



(12) **United States Patent**
Cagle et al.

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- (54) **METHOD OF TREATING OPHTHALMIC INFECTIONS WITH MOXIFLOXACIN COMPOSITIONS**
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(57) **ABSTRACT**

Ophthalmic, otic and nasal compositions containing a new class of antibiotics (e.g., moxifloxacin) are disclosed. The compositions preferably also contain one or more anti-inflammatory agents. The compositions may be utilized to treat ophthalmic, otic and nasal conditions by topically applying the compositions to the affected tissues.

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- DTX4014: Demonstrative—Comparison of Ingredients Chart in *Bayer Healthcare AG, Alcon, Inc., and Alcon Research, Ltd. v. Teva Pharmaceuticals USA, Inc.* (Civil Action No. 06-234 SLR) (Defendants' Exhibit List).
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**METHOD OF TREATING OPHTHALMIC
INFECTIONS WITH MOXIFLOXACIN
COMPOSITIONS**

CLAIM FOR PRIORITY

The present application is a continuation of U.S. patent application Ser. No. 10/200,868 filed Jul. 22, 2002 (now U.S. Pat. No. 6,716,830), which is a continuation of U.S. patent application Ser. No. 09/646,797 filed Sep. 22, 2000, (now abandoned), which is the National Stage of International Application Ser. No. PCT/US99/22622 filed Sep. 29, 1999, which claims benefit under 35 U.S.C. §119(e) of U.S. Provisional Application Ser. Nos. 60/102,504 and 60/102,506 filed on Sep. 30, 1998.

BACKGROUND OF THE INVENTION

The present invention is directed to the provision of topical antibiotic pharmaceutical compositions for the treatment of ophthalmic, otic and nasal infections, particularly bacterial infections, and to methods of treating ophthalmic, otic and nasal infections by applying those compositions to the affected tissues. The compositions and methods of the invention are based on the use of a new class of antibiotics. The compositions of the present invention may also contain one or more anti-inflammatory agents.

The use of quinolone antibiotics to treat infections represents the current state of the art in the field of ophthalmic pharmaceutical compositions and methods of treatment. For example, a topical ophthalmic composition containing the quinolone ciprofloxacin is marketed by Alcon Laboratories, Inc. under the name CILOXAN™ (Ciprofloxacin 0.3%) Ophthalmic Solution. The following quinolones have also been utilized in ophthalmic antibiotic compositions:

Quinolone	Product	Manufacturer
Ofloxacin	OCUFLOX™	Allergan
Norfloxacin	CHIBROXIN™	Merek
Lomefloxacin	LOMEFLOX™	Senju

The foregoing quinolone antibiotic compositions are generally effective in treating ophthalmic infections, and have distinct advantages over prior ophthalmic antibiotic compositions, particularly those having relatively limited spectrums of antimicrobial activity, such as: neomycin, polymyxin B, gentamicin and tobramycin, which are primarily useful against gram negative pathogens; and bacitracin, gramicidin, and erythromycin, which are primarily active against gram positive pathogens. However, despite the general efficacy of the ophthalmic quinolone therapies currently available, there is a need for improved compositions and methods of treatment based on the use of antibiotics that are more effective than existing antibiotics against key ophthalmic pathogens, and less prone to the development of resistance by those pathogens.

There is an even greater need for effective topical compositions and methods for treating otic and nasal infections, particularly bacterial infections. The use of oral antibiotics to treat otic infections in children has limited efficacy, and creates a serious risk of pathogen resistance to the orally administered antibiotics.

Ophthalmic, otic and nasal infections are frequently accompanied by inflammation of the infected ophthalmic, otic and nasal tissues and perhaps even surrounding tissues. Similarly, ophthalmic, otic and nasal surgical procedures that create a risk of microbial infections frequently also cause inflammation of the affected tissues. Thus, there is also a need for ophthalmic, otic and nasal pharmaceutical compositions that combine the anti-infective activity of one or more antibiotics with the anti-inflammatory activity of one or more steroid or non-steroid agents in a single composition.

SUMMARY OF THE INVENTION

The invention is based on the use of a potent new class of antibiotics to treat ophthalmic, otic and nasal infections, as well as the prophylactic use of these antibiotics following surgery or other trauma to ophthalmic, otic or nasal tissues. The compositions of the present invention may also be administered to the affected tissues during ophthalmic, otic or nasal surgical procedures to prevent or alleviate post-surgical infection.

The compositions preferably also contain one or more anti-inflammatory agents to treat inflammation associated with infections of ophthalmic, otic or nasal tissues. The anti-inflammatory component of the compositions is also useful in treating inflammation associated with physical trauma to ophthalmic, otic or nasal tissues, including inflammation resulting from surgical procedures. The compositions of the present invention are therefore particularly useful in treating inflammation associated with trauma to ophthalmic, otic or nasal tissues wherein there is either an infection or a risk of an infection resulting from the trauma.

Examples of ophthalmic conditions that may be treated with the compositions of the present invention include conjunctivitis, keratitis, blepharitis, dacryocystitis, hordeolum and corneal ulcers. The compositions of the invention may also be used prophylactically in connection with various ophthalmic surgical procedures that create a risk of infection.

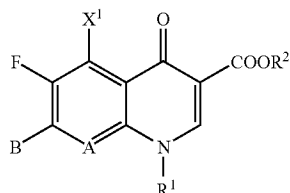
Examples of otic conditions that may be treated with the compositions of the present invention include otitis externa and otitis media. With respect to the treatment of otitis media, the compositions of the present invention are primarily useful in cases where the tympanic membrane has ruptured or tympanostomy tubes have been implanted. The compositions may also be used to treat infections associated with otic surgical procedures, such as tympanostomy, or to prevent such infections.

The compositions of the present invention are specially formulated for topical application to ophthalmic, otic and nasal tissues. The compositions are preferably sterile, and have physical properties (e.g., osmolality and pH) that are specially suited for application to ophthalmic, otic and nasal tissues, including tissues that have been compromised as the result of preexisting disease, trauma, surgery or other physical conditions.

DETAILED DESCRIPTION OF THE INVENTION

The antibiotics used in the compositions and methods of the present invention have the following formula:

3



wherein:

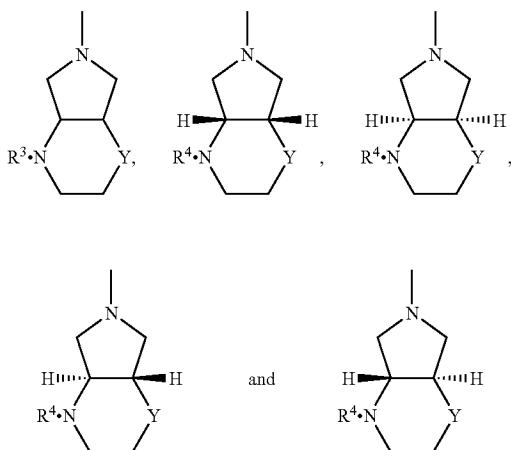
A is CH, CF, CCl, C—OCH₃, or N;

X¹ is H, halogen, NH₂, or CH₃;

R¹ is C₁ to C₃ alkyl, FCH₂CH₂, cyclopropyl or phenyl, optionally mono-, di- or tri-substituted by halogen, or A and R¹ together can form a bridge of formula C—O—CH₂—CH (CH₃);

R² is H, C₁ to C₃ alkyl (optionally substituted by OH, halogen or NH₂), or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl; and

B is a selected from the group consisting of:



wherein:

Y is O or CH₂;

R³ is C₂-C₅ alkoxy, CH₂—CO—C₆H₅, CH₂CH₂CO₂R', R'O₂C—CH=C—CO₂R', CH=CH—CO₂R' or CH₂CH₂—CN,

wherein:

R' is H or C₁ to C₃ alkyl;

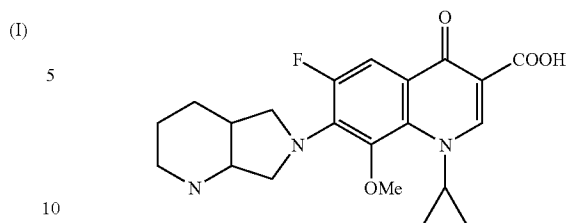
R⁴ is H, C₁ to C₃ alkyl, C₂-C₅ alkoxy, CH₂—CO—C₆H₅, CH₂CH₂CO₂R', R'O₂C—CH=C—CO₂R', CH=CH—CO₂R', CH=CH—CO₂R', CH₂CH₂—CN or 5-methyl-2-oxo-1,3-dioxol-4-yl-methyl,

wherein:

R' is H or C₁ to C₃ alkyl; and their pharmaceutically useful hydrates and salts.

The compound Moxifloxacin is most preferred. Moxifloxacin has the following structure:

4



Further details regarding the structure, preparation, and physical properties of Moxifloxacin and other compounds of formula (I) are provided in U.S. Pat. No. 5,607,942.

The concentrations of the antibiotics of formula (I) in the compositions of the present invention will vary depending on the intended use of the compositions (e.g., treatment of existing infections or prevention of post-surgical infections), and the relative antimicrobial activity of the specific antibiotic selected. The antimicrobial activity of antibiotics is generally expressed as the minimum concentration required to inhibit the growth of a specified pathogen. This concentration is also referred to as the "minimum inhibitory concentration" or "MIC". The term "MIC90" refers to the minimum concentration of antibiotic required to inhibit the growth of ninety percent (90%) of the strains of a species. The concentration of an antibiotic required to totally kill a specified bacteria is referred to as the "minimum bactericidal concentration" or "MBC". The minimum inhibitory concentration of Moxifloxacin for several bacteria commonly associated with ophthalmic, otic and nasal infections are provided in the following table:

Microorganism	MIC ₉₀
<i>S. aureus</i> /methicillin sensitive	0.13
<i>S. aureus</i> /methicillin resistant	4.0
<i>S. aureus</i> /quinolone resistant	4.0
<i>S. epidermidis</i> /methicillin sensitive	0.25
<i>S. epidermidis</i> /methicillin resistant	4.0
<i>S. pneumoniae</i> /penicillin sensitive	0.25
<i>S. pneumoniae</i> /penicillin resistant	0.25
<i>P. aeruginosa</i>	8.0
<i>H. influenzae</i> /β-lactamase positive	0.06
<i>H. influenzae</i> /β-lactamase negative	0.06

All of the foregoing concentrations are expressed as micrograms per milliliter ("mcg/ml").

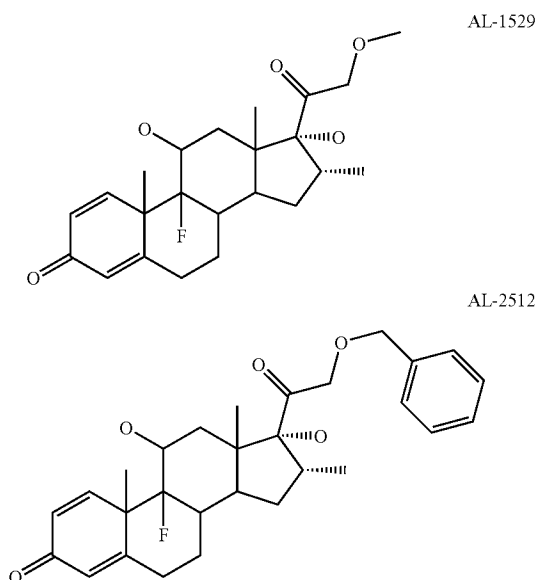
The appropriate antibiotic concentration for ophthalmic compositions will generally be an amount of one or more antibiotics of formula (I) sufficient to provide a concentration in the aqueous humor and lacrimal fluid of the eye equal to or greater than the MIC90 level for the selected antibiotic(s), relative to gram-negative and gram-positive organisms commonly associated with ophthalmic infections. The appropriate concentration for otic and nasal compositions will generally be an amount of one or more antibiotics of formula (I) sufficient to provide a concentration in the infected tissues equal to or greater than the MIC90 level for the selected antibiotic(s), relative to gram-negative and gram-positive organisms commonly associated with otic or nasal infections. Such amounts are referred to herein as "an antimicrobial effective amount". The compositions of the present invention will typically contain one or more compounds of formula (I) in a concentration of from about 0.1 to about 1.0 percent by weight ("wt. %") of the compositions.

5

The compositions of the present invention may also contain one or more anti-inflammatory agents. The anti-inflammatory agents utilized in the present invention are broadly classified as steroidal or non-steroidal. The preferred steroidal anti-inflammatory agents are glucocorticoids.

The preferred glucocorticoids for ophthalmic and otic use include dexamethasone, loteprednol, rimexolone, prednisolone, fluorometholone, and hydrocortisone. The preferred glucocorticoids for nasal use include mometasone, fluticasone, beclomethasone, flunisolide, triamcinolone and budesonide.

The dexamethasone derivatives described in U.S. Pat. No. 5,223,493 (Boltralik) are also preferred steroidal anti-inflammatory agents, particularly with respect to compositions for treating ophthalmic inflammation. The following compounds are especially preferred:



These compounds are referred to herein as “21-ether derivatives of dexamethasone”. The 21-benzyl ether derivative (i.e., compound AL-2512) is particularly preferred.

The preferred non-steroidal anti-inflammatory agents are: prostaglandin H synthetase inhibitors (Cox I or Cox II), also referred to as cyclooxygenase type I and type II inhibitors, such as diclofenac, flurbiprofen, ketorolac, suprofen, nepafenac, amfenac, indomethacin, naproxen, ibuprofen, bromfenac, ketoprofen, meclofenamate, piroxicam, sulindac, mefanamic acid, diflusal, oxaprozin, tolmetin, fenoprofen, benoxaprofen, nabumetome, etodolac, phenylbutazone, aspirin, oxyphenbutazone, NCX-4016, HCT-1026, NCX-284, NCX-456, tenoxicam and carprofen; cyclooxygenase type II selective inhibitors, such as NS-398, vioxx, celecoxib, P54, etodolac, L-804600 and S-33516; PAF antagonists, such as SR-27417, A-137491, ABT-299, apafant, bepafant, minopafant, E-6123, BN-50727, nupafant and modipafant; PDE IV inhibitors, such as ariflo, torbafylline, rolipram, filaminast, piclamilast, cipamfylline, CG-1088, V-11294A, CT-2820, PD-168787, CP-293121, DWP-205297, CP-220629, SH-636, BAY-19-8004, and roflumilast; inhibitors of cytokine production, such as inhibitors of the NFκB transcription factor; or other anti-inflammatory agents known to those skilled in the art.

6

The concentrations of the anti-inflammatory agents contained in the compositions of the present invention will vary based on the agent or agents selected and the type of inflammation being treated. The concentrations will be sufficient to reduce inflammation in the targeted ophthalmic, otic or nasal tissues following topical application of the compositions to those tissues. Such an amount is referred to herein as “an anti-inflammatory effective amount”. The compositions of the present invention will typically contain one or more anti-inflammatory agents in an amount of from about 0.01 to about 1.0 wt. %.

The compositions are typically administered to the affected ophthalmic, otic or nasal tissues by topically applying one to four drops of a sterile solution or suspension, or a comparable amount of an ointment, gel or other solid or semisolid composition, one to four times per day. However, the compositions may also be formulated as irrigating solutions that are applied to the affected ophthalmic, otic or nasal tissues during surgical procedures.

The ophthalmic, otic and nasal compositions of the present invention will contain one or more compounds of formula (I) and preferably one or more anti-inflammatory agents, in pharmaceutically acceptable vehicles. The compositions will typically have a pH in the range of 4.5 to 8.0. The ophthalmic compositions must also be formulated to have osmotic values that are compatible with the aqueous humor of the eye and ophthalmic tissues. Such osmotic values will generally be in the range of from about 200 to about 400 milliosmoles per kilogram of water (“mOsm/kg”), but will preferably be about 300 mOsm/kg.

Ophthalmic, otic and nasal pharmaceutical products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: polyquaternium-1, benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, or other agents known to those skilled in the art. The use of polyquaternium-1 as the antimicrobial preservative is preferred. Typically such preservatives are employed at a level of from 0.001% to 1.0% by weight.

The solubility of the components of the present compositions may be enhanced by a surfactant or other appropriate co-solvent in the composition. Such co-solvents include polysorbate 20, 60, and 80, polyoxyethylene/polyoxypropylene surfactants (e.g., Pluronic F-68, F-84 and P-103), cyclodextrin, or other agents known to those skilled in the art. Typically such co-solvents are employed at a level of from 0.01% to 2% by weight.

The use of viscosity enhancing agents to provide the compositions of the invention with viscosities greater than the viscosity of simple aqueous solutions may be desirable to increase ocular absorption of the active compounds by the target tissues or increase the retention time in the eye, ear or nose. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art. Such agents are typically employed at a level of from 0.01% to 2% by weight.

7

The following examples are provided to further illustrate the ophthalmic, otic and nasal compositions of the present invention.

EXAMPLE 1

Ophthalmic/Otic/Nasal Solution

Ingredient	Amount (wt. %)
Moxifloxacin	0.35
Sodium Acetate	0.03
Acetic Acid	0.04
Mannitol	4.60
EDTA	0.05
Benzalkonium Chloride	0.006
Water	q.s. 100

EXAMPLE 2

Ophthalmic/Otic/Nasal Suspension

Ingredient	Amount (wt. %)
Moxifloxacin	0.3
Dexamethasone, Micronized USP	0.10
Benzalkonium Chloride	0.01
Edetate Disodium, USP	0.01
Sodium Chloride, USP	0.3
Sodium Sulfate, USP	1.2
Tyloxapol, USP	0.05
Hydroxyethylcellulose	0.25
Sulfuric Acid and/or Sodium Hydroxide, NF	q.s. for pH adjustment to 5.5
Purified Water, USP	q.s. to 100

EXAMPLE 3

Ophthalmic Ointment

Ingredient	Amount (wt. %)
Moxifloxacin	0.35
Mineral Oil, USP	2.0
White petrolatum, USP	q.s. 100

EXAMPLE 4

Ophthalmic Ointment

Ingredient	Amount (wt. %)
Moxifloxacin	0.3
Fluorometholone Acetate, USP	0.1
Chlorobutanol, Anhydrous, NF	0.5
Mineral Oil, USP	5
White Petrolatum, USP	q.s. 100

8

The invention has been described herein by reference to certain preferred embodiments. However, as obvious variations thereon will become apparent to those skilled in the art, the invention is not to be considered as limited thereto.

5 What is claimed is:

1. A method of treating ophthalmic infections, which comprises topically applying to the eye a therapeutically effective amount of a pharmaceutical composition comprising moxifloxacin or a pharmaceutically useful hydrate or salt thereof in a concentration of 0.1 to 1.0 wt. % of moxifloxacin and a pharmaceutically acceptable vehicle therefor.

2. A method according to claim 1, wherein the composition further comprises a steroidal or non-steroidal anti-inflammatory agent.

3. A method according to claim 2, wherein the anti-inflammatory agent comprises a steroidal agent.

4. A method according to claim 3, wherein the steroidal agent comprises a glucocorticoid.

5. A method according to claim 4, wherein the glucocorticoid is selected from the group consisting of dexamethasone, rimexolone, prednisolone, fluorometholone, hydrocortisone, mometasone, fluticasone, beclormethasone, flunisolide, triamcinolone, budesonide, and combinations thereof.

6. A method according to claim 4, wherein the glucocorticoid comprises dexamethasone.

7. A method according to claim 4, wherein the glucocorticoid comprises a 21-ether derivative of dexamethasone.

8. A method according to claim 4, wherein the glucocorticoid comprises a 21-benzyl ether derivative of dexamethasone.

9. A method according to claim 2, wherein the anti-inflammatory agent comprises a non-steroidal agent selected from the group consisting of prostaglandin H synthetase inhibitors, cyclooxygenase type II selective inhibitors, PAF antagonists, PDE IV inhibitors, and combinations thereof.

10. A method according to claim 9, wherein the non-steroidal agent comprises a prostaglandin H synthetase inhibitor.

11. A method according to claim 10, wherein the prostaglandin H synthetase inhibitor comprises nepafenac.

12. A method according to claim 10, wherein the prostaglandin H synthetase comprises ketorolac.

13. A method according to claim 10, wherein the prostaglandin H synthetase comprises diclofenac.

14. A method according to claim 9, wherein the non-steroidal agent comprises a cyclooxygenase type II selective inhibitor.

15. A method according to claim 1, wherein the composition is applied to the eye in connection with the treatment of a condition selected from the group consisting of conjunctivitis, keratitis, blepharitis, dacryocystitis, hordeolum, corneal ulceration, and combinations thereof.

16. A method according to any one of claims 1-14, wherein the composition is applied to the eye in connection with an ophthalmic surgical procedure.

17. A method according to any one of claims 1-15, wherein the composition contains moxifloxacin or a pharmaceutically useful hydrate or salt thereof at a concentration of about 0.35 wt. % of moxifloxacin.

18. A method according to any one of claims 1-15, wherein the composition is applied to the eye in connection with the treatment of conjunctivitis.

19. A method according to claim 17, wherein the composition is applied to the eye in connection with the treatment of conjunctivitis.

20. A method according to claim 1, wherein the composition is a liquid that contains sodium chloride.

21. A method according to claim 20, wherein the composition further comprises at least one of a viscosity enhancing agent and a surfactant.

22. A method according to claim 1, wherein the composition has a pH in the range of from 4.5 to 8.0.

23. A method according to claim 22, wherein the composition has a pH in the range of from 5.5 to 8.0.

24. A method according to claim 1, wherein the composition has an osmotic value compatible with the aqueous humor of the eye and ocular tissue and in the range of from about 200 to about 400 milliosmoles per kilogram of water.

25. A method according to claim 1, wherein the composition has an osmotic value compatible with the aqueous humor of the eye and ocular tissue and in the range of from about 200 to about 300 milliosmoles per kilogram of water.

26. A method according to claim 25, wherein the osmotic value is about 300 milliosmoles per kilogram of water.

27. A method according to claim 1, wherein the composition contains a preservative at a concentration of from 0.001 to 1.0 wt. %.

28. A method according to claim 1, wherein the composition is a sterile solution provided in a multi-dose form.

29. A method according to claim 28, wherein the composition is applied to the eye in connection with the treatment of conjunctivitis.

30. A method according to claim 18, wherein the composition inhibits the growth of *S. aureus* and contains moxifloxacin or a pharmaceutically useful hydrate or salt thereof in an amount sufficient to provide a moxifloxacin concentration in the lacrimal fluid and aqueous humor of the eye of at least about 0.13 micrograms per milliliter.

31. A method according to claim 18, wherein the composition inhibits the growth of *S. epidermidis* and contains moxifloxacin or a pharmaceutically useful hydrate or salt thereof in an amount sufficient to provide a moxifloxacin concentration in the lacrimal fluid and aqueous humor of the eye of at least about 0.25 micrograms per milliliter.

32. A method according to claim 29, wherein the composition inhibits the growth of *S. pneumoniae* and contains moxifloxacin or a pharmaceutically useful hydrate or salt thereof in an amount sufficient to provide a moxifloxacin concentration in the lacrimal fluid and aqueous humor of the eye of at least about 0.25 micrograms per milliliter.

33. A method according to claim 1, wherein the composition is applied to the eye in connection with the treatment of keratitis and wherein the composition inhibits the growth of *P. aeruginosa* and contains moxifloxacin or a pharmaceutically useful hydrate or salt thereof in an amount sufficient to provide a moxifloxacin concentration in the lacrimal fluid and aqueous humor of the eye of at least about 0.25 micrograms per milliliter.

34. A method according to claim 18, wherein the composition wherein the composition inhibits the growth of *H. influenzae* and contains moxifloxacin or a pharmaceutically useful hydrate or salt thereof in an amount sufficient to provide a moxifloxacin concentration in the lacrimal fluid and aqueous humor of the eye of at least about 0.06 micrograms per milliliter.

35. A method according to claim 1, wherein the composition is a sterile solution having a pH in the range of from 4.5 to 8.0; wherein the composition has an osmotic value compatible with the aqueous humor of the eye and ocular tissues, including tissues that may have been compromised as the result of preexisting disease, trauma, surgery or other physical conditions, said osmotic value being in the range of from about 200 to about 400 milliosmoles per kilogram of water.

36. A method according to claim 35, wherein the pH is from 5.5 to 8.

37. A method according to claim 35, wherein the osmotic value is about 300.

38. A method according to claim 35, wherein the solution also contains sodium chloride.

39. A method according to claim 38, wherein the composition is applied to the eye in connection with the treatment of conjunctivitis.

40. A method according to claim 35, wherein the composition is applied to the eye in connection with the treatment of conjunctivitis.

41. A method according to claim 39, wherein the composition inhibits the growth of at least one pathogen selected from the group consisting of *S. aureus*, *S. epidermidis*, *S. pneumoniae*, *P. aeruginosa*, and *H. influenzae*.

42. A method according to claim 35, wherein the composition is applied to the eye in connection with an ophthalmic surgical procedure.

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