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PATENT NUMBER and ISSUE DATE
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APPLICATION NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
13/086,950					

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NOTICE OF ALLOWANCE MAILED		Assistant Examiner	CLAIMS ALLOWED	
			Total Claims	Print Claim for O.G
ISSUE FEE			DRAWING	
Amount Due	Date Paid		Sheets Drwg. / Figs.Drwg. / Print Fig.	
☐ TERMINAL DISCLAIMER		Primary Examiner	Application Examiner	
		PREPARED FOR ISSUE		

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APOTEX 1010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Bhagwati P. Kabra et al.

U.S. Serial No.: TBD

Confirmation No.: TBD

Filed: 15 April 2011

Examiner: TBD

Group Art Unit: TBD

CERTIFICATE OF FILING VIA EFS-WEB

I hereby certify that this correspondence is being submitted to the Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 via EFS-Web on this date:

April 14, 2011.

By: /Barbara McKenzie/
Barbara McKenzie

For: SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

PRELIMINARY AMENDMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir or Madam:

Please enter the following amendments prior to formal examination of the above-identified application.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims that begins on page 3 of this paper.

Amendments to the Drawings are reflected in the listing of claims that begins on page 6 of this paper.

Remarks begin on page 9 of this paper.

FIG. 1

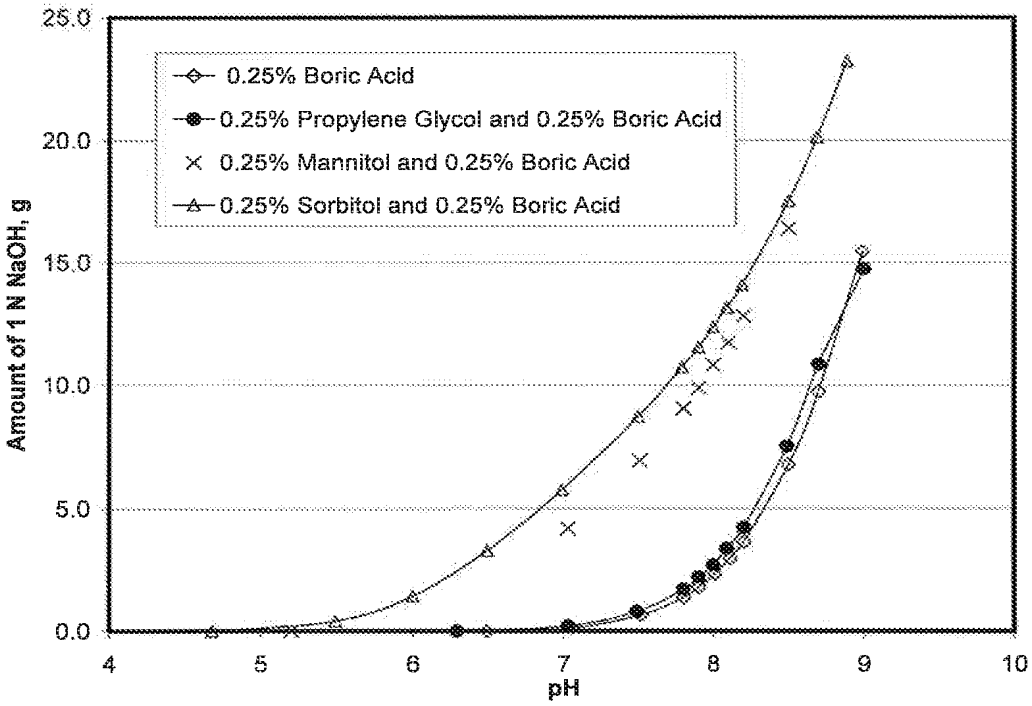

25.0
20.0
15.0
10.0
5.0
0.0
Amount of 1 N NaOH, g
4
5
6
7
8
9
10
pH
0.25% Boric Acid
0.25% Propylene Glycol and 0.25% Boric Acid
0.25% Mannitol and 0.25% Boric Acid
0.25% Sorbitol and 0.25% Boric Acid

FIG. 2

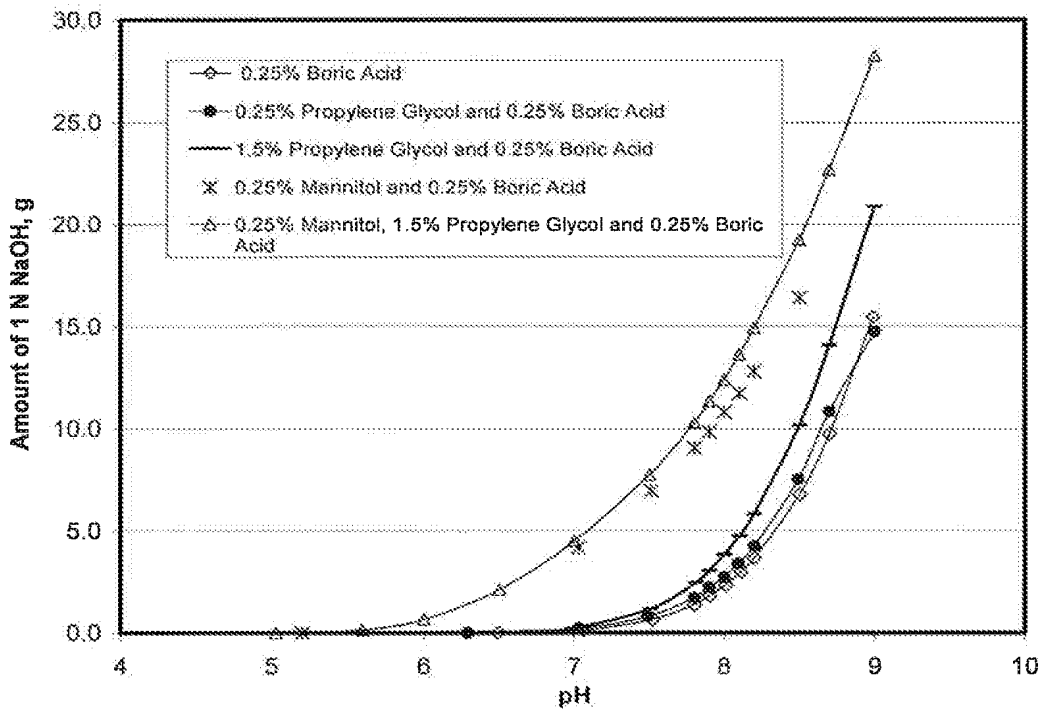
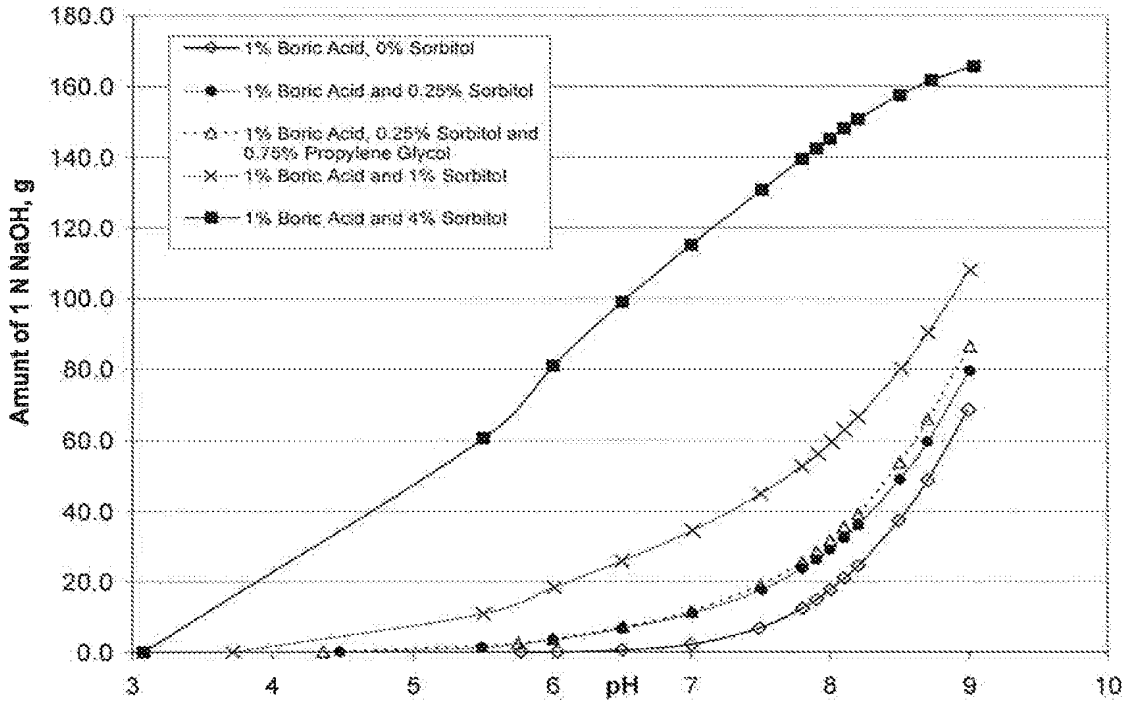

30.0
25.0
20.0
15.0
10.0
5.0
0.0
Amount of 1 N NaOH, g
4
5
6
7
8
9
10
pH
0.25% Boric Acid
0.25% Propylene Glycol and 0.25% Boric Acid
1.5% Propylene Glycol and 0.25% Boric Acid
0.25% Mannitol and 0.25% Boric Acid
0.25% Mannitol, 1.5% Propylene Glycol and 0.25% Boric Acid

FIG. 3


180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
Amount of 1 N NaOH, g
3
4
5
6
pH
7
8
9
10
1% Boric Acid, 0% Sorbitol
1% Boric Acid and 0.25% Sorbitol
1% Boric Acid, 0.25% Sorbitol and 0.75% Propylene Glycol
1% Boric Acid and 1% Sorbitol
1% Boric Acid and 4% Sorbitol

REMARKS

By this amendment, Applicants have canceled claims 1-18 and added claims 19-31. Applicants believe claims 19-31 are in condition for allowance.

CONCLUSION

Should the Examiner have any questions regarding this Amendment, please feel free to contact the undersigned attorney at the phone number listed below.

Respectfully submitted,

Alcon Research, Ltd.

April 14, 2011

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SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

Cross-Reference to Related Applications

The present application claims priority based on U.S. Provisional Patent Application Serial Nos. 60/827,411 filed September 28, 2006, and 60/826,529, filed September 21, 2006.

Background of the Invention

The present invention is directed to self-preserved pharmaceutical compositions. More specifically, the invention is directed to the provision of aqueous, multi-dose pharmaceutical compositions that have been formulated so as to have sufficient antimicrobial activity to satisfy the preservation efficacy requirements of the United States Pharmacopeia ("USP") and analogous guidelines in other countries, without requiring a conventional antimicrobial preservative, such as benzalkonium chloride, polyquaternium-1, hydrogen peroxide (e.g., sodium perborate), or chorine-containing agents. The ability to achieve self-preservation is based on a unique combination of formulation components and criteria.

Many pharmaceutical compositions are required to be sterile (i.e., free of bacteria, fungi and other pathogenic microorganisms). Examples of such compositions include: solutions and suspensions that are injected into the bodies of humans or other mammals; creams, lotions, solutions or other preparations that are topically applied to wounds, abrasions, burns, rashes, surgical incisions, or other conditions where the skin is not intact; and various types of compositions that are applied either directly to the eye (e.g., artificial tears, irrigating solutions, and drug products), or are applied to devices that will come into contact with the eye (e.g., contact lenses).

The foregoing types of compositions can be manufactured under sterile conditions via procedures that are well known to those skilled in the art. However, once the packaging for a product is opened, such that the composition contained therein is exposed to the atmosphere and other sources of potential microbial contamination (e.g., the hands of a human patient), the sterility of the product may be

compromised. Such products are typically utilized multiple times by the patient, and are therefore frequently referred to as being of a "multi-dose" nature.

Due to the frequent, repeated exposure of multi-dose products to the risk of microbial contamination, it is necessary to employ a means for preventing such contamination from occurring. The means employed may be: (i) a chemical agent that prevents the proliferation of microbes in a composition, which is referred to herein as an "antimicrobial preservative"; or (ii) a packaging system that prevents or reduces the risk of microbes reaching a pharmaceutical composition within a container.

Prior multi-dose ophthalmic compositions have generally contained one or more antimicrobial preservatives in order to prevent the proliferation of bacteria, fungi and other microbes. Such compositions may come into contact with the cornea either directly or indirectly. The cornea is particularly sensitive to exogenous chemical agents. Consequently, in order to minimize the potential for harmful effects on the cornea, it is preferable to use anti-microbial preservatives that are relatively non-toxic to the cornea, and to use such preservatives at the lowest possible concentrations (i.e., the minimum amounts required in order to perform their anti-microbial functions).

Balancing the anti-microbial efficacy and potential toxicological effects of anti-microbial preservatives is sometimes difficult to achieve. More specifically, the concentration of an antimicrobial agent necessary for the preservation of ophthalmic formulations from microbial contamination may create the potential for toxicological effects on the cornea and/or other ophthalmic tissues. Using lower concentrations of the anti-microbial agents generally helps to reduce the potential for such toxicological effects, but the lower concentrations may be insufficient to achieve the required level of biocidal efficacy (i.e., antimicrobial preservation).

The use of an inadequate level of antimicrobial preservation may create the potential for microbial contamination of the compositions and ophthalmic infections resulting from such contaminations. This is also a serious problem, since ophthalmic infections involving *Pseudomonas aeruginosa* or other virulent microorganisms can lead to loss of visual function or even loss of the eye.

Thus, there is a need for a means of enhancing the activity of anti-microbial agents so that very low concentrations of the agents can be utilized without increasing the potential for toxicological effects or subjecting patients to unacceptable risks of microbial contamination and resulting ophthalmic infections.

Ophthalmic compositions are generally formulated as isotonic, buffered solutions. One approach to enhancing the anti-microbial activity of such compositions is to include multi-functional components in the compositions. In addition to performing their primary functions, these multi-functional components also serve to enhance the overall anti-microbial activity of the compositions.

The following publications may be referred to for further background regarding the use of multi-functional components to enhance the antimicrobial activity of ophthalmic compositions:

1. U.S. Patent No. 5,817,277 (Mowrey-McKee, et al; tromethamine);
2. U.S. Patent No. 6,503,497 (Chowhan, et al.; borate/polyol complexes);
3. U.S. Patent No. 5,741,817 (Chowhan, et al.; low molecular weight amino acids such as glycine);
4. U.S. Patent No. 6,319,464 (Asgharian; low molecular weight amino alcohols);
5. U.S. Patent Application Publication No. US 2002/0122831 A1 (Mowrey-McKee, et al.; bis-aminopolyols);
6. U.S. Patent No. 6,348,190 (Illes, et al.; zinc); and
7. JP 2003-104870 (zinc).

The use of zinc to enhance the antimicrobial activity of pharmaceutical compositions, including ophthalmic solutions, is well known. See, for example, the following articles and patent publications, as well as U.S. Patent No. 6,348,190 and JP 2003-104870, cited above:

McCarthy, "Metal Ions and Microbial Inhibitors", Cosmetic & Toiletries, 100:69-72 (Feb. 1985);

Zeelie, et al., "The Effects of Selected Metal Salts on the Microbial Activities of Agents used in the Pharmaceutical and Related Industries", Metal Compounds in Environment and Life, 4:193-200 (1992);

Zeelie, et al., "Effects of Copper and Zinc Ions on the Germicidal Properties of Two Popular Pharmaceutical Antiseptic Agents, Cetylpyridinium Chloride and Povidone-iodine", Analyst, 123:503-507 (March 1998);

McCarthy, et al., "The Effect of Zinc Ions on the Antimicrobial Activity of Selected Preservatives", Journal of Pharmacy and Pharmacology, Vol. 41 (1989);

U.S. Patent No. 6,482,799 (Tuśe, et al.);

U.S. Patent No. 5,320,843 (Raheja, et al.);

U.S. Patent No. 5,221,664 (Berkowitz, et al.);

U.S. Patent No. 6,034,043 (Fujiwara, et al.);

U.S. Patent No. 4,522,806 (Muhlemann, et al.);

U.S. Patent No. 6,017,861 (Fujiwara, et al.); and

U.S. Patent No. 6,121,315 (Nair, et al.).

The present invention is directed to the provision of improved preservative systems containing zinc ions.

The compositions of the present invention are multi-dose products that do not require a conventional antimicrobial preservative (e.g., benzalkonium chloride), and yet are preserved from microbial contamination. Such compositions have been referred to in the art as being "preservative free" (see, e.g., U.S. Patent No. 5,597,559 issued to Olejnik, et al.). Compositions that are preserved from microbial contamination as a result of the inherent antimicrobial activity of one or more components of the compositions are also referred to in the art as being "self-preserved" (see, e.g., U.S. Patent No. 6,492,361 issued to Muller, et al.).

The following publication may be referred to for further background regarding pharmaceutical compositions that are "preservative-free" or "self-preserving": Kabara, et al., Preservative-Free and Self-Preserving Cosmetics and Drugs – Principles and Practice, Chapter 1, pages 1-14, Marcel Dekker, Inc. (1997).

The multi-dose compositions of the present invention, which do not contain a conventional antimicrobial preservative, are referred to herein as being "self-preserved".

Summary of the Invention

The present invention is directed to the self-preservation of aqueous ophthalmic compositions via the use of very low concentration of zinc ions. The present invention is based in part on the finding that in order to utilize low concentrations of zinc ions to self-preserve multi-dose ophthalmic compositions having ophthalmically acceptable pH and osmolality values, certain formulation parameters must be maintained. Specifically, the concentration of buffering anions utilized to maintain the pH within an ophthalmically acceptable range must be limited to an amount of 15 millimolar ("mM") or less in order to avoid interfering with the anti-microbial activity of the zinc ions.

In addition, it has been determined that the antimicrobial activity of the zinc-containing compositions of the present invention can be further enhanced by the use of zinc ions in combination with borate or a borate/polyol complex, and that if such a combination is utilized, the use of propylene glycol is strongly preferred, so as to avoid ionic interactions between anionic species generated by other polyols (e.g., sorbitol) and the zinc cations.

It has also been determined that the performance of the zinc-based preservative systems of the present invention is further enhanced by: (i) limiting the amount of multivalent metal cations other than zinc (e.g., calcium and magnesium) in the compositions of the present invention; and (ii) limiting the amount of ionized salts (e.g., sodium chloride and potassium chloride) in said compositions. As described in greater detail below, the compositions of the present invention are preferably free of or substantially free of both ionized salts and multivalent metal cations other than zinc.

The self-preserved, multi-dose compositions of the present invention have several advantages over existing ophthalmic formulations that are either: (i) packaged as a "single dose" or "unit of use" product, so as to avoid the inclusion of any antimicrobial preservative (e.g., BION®TEARS Lubricant Eye Drops, which is marketed by Alcon Laboratories, Inc.), or (ii) preserved by means of a so-called "disappearing" preservatives, such as the chlorite-based system described in U.S. Patent Nos. 5,424,078; 5,736,165; 6,024,954; and 5,858,346 (e.g., the artificial tears product "REFRESH™ Tears", which is marketed by Allergan), or the peroxide-containing system described in U.S. Patent Nos. 5,607,698; 5,683,993; 5,725,887; and

5,858,996 (e.g., the artificial tear product "GenTeal™ Tears", which is marketed by CIBAVision).

Unlike these existing products, the multi-dose ophthalmic compositions of the present invention are able to satisfy the USP preservative efficacy requirements, as well as analogous requirements in other countries, including the Japanese Pharmacopoeia ("JP") and European Pharmacopoeia ("EP") preservative efficacy standards, without employing any conventional antimicrobial preservatives, such as chlorite or hydrogen peroxide.

The above-discussed findings regarding the zinc may be applied to enhance the antimicrobial activity of various types of pharmaceutical compositions. However, the present invention is particularly directed to the provision of aqueous ophthalmic solutions that are effective in preventing microbial contamination in the absence of conventional antimicrobial preservatives, such as benzalkonium chloride ("BAC"), polyquaternium-1, chlorite or hydrogen peroxide.

Brief Description of the Drawings

Figures 1-3 are graphs showing the interaction of boric acid and various polyols.

Detailed Description of the Invention

The pharmaceutical compositions of the present invention contain zinc ions at a concentration of 0.04 to 0.9 millimoles/liter ("mM"), preferably 0.04 to 0.4 mM and most preferably 0.1 to 0.4 mM. The use of this very low concentration is particularly desirable in ophthalmic pharmaceutical compositions containing therapeutically active agents, such as prostaglandin analogues used to control intraocular pressure (e.g., travoprost), because at higher concentrations the zinc ions may produce an astringent effect when applied to the eye. The zinc ions are preferably provided in the form of zinc chloride, at a concentration of 0.0005 to 0.012 percent by weight/volume ("w/v%"), preferably 0.0005 to 0.005 w/v% and most preferably 0.001 to 0.005 w/v%.

The zinc may be provided in various forms, such as zinc chloride, zinc sulfate, zinc acetate or zinc carbonate. The use of zinc chloride is preferred.

As indicated above, the present invention is based on part on a finding that anionic agents utilized to buffer the compositions of the present invention may interfere with the ability of zinc to exert antimicrobial activity. Such interference can be very detrimental to the ability of the compositions to maintain sufficient antimicrobial activity to meet preservative efficacy standards, particularly in view of the very low concentrations of zinc utilized in the present invention. Accordingly, it has been determined that the total concentration of anionic species in the compositions of the present invention should be limited. Specifically, it is preferred that the total concentration of anionic species, particularly buffering anions, should be limited to an amount of less than 15 mM, more preferably less than 10 mM, and most preferably less than 5 mM. For simplicity and clarity, the concentration of buffering anionic species in this patent application will be represented by the concentration of monovalent cations (such as sodium) that are present or needed to bring the pH to the specified value.

As utilized herein, the phrase "less than" relative to a specified concentration (e.g., 15 mM) means that the specified component (e.g., buffering anions) is either not present in the composition at all or is present at a concentration less than the specified limit (e.g., 15 mM).

It has been determined that multivalent buffering anions, particularly citrate and phosphate, have a significant adverse effect on the antimicrobial activity of the zinc-based preservative systems described herein. The compositions of the present invention therefore preferably do not contain any multivalent buffering anions, other than borate-polyol complexes, which may be multivalent under certain conditions (e.g., pH and/or borate: polyol ratio), or are substantially free of such buffering anions. As utilized herein, the phrase "substantially free of multivalent buffering anions" means that the composition either does not contain any multivalent buffering anions or contains an amount of said anions that does not inhibit the ability of the composition to satisfy specified preservative efficacy standards (e.g., USP, EP or JP). The amount of multivalent buffering anions in the compositions of the present invention is preferably less than 5 mM, with said concentration being determined in the same manner as specified in the preceding paragraph.

As indicated above, it has been determined that the antimicrobial activity of the zinc-based preservative systems of the present invention is also adversely affected by other divalent cations, such as calcium and magnesium. The antimicrobial activity of divalent zinc ions (Zn^{2+}) is based upon the ability of the ions to competitively bind and

inactivate macromolecular complexes that are critical to the central metabolic activity of the prokaryotic cell. In order for Zn^{2+} to kill, it must first gain access to the cytoplasm and its charge density prevents its diffusion across the membrane at a physiologically significant rate. Therefore, the ability of Zn^{2+} ions to enter the cell must be facilitated by membrane transport proteins. Access to these transport proteins can be competitively inhibited by multivalent metal cations, particularly Mg^{2+}, Ca^{2+}, Mn^{2+}, Ni^{2+}, and Co^{2+}. Thus, increasing the extracellular concentration of these inhibitory cations diminishes the capacity of Zn^{2+} ions to gain access to the cytoplasm and subsequently reduces its cytotoxic activity to the microorganism.

In view of the potential interference of multivalent metal cations other than zinc, the compositions of the present invention preferably do not contain such cations or are substantially free of said cations. As utilized herein, the phrase "substantially free of multivalent metal cations other than zinc" means that the composition either does not contain such cations or contains an amount of said cations that does not inhibit the ability of the composition to satisfy specified preservative efficacy standards (e.g., USP, EP or JP). The amount of multivalent metal cations other than zinc in the compositions of the present invention is preferably less than 5 mM.

It has also been determined that ionized salts (e.g., sodium chloride and potassium chloride) adversely affect the antimicrobial activity of the preservative systems described herein. Accordingly, the compositions of the present invention preferably do not contain ionized salts, or are substantially free of ionized salts. As utilized herein, the phrase "substantially free of ionized salts" means that the composition either does not contain any ionized salt or contains an amount of ionized salt that does not inhibit the ability of the composition to satisfy specified efficacy standards (e.g., USP, JP or EP). The amount of ionized salt contained in the compositions of the present invention is preferably less than 50 mM.

As used herein, the term "borate" includes boric acid, sodium borate and potassium borate. The use of borates containing divalent cations (e.g., calcium borate) may adversely affect the antimicrobial action of zinc ions, by competing with zinc for binding sites on the cell walls of bacterial and other microbes, and is therefore should be avoided. For the same reason, the self-preserved compositions of the present invention are preferably free of or substantially free of other sources of divalent cations, such as calcium chloride.

The self-preserved compositions of the present invention preferably contain one or more borates in an amount of from about 0.1 to about 2.0% w/v, more preferably 0.3 to 1.5% w/v, and most preferably 0.5 to 1.2% w/v.

As used herein, the term "polyol" includes any compound having at least one hydroxyl group on each of two adjacent carbon atoms that are not in *trans* configuration relative to each other. The polyols can be linear or cyclic, substituted or unsubstituted, or mixtures thereof, so long as the resultant complex is water soluble and pharmaceutically acceptable. Examples of such compounds include: sugars, sugar alcohols, sugar acids and uronic acids. Preferred polyols are sugars, sugar alcohols and sugar acids, including, but not limited to: mannitol, glycerin, xylitol, sorbitol and propylene glycol.

As indicated above, the use of propylene glycol is particularly preferred in order to limit the presence of anionic species. Boric acid interacts with polyols, such as glycerol, propylene glycol, sorbitol and mannitol, to form borate polyol complexes. The type and ratio of such complexes depends on the number of OH groups of a polyol on adjacent carbon atoms that are not in trans configuration relative to each other. For example, propylene glycol has only one OH group on each of two adjacent carbon atoms that are not in trans configuration. Consequently, one molecule of boric acid will interact and form a complex with one or two molecules of propylene glycol, resulting in a monovalent anion. However, in the case of sorbitol, mannitol and other sugar-type polyols, this interaction is much more complex, because one molecule of such polyols can complex with two molecules of borate and then further complex with two additional molecules of the polyol, resulting in a multivalent anion.

When borate is present in the compositions of the present invention, the compositions preferably also contain one or more polyols, at a total concentration of 0.25 to 2.5% w/v. The polyol preferably is propylene glycol at a concentration of 0.25 to 1.80% w/v, preferably 0.25 to 1.25% w/v. Although less preferable than propylene glycol, sorbitol and mannitol are also preferred polyols, and preferably are used at a concentration of 0.05 to 0.75% w/v, preferably 0.05 to 0.5% w/v.

The compositions of the present invention preferably contain borate or a borate/polyol complex, most preferably a borate/polyol complex wherein the polyol portion of the complex is propylene glycol or a combination of propylene glycol and sorbitol. The preference for propylene glycol is based on a discovery that sorbitol and other polyols have a greater tendency to form anionic species at pH values of 7.5 or

less, and that such anionic species may interfere with the antimicrobial activity of zinc. The graphs shown in Figures 1-3 demonstrate that sorbitol has a much higher tendency to form anionic species in the presence of boric acid, compared to propylene glycol.

The data shown in Figures 1-3 were compiled as follows: A 1 Kg solution containing the given concentrations of boric acid and propylene glycol or sorbitol or mannitol was prepared and the initial pH of the solution was determined. 1 N NaOH was then added to adjust the pH. The cumulative amount of sodium hydroxide used to adjust pH to different values was then recorded.

As explained above, boric acid interacts and forms an ionic complex with species containing several hydroxyl groups, such as mannitol and sorbitol. However, the interaction between boric acid and propylene glycol is more limited than with other polyols. This is represented by the amount of sodium hydroxide needed to adjust pH, as shown in Figure 1. Sorbitol and mannitol significantly shift the curve relative to the amount of NaOH required to lower pH, whereas propylene glycol only slightly shifts the curve. This is further evident in Figure 2.

The present invention is particularly directed to the provision of multi-dose, self-preserved ophthalmic compositions that have sufficient antimicrobial activity to allow the compositions to satisfy the USP preservative efficacy requirements, as well as other preservative efficacy standards for aqueous pharmaceutical compositions, without a conventional antimicrobial preservative.

The preservative efficacy standards for multi-dose ophthalmic solutions in the U.S. and other countries/regions are set forth in the following table:

Preservative Efficacy Test ("PET") Criteria
(Log Order Reduction of Microbial Inoculum Over Time

	Bacteria	Fungi
USP 27	A reduction of 1 log (90%), by day 7; 3 logs (99.9%) by day 14; and no increase after day 14	The compositions must demonstrate over the entire test period, which means no increases of 0.5 logs or greater, relative to the initial inoculum.
Japan	3 logs by 14 days; and no increase from day 14 through day 28.	No increase from initial count at 14 and 28 days
Ph. Eur. A[1]	A reduction of 2 logs (99%) by 6 hours; 3 logs by 24 hours; and no recovery after 28 days	A reduction of 2 logs (99%) by 7 days, and no increase thereafter
Ph. Eur. B	A reduction of 1 log at 24 hours; 3 logs by day 7; and no increase thereafter	A reduction of 1 log (90%) by day 14, and no increase thereafter
FDA/ISO 14730	A reduction of 3 logs from initial challenge at day 14; and a reduction of 3 logs from rechallenge	No increase higher than the initial value at day 14, and no increase higher than the day 14 rechallenge count through day 28.

[1]There are two preservative efficacy standards in the European Pharmacopoeia ' "A" and "B".

The standards identified above for the USP 27 are substantially identical to the requirements set forth in prior editions of the USP, particularly USP 24, USP 25 and USP 26.

The compositions of the present invention may optionally also include one or more low molecular weight amino alcohols as buffering agents. The amino alcohols which may be utilized in the present invention are water-soluble and have a molecular weight in the range of from about 60 to about 200. The following compounds are representative of the low molecular weight amino alcohols which may be utilized in the present invention: 2-amino-2-methyl-1-propanol (AMP), 2-dimethylamino-methyl-1-propanol (DMAMP), 2-amino-2-ethyl-1,3-propanediol (AEPD), 2-amino-2-

methyl-1,3-propanediol (AMPD), 2-amino-1-butanol (AB). "AMP (95%)", which refers to 95% pure AMP and 5% water, is the most preferred low molecular weight amino alcohol of the present invention. These amino alcohols are available commercially from Angus Chemical Company (Buffalo Grove, Illinois). Tromethamine may also be utilized in the compositions of the present invention.

The amount of amino alcohol used will depend on the molecular weight of the amino alcohol selected, and the presence (or absence) of other ingredients in the composition (e.g., chelating agents, buffering agents and/or tonicity agents). The amino alcohol will generally be present in an amount necessary to enhance the antimicrobial activity of an aqueous self-preserved pharmaceutical composition of the type described herein. The amount of amino alcohol required for a particular composition can be determined through comparative testing. The above-described amino alcohols are also utilized in the compositions of the present invention to neutralize the pH of the borate or borate/polyol complex, or bring the composition to the desired pH level. The amount of amino alcohol required for this purpose is a function of the particular borate or borate/polyol mixture selected and the concentration thereof. In general, the self-preserved compositions of the present invention may optionally contain one or more amino alcohols at a total concentration of from about 0.01 to about 2.0 percent by weight/volume ("%w/v"), and preferably from 0.1 to 1.0 %w/v.

The zinc, zinc/borate, zinc/polyol and zinc/borate/polyol systems described herein may be included in various types of pharmaceutical compositions to enhance anti-microbial activity and self-preserve the compositions, such as ophthalmic, otic, nasal and dermatological compositions, but is particularly useful in ophthalmic compositions. Examples of such compositions include: ophthalmic pharmaceutical compositions, such as topical compositions used in the treatment of glaucoma, infections, allergies or inflammation; compositions for treating contact lenses, such as cleaning products and products for enhancing the ocular comfort of patients wearing contact lenses; and various other types of ophthalmic compositions, such as ocular lubricating products, artificial tears, astringents, and so on. The compositions may be aqueous or non-aqueous, but will generally be aqueous.

The compositions of the present invention may contain various types of therapeutic agents. However, the invention is most useful relative to therapeutic agents that are nonionic, since nonionic agents do not interfere with the antimicrobial activity of zinc cations in solution. Cationic therapeutic agents may also be utilized in

the compositions, particularly if the agent is included in the compositions in free base form or in the form of a salt with a monovalent anion, such as a hydrochloride salt. Cationic therapeutic agents that are included in the compositions in the form of a salt of a multivalent anion may interfere with the antimicrobial activity of the zinc preservative systems described herein, depending on the concentration of the anion. Such interference must be considered when selecting therapeutic agents that are suitable for use in the compositions of the present invention. Similarly, the use of therapeutic agents that are anionic may be considered; however, such agents may interfere with the activity of zinc ions, depending on the concentration of the agent and its dissociation constant.

Examples of therapeutic agents that may be contained in the ophthalmic compositions of the present invention include prostaglandin analogs (e.g., latanoprost, travoprost and unoprostone), hypotensive lipids (e.g., bimatoprost), and glucocorticoids (e.g., prednisolone, dexamethasone and lotoporednol).

The present invention is particularly directed to the provision of self-preserved, multi-dose ophthalmic compositions in connection with the treatment of conditions wherein the cornea or adjacent ocular tissues are irritated, or conditions requiring frequent application of a composition, such as in the treatment of dry eye patients. The self-preserved compositions of the present invention are therefore particularly useful in the field of artificial tears, ocular lubricants, and other compositions used to treat dry eye conditions, as well as other conditions involving ocular inflammation or discomfort.

The compositions of the present invention will generally be formulated as sterile aqueous solutions. The compositions of the present invention are also formulated so as to be compatible with the eye and/or other tissues to be treated with the compositions. The ophthalmic compositions intended for direct application to the eye will be formulated so as to have a pH and tonicity that are compatible with the eye.

The compositions will have a pH in the range of 4 to 9, preferably 5.5 to 8.5, and most preferably 5.5 to 8.0. It has been determined that a slightly alkaline pH increases the antimicrobial activity of the compositions of the present invention. The use of a pH in the range of 7.0 to 8.0 is therefore preferred.

The compositions will have an osmolality of 200 to 350 milliosmoles per kilogram (mOsm/kg), more preferably 250 to 330 mOsm/kg. As indicated above, the use of nonionic osmolality-adjusting agents is preferred, as ionic salts such as sodium chloride have been found to reduce the antimicrobial activity of the zinc-based preservative systems described herein. The use of propylene glycol, glycerol, xylitol or combinations thereof as nonionic osmolality adjusting agents is particularly preferred. Boric acid may also be utilized as an osmolality-adjusting agent in the compositions of the present invention. Boric acid, if utilized, will be present in the compositions as a mixture of ionic and nonionic species.

The compositions of the present invention may contain various types of pharmaceutical excipients, such as surfactants, viscosity-modifying agents and so on, provided that such excipients are non-ionic. The use of excipients that are cationic or anionic is not preferred, since such ionic agents may interfere with the zinc-based preservation systems described herein. This is particularly true with respect to anionic excipients. Accordingly, the compositions of the present invention are preferably free of or substantially free of anionic excipients.

In the event cationic or anionic excipients are utilized, the amount of excipient contained in the compositions must be limited to an amount that does not inhibit the ability of the composition to meet the applicable preservative efficacy requirements (e.g., USP, JP and/or EP) and adjustments to the formulation properties may be required. For example, the nonionic surfactant polyoxyl 40 hydrogenated castor oil can be used for solubilization or stabilization of drugs, such as travoprost. However, it has been determined that 12-hydroxy stearic acid, an anionic compound that has been determined to be present as an impurity and potential degradation product of the excipient polyoxyl 40 hydrogenated castor oil, interacts with zinc and forms particles. In order to avoid particle formation throughout the commercial shelf-life of a composition containing these components, the pH of the composition needs to be in the range 5.0 to 6.0, preferably in the range 5.5 to 5.9. These finding are further illustrated in Example Y, below.

One or more conventional antimicrobial preservatives (e.g., benzalkonium chloride and polyquaternium-1) can be present in the compositions of the present invention, if desired, but the compositions preferably do not contain any conventional antimicrobial preservatives. If utilized, such preservatives can be present in conventional amounts, but in view of the self-preserving properties of the compositions of the present invention, such conventional antimicrobial preservatives

can also be utilized in much lower concentrations than would be required to satisfy preservative efficacy requirements if only the conventional antimicrobial preservative were present. Since the present compositions can be a self-preserved composition, if an anti-microbial preservative is present as an option, the amount can be an amount that would not be effective alone as an antimicrobial preservative agent. However, the overall composition would have sufficient antimicrobial activity to satisfy USP/FDA/ISO preservative efficacy requirements.

Preferably the conventional antimicrobial preservative, if present, is not anionic and if anionic, it is preferred that the amount should be low enough to not substantially interfere with the antimicrobial activity of the preservative systems described herein.

Applicants specifically incorporate the entire contents of all cited references in this disclosure. Further, when an amount, concentration, or other value or parameter is given as either a range, preferred range, or a list of upper preferable values and lower preferable values, this is to be understood as specifically disclosing all ranges formed from any pair of any upper range limit or preferred value and any lower range limit or preferred value, regardless of whether ranges are separately disclosed. Where a range of numerical values is recited herein, unless otherwise stated, the range is intended to include the endpoints thereof, and all integers and fractions within the range. It is not intended that the scope of the invention be limited to the specific values recited when defining a range.

Other embodiments of the present invention will be apparent to those skilled in the art from consideration of the present specification and practice of the present invention disclosed herein. It is intended that the present specification and examples be considered as exemplary only with a true scope and spirit of the invention being indicated by the following claims and equivalents thereof.

The following examples are presented to further illustrate selected embodiments of the present invention. The formulations shown in the examples were prepared using procedures that are well-known to persons of ordinary skill in the field of ophthalmic pharmaceutical compositions.

Antimicrobial preservative effectiveness as set forth by the examples *infra* was determined using an organism challenge test according to the methods described in the United States Pharmacopeia 24 (USP) for category 1A products. Samples were

inoculated with known levels of one or more of the following: gram-positive vegetative bacteria (*Staphylococcus aureus* ATCC 6538), gram-negative vegetative bacteria (*Pseudomonas aeruginosa* ATCC 9027 and *Escherichia coli* ATCC 8739), yeast (*Candida albicans* ATCC 10231) and mold (*Aspergillus niger* ATCC 16404). The samples were then pulled at specified intervals to determine if the antimicrobial preservative system was capable of killing or inhibiting the propagation of organisms purposely introduced into the formulation. The rate or level of antimicrobial activity determines compliance with the USP preservative efficacy standards for the cited categories of preparations. In some instances, the PET screen test was conducted for only 7 days, rather than 14 or 28 days, with additional time points of 6 and 24 hours being added to evaluate preservative efficacy relative to Ph. Eur. B. criteria. This modified PET screen test has been shown to be a reliable test for determining whether a composition will meet USP or Ph. Eur. B criteria.

Table 1

Preservative Standards for U.S. Category 1A Products presented as Log Reduction of Organism Population

Time Pulls	24 Hours	7 days	14 days	28 days
For Bacteria (*S. aureus, P. aeruginosa, and E. coli*)				
Ph. Eur. B	1.0	3.0	NI	NI
USP	NA	1.0	3.0	NI
For Fungi (*C. albicans and A. niger*)				
Ph. Eur. B	NA	NA	1.0	NI
USP	NA	NI	NI	NI

NI = No increase at this or any following time pulls

NA = Time point not required for applicable standard (e.g., USP or Ph. Eur. B)

As shown in Table 1, the USP 24 Antimicrobial Effectiveness Test requires that compositions containing Category 1A products have sufficient anti-bacterial activity to reduce an initial inoculum of approximately 10^5 to 10^6 bacteria by one log (i.e., a 90% reduction in the microorganism population) over a period of seven (7) days and by three logs (i.e., a 99.9% reduction in the microorganism population) over a period of fourteen (14) days, and requires that there cannot be any increase in the microorganism population following the conclusion of the fourteen day period. Relative to fungi, the USP standards require that the compositions maintain stasis (i.e., no growth) relative to the population of the initial inoculum over the entire 28 day test

period. A category 1A product is an injection, or other parenteral including emulsions, otic, sterile nasal products and ophthalmic products made with aqueous bases or vehicles.

The margin of error in calculating microorganism populations is generally accepted to be +/-0.5 logs. Accordingly, the term "stasis", as utilized herein relative to the above-discussed USP standards, means that the initial population cannot increase by more than 0.5 log orders, relative to the initial population.

Examples A - E

The formulations of Examples A-E were evaluated to determine the effect of buffering anions on preservative efficacy. As discussed in greater detail below, the formulations of Examples A and B do not contain buffering agents. Although these formulations satisfied the USP preservative efficacy requirements, the presence of a buffering system is highly desirable, so as to prevent pH drift over the life of a commercial product (i.e., a period of up to two years or more). The formulation of Example C include a borate/polyol buffering system, but the system has minimal buffering capacity. As with the formulations of Examples A and B, the formulation of Example C satisfied the USP requirements. The formulations of Examples D and E contain significantly greater concentrations of buffering agents and consequently a higher buffering capacity. However, the relatively large amount of buffering anions present resulted in a failure of the formulations to satisfy preservative efficacy requirements. Thus, a comparison of Examples A-E demonstrates the need to balance the requirements for an effective buffering system with the antimicrobial activity required to satisfy preservative efficacy requirements.

The formulation of Example A does not have any buffering ingredient. The amount of sodium hydroxide used in the formulation (0.2 mM) to adjust pH is minimal, which means that the buffering anion concentration is very low. This formulation containing 0.18 mM zinc (0.0025% zinc chloride) meets USP preservation criteria, but is not desirable from a commercial perspective due to the lack of buffering capacity.

Though the formulation of Example B contains boric acid, it does not have buffering capacity as the pKa of boric acid (alone) is much higher than 6. The amount of sodium hydroxide used in the formulation (0.3 mM) to adjust pH is minimal. This formulation containing 0.18 mM zinc (0.0025% zinc chloride) meets USP

preservation criteria, but is not commercially desirable due to the lack of buffering capacity.

The formulation of Example C includes two excipients, boric acid and propylene glycol, which together add significantly to the osmolality of the composition and provide minimal buffering capacity. The amount of sodium hydroxide required in this formulation to adjust pH (0.5 mM) is somewhat higher than for the formulations of Examples A and B, but still very low compared to the limits specified herein (i.e., less than 15 mM, more preferably less than 5 mM). This formulation, containing 0.18 mM Zinc (0.0025% zinc chloride), meets USP preservation criteria, but the buffering capacity is not ideal relative to commercial viability.

Adding boric acid and sorbitol in the amounts indicated for the formulations of Examples D and E provides significant buffering capacity, but results in very high buffering anion concentrations (i.e., 77 and 49 mM, respectively). Example D does not meet USP preservation criteria for either *S. aureus* or *E. coli* at days 7 and 14. Example E does not meet USP preservation criteria for *S. aureus* at day *14* or for *E. coli* at days 7 and 14. These results demonstrate that the addition of significant amounts of buffering anions disrupted the preservation activity of the compositions. Thus, although the buffering systems of the formulations in Examples D and E are commercially viable, the preservative systems do not satisfy USP requirements and consequently would not be acceptable for a commercial product subject to the USP requirements or similar requirements in countries other than the U.S.

Example	A	B	C	D	E
FID	107339	107340	107431	106737	106757
Lot Number	04-37152	04-37160-1	04-37290	04-36171	04-36176
Ingredient	**Concentration (w/v %)**				
Travoprost	0.004	0.004	0.004	0.004	0.004
Polyoxyl 40 Hydrogenated Castor Oil (HCO-40)	0.5	0.5	0.5	0.5	0.5
Zinc Chloride	0.0025	0.0025	0.0025	0.0025	0.0025
Boric Acid	None	1	1	1	0.5
Sorbitol	0.25	None	None	3.8	3.2
Propylene Glycol	0.75	None	0.75	None	None
Sodium Hydroxide, and/or Hydrochloric Acid	Adjust pH to 6.0	Adjust pH to 6.0	Adjust pH to 6.0	Adjust pH to 6.0	Adjust pH to 6.0
Purified Water	QS 100 %	QS 100 %	QS 100 %	QS 100 %	QS 100 %
Osmolality	113	Not tested	274	291	208
Monovalent cation (Na) conc. needed to adjust pH of buffering anions	0.2 mM	0.3 mM	0.5 mM	77 mM	49 mM
Microorganism	**Log Order Reductions**				
S. aureus					
7 D	5.0	5.0	4.7	0.9	1.1
14 D	5.0	5.0	4.7	1.8	2.3
28 D	5.0	5.0	4.7	4.4	4.7
P.aeruginosa					
7 D	5.0	5.0	4.9	2.1	4.0
14 D	5.0	5.0	4.9	4.3	4.9
28 D	5.0	5.0	4.9	5.1	4.9
E. coli					
7 D	5.0	5.0	4.5	0.9	0.9
14 D	5.0	5.0	5.1	1.4	2.1
28 D	5.0	5.0	5.1	5.2	4.9
C. albican					
7 D	1.4	0.0	0.0	0.3	0.1
14 D	3.3	0.6	0.2	0.4	0.6
28 D	3.4	4.9	0.9	0.7	1.5
A. niger					
7 D	0.0	1.4	0.7	3.4	2.7
14 D	0.7	2.2	0.2	3.7	3.7
28 D	0.6	2.3	0.5	4.9	4.3

Examples F through J

In these examples, the amount of sorbitol was reduced to 1%, while keeping the boric acid concentration at 1%, in order to reduce the concentration of buffering anionic species. In addition, examples G, I, and J contain 0.75% propylene glycol. All five examples have an anionic buffer concentration of about 19 mM.

The compositions of Examples F and G contain 0.18 mM of zinc. These have much better anti-microbial activity against *S. Aureus* than the formulations of Examples D and E, above. Specifically, the compositions of Examples F and G meet USP preservation criteria for *S. aureus*. However, although the antimicrobial activity against *E. coli* at zinc concentrations of 0.18 mM (Examples F and G) and 0.36 mM (Example H and I) is improved, compared to examples D and E, it is not sufficient to consistently meet USP preservation criteria at day 14. Increasing the zinc concentration to 1.8 mM (Example J) improved the antimicrobial activity of the solution, so as to allow it to meet USP criteria. However, as indicated above, such higher concentration of zinc are not preferred in ophthalmic products, as zinc may provide astringent activity at these concentrations.

All of the formulations of Examples F-J contained anionic buffer concentrations of 19 mM, which is greater than the preferred limit of 15 mM specified herein. The fact that these compositions were not able to consistently meet or exceed the USP preservative efficacy requirements, even at relatively high zinc concentrations, further demonstrates the importance of limiting the concentration of buffering anions.

Example	F	G	H	I	J
FID	106039	106755	107038	107039	107099
Lot Number	04-36405	04-36173	04-36479	04-36476	04-36632
Ingredient	**Concentration (w/v %)**				
Travoprost	0.004	0.004	0.004	0.004	0.004
Polyoxyl 40 Hydrogenated Castor Oil (HCO-40)	0.5	0.5	0.5	0.5	0.5
Zinc Chloride	0.0025	0.0025	0.005	0.005	0.025
Boric Acid	1	1	1	1	1
Sorbitol	1	1	1	1	1
Propylene Glycol	None	0.6	None	0.6	0.6
Sodium Hydroxide, and/or Hydrochloric Acid	Adjust pH to 6.0	Adjust pH to 6.0	Adjust pH to 6.0	Adjust pH to 6.0	Adjust pH to 6.0
Purified Water	QS 100 %	QS 100 %	QS 100 %	QS 100 %	QS 100 %
Osmolality	--	279	204	288	291
Monovalent cation (Na) conc. needed to adjust pH of buffering anions	19 mM	19 mM	19 mM	19 mM	19 mM
Microorganism	**Log Order Reductions**				
S. aureus					
7 D	2.1	2.2	1.7	3.4	4.4
14 D	3.7	4.4	4.0	3.7	5.1
28 D	5.0	5.2	5.0	5.0	5.1
P.aeruginosa					
7 D	2.6	3.2	3.0	3.4	4.9
14 D	4.6	5.1	4.7	4.6	4.9
28 D	5.0	5.1	5.0	5.0	4.9
E. coli					
7 D	1.7	1.7	1.4	1.5	3.4
14 D	*2.3*	*2.8*	3.0	*2.3*	4.9
28 D	5.1	5.2	5.1	5.1	4.9
C. albican					
7 D	0.2	0.3	0.2	0.2	0.7
14 D	0.1	0.4	0.2	0.9	1.0
28 D	0.4	0.7	0.6	1.3	1.2
A. niger					
7 D	3.0	2.7	3.0	3.0	3.4
14 D	3.1	3.6	3.7	3.0	3.6
28 D	3.7	4.3	3.8	3.8	3.6

Examples K through N

In these examples, the amount of sorbitol was reduced to 0.25%, while keeping the boric acid concentration at 1%, in order to reduce the concentration of buffering anionic species. In addition, the compositions of Examples L-N contain 0.75% propylene glycol. The formulations of Examples K and L have an anionic buffer concentration of about 4 mM, which is within the preferred range of less than 5 mM specified herein. The antimicrobial activity of these compositions against *E. coli* at a zinc concentration of 0.18 mM (0.0025 w/v%) is significantly improved, relative to the activity of the formulations in Examples F-J, and the compositions meet USP preservation criteria. In examples M and N, the pH was adjusted to 5.5 and 6.5, respectively, while maintaining the USP preservation efficacy. The results obtained with the formulations of Examples K through N, which are representative of the compositions of the present invention, further demonstrate the importance of limiting the concentration of buffering anions, relative to satisfying preservative efficacy requirements.

Example	K	L	M	N
FID	107046	**107047**	**109032**	**109033**
Lot Number	04-36523	37157-3	05-40452	05-40453
Ingredient				
Travoprost	0.004	0.004	0.004	0.004
Polyoxyl 40 Hydrogenated Castor Oil (HCO-40)	0.5	0.5	0.5	0.5
Zinc Chloride	0.0025	0.0025	0.0025	0.0025
Boric Acid	1	1	1	1
Sorbitol	0.25	0.25	0.25	0.25
Propylene Glycol	None	0.75	0.75	0.75
Sodium Hydroxide, and/or Hydrochloric Acid	Adjust pH to 6.0	Adjust pH to 6.0	Adjust pH to 5.5	Adjust pH to 6.5
Purified Water	QS 100 %	QS 100 %	QS 100 %	QS 100 %
Osmolality	176	272	283	278
Monovalent cation (Na) conc. needed to adjust pH of buffering anions	3.9 mM	4.1 mM	2 mM	7.5 mM
Microorganism		**Log Order Reductions**		
S. aureus				
7 D	2.6	4.1	3.2	3.4
14 D	4.7	5.0	4.8	4.8
28 D	5.0	5.0	4.8	4.8
P.aeruginosa				4.9
7 D	4.6	4.5	4.9	4.9
14 D	5.0	5.0	4.9	4.9
28 D	5.0	5.0	4.9	
E. coli				
7 D	2.7	1.9	3.4	3.4
14 D	5.1	5.0	4.9	4.9
28 D	5.1	5.0	4.9	4.9
C. albican				
7 D	0.1	0.2	0.1	0.2
14 D	0.1	0.6	0.3	0.4
28 D	0.4	1.0	0.9	1.3
A. niger				
7 D	2.2	2.3	2.7	2.6
14 D	2.3	3.8	3.1	2.6
28 D	3.0	3.5	3.8	2.8

Examples O and P

In these examples, the amount of boric acid was reduced. The formulations meet USP preservation criteria and are representative of the compositions of the present invention.

Example	O	P
FID	**107519**	**107520**
Lot Number	04-37442	04-37443
Ingredient	**Concentration (w/v %)**	
Travoprost	0.004	0.004
Polyoxyl 40 Hydrogenated Castor Oil (HCO-40)	0.5	0.5
Zinc Chloride	0.0025	0.0025
Boric Acid	0.3	0.15
Sorbitol	0.25	0.125
Propylene Glycol	1.6	1.6
Sodium Hydroxide, and/or Hydrochloric Acid	Adjust pH to 6.0	Adjust pH to 6.0
Purified Water	QS 100 %	QS 100 %
Osmolality	281	247
Sodium Hydroxide conc.	2.2 mM	0.5 mM
Monovalent cation (Na) conc. needed to adjust pH of buffering anions	2.2 mM	0.5 mM
Microorganism	**Log Order Reductions**	
S. aureus		
7 D	4.9	5.0
14 D	4.9	5.0
28 D	4.9	5.0
P.aeruginosa		
7 D	5.0	5.0
14 D	5.0	5.0
28 D	5.0	5.0
E. col		
7 D	5.1	5.1
14 D	5.1	5.1
28 D	5.1	5.1
C. albican		
7 D	0.3	0.2
14 D	0.9	1.0
28 D	1.5	2.0
A. niger		
7 D	2.6	2.6
14 D	3.0	2.3
28 D	3.7	2.6

Examples Q and R

The preservation of formulations containing 0.18 mM zinc (0.0025% zinc chloride), with or without boric acid. was evaluated. The results show that antimicrobial activity was greater with the presence of boric acid/polyols. However, the formulation of Example R exhibited sufficient activity to satisfy USP preservative efficacy requirements, even though it did not contain boric acid. The ability of the formulation of Example R to meet preservative efficacy requirements is believed to be attributable in part to the fact that the formulation: (i) did not contain any multivalent anionic buffering agents and (ii) contained a non-ionic agent (i.e., propylene glycol) as the principal osmolality adjusting agent. The formulations of Examples Q and R are representative of the compositions of the present invention.

Examples		Q	R
FID		112306	112308
Lot Number		07-47316	07-47318
Ingredients		Concentration (w/v %)	
Zinc Chloride		0.0025	0.0025
Tromethamine		None	0.13
Propylene Glycol		1.6	1.6
Boric Acid		0.25	None
Mannitol		0.1	None
Sodium Hydroxide, and/or Hydrochloric Acid		Adjust pH to 7.5	Adjust pH to 7.5
Purified Water		QS 100%	QS 100%
Osmolality (mOsm/kg)		261	232
Sodium Hydroxide concentration		4.4 mM NaOH	None
Monovalent Cation (sodium) needed to adjust pH of buffering anions		4.4 mM NaOH	*
Microorganism		Log Order Reductions	
S. Aureus	6 Hours	0.5	1.4
	24 Hours	2.6	3.5
	7 Days	5.1	5.1
	14 Days	NT	NT
	28 Days	NT	NT
Pseudomonas A	6 Hours	1.4	2.8
	24 Hours	4.0	3.8
	7 Days	5.1	5.1
	14 Days	NT	NT
	28 Days.	NT	NT
E. Coli	6 Hours	0.8	0.7
	24 Hours	1.5	1.7
	7 Days	5.1	5.1
	14 Days	NT	NT
	28 Days.	NT	NT
Candida A.	7 Days	0.9	0.3
	14 Days	NT	NT
	28 Days.	NT	NT
A. Niger	7 Days	1.7	0.4
	14 Days	NT	NT
	28 Days.	NT	NT

* This formulation does not contain any buffering anion. However, it contains a buffering cation, tromethamine. pH is adjusted using 8.8 mM HCl.

NT = Not Tested

5

Examples Q and S

A comparison of the formulations of Examples Q and S demonstrates that the preservation efficacy of formulations containing 0.18 mM zinc (0.0025% zinc chloride) is reduced in the presence of low levels of a multivalent metal cation, i.e., calcium. However, the amount of multivalent metal cation in the formulation of Example S (i.e., 2.3 mM), which is less than the upper limit specified herein (i.e., less than 5 mM), was not great enough to significantly inhibit the preservative efficacy of the formulation. The formulations of Examples Q and S are representative of the compositions of the present invention.

Examples		Q	S
FID		112306	112307
Lot Number		07-47316	07-47317
Ingredients		Concentration (w/v %)	
Zinc Chloride		0.0025	0.0025
Calcium Chloride		None	0.025
Propylene Glycol		1.6	1.6
Boric Acid		0.25	0.25
Mannitol		0.1	0.1
Sodium Hydroxide, and/or Hydrochloric Acid		Adjust pH to 7.5	Adjust pH to 7.5
Purified Water		QS 100%	QS 100%
Osmolality (mOsm/kg)		261	264
Sodium Hydroxide Conc.		4.4 mM	4.5 mM
Monovalent Cation (Sodium) needed to adjust pH of buffering anions		4.4 mM	4.5 mM
Microorganism		Log Order Reductions	
S. Aureus	6 Hours	0.5	0.2
	24 Hours	2.6	1.2
	7 Days	5.1	5.1
	14 Days	NT	NT
	28 Days	NT	NT
Pseudomonas A	6 Hours	1.4	0.6
	24 Hours	4.0	0.8
	7 Days	5.1	5.1
	14 Days	NT	NT
	28 Days.	NT	NT
E. Coli	6 Hours	0.8	0.6
	24 Hours	1.5	0.7
	7 Days	5.1	5.1
	14 Days	NT	NT
	28 Days.	NT	NT
Candida A.	7 Days	0.9	0.6
	14 Days	NT	NT
	28 Days.	NT	NT
A. Niger	7 Days	1.7	1.4
	14 Days	NT	NT
	28 Days.	NT	NT

NT = Not Tested

Examples Q, T and U

A comparison of the results obtained with the formulations of Examples Q, T and U demonstrates that preservation efficacy improves as the zinc chloride concentration is increased from 0.18 mM zinc (0.0025% zinc chloride) to 1.8 mM zinc (0.025% zinc chloride). All three formulations satisfied USP preservative efficacy requirements. However, the formulation of Example Q (0.18 mM zinc) did not clearly satisfy the Ph. Eur. B. requirements. The formulations of Examples T and U (0.88 and 1.8 mM of zinc, respectively) did clearly satisfy the Ph. Eur. B requirements; however, the use of higher concentrations of zinc (i.e., 1.8 mM in Example U) is not desirable, as such concentrations may product an astringent affect when applied to the eye. The zinc concentration utilized in the formulation of Example U is outside the range specified herein (i.e., 0.04 to 0.9 mM). Consequently, the formulations of Examples Q and T are representative of the compositions of the present invention, while the formulation of Example U is comparative.

Examples		Q	T	U
FID		112306	112294	112148
Lot Number		07-47316	07-47278	07-46931
Ingredients		Concentration (w/v %)		
Zinc Chloride		0.0025	0.012	0.025
Propylene Glycol		1.6	1.6	1.6
Boric Acid		0.25	0.25	0.25
Mannitol		0.1	0.1	0.1
Sodium Hydroxide, and/or Hydrochloric Acid		Adjust pH to 7.5	Adjust pH to 7.5	Adjust pH to 7.5
Purified Water		QS 100%	QS 100%	QS 100%
Osmolality (mOsm/kg)		261	261	265
Sodium Hydroxide Conc.		4.4 mM	4.4 mM	4.6 mM
Monovalent Cation (Sodium) needed to adjust pH of buffering anions		4.4 mM	4.4 mM	4.6 mM
Microorganism		Log Order Reductions		
S. Aureus	6 Hours	0.5	1.2	2.6
	24 Hours	2.6	3.5	4.3
	7 Days	5.1	5.0	5.0
	14 Days	NT	NT	NT
	28 Days	NT	NT	NT
Pseudomonas A	6 Hours	1.4	1.3	2.7
	24 Hours	4.0	3.3	4.5
	7 Days	5.1	4.9	5.0
	14 Days	NT	NT	NT
	28 Days.	NT	NT	NT
E. Coli	6 Hours	0.8	0.8	1.0
	24 Hours	1.5	1.6	1.8
	7 Days	5.1	5.0	5.0
	14 Days	NT	NT	NT
	28 Days.	NT	NT	NT
Candida A.	7 Days	0.9	2.8	5.0
	14 Days	NT	NT	NT
	28 Days.	NT	NT	NT
A. Niger	7 Days	1.7	1.3	1.6
	14 Days	NT	NT	NT
	28 Days.	NT	NT	NT

NT = Not Tested

Examples U, V and W

A comparison of the results obtained with the formulations of Examples U, V and W demonstrates the effect of pH on the antimicrobial activity of the zinc-based preservative systems of the present invention. Specifically, even at a high zinc concentration (i.e., 1.8 mM), the formulation of Example V (pH 5.5) did not satisfy the Ph. Eur. B. preservative efficacy requirements, but the same formulation did satisfy those requirements when the pH was increased to 6.5 (Example W) or 7.5 (Example U). These results demonstrate the preference for use of a slightly alkaline pH in the compositions of the present invention, as specified above. This preference is of even greater importance when concentrations of zinc lower than 1.8 mM are utilized, as in the compositions of the present invention.

Examples		V	W	U
FID		112286	112287	112148
Lot Number		07-47249	07-47632	07-46931
Ingredients		Concentration (w/v %)		
Zinc Chloride		0.025	0.025	0.025
Propylene Glycol		1.6	1.6	1.6
Boric Acid		0.25	0.25	0.25
Mannitol		0.1	0.1	0.1
Sodium Hydroxide, and/or Hydrochloric Acid		Adjust pH to 5.5	Adjust pH to 6.5	Adjust pH to 7.5
Purified Water		QS 100%	QS 100%	QS 100%
Osmolality (mOsm/kg)		263	265	265
Sodium Hydroxide Conc.		0.1 mM	1.0 mM	4.6 mM
Monovalent Cation (Sodium) needed to adjust pH of buffering anions		0.1 mM	1.0 mM	4.6 mM
Microorganism		Log Order Reductions		
S. Aureus	6 Hours	0.1	0.2	2.6
	24 Hours	0.2	2.3	4.3
	7 Days	4.2	5.0	5.0
	14 Days	NT	NT	NT
	28 Days	NT	NT	NT
Pseudomonas A	6 Hours	1.2	1.4	2.7
	24 Hours	2.1	3.2	4.5
	7 Days	4.9	4.9	5.0
	14 Days	NT	NT	NT
	28 Days.	NT	NT	NT
E. Coli	6 Hours	0.4	0.5	1.0
	24 Hours	0.9	1.3	1.8
	7 Days	2.2	5.0	5.0
	14 Days	NT	NT	NT
	28 Days.	NT	NT	NT
Candida A.	7 Days	1.0	2.0	5.0
	14 Days	NT	NT	NT
	28 Days.	NT	NT	NT
A. Niger	7 Days	2.3	2.0	1.6
	14 Days	NT	NT	NT
	28 Days.	NT	NT	NT

NT = Not Tested

Example X

The formulation of Example X, which is representative of the compositions of the present invention, contained zinc at a concentration of 0.29 mM, had an alkaline pH and satisfied the USP and Ph. Eur. B. preservative efficacy requirements. These results further demonstrate the basis for the above-specified preference for the use of a slightly alkaline pH in the compositions of the present invention.

Example		X
FID		112736
Lot Number		07-48252
Ingredients		Concentration (w/v %)
Zinc Chloride		0.004
Propylene Glycol		1.7
Boric Acid		0.25
Tromethamine, and/or HC1		Adjust pH to 8.0
Purified Water		QS 100%
Osmolality (mOsm/kg)		265
Tromethamine concentration mM		12.4
Monovalent Cation (Tromethamine) Needed to adjust pH of buffering ıs*		8.2
Microorganism		Log Order Reductions
S. Aureus	6 Hours	1.9
	24 Hours	3.9
	7 Days	4.9
	14 Days	4.9
	28 Days	4.9
Pseudomonas A	6 Hours	2.2
	24 Hours	3.0
	7 Days	4.7
	14 Days	4.7
	28 Days.	4.7
E. Coli	6 Hours	0.8
	24 Hours	1.5
	7 Days	3.9
	14 Days	5.0
	28 Days.	5.0
Candida A.	7 Days	2.1
	14 Days	2.9
	28 Days.	4.1
A. Niger	7 Days	0.9
	14 Days	1.9
	28 Days.	1.8

* Calculated using pKa of 8.3

Example Y

12-Hydroxystearic acid (HSA) is an impurity and potential degradation product of the excipient polyoxyl 40 hydrogenated castor oil ("HCO-40"). Above a threshold concentration of HSA, zinc ions interact with HSA to form zinc di-12-hydroxystearate particles. This particulate matter formation is not acceptable for an ophthalmic solution. A study was conducted to assess the effect of pH on particulate matter formation in freshly prepared samples of the composition shown in Table Y-1 below. The potential for particulate formation was evaluated by adding varying amounts of HCO-40 to the composition. The results presented in Table Y-2 below show that as pH is decreased, a higher level of HSA is required to form particles. Thus, a lower pH is preferred for a composition containing the surfactant HCO-40 and zinc ions, so that the composition remains free from particulate matter formation throughout its shelf-life. The preferred pH range for such compositions is 5.0 to 6.0. The most preferred pH range for such compositions is 5.5 to 5.9.

Table Y-1:

Composition of used for the study effect of pH on zinc di-12-hydroxystearate particulate matter formation [a]

Component	Concentration W/V%
Travoprost	0.004%
Polyoxyl 40 Hydrogenated Castor Oil (HCO-40)	0.5%
Boric Acid	1.0%
Zinc Chloride	0.0025%
Sorbitol	0.25%
Propylene Glycol	0.75%
Sodium Hydroxide/ Hydrochloric Acid	Adjust pH.[b]
Purified Water	q.s. 100%

[a] These samples were spiked with HSA.

[b] pH was adjusted to pre-determined values between 5.5 to 6.5

Table Y-2

Relationship Between pH and Particulate Matter Formation (by Microscopic Observation) in Freshly Prepared Samples of Composition Containing HSA at Room Temperature

Total Concentration of HSA	pH at which Particulate Matter [a] was not formed	pH at which Particulate Matter [a] was formed
5 ppm	6.00	6.10[b]
6.5 ppm	5.75	5.90
8 ppm	5.58	5.75

[a] Based on microscopic observation of white crystalline particles.
[b] Particles observed visually; hence were not checked microscopically.

Example Z:

The formulation shown below represents a further example of a self-preserved pharmaceutical composition of the present invention.

Example	**Z**
Ingredients	**Conc. (w/v%)**
Olopatadine Hydrochloride	0.111
Propylene glycol	0.3
Boric Acid	1.0
Sodium Chloride	*0.17*
Zinc Chloride	0.0025
Sodium Hydroxide	
Hydrochloric Acid	Adjust pH 7.0
Purified Water	QS 100

II. Physical Parameters	
Osmolality (mOsm/kg)	267,268
Monovalent cation (Na) concentration needed to adjust pH of buffering anions	6.9 mM

PET Results	**6h**	**24h**	**7d**	**14d**	**28d**
S.aureus	0.0	0.2	4.4	4.9	4.9
P. aeruginosa	0.4	1.3	3.7	4.9	4.9
E. coli	0.7	0.8	5.0	5.0	5.0
C. albicans			0.1	0.5	1.3
A. niger			1.5	1.8	1.3

Examples AA through AD

The formulations in Examples AA and AB contain borate/polyol buffers, whereas the formulations in Example AC and AD contain citrate and phosphate buffers, respectively. All formulations contain 0.11 mM zinc (0.0015% zinc chloride). The formulations in Examples AA and AB, which are representative of the compositions of the present invention, satisfied USP preservative efficacy requirements for the microorganisms tested. The formulations in Examples AC and AD failed to satisfy the USP preservative efficacy requirements, relative to all microorganisms tested. The formulations in Examples AC and AD contained multivalent buffering anions (i.e., citrate and phosphate, respectively) at concentrations of greater than 5 mM. These results demonstrate the importance of limiting the concentration of multivalent buffering anions in the compositions of the present invention.

Example		AA	AB	AC	AD
FID		109997	110009	110002	110013
Lot Number		05-42424	05-42421	05-42428	05-42432
Ingredient					
Polyoxyl 40 Hydrogenated Castor Oil (HCO-40)		0.5	0.5	0.5	0.5
Zinc Chloride		0.0015	0.0015	0.0015	0.0015
Boric Acid		1	1	None	None
Propylene Glycol		0.4	0.4	0.4	0.4
Sodium Chloride		None	0.2	None	None
Sodium Citrate (Dihydrate)		None	None	0.215	None
Dibasic Sodium Phosphate (Anhydrous)		None	None	None	0.156
Sodium Hydroxide, and/or Hydrochloric Acid		Adjust pH to 7.0	Adjust pH to 7.0	Adjust pH to 7.0	Adjust pH to 7.0
Purified Water		QS 100 %	QS 100 %	QS 100 %	QS 100 %
Osmolality		210	270	76	85
Monovalent cation (Na) conc. needed to adjust pH of buffering anions		4.4 mM	4.7 mM	20.4 mM*	15.8 mM*
Microorganism		**Log Order Reductions**			
S. aureus	7 D	4.8	4.8	*0.9*	*0.9*
	14 D	4.8	4.8	4.8	3.5
	28 D	4.8	4.8	4.8	4.3
P.aeruginosa	7 D	4.9	4.9	*0.4*	*-0.3*
	14 D	4.9	4.9	*0.5*	*-0.4*
	28 D	4.9	4.9	*0.3*	*-0.2*
E. col	7 D	4.4	4.4	*-0.6*	*-0.9*
	14 D	4.4	4.4	*-0.4*	*-0.8*
	28 D	4.4	4.4	*-0.3*	*-0.5*
C. albican	7 D	NT	NT	NT	NT
	14 D	NT	NT	NT	NT
	28 D	NT	NT	NT	NT
A. niger	7 D	NT	NT	NT	NT
	14 D	NT	NT	NT	NT
	28 D	NT	NT	NT	NT

* Calculated based on Pka and concentration of buffer used.

5

We Claim:

1. A multi-dose, self-preserved ophthalmic composition, comprising zinc ions at a concentration of 0.04 to 0.9 mM, wherein the concentration of anionic species present in the composition is less than 15 mM.

2. A composition according to Claim 1, wherein the composition further comprises an antimicrobial effective amount of borate.

3. A composition according to Claim 1, wherein the composition further comprises a borate/polyol complex.

4. A composition according to Claim 3, wherein the polyol utilized in the borate/polyol complex is propylene glycol.

5. A composition, according to Claim 3, wherein the polyol utilized in the borate/polyol complex is propylene glycol and sorbitol.

6. A composition according to Claim 1, wherein the composition comprises zinc ions at a concentration of 0.04 to 0.4 mM.

7. A composition according to Claim 6, wherein the concentration of buffering anions in the composition is less than 5 mM.

8. A composition according to Claim 1, wherein the concentration of multivalent metal cations other than zinc in the composition is less than 5 mM.

9. A composition according to Claim 1, wherein the concentration of ionized salts in the composition is less than 50 mM.

10. A composition according to Claim 1, wherein: (i) the concentration of zinc ions in the composition is 0.1 to 0.4 mM; (ii) the concentration of multivalent buffering anions in the composition is less than 5 mM; (iii) the concentration of multivalent metal cations in the composition is less than 5 mM; and (iv) the concentration of ionized salts in the composition is less than 50 mM.

11. In a method of enhancing the antimicrobial activity of an aqueous ophthalmic composition by including zinc ions in said composition, the improvement which comprises utilizing the zinc ions in the composition at a concentration of 0.04 to 0.9 mM and limiting the concentration of buffering anions in the composition to less than 15 mM.

12. The method of Claim 11, wherein the improvement further comprises including a borate/polyol complex in said composition.

13. The method of Claim 12, wherein the polyol utilized in said borate/polyol complex is propylene glycol.

14 The method of Claim 11, wherein the concentration of zinc ions in the composition is 0.04 to 0.4 mM.

15. The method of Claim 14, wherein the concentration of buffering anions is less than 5 mM.

16. The method of Claim 11, wherein the improvement further comprises limiting the concentration of multivalent cations other than zinc in the composition to less than 5 mM.

17. The method of Claim 11, wherein the improvement further comprises limiting the concentration of ionized salts in the composition to less than 50 mM.

18. The method of Claim 11, wherein zinc ions are utilized at a concentration of 0.1 to 0.4 mM, the concentration of multivalent buffering anions in the composition is limited to a concentration of less than 5 mM, the concentration of multivalent metal cations other than zinc in the composition is limited to a concentration of less than 5 mM, and the concentration of ionized salts in the composition is limited to a concentration of less than 50 mM.

Abstract

The present invention is directed to the provision of multi-dose, self-preserved ophthalmic compositions. The compositions possess sufficient antimicrobial activity to satisfy USP preservative efficacy requirements, as well as similar preservative standards (e.g., EP and JP), without requiring the presence of conventional anti-microbial preservative agents, such as benzalkonium chloride. The compositions are effectively preserved by a balanced ionic buffer system containing zinc ions at a concentration of 0.04 to 0.9 mM, preferably 0.04 to 0.4 mM. One aspect of the balanced buffer system is limitation of the amount of buffering anions present to a concentration of 15 mM or less, preferably 5 mM or less. In a preferred embodiment, the compositions also contain borate or, most preferably, one or more borate/polyol complexes. The use of propylene glycol as the polyol in such complexes is strongly preferred. Limiting the amount of divalent metals other than zinc and the amount of ionized salts present has also been determined to be important to maximize the antimicrobial activity of the balanced buffer systems.

FIG. 1

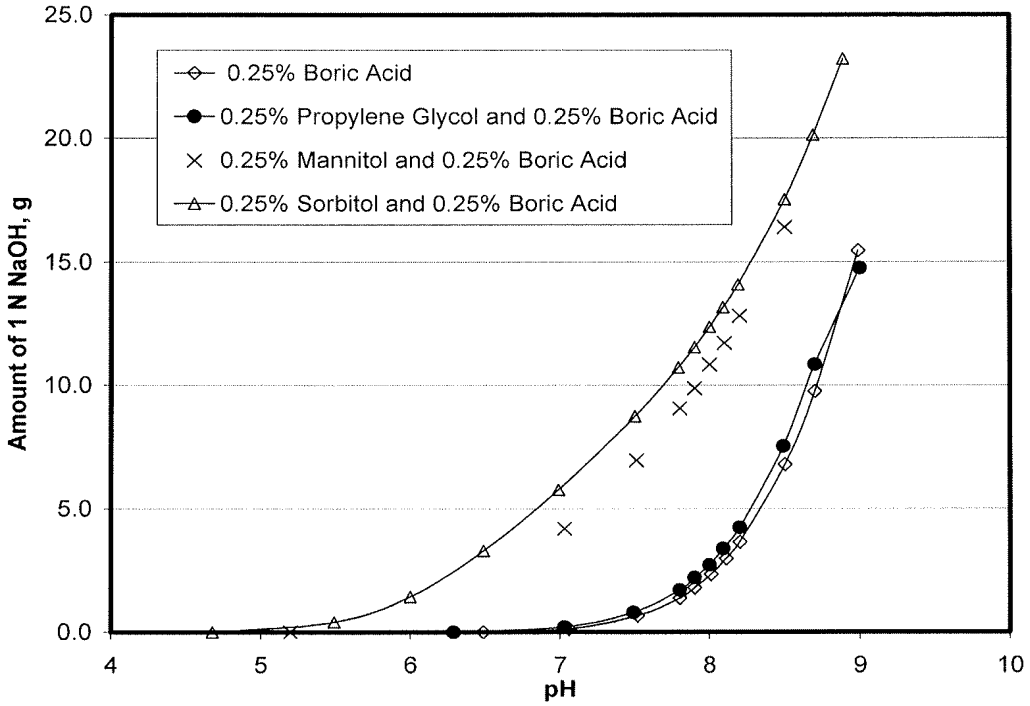

Figure 1: Amount of 1 N Sodium Hydroxide needed to adjust pH of 1Kg solution of Boric Acid (0.25%) in presence of mannitol, sorbitol or propylene glycol.

FIG. 2

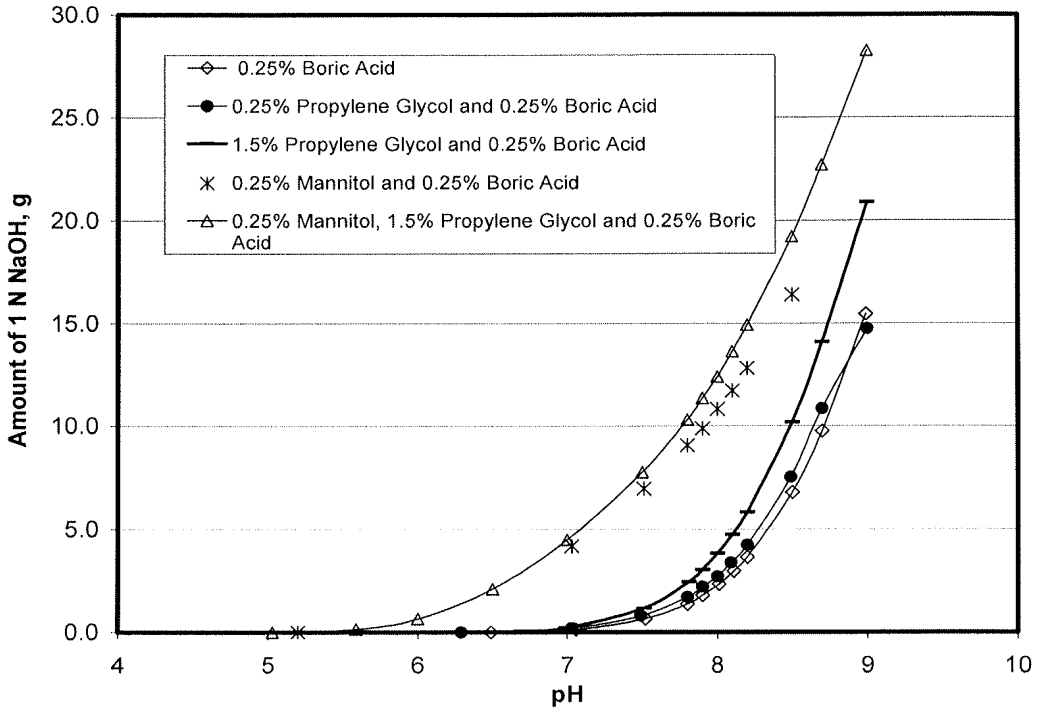

Figure 2: Amount of 1 N Sodium Hydroxide needed to adjust pH of 1Kg solution of Boric Acid (0.25%) in presence of propylene glycol.

FIG. 3

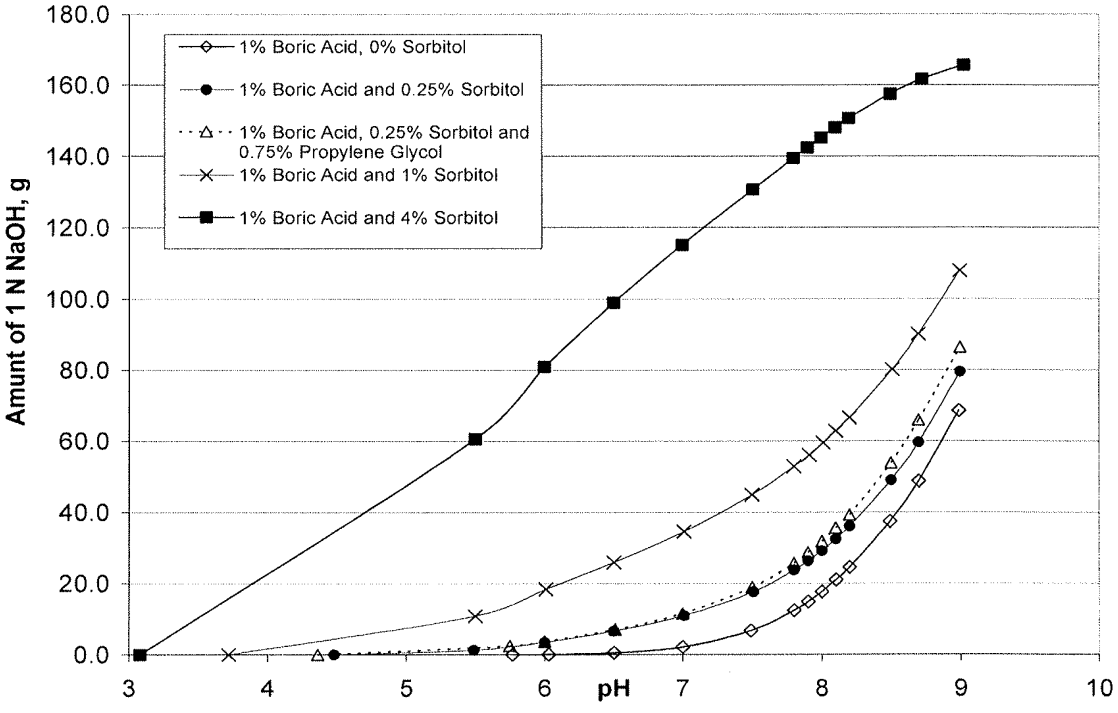

Figure 3: Amount of 1 N Sodium Hydroxide needed to adjust pH of 1Kg solution Boric Acid (1%) in presence of different concentrations of sorbitol...

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled:

SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

described and claimed herewith and further identified as Attorney Docket No. 3205 US the specification of which (check one)

(X) is attached hereto.

( ) was filed by an authorized person on my behalf on _____, as Application Serial No. _____ and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is known to me to be material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT international application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s):			Priority Claimed	
Application Number	**Country**	**Filed (Month/Day/Year)**	**Yes**	**No**

I hereby claim the benefit under 35 USC §119(e) of any United States provisional application(s) listed below.

Prior Provisional Application(s):		Priority Claimed	
Application Number	**Filed (Month/Day/Year)**	**Yes**	**No**
60/827,411	**09/28/06**	**X**	
60/826,529	**09/21/06**	**X**	

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s), or Section 365(c) of any PCT international application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, Section 112. I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Prior U.S. Application(s):		Status: Patent, Pending, Abandoned
Application Number	**Filed (Month/Day/Year)**	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint those patent practitioners associated with Customer No. **26356** as my attorneys, with full power of substitution and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith.

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Docket No. 3205 US

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Bhagwati P. Kabra
Filer:	Scott Chapple/Barbara McKenzie
Attorney Docket Number:	3205 US A

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	330	330
Utility Search Fee	1111	1	540	540
Utility Examination Fee	1311	1	220	220
Pages:				
Claims:				
Claims in excess of 20	1202	8	52	416
Multiple dependent claims	1203	1	390	390
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1896**

Electronic Acknowledgement Receipt

EFS ID:	9882608
Application Number:	13086950
International Application Number:	
Confirmation Number:	5197
Title of Invention:	SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Bhagwati P. Kabra
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	3205 US A
Receipt Date:	14-APR-2011
Filing Date:	
Time Stamp:	16:12:25
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1896
RAM confirmation Number	2714
Deposit Account	010682
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	3205_US_A_ADS_041411.pdf	1032089 5800450707aed3a85d01173602395af7259b04f4	no	5
Warnings:					
Information:					
2		3205_US_A_PrelAmend_041411.pdf	290076 7e1b569c3dbae4bba9e545d0b1eeac6ce7726476	yes	9

Multipart Description/PDF files in .zip description

Document Description	Start	End
Preliminary Amendment	1	1
Specification	2	2
Claims	3	5
Drawings-only black and white line drawings	6	8
Applicant Arguments/Remarks Made in an Amendment	9	9

Warnings:					
Information:					
3		3205US_Appln_092007.pdf	2303938 5539b241ed97e9d5d87c4e44a5250eda88789fd5	yes	45

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	39
Claims	40	41
Abstract	42	42
Drawings-only black and white line drawings	43	45

Warnings:

Information:					
4	Oath or Declaration filed	3205US_copy_Oath-Decl.pdf	123929 c4ebf1e9e886121d99f09e26fd98d56154e50239	no	4
Warnings:					
Information:					
5	Fee Worksheet (PTO-875)	fee-info.pdf	38511 91bb6b6e24df9fb9c1d725dae4a057c53dc8ffaa	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	3788543	

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/14 (11-08)
Approved for use through 09/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	3205 US A
	Application Number	
Title of Invention	Self-Preserved Aqueous Pharmaceutical Compositions	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

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Citizenship under 37 CFR 1.41(b)[i] US

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Applicant 3 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	3205 US A
	Application Number	
Title of Invention	Self-Preserved Aqueous Pharmaceutical Compositions	

Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	10308 Lisa Jean Drive				
Address 2					
City	Crowley	**State/Province**	TX		
Postal Code	76036	**Country**i	US		

Applicant 4 Remove

Applicant Authority (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	**Given Name**	**Middle Name**	**Family Name**	**Suffix**
	Wesley	Wehsin	Han	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Arlington	**State/Province**	TX	**Country of Residence** i	US
Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	2400 Winding Hollow Lane				
Address 2					
City	Arlington	**State/Province**	TX		
Postal Code	76006	**Country**i	US		

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	26356		
Email Address	Scott.Chapple@AlconLabs.com	Add Email	Remove Email

Application Information:

Title of the Invention	Self-Preserved Aqueous Pharmaceutical Compositions		
Attorney Docket Number	3205 US A	**Small Entity Status Claimed**	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)		**Suggested Figure for Publication (if any)**	

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	3205 US A
	Application Number	
Title of Invention	Self-Preserved Aqueous Pharmaceutical Compositions	

Publication Information:

☐	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐	**Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S. C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	26356		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	11/858781	2007-09-20
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
11/858781	non provisional of	60/827411	2006-09-28
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
11/858781	non provisional of	60/826529	2006-09-21

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

Remove

Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			◉ Yes ○ No

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	3205 US A
	Application Number	
Title of Invention	Self-Preserved Aqueous Pharmaceutical Compositions	

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1 Remove

If the Assignee is an Organization check here. ☒

Organization Name	Alcon Research, Ltd.		
Mailing Address Information:			
Address 1	6201 South Freeway		
Address 2			
City	Fort Worth	**State/Province**	TX
Country [i] US		Postal Code	76134-2009
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the **Add** button. Add

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, Reg. #46,287/			Date (YYYY-MM-DD)	2011-04-14
First Name	Scott	Last Name	Chapple	Registration Number	46287

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph beginning at page 1, line 6, as follows:

-- The present application is a continuation of U.S. Serial No. 11/858,781, filed September 20, 2007, which claims priority based on U.S. Provisional Patent Application Serial Nos. 60/827,411 filed September 28, 2006, and 60/826,529, filed September 21, 2006, the disclosure of which is specifically incorporated by reference herein. --

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

Claim 1-18 (canceled)

Claim 19 (new): A multi-dose, self-preserved ophthalmic solution, comprising:
a therapeutically effective amount of an ophthalmically acceptable therapeutic agent;
zinc ions at a concentration of 0.1 to 0.4 mM;
borate at a concentration of 0.5 to 1.2% w/v; and
polyol at a concentration 0.25 to 2.5% w/v;
wherein: (i) the concentration of anionic species in the solution is less than 15 mM; (ii) the concentration of multivalent buffering anions in the solution is less than 5 mM; (iii) the concentration of multivalent metal cations other than zinc in the solution is less than 5 mM; and (iv) the solution exhibits sufficient antimicrobial activity to allow the solution to satisfy USP 27 preservative efficacy requirements.

Claim 20 (new): A solution according to Claim 19, wherein the zinc ions are provided in the form of zinc chloride in the solution at a concentration of 0.001 to 0.005% w/v.

Claim 21 (new): A solution according to Claim 19, wherein the polyol is comprised of at least one polyol selected from the group consisting of mannitol, glycerin, xylitol, sorbitol, propylene glycol.

Claim 22 (new): A solution according to Claim 19, wherein the polyol includes propylene glycol, sorbitol or both.

Claim 23 (new): A solution according to Claim 19, wherein the polyol comprises propylene glycol at a concentration of 0.25 to 1.25% w/v and sorbitol at a concentration of 0.05 to 0.5% w/v.

Claim 24 (new): A solution according to Claim 19, wherein the borate consists of boric acid.

Claim 25 (new): A solution according to Claim 19, wherein the solution has a pH from 5.5 to 5.9.

Claim 26 (previously presented): A solution according to Claim 19, further comprising a non-ionic surfactant.

Claim 27 (new): A solution according to any one of Claims 19 through 26, wherein the therapeutic agent is a prostaglandin analog.

Claim 28 (new): A solution according to any one of Claims 19 through 26 wherein the therapeutic agent is travoprost.

Claim 29 (new): A multi-dose, self-preserved ophthalmic solution, comprising:

(a) a therapeutically effective amount of travoprost;

(b) a non-ionic surfactant;

(c) zinc chloride at a concentration of 0.001 to 0.005% w/v;

(d) boric acid at a concentration of 0.5 to 1.2% w/v;

(e) propylene glycol at a concentration of 0.25 to 1.25% w/v; and

(f) sorbitol at a concentration of 0.05 to 0.5% w/v.;

wherein: (i) the solution has a pH from 5.5 to 5.9; (ii) the concentration of anionic species in the solution is less than 10 mM; (iii) the concentration of multivalent buffering anions in the solution is less than 5 mM; and (iv) the concentration of multivalent metal cations other than zinc in the solution is less than 5 mM; and (v) the solution exhibits sufficient antimicrobial activity to satisfy USP 27 preservative efficacy requirements based solely on the anti-microbial properties of one or more of components (a) - (f) together with the pH of the solution.

Claim 30 (new): A solution according to Claim 29 wherein the solution does not contain multivalent buffering anions and does not contain multivalent cations other than zinc.

Claim 31 (new): A multi-dose ophthalmic solution, consisting essentially of:

(a) travoprost at a concentration of 0.004% w/v;

(b) zinc chloride at a concentration of 0.0025% w/v;

(c) polyoxyl 40 hydrogenated castor oil at a concentration of 0.5% w/v;

(d) boric acid at a concentration of 1.0% w/v;

(e) propylene glycol at a concentration of 0.75% w/v;

(f) sorbitol at a concentration of 0.25% w/v;

(g) sodium hydroxide and/or hydrochloric acid in an amount sufficient to cause the solution to have a pH from 5.5 to 5.9; and

(h) water;

wherein: (i) the concentration of anionic species in the solution is less than 10 mM; (ii) the solution does not contain multivalent buffering anions; and (iii) the solution does not contain multivalent cations other than zinc.

Claim 32 (new): A solution according to Claim 31 wherein the solution exhibits sufficient antimicrobial activity to satisfy USP 27 preservative efficacy requirements based solely on the anti-microbial properties of one or more of components (a) - (f) together with the pH of the solution.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/086,950

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	330
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	540
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	220
TOTAL CLAIMS (37 CFR 1.16(i))	28 minus 20 =	* 8			OR	x 52 =	416
INDEPENDENT CLAIMS (37 CFR 1.16(h))	3 minus 3 =	*				x 220 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $270 ($135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							390
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1896

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/086,950	04/14/2011	1722	1896	3205 US A	14	3

CONFIRMATION NO. 5197

26356
ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

FILING RECEIPT

OC000000047379288

Date Mailed: 04/29/2011

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Bhagwati P. Kabra, Euless, TX;
Masood A. Chowhan, Arlington, TX;
L. Wayne Schneider, Crowley, TX;
Wesley Wehsin Han, Arlington, TX;

Assignment For Published Patent Application

ALCON RESEARCH, LTD., Fort Worth, TX

Power of Attorney: The patent practitioners associated with Customer Number 26356

Domestic Priority data as claimed by applicant

This application is a CON of 11/858,781 09/20/2007
which claims benefit of 60/827,411 09/28/2006
and claims benefit of 60/826,529 09/21/2006

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 04/27/2011

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/086,950**

Projected Publication Date: 08/11/2011

Non-Publication Request: No

Early Publication Request: No

Title

Self-Preserved Aqueous Pharmaceutical Compositions

Preliminary Class

430

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

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MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

Substitute for Form PTO-1360
(For use with Form PTO/SB/06)

Application Number	Filing Date
13086950	

Applicant(s) Bhagwati Kabra

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	---	---				
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Total Indep	3		0		0	
Total Depend	25	↵	0	↵	0	↵
Total Claims	28		0		0	

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PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	13086950
Filing Date	2011-04-14
First Named Inventor	Bhagwati P. Kabra
Art Unit	1613
Examiner Name	Arnold, Ernst V.
Attorney Docket Number	3205 US A

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4522806		1985-06-11	Muhlemann et al.	
	2	5130298		1992-07-14	Cini et al.	
	3	5221664		1993-06-22	Berkowitz et al.	
	4	5320843		1994-06-14	Raheja et al.	
	5	5352708		1994-10-04	Woodward et al.	
	6	5424078		1995-06-13	Dziabo et al.	
	7	5460834		1995-10-24	Bhagat	
	8	5597559		1997-01-28	Olejnik et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13086950
	Filing Date	2011-04-14
	First Named Inventor	Bhagwati P. Kabra
	Art Unit	1613
	Examiner Name	Arnold, Ernst V.
	Attorney Docket Number	3205 US A

	9	5607698		1997-03-04	Martin et al.	
	10	5683993		1997-11-04	Tsao	
	11	5725887		1998-03-10	Martin et al.	
	12	5736165		1998-04-07	Ripley et al.	
	13	5741817		1998-04-21	Chowhan et al.	
	14	5817277		1998-10-06	Mowrey-McKee et al.	
	15	5820822		1998-10-13	Kross	
	16	5858346		1999-01-12	Vehige et al.	
	17	5858996		1999-01-12	Tsao	
	18	6017861		2000-01-25	Fujiwara et al.	
	19	6024954		2000-02-15	Park et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13086950
	Filing Date	2011-04-14
	First Named Inventor	Bhagwati P. Kabra
	Art Unit	1613
	Examiner Name	Arnold, Ernst V.
	Attorney Docket Number	3205 US A

	20	6034043		2000-03-07	Fujiwara et al.	
	21	6121315		2000-09-19	Nair et al.	
	22	6143799		2000-11-07	Chowhan et al.	
	23	6319464		2001-11-20	Asgharian	
	24	6348190		2002-02-19	Illes et al.	
	25	6482799		2002-11-19	Tusé et al.	
	26	6492361		2002-12-10	Muller et al.	
	27	6503497		2003-01-07	Chowhan et al.	
	28	6583124		2003-06-24	Asgharian	
	29	7074827		2006-07-11	Ueno	
	30	7445771		2008-11-04	Dassanayake et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13086950
	Filing Date	2011-04-14
	First Named Inventor	Bhagwati P. Kabra
	Art Unit	1613
	Examiner Name	Arnold, Ernst V.
	Attorney Docket Number	3205 US A

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20020122831		2002-09-05	Mowrey-McKee et al.	
	2	20020123482		2002-09-05	Chowhan et al.	
	3	20050129771		2005-06-16	Asgharian	
	4	20050214382		2005-09-29	Xia et al.	
	5	20060205725		2006-09-14	Ueno	
	6	20070212420		2007-09-13	Xia et al.	
	7	20070297990		2007-12-27	Shah et al.	
	8	20100227003		2010-09-09	Shah et al.	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13086950
	Filing Date	2011-04-14
	First Named Inventor	Bhagwati P. Kabra
	Art Unit	1613
	Examiner Name	Arnold, Ernst V.
	Attorney Docket Number	3205 US A

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2003-104870	JP		2003-04-09	Yuka		☒
	2	95/13050	WO		1995-05-18	Ciba-Geigy AG		☐
	3	98/10773	WO		1998-03-19	Richter Gedeon		☐
	4	2005/097067	WO		2005-10-20	Bausch & Lomb Inc.		☐
	5	2007/106723	WO		2007-09-20	Bausch & Lomb Inc.		☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	BRUCE GRAHN et al., 4-2001, "Zinc and the eye", Journal Of The American College Of Nutrition, Vol. 20, No. 2, 106-11	☐
	2	GUTTMAN, "Liquid gel therapy broadens role of dry eye product line", Ophthalmologytimes.com, 2006, pgs 33-34 and copyright notice	☐
	3	Illustration of packaging for Systane® free	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13086950
	Filing Date	2011-04-14
	First Named Inventor	Bhagwati P. Kabra
	Art Unit	1613
	Examiner Name	Arnold, Ernst V.
	Attorney Docket Number	3205 US A

	4	KABARA et al., 1997, Preservative-Free and Self-Preserving Cosmetics and Drugs – Principles and Practice, Chapter 1, pages 1-14, Marcel Dekker, Inc.	☐
	5	MCCARTHY et al., 1989, "The Effect of Zinc Ions on the Antimicrobial Activity of Selected Preservatives", Journal of Pharmacy and Pharmacology, Vol. 41, 114P	☐
	6	MCCARTHY, 1985, "Metal Ions as Microbial Inhibitors", Cosmetic & Toiletries, 100:69-72	☐
	7	PCT International Search Report for corresponding International Application No. PCT/US2007/079082 with mailing date April 7, 2008	☐
	8	PCT Written Opinion for corresponding International Application No. PCT/US2007/079082 with mailing date April 7, 2008	☐
	9	ZEELIE et al., 1992, "The Effects of Selected Metal Salts on the Microbial Activities of Agents used in the Pharmaceutical and Related Industries", Metal Compounds in Environment and Life, 4, 193-200	☐
	10	ZEELIE et al., 1998, "Effects of copper and zinc ions on the germicidal properties of two popular pharmaceutical antiseptic agents cetylpyridinium chloride and povidone-iodine", Analyst, 123, 503-507	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13086950
	Filing Date	2011-04-14
	First Named Inventor	Bhagwati P. Kabra
	Art Unit	1613
	Examiner Name	Arnold, Ernst V.
	Attorney Docket Number	3205 US A

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, Reg. #46,287/	Date (YYYY-MM-DD)	2011-07-13
Name/Print	Scott A. Chapple	Registration Number	46,287

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
3205PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2007/079082	20/09/2007	21/09/2006
Applicant		
ALCON MANUFACTURING, LTD.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 1
      [X] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

Form PCT/ISA/210 (first sheet) (April 2007)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/079082

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K47/02 A61K47/10 A61K47/26

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)
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 2005/097067 A (BAUSCH & LOMB [US]; XIA ERNING [US]; SALAMONE JOSEPH C [US]; BORAZJANI) 20 October 2005 (2005-10-20) page 3, line 28 - page 5, line 11; claims 1-4,8-18; examples 2-4,8-18	1-18
X	WO 98/10773 A (RICHTER GEDEON VEGYESZET [HU]; ILLES JANOS [HU]; NESMELYI ERZSEBET [HU) 19 March 1998 (1998-03-19) page 19, line 1 - page 20, line 3; claims 1-12; examples 4,5	1,6-11, 14-18
Y		2-5,12, 13
Y	US 2002/098160 A1 (CHOWHAN MASOOD [US] ET AL) 25 July 2002 (2002-07-25) paragraphs [0011] - [0015]; claims 1-24	2-5,12, 13

-/--

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"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	Date of mailing of the international search report
28 March 2008	07/04/2008

Name and mailing address of the ISA/	Authorized officer
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	Rauter, Anton

3

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2007/106723 A (BAUSCH & LOMB [US]; DOBIE ALYCE K [US]; KLEIBER TAMMY J [US]; LAVOIE P) 20 September 2007 (2007-09-20) page 7, line 18 - page 8, line 16; claims 1-36	1,5-11, 14-18
A	GRAHN BRUCE H ET AL: "Zinc and the eye" April 2001 (2001-04), JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION, AMERICAN COLLEGE OF NUTRION, WILMINGTON, NC, US, PAGE(S) 106-118 , XP002334806 ISSN: 0731-5724 the whole document	1-18

3

INTER[illegible]TIONAL SEARCH REPORT

Information on patent family members

In[illegible]tional application No
PCT/US2007/079082

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005097067 A	20-10-2005	AU 2005231147 A1	20-10-2005
		BR PI0509363 A	11-09-2007
		CA 2560724 A1	20-10-2005
		CN 1938003 A	28-03-2007
		EP 1734923 A1	27-12-2006
		JP 2007530685 T	01-11-2007
		KR 20060135006 A	28-12-2006
		US 2005214382 A1	29-09-2005
WO 9810773 A	19-03-1998	AT 254922 T	15-12-2003
		AU 4469197 A	02-04-1998
		CN 1230117 A	29-09-1999
		DE 69726457 D1	08-01-2004
		DE 69726457 T2	26-08-2004
		DK 964687 T3	08-03-2004
		EP 0964687 A1	22-12-1999
		ES 2212131 T3	16-07-2004
		HU 9602498 A2	28-04-1998
		JP 2001500860 T	23-01-2001
		KR 20000036098 A	26-06-2000
		PT 964687 T	27-02-2004
		RU 2204394 C2	20-05-2003
		UA 66766 C2	15-08-2000
		US 6348190 B1	19-02-2002
US 2002098160 A1	25-07-2002	NONE	
WO 2007106723 A	20-09-2007	US 2007212420 A1	13-09-2007

ATENT COOPERATION TRE Y

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2007/079082	20.09.2007	21.09.2006

International Patent Classification (IPC) or both national classification and IPC
INV. A61K9/00 A61K47/02 A61K47/10 A61K47/26

Applicant
ALCON MANUFACTURING, LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Rauter, Anton Telephone No. +49 89 2399-8645

Form (PCT/ISA/237) (Cover Sheet) (April 2005)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-18
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item V.

1 Reference is made to the following documents:

D1 : WO 2005/097067 A (BAUSCH &; LOMB [US]; XIA ERNING [US]; SALAMONE JOSEPH C [US]; BORAZJANI) 20 October 2005 (2005-10-20)

D2 : WO 98/10773 A (RICHTER GEDEON VEGYESZET [HU]; ILLES JANOS [HU]; NESMELYI ERZSEBET [HU) 19 March 1998 (1998-03-19)

D3: US 2002/0098160 (ALCON RESEARCH, LTD.)

2 INDEPENDENT CLAIMS 1 AND 11

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of the said claims is not new in the sense of Article 33(2) PCT.

The claimed composition comprises
- zinc ions in a concentration of 0,04 - 0,9 mM, and
- anionic species < 15 mM.

D1 discloses such products, as can *eg* be taken from claim 16 or the Examples. There is no necessity that anionic species are present according to claim 1 of D1. Anyway, the products disclosed according to the Examples do comprise anionic species in the presently specified amounts of less than 15 mM (if the percentages are converted into moles). With respect to present independent method claim 11, your attention is drawn to the fact that the whole disclosure of D1 is directed to the enhancement of antimicrobial activity of aqueous ophthalmic compositions by including zinc ions. Further novelty destroying prior art can be taken from D2.

3. DEPENDENT CLAIMS 2-10 and 12-18

The said dependent claims do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT). The citations D1

and D2 disclose products comprising the further specified zinc concentrations as well as borate/polyol complexes, and D3 suggests further details in relation to the latter components .

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 2007/106723	20.09.2007	09.03.2007	10.03.2006

Electronic Acknowledgement Receipt

EFS ID:	10505711
Application Number:	13086950
International Application Number:	
Confirmation Number:	5197
Title of Invention:	Self-Preserved Aqueous Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Bhagwati P. Kabra
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	3205 US A
Receipt Date:	13-JUL-2011
Filing Date:	14-APR-2011
Time Stamp:	08:31:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	3205_US_A_IDS_071311.pdf	102072 4445225000c3a6c88dc80556c0456ccc6fb24de7	no	3

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	3205_US_A_IDS-08a_071311.pdf	614665 f19a20714a7ef6c106f9d76591962bbe7cac8118	no	8
Warnings:					
Information:					
3	Foreign Reference	JP_2003_104870_A1_machine-translation.pdf	1165439 e39c3f83adc7ec8f3bdcf416f79dae3ca9e5144c	no	20
Warnings:					
Information:					
4	Foreign Reference	WO_95_013050_A1.pdf	899311 6ed3c2abcd69afb554163949e690c09f31e35340	no	23
Warnings:					
Information:					
5	Foreign Reference	WO_98_010773_A1.pdf	1094400 70ef6115f96fbb92512528529584633aa07adcb9	no	31
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Information:					
6	Foreign Reference	WO_05_097067_A1.pdf	1851911 09ef491e2103f61292d1affcd377fedf0070e7f0	no	36
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Information:					
7	Foreign Reference	WO_07_106723_A2.pdf	2197756 e0118b98dd4e75ee4e52c42fdb4171cc8ae4b675	no	54
Warnings:					
Information:					
8	Non Patent Literature	GRAHN_Bruce_et_aL_2001_JACN_106-118.pdf	1046135 d88da65a732fa5caf3e1fea4d70c60a9cc0b3a34	no	13
Warnings:					
Information:					
9	Non Patent Literature	GUTTMAN_2006_OphthalmologyTimes.pdf	317495 fbd8f87e6f130a7d13891e754fe1214a2957fc62	no	3
Warnings:					
Information:					
10	Non Patent Literature	Systane_Free_Packaging.pdf	117195 904505e9423f466bbc071a7252b4a37b737d34f5	no	1
Warnings:					
Information:					

11	Non Patent Literature	KABARA_et_al_1997_PreservativeFree_1-14.pdf	1119845 3806fb2237c7f67baf64bd21637384604ba0b8f3	no	24
Warnings:					
Information:					
12	Non Patent Literature	McCARTHY_et_al_1989_JPP_41_114P.pdf	168868 924ab00001ceea122201e234ec44220037552168	no	1
Warnings:					
Information:					
13	Non Patent Literature	McCARTHY_et_al_1985_CT_100_69-72.pdf	408963 f0bd918bda22e2284bb396b48e2ef8d97f0b6fbf	no	4
Warnings:					
Information:					
14	Non Patent Literature	PCT-US2007-079082_Search_Rpt.pdf	151432 06e90888972b442c4fac35314af65f82d139682c	no	4
Warnings:					
Information:					
15	Non Patent Literature	PCT-US2007-079082_Written_Opinion.pdf	168208 542b0e8aa688a9d8e4db617dd614f1ffe623ae1f	no	5
Warnings:					
Information:					
16	Non Patent Literature	ZEELIE_et_al_1992_MCEL_4_193-200.pdf	567484 77004f2c72d772bbffe3db7fd7f7a82c36b43ed3	no	8
Warnings:					
Information:					
17	Non Patent Literature	ZEELIE_et_al_1998_Analyst_123_503-507.pdf	405364 bc6f5ccea4c9ac7a998b12546f81d9365de7b950	no	5
Warnings:					
Information:					
			Total Files Size (in bytes):	12396543	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Bhagwati P. Kabra et al.

U.S. Serial No.: 13/086,950

Confirmation No.: 5197

Filed: April 14, 2011

Examiner: Arnold, Ernst V.

Group Art Unit: 1613

For: Self-Preserved Aqueous Pharmaceutical Compositions

CERTIFICATE OF FILING VIA EFS-WEB

I hereby certify that this correspondence is being submitted to the Mail Stop Amendment; Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 via EFS-Web on this date:

July 13, 2011.

By: /Barbara McKenzie/
Barbara McKenzie

INFORMATION DISCLOSURE STATEMENT PURSUANT TO 37 C.F.R. 1.56, 1.97(b)(3), AND 1.98

Mail Stop Amendment
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with Rules 56, 97 and 98 of the Rules of Practice in Patent Cases (37 C.F.R. § 1.56, 1.97(b)(3) and 1.98), enclosed is Form PTO/SB/08a Information Disclosure Statement by Applicant.

Because the PTO has waived the requirement under 37 CFR 1.98(a)(2) to submit copies of each cited U.S. patent and patent application publication in all U.S. national patent applications filed after June 30, 2003, none are enclosed. Only copies of cited foreign patent documents and non-patent literature are enclosed. Applicants do not concede that these materials constitute prior art within the meaning of the United States patent statutes.

This Information Disclosure Statement includes an article and an illustration of packaging for a product named Systane Free Lubricant Eye Drops Liquid Gel, which was marketed by Alcon. It is believed that Alcon's first commercial sale of this product occurred on December 14, 2005. The product is not currently sold; it was withdrawn from the market in December 2006. The formulation of the product was as follows:

Component	Concentration	Units
Hydroxypropyl Guar 8a	0.16% to 0.19%	W/V %
Boric Acid	0.7%	W/V %
Sorbitol	1.4%	W/V %
Polyethylene Glycol (400)	0.4%	W/V %
Propylene Glycol	0.3%	W/V %
Potassium Chloride	0.12%	W/V %
Sodium Chloride	0.1%	W/V %
Calcium Chloride (Dihydrate)	0.0053%	W/V %
Magnesium Chloride (Hexahydrate)	0.0064%	W/V %
Zinc Chloride	0.0015%	W/V %
2-Amino-2-Methyl-Propanol (Amp)	0.57%	W/V %
Hydrochloric Acid (1n)	0.15%	W/V %
Sodium Hydroxide	adjust pH to 7.9	W/V %
Purified Water	qs to 100%	W/V %

Formulation Comments:

$ZnCl_2$ may be added in up to 5% xs to compensate for manufacturing losses.

Applicants requests that the listed references be considered during prosecution of this application and that the references appear among the "References Cited" on any patent issuing from the application.

This statement is filed before the mailing of a first Office Action on the merits pursuant to 37 C.F.R. § 1.97(b), and therefore no fee for the consideration of this statement is enclosed herewith. However, the Commissioner is hereby authorized to charge any amount required for the consideration of this statement to Deposit Account No. 010682 of Alcon Research, Ltd.

Respectfully submitted,

July 12, 2011
Date

Scott A. Chapple
Registration No. 46,287

Address for Correspondence:
Alcon Research, Ltd.
Attn: Scott A. Chapple
6201 S. Freeway, TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-5288

Attorney Docket: 3205 US A

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/086,950	04/14/2011	Bhagwati P. Kabra	3205 US A

CONFIRMATION NO. 5197

PUBLICATION NOTICE

26356
ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

OC000000049258045

Title: Self-Preserved Aqueous Pharmaceutical Compositions

Publication No.US-2011-0195132-A1
Publication Date:08/11/2011

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13086950
Filing Date	2011-04-14
First Named Inventor	Bhagwati P. Kabra
Art Unit	1613
Examiner Name	Arnold, Ernst V.
Attorney Docket Number	3205 US A

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					

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U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13086950
	Filing Date	2011-04-14
	First Named Inventor	Bhagwati P. Kabra
	Art Unit	1613
	Examiner Name	Arnold, Ernst V.
	Attorney Docket Number	3205 US A

	1	USSN 12/441,995 Office Action dated September 16, 2011	☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13086950
	Filing Date	2011-04-14
	First Named Inventor	Bhagwati P. Kabra
	Art Unit	1613
	Examiner Name	Arnold, Ernst V.
	Attorney Docket Number	3205 US A

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, Reg. #46,287/	Date (YYYY-MM-DD)	2011-10-03
Name/Print	Scott A. Chapple	Registration Number	46,287

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	11098722
Application Number:	13086950
International Application Number:	
Confirmation Number:	5197
Title of Invention:	Self-Preserved Aqueous Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Bhagwati P. Kabra
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	3205 US A
Receipt Date:	03-OCT-2011
Filing Date:	14-APR-2011
Time Stamp:	14:46:04
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	3205_US_A_IDS_S1_100311.pdf	82865 dbb1c9ac19a79abb3e9a3e6870e6f888ffc84b35	no	2

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Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	3205_US_A_IDS-S1_08a_100311.pdf	612392 9df3c376f838ace3f31577b15f70ab38ac6694b9	no	4

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3	Non Patent Literature	USSN_12-441995_091611_OA.pdf	364277 a68473c4821dc4e6b5fc33037501582bd88b4310	no	10

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Information:

Total Files Size (in bytes):	1059534

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New International Application Filed with the USPTO as a Receiving Office

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Bhagwati P. Kabra et al.

U.S. Serial No.: 13/086,950

Confirmation No.: 5197

Filed: April 14, 2011

Examiner: Arnold, Ernst V.

Group Art Unit: 1613

For: Self-Preserved Aqueous Pharmaceutical Compositions

CERTIFICATE OF FILING VIA EFS-WEB

I hereby certify that this correspondence is being submitted to the Mail Stop Amendment; Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 via EFS-Web on this date:

October 3, 2011.

By: /Barbara McKenzie/
Barbara McKenzie

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT PURSUANT TO 37 C.F.R. 1.56, 1.97(b)(3), AND 1.98

Mail Stop Amendment
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with Rules 56, 97 and 98 of the Rules of Practice in Patent Cases (37 C.F.R. § 1.56, 1.97(b)(3) and 1.98), enclosed is Form PTO/SB/08a Information Disclosure Statement by Applicant.

Because the PTO has waived the requirement under 37 CFR 1.98(a)(2) to submit copies of each cited U.S. patent and patent application publication in all U.S. national patent applications filed after June 30, 2003, none are enclosed. Only copies of cited foreign patent documents and non-patent literature are enclosed. Applicants do not concede that these materials constitute prior art within the meaning of the United States patent statutes.

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This statement is filed before the mailing of a first Office Action on the merits pursuant to 37 C.F.R. § 1.97(b), and therefore no fee for the consideration of this statement is enclosed herewith. However, the Commissioner is hereby authorized to charge any amount required for the consideration of this statement to Deposit Account No. 010682 of Alcon Research, Ltd.

Respectfully submitted,

October 3, 2011
Date

Scott A. Chapple
Registration No. 46,287

Address for Correspondence:
Alcon Research, Ltd.
Attn: Scott A. Chapple
6201 S. Freeway, TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-5288

Attorney Docket: 3205 US A

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13086950
Filing Date	2011-04-14
First Named Inventor	Bhagwati P. Kabra
Art Unit	1613
Examiner Name	Arnold, Ernst V.
Attorney Docket Number	3205 US A

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13086950
	Filing Date	2011-04-14
	First Named Inventor	Bhagwati P. Kabra
	Art Unit	1613
	Examiner Name	Arnold, Ernst V.
	Attorney Docket Number	3205 US A

	1	USSN 12/441,742 Office Action dated July 28, 2011	☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13086950
	Filing Date	2011-04-14
	First Named Inventor	Bhagwati P. Kabra
	Art Unit	1613
	Examiner Name	Arnold, Ernst V.
	Attorney Docket Number	3205 US A

CERTIFICATION STATEMENT

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☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, Reg. #46,287/	Date (YYYY-MM-DD)	2011-10-17
Name/Print	Scott A. Chapple	Registration Number	46,287

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	11200200
Application Number:	13086950
International Application Number:	
Confirmation Number:	5197
Title of Invention:	Self-Preserved Aqueous Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Bhagwati P. Kabra
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	3205 US A
Receipt Date:	17-OCT-2011
Filing Date:	14-APR-2011
Time Stamp:	15:09:21
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	3205_US_A_IDS-S2_101711.pdf	81976 c0398010072b0df7f52ee939a5767ef540f13b50	no	2

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	3205_US_A_IDS-S2_08a_101711.pdf	612461 87f0e1fc2bcbdfc834bd1bf682eb72fabf9fe04e	no	4

Warnings:

Information:

A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.

3	Non Patent Literature	USSN_12-441742_OA_7-28-2011.pdf	568356 f0e50ff2035c1644399f95a7da3845746 5f29ea2	no	16

Warnings:

Information:

Total Files Size (in bytes):	1262793

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Bhagwati P. Kabra et al.

U.S. Serial No.: 13/086,950

Confirmation No.: 5197

Filed: April 14, 2011

Examiner: Arnold, Ernst V.

Group Art Unit: 1613

For: Self-Preserved Aqueous Pharmaceutical Compositions

CERTIFICATE OF FILING VIA EFS-WEB

I hereby certify that this correspondence is being submitted to the Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 via EFS-Web on this date:

October 17, 2011.

By: /Barbara McKenzie/
Barbara McKenzie

SECOND INFORMATION DISCLOSURE STATEMENT PURSUANT TO 37 C.F.R. 1.56, 1.97(b)(3), AND 1.98

Mail Stop Amendment
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with Rules 56, 97 and 98 of the Rules of Practice in Patent Cases (37 C.F.R. § 1.56, 1.97(b)(3) and 1.98), enclosed is Form PTO/SB/08a Information Disclosure Statement by Applicant.

Because the PTO has waived the requirement under 37 CFR 1.98(a)(2) to submit copies of each cited U.S. patent and patent application publication in all U.S. national patent applications filed after June 30, 2003, none are enclosed. Only copies of cited foreign patent documents and non-patent literature are enclosed. Applicants do not concede that these materials constitute prior art within the meaning of the United States patent statutes.

Applicants requests that the listed references be considered during prosecution of this application and that the references appear among the "References Cited" on any patent issuing from the application.

This statement is filed before the mailing of a first Office Action on the merits pursuant to 37 C.F.R. § 1.97(b), and therefore no fee for the consideration of this statement is enclosed herewith. However, the Commissioner is hereby authorized to charge any amount required for the consideration of this statement to Deposit Account No. 010682 of Alcon Research, Ltd.

Respectfully submitted,

October 17, 2011
Date

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Registration No. 46,287

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Attorney Docket: 3205 US A

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/086,950	04/14/2011	Bhagwati P. Kabra	3205 US A	5197

26356 7590 02/27/2012

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FORT WORTH, TX 76134

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1613	
MAIL DATE	DELIVERY MODE
02/27/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	13/086,950	KABRA ET AL.	
	Examiner	Art Unit	
	ERNST ARNOLD	1613	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *19-32* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *19-32* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☒ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *14 April 2011* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/17/11,10/3/11,7/13/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18 have been cancelled. Claims 19-32 are pending and under examination.

Priority

The Examiner cannot find support for the limitations, for example, “the concentration of multivalent metal cations other than zinc in the solution is less than 5 mM"; and "the solution does not contain multivalent cations other than zinc” in the provisional documents and therefore the instant Application is only afforded the effective filing date of the parent application 11/858781 on 9/20/2007.

Specification

The disclosure is objected to because of the following informalities: Figures 1,2 and 3 are directed to:

> Figure 1: Amount of 1 N Sodium Hydroxide needed to adjust pH of 1Kg solution of Boric Acid (0.25%) in presence of mannitol, sorbitol or propylene glycol.

> Figure 2: Amount of 1 N Sodium Hydroxide needed to adjust pH of 1Kg solution of Boric Acid (0.25%) in presence of propylene glycol.

> Figure 3: Amount of 1 N Sodium Hydroxide needed to adjust pH of 1Kg solution Boric Acid (1%) in presence of different concentrations of sorbitol...

But the specification states on page 6:

Brief Description of the Drawings

* Figures 1-3 are graphs showing the interaction of boric acid and various polyols.

The specification and the Figures are not in agreement.

Appropriate correction is required. The Examiner also assumes Applicant will note the plurality of periods in caption of Figure 3 and correct that as well.

Information Disclosure Statement

References without a date have not been considered and a line has been drawn through the reference.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 19-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xia et al. (US 2005/0214382: IDS reference 4) and Asgharian (US 6319464: IDS reference 23) and Chowhan et al. (US 6503497: IDS reference 27) and Deaciuc et al. (US 20060270735) as evidenced by Sherman (US 5843891).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicant claims, for example:

Claim 19 (new): A multi-dose, self-preserved ophthalmic solution, comprising:
a therapeutically effective amount of an ophthalmically acceptable therapeutic agent;
zinc ions at a concentration of 0.1 to 0.4 mM;
borate at a concentration of 0.5 to 1.2% w/v; and
polyol at a concentration 0.25 to 2.5% w/v;
wherein: (i) the concentration of anionic species in the solution is less than 15 mM; (ii) the concentration of multivalent buffering anions in the solution is less than 5 mM; (iii) the concentration of multivalent metal cations other than zinc in the solution is less than 5 mM; and (iv) the solution exhibits sufficient antimicrobial activity to allow the solution to satisfy USP 27 preservative efficacy requirements.

The Examiner notes that instant claim 31 uses the transitional language of "consisting essentially of". Please note from MPEP 2111.03: For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of

what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355.

Determination of the scope and content of the prior art

(MPEP 2141.01)

Xia et al. teach ophthalmic compositions with a preservative effective amount of a zinc compound comprising water (Abstract and claims 14 and 29). Xia et al. teach compositions with a minimum of about 0.001 wt% to a maximum of about 1 wt% of a zinc compound such as **zinc chloride** in the composition (claims 14-17, 29-43 and 55-66 and [0021]). Please note that no other anions or multivalent cations are required in the composition and therefore their concentrations are less than 15 mM and 5 mM respectively. Also note that while Xia et al. report amounts in terms of wt% and Applicant claims w/v% and the solute is dissolved in water where 100 ml is equal to approximately 100 g then w/v% is no different from w/w%. In other words, a solution with 1 g of solute dissolved in a final volume of 100 ml aqueous solution may also be considered 1% w/w. By extension, since zinc chloride is $ZnCl_2$ then the amount in 100 ml of aqueous solution where 1 ml is about 1g:

0.001 g $ZnCl_2$/136.3 g/mol $ZnCl_2$ = 7.33 X 10^{-6} mol $ZnCl_2$/0.1 L = 0.0733 mM $ZnCl_2$

1.0 g $ZnCl_2$/136.3 g/mol $ZnCl_2$ = 0.00733 mol $ZnCl_2$/0.1 L = 73.3 mM $ZnCl_2$

Since the term "about" was used by Xia et al., those numbers have 'wiggle room' above and below the calculated values. Thus, Xia et al. provide a teaching with sufficient specificity to select a composition with zinc chloride with "about 0.001 wt%" which reads on the instantly claimed lower value of 0.1 mM.

Indeed, Xia et al. teach using various zinc concentrations ranging from 0.05 to 0.025 to 0.0125 and 0.0065 in Tables 9-11 on pages 8 and 9.

0.0065 g $ZnCl_2$/136.3 g/mol $ZnCl_2$ = 4.76 X 10^{-5} mol $ZnCl_2$/0.1 L = 0.476 mM $ZnCl_2$

Consequently, the instantly claimed range for the zinc ions is bracketed with sufficient specificity by the reference. Single or multi-dose is irrelevant because it is at the discretion of the practitioner as to what constitutes a dose. Thus, a 100 ml sample could be a large single dose or 100 smaller 1 ml doses.

Xia et al. teach the addition of other agents such as therapeutic agents including **prostaglandins** (claims 28, 43 and [0051]) as well as tonicity adjusting agents, buffering agents, **pH adjusting agents** and viscosity adjusting agents.

Borate and boric acid are present at 0.090 and 0.85 wt% respectively (Tables 9-11 pages 8-9) and borate buffers are preferred and can be present from about 0.05 wt% to a maximum of about 2.5 wt% [0050]. Please note that in aqueous solution, boric acid will exist in equilibrium with borate.

Glycerin, a polyol, can be included with **non-ionic surfactants** [0054] as well as **propylene glycol** [0056].

The **pH of the composition** has a minimum of about 5 and about 6 [0050] thus embracing the instantly claimed ranges of pH.

Asgharian teaches multi-dose ophthalmic compositions that contain borate/polyol buffer system (Abstract and claims 5-12) where: "The compositions of the present invention preferably contain one or more borates in an amount of from about 0.01 to about 2.0% w/v, more preferably from about 0.3 to 1.2% w/v, and one or more polyols in an amount of from about 0.01 to 5.0%

w/v," (column 5, lines 22-26). Asgharian teaches the polyol as mannitol, glycerin, xylitol and sorbitol with sorbitol being preferred (column 5, lines 12-17). Asgharian teaches that the addition of one or more polyols to a borate buffer enhances the anti-microbial activity of the composition (column 2, lines 42-48). Asgharian teaches NaOH and HCl as a pH adjusting agents (Examples 5-7 and claim 12, for example).

Chowhan et al. teach in the Abstract: "Water-soluble borate-polyol complexes are useful as buffers and/or antimicrobials in aqueous ophthalmic compositions, including those containing polyvinyl alcohol. These compositions have greater antimicrobial activity than comparable compositions containing typical borate buffers and unexpectedly increase the antimicrobial efficacy of other antimicrobial agents when used in combination."

Chowhan et al. teach that ophthalmic compositions are generally formulated to have a pH between about 4.0 and 8.0 (column 1, lines 28-30) and Chowhan et al. teach using NaOH/HCl to adjust the pH (Example 1 and 5-7).

Chowhan et al. teach polyols such as mannitol, glycerin and propylene glycol to be mixed with boric acid (column 2, lines 20-23 and Example 1, Formulations A-H; Examples 2 and 3, Formulations 1-19) with the aqueous ophthalmic compositions comprising 0.05 to 6.0 wt% of a water soluble borate-polyol complex in a molar ratio of borate and polyol of 1:0.1 to 1:10, for example (claims 1-38).

Deaciuc et al. teach ophthalmic compositions comprising **0.004% w/v of travoprost**, boric acid and the polyol mannitol where the pH is in the range of 5.0 to 7.5 (claims 1-21). Diaciuc et al. direct the artisan to using the surfactant cremaphor RH40 in **0.5% w/v** [0070 and

Table 1, F4-F6] which is **polyoxyl 40 hydrogentated castor oil** as evidenced by Sherman (column 4, lines 34-36).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and Xia et al. is that Xia et al. do not expressly teach an embodiment with the instantly claimed amounts of sorbitol and propylene glycol in the composition that satisfies USP 27 preservative efficacy requirements or the use of NaOH and/or HCl to adjust the pH. This deficiency in Xia et al. is cured by the teachings of Asgharian and Chowhan et al.

2. The difference between the instant application and Xia et al. is that Xia et al. do not expressly teach an embodiment with the instantly claimed amounts of travoprost and polyoxyl 40 hydrogentated castor oil. This deficiency in Xia et al. is cured by the teachings of Deaciuc et al. as evidenced by Sherman.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to add the instantly claimed amounts of sorbitol and propylene glycol in the composition that satisfies USP 27 preservative efficacy requirements or the add NaOH and/or HCl to adjust the pH**,** as suggested by Asgharian and Chowhan et al., to the composition of Xia et al. and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because it is well known in the art that the addition of polyols to borate buffer preservative systems enhances the antimicrobial activity of the composition. The ordinary artisan recognizing that Xia already teach adding polyols such as proplylene glycol and glycerine with the further knowledge of the beneficial enhancement by the addition of the polyols to the composition as taught by Asgharian and Chowhan et al., would desire the best preservative composition and add the instantly claimed polyols to the composition. It is simply routine optimization to determine the amount of each polyol in order to satisfy USP 27 preservative efficacy requirements which is intrinsically met by the combination of the antimicrobial properties of any of the components that have antimicrobial properties and the pH. Furthermore, Xia et al. already suggest adding pH adjusting agents and both Chowhan et al. and Asgharian suggests adding NaOH or HCl to provide pH adjustment and therefore it is just optimization to the desired pH of between 5.5 and 5.9.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to add the instantly claimed amounts of travoprost and polyoxyl 40 hydrogentated castor oil**,** as suggested by Deaciuc et al. as evidenced by Sherman, to the composition of Xia et al., and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Xia et al. already suggest adding prostaglandins and surfactants and the art of Deaciuc et al. provides sufficient specificity to the type of prostaglandin and surfactant in the same amounts as instantly claimed to add to ophthalmic compositions. The predictable result is a travoprost ophthalmic composition.

This rejection is based on the well-established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, *In re Sussman*, 1943 C.D. 518. From MPEP 2143 A: "…all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. *KSR*, 550 U.S. at ___, 82 USPQ2d at 1395; *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 282, 189 USPQ 449, 453 (1976); *Anderson 's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 62-63, 163 USPQ 673, 675 (1969); *Great Atlantic & P. Tea Co. v. Supermarket Equipment Corp.*, 340 U.S. 147, 152, 87 USPQ 303, 306 (1950)."

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

1. Claims 19-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11, 14, 15, 17, 21 and 23-26 of copending Application No. 12/441995. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn to borate/polyol

multi-dose self preserved ophthalmic compositions comprising zinc, borate and polyol such as sorbitol and propylene glycol, and travoprost.

The copending does not expressly teach satisfying USP 27 preservative efficacy requirements or the exact amounts of the polyols and travoprost in the composition.

However, the same ingredients making both compositions and therefore the copending application will satisfy not only USP 26 but also USP 27 preservative efficacy requirements. The amount of each ingredient is merely routine optimization to achieve the desired effect. Consequently, the ordinary artisan would have recognized the obvious variation of the instant subject matter over the copending subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

2. Claims 19-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-29 of copending Application No. 11/858781. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn to borate/polyol multi-dose self preserved ophthalmic compositions comprising zinc, borate and polyol such as sorbitol and propylene glycol, polyoxyl 40 hydrogenated castor oil and travoprost at the same pH of 5.5 to 5.9.

Consequently, the ordinary artisan would have recognized the obvious variation of the instant subject matter over the copending subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (7:15 am-4:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Kwon can be reached on 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ernst V Arnold/
Primary Examiner, Art Unit 1613

Notice of References Cited	Application/Control No. 13/086,950	Applicant(s)/Patent Under Reexamination KABRA ET AL.	
	Examiner ERNST ARNOLD	Art Unit 1613	Page 1 of 1

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*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-5,843,891	12-1998	Sherman, Bernard C.	424/456
*	B	US-2006/0270735	11-2006	Deaciuc et al.	514/530
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
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(Not for submission under 37 CFR 1.99)

Application Number	13086950
Filing Date	2011-04-14
First Named Inventor	Bhagwati P. Kabra
Art Unit	1613
Examiner Name	Arnold, Ernst V.
Attorney Docket Number	3205 US A

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	Examiner Name	Arnold, Ernst V.
	Attorney Docket Number	3205 US A

	1	USSN 12/441,995 Office Action dated September 16, 2011	☐

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☒ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, Reg. #46,287/	Date (YYYY-MM-DD)	2011-10-03
Name/Print	Scott A. Chapple	Registration Number	46,287

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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First Named Inventor	Bhagwati P. Kabra
Art Unit	1613
Examiner Name	Arnold, Ernst V.
Attorney Docket Number	3205 US A

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	Attorney Docket Number	3205 US A

	1	USSN 12/441,742 Office Action dated July 28, 2011	☐

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	1	4522806		1985-06-11	Muhlemann et al.	
	2	5130298		1992-07-14	Cini et al.	
	3	5221664		1993-06-22	Berkowitz et al.	
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	7	5460834		1995-10-24	Bhagat	
	8	5597559		1997-01-28	Olejnik et al.	

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	9	5607698		1997-03-04	Martin et al.	
	10	5683993		1997-11-04	Tsao	
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	13	5741817		1998-04-21	Chowhan et al.	
	14	5817277		1998-10-06	Mowrey-McKee et al.	
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	19	6024954		2000-02-15	Park et al.	

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	20	6034043		2000-03-07	Fujiwara et al.	
	21	6121315		2000-09-19	Nair et al.	
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	29	7074827		2006-07-11	Ueno	
	30	7445771		2008-11-04	Dassanayake et al.	

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	1	20020122831		2002-09-05	Mowrey-McKee et al.	
	2	20020123482		2002-09-05	Chowhan et al.	
	3	20050129771		2005-06-16	Asgharian	
	4	20050214382		2005-09-29	Xia et al.	
	5	20060205725		2006-09-14	Ueno	
	6	20070212420		2007-09-13	Xia et al.	
	7	20070297990		2007-12-27	Shah et al.	
	8	20100227003		2010-09-09	Shah et al.	

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	Application Number	13086950
	Filing Date	2011-04-14
	First Named Inventor	Bhagwati P. Kabra
	Art Unit	1613
	Examiner Name	Arnold, Ernst V.
	Attorney Docket Number	3205 US A

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2003-104870	JP		2003-04-09	Yuka		☒
	2	95/13050	WO		1995-05-18	Ciba-Geigy AG		☐
	3	98/10773	WO		1998-03-19	Richter Gedeon		☐
	4	2005/097067	WO		2005-10-20	Bausch & Lomb Inc.		☐
	5	2007/106723	WO		2007-09-20	Bausch & Lomb Inc.		☐

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	1	BRUCE GRAHN et al., 4-2001, "Zinc and the eye", Journal Of The American College Of Nutrition, Vol. 20, No. 2, 106-11	☐
	2	GUTTMAN, "Liquid gel therapy broadens role of dry eye product line", Ophthalmologytimes.com, 2006, pgs 33-34 and copyright notice	☐
	3	~~Illustration of packaging for Systane® free~~	☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	Bhagwati P. Kabra
	Art Unit	1613
	Examiner Name	Arnold, Ernst V.
	Attorney Docket Number	3205 US A

	4	KABARA et al., 1997, Preservative-Free and Self-Preserving Cosmetics and Drugs – Principles and Practice, Chapter 1, pages 1-14, Marcel Dekker, Inc.	☐
	5	MCCARTHY et al., 1989, "The Effect of Zinc Ions on the Antimicrobial Activity of Selected Preservatives", Journal of Pharmacy and Pharmacology, Vol. 41, 114P	☐
	6	MCCARTHY, 1985, "Metal Ions as Microbial Inhibitors", Cosmetic & Toiletries, 100:69-72	☐
	7	PCT International Search Report for corresponding International Application No. PCT/US2007/079082 with mailing date April 7, 2008	☐
	8	PCT Written Opinion for corresponding International Application No. PCT/US2007/079082 with mailing date April 7, 2008	☐
	9	ZEELIE et al., 1992, "The Effects of Selected Metal Salts on the Microbial Activities of Agents used in the Pharmaceutical and Related Industries", Metal Compounds in Environment and Life, 4, 193-200	☐
	10	ZEELIE et al., 1998, "Effects of copper and zinc ions on the germicidal properties of two popular pharmaceutical antiseptic agents cetylpyridinium chloride and povidone-iodine", Analyst, 123, 503-507	☐

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Examiner Signature	/Ernst Arnold/	Date Considered	02/24/2012

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1	"20050214382".pn. and (surfactant or nonionic)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/24 07:12
L2	2	"20050214382".pn. and (USP or efficacy)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/24 07:14
L3	1	"20050214382".pn. and (sodium adj chloride)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/24 07:30
L7	2	"6319464".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/24 07:36
L8	2	"6319464".pn. and (sorbitol or polyol or zinc or borate)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/24 07:37
L9	53	(travoprost and ophthalmic).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/24 07:58
L10	15	l9 and (borate or boric).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/24 07:59
L11	11	l10 and @ad<"20070920"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/24 07:59
L12	42	((hydrogenated with castor) and ophthalmic).clm.	US-PGPUB; USPAT;	OR	ON	2012/02/24 08:49

			USOCR; FPRS; EPO; JPO; DERWENT			
L13	33	l12 and @ad<"20070920"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/24 08:50
L14	13	l13 and (polyoxy or polyoxyl)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/24 08:50
L15	1	l14 and travoprost	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/24 08:52
L16	4	((Cremaphor adj RH40) and (tear or eye or ophthalmic).clm.)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/24 08:56
L17	4	l16 and @ad<"20070920"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/24 08:56
L18	2	"20050214382".pn. and (NaOH or HCl or pH)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/24 09:35
L19	1	"6319464".pn. and (NaOH or HCl or pH)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/24 09:37
L20	2	"6503497".pn. and (NaOH or HCl or pH)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/24 09:45
L21	2	"20050214382".pn. and (water or aqueous)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/24 10:03
L22	2	"20060270735".pn.	US-PGPUB; USPAT;	OR	ON	2012/02/24 10:17

			USOCR; FPRS; EPO; JPO; DERWENT			
S1	0	"6211238".pn. and zinc	USPAT	OR	OFF	2012/02/23 13:42
S2	1	"6211238".pn.	USPAT	OR	ON	2012/02/23 13:42
S3	634	(((kabra or chowhan or schneider or han).in. or "alcon.as.") and (zinc and (borate or boric) and (polyol or mannitol or glycerin or glycerol or xylitol or sorbitol or (propylene adj glycol))))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 13:50
S4	8	(((kabra or chowhan or schneider or han).in. or "alcon.as.") and (zinc and (borate or boric) and (polyol or mannitol or glycerin or glycerol or xylitol or sorbitol or (propylene adj glycol))).clm.)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 13:51
S5	1	"20020123482".pn. and (zinc and polyol and (borate or borax or boric))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 14:12
S6	3903	(zinc and (borate or boric) and (polyol or mannitol or glycerin or glycerol or xylitol or sorbitol or (propylene adj glycol)).clm.)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 14:16
S7	1	"20080075790".pn. and (amount with anions)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 14:49
S8	1	"20080075790".pn. and ((amount with anion) and (multivalent with cation))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 14:58
S9	0	"6503497".pn. and zinc and borate	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 15:07
S10	0	"6503497".pn. and zinc	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 15:07
S11	3	"6503497".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO;	OR	ON	2012/02/23 15:07

			JPO; DERWENT			
S12	2	"7445771".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 15:16
S13	2	"5460834".pn.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 15:18
S14	2	"20110195132".pn. and ("0.001" or "0.005" or "0.005%" or "0.5" or "1.2%" or "0.25" or "1.25%")	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 15:50
S15	1	"5597559".pn. and zinc	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 15:53
S16	78	((tear or (artificial with tear) or ophthalmic).clm. and (zinc with (amount or concentration)) and zinc.clm.)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 17:12
S17	62	S16 and @ad<"20070920"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 17:12
S18	87	(bion with tear)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 18:18
S19	16	S18 and (ZnCl2 or (zinc with chloride))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 18:19
S20	5	S19 and @ad<"20070920"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 18:19
S21	2	(zinc and (boric or borate) and (polyol or mannitol or glycerol or glycerin or xylitol or sorbitol or glycol) and (artificial with tear)).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO;	OR	ON	2012/02/23 18:30

			JPO; DERWENT			
S22	2	S21 and @ad<"20070920"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 18:30
S23	777	((zinc with preservative) and (zinc with (amount or concentration)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 18:33
S24	519	S23 and @ad<"20070920"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 18:33
S25	37	S24 and ((zinc with preservative) and (zinc with (amount or concentration))).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 18:33
S26	1	"20050214382".pn. and ((borate or boric) and (polyol or mannitol or glycerin or glycerol or xylitol or sorbitol or (propylene adj glycol)))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 19:15
S27	0	S26 and sorbitol	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 19:15
S28	2	"20050214382".pn. and (prostaglandin or travoprost)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 19:16
S29	87	((sorbitol or glucitol or sorbogem or sorbo) and (propanediol or (propylene adj glycol) or ((methyl adj ethyl) adj glycol)) and (tear or ophthalmic)).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 19:20
S30	60	S29 and @ad<"20070920"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/02/23 19:20
S31	60	S30 and ((sorbitol or glucitol or sorbogem or sorbo) and (propanediol or (propylene adj glycol) or ((methyl adj ethyl) adj glycol)) and (tear or	US-PGPUB; USPAT; USOCR; FPRS; EPO;	OR	ON	2012/02/23 19:21

		ophthalmic))	JPO; DERWENT				

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	13086950	KABRA ET AL.
	Examiner	Art Unit
	ERNST ARNOLD	1613

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
inventor/assignee name EAST/PALM	2/24/12	eva
EAST all databases	2/24/12	eva

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Bhagwati P. Kabra et al.

U.S. Serial No.: 13/086,950

Confirmation No.: 5197

Filed: April 14, 2011

Examiner: Arnold, Ernst V.

Group Art Unit: 1613

CERTIFICATE OF FILING VIA EFS-WEB

I hereby certify that this correspondence is being submitted to the Mail Stop Amendment; Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 via EFS-Web on this date:

May 17, 2012.

By: /Barbara McKenzie/
Barbara McKenzie

For: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

AMENDMENT AND RESPONSE

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This paper is submitted in response to the Office Action dated February 27, 2012 for which the three month deadline for filing a response is May 27, 2012.

Applicants believe that no extension of time is required. However, if the U.S. Patent Office deems any fees to be deficient or absent, this paragraph is a request and authorization to deduct such fees from Alcon Research, Ltd. Deposit Account No. **010682.**

Applicants respectfully request the Examiner to consider the following remarks relative to the above-identified application.

A listing of claims begins on page 2 hereof.

Remarks begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

Claims 1-18 (canceled)

Claim 19 (currently amended): A multi-dose, self-preserved ophthalmic solution, comprising:

a therapeutically effective amount of an ophthalmically acceptable therapeutic agent;
zinc ions at a concentration of 0.1 to 0.4 mM;
borate at a concentration of 0.5 to 1.2% w/v; ~~and~~
propylene glycol at a concentration of 0.25 to 1.25 %; and
sorbitol at a concentration of 0.05 to 0.5% w/v;
~~polyol at a concentration 0.25 to 2.5% w/v;~~
wherein: (i) the concentration of anionic species in the solution is less than 15 mM; (ii) the concentration of multivalent buffering anions in the solution is less than 5 mM; (iii) the concentration of multivalent metal cations other than zinc in the solution is less than 5 mM; and (iv) the solution exhibits sufficient antimicrobial activity to allow the solution to satisfy USP 27 preservative efficacy requirements.

Claim 20 (previously presented): A solution according to Claim 19, wherein the zinc ions are provided in the form of zinc chloride in the solution at a concentration of 0.001 to 0.005% w/v.

Claim 21-23 (canceled)

Claim 24 (previously presented): A solution according to Claim 19, wherein the borate consists of boric acid.

Claim 25 (previously presented): A solution according to Claim 19, wherein the solution has a pH from 5.5 to 5.9.

Claim 26 (previously presented): A solution according to Claim 19, further comprising a non-ionic surfactant.

Claim 27 (currently amended): A solution according to any one of Claims 19, 24, 25 or 26 ~~through 26~~, wherein the therapeutic agent is a prostaglandin analog.

Claim 28 (currently amended): A solution according to any one of Claims 19, 24, 25 or 26 ~~through 26~~ wherein the therapeutic agent is travoprost.

Claim 29 (previously presented): A multi-dose, self-preserved ophthalmic solution, comprising:

(a) a therapeutically effective amount of travoprost;

(b) a non-ionic surfactant;

(c) zinc chloride at a concentration of 0.001 to 0.005% w/v;

(d) boric acid at a concentration of 0.5 to 1.2% w/v;

(e) propylene glycol at a concentration of 0.25 to 1.25% w/v; and

(f) sorbitol at a concentration of 0.05 to 0.5% w/v;

wherein: (i) the solution has a pH from 5.5 to 5.9; (ii) the concentration of anionic species in the solution is less than 10 mM; (iii) the concentration of multivalent buffering anions in the solution is less than 5 mM; and (iv) the concentration of multivalent metal cations other than zinc in the solution is less than 5 mM; and (v) the solution exhibits sufficient antimicrobial activity to satisfy USP 27 preservative efficacy requirements based solely on the anti-microbial properties of one or more of components (a) – (f) together with the pH of the solution.

Claim 30 (previously presented): A solution according to Claim 29 wherein the solution does not contain multivalent buffering anions and does not contain multivalent cations other than zinc.

Claim 31 (previously presented): A multi-dose ophthalmic solution, consisting essentially of:

(a) travoprost at a concentration of 0.004% w/v;

(b) zinc chloride at a concentration of 0.0025% w/v;

(c) polyoxyl 40 hydrogenated castor oil at a concentration of 0.5% w/v;

(d) boric acid at a concentration of 1.0% w/v;

(e) propylene glycol at a concentration of 0.75% w/v;

(f) sorbitol at a concentration of 0.25% w/v;

(g) sodium hydroxide and/or hydrochloric acid in an amount sufficient to cause the solution to have a pH from 5.5 to 5.9; and

(h) water;

wherein: (i) the concentration of anionic species in the solution is less than 10 mM; (ii) the solution does not contain multivalent buffering anions; and (iii) the solution does not contain multivalent cations other than zinc.

Claim 32 (previously presented): A solution according to Claim 31 wherein the solution exhibits sufficient antimicrobial activity to satisfy USP 27 preservative efficacy requirements based solely on the anti-microbial properties of one or more of components (a) – (f) together with the pH of the solution.

REMARKS

Applicants thank Examiner Arnold for the courtesies extended to the undersigned during a telephonic Interview conducted on May 16, 2012. The Office Action rejected claims 19-32. By this amendment, Applicants have amended the specification, amended claims 19, 27 and 28 and have canceled claims 21-23. Applicants respectfully request reconsideration based upon the discussion provided below. Applicants believe the claims of the present application are novel and non-obvious relative to the prior art.

I. Objections to the Specification

The Office Action objected to the Specification suggesting that the description in the actual figures did not correspond to the description in the Brief Description of Drawings. Without acquiescing in this objection, Applicants have amended the Brief Description of Drawings to overcome the objection. Applicants also submit herewith replacement pages of drawings to place proper numbering at the top of the drawings and to remove the descriptions under the drawings since they are now in the specification.

II. Claim Rejections under 35 USC 103

The Office Action rejected claims 19-32 under 35 USC 103(a) as being obvious over Xia et al. (US 2005/0214382) in view of one or more of the following references: Asgharian (US 6319464); Chowhan et al. (US 6503497); Deaciuc et al. (US 20060270735); and Sherman (US 5843891). Applicants respectfully request reconsideration of these rejections. Below, Applicants briefly review a primary advantage of the subject matter of the claims of the present application and then provide reasoning as to the patentability of the claimed subject matter relative to the cited prior art.

Advantage of the Subject Matter of the Claims

The subject matter of the claims of the present application represents a significant advance in preservation of ophthalmic compositions. The subject matter represents a novel zinc-based preservative system that achieves desired preservation of an ophthalmic composition using a very low concentration of zinc. The preservation system relies upon the maintenance of a low concentration of anionic species in the ophthalmic composition to provide that composition with the ability to pass United States Pharmacopeia preservation standards while using the very low concentration of zinc and no conventional anti-microbial

preservative.

Subject Matter of the Claims Relative to the Cited Prior Art

The Office Action specifically defines that which the Examiner believes to be the difference between the claims of the present application and the prior art. As part of that definition, the Office Action, at page 7 thereof, reads:

> The difference between the instant application and Xia et al. is that Xia et al. do not expressly teach an embodiment with the instantly claimed amounts of sorbitol and propylene glycol in the composition that satisfies USP 27 preservative efficacy requirements or the use of NaOH and/or HCl to adjust the pH. This deficiency in Xia et al. is cured by the teachings of Asgharian and Chowhan et al.

Applicants suggest that this definition of differences is not complete. Applicants respectfully request reconsideration of this definition of the differences between the prior art and the subject matter of the claims of the present application and reconsideration of whether Asgharian and Chowhan et al. actually cure the deficiencies in the disclosure of Xia et al.

In addition to the differences identified by the Examiner in the Office Action, each of the claims of the present application specifically recites a concentration range of zinc ions (i.e., 0.04 mM to 0.4 mM) and recites an upper limit to the concentration of anionic species (e.g., 15mM). These recitations represent important differences between the subject matter of the claims of the present application and the prior art, particularly Xia et al. This is particularly the case when these recitations are considered in conjunction with the other differences recited by the Examiner in the Office Action.

In regard to Xia et al., the Office Action states, at page 5 thereof, that "no other anions or multivalent cations [other than those from zinc chloride] are required in the composition and therefore their concentrations are less than 15 mM and 5mM respectively." The skilled artisan, however, would read Xia et al. much differently and would not come to the same conclusion suggested by the Office Action. Paragraph 45 of Xia et al. reads as follows:

> The aqueous solutions of the present invention are typically adjusted with tonicity agents to approximate the tonicity of normal lacrimal fluids (approximately equivalent to a 0.9 wt. % solution of sodium chloride or 2.8 wt. % glycerol solution). Typically, the solutions are hypotonic or substantially isotonic with physiological saline used alone or in

combination with other adjusting agents ...

Xia et al. then go on to provide a total of twenty specific examples of formulations, each having a concentration of 0.220 wt% of sodium chloride (NaCl) or greater. In doing so, Xia et al. express a very clear preference for producing osmolality in their compositions with high concentrations of NaCl and, more particularly, concentrations of NaCl that cause the anionic species of the formulation of Xia et al. to be greater than 15 mM (see calculations below).

0.220 wt% NaCl = 0.00220 mg NaCl per mg of solution, 1 g of solution = almost exactly 1 ml of solution
Thus, 0.220 wt% NaCl = 0.00220 mg NaCl per ml or 2.20 g NaCl per liter, molar mass NaCl = 58.4 g/mol
2.20 g/L ÷ 58.4 g/mol = 0.0377 M NaCl = 37.7 mM NaCl or 37.7 mM of anionic species chloride.

Thus, the concentration of anionic species in the Xia et al. formulations from NaCl alone is approximately 37.7 mM, which is more than twice the upper limit of the total concentration of anionic species recited in the claims of the present application.

Based on the disclosure of Xia et al., the skilled artisan would read Xia et al. to suggest that their compositions should include a substantial amount of NaCl. The skilled artisan would read Xia et al. to suggest that their composition should include an amount of NaCl that would cause those compositions to have a concentration of anionic species substantially higher than the limit recited in the claims of the present application. As such, the skilled artisan would never read Xia et al. as disclosing or suggesting a composition with an upper limit of anionic species of 5 mM or even 15 mM.

In addition to the above, Xia et al. provide no recognition of the deleterious effect of anionic species upon the ability of zinc to provide preservation efficacy and actually encourage the use of anionic species in their composition. Paragraphs 22 and 24 of Xia et al. read:

> ... The compositions of the present invention include a polycationic material. The term "polycation" material denotes a material having multiple cationic moieties, such as quaternary ammonium groups, in the same molecule.

> In general, polyquaternium polymers suitable for use in the present invention are a well-known class of polymers of which many variations are commercially available. The polyquaternium polymer preferably includes an ophthalmologically suitable anionic organic or inorganic counterion. A preferred counterion may include, but are not limited to fluoride ions, chloride ions, bromide ions, iodide ions and the like.

Thus, Xia et al. teach toward the inclusion of anions as counterions in their composition. Again, the skilled artisan would never read Xia et al. as disclosing or suggesting a composition with an upper limit of anionic species of 5 mM or even 15 mM.

The Office Action asserts, at page 4 thereof, that Xia et al. teach compositions with a concentration of zinc at a minimum of about 0.001 wt% to a maximum of about 1 wt%. While this range admittedly at least overlaps with the range of zinc ions (i.e., 0.04 mM to 0.4 mM) recited in the claims of the present application, it does not end the inquiry into the scope and content of the prior art or the differences between the prior art and the claimed subject matter. The true difference between the subject matter of the claims of the present application and Xia et al. is that the present application provides a composition that passes U.S. Pharmacopeia preservation standards using a preservative system that combines borate and polyol with very low concentrations of zinc, as recited in the claims of the present application.

Xia et al. provide no teaching of whether it is possible to pass U.S. Pharmacopeia standards with a concentration of zinc ions that is from 0.04 to 0.4 mM, and certainly does not teach how to do so. As suggested by the Office Action, at page 5 thereof, Tables 9-11 of Xia et al. teach zinc wt.% concentration ranges "from 0.05 to 0.025 to 0.0125 and 0.0065" and as calculated in the office action, the lowest concentration of 0.0065 is close to 0.476 mM of zinc ions. However, this concentration of zinc ions does not overlap with the concentration of zinc ions recited in the claims of the present application. Further, Xia et al. do not teach the ability to pass U.S. Pharmacopeia standards at zinc concentrations below 0.0065 wt%. In contrast, the zinc-based preservation system taught in the present application combines low concentrations of zinc with 0.1 – 2.0% of borate and 0.25 – 2.5% of polyol (i.e., propylene glycol and sorbitol) to create compositions that pass U.S. Pharmacopeia preservation efficacy standards at $ZnCl_2$ concentrations of 0.0025 w/v%, which is substantially lower than the 0.0065 wt % disclosed in Xia et al.

The compositions of the present application are able to pass the U.S. Pharmacopeia

preservation efficacy standard with substantially lower concentrations of zinc than those exemplified in Xia et al. by limiting the concentration of anionic species to 15 mM or less, as recited in all of Applicants' claims. Moreover, Xia et al. do not disclose or suggest controlling the concentration of multivalent buffering anions less than 5 mM or the concentration of multivalent metal cations other than zinc less than 5mM, as recited in some of Applicants' dependent claims.

Secondary References

None of the secondary references cited by the Office Action can overcome the above deficiencies of Xia et al. None of the cited secondary references, alone or in combination, teaches the presently claimed preservation system. None of these references discloses or suggests the maintenance of anionic species below a certain concentration significantly improves the ability of a zinc-based preservative system containing borate and polyol to provide preservation efficacy at a very low concentration of zinc ions. Moreover, this information is not part of the ordinary knowledge of the skilled artisan at the time of filing the present application.

There is a long history of attempts to provide zinc-based preservation systems that pass preservation efficacy standards using zinc. Olejnik (US 5597559), which was discussed in the first Notice of Allowance issued for this application, illustrates just how difficult it has been to provide preservation efficacy with zinc-based preservation systems[1]. As discussed above, the subject matter of the claims of the present application represents a significant advance relative to these past efforts.

Moreover, the Office Action suggests that, "it is simply routine optimization to determine the amount of each polyol in order to satisfy USP 27 preservative efficacy requirements which is intrinsically met by the combination of antimicrobial properties and the pH." Applicants suggest that this statement lacks merit. In particular, the references cited by the Office Action do not specifically teach the particular combination of polyols at the ranges now recited in the claims (i.e., propylene glycol in the composition at a concentration of 0.25 to 1.25% w/v and sorbitol in the composition at a concentration of 0.05 to 0.5% w/v) in conjunction with a low concentration of zinc ions and a low concentration of anionic species to achieve the surprising high degree of preservative efficacy shown by the data of the present

[1] The first Notice of Allowance reads, "... it is surprising that Applicant can use about half as much zinc as Olejnik et al. (US 5597559) and obtain a much greater duration of preservative effect. In contrast Olejnik et al. teach only 72 hours of efficacy, which clearly does not meet USP 27 standards ..."

application. This is particularly the case since the particular combination of polyols recited along with the borate and the zinc achieve this high degree of preservation efficacy without any substantial assistance from any other antimicrobial agents.

Based on the above, Applicants respectfully request reconsideration of the subject matter that is actually taught by Xia et al. and how the differences between the subject matter of Xia et al. and the subject matter of the claims of the present application show that the claims of the present application represent a significant advance over Xia et al. Applicants further respectfully request reconsideration of whether any of the secondary references provide teachings that, even when considered in conjunction with the ordinary knowledge of the skilled artisan, would lead a skilled artisan to the subject matter of the claims of the present application. Finally, Applicants respectfully request that the claims of the present application be given a Notice of Allowance so that Letters Patent may be issued.

Obviousness Type Double Patenting

The Office Action rejected claims of the present application on the ground of nonstatutory obviousness-type double patenting in view of U.S. Patent Application Serial No. 12/441,995 and U.S. Patent Application Serial No. 11/858,781. Without acquiescing in these rejections, Applicants have filed terminal disclaimers herewith to overcome the rejections.

CONCLUSION

Should the Examiner have any questions regarding this Amendment, please feel free to contact the undersigned attorney at the phone number listed below.

Respectfully submitted,

Alcon Research, Ltd.

May 17, 2012

Scott A. Chapple
Reg. No. 46,287

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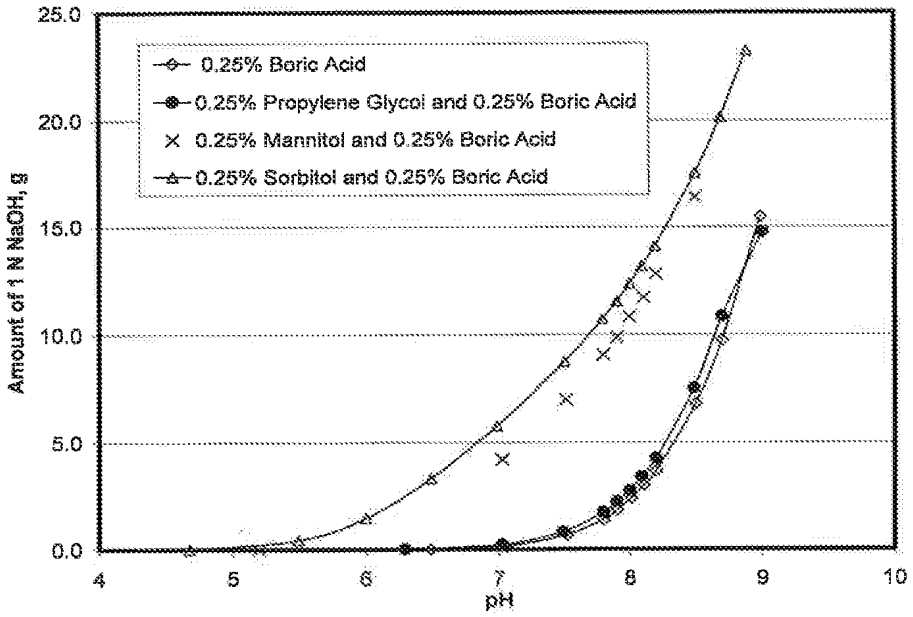
Alcon Research, Ltd.
6201 S. Freeway, TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-5288

Attorney Docket: 3205US

REPLACEMENT SHEET

1 / 3

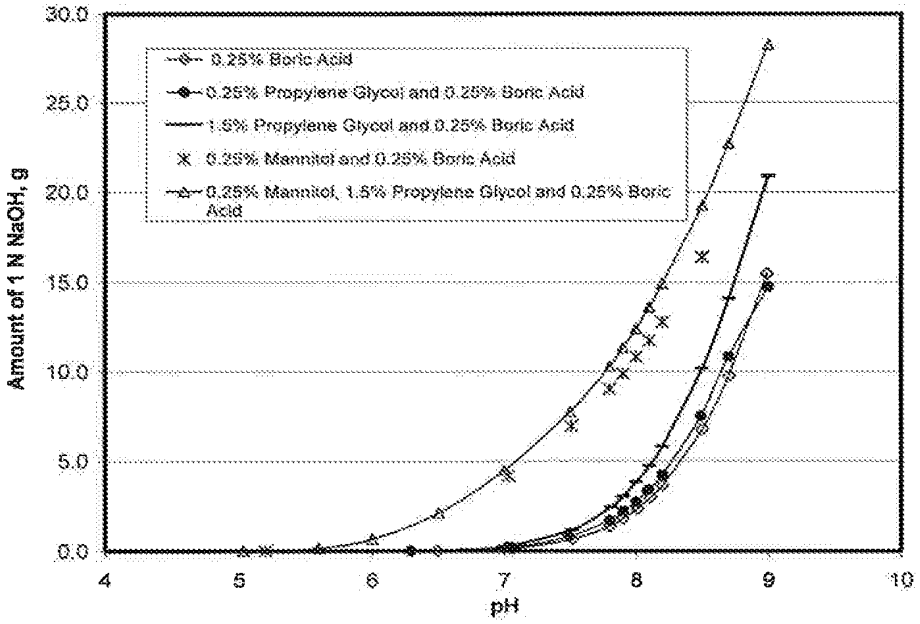
FIG. 1



REPLACEMENT SHEET

2 / 3

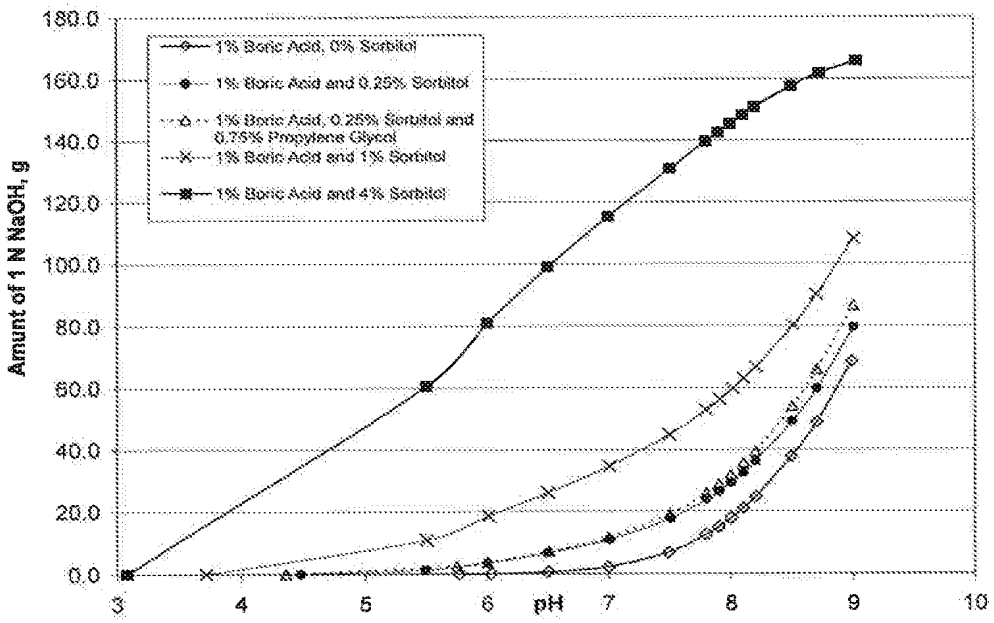
FIG. 2



REPLACEMENT SHEET

3 / 3

FIG. 3



PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13086950
Filing Date	2011-04-14
First Named Inventor	Bhagwati P. Kabra
Art Unit	1613
Examiner Name	Arnold, Ernst V.
Attorney Docket Number	3205 US A

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13086950
	Filing Date	2011-04-14
	First Named Inventor	Bhagwati P. Kabra
	Art Unit	1613
	Examiner Name	Arnold, Ernst V.
	Attorney Docket Number	3205 US A

	1	HOFFMAN H.M. et al., "Pre-clinical in vitro Testing of an Artificial Tear Formulation with a Novel Preservation System", poster presentation at the annual meeting of the Association for Research In Vision And Ophthalmology (ARVO), Ft. Lauderdale, FL., April 30, 2006	☐
	2	Illustration of packaging for Systane® Free, March 7, 2006	☐
	3	SYSTANE® FREE promotional document (minimal-blur) published on or about January 1, 2006	☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13086950
	Filing Date	2011-04-14
	First Named Inventor	Bhagwati P. Kabra
	Art Unit	1613
	Examiner Name	Arnold, Ernst V.
	Attorney Docket Number	3205 US A

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☒ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Scott A. Chapple, Reg. #46,287/	Date (YYYY-MM-DD)	2012-05-17
Name/Print	Scott A. Chapple	Registration Number	46,287

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

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Electronic Patent Application Fee Transmittal

Application Number:	13086950
Filing Date:	14-Apr-2011
Title of Invention:	Self-Preserved Aqueous Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Bhagwati P. Kabra
Filer:	Scott Chapple/Barbara McKenzie
Attorney Docket Number:	3205 US A

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
Statutory or terminal disclaimer	1814	2	160	320
		Total in USD ($)		**500**

Electronic Acknowledgement Receipt

EFS ID:	12808423
Application Number:	13086950
International Application Number:	
Confirmation Number:	5197
Title of Invention:	Self-Preserved Aqueous Pharmaceutical Compositions
First Named Inventor/Applicant Name:	Bhagwati P. Kabra
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	3205 US A
Receipt Date:	17-MAY-2012
Filing Date:	14-APR-2011
Time Stamp:	18:18:47
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$500
RAM confirmation Number	5186
Deposit Account	010682
Authorized User	

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		3205_US_A_Amend_051712.pdf	659881 6041bd885e5d2c2cb616844c8de9ddad93e82c75	yes	15

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Specification	2	2
Claims	3	5
Applicant Arguments/Remarks Made in an Amendment	6	12
Drawings-only black and white line drawings	13	15

Warnings:

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2	Terminal Disclaimer Filed	3205_US_A_USSN_11-858781_sb25_051712.pdf	96377 262aa97d077c89d11e95dc7f3f4a2714ac3692c1	no	1

Warnings:

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3	Assignee showing of ownership per 37 CFR 3.73(b).	3205_US_A_USSN_11-858781_sb96_051712.pdf	90223 ef150ff91af43fdd7e0afd5000c53dfff733de3a	no	1

Warnings:

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4	Terminal Disclaimer Filed	3205_US_A_USSN_12-441995_sb25_051712.pdf	96525 7ec160a329e0a3acc9d8b3568c86c312bf654c17	no	1

Warnings:

Information:

5	Assignee showing of ownership per 37 CFR 3.73(b).	3205_US_A_USSN_12-441995_sb96_051712.pdf	87126 448df817b3143ea94de217664c4069bb754d60da	no	1

Warnings:

Information:

6	Transmittal Letter	3205_US_A_IDS-S3_051712.pdf	74765 c010b34bbcf0d9dd251cc16a2f97fd266f2c17e4	no	2
Warnings:					
Information:					
7	Information Disclosure Statement (IDS) Form (SB08)	3205_US_A_IDS-S3_08a_051712.pdf	612702 5ba747d2cd2cc267faaa974cdbb7de7665ea47d3	no	4
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8	Non Patent Literature	Hoffman_et_al_2006-04-30.pdf	263962 70f7c59d27cbba45054ea327b8586fc267d03d65	no	1
Warnings:					
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9	Non Patent Literature	Systane_Free_Packaging.pdf	117195 904505e9423f466bbc071a7252b4a37b737d34f5	no	1
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10	Non Patent Literature	Systane_Free_promotional_2006.pdf	202005 b426e99c7ccce7f1fa31f7e6c15f88e3164e09e2	no	2
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11	Fee Worksheet (SB06)	fee-info.pdf	31728 609a43afa0859fffaa301c1af1cc5bb98e031e2a	no	2
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National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

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PTO/SB/25 (08-11)
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TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION	Docket Number (Optional) 3205 US A

In re Application of: Bhagwati P. Kabra et al.

Application No.: 13/086,950

Filed: April 14, 2011

For: Self-Preserved Aqueous Pharmaceutical Compositions

The owner*, Alcon Research, Ltd., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number 11/858,781, filed September 20, 2007, as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

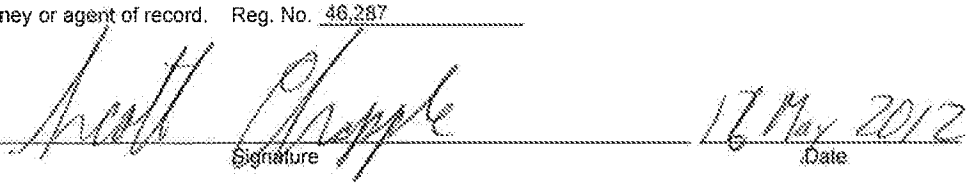
In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said **reference** application, "as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application," in the event that: any such patent: granted on the pending **reference** application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 46,287



Signature — Date: 12 Dec 2012

Scott A. Chapple
Typed or printed name

817-615-5288
Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

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*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this statement. See MPEP § 324.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Alcon Research, Ltd.

Application No./Patent No.: 11/858,781 Filed/Issue Date: September 20, 2007

Titled: Self-Preserved Aqueous Pharmaceutical Compositions

Alcon Research, Ltd., a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. [X] the assignee of the entire right, title, and interest in;

2. [ ] an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. [ ] the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made) the patent application/patent identified above, by virtue of either:

A. [ ] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. [X] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Inventors To: Alcon Manufacturing, Ltd.

The document was recorded in the United States Patent and Trademark Office at
Reel 019856, Frame 0532, or for which a copy thereof is attached.

2. From: Alcon Manufacturing, Ltd. To: Alcon Research, Ltd.

The document was recorded in the United States Patent and Trademark Office at
Reel 021266, Frame 0729, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet(s).

[ ] As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature

16 May 2012
Date

Scott A. Chapple
Printed or Typed Name

Attorney/Agent of Record
Title

PTO/SB/25 (08-11)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING "REFERENCE" APPLICATION

Docket Number (Optional): 3205 US A

In re Application of: Bhagwati P. Kabra et al.

Application No.: 13/086,950

Filed: April 14, 2011

For: Self-Preserved Aqueous Pharmaceutical Compositions

The owner*, Alcon Research, Ltd., of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending **reference** Application Number 12/441,995, filed March 19, 2009, as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the **reference** application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

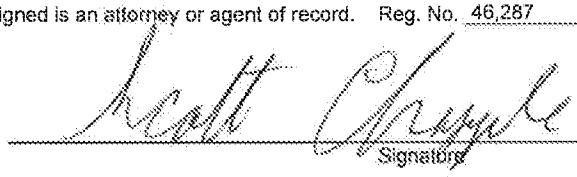
In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said **reference** application, "as the term of any patent granted on said **reference** application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending **reference** application," in the event that: any such patent: granted on the pending **reference** application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of a business/organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the business/organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 46,287



Signature

16 May 2012
Date

Scott A. Chapple
Typed or printed name

817-615-5286
Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this statement. See MPEP § 324.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Alcon Research, Ltd.

Application No./Patent No.: 12/441,995 Filed/Issue Date: March 19, 2009

Titled: Self-Preserved Aqueous Pharmaceutical Compositions

Alcon Research, Ltd. , a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 002420, Frame 0803, or for which a copy therefore is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature — Date: 11 May 2012

Scott A. Chapple — Attorney/Agent of Record

Printed or Typed Name — Title

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Bhagwati P. Kabra, et al.

U.S. Serial No. 13/086,950

Confirmation No.: 5197

Filed: April 14, 2011

Examiner: Arnold, Ernst V.

Group Art Unit: 1613

For: SELF PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

CERTIFICATE OF FILING VIA EFS-WEB

I hereby certify that this correspondence is being submitted to the Mail Stop Amendments; Commissioner for Patents, P.O. Box 1450, Alexandria, VA. 22313-1450 via EFS-Web on this date:
May 17, 2012.

By: /Barbara McKenzie/
Barbara McKenzie

THIRD INFORMATION DISCLOSURE STATEMENT PURSUANT TO 37 C.F.R. 1.56, 1.97(b)(3), AND 1.98

Mail Stop Amendment
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to the duty of disclosure under 37 C.F.R. § 1.97(c), Applicants submit the attached PTO Form PTO/SB/08a. Neither a final Office Action under §1.113 nor a notice of allowance under §1.311 have been issued in the above-referenced application.

This Information Disclosure Statement cites three references. Each of the three references relates to Systane® Free, an artificial tear product marketed by the assignee of the present application. The composition of Systane® Free was disclosed in detail in the Information Disclosure Statement that was filed in present application on July 13, 2011.

Because the PTO has waived the requirement under 37 CFR 1.98(a)(2) to submit copies of each cited U.S. patent and patent application publication in all U.S.

national patent applications filed after June 30, 2003, none are enclosed. Only copies of cited foreign patent documents and non-patent literature are enclosed.

Applicants request that the listed references be considered during prosecution of this application, and that the references appear among the "References Cited" on any patent issuing herefrom.

The requisite fee under 37 C.F.R. §1.17(p) has been charged to Deposit Account No. 010682 via EFS Web.

Respectfully submitted,

ALCON RESEARCH, LTD.

May 17, 2012

Scott A. Chapple
Reg. No. 46,287

ADDRESS FOR CORRESPONDENCE:
Alcon Research, Ltd.
Scott A. Chapple, IP Legal
6201 South Freeway, TB4-8
Fort Worth, TX 76134-2099
Phone: 817-615-5288

Docket No. 3205 US A

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/086,950	Filing Date 04/14/2011	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	05/17/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 11	Minus	** 20	= 0	X $ =		OR	X $60=	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $ =		OR	X $250=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/BRUCE HARRISON/

AMENDMENTS TO THE SPECIFICATION

Please revise the paragraph beginning at page 6, line 20 as follows:

~~Figures 1-3 are graphs showing the interaction of boric acid and various polyols.~~

Figure 1 is a graph showing the amount of 1' N Sodium Hydroxide needed to adjust pH of 1Kg solution of Boric Acid (0.25%) in presence of mannitol, sorbitol or propylene glycol.

Figure 2 is a graph showing the amount of 1 N Sodium Hydroxide needed to adjust pH of 1Kg solution of Boric Acid (0.25%) in presence of propylene glycol.

Figure 3 is a graph showing the amount of 1 N Sodium Hydroxide needed to adjust pH of 1Kg solution Boric Acid (1%) in presence of different concentrations of sorbitol.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	13/086,950	KABRA ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 5/17/12	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

Janice Ford

terminals approved

U.S. Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

26356 7590 07/31/2012

ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

EXAMINER
ARNOLD, ERNST V

ART UNIT	PAPER NUMBER
1613	

DATE MAILED: 07/31/2012

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/086,950	04/14/2011	Bhagwati P. Kabra	3205 US A	5197

TITLE OF INVENTION: SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	10/31/2012

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

26356 7590 07/31/2012

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FORT WORTH, TX 76134

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/086,950	04/14/2011	Bhagwati P. Kabra	3205 US A	5197

TITLE OF INVENTION: SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	10/31/2012

EXAMINER	ART UNIT	CLASS-SUBCLASS
ARNOLD, ERNST V	1613	424-078040

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/086,950	04/14/2011	Bhagwati P. Kabra	3205 US A	5197

26356 7590 07/31/2012

ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134

EXAMINER	
ARNOLD, ERNST V	

ART UNIT	PAPER NUMBER
1613	

DATE MAILED: 07/31/2012

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)

(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No.	Applicant(s)	
	13/086,950	KABRA ET AL.	
	Examiner	Art Unit	
	ERNST ARNOLD	1613	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *5/17/12*.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *19, 20 and 24-32 [renumbered as 1-11]* .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 5/17/12
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Ernst V Arnold/
Primary Examiner, Art Unit 1613

DETAILED ACTION

Claims 1-18 and 21-23 have been cancelled. Claims 19, 20 and 24-32 are pending and under examination.

Drawings

The drawings were received on 5/17/12. These drawings are ACCEPTED.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 5/17/12 was filed after the mailing date of the OFFICE ACTION on 2/27/12. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Terminal Disclaimer

The terminal disclaimers filed on 5/17/12 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration dates of applications 11/858781 and 12/441995 have been reviewed and are accepted. The terminal disclaimers have been recorded.

Withdrawn rejections:

Applicant's amendments and arguments filed 5/17/12 are acknowledged and have been fully considered. The Examiner has re-weighed all the evidence of record. Any rejection and/or objection not specifically addressed below is herein withdrawn. Claims 19-32 were rejected under 35 U.S.C. 103(a) as being unpatentable over Xia et al. (US 2005/0214382: IDS reference 4) and Asgharian (US 6319464: IDS reference 23) and Chowhan et al. (US 6503497: IDS reference 27) and Deaciuc et al. (US 20060270735) as evidenced by Sherman (US 5843891). Applicant's amendments and arguments are sufficient to overcome this rejection and it is withdrawn by the Examiner.

Allowable Subject Matter

The following is an examiner's statement of reasons for allowance: the closest prior art of Xia et al. (US 2005/0214382: IDS reference 1 filed on 4/29/11) does not teach or suggest, alone or in combination, the instant multi-dose, self-preserved ophthalmic composition with less than 15 mM anionic species and the specific amounts of propylene glycol and sorbitol as instantly claimed. There is no suggestion or motivation in the art to optimize both of these specific components in the amounts instantly claimed in combination with the ensemble of other components in the multi-dose, self-preserved ophthalmic composition. Therefore, the Examiner deems the instant invention free of the art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue

fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

Claims 19, 20 and 24-32 [renumbered as 1-11] are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERNST ARNOLD whose telephone number is (571)272-8509. The examiner can normally be reached on M-F 7:15-4:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Kwon can be reached on 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ernst V Arnold/
Primary Examiner, Art Unit 1613

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L3	44	424/405.ccls. and (zinc and (boric or borate) and sorbitol and (propylene adj glycol))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/07/16 10:17
L4	49	424/641.ccls. and (zinc and (boric or borate) and sorbitol and (propylene adj glycol))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/07/16 10:17
L5	0	424/657.ccls. and (zinc and (boric or borate) and sorbitol and (propylene adj glycol))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/07/16 10:17
L6	15	424/659.ccls. and (zinc and (boric or borate) and sorbitol and (propylene adj glycol))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/07/16 10:17
L7	13	424/660.ccls. and (zinc and (boric or borate) and sorbitol and (propylene adj glycol))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/07/16 10:18
L8	16	424/78.04.ccls. and (zinc and (boric or borate) and sorbitol and (propylene adj glycol))	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/07/16 10:18
L11	38	424/405.ccls. and (zinc and (boric or borate) and sorbitol and (propylene adj glycol)) and @ad<"20070920"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/07/16 10:19
L12	28	424/641.ccls. and (zinc and (boric or borate) and sorbitol and (propylene adj glycol)) and @ad<"20070920"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/07/16 10:19
L13	0	424/657.ccls. and (zinc and (boric or borate) and sorbitol and (propylene adj glycol)) and @ad<"20070920"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/07/16 10:19
L14	7	424/659.ccls. and (zinc and (boric or borate) and sorbitol and (propylene adj glycol)) and @ad<"20070920"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/07/16 10:20
L15	7	424/660.ccls. and (zinc and (boric or borate) and sorbitol and (propylene adj glycol)) and @ad<"20070920"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/07/16 10:20
L16	26	l11 and (sorbitol with propylene)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/07/16 10:21

L17	17	l12 and (sorbitol with propylene)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2012/07/16 10:22

7/ 16/ 2012 10:51:17 AM
C:\ Users\ earnold\ Documents\ EAST\ Workspaces\ 11858781i.wsp

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13086950	KABRA ET AL.
	Examiner	Art Unit
	ERNST ARNOLD	1613

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/16/2012								
	1	-								
	2	-								
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	29	=								
	30	=								
	31	=								
	32	=								

Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
13086950	KABRA ET AL.
Examiner	**Art Unit**
ERNST ARNOLD	1613

ORIGINAL		INTERNATIONAL CLASSIFICATION									
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED				
424	78.04	A	6	1	K	31 / 74 (2006.01.01)	A	0	1	N	25 / 00 (2006.01.01)
		A	6	1	K	33 / 32 (2006.01.01)	A	0	1	N	59 / 16 (2006.01.01)
		A	6	1	K	33 / 22 (2006.01.01)	A	0	1	N	59 / 14 (2006.01.01)

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
424	405	641	657	659	660
514	912				

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	19														
2	20														
3	24														
4	25														
5	26														
6	27														
7	28														
8	29														
9	30														
10	31														
11	32														

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 11	
/ERNST ARNOLD/ Primary Examiner.Art Unit 1613 (Primary Examiner)	7/16/12 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13086950	KABRA ET AL.
	Examiner	Art Unit
	ERNST ARNOLD	1613

SEARCHED			
Class	Subclass	Date	Examiner
424	78.04, 405, 641, 657, 650, 660 text limited	7/16/12	eva

SEARCH NOTES		
Search Notes	Date	Examiner
inventor/assignee name EAST/PALM	2/24/12	eva
EAST all databases	2/24/12	eva
search update EAST	7/16/12	eva

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner
USPGPUB TEXT SEARCH	EAST	7/16/12	EVA

EAST Search History

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	54	(zinc and (boric or borate) and (sorbitol and (propylene adj glycol))).clm.	US-PGPUB; USPAT; UPAD	OR	ON	2012/07/16 10:13
L2	8	l1 and (eye or ophthalmic).clm.	US-PGPUB; USPAT; UPAD	OR	ON	2012/07/16 10:14
L9	18172	"l6" and @ad<"20070920"	US-PGPUB; USPAT; UPAD	OR	ON	2012/07/16 10:18
L10	18172	"l6" and @ad<"20070920"	US-PGPUB; USPAT; UPAD	OR	ON	2012/07/16 10:19

7/ 16/ 2012 10:51:35 AM
C:\ Users\ earnold\ Documents\ EAST\ Workspaces\ 11858781i.wsp

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BIB DATA SHEET

CONFIRMATION NO. 5197

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/086,950	04/14/2011 RULE	424	1613	3205 US A

APPLICANTS

Bhagwati P. Kabra, Euless, TX;
Masood A. Chowhan, Arlington, TX;
L. Wayne Schneider, Crowley, TX;
Wesley Wehsin Han, Arlington, TX;

**** CONTINUING DATA ***************************

This application is a CON of 11/858,781 09/20/2007
which claims benefit of 60/827,411 09/28/2006
and claims benefit of 60/826,529 09/21/2006

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

04/27/2011

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /Ernst V Arnold / Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		TX	3	11 ~~44~~	3

ADDRESS

ALCON
IP LEGAL, TB4-8
6201 SOUTH FREEWAY
FORT WORTH, TX 76134
UNITED STATES

TITLE

Self-Preserved Aqueous Pharmaceutical Compositions

FILING FEE RECEIVED		
1896	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13086950
Filing Date	2011-04-14
First Named Inventor	Bhagwati P. Kabra
Art Unit	1613
Examiner Name	Arnold, Ernst V.
Attorney Docket Number	3205 US A

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	1							☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13086950
	Filing Date	2011-04-14
	First Named Inventor	Bhagwati P. Kabra
	Art Unit	1613
	Examiner Name	Arnold, Ernst V.
	Attorney Docket Number	3205 US A

/E.A./	1	HOFFMAN H.M. et al., "Pre-clinical in vitro Testing of an Artificial Tear Formulation with a Novel Preservation System", poster presentation at the annual meeting of the Association for Research In Vision And Ophthalmology (ARVO), Ft. Lauderdale, FL., April 30, 2006	☐
/E.A./	2	Illustration of packaging for Systane® Free, March 7, 2006	☐
/E.A./	3	SYSTANE® FREE promotional document (minimal-blur) published on or about January 1, 2006	☐

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EXAMINER SIGNATURE

Examiner Signature	/Ernst Arnold/	Date Considered	07/16/2012

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

26356 7590 07/31/2012

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6201 SOUTH FREEWAY
FORT WORTH, TX 76134

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Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

Barbara McKenzie (Depositor's name)
(Signature)
October 31, 2012 (Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/086,950	04/14/2011	Bhagwati P. Kabra	3205 US A	5197

TITLE OF INVENTION: SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1740	$300	$0	$2040	10/31/2012

EXAMINER	ART UNIT	CLASS-SUBCLASS
ARNOLD, ERNST V	1613	424-078040

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Scott A. Chapple
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Alcon Research, Ltd.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Fort Worth, Texas

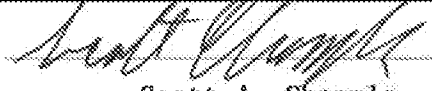
Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☒ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 010682 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
- ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature  Date October 31, 2012

Typed or printed name Scott A. Chapple Registration No. 46,287

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Electronic Patent Application Fee Transmittal

Application Number:	13086950
Filing Date:	14-Apr-2011
Title of Invention:	SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Bhagwati P. Kabra
Filer:	Scott Chapple/Barbara McKenzie
Attorney Docket Number:	3205 US A

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	1501	1	1770	1770
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2070**

Electronic Acknowledgement Receipt

EFS ID:	14111796
Application Number:	13086950
International Application Number:	
Confirmation Number:	5197
Title of Invention:	SELF-PRESERVED AQUEOUS PHARMACEUTICAL COMPOSITIONS
First Named Inventor/Applicant Name:	Bhagwati P. Kabra
Customer Number:	26356
Filer:	Scott Chapple/Barbara McKenzie
Filer Authorized By:	Scott Chapple
Attorney Docket Number:	3205 US A
Receipt Date:	31-OCT-2012
Filing Date:	14-APR-2011
Time Stamp:	12:22:17
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2070
RAM confirmation Number	7601
Deposit Account	010682
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

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Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	32278 0c4cb3989034c3930cbf2413d53860656689468f	no	2
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13/086,950	12/04/2012	8323630	3205 US A	5197

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ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

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