

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
8 December 2005 (08.12.2005)

PCT

(10) International Publication Number
WO 2005/115487 A1

(51) International Patent Classification⁷: **A61L 12/14**,
C11D 3/00, A01N 47/44, A61K 31/155

(21) International Application Number:
PCT/US2005/016181

(22) International Filing Date: 10 May 2005 (10.05.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/850,017 20 May 2004 (20.05.2004) US

(71) Applicant (for all designated States except US): **BAUSCH & LOMB INCORPORATED** [US/US]; One Bausch & Lomb Place, Rochester, NY 14604-2701 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **XIA, Erning** [US/US]; 93 Chippenham Drive, Penfield, NY 14526 (US). **SALAMONE, Joseph, C.** [US/US]; 8 Woodcliff Terrace, Fairport, NY 14450 (US).

(74) Agents: **LAVOIE, Paul, T.** et al.; Bausch & Lomb Incorporated, One Bausch & Lomb Place, Rochester, NY 14604-2701 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,

MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— as to the identity of the inventor (Rule 4.17(i)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Published:

— with international search report

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

(54) Title: ENHANCED DISINFECTING COMPOSITIONS FOR MEDICAL DEVICE TREATMENTS

(57) Abstract: The use of one or more compositions of one or more disinfecting agents at a relatively high pH to disinfect contact lenses and preserve ophthalmic lens compositions is described. Ophthalmic lens solutions containing one or more compositions of one or more disinfecting agents at a relatively high pH and methods of making and using the same are also described.



WO 2005/115487 A1

ENHANCED DISINFECTING COMPOSITIONS FOR MEDICAL DEVICE TREATMENTS

Field of the Invention:

The present invention is directed toward the use of a disinfecting composition in a buffered solution having a pH above about 7.5 for enhanced disinfection and preservation. More particularly, the present invention is directed toward the use of one or more compositions having a reduced amount of one or more disinfecting agents in a solution having a higher pH, above about 7.5, for enhanced rapid disinfection and/or enhanced preservation of ophthalmic solutions and devices.

Background of the Invention:

Contact lenses in wide use today fall into two general categories, hard and soft. The hard or rigid corneal type lenses are formed from materials prepared by the polymerization of acrylic esters, such as poly(methyl methacrylate) (PMMA). The gel, hydrogel or soft type lenses are made by polymerizing such monomers as 2-hydroxyethyl methacrylate (HEMA) or, in the case of extended wear lenses, by polymerizing silicon-containing monomers or macromonomers. Both the hard and soft types of contact lenses are exposed to a broad spectrum of microbes during normal wear and become soiled relatively quickly. Contact lenses whether hard or soft therefore require routine cleaning and disinfecting. Failure to routinely clean and disinfect contact lenses properly can lead to a variety of problems ranging from mere discomfort when being worn to serious ocular infections. Ocular infections caused by virulent microbes such

as *Pseudomonas aeruginosa* can lead to loss of the infected eye(s) if left untreated or if allowed to reach an advanced stage before initiating treatment.

U.S. Patent Number 4,758,595 discloses a contact lens disinfectant and preservative containing a biguanide or a water-soluble salt thereof in combination with a buffer, preferably a borate buffer, e.g., boric acid, sodium borate, potassium tetraborate, potassium metaborate or mixtures of the same.

U.S. Patent Number 4,361,548 discloses a contact lens disinfectant and preservative containing dilute aqueous solutions of a polymer; namely, dimethyldiallylammonium chloride (DMDAAC) having molecular weights ranging from about 10,000 to 1,000,000. Amounts of DMDAAC homopolymer as low as 0.00001 percent by weight may be employed when an enhancer, such as thimerosal, sorbic acid or phenylmercuric salt is used therewith. Although lens binding and concomitant eye tissue irritation with DMDAAC were reduced, it was found in some users to be above desirable clinical levels.

Despite the availability of various commercially available contact lens disinfecting systems such as heat, hydrogen peroxide, biguanides, polymeric biguanides, quaternary ammonium polymers, amidoamines and other chemical agents, there continues to be a need for improved disinfecting systems. Such improved disinfecting systems include systems that are simple to use, are effective against a broad spectrum of microbes, are non-toxic and do not cause ocular irritation as the result of binding to the contact lens material. There is a particular need in the field of contact lens disinfection and ophthalmic composition preservation for safe and effective chemical agents with antimicrobial activity.

Summary of the Invention:

The present invention relates to compositions useful for no-rub cleaning of contact lenses, for rapidly disinfecting medical devices such as contact lenses, for preserving solutions such as ophthalmic solutions, pharmaceuticals, artificial tears and comfort drops against microbial contamination, and for preserving medical devices such as contact lenses. Compositions of the present invention are suitable for use with all types of contact lenses, including rigid gas permeable contact lenses. Compositions of the present invention may be formulated into no-rub contact lens cleaning solutions, which eliminate the need for manual rubbing of contact lenses during cleaning and provide rapid disinfection of contact lenses. For purposes of the present invention, "rapid disinfection" and "rapidly disinfecting" are defined as a microorganism reduction of at least about one log in about one hour. No-rub cleaning and rapid disinfection of contact lenses leads to higher user compliance and greater universal appeal than traditional contact lens disinfecting and cleaning solutions.

Compositions formulated in accordance with the present invention include a relatively lower level, or a reduced amount, of one or more disinfecting agents in solution at a relatively higher pH, above about 7.5, for enhanced, rapid disinfection and/or enhanced preservation. Such solutions including one or more compositions of the present invention at a higher pH, above about 7.5, are useful for cleaning, disinfecting, soaking, rinsing, wetting and conditioning all types of contact lenses, including rigid gas permeable contact lenses. The higher pH of

solutions of the present invention allows for the use of a relatively lowered level, or a reduced amount, of one or more disinfecting agents while still achieving effective disinfection and/or preservation of ophthalmic solutions and devices. Due to the presence of a lower level or a reduced amount of one or more disinfecting agents, lens wearer comfort is increased.

The subject relatively low-level disinfecting agent-containing compositions are useful in the manufacture of multi-purpose solutions that are non-toxic, simple to use, do not cause ocular irritation and enable no-rub contact lens cleaning.

Accordingly, it is an object of the present invention to provide compositions with enhanced disinfecting activity useful in the manufacture of ophthalmic disinfecting systems.

Another object of the present invention is to provide a method for using compositions with enhanced disinfecting activity in the disinfection of medical devices.

Another object of the present invention is to provide compositions with enhanced disinfecting activity useful in ophthalmic systems for disinfecting contact lenses.

Another object of the present invention is to provide compositions with enhanced disinfecting activity useful in preserving ophthalmic systems from microbial contamination.

Another object of the present invention is to provide compositions with enhanced disinfecting activity useful in ophthalmic systems for disinfecting contact lenses with reduced or eliminated eye irritation.

Another object of the present invention is to provide a method of making compositions with enhanced disinfecting activity useful in ophthalmic systems.

Still another object of the present invention is to provide a method of making compositions with enhanced disinfecting activity useful as disinfecting and preservative agents.

These and other objectives and advantages of the present invention, some of which are specifically described and others that are not, will become apparent from the detailed description and claims that follow.

Detailed Description of the Invention:

Compositions of the present invention can be used with all contact lenses such as conventional hard and soft lenses, as well as rigid and soft gas permeable lenses. Such suitable lenses include both hydrogel and non-hydrogel lenses, as well as silicone and fluorine-containing lenses. The term "soft contact lens" as used herein generally refers to those contact lenses that readily flex under small amounts of force. Typically, soft contact lenses are formulated from polymers having a certain proportion of repeat units derived from monomers such as 2-hydroxyethyl methacrylate and/or other hydrophilic monomers, typically crosslinked with a crosslinking agent. However, newer soft lenses, especially for extended wear, are being made from high-Dk silicone-containing materials.

Compositions of the present invention include one or more disinfecting agents. Suitable disinfecting agents for use in the present invention include for example but are not limited to 1,1'-hexamethylene-bis[5-(p-

chlorophenyl)biguanide] (Chlorhexidine) or water soluble salts thereof, 1,1'-hexamethylene-bis[5-(2-ethylhexyl)biguanide] (Alexidine) or water soluble salts thereof, poly(hexamethylene biguanide) (PHMB) or water soluble salts thereof, polyquaternium-1 and quaternary ammonium compounds of low and high molecular weight. Biguanides are described in U.S. Patent Numbers: 5,990,174; 4,758,595 and 3,428,576, each incorporated herein in its entirety by reference. The preferred disinfecting agents due to their ready commercial availability are poly(aminopropyl biguanide) (PAPB), also commonly referred to as poly(hexamethylene biguanide) (PHMB), and 1,1'-hexamethylene-bis[5-(2-ethylhexyl)biguanide] (Alexidine).

Compositions of the present invention comprise a five to thirty percent reduction in the amount of one or more disinfecting agents employed over that of commercially available products. Since the subject compositions comprise five to thirty percent smaller amount of one or more disinfecting agents, it is surprising that the subject compositions exhibit enhanced disinfecting and/or preservative effect. For purposes of the present invention, "enhanced disinfection" and "enhanced preservation" is defined as effective disinfection and effective preservation with lower levels or reduced amounts of one or more disinfecting agents. Standard total amounts of disinfecting agents in lens care solutions are in the range of 0.5 parts per million (ppm) to 15 ppm. Accordingly, compositions of the present invention comprise about 0.35 ppm to about 14.25 ppm, and more preferably about 0.35 ppm to about 10.5 ppm of one or more disinfecting agents.

One or more compositions of the present invention are used in solutions having a relatively higher pH, above about 7.5, and more preferably from above about 7.5 to about 11.0, and more preferably from above about 7.5 to about 8.25. Such solutions of the present invention comprise a five to twenty percent increase in pH over that of commercially available products. Solutions of the present invention are useful as no-rub contact lens care solutions for rapid disinfection of contact lenses. For such purposes, compositions of the present invention are preferably in solution in a sufficient concentration to destroy harmful microorganisms on the surface of a contact lens within a recommended minimum soaking time. This recommended minimum soaking time is included in the package instructions for use of the solution. The term "disinfecting solution" does not exclude the possibility that the solution may also be useful as a preserving solution, or that the disinfecting solution may be useful for other purposes such as daily cleaning, rinsing, and storage of contact lenses, depending on the particular formulation containing the subject compositions. Additionally, compositions of the present invention can be used in conjunction with other known disinfecting or preserving agents if desired.

Compositions of the present invention in solution are physiologically compatible or "ophthalmically safe" for use with contact lenses. Ophthalmically safe as used herein means that a contact lens treated with or in the subject solution is generally suitable and safe for direct placement on the eye without rinsing. The subject solutions are safe and comfortable for daily contact with the eye via a contact lens that has been wetted with the solution. An ophthalmically safe solution has a tonicity and pH that is compatible with the eye and comprises

materials, and amounts thereof, that are non-cytotoxic according to ISO (International Standards Organization) standards and U.S. FDA (Food and Drug Administration) regulations. The solution should be sterile in that the absence of microbial contaminants in the product prior to release should be statistically demonstrated to the degree necessary for such products.

Compositions of the present invention may optionally include one or more aminoalcohol buffers, such as ethanolamine buffers, present in a total amount of from approximately 0.02 to approximately 3.0 percent by weight based on the total weight of the composition. Suitable aminoalcohol buffers include for example but are not limited to monoethanolamine (MEA), diethanolamine (DEA), triethanolamine (TEA), 2-amino-2-methyl-1,3-propanediol (AMPD), 2-dimethylamino-2-methyl-1-propanediol (DMAMP), 2-amino-2-ethylpropanol (AEP), 2-amino-1-butanol (AB) and 2-amino-2-methyl-1-propanol (AMP), but preferably MEA, DEA or TEA.

Compositions of the present invention likewise include one or more tonicity agents to approximate the osmotic pressure of normal lachrymal fluids, which is equivalent to a 0.9 percent solution of sodium chloride or 2.5 percent glycerin solution. Examples of suitable tonicity agents include but are not limited to sodium and potassium chloride, dextrose, mannose, glycerin, propylene glycol, calcium and magnesium chloride. These agents are typically used individually in amounts ranging from about 0.01 to 2.5 percent w/v and, preferably, from about 0.2 to about 1.5 percent w/v. Preferably, the tonicity agent is employed in an amount to provide a final osmotic value of 200 to 450

mOsm/kg and more preferably between about 220 to about 350 mOsm/kg, and most preferably between about 220 to about 320 mOsm/kg.

Compositions of the present invention when in solution likewise include one or more buffers or a buffering system, in addition to or in place of the aminoalcohol buffer, to adjust the final pH of the solution. Suitable buffers include for example but are not limited to phosphate buffers, borate buffers, tris(hydroxymethyl)aminomethane (Tris) buffers, bis(2-hydroxyethyl)imino-tris(hydroxymethyl)methane (bis-Tris) buffers, citrate buffers, sodium bicarbonate, and combinations thereof. A suitable buffering system for example may include at least one phosphate buffer and at least one borate buffer, which buffering system has a buffering capacity of 0.01 to 0.5 mM, preferably 0.03 to 0.45, of 0.01 N of HCl and 0.01 to 0.3, preferably 0.025 to 0.25, of 0.01 N of NaOH to change the pH one unit. Buffering capacity is measured by a solution of the buffers only.

Compositions of the present invention may optionally include one or more cationic polysaccharides. One or more cationic polysaccharides are present in the subject compositions in a total amount of from approximately 0.001 to approximately 0.5 percent by weight based on the total weight of the composition, but more preferably from about 0.005 to about 0.05 percent by weight. Suitable cationic polysaccharides for use in compositions of the present invention include for example but are not limited to variations of polyquaternium-10 such as for example but not limited to Polymer JR 125TM (Dow Chemical Company, Midland, Michigan) having a 2 percent solution viscosity of 75-125 cPs and 1.5 to 2.2 percent nitrogen, Polymer JR 400TM (Dow Chemical

Company) having a 2 percent solution viscosity of 300 to 500 cPs and 1.5 to 2.2 percent nitrogen, Polymer JR 30MTM (Dow Chemical Company) having a 1 percent solution viscosity of 1,000 to 2,500 cPs and 1.5 to 2.2 percent nitrogen, Polymer LR 400TM (Dow Chemical Company) having a 2 percent solution viscosity of 300 to 500 cPs and 0.8 to 1.1 percent nitrogen, Polymer LR 30MTM (Dow Chemical Company) having a 1 percent solution viscosity of 1,250 to 2,250 cPs and 0.8 to 1.1 percent nitrogen, and Polymer LKTM (Dow Chemical Company) having a 2 percent solution viscosity of 300 to 500 cPs and 0.8 to 1.1 percent nitrogen. The preferred cationic polysaccharide for use in the present invention is Polymer JR 125TM or Polymer JR 400TM.

Compositions of the present invention may likewise optionally include one or more surfactants that have known advantages in terms of cleaning efficacy and comfort. Surfactants are present in the subject compositions in a total amount of from approximately 0.001 to approximately 25.0 percent by weight based on the total weight of the composition, but more preferably from about 0.001 to about 5.0 percent by weight. Suitable surfactants include for example but are not limited to sugar-containing polyethers, aliphatic or aromatic hydrocarbon-containing polyethers, polyethers based upon poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide), i.e., (PEO-PPO-PEO), or poly(propylene oxide)-poly(ethylene oxide)-poly(propylene oxide), i.e., (PPO-PEO-PPO), or a combination thereof. PEO-PPO-PEO and PPO-PEO-PPO are commercially available under the trade names PluronicTM, R-PluronicTM, TetronicsTM and R-TetronicsTM (BASF Wyandotte Corp., Wyandotte, Michigan) and are further described in U.S. Patent Number 4,820,352 incorporated herein

in its entirety by reference. Suitable surfactants for use in the present composition should be soluble in the lens care solution, not become turbid, and should be non-irritating to eye tissues.

Optionally, it may also be desirable to include one or more water-soluble viscosity agents in the subject composition. Because of the demulcent effect of viscosity agents, the same have a tendency to enhance the lens wearer's comfort by means of a film on the lens surface cushioning impact against the eye. Suitable viscosity agents include for example but are not limited to water-soluble cellulose polymers like hydroxyethyl cellulose, hydroxypropyl cellulose or carboxymethyl cellulose, povidone, poly(vinyl alcohol), poly(ethylene glycol), poly(ethylene oxide) and the like. Viscosity agents may be employed in amounts ranging from about 0.01 to about 4.0 weight percent or less.

Compositions of the present invention may optionally include one or more sequestering agents to bind metal ions, which in the case of ophthalmic solutions, might otherwise react with protein deposits and collect on contact lenses. Suitable sequestering agents include for example but are not limited to ethylenediaminetetraacetic acid (EDTA) and its salts. Another useful class of sequestering agents are phosphonates or hydroxyalkylphosphonates (HAP), such as those disclosed in U.S. Patent No. 5,858,937 (Richards et al.), available under the trade name Dequest® (Monsanto Co., St. Louis, Missouri), and most preferably tetra sodium etidronate available under the trade name Dequest® 2016 (Monsanto Co.). Sequestering agents are preferably used in amounts ranging from about 0.01 to about 0.2 weight percent.

The compositions of the present invention are described in still greater detail in the examples that follow.

EXAMPLE 1 – Effect of pH on Biocidal Efficacy:

Sample solutions for testing the effect of pH on biocidal efficacy, were prepared in accordance with the formulations set forth below in Table 1.

TABLE 1
Test Sample Solutions

Ingredients W/W Percent	1	2	Sample 3	4	5	6
Triethanolamine HCl	1.00	0.90	0.80	0.60	0.40	0.10
Triethanolamine BASE	0.10	0.20	0.30	0.50	0.70	1.00
Sodium Chloride	0.33	0.36	0.36	0.36	0.41	0.41
Alexidine 2HCl (ppm)	3.50	3.50	3.50	3.50	3.50	3.50
pH	7.03	7.36	7.58	7.92	8.23	8.94

Test solutions prepared in accordance with the formulations set forth above in Table 1, were tested to determine the effect of pH on biocidal efficacy. Test solutions prepared in accordance with Table 1 above, were each tested for ISO/FDA microbial biocidal efficacy using five FDA/ISO challenge microorganisms, i.e., three bacteria and two fungi. Primary acceptance criteria established for bacteria require that the number of viable bacteria, recovered per ml, shall be reduced by a value not less than 3.0 logs within the minimum recommended disinfection period. Primary acceptance criteria established for yeasts and molds require that the number of viable yeasts and molds, recovered per ml, shall be reduced by a value of not less than 1.0 logs within the minimum

recommended disinfection time with no increase at not less than four times the minimum recommended disinfection time within an experimental error of ± 0.5 logs. Secondary acceptance criteria for bacteria requires that there is a combined log reduction for the mean values of all three bacteria of not less than 5.0 logs within the recommended disinfection period. The minimum acceptable mean log reduction for any single bacterial type is 1.0 log. Stasis for the yeast and mold must be observed for the minimum recommended disinfection period. Results of the ISO/FDA microbial biocidal efficacy testing of the subject test solutions are set forth below in Table 2.

TABLE 2
Biocidal Efficacy With Varying pH

ISO Agent	Hours	Log Reduction of Sample					
		1	2	3	4	5	6
<i>Staphylococcus aureus</i> (ATCC 6538)	1	3.6	3.3	3.9	3.8	>4.6	>4.6
	4	>4.6	>4.6	>4.6	>4.6	>4.6	>4.6
<i>Pseudomonas aeruginosa</i> (ATCC 9027)	1	3.4	3.9	4.8	4.1	4.8	4.8
	4	>4.8	>4.8	>4.8	>4.8	>4.8	>4.8
<i>Serratia marcescens</i> (ATCC 13880)	1	3.0	3.8	3.8	3.8	3.5	4.5
	4	>4.7	>4.7	>4.7	>4.7	>4.7	>4.7
<i>Candida albicans</i> (ATCC 10231)	1	2.1	2.5	2.5	2.5	3.3	2.8
	4	2.5	4.4	4.4	4.2	4.3	4.7
<i>Fusarium solani</i> (ATCC 36031)	1	3.1	3.2	3.2	3.0	2.9	1.8
	4	3.7	4.0	4.0	3.4	3.9	3.3

The results of the biocidal efficacy with varying pH study show that biocidal efficacy increases significantly when the pH of the test solution

increases. This is particularly evident at the one-hour time point, with the exception of *Fusarium solani*.

EXAMPLE 2 – Effect of Triethanolamine Buffer Strength/Capacity on Biocidal Efficacy:

Sample solutions for testing the effect of triethanolamine (TEA) buffer strength/capacity on biocidal efficacy were prepared in accordance with the formulations set forth below in Table 3.

TABLE 3

Test Sample Solutions

Ingredients W/W Percent	7	8	Sample 9	10
Triethanolamine HCl	0.470	0.705	0.940	1.410
Triethanolamine BASE	0.075	0.100	0.150	0.225
Sodium Chloride	0.52	0.45	0.36	0.19
Alexidine 2HCl (ppm)	3.00	3.00	3.00	3.00
pH	7.00	7.00	7.00	7.00

TABLE 3 - Continued**Test Sample Solutions**

Ingredients W/W Percent	11	Sample 12	13	14
Triethanolamine HCl	0.470	0.705	0.940	1.410
Triethanolamine BASE	0.075	0.100	0.150	0.225
Sodium Chloride	0.52	0.45	0.36	0.19
Alexidine 2HCl (ppm)	4.00	4.00	4.00	4.00
pH	7.00	7.00	7.00	7.00

Test solutions prepared in accordance with the formulations set forth above in Table 3 were tested to determine the effect of TEA buffer strength/capacity on biocidal efficacy. Test solutions prepared in accordance with Table 3 above were each tested for ISO/FDA microbial biocidal efficacy using five FDA/ISO challenge microorganisms, i.e., three bacteria and two fungi. Primary acceptance criteria established for bacteria require that the number of viable bacteria, recovered per ml, shall be reduced by a value not less than 3.0 logs within the minimum recommended disinfection period. Primary acceptance criteria established for yeasts and molds require that the number of viable yeasts and molds, recovered per ml, shall be reduced by a value of not less than 1.0 logs within the minimum recommended disinfection time with no increase at not less than four times the minimum recommended disinfection time within an experimental error of +/- 0.5 logs. Secondary acceptance criteria for bacteria requires that there is a combined log reduction for the mean values of all three

bacteria of not less than 5.0 logs within the recommended disinfection period.

The minimum acceptable mean log reduction for any single bacterial type is 1.0 log. Stasis for the yeast and mold must be observed for the minimum recommended disinfection period. Results of the ISO/FDA microbial biocidal efficacy testing of the subject test solutions are set forth below in Table 4.

TABLE 4

Biocidal Efficacies With Varying TEA Buffer Strength/Capacity

ISO Agent	Hours	Log Reduction of Sample			
		7	8	9	10
<i>Staphylococcus aureus</i>					
(ATCC 6538)	1	2.2	2.0	2.3	2.0
	4	4.3	3.6	3.8	3.4
<i>Pseudomonas aeruginosa</i>					
(ATCC 9027)	1	3.2	3.0	3.2	3.1
	4	>4.7	4.3	>4.7	>4.7
<i>Serratia marcescens</i>					
(ATCC 13880)	1	2.8	3.1	3.1	3.4
	4	4.3	>4.7	4.2	4.7
<i>Candida albicans</i>					
(ATCC 10231)	1	1.2	1.5	1.7	2.1
	4	2.0	2.3	2.9	3.8
<i>Fusarium solani</i>					
(ATCC 36031)	1	2.5	2.2	2.4	3.0
	4	2.4	3.9	4.4	3.0

TABLE 4 - Continued

Biocidal Efficacies With Varying TEA Buffer Strength/Capacity

ISO Agent	Hours	Log Reduction of Sample			
		11	12	13	14
<i>Staphylococcus aureus</i>					
(ATCC 6538)	1	3.0	2.7	2.9	2.7
	4	4.0	4.7	>4.7	4.5
<i>Pseudomonas aeruginosa</i>					
(ATCC 9027)	1	3.5	3.2	3.6	3.9
	4	>4.7	>4.7	>4.7	>4.7
<i>Serratia marcescens</i>					
(ATCC 13880)	1	3.1	3.4	3.4	3.5
	4	>4.7	>4.7	>4.7	>4.7
<i>Candida albicans</i>					
(ATCC 10231)	1	1.7	2.0	2.1	2.8
	4	2.7	3.3	3.9	4.2
<i>Fusarium solani</i>					
(ATCC 36031)	1	3.2	2.9	4.4	3.0
	4	4.4	>4.6	4.1	>4.6

The results of the biocidal efficacy with varying TEA buffer strength/capacity study show that biocidal efficacy increases significantly when the buffer capacity of the test solution increases. This is particularly evident at both the one- and four-hour time points for *Candida albicans*.

EXAMPLE 3 – Effect of Mixed Buffers at High pH on Biocidal Efficacy:

Sample solutions for testing the effect of mixed buffers of TEA and borate at a relatively high pH on biocidal efficacy, were prepared in accordance with the formulations set forth below in Table 5.

TABLE 5
Test Sample Solutions

Ingredients W/W Percent	Sample 15	Sample 16	17
Boric Acid	1.500	1.500	1.500
Triethanolamine BASE	1.000	1.000	1.000
Tetra sodium etidronate	0.100	0.100	0.100
Polyquaternium-10	0.020	0.020	0.020
Pluronic F127	2.000	2.000	2.000
Tetronic 1107	1.000	1.000	1.000
Alexidine 2HCl (ppm)	3.000	3.500	4.000
pH	7.7	7.7	7.7

Test solutions prepared in accordance with the formulations set forth above in Table 5 were tested to determine the effect of mixed buffers of TEA and borate at a relatively high pH on biocidal efficacy. Test solutions prepared in accordance with Table 5 above, were each tested for ISO/FDA microbial biocidal efficacy using five FDA/ISO challenge microorganisms, i.e., three bacteria and two fungi. Primary acceptance criteria established for bacteria require that the number of viable bacteria, recovered per ml, shall be reduced by a value not less than 3.0 logs within the minimum recommended disinfection period. Primary

acceptance criteria established for yeasts and molds require that the number of viable yeasts and molds, recovered per ml, shall be reduced by a value of not less than 1.0 logs within the minimum recommended disinfection time with no increase at not less than four times the minimum recommended disinfection time within an experimental error of ± 0.5 logs. Secondary acceptance criteria for bacteria requires that there is a combined log reduction for the mean values of all three bacteria of not less than 5.0 logs within the recommended disinfection period. The minimum acceptable mean log reduction for any single bacterial type is 1.0 log. Stasis for the yeast and mold must be observed for the minimum recommended disinfection period. Results of the ISO/FDA microbial biocidal efficacy testing of the subject test solutions are set forth below in Table 6.

TABLE 6

Biocidal Efficacies With Mixed Buffers and High pH

ISO Agent	Hours	Log Reduction of Sample		
		15	16	17
<i>Staphylococcus aureus</i>				
(ATCC 6538)	1	4.5	4.8	4.5
	4	4.2	4.1	4.5
<i>Pseudomonas aeruginosa</i>				
(ATCC 9027)	1	4.2	4.4	4.4
	4	4.4	4.6	4.4
<i>Serratia marcescens</i>				
(ATCC 13880)	1	4.2	3.4	>4.2
	4	4.0	3.9	>4.2

TABLE 6 - Continued

TABLE 6

Biocidal Efficacies With Mixed Buffers and High pH

ISO Agent	Hours	Log Reduction of Sample		
		15	16	17
<i>Candida albicans</i>				
(ATCC 10231)	1	>4.7	>4.7	>4.7
	4	>4.7	>4.7	>4.7
<i>Fusarium solani</i>				
(ATCC 36031)	1	>4.4	>4.4	>4.4
	4	>4.4	>4.4	>4.4

The results of the biocidal efficacy with mixed buffers at a high pH study show that biocidal efficacy increases significantly when the pH is at 7.7. This is particularly evident in the case of yeast and mold.

EXAMPLE 4 – Effect of Mixed Buffers at High pH on Biocidal Efficacy:

Sample solutions for testing the effect of mixed buffers of TEA and borate at a neutral pH on biocidal efficacy, were prepared in accordance with the formulations set forth below in Table 7.

TABLE 7
Test Sample Solutions

Ingredients W/W Percent	Sample 18	Sample 19	20
Boric Acid	1.300	1.300	1.300
Triethanolamine BASE	0.700	0.700	0.700
Tetra sodium etidronate	0.100	0.100	0.100
Polyquaternium-10	0.020	0.020	0.020
Pluronic F127	2.000	2.000	2.000
Tetronic 1107	1.000	1.000	1.000
Alexidine 2HCl (ppm)	3.000	3.500	4.000
pH	7.0	7.0	7.0

Test solutions prepared in accordance with the formulations set forth above in Table 7 were tested to determine the effect of mixed buffers of TEA and borate at a neutral pH on biocidal efficacy. Test solutions prepared in accordance with Table 7 above were each tested for ISO/FDA microbial biocidal efficacy using five FDA/ISO challenge microorganisms, i.e., three bacteria and two fungi. Primary acceptance criteria established for bacteria require that the number of viable bacteria, recovered per ml, shall be reduced by a value not less than 3.0 logs within the minimum recommended disinfection period. Primary acceptance criteria established for yeasts and molds require that the number of viable yeasts and molds, recovered per ml, shall be reduced by a value of not less than 1.0 logs within the minimum recommended disinfection time with no increase at not less than four times the minimum recommended disinfection time

within an experimental error of +/- 0.5 logs. Secondary acceptance criteria for bacteria requires that there is a combined log reduction for the mean values of all three bacteria of not less than 5.0 logs within the recommended disinfection period. The minimum acceptable mean log reduction for any single bacterial type is 1.0 log. Stasis for the yeast and mold must be observed for the minimum recommended disinfection period. Results of the ISO/FDA microbial biocidal efficacy testing of the subject test solutions are set forth below in Table 8.

TABLE 8

Biocidal Efficacies With Mixed Buffers and Neutral pH

ISO Agent	Hours	Log Reduction of Sample		
		18	19	20
<i>Staphylococcus aureus</i>				
(ATCC 6538)	1	4.1	4.1	4.6
	4	4.2	>4.8	4.0
<i>Pseudomonas aeruginosa</i>				
(ATCC 9027)	1	4.4	4.7	4.3
	4	4.1	4.7	4.9
<i>Serratia marcescens</i>				
(ATCC 13880)	1	2.0	2.7	>4.2
	4	3.2	3.7	3.2
<i>Candida albicans</i>				
(ATCC 10231)	1	4.4	3.4	4.3
	4	>4.7	>4.7	>4.7
<i>Fusarium solani</i>				
(ATCC 36031)	1	2.8	>4.4	>4.4
	4	>4.4	>4.4	>4.4

The results of the biocidal efficacy with mixed buffers at a neutral pH study show that biocidal efficacy decreases significantly in a mixed buffer system when the pH is at 7.0 as used in Example 3.

EXAMPLE 5 – Effect of Mixed Buffers at Neutral pH on Biocidal Efficacy:

[0042] Sample solutions for testing the effect of mixed buffers of phosphate and borate at a neutral pH on biocidal efficacy, were prepared in accordance with the formulations set forth below in Table 9.

TABLE 9
Test Sample Solutions

Ingredients W/W Percent	21	Sample 22	23
Boric Acid	0.850	0.850	0.850
Sodium Phosphate (monobasic)	0.150	0.150	0.150
Sodium Phosphate (dibasic)	0.420	0.420	0.420
Tetra sodium etidronate	0.100	0.100	0.100
Polyquaternium-10	0.020	0.020	0.020
Pluronic F127	2.000	2.000	2.000
Tetronic 1107	1.000	1.000	1.000
Alexidine 2HCl (ppm)	3.500	4.000	4.500
pH	7.0	7.0	7.0

Test solutions prepared in accordance with the formulations set forth above in Table 9 were tested to determine the effect of mixed buffers of phosphate and borate at a neutral pH on biocidal efficacy. Test solutions prepared in accordance with Table 9 above, were each tested for ISO/FDA microbial biocidal efficacy using five FDA/ISO challenge microorganisms, i.e.,

three bacteria and two fungi. Primary acceptance criteria established for bacteria require that the number of viable bacteria, recovered per ml, shall be reduced by a value not less than 3.0 logs within the minimum recommended disinfection period. Primary acceptance criteria established for yeasts and molds require that the number of viable yeasts and molds, recovered per ml, shall be reduced by a value of not less than 1.0 logs within the minimum recommended disinfection time with no increase at not less than four times the minimum recommended disinfection time within an experimental error of ± 0.5 logs. Secondary acceptance criteria for bacteria requires that there is a combined log reduction for the mean values of all three bacteria of not less than 5.0 logs within the recommended disinfection period. The minimum acceptable mean log reduction for any single bacterial type is 1.0 log. Stasis for the yeast and mold must be observed for the minimum recommended disinfection period. Results of the ISO/FDA microbial biocidal efficacy testing of the subject test solutions are set forth below in Table 10.

TABLE 10**Biocidal Efficacies With Mixed Buffers and Neutral pH**

ISO Agent	Hours	Log Reduction of Sample		
		21	22	23
<i>Staphylococcus aureus</i>				
(ATCC 6538)	1	3.0	3.6	3.9
	4	>4.9	>4.9	>4.9
<i>Pseudomonas aeruginosa</i>				
(ATCC 9027)	1	>5.0	4.2	>5.0
	4	>5.0	>5.0	>5.0

TABLE 10 - Continued

TABLE 10

Biocidal Efficacies With Mixed Buffers and Neutral pH

ISO Agent	Hours	Log Reduction of Sample		
		21	22	23
<i>Serratia marcescens</i>				
(ATCC 13880)	1	2.9	3.1	3.8
	4	4.5	>4.5	>4.5
<i>Candida albicans</i>				
(ATCC 10231)	1	2.6	2.9	3.1
	4	3.6	4.2	4.4
<i>Fusarium solani</i>				
(ATCC 36031)	1	4.5	>4.5	>4.5
	4	>4.5	>4.5	>4.5

The results of the biocidal efficacy with mixed buffers at a neutral pH study show that biocidal efficacy is significantly lower at a pH of 7.0 than at a pH of 7.6 (see Example 6 below). This is particularly true in the case of *Candida albicans*.

EXAMPLE 6 – Effect of Mixed Buffers at High pH on Biocidal Efficacy:

Sample solutions for testing the effect of mixed buffers of phosphate and borate at a relatively high pH on biocidal efficacy, were prepared in accordance with the formulations set forth below in Table 11.

TABLE 11
Test Sample Solutions

Ingredients W/W Percent	24	Sample 25	26
Boric Acid	0.385	0.385	0.385
Sodium Phosphate (monobasic)	0	0	0
Sodium Phosphate (dibasic)	0.420	0.420	0.420
Tetra sodium etidronate	0.100	0.100	0.100
Polyquaternium-10	0.020	0.020	0.020
Pluronic F127	2.000	2.000	2.000
Tetronic 1107	1.000	1.000	1.000
Alexidine 2HCl (ppm)	3.500	4.000	4.500
pH	7.6	7.6	7.6

Test solutions prepared in accordance with the formulations set forth above in Table 11 were tested to determine the effect of mixed buffers of phosphate and borate at a high pH on biocidal efficacy. Test solutions prepared in accordance with Table 11 above were each tested for ISO/FDA microbial biocidal efficacy using five FDA/ISO challenge microorganisms, i.e., three bacteria and two fungi. Primary acceptance criteria established for bacteria require that the number of viable bacteria, recovered per ml, shall be reduced by a value not less than 3.0 logs within the minimum recommended disinfection period. Primary acceptance criteria established for yeasts and molds require that the number of viable yeasts and molds, recovered per ml, shall be reduced

by a value of not less than 1.0 logs within the minimum recommended disinfection time with no increase at not less than four times the minimum recommended disinfection time within an experimental error of +/- 0.5 logs. Secondary acceptance criteria for bacteria requires that there is a combined log reduction for the mean values of all three bacteria of not less than 5.0 logs within the recommended disinfection period. The minimum acceptable mean log reduction for any single bacterial type is 1.0 log. Stasis for the yeast and mold must be observed for the minimum recommended disinfection period. Results of the ISO/FDA microbial biocidal efficacy testing of the subject test solutions are set forth below in Table 12.

TABLE 12
Biocidal Efficacies With Mixed Buffers and High pH
Log Reduction of

ISO Agent	Hours	Sample		
		24	25	26
<i>Staphylococcus aureus</i>				
(ATCC 6538)	1	4.6	4.3	4.9
	4	>4.9	>4.9	>4.9
<i>Pseudomonas aeruginosa</i>				
(ATCC 9027)	1	>5.0	>5.0	4.5
	4	>5.0	>5.0	>5.0
<i>Serratia marcescens</i>				
(ATCC 13880)	1	2.7	3.4	3.1
	4	>4.5	>4.5	4.5
<i>Candida albicans</i>				
(ATCC 10231)	1	2.6	3.0	>4.6
	4	4.6	>4.6	>4.6
<i>Fusarium solani</i>				
(ATCC 36031)	1	4.5	4.5	>4.5
	4	>4.5	>4.5	>4.5

The results of the biocidal efficacy with mixed buffers at a high pH study show that biocidal efficacy is significantly increased at a pH of 7.6 than at a pH of 7.0 (see Example 5 above).

One or more disinfecting agent-containing compositions of the present invention are useful as contact lens care solutions for disinfecting contact lenses. An effective disinfecting amount of disinfecting agent is an amount that will at least partially reduce the microorganism population in the formulations employed. Preferably, disinfecting amount is that which will reduce the microbial burden of representative bacteria by two log orders in four hours and more preferably by one log order in one hour. Most preferably, a disinfecting amount is an amount that will eliminate the microbial burden on a contact lens when used according to its regimen for the recommended soaking time as established by ISO (International Standards for Ophthalmic Optics)/FDA Stand-Alone Procedures for Disinfection Test (ISO/DIS 14729; 2001). Typically, such agents are present in concentrations ranging from about 0.00001 to about 0.5 percent weight/volume (w/v), and more preferably, from about 0.00003 to about 0.5 percent w/v. Unexpectedly, when used at a high pH, i.e., above about 7.5, a smaller amount of disinfecting agent, i.e., a 5 to 30 percent reduction and more preferably a 15 to 30 percent reduction, is required to achieve a disinfecting amount.

As stated above, contact lenses or similar medical devices are disinfected by contacting the lens with a solution of one or more compositions of the present composition. Although this may be accomplished by simply soaking a lens in the subject solution, if desired, a few drops of the solution may be initially placed on

each side of the lens prior to rubbing the lens for a period of time, for example, approximately 20 seconds. The lens can then be subsequently immersed within several milliliters of the subject solution. Preferably, the lens is permitted to soak in the solution for at least four hours. The lenses are then removed from the solution, rinsed with the same or a different solution, for example a preserved isotonic saline solution and then replaced on the eye.

Solutions containing one or more compositions of the present invention may be formulated into specific contact lens care products for use as customary in the field of ophthalmology. Such products include but are not limited to wetting solutions, soaking solutions, cleaning and conditioning solutions, as well as multipurpose type lens care solutions and in-eye cleaning and conditioning solutions.

While the invention has been described in conjunction with specific examples thereof, this is illustrative only. Accordingly, many alternatives, modifications, and variations will be apparent to those skilled in the art in the light of the foregoing description and it is, therefore, intended to embrace all such alternatives, modifications, and variations as to fall within the spirit and scope of the appended claims.

We claim:

1. A composition comprising:
a reduced volume disinfecting amount of one or more disinfecting agents at a high pH.
2. The composition of claim 1 wherein said high pH is above about 7.5.
3. The composition of claim 1 wherein said high pH is above about 7.5 to about 8.5.
4. The composition of claim 1 wherein said high pH is above about 7.5 to about 8.25.
5. The composition of claim 1 wherein said one or more disinfecting agents are selected from the group consisting of 1,1'-hexamethylene-bis[5-(p-chlorophenyl)biguanide], water soluble salts of 1,1'-hexamethylene-bis[5-(p-chlorophenyl)biguanide], 1,1'-hexamethylene-bis[5-(2-ethylhexyl)biguanide], water soluble salts of 1,1'-hexamethylene-bis[5-(2-ethylhexyl)biguanide], poly(hexamethylene biguanide), water soluble salts of poly(hexamethylene biguanide), polyquaternium-1 and quaternary ammonium compounds of low and high molecular weight.
6. The composition of claim 1 wherein said one or more disinfecting agents include 1,1'-hexamethylene-bis[5-(p-chlorophenyl)biguanide] or salts thereof.
7. The composition of claim 1 wherein said reduced volume disinfecting amount of said one or more disinfecting agents is a standard volume reduced by 5 to 30 percent.

8. A method of producing the composition of claim 1 comprising:
combining a reduced volume disinfecting amount of one or more disinfecting agents at a high pH.
9. The method of claim 8 wherein said high pH is above about 7.5.
10. The method of claim 8 wherein said high pH is above about 7.5 to about 8.5.
11. The method of claim 8 wherein said high pH is above about 7.5 to about 8.25.
12. The method of claim 8 wherein said one or more disinfecting agents are selected from the group consisting of 1,1'-hexamethylene-bis[5-(p-chlorophenyl)biguanide], water soluble salts of 1,1'-hexamethylene-bis[5-(p-chlorophenyl)biguanide], 1,1'-hexamethylene-bis[5-(2-ethylhexyl)biguanide], water soluble salts of 1,1'-hexamethylene-bis[5-(2-ethylhexyl)biguanide], poly(hexamethylene biguanide), water soluble salts of poly(hexamethylene biguanide), polyquaternium-1 and quaternary ammonium compounds of low and high molecular weight.
13. The method of claim 8 wherein said one or more disinfecting agents include 1,1'-hexamethylene-bis[5-(p-chlorophenyl)biguanide] or salts thereof.
14. The method of claim 8 wherein said reduced volume disinfecting amount of said one or more disinfecting agents is a standard volume reduced by 5 to 30 percent.
15. A solution comprising one or more compositions of claim 1.
16. The solution of claim 15 wherein said high pH is above about 7.5.

17. The solution of claim 15 wherein said high pH is above about 7.5 to about 8.5.
18. The solution of claim 15 wherein said high pH is above about 7.5 to about 8.25.
19. The solution of claim 15 wherein said solution includes one or more buffers or buffering systems.
20. The solution of claim 15 wherein said solution includes one or more buffers or buffering systems selected from the group consisting of phosphate buffers, borate buffers, tris(hydroxymethyl)aminomethane (Tris) buffers, bis(2-hydroxyethyl)imino-tris(hydroxymethyl)methane (bis-Tris) buffers, sodium bicarbonate, citrate buffers, aminoalcohol buffers and combinations thereof.
21. The solution of claim 15 wherein said solution includes one or more tonicity agents.
22. The solution of claim 15 wherein said solution includes one or more tonicity agents selected from the group consisting of sodium chloride, potassium chloride, dextrose, mannose, glycerin, propylene glycol, calcium chloride and magnesium chloride.
23. The solution of claim 15 wherein said solution includes one or more surfactants.
24. The solution of claim 15 wherein said solution includes one or more surfactants selected from the group consisting of polyethers based upon poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide), poly(propylene oxide)-poly(ethylene oxide)-poly(propylene oxide), sugar-

containing polyethers, aliphatic or aromatic hydrocarbon-containing polyethers and combinations thereof.

25. The solution of claim 15 wherein said solution includes one or more viscosity agents.
26. The solution of claim 15 wherein said solution includes one or more viscosity agents selected from the group consisting of water-soluble cellulose polymers, povidone, poly(vinyl alcohol), poly(ethylene glycol) and poly(ethylene oxide).
27. The solution of claim 15 wherein said solution includes one or more aminoalcohol buffers.
28. The solution of claim 15 wherein said solution includes one or more aminoalcohol buffers selected from the group consisting of monoethanolamine, diethanolamine, triethanolamine, 2-amino-2-methyl-1,3-propanediol, 2-dimethylamino-2-methyl-1-propanediol, 2-amino-2-ethylpropanol, 2-amino-1-butanol and 2-amino-2-methyl-1-propanol.
29. The solution of claim 15 wherein said solution includes one or more cationic polysaccharides.
30. The solution of claim 15 wherein said solution includes one or more cationic polysaccharides selected from the group consisting of variations of polyquaternium-10.
31. The solution of claim 15 wherein said solution includes one or more sequestering agents.

32. The solution of claim 15 wherein said solution includes one or more sequestering agents selected from the group consisting of phosphonates, ethylenediaminetetraacetic acid and salts of ethylenediaminetetraacetic acid.
33. A method of using the solution of claim 15 comprising:
contacting a surface of a contact lens with said solution for a period of time suitable to eliminate a microbial burden on said contact lens.
34. A method of producing the solution of claim 15 comprising:
adding a reduced volume disinfecting amount of said one or more disinfecting agents to a solution at a high pH.
35. An improved disinfecting composition including one or more disinfecting agents in solution wherein the improvement comprises:
a reduced volume disinfecting amount of said one or more disinfecting agents at a high pH to achieve increased biocidal efficacy.
36. The improved composition of claim 35 wherein said high pH is above about 7.5.
37. The improved composition of claim 35 wherein said high pH is above about 7.5 to about 8.5.
38. The improved composition of claim 35 wherein said high pH is above about 7.5 to about 8.25.
39. The improved composition of claim 35 wherein said one or more disinfecting agents are selected from the group consisting of 1,1'-hexamethylene-bis[5-(p-chlorophenyl)biguanide], water soluble salts of 1,1'-hexamethylene-bis[5-(p-chlorophenyl)biguanide], 1,1'-hexamethylene-

bis[5-(2-ethylhexyl)biguanide], water soluble salts of 1,1'-hexamethylene-bis[5-(2-ethylhexyl)biguanide], poly(hexamethylene biguanide), water soluble salts of poly(hexamethylene biguanide), polyquaternium-1 and quaternary ammonium compounds of low and high molecular weight.

40. The improved composition of claim 35 wherein said one or more disinfecting agents include 1,1'-hexamethylene-bis[5-(p-chlorophenyl)biguanide] or salts thereof.
41. The improved composition of claim 35 wherein said reduced volume disinfecting amount of said one or more disinfecting agents is a standard volume reduced by 5 to 30 percent.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2005/016181

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61L12/14 C11D3/00 A01N47/44 A61K31/155		
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) IPC 7 A61L C11D A01N A61K		
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		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/053479 A (BAUSCH & LOMB INCORPORATED) 3 July 2003 (2003-07-03) example 3	1-41
X	WO 2004/030715 A (BAUSCH & LOMB INCORPORATED) 15 April 2004 (2004-04-15) page 1, lines 4-17 page 7, lines 8-15 page 12, line 26 - page 14, line 27	1-26, 29-41
X	US 2002/004466 A1 (XIA ERNING ET AL) 10 January 2002 (2002-01-10) paragraphs '0001!, '0008!, '0009!, '0018! - '0023!, '0025! - '0027!	1-24, 31-41
-/--		
☒ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in 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 *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family		
Date of the actual completion of the international search 21 July 2005		Date of mailing of the international search report 29/07/2005
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Jochheim, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2005/016181

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with Indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/013624 A1 (GRAHAM RICHARD ET AL) 16 January 2003 (2003-01-16) paragraphs '0001!, '0007! - '0013!, '0019!, '0025!, '0027!, '0029! -----	1-26, 29-41
X	WO 99/24543 A (BAUSCH & LOMB INCORPORATED) 20 May 1999 (1999-05-20) claim 1; examples 1,2 -----	1-26, 29-41

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2005/016181

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03053479	A	03-07-2003	AU 2002364724 A1	09-07-2003
			BR 0215144 A	03-11-2004
			CA 2473935 A1	03-07-2003
			EP 1458420 A2	22-09-2004
			JP 2005513546 T	12-05-2005
			WO 03053479 A2	03-07-2003
			US 2003153475 A1	14-08-2003
WO 2004030715	A	15-04-2004	AU 2003270504 A1	23-04-2004
			CA 2500540 A1	15-04-2004
			EP 1545641 A1	29-06-2005
			WO 2004030715 A1	15-04-2004
US 2002004466	A1	10-01-2002	WO 02064715 A2	22-08-2002
			AU 7478800 A	30-04-2001
			BR 0014619 A	18-06-2002
			CA 2384652 A1	05-04-2001
			CN 1376082 A	23-10-2002
			EP 1229976 A1	14-08-2002
			JP 2003510173 T	18-03-2003
			WO 0123066 A1	05-04-2001
			US 2002132971 A1	19-09-2002
			US 6423820 B1	23-07-2002
US 2003013624	A1	16-01-2003	US 2002035045 A1	21-03-2002
			US 6319883 B1	20-11-2001
			US 6063745 A	16-05-2000
			US 2003129083 A1	10-07-2003
			AU 745778 B2	28-03-2002
			AU 1705899 A	15-06-1999
			BR 9815009 A	03-10-2000
			CA 2311660 A1	03-06-1999
			CN 1279618 A	10-01-2001
			EP 1034005 A1	13-09-2000
			JP 2001523850 T	27-11-2001
			WO 9926669 A1	03-06-1999
WO 9924543	A	20-05-1999	AU 737541 B2	23-08-2001
			AU 1583899 A	31-05-1999
			BR 9814012 A	26-09-2000
			CA 2307566 A1	20-05-1999
			CN 1278863 A	03-01-2001
			EP 1030903 A1	30-08-2000
			JP 2001522673 T	20-11-2001
			WO 9924543 A1	20-05-1999
			US 6153568 A	28-11-2000