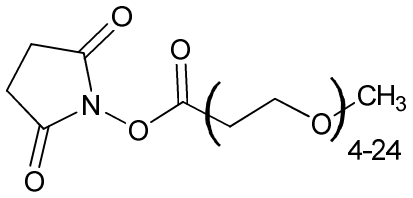
[0044] In another embodiment, the γ-crystallin charge masking agent is a bifunctional molecule containing a leaving group covalently linked to a molecular bristle. The bifunctional molecule interacts with charges on the γ-crystallin molecules, such as positively charged lysine and arginine residues and negatively charged glutamate and aspartate residues. The molecular bristle is a hydrophilic, water-soluble species that provides distance between the γ-crystallin molecules, preventing aggregation. Without being held to theory, it is believed that the bifunctional molecule reacts and effectively puts the molecular bristle onto the protein, and the leaving group is expelled during the reaction. The covalently attached molecular bristle prevents aggregation of the γ-crystallin molecules. Without being held to theory, it is believed that the bifunctional molecules described herein may also act as β-crystallin interaction inhibitors.

[0045] Exemplary leaving groups (also called reactive groups) include succinimide and carboxylic acid functional groups, specifically N-hydroxysuccinimide and COOH. In some embodiments, the leaving group is biocompatible. Other examples of leaving groups include isocyanate, isothiocyanate, sulfonyl chloride, aldehyde, carbodiimide, acyl azide, anhydride, fluorobenzene, carbonate, N-hydroxysuccinimide ester, imidoester, epoxide, and fluorophenyl ester. Figure 17 shows embodiments of leaving groups wherein the R group is the molecular bristle. When the bifunctional molecule contains COOH, water leaves when it reacts with a protein's amine group. When the bifunctional molecule contains N-hydroxysuccinimide water is not released. In an NH_2 reaction, water leaves when NH_2 reacts with a COOH group on the protein.

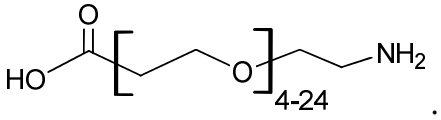
[0046] Exemplary molecular bristles include linear or branched poly(ethylene glycol) having 4 or more oxyethylene groups, such as 4 to 200 oxyethylene groups. Also included

are modified poly(ethylene glycol) such as alkoxy- and aryloxy poly(ethylene glycol) having 4 to 200, specifically 4 to 24 oxyethylene, alkloxy ethylene or aryloxy ethylene groups. Alternative molecular bristles include poly(2-hydroxypropyl methacrylamide) (HPMA), poly(2-hydroxyethyl methacrylate) (HEMA), poly(2-oxazilines), poly(m-phosphocholine), polylysine, and poly(glutamic acid). Figure 18 shows embodiments of molecular bristles. In one embodiment, the molecular bristle has a number average molecular weight of 150 to 8000.

[0047] In a specific embodiment, the bifunctional γ-crystallin charge masking agent is:



Or



.

[0048] In one embodiment, the bifunctional γ-crystallin charge masking agents described herein are also useful in the treatment of diseases relating to protein folding such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. In a specific embodiment, the bifunctional γ-crystallin charge masking agents are administered as oral compositions.

[0049] In one embodiment, the γ-crystallin charge masking agent is not a polypeptide. "Polypeptide", "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymers.

[0050] An advantage of the γ-crystallin charge masking agents described herein is that they are expected to be effective in the presence of post-translational modifications of γ-crystallins, including, for example, transamidation, oxidation, modified and dysfunctional connexins, and high concentrations of inorganic and organic ions such as Ca^{+2}.

the bifunctional molecules described herein, is about 0.001 g to about 0.1 g. Specifically, the effective presbyopia -inhibiting amount is about 0.01 g to about 0.05 g.

[0054] As used herein the term “ophthalmic composition” refers to a pharmaceutically acceptable formulation, delivery device, mechanism or system suitable for administration to the eye. The term “ophthalmic compositions” includes but are not limited to solutions, suspensions, gels, ointments, sprays, depot devices or any other type of formulation, device or mechanism suitable for short term or long term delivery of β_L-crystallin electrostatic interaction inhibitors to the eye. In contrast to oral formulations, for example, ophthalmic compositions exhibit specific technical characteristics associated with their application to the eyes, including the use of pharmaceutically acceptable ophthalmic vehicles that avoid inducing various reactions such as, for example, irritation of the conjunctiva and cornea, closure of the eyelids, secretion of tears and painful reactions. Specific ophthalmic compositions are advantageously in the form of ophthalmic solutions or suspensions (i.e., eye drops), ophthalmic ointments, or ophthalmic gels containing β_L–crystallin electrostatic interaction inhibitors. Depending upon the particular form selected, the compositions may contain various additives such as buffering agents, isotonizing agents, solubilizers, preservatives, viscosity-increasing agents, chelating agents, antioxidizing agents, antibiotics, sugars, and pH regulators.

[0055] Examples of preservatives include, but are not limited to chlorobutanol, sodium dehydroacetate, benzalkonium chloride, pyridinium chlorides, phenethyl alcohols, parahydroxybenzoic acid esters, benzethonium chloride, hydrophilic dihalogenated copolymers of ethylene oxide and dimethyl ethylene-imine, mixtures thereof, and the like. The viscosity-increasing agents may be selected, for example, from methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, hydroxypropylmethylcellulose, polyvinyl alcohol, carboxymethylcellulose, chondroitin sulfate, and salts thereof. Suitable solubilizers include, but are not limited to, poly(oxyethylene) hydrogenated castor oil, poly(ethylene glycol), polysorbate 80, and poly(oxyethylene monostearate). Typical chelating agents include, but are not limited to, sodium edetate, citric acid, salts of diethylenetriamine pentaacetic acid, diethylenetriamine pentamethylenephosphonic acid, and stabilizing agents such as sodium edetate and sodium hydrogen sulfite.

[0056] Exemplary buffers include, but are not limited to borate buffers, phosphate buffers, carbonate buffers, acetate buffers and the like. The concentration of buffer in the ophthalmic compositions may vary from about 1 mM to about 150 mM or more, depending on the particular buffer chosen.

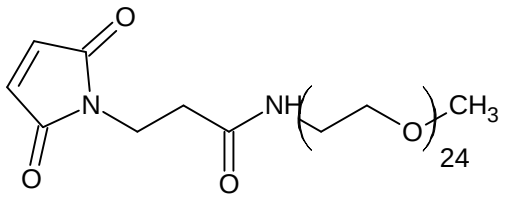
[0057] As used herein, the term “vehicle” is intended to include a carrier, diluent or excipient suitable for ophthalmic use. “Excipient” refers to an ingredient that provides one or more of bulk, imparts satisfactory processing characteristics, helps control the dissolution rate, and otherwise gives additional desirable characteristics to the compositions. In particular, the excipients are selected such that the ophthalmic composition does not trigger a secretion of tears that will entrain the active ingredient. Acceptable excipients are well known to a person skilled in the art, who will know how to select them depending on the desired formulation.

[0058] In one embodiment, the γ-crystallin charge masking agent is administered in the form of an ophthalmic device, such as a contact lens or a punctal plug. Suitable ophthalmic devices included biocompatible devices with a corrective, cosmetic or therapeutic quality.

[0059] In one embodiment, the γ-crystallin charge masking agent may be adhered to, incorporated into or associated with a contact lens, optionally as a controlled-release composition. The contact lens may be produced using the known materials, for example hydrogels, silicone hydrogels, silicone elastomers and gas permeable materials such as poly(methylmethacrylate) (PMMA), methacrylic acid ester polymers, copolymers of oligosiloxanylalkyl(meth)acrylate monomers/methacrylic acid and the like. Specific examples of materials for water-containing soft ophthalmic lenses include those described in U.S. Pat. No. 5,817,726, 2-hydroxyethyl methacrylate polymers as described in U.S. Pat. No. 5,905,125, ophthalmic lens materials as described in European Patent Application No. 781,777, the hydrogel lens which is coated with a lipid layer in advance as described in U.S. Pat. No. 5,942,558; all incorporated herein for their teachings regarding contact lenses. Generally used contact lens such as hard or rigid cornea-type lens, and gel, hydrogel or soft-type lens which are produced from the above known materials may be used.

[0060] It is common in the contact lens industry to characterize contact lenses into two major categories; conventional and silicone hydrogels. The conventional based hydrogels started as poly(hydroxyethyl methacrylate) (poly HEMA) and evolved to polyHEMA copolymers with other hydrophilic moieties such as n-vinyl pyrrolidone (nVP), acrylamide, dimethyl acrylamide, and methacrylated phosphorylcholines. Polyvinyl alcohol lenses may also be employed.

[0061] The silicone hydrogels (SiH) typically consist of copolymers of methacrylated or meth(acrylamide) silicone monomers, prepolymers or macromers with typical conventional hydrogel monomers. Examples of silicone monomers include “Tris” that is 3-[Tris(trimethylsiloxy)silyl]propyl methacrylate, alkyl



MMPEG24

[0110] The MALDI-TOF spectra of ɣ-crystallin modified with MMPEG24 showed three distinct peaks can be observed with minimal to no unmodified ɣ-crystallin. (data not shown) Four ɣD-crystallin peaks were observed at 23187, 24426, 25666 m/z corresponding to 1, 2, and 3 modifications. In the case of ɣS-crystallin peaks were observed at 23565, 24426, and 25666 m/z corresponding to 1, 2, and 3 modifications. The highest relative intensity for both crystallin proteins occurred at 2 modifications.

[0111] Excellent agreement is again seen between the native and PEGylated ɣ-crystallin proteins. It is known that in some instances the thiol groups of cysteine are involved in intramolecular disulfide bonding which give structural integrity providing the secondary structure. As both MM modified ɣD- and ɣS-crystallin spectra show a secondary structure similar to native ɣ-crystallin state it was concluded that the modification did not alter the proteins structure. (data not shown)

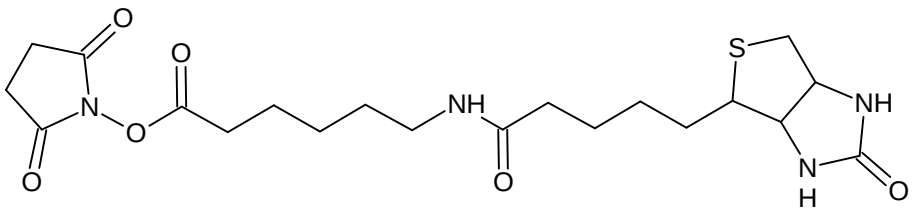
[0112] PEGylating ɣ-crystallin through its cysteine residues did not prevent aggregation. The NICF curves (data not shown) have an angular dependence which resulted in the distribution function having two distinct sets of peaks (Figure 13). The Γ versus q^2 graph showed two slopes with a linear angular dependence indicating the presence of a slow and fast diffusion coefficient. (data not shown) At 37°C, the slow mode resulted in an R_h of 80nm for ɣD-crystallin and 85nm for ɣS-crystallin. The large size indicateed that the protein was aggregating in solution. The fast mode corresponded to monomeric ɣ-crystallin protein, with an R_h of 2.8nm and 3.0 nm for ɣD- and ɣS-crystallin at 37°C.

[0113] The fact that PEGylation via maleimide functionality did not prevent aggregation provides critical information regarding the formation of ɣ-crystallin aggregates. Due to MMPPEG24 and NHSPEG24 both resulting in a similar number of modifications the surface coverage and spacer groups around the ɣ-crystallin proteins must also be similar. The aggregate observed with MMPEG24 modification demonstrates that prevention of aggregation cannot be entirely dependent on hydrophilic spacer molecules.

[0114] A key insight into the aggregation mechanism is gained in realizing that PEGylating the protein via uncharged amino acids does not prevent aggregation. The key difference between MMPEG and NHSPEG or CAPEG is that PEGylation via maleimide reaction does not target charged amino acids of the protein. Without being held to theory, this suggests that surface charge and electrostatics play a major role in the formation of aggregates and must be targeted when disrupting aggregation.

Example 7- Chemical Modification of ɣD- and ɣS- crystalline with BIOTIN

[0115] Biotin is a molecule commonly used for protein modification due to its high binding affinity for avidin. Proteins can be tagged with biotin, undergo reactions *in vivo* or *in vitro*, then be separated or purified from the bulk using an avidin column. The NHSBiotin molecule was chosen because it reacts through the same mechanism as PEG4 and PEG24 however the added molecule will no longer be hydrophilic but rather contain a highly charged end group. The molecular weight added per unit is 226.38 g/mole with a spacer arm of 1.38 nm.



NHSBiotin

[0116] The ɣ-crystallin proteins were successfully modified with biotin as shown in the MALDI-TOF. (data not shown) ɣD-crystallin's peak modification was eight units (23758 m/z) while ɣS-crystallin's peak occurrence was four units (23325 m/z). Both systems show no unmodified ɣ-crystallin indicating reaction conditions were sufficient for thorough modification.

[0117] The CD spectra showed a sizeable shift upwards as compared with the native structure of the protein. (data not shown) A shallower well was observed around 220 nm which goes against the trend of good correlation between modification and secondary structure. The change in spectra could be an indication that the secondary structure of the

proteins has been perturbed by the modification. Despite the shift in spectra, the overall shape of the curve is similar and there was no indication of a disordered or random coil.

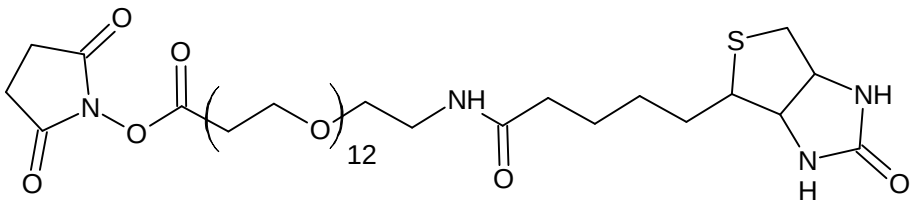
[0118] Aggregation of ɣ-crystallin protein was observed for ɣ-crystallin modified with biotin. The NICF showed a slow and a fast mode which resulted in the distribution function having two sets of peaks (Figure 14). Angular dependence of the distribution function can be seen in the Γ versus q^2 graph, where a qualitative difference was seen between the slow and fast modes. At 22°C, the R_h of the fast and slow modes were 2.8nm and 150nm for ɣD-crystallin, while for ɣS-crystallin these values were 2.6nm and 180nm. A slow and fast mode was also observed at 37°C with the R_h values being similar to those at 22°C.

[0119] The aggregation of ɣ-crystallin modified with NHSBiotin shows that the functionality of the modifying molecule (i.e., the molecular bristle) is important. Mechanistically, biotin modified ɣ-crystallin is in the same manner as NHSPEG. Only modifying charged amino acids of ɣ-crystallin is thus not sufficient in preventing aggregation. A comparable degree of modification occurred with biotin and PEG4 meaning a similar shift of the protein's isoelectric point. Due to aggregation occuring in the case of ɣ-crystallin modified with biotin it is not sufficient to purely shift the isoelectric point of the ɣ-crystallin protein to prevent aggregation. DLS measurements of the biotinylated system also further support the notion that aggregation cannot be prevented merely by adding spacer molecules onto the surface of ɣ-crystallin.

[0120] The stark contrast in chemical properties between PEG and biotin is the reason one prevents aggregation and the other does not. PEG is a flexible hydrophilic molecule whereas the biotin functionaly is capable of hydrogen bonding and stabilizing a negative charge. The properties of PEG thus help the solubility of proteins whereas biotin would contribute to the hydrophobic and electrostatic nature of the aggregates.

Example 8- Chemical Modification of ɣD- and ɣS- crystalline with BIOTIN-PEG

[0121] Modifying ɣ-crystallin proteins with biotin resulted in aggregation so it was proposed to use NHSBiotinPEG which incorporates a hydrophilic spacer between the protein and biotin functionality. It was proposed that the hydrophilic nature of PEG would be the key factor in the prevention of ɣ-crystallin aggregation. The NHS functionalization is used to keep the reaction mechanism constant. The molecular weight added per unit was 825.64 g/mol and the spacer arm was 5.6 nm.



NHSBiotinPEG12

[0122] An appreciable shift in molecular weight was observed in MALDI-TOF indicating modification of the ɣ-crystallin proteins with BiotinPEG12. (data not shown) ɣD-crystallin had three distinct peaks observable at 22760, 23582, and 24404 m/z corresponding to one, two, and three modifications. The resolution of ɣS-crystallin provided MALDI-TOF peaks at 23001, 23816, 24669, 25470, and 26122 m/z corresponding to one-five modifications. The MALDI-TOF spectra also showed no unmodified ɣ-crystallin demonstrating sufficient reaction conditions.

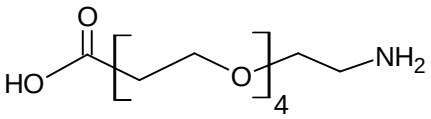
[0123] The modified ɣ-crystallin protein's secondary structure was in good agreement with that of the native ɣ-crystallin as seen in the CD spectra. (data not shown) The well observed with CD spectra for ɣ-crystallin modified with just biotin was no longer evident. The PEG portion of the modification most likely allowed for increased solubility in addition to providing a spacer between the protein and biotin functionality.

[0124] Despite the incorporation of PEG on the biotin functionality there was still aggregate present in solution as can be seen in the slow and fast mode of the NICF. (data not shown) The distribution function (Figire 15) contained two sets of peaks that demonstrate an angular dependence. The Γ versus q^2 graph clearly showed two distinct linear fits, the slope of which provide a slow and fast diffusive mode. (data not shown) The fast diffusion coefficient corresponds to the monomeric ɣ-crystallin where ɣD-crystallin had an R_h of 2.7nm at 22°C, while ɣS-crystallin had the value was 2.6nm. The slow diffusion coefficient represented the large aggregate present in solution with an R_h of 105nm for ɣD-crystallin and 115nm for ɣS-crystallin at 22°C. Aggregate of a similar R_h was also observed at 37°C.

[0125] The use of PEG as a spacer between the protein and biotin functionality did not aid in preventing aggregation. Without being held to theory and with reference to the discussion earlier concerning biotin shifting the isoelectric point of ɣ-crystallin, these experimental results also suggest hydrophobics to dominate over electrostatics in aggregates

Methods: Harvesting and characterization of human cadaver lenses

[0133] Within about 24 hours of death, the eyeball is harvested, sliced and the vitreous is removed. The lens is excised and placed in an incubation medium called Optisol®. Optisol® is a corneal storage medium conatining chondroitin sulfate, dextran 40, optisol base powder, sodium bicarbonate, gentamycin, amino acids, sodium pyruvate, L-glutamine, 2-mercaptoethanol and purified water. OD is the right eye and OS is the left eye.



CAPEG4

[0134] Lens opacities are classified according to the LOCS III system. LOCS III measurements are taken with a slit lamp miroscope. The LOCS III contains an expanded set of standards selected from the Longitudinal Study of Cataract slide library at the Center for Clinical Cataract Research, Boston, Mass. It includes six slit lamp images for grading nuclear color (NC) and nuclear opalescence (NO), five retroillumination images for grading cortical cataract (C), and five retroillumination images for grading posterior subcapsular (P) cataract. Cataract severity is graded on a decimal scale, with the standards have regularly spaced intervals on the scale.

Example 10: Testing of CAPEG4 in human cadaver lenses- transport across the epithelium

[0135] The transport of the CAPEG4 across an epithelium construct was studied. The epithelium is the outer layer of the cornea and transport across the epithelium has proven to be challenging. The goal was to demonstrate the CAPEG4 construct could be used in a eye drop formulation for transport through the front of the eye.

[0136] Specifically, the CAPEG4 construct in solution was added to the top of an apparatus containing culture medium and an epithelium construct. (Figure 19). The epithelium construct consists of a layer(s) of human corneal epithelial cells. Aliquots were taken at the top and the bottom of the cultre medium from 15 to 120 minutes. Figure 20 shows the CAPEG4 that was transported to the bottom of the cell.

[0137] Figure 21 shows the pH of Optisol® versus the mg/ml of added CAPEG4. The data is also presented in tables 5a and 5b. Overall, it is demonstrated that the reduction in corticle and posterior subcapsular cataracts is due to the CAPEG4 and not a pH effect of the

medium because here was no reduction in corticle cataracts by simply changing (lowering) the pH of the Optisol® media with citric acid to the same pH of Optisol® containing the CaPEG amine. Reduction in opacity required the presence of the active agent.

Table 5a: 1 mg/ml CAPEG4

Time	**Top**		**Bottom**		
Min	mcg/well	Average	mcg/well	Average	% (stock)
15	427 472	449	4 22	13	2.4
30	448 445	446	26 37	31	5.8
60	454 388	421	8 11	9	1.7
45	459 428	443	9 8	8	1.5
90	467 459	463	17 45	31	5.7
120	453 510	481	21 30	25	4.7
1000 mcg/mL	543	543			
Time 0 harvest:	446 453	450	4 3	3	0.6

Table 5b: 16 mg/mL CAPEG4

Time	**Top**		**Bottom**		
Min	mcg/well	Average	mcg/well	Average	% (stock)
15	5842 6908	6375	58 62	60	0.7
30	6099 6526	6312	93 105	99	1.2
60	6450 7494	6972	160 139	149	1.8
45	6313 6356	6335	677 418	548	6.7
90	6122 6792	6457	525 na	525	6.4
16000 mcg/mL	8186	8186			
Blank insert at 15 min	7857	7857	1837	1837	23

Example 11: Testing of CAPEG4 with human cadaver lenses- reduction of cataracts in human cadaver lenses

[0138] In all cases, the control is Optisol® medium. The remaining data points are for isolated human cadaver lenses treated with CAPEG4 solutions with Optisol®.

[0139] Table 6 shows the results for lenses incubated with control medium or 10 mg/mL CAPEG4 versus time. In table 6, under the heading cortical, there is a LOCS III grade of 1.0, 1.0 and 0.9 for a lens incubated with 10 mg/ml CAPEG4. The LOCS grades for the control are 1.0, 1.2 and 0.9. At 10 mg/mL there was no significant change in the experimental versus control samples.

Table 6- LOCS III Grading of cataracts incubated with Optisol® or 10 mg/ml CAPEG4 versus time

[CaPEG] (mg/mL)	Time (HR)	Cortical	NO	NC	PS
10 (OD)	0	1.0	5.0	5.0	0.9
Control (OS) Optisol Only	0	1.2	5.0	5.0	0.9
10	24	1.0	5.0	5.0	0.9
Control Optisol Only	24	1.2	5.0	5.0	0.9
10	72	0.9	5.0	5.0	0.9
Control	72	0.9	5.0	5.0	1.0

[0140] Table 7 shows the results for lenses incubated with control medium or 50 mg/mL CAPEG4 versus time. In table 7, under the heading cortical, there is a LOCS III grade of 1.0 for all samples and a Nuclear opalescence (NO) grade of 2.0 for all samples. There were no significant differences between the controls and 50 mg/mL incubation up tp 72 hours for cortical cataracts or for NO. Nuclear color (NC) increased slightly with time for both the control and upon incubation in the 50 mg/mL CAPEG4 solution. There was a slight improvement in posterior subcapsular cataract from 1.1 to 0.9 at o0 and 24 hours, respectively.

Table 7- LOCS III Grading of cataracts incubated with Optisol® or 50 mg/ml CAPEG4 versus time

[CaPEG] (mg/mL)	Time (HR)	Cortical	NO	NC	PS
50 (OD)	0	1.0	2.0	1.7	1.1
Control (OS) Optisol Only	0	1.0	2.0	1.8	0.9
50	24	1.0	2.0	1.7	0.9
Control Optisol Only	24	1.0	2.0	1.8	0.9
50	72	1.0	2.0	1.9	0.9
Control	72	1.0	2.0	2.0	0.9

[0141] Table 8 shows the results for lenses incubated with control medium or 100 mg/mL CAPEG4 versus time. There is a decrease in opalescence (NO from 1.8 to 1.2) at 0 and 24 hours, respectively for CAPEG4 incubation and minor improvements in cortical and nuclear color up to 72 hours.

Table 8- LOCS III Grading of cataracts incubated with Optisol® or 100 mg/ml CAPEG4 versus time

[CaPEG] (mg/mL)	Time (HR)	Cortical	NO	NC	PS
100 (OD)	0	3.0	1.8	1.3	0.9
Control (OS) Optisol Only	0	0.9	1.9	1.5	0.9
100	24	2.9	1.2	1.1	0.9
Control Optisol Only	24	0.9	1.8	2.0	0.9
100	72	2.7	1.2	1.1	0.9
Control	72	0.9	1.9	**2.0**	0.9

[0142] Table 9 is a repeat of the experiment in Table 8 with different eyes. Under PS (Posterior subcapsular cataracts) the sample incubated at 100 mg/ml CAPEG4 had values of 1.8, 1.5, and 1.0 at 0, 24 and 72 hours, respectively. There was also a reduction in cortical cataracts from 3.0 to 2.6 to 2.0 at 0, 24, and 72 hours, respectively.

Table 9- LOCS III Grading of cataracts incubated with Optisol® or 100 mg/ml CAPEG4 versus time

[CaPEG] (mg/mL)	Time (HR)	Cortical	NO	NC	PS
100 (OD)	0	3.0	3.0	3.0	1.8
Control (OS) Optisol Only	0	1.0	3.0	3.0	1.5
100	24	2.6	3.0	3.0	1.5
Control Optisol Only	24	1.0	3.0	3.0	1.5
100	72	2.0	3.0	3.2	1.0
Control	72	1.0	3.0	3.1	1.5

[0143] Table 10 shows the results for lenses incubated with control medium or 200 mg/mL CAPEG4 versus time. Cortical cataracts were reduced from 2.5 to 2.2 to 2.0 at 0, 24, and 72 hours, respectively. The control also exhibit a slight reduction in cortical cataracts from 3.3 to 3.0 at 24 and 72 hours, respectively.

Table 10- LOCS III Grading of cataracts incubated with Optisol® or 200 mg/ml CAPEG4 versus time

[CaPEG] (mg/mL)	Time (HR)	Cortical	NO	NC	PS
200 (OD)	0	2.5	2.4	2.4	0
Control (OS) Optisol Only	0	3.3	2.5	2.5	0
200	24	2.2	2.4	2.4	0
Control Optisol Only	24	3.3	2.5	2.5	0
200	72	2.0	2.4	2.4	0
Control	72	3.0	2.5	2.5	0

[0144] Table 11 shows the results for lenses incubated with control medium or 200 mg/mL CAPEG4 versus time. The only decrease in cataract was observed in cortical cataracts for the CAPEG4 solution going from 1.3 to 1.0 to 0.9 at 0, 24, and 72 hours, respectively.

Table 11- LOCS III Grading of cataracts incubated with Optisol® or 200 mg/ml CAPEG4 (in Optisol®) versus time

[CaPEG] (mg/mL)	Time (HR)	Cortical	NO	NC	PS
200 (OD)	0	1.3	3.2	2.8	0.9
Control (OS) Optisol Only	0	1.4	3.2	3.0	0.9
200	24	1.0	3.2	2.8	0.9
Control Optisol Only	24	1.4	3.2	3.0	0.9
200	72	0.9	3.2	2.8	0.9
Control	72	1.4	3.2	3.0	0.9

[0145] Table 12 shows the results of changing the pH of Optisol® with no added CAPEG4. The pH was lowered via the addition of citric acid. There was no effect of changing the pH of the Optisol® on the cataracts.

Table 12: Efect of pH of Optisol® on cataracts

pH	Time (HR)	Cortical	NO	NC	PS
6.470 (OD)	0	2.0	5.0	5.2	0.9
6.085 (OD)	0	2.7	2.3	2.0	0.9
6.470	24	2.0	5.0	5.2	0.9
6.075	24	2.7	2.3	2.0	0.9
6.470	72	2.0	5.0	5.2	0.9
6.075	72	2.7	2.3	2.0	0.9

[0146] For cadaver lens studies, the different starting point for LOCSIII grade is due to the varying starting condition in the patients. As the concentration of the CAPEG4 solutions in Optisol increased, wrinkling of the lens capsule was observed and subjectively exhibited some loss of lens volume.

[0147] The terms “a” and “an” do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. The term “or” means “and/or”. The terms “comprising”, “having”, “including”, and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to”). All ranges disclosed herein are inclusive and combinable.

[0148] Embodiments are described herein, including the best modes known to the inventors. Variations of such embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The skilled artisan is expected to employ such variations as appropriate, and the disclosed methods are expected to be practiced otherwise than as specifically described herein. Accordingly, all modifications and equivalents of the

CLAIMS

1. Use of an ophthalmic composition in the manufacture of a medicament for inhibiting or reversing the progression of cataract formation, presbyopia, or age related degeneration of a crystalline lens in an eye, wherein the composition is to contact the eye, including the crystalline lens, said composition comprising at least one γ-crystallin charge masking agent,

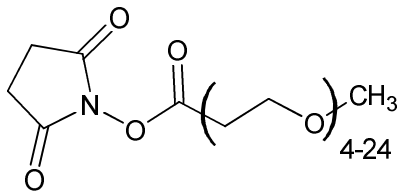
wherein the γ-crystallin charge masking agent is a bifunctional molecule containing a reactive group covalently linked to a molecular bristle,

wherein the reactive group is NH_2, a succinimide, a carboxylic acid, isocyanate, isothiocyanate, sulfonyl chloride, aldehyde, carbodiimide, acyl azide, anhydride, fluorobenzene, carbonate, N-hydroxysuccinimide ester, imidoester, epoxide and fluorophenyl ester, and

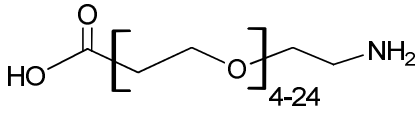
wherein the molecular bristle is a polyethylene glycol, an alkoxy-polyethylene glycol, or an alkoxypolyethylene glycol having 4 to 200 oxyethylene, alkoxyethylene or aryloxyethylene groups; poly(2-hydroxypropyl)methacrylamide (HPMA); poly(2-hydroxyethyl)methacrylate (HEMA);a ply(2-oxaziline), poly(m-phosphocholine, poly lysine, or poly glutamic acid, the molecular bristle having a molecular weight of 150 to 8000.

2. The use according to claim 1, wherein the reactive group is NH_2, N-hydroxysuccinimide or COOH.

3. The use according to claim 1, wherein the γ-crystallin charge masking agent is



or



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4. The use according to any one of claims 1 to 3, wherein the medicament is an eye drop or is to be administered with an ophthalmic device.

5. The use according to claim 4, wherein the ophthalmic device is a contact lens or a punctal plug.

6. The use according to any one of claims 1 to 3, wherein said medicament is to be administered by injection, iontophoresis or ultrasound enhancement.

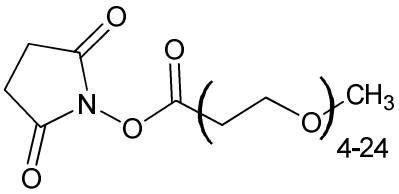
7. An ophthalmic composition comprising a bifunctional molecule containing a reactive group covalently linked to a molecular bristle and an ophthalmically acceptable excipient,

wherein the reactive group is NH_2, a succinimide, a carboxylic acid, isocyanate, isothiocyanate, sulfonyl chloride, carbodiimide, acyl azide, fluorobenzene, carbonate, N-hydroxysuccinimide ester, imidoester, and fluorophenyl ester, and

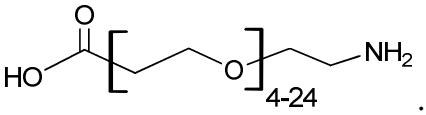
wherein the molecular bristle is a polyethylene glycol, an alkoxy-polyethylene glycol, or an alkoxypolyethylene glycol having 4 to 200 oxyethylene, alkoxyethylene or aryloxyethylene groups; poly(2-hydroxypropyl)methacrylamide (HPMA); poly(2-hydroxyethyl)methacrylate (HEMA);a ply(2-oxaziline), poly(m-phosphocholine, poly lysine, or poly glutamic acid, the molecular bristle having a molecular weight of 150 to 8000.

8. The ophthalmic composition of claim 7, wherein the reactive group is NH_2, N-hydroxysuccinimide or COOH.

9. The ophthalmic composition of claim 7, wherein the bifunctional molecule is



or



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10. The ophthalmic composition of claim 7, wherein the ophthalmic composition is an eye drop or comprised within an ophthalmic device.

11. The ophthalmic composition of claim 10, wherein the ophthalmic device is a contact lens or a punctal plug.