OPHTHALMIC SOLUTIONS DISPLAYING IMPROVED EFFICACY

Related Applications

This application claims priority from US provisional application serial no. 61/037894, which is incorporated by reference in its entirety.

Background of the Invention

There are many commercially available ophthalmic solutions. The solutions should provide disinfection against a variety of bacteria and fungi, which can come in contact with the eye and devices which reside on the eye, such as contact lenses. The solutions must remain free from contamination during the use life of the solution. To meet this requirement solutions either contain a preservative component or are sterile packaged in single use dosages. For contact lens cleaning and care solutions, and over the counter eye drops, multidose containers are popular. These solutions require the inclusion of preservatives (for eye drops) and disinfecting compositions (for contact lens cleaning and care solutions).

Hydrogen peroxide has been used as disinfectant or preservative in ophthalmic solutions. However, hydrogen peroxide is not stable, and must either be included in concentrations which sting the eye or the solutions must contain additional components to stabilize the hydrogen peroxide. Compounds disclosed to be useful as peroxide stabilizers include phosphonates, phosphates, and stannates, and specific examples physiologically compatible salts of phosphonic acids such as diethylenetriamine pentamethylenephosphonic acid. Amino polycarboxylic acid chelating agents, such as ethylene diamine tetraacetic acid have also been disclosed.

Diethylenetriamine pentamethylenephosphonic acid (PTPPA) and ethylenediamine tetraacetic acid (EDTA) are cyctotoxic at relatively low levels and have low pH. Thus, these stabilizers can be included only in small amounts, and require the addition of neutralizing agents to provide a solution which is compatible with the human eye.

Accordingly, for solutions which are instilled directly in the eye, or for contact cleaning and care solutions which do not need to be rinsed off before the lens is placed on the eye, additional hydrogen peroxide stabilizers are desired.

Summary of the Invention

The present invention relates to ophthalmic compositions comprising a pH between about 6 and about 8 and about 50 to about 1500 ppm hydrogen peroxide, about 100 ppm to about 2000 ppm of at least one chlorite compound and about 20 to 100 ppm of at least one saturated, polymeric quaternium salt.

The present invention further relates to ophthalmic solutions comprising the components listed in Table 1, in the amounts listed in Table 1.

Description of the Invention

The present invention relates to novel ophthalmic solutions comprising low concentrations of hydrogen peroxide. The present invention further relates to ophthalmic solutions comprising small concentrations of hydrogen peroxide which are storage stable.

As used herein storage stable, means that under storage conditions, such as temperatures of less than about 40°C, the solution loses less than thirty percent of the hydrogen peroxide in said solution over thirty days, and in some embodiments less than about 25% in thirty days.

Ophthalmic compositions are any composition which can be directly instilled into an eye, or which can be used to soak, clean, rinse, store or treat any ophthalmic device which can be used placed in or on the eye. Examples of ophthalmic compositions include ophthalmic device packing solutions, cleaning solutions, conditioning solutions, storage solutions, eye drops, eye washes, as well as ophthalmic suspensions, gels and ointments and the like. In one embodiment of the present invention, the ophthalmic composition is an ophthalmic solution.

Ophthalmic devices include any devices which can be placed on the eye, or any part of the eye, such as, but not limited to under the eyelid or in the punctum. Examples of ophthalmic devices include contact lenses, ophthalmic bandages, ophthalmic inserts, punctal plugs and the like.

The ophthalmic compositions of the present invention comprise between about 50 to about 1000 ppm hydrogen peroxide. In some embodiments the hydrogen peroxide is present in concentrations between about 100 and about 500 ppm, and in other embodiments, between about 100 and about 300 ppm.

Alternatively, the composition may include a source of hydrogen peroxide. Suitable hydrogen peroxide sources are known, and include peroxy compounds which are hydrolyzed in water. Examples of hydrogen peroxide sources include alkali metal perborates or percarbonates such as sodium perborate and sodium percarbonate.

It has been found that ophthalmic composition comprising hydrogen peroxide in the amounts described above may be stabilized by including between about 0.005 wt% (50 ppm) to about 0.15 wt % (1500 ppm), and in some embodiments from about 100 to about 1000 ppm of at least one ophthalmically compatible stabilizer, such as at least one salt of diethylenetriamine pentaacetic acid comprising at least one calcium salt, zinc salt or mixed calcium/zinc salt of diethylenetriamine pentaacetic acid. As used herein, the term calcium salt, zinc salt or mixed calcium/zinc salt means that the DTPA comprises at least one of the specified cations. So for example, calcium salts of DTPA include DTPA salts which comprise at least one calcium ion. Examples include dicalcium salts of DTPA, dicalcium-trisodium salts of DTPA, monozinc salts of DTPA, and mixtures thereof. The salts of the present invention may further comprise any additional ophthalmically compatible cations such as sodium, magnesium, combinations thereof and the like. In one embodiment the DTPA salt comprises dicalcium DTPA. The concentration of the diethylenetriamine pentaacetic acid salt is between about 50 and about 1000 ppm.

The DTPA salts may formed separately and added to the solution or pentetic acid (diethylenetriamine pentaacetic acid) and a hydroxide salt of the desired cation

may be added to the solution in a stoichiometric amount to form the desired DTPA salt in situ.

Dicalcium diethylenetriamine pentaacetic acid has been found to be at least as effective, and at some concentrations more effective at stabilizing hydrogen peroxide-containing ophthalmic solutions than diethylenetriamine pentamethylenephosphonic acid (DTPPA). Dicalcium diethylenetriamine pentaacetic acid is also less cytotoxic and has a more neutral pH than does DTPPA.

The ophthalmic compositions of the present invention also have a pH of between about 6 and 8, and in some embodiments between about 6.5 and about 7.5. This allows the compositions of the present invention to be instilled directly in the eye, and to be used on ophthalmic devices that are to be placed in the ocular environment.

The ophthalmic compositions may further comprise at least one additional peroxide stabilizer. Any known peroxide stabilizer may be used, so long as it is not cytotoxic at the concentrations being used, and is compatible with the other ophthalmic composition components. For example, the additional peroxide stabilizer should not interfere with the functioning of any other components included in the composition, and should not react with any other components. Examples of suitable additional peroxide stabilizers include phosphonates, phosphates, ethylene diamine tetraacetic acid, nitrilo triacetic acid, ophthalmically compatible water soluble salts of any of the foregoing, mixtures thereof, and the like. In one embodiment the additional peroxide stabilizer comprises DTPPA or least one pharmaceutically acceptable salt of DTPPA.

The at least one additional peroxide stabilizer may be present in concentrations up to about 1000 ppm, and in some embodiments between about 100 and about 500 ppm. When the additional peroxide stabilizer comprises DTPPA or at least one pharmaceutically acceptable salt of DTPPA, it is present in a concentration up to about 1000 ppm, and in some embodiments between about 100 ppm to about 500 ppm.

The ophthalmic compositions of the present invention may further comprise additional components such as, but not limited to pH adjusting agents, tonicity adjusting agents, buffering agents, active agents, lubricating agents, disinfecting agents, viscosity

adjusting agents, surfactants and mixtures thereof. When the ophthalmic composition is an ophthalmic solution, all components in the ophthalmic solution of the present invention should be water-soluble. As used herein, water soluble means that the components, either alone or in combination with other components, do not form precipitates or gel particles visible to the human eye at the concentrations selected and across the temperatures and pH regimes common for manufacturing, sterilizing and storing the ophthalmic solution.

The pH of the ophthalmic composition may be adjusted using acids and bases, such as mineral acids, such as, but not limited to hydrochloric acid and bases such as sodium hydroxide.

The tonicity of the ophthalmic composition may be adjusted by including tonicity adjusting agents. In some embodiments it is desirable for the ophthalmic composition to be isotonic, or near isotonic with respect to normal, human tears. Suitable tonicity adjusting agents are known in the art and include alkali metal halides, phosphates, hydrogen phosphate and borates. Specific examples of tonicity adjusting agents include sodium chloride, potassium chloride, calcium chloride, magnesium chloride, zinc chloride, combinations thereof and the like.

The ophthalmic composition may further comprise at least one buffering agent which is compatible with diethylenetriamine pentaacetic acid salt. Examples of suitable buffering agents include borate buffers, phosphate buffers, sulfate buffers, combinations thereof and the like. In one embodiment the buffering agent comprises borate buffer. In another embodiment, the buffering agent comprises phosphate buffer. Specific examples include borate buffered saline and phosphate buffered saline.

The ophthalmic composition may also comprise at least one disinfecting agent in addition to hydrogen peroxide. The disinfecting agent should not cause stinging or damage to the eye at use concentrations and should be inert with respect to the other composition components. Suitable disinfecting components include polymeric biguanides, polymeric quarternary ammonium compounds, chlorites, bisbiguanides, quarternary ammonium compounds and mixtures thereof.

In one embodiment, the disinfecting component comprises at least one chlorite compound. Suitable chlorite compounds include water soluble alkali metal chlorites, water soluble alkaline metal chlorites and mixtures thereof. Specific examples of chlorite compounds include potassium chlorite, sodium chlorite, calcium chlorite, magnesium chlorite and mixtures thereof. In one embodiment the chlorite compound comprises sodium chlorite.

Suitable concentrations for the chlorite compound include concentrations between about 100 and about 2000 ppm, in some embodiments between about 100 and about 1000 ppm, in other embodiments between about 100 and about 500 ppm and in other embodiments between about 200 and about 500 ppm.

Combinations of suitable peroxide/chlorite disinfecting agents are disclosed in US6,488,965, US6,592,907, US20060127497, US2004/0037891, US 2007/0104798. These patents as well as all other patent disclosed herein are hereby incorporated by reference in their entirety.

The ophthalmic compositions of the present invention may further comprise at least one additional disinfecting compound selected from the group consisting of fully saturated, polymeric quaternium salts such as poly[oxyethylene(-dimethylimino)ethylene-(dimethylimino)ehthylene dichloride (CAS designation of 31512-74-0, and referred to herein as "Polyquaternium-42"), disclosed in US 5,300,296 and US 5380,303. The polymeric quaternium salts are desirably fully saturated to insure they are stable in the presence of the hydrogen peroxide. The fully saturated, polymeric quaternium salts may be present in the solution in amounts between about 10 to about 100 ppm, and in some embodiments from about 25 to about 100 ppm. It has been found that when at least one fully saturated, polymeric quaternium salts such as Polyqaternium-42 is included in an ophthalmic solution along with hydrogen peroxide and chlorite the resulting solutions display surprisingly improved antifungal properties, particularly against *fusarium solani.*

One or more lubricating agents may also be included in the ophthalmic composition. Lubricating agents include water soluble cellulosic compounds,

hyaluronic acid, and hyaluronic acid derivatives, chitosan, water soluble organic polymers, including water soluble polyurethanes, polyethylene glycols, combinations thereof and the like. Specific examples of suitable lubricating agents include polyvinyl pyrrolidone ("PVP"), hydroxypropyl methyl cellulose, carboxymethyl cellulose, glycerol, propylene glycol, 1,3-propanediol, polyethylene glycols, mixtures there of and the like. Generally lubricating agents have molecular weights in excess of 100,000. When glycerol, propylene glycol and 1,3-propanediol are used as lubricating agents, they may have molecular weights lower than 100,000.

When a lubricating agent is used, it may be included in amounts up to about 5 weight %, and in some embodiments between about 100 ppm and about 2 weight%.

One or more active agent may also be incorporated into the ophthalmic solution. A wide variety of therapeutic agents may be used, so long as the selected active agent is inert in the presence of peroxides. Suitable therapeutic agents include those that treat or target any part of the ocular environment, including the anterior and posterior sections of the eye and include pharmaceutical agents, vitamins, nutraceuticals combinations thereof and the like. Suitable classes of active agents include antihistamines, antibiotics, glaucoma medication, carbonic anhydrase inhibitors, anti-viral agents, anti-inflammatory agents, non-steroid anti-inflammatory drugs, antifungal drugs, anesthetic agents, miotics, mydriatics, immunosuppressive agents, antiparasitic drugs, anti-protozoal drugs, combinations thereof and the like. When active agents are included, they are included in an amount sufficient to product the desired therapeutic result (a "therapeutically effective amount").

The ophthalmic composition of the present invention may also include one or more surfactant, detergent or mixture thereof. Suitable examples include tyloxapol, poloxomer (poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide)) type surfactants which are commercially available from BASF and poloxamine type surfactants (non-ionic, tetrafunctional block copolymers based on ethylene oxide/propylene oxide, terminating in primary hydroxyl groups, commercially available from BASF, under the tradename Tetronic). A specific example is Pluronic F-147 and

Tetronic 1304. Tyloxapol is a non-ionic, low molecular weight surfactant, and is fully soluble in the phosphate buffers. Tyloxapol is a detergent commercially available from Pressure Chemical Company. In embodiments where tyloxapol is included, it is included in amounts between about 500 to about 2000 ppm.

Surfactants may be used in amounts up to about 5 weight%, and in some embodiments up to about 2 weight%.

Some surfactants may also act as disinfectant enhancers. Disinfectant enhancers for the solutions of the present application include C_{5-20} polyols, such as 1,2-octanediol (caprylyl glycol), glycerol monocaprylate, sorbitan monolaurate (TWEEN 80) combinations thereof and the like. Disinfectant enhancers may be present in amounts from about 50 to about 2000 ppm.

Additionally, the ophthalmic composition may comprise one or more viscosity adjusting agent or thickener. Suitable viscosity adjusting agents are known in the art and include polyvinyl alcohol, polyethylene glycols, guar gum, combinations thereof and the like. The viscosity adjusting agent may be used in amounts necessary to achieve the desired viscosity.

It will be appreciated that all the components at the concentrations they are used herein, will be soluble in buffered solutions, compatible with the other solution components and will not cause ocular pain or damage.

Examples of ophthalmic solutions according to the present invention are disclosed in Tables 1 and 2.

Table 1

Component	**Chemical Formula**	**Concentration**
Hydrogen Peroxide	H_2O_2	50-1000 ppm 100-500 ppm 100 to 300 ppm

Sodium Chlorite	$NaClO_2$	100-2000 ppm 100-1000 ppm 100-500 ppm 200 to 500 ppm
Polyquaternium-42 (WSCP, polixetonium)	$(CH_{10}H_{24}N_2O.2Cl)_n$	10-100 ppm 25 to 100 ppm
Polyvinylpyrrolidone K90 (PVP, Povidone)	$(C_6H_9NO)_n$	0.1 to 1.0 %
Diethylenetriamine pentaacetic Acid (DTPA)	$C_{14}H_{23}N_3O_{10}$	50-500 ppm 100 to 500 ppm
Boric Acid	$B(OH)_3$	0.15 to 1.00 %
Sodium Borate	$Na_2B_4O_7{\cdot}10H_2O$	
Caprylyl Glycol (1,2-octanediol)	$C_8H_{18}O_2$	50 to 1000 ppm
Glycerol Monolaurate	$C_{15}H_{30}O_4$	50 to 1000 ppm
Poloxamer 407	$OH(C_2H_4O)_{101}(C_3H_6)_{56}$-$(C_2H_4O)_{101}H$	0.1 to 1.5%
Sodium Chloride	NaCl	Adjusted to Tonicity
Water	H_20	Q.S.

Table 2

Component	**Chemical Formula**	**Concentration**
Hydrogen Peroxide	H_2O_2	50-500 ppm
Sodium Chlorite	$NaClO_2$	100-1000 ppm
Polyquaternium-42 (WSCP, polixetonium)	$(CH_{10}H_{24}N_2O.2Cl)_n$	10-100 ppm 25 to 100 ppm
Polyvinylpyrrolidone K90 (PVP, Povidone)	$(C_6H_9NO)_n$	500 to 2500 ppm
DTPA, monocalcium salt	$CaC_{14}H_{23}N_3O_{10}$	0 to 1,000 ppm
Potassium Phosphate, monobasic	KH_2PO_4	0.15 to 0.5 %

Sodium Phosphate, Dibasic	$Na_2HPO_4 \cdot 2H_2O$	
Poloxamer 407	$OH(C_2H_4O)_{101}(C_3H_6)_{56}-(C_2H_4O)_{101}H$	500 – 10,000 ppm
Tyloxapol	$(C_{14}H_{22}O \cdot C_2H_4O \cdot CH_2O)$	250 – 5,000 ppm
Sodium Citrate	$Na_3C_6H_5O_7 \cdot 2H_2O$	0.065 - 0.65%
Sodium Chloride	NaCl	Adjusted to Tonicity
Purified Water	H_20	Q.S.

Ophthalmic solutions of the present invention may be formed by mixing the selected components with water. Other ophthalmic compositions may be formed by mixing the selected components with a suitable carrier.

In order to illustrate the invention the following examples are included. These examples do not limit the invention. They are meant only to suggest a method of practicing the invention. Those knowledgeable in contact lenses as well as other specialties may find other methods of practicing the invention. However, those methods are deemed to be within the scope of this invention.

Examples

Examples 1-3 & Comparative Examples 1 and 2

The base solution shown in Table 3, below was made as follows. HPMC was weighed into about 100 ml deionized water and gently heated to allow all of the material to dissolve. The HPMC solution was allowed to cool and an additional ~500 ml deionized water was added.

NaCl, boric acid, and poloxamer, were added to the solution in the amount listed in Table 3. Dequest 2060 (CAS 15827-60-8, from Fluka Sigma Aldrich) the dicalcium salt of DTPA (ISP Columbus) or a mixture of the two, were added in the amount listed in Table 4. The solution was mixed thoroughly until all components were fully

dissolved. The solution was titrated with NaOH solution (0.1N) until the pH was 7.2 – 7.4.

Deionized water was added to make up a total of approximately 950 ml. The pH was checked and corrected to 7.2-7.4, if necessary. Sodium chlorite and hydrogen peroxide were added in the amounts listed in Table 3 and mixed thoroughly. The pH was rechecked and neutralized with NaOH solution as necessary. Deionized water was added to make up to 1000 g total. The solutions were stored in opaque polypropylene or high density polyethylene containers.

Table 3

Component	Source	Weight (gm)
NaCl	Fisher Science ED	7.5
Boric Acid	Fisher Science ED	1.5
Poloxamer F-127	BASF	1
Hydroxylpropyl methyl cellulose (HPMC)	Acros Organics	1.5
Sodium chlorite	Acros	0.5
Hydrogen peroxide (30%)	Fisher Scientific	0.83
Purified water		Q.S. 1000

100 g aliquots of the solution containing the amounts of DTPPA, DTPA or both, as shown in Table 4, below, were placed in opaque plastic containers and labeled.

A 5 ml sample from each container was removed and analyzed for hydrogen peroxide using the metavanadate colorimetric method, according to the method disclosed in Talanta, vol. 66, issue 1, pg 86-91, March 31, 2005. This is the baseline (t=0) hydrogen peroxide concentration, reported in the fourth column of Table 4, below. Each container was weighed, and the baseline weights were recorded. The containers were stored at 40°C. At each of the intervals shown in Table 4, each container was weighed and 5 ml sample was removed for hydrogen peroxide determination as described above. The results

are shown in Table 4. The value for Δppm was calculated by subtracting the concentration hydrogen peroxide in each solution measured at the time shown in Table 4, and subtracting from the original hydrogen peroxide concentration for that sample. The % Δ was calculated by dividing the concentration of hydrogen peroxide in each solution measured at the time shown in Table 4, by the original hydrogen peroxide concentration for that sample.

Examples 4-9 and Comparative Examples 3-4

Examples 1-3 and Comparative Example 1 were repeated, except that 5ppm of either iron sulfate or copper sulfate were added after the addition of stabilizer, but before the chlorite. Peroxide stability was evaluated as in Examples 1-3 and the results are shown in Tables 5 (copper) and 6 (iron), below.

Table 4

Ex#	DTPPA (mmol/100ml)	DTPA (mmol/100ml)	Initial $[H_2O_2]$ ppm	Day 4 $[H_2O_2]$		Day 9 $[H_2O_2]$		Day 16 $[H_2O_2]$		Day 29 $[H_2O_2]$		Day 36 $[H_2O_2]$	
				Δ ppm	% Δ	Δ ppm	% Δ	Δ ppm	% Δ	Δ ppm	%	Δ ppm	% Δ
CE1	0	0	252	-15	6	-21	8	-38	15	-64	25	-76	30
CE2	0.02	0	243	-15	6	-22	9	-39	16	-64	26	-71	29
2	0	0.02	257	-17	7	-15	6	-31	12	-55	21	-64	25
3	0.01	0.01	258	-16	6	-17	7	-35	14	-59	23	-67	26

Table 5: Copper addition (5ppm)

Ex#	DTPPA (mmol/100ml)	DTPA (mmol/100ml)	Initial $[H_2O_2]$ ppm	Day 4 $[H_2O_2]$		Day 9 $[H_2O_2]$		Day 16 $[H_2O_2]$		Day 29 $[H_2O_2]$		Day 36 $[H_2O_2]$	
				Δ ppm	% Δ	Δ ppm	% Δ	Δ ppm	% Δ	Δ ppm	%	Δ ppm	% Δ
CE3	0	0	179	-179	100	NA	100	NA	100	NA	100	NA	100
4	0.02	0	243	-22	9	-24	10	-42	17	-66	27	-74	30
5	0	0.02	250	-12	5	-14	6	-28	11	-50	20	-60	24
6	0.01	0.01	239	-15	6	-14	6	-30	13	-54	23	-61	26

Table 6: Iron addition (5ppm)

Ex#	DTPPA (mmol/100ml)	DTPA (mmol/100ml)	Initial $[H_2O_2]$ ppm	Day 4 $[H_2O_2]$		Day 9 $[H_2O_2]$		Day 16 $[H_2O_2]$		Day 29 $[H_2O_2]$		Day 36 $[H_2O_2]$	
				Δ ppm	% Δ	Δ ppm	% Δ	Δ ppm	% Δ	Δ ppm	%	Δ ppm	% Δ
CE4	0	0	250	-34	14	-35	14	-54	22	-80	32	-90	36
7	0.02	0	244	-16	7	-18	7	-35	14	-55	23	-63	26
8	0	0.02	251	-15	6	-17	7	-36	14	-62	25	-71	28

9	0.01	0.01	254	-16	6	-14	6	-31	12	-56	22	-63	25

The data in Table 4 above shows that peroxide solutions which are stabilized with the dicalcium salt of DTPA lose less peroxide than unstabilized solutions or solutions stabilized with DTPPA. The stabilized solutions of the present invention lose less than 25% and in some cases less than about 20% peroxide over about 30 days at 40°C. The data in Tables 5 and 6 show that peroxide solutions which are stabilized with the dicalcium salt of DTPA lose substantially less peroxide than unstabilized solutions. None of the solutions lost more than about 0.4 g due to evaporation during the course of the evaluation.

Examples 10-11

Example 2 was repeated except that the concentration of the dicalcium salt of DTPA was varied as shown in Table 7, below, and the pH was not adjusted after the addition of the DTPA salt. At the intervals listed in Table 7, below, samples were withdrawn and tested as described for Example 2.

Table 7

Ex #	DTPA (gm)	Initial $[H_2O_2]$ ppm	Day 7		Day 18 $[H_2O_2]$		Day 29 $[H_2O_2]$		Day 48 $[H_2O_2]$	
			Δ ppm	% Δ	Δ ppm	% Δ	Δ ppm	% Δ	Δ ppm	% Δ
CE 1	0	257	-25	10	-69	27	-103	40	-132	51
4	0.01	259	-13	5	-31	12	-48	19	-79	30
5	0.025	263	-15	6	-36	14	-53	20	-84	32

Examples 12-17

The base solution shown in Table 8, below was made as follows. PVP and poloxamer were weighed into about 100 ml deionized water and gently heated to allow all of the material to dissolve. The PVP solution was allowed to cool and an additional ~500 ml deionized water was added.

NaCl and boric acid were added to the solution in the amount listed in Table 8. The dicalcium salt of DTPA (ISP Columbus) was added in the amount listed in Table 9. The solution was mixed thoroughly until all components were fully dissolved. The solution was titrated with NaOH solution (0.1N) until the pH was 7.2 – 7.4.

Deionized water was added to make up a total of approximately 950 ml. The pH was checked and corrected to 7.2-7.4, if necessary. Sodium chlorite and hydrogen peroxide were added in the amounts listed in Table 8 and mixed thoroughly. The pH was rechecked and neutralized with NaOH solution as necessary. Deionized water was added to make up to 1000 g total. The solutions were stored in opaque polypropylene or high density polyethylene containers.

Table 8

Component	Source	Weight (gm)
NaCl	Fisher Science ED	7.5
H_3BO_3	Fisher Science ED	4.5
$Na_2B_4O_7 \bullet 10H_2O$	Fisher Science ED	0.25
Poloxamer F-127	BASF	1
Polyvinylpyrrolidone K90 (PVP)	ISP	1.5
Sodium chlorite	Acros	0.5
Hydrogen peroxide (30%)	Fisher Scientific	0.7
Purified water		Q.S. 1000

The contact lens disinfection solutions from Examples 12-17 and Comparative Examples 5 & 6 were tested for antimicrobial efficacy using the stand-alone procedure described in ISO 14729. Each solution was challenged with five different organisms. Bacteria used were *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Serratia marcescens.* Fungi used were *Candida albicans* and *Fusarium solani.* Test organisms were cultured from representative ATCC strains as described in ISO 14729.

A ten milliliter aliquot of the test contact lens disinfection solution was placed in a sterile borosilicate glass or polypropylene screw cap test tube. To this solution was

added a 0.01 – 0.1 milliliter aliquot of a suspension of the representative test organism in organic soil. This initial inoculum of the test organism was between $1x10^5$ and $1x10^6$ CFU/ml upon dilution with the test solution. Aliquots of the solution were taken at 25%, 50%, 75% and 100% of the minimum recommended disinfection time, MRDT, for the test contact lens disinfection solution. The residual disinfectant activity of each aliquot was neutralized and the solution plated for microbe enumeration. An additional time point of 400% of the minimum recommended disinfection time was tested for each fungi. Log reductions for each organism were calculated for each time point tested by subtracting the remaining viable organisms from the initial inoculum. The primary criteria for microbial reduction is 3.0 log (99.9%) for the bacteria and 1.0 log (90.0%) for the fungi, within the minimum recommended disinfection time

The results are shown in Table 9, below.

Table 9

Ex	[PQ-42] ppm	[DTPA] ppm	Log reduction @ MRDT				
			PA	SA	SM	CA	FS
12	25	300	>4.8	4.6	4.7	0.5	0.9
13	50	300	>4.8	4.6	4.7	0.4	1.4
14	75	300	>4.8	4.6	4.7	0.5	1.7
15	25	750	>4.8	4.3	4.5	0.4	1
16	50	750	>4.8	4.4	4.7	0.5	1.4
17	75	750	>4.8	4.3	4.7	0.5	1.7

PQ-42 – Polyquaternium-42
PA - *pseudomonas aeruginosa*
SA - *staph aureus*
SM - *serratia marcescens*
CA - *candida albicans*
FS - *fusarium solani*

Comparative Examples 5-8

Examples 12 and 13 were repeated except that either no hydrogen peroxide and chlorite were added or no Polyquaternium-42 was added. Table 10 shows the concentrations of sodium chlorite, peroxide and Polyquternium-42 used in the

comparative Examples, and in Examples 12 and 13. The activity against bacteria and fungi was measured as described in Examples 12-13, and the results are listed in Table 10 along with the results for Examples 12 and 13.

Ex	Chlorite ppm	[PQ-42] ppm	[H2O2] ppm	Log reduction @ MRDT				
				PA	SA	SM	CA	FS
12	500	25	200	>4.8	4.6	4.7	0.5	0.9
CE5	500	0	200	>4.8	1.1	2	0.6	-0.07
13	500	50	200	>4.8	4.6	4.7	0.4	1.4
CE6	0	50	0	0.5	3.7	1.6	-0.3	0.7

PQ-42 – Polyquaternium-42
PA - *pseudomonas aeruginosa*
SA - *staph aureus*
SM - *serratia marcescens*
CA - *candida albicans*
FS - *fusarium solani*

Comparing Examples 12 and 13, which contain both hydrogen peroxide/chlorite and Polyquaternium-42 to Comparative Examples 5 (no Polyquaternium-42) and 6 (no hydrogen peroxide/chlorite), it can be seen that there is a surprising increase in antifungal activity with respect to *fusarium solani*. The peroxide/chlorite disinfectant displays no reduction in *fusarium solani* and at 50 ppm Polyquaternium-42 displays a 0.7 log reduction. However, the combination of the peroxide/chlorite disinfectant and Polyquaternium-42 at 50 ppm displays a 1.4 log reduction in *fusarium solani*, which is greater than the 1 log reduction required for ophthalmic solution efficacy.

WE CLAIM:

1. An ophthalmic composition comprising a pH between about 6 and about 8 and about 50 to about 1000 ppm hydrogen peroxide, about 100 ppm to about 2000 ppm of at least one chlorite compound and about 10 to 100 ppm of at least one saturated, polymeric quaternium salt.

2. The composition of claim 1 wherein said hydrogen peroxide is present in a concentration between about 100 and about 500 ppm.

3. The composition of claim 1 wherein said hydrogen peroxide is present in a concentration between about 100 and about 300 ppm.

4. The composition of claim 1 wherein said pH is between about 6.5 about 7.5.

5. The composition of claim 1 further comprising at least one stabilizer.

6. The composition of claim 5 wherein said at least one stabilizer is selected from the group consisting of diethylenetriamine pentaacetic acid salt, selected from the group consisting of calcium salts of diethylenetriamine pentaacetic acid, zinc salts of diethylenetriamine pentaacetic acid and mixed calcium/zinc salts of diethylenetriamine pentaacetic acid

7. The solution of claim 5 wherein said diethylenetriamine pentaacetic acid is present in a concentration between about 50 and about 1500 ppm.

8. The composition of claim 1 further comprising water.

9. The composition of claim 5 wherein said chelating agent comprises diethylenetriamine pentamethylenephosphonic acid.

10. The composition of claim 9 wherein said diethylenetriamine pentamethylenephosphonic acid is present in a concentration between about 100 and about 1000 ppm.

11. The composition of claim 9 wherein said diethylenetriamine entamethylenephosphonic acid is present in a concentration between about 100 ppm to about 500 ppm.

12. The composition of claim 5 comprising at least two chelating agents.

13. The composition of claim 1 further comprising at least one additional component selected from the group consisting of tonicity adjusting agents, buffering agents, active agents, lubricating agents, disinfecting agents, surfactants and mixtures thereof.

14. The composition of claim 13 further comprising a buffering agent selected from the group consisting of borate buffers, phosphate buffers, sulfate buffers, and mixtures thereof.

15. The composition of claim 14 wherein said buffering agent comprises borate buffer or phosphate buffer.

16. The composition of claim 1 wherein said at least one saturated, polymeric quaternium salt comprises poly[oxyethylene(-dimethylimino)ethylene-(dimethylimino)ehthylene dichloride.

17. The composition of claim 1 wherein said at least one chlorite compound is present in an amount of about 100 ppm to about 1000 ppm.

18. The composition of claim 17 wherein said chlorite compound is selected from the group consisting of water soluble alkali metal chlorites, water soluble alkaline metal chlorites and mixtures thereof.

19. The composition of claim 17 wherein said chlorite compound is selected from the group consisting of potassium chlorite, sodium chlorite, calcium chlorite, magnesium chlorite and mixtures thereof.

20. The composition of claim 17 wherein said chlorite compound comprises sodium chlorite.

21. The composition of claim 17 wherein said chlorite compound is present in an amount between about 100 and about 500 ppm.

22. The composition of claim 20 wherein said chlorite compound is present in an amount between about 200 and about 500 ppm.

23. The composition of claim 7 wherein said diethylenetriamine pentaacetic acid is present in an amount between about 100 and about 1,000 ppm.

24. The composition of claim 1 further comprising about 0.1 to about 1 weight % of at least one lubricating agent.

25. The composition of claim 1 wherein said composition is an ophthalmic solution.

26. The composition of claim 24 wherein said lubricating agent comprises polyvinyl pyrrolidone.

27. The composition of claim 1 further comprising at least one disinfection enhancer.

28. The composition of claim 27 wherein said at least one disinfection enhancer is selected from the group consisting of C_{5-20} polyols.

29. The composition of claim 27 wherein said at least one disinfection enhancer is present in an amount between about 50 ppm and about 2000 ppm and is selected from the group consisting of 1,2-octanediol, glycerol monocaprylate, sorbitan monolaurate (TWEEN 80) and mixtures thereof.