IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
FORT WORTH DIVISION

ALCON MANUFACTURING, LTD. and ALCON LABORATORIES, INC., Plaintiffs, v. CYNACON/OCuSOFT, INC., OCuSOFT INC., OCuSOFT II INC., and ALTAIRE PHARMACEUTICALS, INC., Defendants.	Civil Action No. 4-06CV-791-Y U.S. District Judge Terry R. Means

FIRST AMENDED COMPLAINT AND DEMAND FOR JURY TRIAL

Plaintiffs Alcon Manufacturing, Ltd. and Alcon Laboratories, Inc. ("Alcon") bring this action for patent infringement and other relief against defendants CYNACON/OCuSOFT, Inc., OCuSOFT Inc., and OCuSOFT II Inc. (individually and collectively "CYNACON/OCuSOFT"), and defendant Altaire Pharmaceuticals, Inc. ("Altaire"), and allege as follows:

PARTIES

1. Plaintiff Alcon Manufacturing, Ltd. is a limited partnership organized under the laws of Texas and maintains its principal place of business at 6201 South Freeway, Fort Worth, Texas 76134. Plaintiff Alcon Laboratories, Inc. is a Delaware corporation and is a general partner in the limited partnership.

2. On information and belief, defendants CYNACON/OCuSOFT are Texas corporations having a principal place of business at 5311 Avenue N, Rosenberg, Texas 77471, mailing address P.O. Box 429, Richmond, Texas 77046-0429, and have manufactured, used, offered for sale, sold, and/or imported ophthalmic compositions, artificial tear solutions, and/or ocular lubricant compositions. CYNACON/OCuSOFT may be served with process by serving their registered agent for service, Mr. Bernard T. Halloran, 2900 Wilcrest Drive, Suite 102, Houston, Texas 77042.

3. Defendant Altaire Pharmaceuticals, Inc. ("Altaire") is a corporation duly organized under the laws of New York. Altaire's principal place of business is located at 311 West Lane, Aquebogue, New York 11931. Altaire is a nonresident of the State of Texas which engages in business in the State of Texas, but does not maintain a regular place of business in the State of Texas and does not have a designated agent for service of process in the State of Texas. Pursuant to TEX. CIV. PRAC. & REM. CODE §§17.044(b), 17.045, and FED. R. CIV. P. 4(e)(1), Altaire may be served with process by serving Mr. Roger Williams, the Secretary of State of Texas, State Capitol, Room 1E.8, Austin, Texas 78701, who then shall immediately mail a copy of the process by registered mail or certified mail, return receipt requested, to Altaire's principal place of business at 311 West Lane, Aquebogue, New York 11931, Attention: any officer/director authorized to accept service on behalf of Altaire.

JURISDICTION AND VENUE

4. This is an action for patent infringement pursuant to the laws as set forth in Title 35 of the United States Code, and particularly, 35 U.S.C. §§ 271, 281, 283, 284 and 285. This Court has exclusive subject matter jurisdiction of this litigation under 28 U.S.C. §§ 1331 and 1338(a).

5. This Court has personal jurisdiction over CYNACON/OCuSOFT because, upon information and belief, they reside in the State of Texas and transact business and have committed infringing acts in this judicial district. In addition, CYNACON/OCuSOFT has purposefully availed themselves of the privilege of acting in this district by, among other things, advertising and selling goods in this district, and on their web site, accessible by Internet users throughout the United States and elsewhere, including those in this district.

6. This Court has personal jurisdiction over Altaire because, upon information and belief, it transacts substantial and continuous business and has committed infringing acts in this judicial district. In addition, Altaire has purposefully availed itself of the privilege of acting in this district by, among other things, arranging for the distribution, sale, and offering for sale of its products in this district, and advertising and selling goods in this district and on its web site, accessible by Internet users throughout the United States and elsewhere, including those in this district.

7. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(b), (c) and 1400(b). Venue is also proper because each defendant is subject to personal jurisdiction and a substantial part of the events giving rise to Alcon's claims occurred in this district. Upon information and belief, each defendant has directed sales efforts and has used, manufactured, distributed, sold, and/or offered for sale in this judicial district various products that are accused of infringement. The unlawful acts committed by defendants have been and are, in whole or in part, conceived, carried out and/or made effective within this district, and the damages suffered by Alcon were suffered, at least in part, within this district. The interstate trade or commerce by defendants described herein is carried out in part within this district.

COUNT I

8. Alcon repeats and realleges the allegations in paragraphs 1-7 as though fully set forth herein.

9. Alcon is the owner and/or the exclusive licensee, and possessor of all substantial rights, including the right to sue for past, present and future infringements for U.S. Patent No. 6,403,609, titled "Ophthalmic Compositions Containing Galactomannan Polymers and Borate" issued June 11, 2002 ("the '609 patent").

10. The '609 patent relates generally to ophthalmic compositions and methods for lubricating an eye as set out in the patent and its claims. A true and correct copy is attached hereto as Exhibit A.

11. The '609 patent is valid and enforceable.

12. Upon information and belief, CYNACON/OCuSOFT infringed the '609 patent by making, using, selling, offering for sale, and/or importing ophthalmic compositions for lubricating an eye covered by one or more claims of the '609 patent.

13. Upon information and belief, by making, using, selling, offering for sale, and/or importing the ophthalmic compositions for lubricating an eye, CYNACON/OCuSOFT also induced infringement of the '609 patent, and has contributed to the infringement of the '609 patent. The CYNACON/OCuSOFT ophthalmic compositions have no substantial non-infringing uses.

14. Upon information and belief, CYNACON/OCuSOFT has willfully engaged in its infringing conduct.

15. As a direct and proximate result of CYNACON/OCuSOFT's infringement, Alcon has been and continues to be injured and has sustained and will continue to sustain substantial damages in an amount not presently known.

16. Alcon has no adequate remedy at law against these acts of patent infringement. Unless CYNACON/OCuSOFT is preliminarily and permanently enjoined from its unlawful and willful infringement of the '609 patent, Alcon will suffer irreparable harm.

17. Upon information and belief, Altaire infringed the '609 patent by making, using, selling, offering for sale, and/or importing ophthalmic compositions for lubricating an eye covered by one or more claims of the '609 patent.

18. Upon information and belief, by making, using, selling, offering for sale, and/or importing the ophthalmic compositions for lubricating an eye, Altaire also induced infringement of the '609 patent, and has contributed to the infringement of the '609 patent. The Altaire ophthalmic compositions have no substantial non-infringing uses.

19. Upon information and belief, Altaire has willfully engaged in its infringing conduct.

20. As a direct and proximate result of Altaire's infringement, Alcon has been and continues to be injured and has sustained and will continue to sustain substantial damages in an amount not presently known.

21. Alcon has no adequate remedy at law against these acts of patent infringement. Unless Altaire is preliminarily and permanently enjoined from its unlawful and willful infringement of the '609 patent, Alcon will suffer irreparable harm.

22. Alcon has incurred and will incur attorney fees, costs and expenses in the prosecution of this action. The circumstances of this dispute create an exceptional case within

the meaning of 35 U.S.C. § 285, and Alcon is entitled to recover its reasonable and necessary fees and expenses.

COUNT II

23. Alcon repeats and realleges the allegations in paragraphs 1-22 as though fully set forth herein.

24. Alcon is the owner and/or the exclusive licensee, and possessor of all substantial rights, including the right to sue for past, present and future infringements for U.S. Patent No. 6,583,124, titled "Ophthalmic Compositions Containing Galactomannan Polymers and Borate" issued June 24, 2003 ("the '124 patent").

25. The '124 patent relates generally to an artificial tear solution and methods of lubricating or moisturizing an eye as set out in the patent and its claims. A true and correct copy is attached hereto as Exhibit B.

26. The '124 patent is valid and enforceable.

27. Upon information and belief, CYNACON/OCuSOFT infringed the '124 patent by making, using, selling, offering for sale, and/or importing artificial tear solutions for lubricating or moisturizing an eye covered by one or more claims of the '124 patent.

28. Upon information and belief, by making, using, selling, offering for sale, and/or importing the artificial tear solutions for lubricating or moisturizing an eye, CYNACON/OCuSOFT also induced infringement of the '124 patent, and has contributed to the infringement of the '124 patent. The CYNACON/OCuSOFT artificial tear solutions have no substantial non-infringing uses.

29. Upon information and belief, CYNACON/OCuSOFT has willfully engaged in its infringing conduct.

30. As a direct and proximate result of CYNACON/OCuSOFT's infringement, Alcon has been and continues to be injured and has sustained and will continue to sustain substantial damages in an amount not presently known.

31. Alcon has no adequate remedy at law against these acts of patent infringement. Unless CYNACON/OCuSOFT is preliminarily and permanently enjoined from its unlawful and willful infringement of the '124 patent, Alcon will suffer irreparable harm.

32. Upon information and belief, Altaire infringed the '124 patent by making, using, selling, offering for sale, and/or importing artificial tear solutions for lubricating or moisturizing an eye covered by one or more claims of the '124 patent.

33. Upon information and belief, by making, using, selling, offering for sale, and/or importing the artificial tear solutions for lubricating or moisturizing an eye, Altaire also induced infringement of the '124 patent, and has contributed to the infringement of the '124 patent. The Altaire artificial tear solutions have no substantial non-infringing uses.

34. Upon information and belief, Altaire has willfully engaged in its infringing conduct.

35. As a direct and proximate result of Altaire's infringement, Alcon has been and continues to be injured and has sustained and will continue to sustain substantial damages in an amount not presently known.

36. Alcon has no adequate remedy at law against these acts of patent infringement. Unless Altaire is preliminarily and permanently enjoined from its unlawful and willful infringement of the '124 patent, Alcon will suffer irreparable harm.

37. Alcon has incurred and will incur attorney fees, costs and expenses in the prosecution of this action. The circumstances of this dispute create an exceptional case within

the meaning of 35 U.S.C. § 285, and Alcon is entitled to recover its reasonable and necessary fees and expenses.

COUNT III

38. Alcon repeats and realleges the allegations in paragraphs 1-37 as though fully set forth herein.

39. Alcon is the owner and/or the exclusive licensee, and possessor of all substantial rights, including the right to sue for past, present and future infringements for U.S. Patent No. 6,838,449, titled "Ophthalmic Compositions Containing Galactomannan Polymers and Borate" issued January 4, 2005 ("the '449 patent").

40. The '449 patent relates generally to an ocular lubricant composition and methods for lubricating or moisturizing an eye as set out in the patent and its claims. A true and correct copy is attached hereto as Exhibit C.

41. The '449 patent is valid and enforceable.

42. Upon information and belief, CYNACON/OCuSOFT infringed the '449 patent by making, using, selling, offering for sale, and/or importing ocular lubricant compositions for lubricating or moisturizing an eye covered by one or more claims of the '449 patent.

43. Upon information and belief, by making, using, selling, offering for sale, and/or importing the ocular lubricant compositions for lubricating or moisturizing an eye, CYNACON/OCuSOFT also induced infringement of the '449 patent, and has contributed to the infringement of the '449 patent. The CYNACON/OCuSOFT ocular lubricant compositions have no substantial non-infringing uses.

44. Upon information and belief, CYNACON/OCuSOFT has willfully engaged in its infringing conduct.

45. As a direct and proximate result of CYNACON/OCuSOFT's infringement, Alcon has been and continues to be injured and has sustained and will continue to sustain substantial damages in an amount not presently known.

46. Alcon has no adequate remedy at law against these acts of patent infringement. Unless CYNACON/OCuSOFT is preliminarily and permanently enjoined from its unlawful and willful infringement of the '449 patent, Alcon will suffer irreparable harm.

47. Upon information and belief, Altaire infringed the '449 patent by making, using, selling, offering for sale, and/or importing ocular lubricant compositions for lubricating or moisturizing an eye covered by one or more claims of the '449 patent.

48. Upon information and belief, by making, using, selling, offering for sale, and/or importing the ocular lubricant compositions for lubricating or moisturizing an eye, Altaire also induced infringement of the '449 patent, and has contributed to the infringement of the '449 patent. The Altaire ocular lubricant compositions have no substantial non-infringing uses.

49. Upon information and belief, Altaire has willfully engaged in its infringing conduct.

50. As a direct and proximate result of Altaire's infringement, Alcon has been and continues to be injured and has sustained and will continue to sustain substantial damages in an amount not presently known.

51. Alcon has no adequate remedy at law against these acts of patent infringement. Unless Altaire is preliminarily and permanently enjoined from its unlawful and willful infringement of the '449 patent, Alcon will suffer irreparable harm.

52. Alcon has incurred and will incur attorney fees, costs and expenses in the prosecution of this action. The circumstances of this dispute create an exceptional case within

the meaning of 35 U.S.C. § 285, and Alcon is entitled to recover its reasonable and necessary fees and expenses.

PRAYER FOR RELIEF

WHEREFORE, Alcon respectfully requests that judgment be entered in its favor and against defendants and that the Court grant the following relief to Alcon:

a. Declare that CYNACON/OCuSOFT has infringed each of the '609, the '124, and the '449 patents;

b. Declare that CYNACON/OCuSOFT's infringement of each of the '609, the '124, and the '449 patents was willful;

c. Preliminarily and permanently enjoin and restrain CYNACON/OCuSOFT, their officers, directors, agents, servants, employees, licensees, successors, assigns, those in active concert and participation with defendants, and all persons acting on their behalf or within their control from making, using, selling, offering to sell, importing, exporting, advertising, or otherwise using, contributing to the use of, or inducing the use of any infringing products or methods;

d. Award Alcon damages adequate to compensate for such acts of infringement;

e. Award Alcon increased damages in an amount not less than three times the amount found by the jury or assessed by this Court for CYNACON/OCuSOFT's willful infringement in accordance with 35 U.S.C. § 284;

f. Declare that Altaire has infringed each of the '609, the '124, and the '449 patents;

g. Declare that Altaire's infringement of each of the '609, the '124, and the '449 patents was willful;

h. Preliminarily and permanently enjoin and restrain Altaire, its officers, directors, agents, servants, employees, licensees, successors, assigns, those in active concert and participation with defendants, and all persons acting on its behalf or within its control from making, using, selling, offering to sell, importing, exporting, advertising, or otherwise using, contributing to the use of, or inducing the use of any infringing products or methods;

i. Award Alcon damages adequate to compensate for such acts of infringement;

j. Award Alcon increased damages in an amount not less than three times the amount found by the jury or assessed by this Court for Altaire's willful infringement in accordance with 35 U.S.C. § 284;

k. Award Alcon its expenses, costs, and attorneys' fees in accordance with 35 U.S.C. § 285; and

l. Award Alcon such other and further relief as is just and proper.

JURY DEMAND

Plaintiffs hereby demand a trial by jury of all issues so triable.

Respectfully submitted,

Date: November 15th, 2006 By: _____

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ATTORNEYS FOR PLAINTIFFS ALCON MANUFACTURING, LTD AND ALCON LABORATORIES, INC.

US006403609B1

(12) **United States Patent**
Asgharian

(10) **Patent No.: US 6,403,609 B1**
(45) **Date of Patent: Jun. 11, 2002**

(54) **OPHTHALMIC COMPOSITIONS CONTAINING GALACTOMANNAN POLYMERS AND BORATE**

(75) Inventor: **Bahram Asgharian**, Arlington, TX (US)

(73) Assignee: **Alcon Manufacturing, Ltd.**, Fort Worth, TX (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/423,762**

(22) PCT Filed: **Jul. 17, 1998**

(86) PCT No.: **PCT/US98/14596**

§ 371 (c)(1),
(2), (4) Date: **Nov. 12, 1999**

(87) PCT Pub. No.: **WO99/06023**

PCT Pub. Date: **Feb. 11, 1999**

Related U.S. Application Data

(60) Provisional application No. 60/054,132, filed on Jul. 29, 1997.

(51) **Int. Cl.**[7] **A61K 31/715**; C07H 1/00

(52) **U.S. Cl.** **514/310**; 514/54; 514/839; 514/912; 514/944; 536/123.1; 536/124; 536/128

(58) **Field of Search** 514/310, 54, 839, 514/912, 944; 536/123.1, 124, 128

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5,972,326 A	10/1999	Galin et al.	424/78.04
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WO	WO 94/10976	5/1994
WO	WO 97/30092	8/1997
WO	WO 99/06023	2/1999

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Power et al., "Gel transition studies on nonideal polymer networks using small amplitude oscillatory rheometry," Journal of Rheology, 1998, vol. 42(5), pp. 1021–1037.*

Ophthalmic Drug Facts '99, Facts and Comparisons, Ch. 3, St. Louis, MO, pp. 25–39 (1999).

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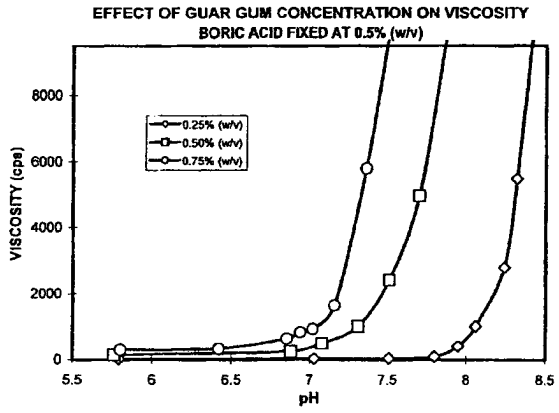
Primary Examiner—Ralph Gitomer
Assistant Examiner—Devesh Khare
(74) *Attorney, Agent, or Firm*—Gregg C. Brown

(57) **ABSTRACT**

The present invention is directed to ophthalmic compositions containing a gelling amount of a combination of galactomannan polysaccharides and borates. The compositions gel or partially gel upon administration to the eye. The present invention also discloses methods of topical ophthalmic administration of the compositions of the eye.

37 Claims, 3 Drawing Sheets



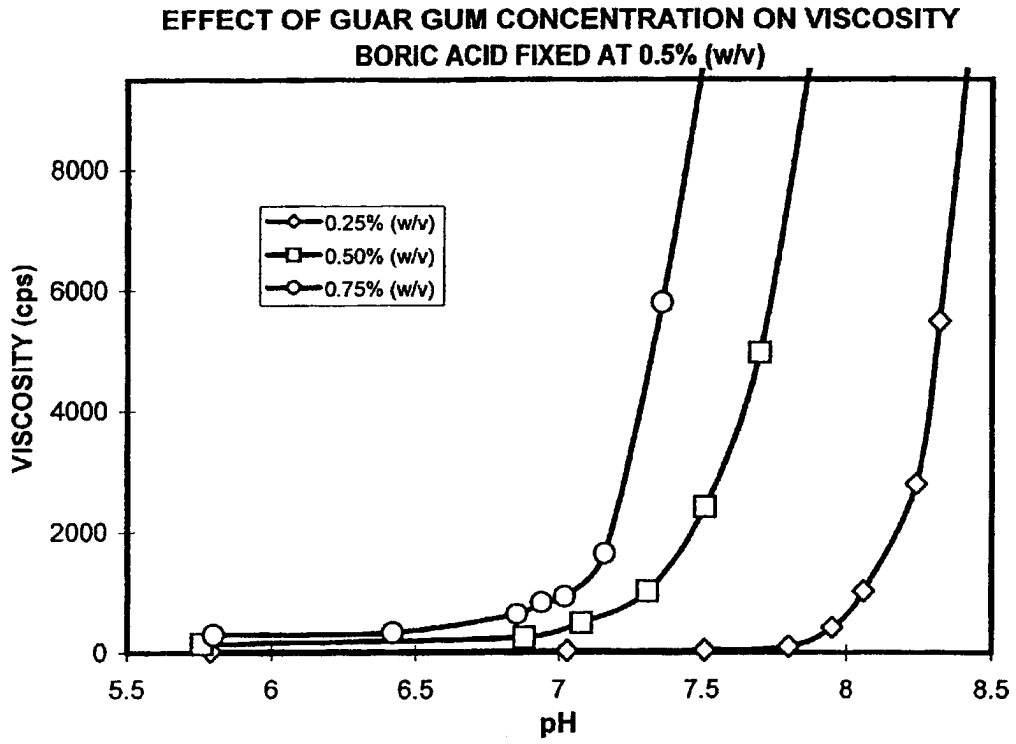

EFFECT OF GUAR GUM CONCENTRATION ON VISCOSITY
BORIC ACID FIXED AT 0.5% (w/v)
VISCOSITY (cps)
8000
6000
4000
2000
0
0.25% (w/v)
0.50% (w/v)
0.75% (w/v)
5.5
6
6.5
7
7.5
8
8.5
pH

FIG. 1

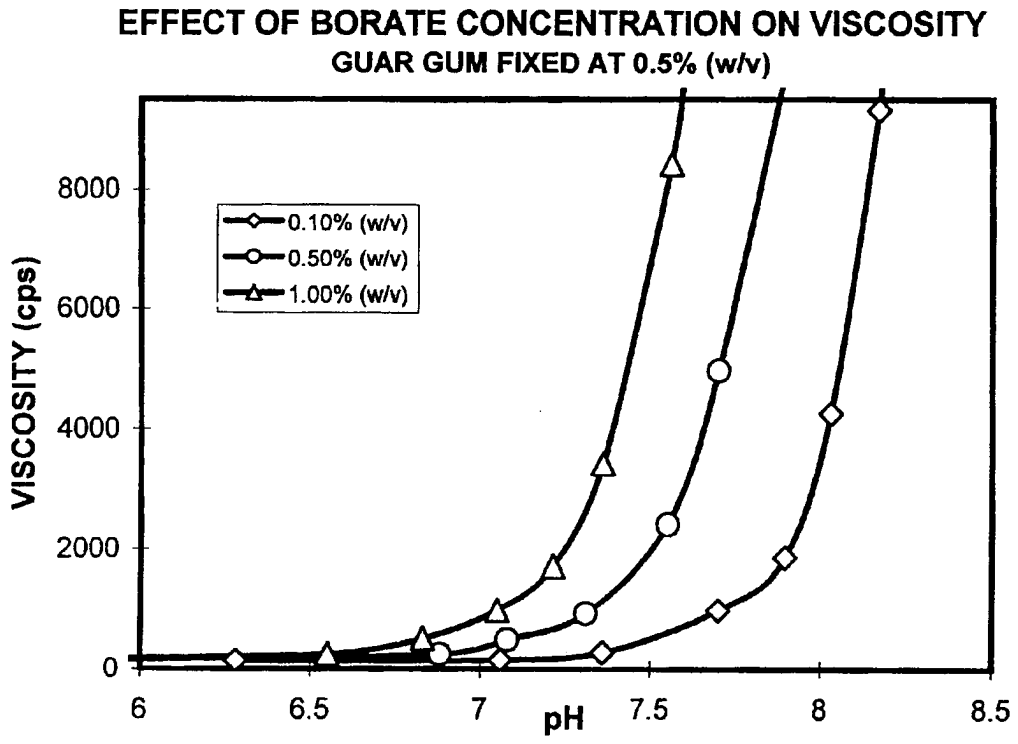

EFFECT OF BORATE CONCENTRATION ON VISCOSITY
GUAR GUM FIXED AT 0.5% (w/v)
VISCOSITY (cps)
8000
6000
4000
2000
0
0.10% (w/v)
0.50% (w/v)
1.00% (w/v)
6
6.5
7
pH
7.5
8
8.5

FIG. 2

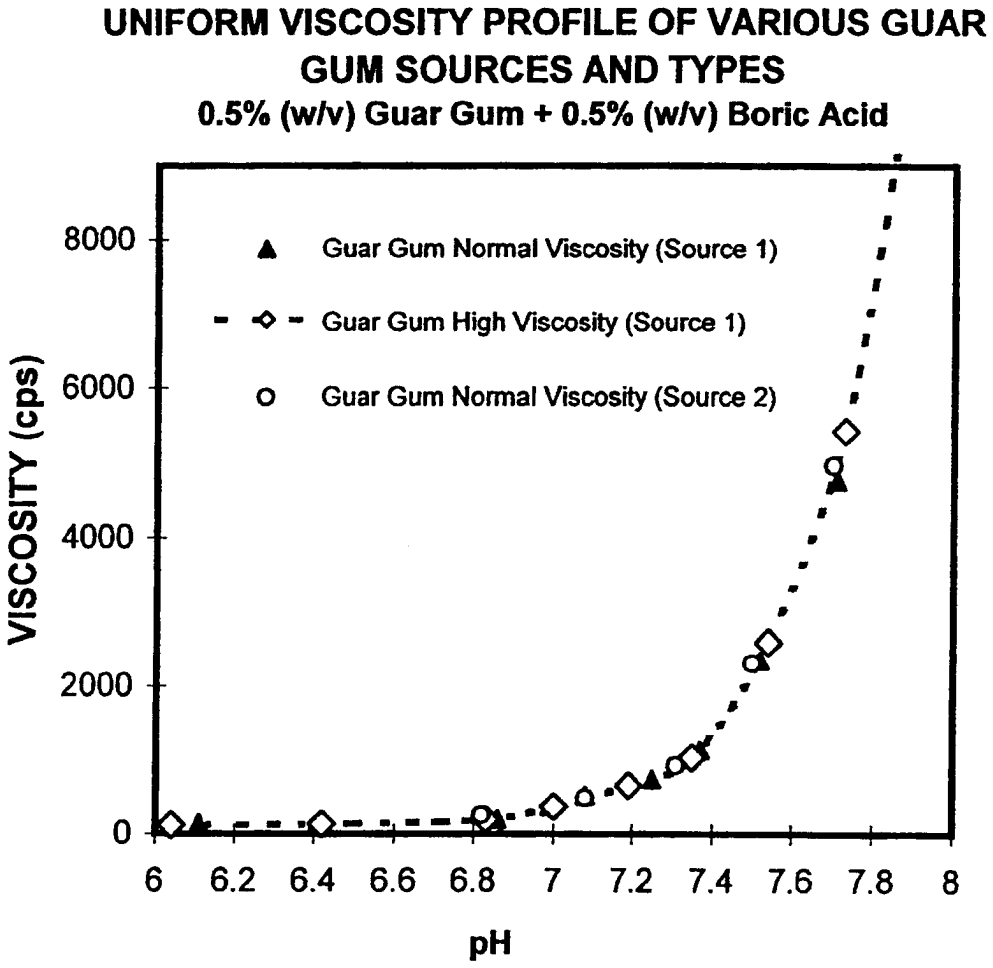

UNIFORM VISCOSITY PROFILE OF VARIOUS GUAR GUM SOURCES AND TYPES
0.5% (w/v) Guar Gum + 0.5% (w/v) Boric Acid
Guar Gum Normal Viscosity (Source 1)
Guar Gum High Viscosity (Source 1)
Guar Gum Normal Viscosity (Source 2)
VISCOSITY (cps)
8000
6000
4000
2000
0
6
6.2
6.4
6.6
6.8
7
7.2
7.4
7.6
7.8
8
pH

FIG. 3

OPHTHALMIC COMPOSITIONS CONTAINING GALACTOMANNAN POLYMERS AND BORATE

This application claims priority from provisional application Ser. No. 60/054,132, filed Jul. 29, 1997.

BACKGROUND OF THE INVENTION

The present invention relates to the use of adjuvants in topical ophthalmic compositions. In particular, the present invention relates to pharmaceutical compositions comprising galactomannan polymers in combination with borates, and methods for the controlled administration of pharmaceutically active agents to patients, wherein the compositions are administered as liquids which thicken to form gels upon instillation into the eye. The transition from liquid to gel is primarily due to the change in pH and ionic strength.

Topical ophthalmic compositions have taken the form of liquids, ointments, gels and inserts. Liquid compositions for drop-wise instillation of pharmaceutically active agents to the eve provide for easy administration, but they do not always provide for an accurate dosage amount, as portions of the liquid are often blinked away during administration or drained down the punctum into the nasal passage. Ointments and gels, which usually reside in the eye longer than a liquid and therefore provide for more accurate administration, often interfere with a patient's vision. Ocular inserts, both bioerodible and non-bioerodible, are also available and allow for less frequent administration of drug. These inserts, however, require complex and detailed preparation and are frequently uncomfortable to the wearer. An additional problem with non-bioerodible inserts is that they must be removed after use.

U.S. Pat. No. 4,136,173 (Pramoda, et al.) discloses the use of therapeutic compositions containing xanthan gum and locust bean gum which are administered in liquid form and gel upon instillation. This reference describes a mechanism for transition from liquid to gel involving pH change. pH sensitive gels such as carbomers, xanthan, gellan, and those described above, need to be formulated at or below the pKa of their acidic groups (typically at a pH of about 2 to 5). Compositions formulated at low pH, however, are irritating to the eye.

The use of locust bean gum to form a gel vehicle for ophthalmic drug delivery is described in U.S. Pat. No. 4,136,177 (Lin, et al.). However, the gels described by Lin, et al. are formed at the time of manufacture, rather than upon application to the eye.

U.S. Pat. No. 4,861,760 (Mazuel, et al.) discloses ophthalmic compositions containing gellan gum which are administered to the eye as non-gelled liquids and gel upon instillation due to a change in ionic strength. These systems do not involve the use of small cross-linking molecules, but instead provide gel characteristics due to self cross-linking during ionic condition changes.

Gels involving the cross-linking of polysaccharides wit h borates are disclosed for use as well fracturing fluids in U.S. Pat. No. 5,082,579 (Dawson), U.S. Pat. No. 5,145,590 (Dawson), and U.S. Pat. No. 5,160,643 (Dawson). These patents describe the use of borates and polysaccharides for industrial oil well excavation.

The ophthalmic use of current gelling liquid systems have a number of drawbacks. For example, natural polymers such as xanthan gum have the disadvantage of lot to lot variability due to variations in source and/or limited manufacturing controls during processing. These variabilities cause significant undesirable changes in the properties of the compound, such as variable gelling characteristics. Thermogelling systems such as polyethylene oxide/polypropylene oxide block copolymers ("PEO/PPO") lose water in order to form gels, and consequently result in turbid gels. Polyvinyl alcohol ("PVA")-borate combination gelling systems need to be formulated at low pH, and therefore, can cause ocular irritation upon instillation. Other gelling systems have viscosity, rehydration and cloud point instability problems associated with autoclaving.

Polyvinyl alcohol crosslinking with borates have been disclosed in U.S. Pat. No. 4,255,415 (Sukhbir et al.). These compositions are pre-formed gels, and are therefore hard to dispense. WIPO Publication No. WO 94/10976 (Goldenberg et al.) discloses a low pH PVA-borate delivery system that does go through liquid/gel transition. This system has the disadvantage, however, of limited gelling effects, and only at certain concentrations of PVA depending on the molecular weight of the PVA utilized. Furthermore, since the crosslinking cites are unlimited with this system, strong local gelation upon addition of base has limited its manufacturing, and therefore, polyvinyl pyrrolidone presumably has been included in these compositions to overcome the shortcoming. The novel gelling system of the present invention does not have the above limitation.

SUMMARY OF THE INVENTION

The present invention is directed to topical ophthalmic compositions comprising galactomannan polymers and borate compounds which provide controlled administration of a drug to the eye. The invention is based on a new gelling system which comprises a galactomannan polysaccharide and a borate crosslinker which forms a gel upon increases in pH and ionic strength. In this novel system, bisdiol borates crosslink with the cis diol groups of the sugar moieties of the polysaccharide. The compositions are administered as liquids or partially gelled liquids (hereinafter "liquids") which thicken to form gels upon instillation into the eye. Alternatively, the compositions may not contain a pharmaceutically active agent, and can be administered to the eye for lubrication or to supplement tears in the treatment of, for example, dry eye.

The present invention galactomannan-borate gelling system has several advantages over other gelling systems. One advantage is that the compositions of the present invention are clear solutions and the resultant gel is also crystal clear. While other systems may become opaque or cloudy upon instillation, the crystal clear gel of the present invention provides greater clarity of vision to the treated eye. The present invention compositions may be formulated at slightly acidic to neutral pH and require only a minor pH change to activate gelation (i.e., about 0.5 to 1.0 pH unit). This feature minimizes possible irritation of the eye resulting from acidic exposure, such as may result with other pH sensitive systems which require a pH change of about 2.4 to about 4.4 pH units (i.e., are formulated with a pH of about 3–5). Galactomannan polymers are also heat stable and show no cloud point even during autoclaving conditions. As such, viscosity and rehydration problems resulting from batch scale up, such as exist with PVA and carbomer polymer systems, are not present with the galactomannan polymer containing compositions of the present invention.

Galactomannan polysaccharides are non-ionic and, in combination with borates at acidic to neutral pH, are also essentially non-ionic. Thus, the polymer system is completely compatible with anionic, neutral and cationic drugs.

Furthermore, the preservative efficacy of the preservatives are not compromised by the presence of the polymer. Typically, the efficacy of benzalkonium chloride or other cationic preservatives are compromised with anionic polymers such as gellan and carageenan, and excess preservative may therefore be needed in those systems. Increases in preservative concentration may also increase irritation and toxicity of the composition.

The galactomannan-borate gelling system of the present invention has other advantages. Galactomannan polymers have a relatively low molecular weight and are therefore easy to manufacture and scale up. Galactomannan polymers are also readily available and have been used in food and personal care products such that the polymers are considered to be safe. Furthermore, control or manipulation of the gelling characteristics of the galactomannan-borate gelling compositions of the present invention is relatively simple as compared with prior art systems. The gelling properties of other single polymer systems, such as ionomers, e.g., gellan and carageenans, and thermogels, e.g., poloxamines and poloxamers, are typically related to the molecular weight and the number of functional groups of the polymers. Thus, in order to change the gel point or degree of gelation of those prior art systems, one would need to modify the base polymer—a labor intensive activity. In contrast, by simply manipulating the borate to galactomannan ratio in the present invention compositions, a wide range of gelling characteristics is available in order to fine tune the compositions to the targeted requirements (see FIGS. 1 and 2). Moreover, as illustrated in FIG. 3, the galactomannans of the present invention (e.g., guar gum) demonstrate excellent gelling consistency and reproducibility, though the type or source of the galactomannan is varied.

Still other advantages are present in the compositions of the present invention. The galactomannan polymer and the borate crosslinker compositions of the present invention are liquids and, therefore, easy to dispense. Some gelling systems such as gellan gum, as disclosed in U.S. Pat. No. 4,861,760 (Mazuel et al.), are thixotropic, which may require shaking to increase the fluidity and ease of dispensing. The present invention compositions contain a relatively low concentration of galactomannan (about 0.2 to 0.5%) as compared to some thermogelling systems such as PEO/PPO block copolymers, which require very high concentrations. Lower concentrations of the gelling polymer provide lower potential toxicity and ease of preservation from microbial contamination over higher concentration systems.

The methods of the present invention involve the topical administration of the galactomannan-borate containing compositions of the present invention.

The present invention is also directed to methods of sterilization of the galactomannans involving autoclaving.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph illustrating the gelling characteristics of various concentrations of guar gum in the presence of borate, relative to pH.

FIG. 2 is a graph illustrating the gelling characteristics of various concentrations of borate in the presence of guar gum, relative to pH.

FIG. 3 is a graph illustrating the uniformity of the gelling characteristics of three different types/sources of guar gum.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to ophthalmic compositions which comprise one or more galactomannan polysaccharide(s) and one or more borate compound(s). The present invention is also directed to methods of using these compositions to treat various ophthalmic disorders including dry eye, glaucoma, ocular hypertension, infection, allergy and inflammation.

The types of galactomannans that may be used in the present invention are typically derived from guar gum, locust bean gum and tara gum. As used herein, the term "galactomannan" refers to polysaccharides derived from the above natural gums or similar natural or synthetic gums containing mannose or galactose moieties, or both groups, as the main structural components. Preferred galactomannans of the present invention are made up of linear chains of (1–4)-β-D-mannopyranosyl units with α-D-galactopyranosyl units attached by (1–6) linkages. With the preferred galactomannans, the ratio of D-galactose to D-mannose varies, but generally will be from about 1:2 to 1:4. Galactomannans having a D-galactose:D-mannose ratio of about 1:2 are most preferred. Additionally, other chemically modified variations of the polysaccharides are also included in the "galactomannan" definition. For example, hydroxyethyl, hydroxypropyl and carboxymethylhydroxypropyl substitutions may be made to the galactomannans of the present invention. Non-ionic variations to the galactomannans, such as those containing alkoxy and alkyl (C1–C6) groups are particularly preferred when a soft gel is desired (e.g., hydroxylpropyl substitutions). Substitutions in the non-cis hydroxyl positions are most preferred. An example of non-ionic substitution of a galactomannan of the present invention is hydroxypropyl guar, with a molar substitution of about 0.4. Anionic substitutions may also be made to the galactomannans. Anionic substitution is particularly preferred when strongly responsive gels are desired.

The borate compounds which may be used in the compositions of the present invention are boric acid and other pharmaceutically acceptable salts such as sodium borate (borax) and potassium borate. As used herein, the term "borate" refers to all pharmaceutically suitable forms of borates. Borates are common excipients in ophthalmic formulations due to good buffering capacity at physiological pH and well known safety and compatibility with a wide range of drugs and preservatives. Borates also have inherent bacteriostatic and fungistatic properties, and therefore aid in the preservation of the compositions.

The present invention compositions comprise one or more galactomannan(s) in the amount of from about 0.1 to 5% weight/volume ("w/v") and borate in the amount of from about 0.05 to 5% (w/v). Preferably, the compositions will contain 0.2 to 2.0% (w/v) of galactomannan and 0.1 to 2.0% (w/v) of a borate compound. Most preferably, the compositions will contain 0.3 to 0.8% (w/v) of galactomannan and 0.25 to 1.0% (w/v) of a borate compound. The particular amounts will vary, depending on the particular gelling properties desired. In general, the borate or galactomannan concentration may be manipulated in order to arrive at the appropriate viscosity of the composition upon gel activation (i.e., after administration). As shown in FIGS. 1 and 2, manipulating either the borate or galactomannan concentration provides stronger or weaker gelation at a given pH. If a strongly gelling composition is desired, then the borate or galactomannan concentration may be increased. If a weaker gelling composition is desired, such as a partially gelling composition, then the borate or galactomannan concentration may be reduced. Other factors may influence the gelling features of the compositions of the present invention, such as the nature and concentration of additional ingredients in

the compositions, such as salts, preservatives, chelating agents and so on. Generally, preferred non-gelled compositions of the present invention, i.e., compositions not yet gel-activated by the eye, will have a viscosity of from about 5 to 1000 cps. Generally, preferred gelled compositions of the present invention, i.e., compositions gel-activated by the eye, will have a viscosity of from about 50 to 50,000 cps.

The galactomannans of the present invention may be obtained from numerous sources. Such sources include guar gum, locust bean gum and tara gum, as further described below. Additionally, the galactomannans may also be obtained by classical synthetic routes or may be obtained by chemical modification of naturally occurring galactomannans.

Guar gum is the ground endosperm of *Cyamopisis tetragonolobus (L.) Taub*. The water soluble fraction (85%) is called "guaran" (molecular weight of 220,000), which consists of linear chains of (1–4)-β-D mannopyranosyl units with α-D-galactopyranosyl units attached by (1–6) linkages. The ratio of D-galactose to D-mannose in guaran is about 1:2. The gum has been cultivated in Asia for centuries and is primarily used in food and personal care products for its thickening property. It has five to eight times the thickening power of starch. Its derivatives, such as those containing hydroxypropyl or hydroxypropyltrimonium chloride substitutions, have been commercially available for over a decade. Guar gum may be obtained, for example, from Rhone-Polulenc (Cranbury, N.J.), Hercules, Inc. (Wilmington, Del.) and TIC Gum, Inc. (Belcamp, Md.).

Locust bean gum or carob bean gum is the refined endosperm of the seed of the carob tree, *ceratonia siliqua*. The ratio of galactose to mannose for this type of gum is about 1:4. Cultivation of the carob tree is old and well known in the art. This type of gum is commercially available and may be obtained from TIC Gum, Inc. (Bekamp, Md.) and Rhone-Polulenc (Cranbury, N.J.).

Tara gum is derived from the refined seed gum of the tara tree. The ratio of galactose to mannose is about 1:3. Tara gum is not produced in the United States commercially, but the gum may be obtained from various sources outside the United States.

In order to limit the extent of cross-linking to provide a softer gel characteristic, chemically modified galactomannans such as hydroxypropyl guar may be utilized. Modified galactomannans of various degree of substitution are commercially available from Rhone-Poulenc (Cranbury, N.J.). Hydroxypropyl guar with low molar substitution (e.g., less than 0.6) is particularly preferred.

Other ingredients may be added to the compositions of the present invention. Such ingredients generally include tonicity adjusting agents, chelating agents, active pharmaceutical agent(s), solubilizers, preservatives, pH adjusting agents and carriers. Other polymer or monomeric agents such as polyethylene glycol and glycerol may also be added for special processing. Tonicity agents useful in the compositions of the present invention may include salts such as sodium chloride, potassium chloride and calcium chloride; non-ionic tonicity agents may include propylene glycol and glycerol; chelating agents may include EDTA and its salts; solubilizing agents may include Cremophor EL® and tween 80; other carriers may include amberlite® IRP-69; pH adjusting agents may include hydrochloric acid, Tris, triethanolamine and sodium hydroxide; and suitable preservatives may include benzalkonium chloride, polyquaternium-1 and polyhexamethylene biguanide. The above listing of examples is given for illustrative purposes and is not intended to be exhaustive. Examples of other agents useful for the foregoing purposes are well known in ophthalmic formulation and are contemplated by the present invention.

Combination of the gelling system of the present invention with prior art gelling systems is also contemplated by the present invention. Such systems may include the inclusion of ionomers, such as xanthan, gellan, carageenan and carbomers, and thermogels, such as ethylhydroxyethyl cellulose.

In general, the compositions of the present invention will be used to administer various pharmaceutically active compounds to the eye. Such pharmaceuticals may include, but are not limited to, anti-hypertensive, anti-glaucoma, neuroprotective, anti-allergy, muco-secretagogue, angiostatic, anti-microbial, pain relieving and anti-inflammatory agents.

Examples of pharmaceutically active agents which may be included in the compositions of the present invention, and administered via the methods of the present invention include, but are not limited to: glaucoma agents, such as betaxolol, timolol, pilocarpine, carbonic anhydrase inhibitors and prostglandins; dopaminergic antagonists; post-surgical antihypertensive agents, such as para-amino clonidine (apraclonidine); anti-infectives, such as ciprofloxacin and tobramycin; non-steroidal and steroidal anti-inflammatories, such as naproxen, diclofenac, suprofen, ketorolac, tetrahydrocortisol and dexamethasone; proteins; growth factors, such as epidermal growth factor; and anti-allergics.

Optionally, the compositions of the present invention may be formulated without a pharmaceutically active compound. Such compositions may be used to lubricate the eye or provide artificial tear solutions to treat, for example, dry eye. In general, artificial tear solutions will contain tonicity agents, polymers and preservatives, as described above. The amount of galactomannan and borate contained in the artificial tear solutions will vary, as described above, but will generally be in the amount of from 0.1 to 3.0% (w/v) and 0.1 to 2.0% (w/v), respectively.

In general, the compositions of the present invention are formulated in two parts. The galactomannan polymer is hydrated and sterilized (Part I). Any pharmaceutical agent(s) and/or other ingredients to be included in the composition are then dissolved in water and sterile filtered (Part II). Parts I and II are then combined and the pH of the resultant mixture is adjusted to the target level, generally 6.0 to 7.0. If the pharmaceutical agent(s) to be included have low water solubility, they will generally be added last. In certain cases, it may be preferred to sterilize the pharmaceutical agent(s) separately, and then aspetically add the agent(s) and other ingredients together.

Sterilization of the galactomannan polysaccharide can be accomplished by autoclaving. Since the polymers undergo depolymerization at the extreme conditions of autoclaving, non-aqueous autoclaving is generally preferred. This can be accomplished by dispersing the polymer in a suitable organic liquid such as low molecular weight polyethylene glycols. The resulting suspension may then be autoclaved to sterilize the polymer. The sterilized polymer is then hydrated aseptically, prior to admixture with the other ingredients.

The following example illustrates a novel method of sterilizing a galactomannan polysaccharide of the present invention:

EXAMPLE 1

Preliminarily, a compounding vessel (20 L stainless steel pressure can), a 0.2 micron sterilizing filter, a receiving

vessel (20 L carboy), a 4.5 micron polishing filter, a 0.2 micron sterilizing filter, a vent filter, and the filling equipment are sterilized by autoclaving.

In a beaker equipped with an overhead agitator, add the weighed amount of polyethylene glycol 400 (200 g). While mixing slowly disperse the weighed amount of hydroxypropyl ("HP")Guar gum (10 g). Mix until completely homogeneous. In a 500 ml Schott bottle, equipped with a magnetic stir bar, weigh exactly 120.0 g of the HPGuar gum/PEG-400 dispersion. Prepare to sterilize by autoclaving. In a second identical 500 ml Schott bottle weigh exactly 120.0 g of the same dispersion. Prepare to use as a dummy during the autoclaving cycle. To both bottles add 1.3 ml of purified water (amount equivalent, by volume, of the microorganism suspension used to inoculate the bottles during the validation study). Mix both bottles for 10 minutes using a magnetic stir plate. Autoclave the HPGuar gum/PEG-400 dispersion using the validated time-temperature cycle of 80 minutes at 125° C.

The other set of ingredients to be included in the final formulation may be prepared separately by various methods known in the art. The resultant mixture can be added by sterile filtration to the compounding vessel, along with the HPGuar gum/PEG-400 preparation.

Aseptically transfer the sterilized HPGuar gum/PEG400 dispersion into the pre-sterilized compounding vessel. Rinse the bottle content with sterilized purified water. Bring the content of the compounding vessel to exactly 95% of the theoretical batch weight (19.0 liters or 19.06 Kg) using sterile room temperature purified water. Allow the HPGuar gum/PEG slurry to hydrate while mixing, at moderate speed, in the compounding vessel for a minimum of 2 hours. Transfer the contents of the compounding vessel through a 4.5 micron pre-sterilized polishing filter into the pre-sterilized receiving vessel equipped with a stir bar. There will be some loss of the contents due to the product held in filter housing and filter cartridge. (If a pressure can is used as compounding vessel, the recommended pressure for clarification filtration is approximately 30 psi.) Check and adjust pH, if necessary, to 6.9–7.1 (target 7.0) using 1N NaOH or 1N HCl. Approximately 3–4 ml of 1N NaOH per 1 liter of final batch weight is needed to achieve the desired pH. QS to final batch weight using sterile purified water. Mix at low speed for a minimum of 30 minutes.

The following examples further illustrate preferred ophthalmic compositions of the present invention:

EXAMPLE 2

The following is an example of a topical ophthalmic composition containing timolol.

Compound	Amount % (w/v)
Timolol Maleate	0.68*
Boric Acid	0.5
Guar Gum	0.5
PEG-400	1.0
Sodium Chloride	0.5
Benzalkonium Chloride	0.01
Sodium Hydroxide/Hydrochloric Acid	QS to pH 6.5
Purified Water	QS

*0.68% Timolol Maleate is equivalent to 0.5% Timolol.

The above formulation is prepared by first preparing a Part I and Part II mixture. The guar gum is first dispersed in PEG-400 and autoclaved as Part I. The other ingredients are dissolved in about 90% of the volume of water and sterile filtered in a receiving vessel as Part II. Part I is then added to Part II aseptically. The pH may then be adjusted aseptically and the batch is then brought to final weight (volume). The combined solution is then passed through a 1.0 μm polish filter, aseptically, to remove the particulates.

EXAMPLE 3

The following is another example of a topical ophthalmic composition containing timolol.

Compound	Amount % (w/v)
Timolol Maleate	0.34*
Boric Acid	0.5
Guar Gum	0.25
Glycerol	1.0
Benzalkonium Chloride	0.005
Sodium Hydroxide/Hydrochloric Acid	QS to pH 7.0
Purified Water	QS

*0.34% Timolol Maleate is equivalent to 0.25% Timolol.

The above composition may be prepared in a similar way as the Example 2 composition.

EXAMPLE 4

The following is an example of an artificial tear solution.

Compound	Amount % (w/v)
Boric Acid	0.5
Hydroxpropyl Guar	0.3
Propylene glycol	1.4
Polyquaternium-1	0.0005
Sodium Hydroxide/Hydrochloric Acid	QS to pH 6.8
Purified Water	QS

The above composition may be prepared in a similar way as the Example 2 composition.

The invention in its broader aspects is not limited to the specific details shown and described above. Departures may be made from such details within the scope of the accompanying claims without departing from the principles of the invention and without sacrificing its advantages.

What is claimed is:

1. A topical ophthalmic composition in the form of a liquid, said liquid composition comprising 0.1 to 5% (w/v) guar or a derivative thereof, 0.05 to 5.0% (w/v) of a borate compound, and water, said liquid composition having a pH such that the liquid composition thickens to form a gel or partial gel when one or more drops of the liquid composition are topically administered to the eye.

2. A topical ophthalmic composition of claim 1, wherein the composition has a slightly acidic to neutral pH.

3. A topical ophthalmic composition of claim 1, wherein the borate compound is selected from the group consisting of boric acid, sodium borate, potassium borate and combinations thereof.

4. A topical ophthalmic composition of claim 3, wherein the composition contains hydroxypropyl guar.

5. A topical ophthalmic composition of claim 4, wherein the hydroxypropyl guar has a molar substitution of less than 0.6.

6. A topical ophthalmic composition of claim 4, wherein the borate compound comprises boric acid.

7. A topical ophthalmic composition of claim 6, wherein the composition comprises hydroxypropyl guar in a concentration of 0.2 to 2.0% (w/v) and boric acid in a concentration of 0.1 to 2.0% (w/v).

8. A topical ophthalmic composition of claim 1, wherein the composition further comprises one or more pharmaceutically active agents.

9. A topical ophthalmic composition of claim 8, wherein the pharmaceutically active agent is selected from the group consisting of: anti-hypertensive, anti-glaucoma, neuroprotective, anti-allergy, muco-secretagogue, angiostatic, anti-microbial, pain-relieving and anti-inflammatory agents.

10. A topical ophthalmic composition of claim 1, wherein the composition has a pH of 6.0 to 7.0.

11. A composition according to any one of the claims 1–9, wherein the composition has a pH of 6.0 to 7.0.

12. A composition according to any one of claims 1–10 wherein the composition is adapted for use as an ocular lubricant or artificial tear composition.

13. A method of lubricating the eye, which comprises topically applying a composition of any one of claims 1–10 to the eye.

14. A sterile ophthalmic pharmaceutical composition, comprising 0.1 to 5% (w/v) of a galactomannan selected from the group consisting of guar and derivatives thereof, 0.05 to 5.0% (w/v) of a borate compound, and water.

15. A sterile ophthalmic composition according to claim 14, wherein the borate compound is selected from the group consisting of boric acid, sodium borate, potassium borate and combinations thereof.

16. A sterile ophthalmic composition according to claim 15, wherein the galactomannan comprises hydroxypropyl guar.

17. A sterile ophthalmic composition according to claim 16, wherein the borate compound comprises boric acid.

18. A sterile ophthalmic composition according to claim 18, wherein the composition contains hydroxypropyl guar in a concentration of 0.2 to 2.0% (w/v) and boric acid in a concentration of 0.1 to 2.0% (w/v).

19. A sterile ophthalmic composition according to any one of claims 14–18, wherein the composition has a slightly acidic to neutral pH.

20. A sterile ophthalmic composition according to any one of claims 14–18, wherein the composition further comprises a pharmaceutically active agent.

21. A sterile ophthalmic composition according to any one of claims 14–18, wherein the composition is adapted for use as an ocular lubricant or artificial tear composition.

22. A method of lubricating the eye, which comprises applying a lubricating amount of a composition of claim 21 to the eye.

23. A method of delivering a pharmaceutical agent to the eye which comprises topically administering to the eye a sterile ophthalmic composition comprising a pharmaceutically active agent, 0.1 to 5% (w/v) of a galactomannan selected from the group consisting of guar and derivatives thereof, 0.05 to 5% (w/v) of a borate compound, and water.

24. A method according to claim 23, wherein the borate compound is selected from the group consisting of boric acid, sodium borate, potassium borate and combinations thereof.

25. A method according to claim 24, wherein the galactomannan comprises hydroxypropyl guar.

26. A method according to claim 25, wherein the composition contains hydroxypropyl guar in a concentration of 0.2 to 2.0% (w/v), and the borate compound comprises boric acid in a concentration of 0.1 to 2.0% (w/v).

27. A method according to claim 23, wherein the pharmaceutically active agent is selected from the group consisting of: anti-hypertensive, anti-glaucoma, neuroprotective, anti-allergy, muco-secretagogue, angiostatic, anti-microbial, pain-relieving and anti-inflammatory agents.

28. A sterile ophthalmic pharmaceutical composition useful as an ocular lubricant or artificial tear composition, comprising 0.1 to 3.0% (w/v) of a galactomannan selected from the group consisting of guar and derivatives thereof, 0.1 to 2.0% (w/v) of a borate compound, and water.

29. A sterile ophthalmic composition according to claim 28, wherein the borate compound is selected from the group consisting of boric acid, sodium borate, potassium borate and combinations thereof.

30. A sterile ophthalmic composition according to claim 29, wherein the galactomannan comprises hydroxypropyl guar.

31. A sterile ophthalmic composition according to claim 28, wherein the borate compound comprises boric acid.

32. A sterile ophthalmic composition according to claim 28, wherein the galactomannan comprises hydroxypropyl guar and the borate compound comprises boric acid.

33. A sterile ophthalmic composition according to any one of claims 28–32, wherein the composition has a slightly acidic to neutral pH.

34. A sterile ophthalmic composition according to claim 33, wherein the composition has a pH of 6 to 7.

35. A method of lubricating an eye, which comprises topically applying to the eye a lubricating amount of a composition according to claim 34.

36. A method of lubricating an eye, which comprises topically applying to the eye a lubricating amount of a composition according to claim 33.

37. A method of lubricating an eye which comprises topically applying to the eye a lubricating amount of a composition according to any one of claims 28–32.

* * * * *

US006583124B2

(12) **United States Patent**
Asgharian

(10) **Patent No.: US 6,583,124 B2**
(45) **Date of Patent: *Jun. 24, 2003**

(54) **OPHTHALMIC COMPOSITIONS CONTAINING GALACTOMANNAN POLYMERS AND BORATE**

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(73) Assignee: **Alcon Manufacturing, Ltd.**, Fort Worth, TX (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(22) Filed: **Apr. 22, 2002**

(65) **Prior Publication Data**

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Related U.S. Application Data

(63) Continuation of application No. 09/423,762, filed as application No. PCT/US98/14596 on Jul. 17, 1998, now Pat. No. 6,403,609.

(60) Provisional application No. 60/054,132, filed on Jul. 29, 1997.

(51) **Int. Cl.**[7] **A61K 33/22**; A61K 31/736

(52) **U.S. Cl.** **514/54**; 514/310; 514/839; 514/912; 514/944; 536/123.1; 536/124; 536/128; 424/659; 424/660

(58) **Field of Search** 514/310, 54, 839, 514/912, 944; 536/123.1, 124, 128; 424/659, 660

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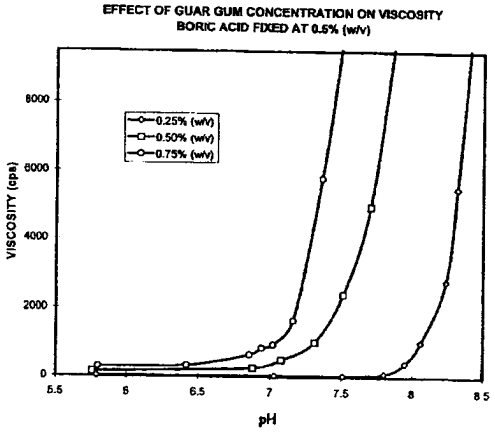
Primary Examiner—Samuel Barts
Assistant Examiner—Devesh Khare
(74) *Attorney, Agent, or Firm*—Gregg C. Brown

(57) **ABSTRACT**

The present invention is directed to ophthalmic compositions containing a gelling amount of a combination of galactomannan polysaccharides and borates. The compositions gel or partially gel upon administration to the eye. The present invention also discloses methods of topical ophthalmic administration of the compositions to the eye.

12 Claims, 3 Drawing Sheets



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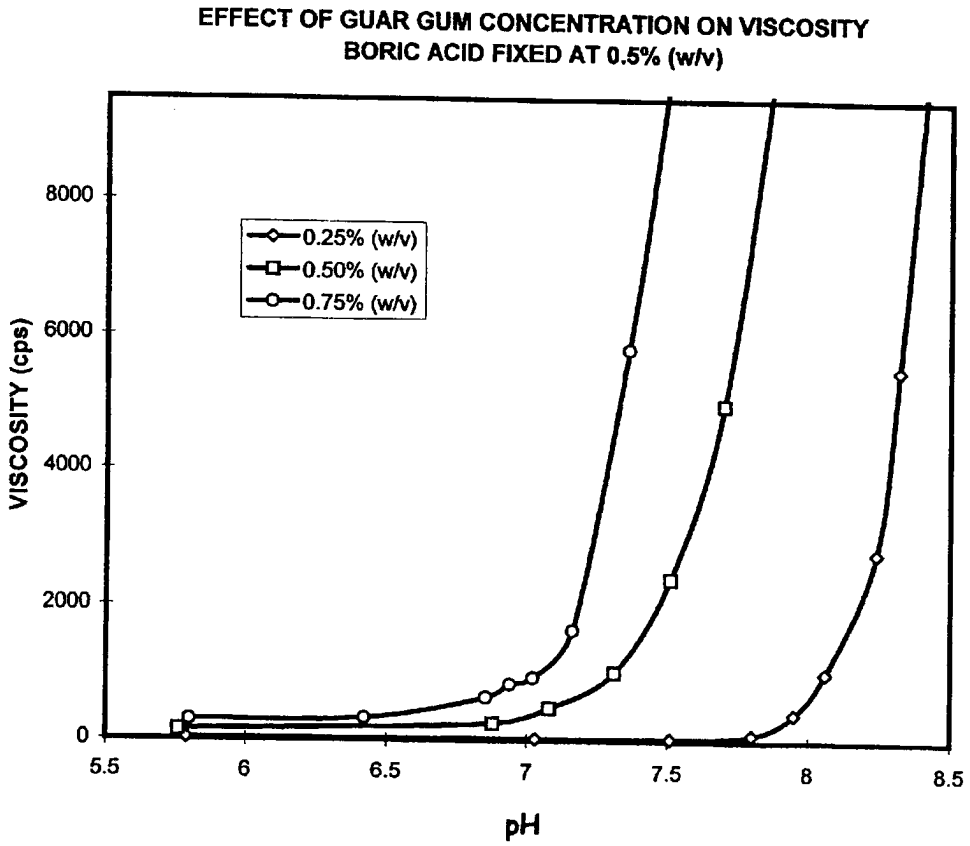
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VISCOSITY (cps)
8000
6000
4000
2000
0
0.25% (w/v)
0.50% (w/v)
0.75% (w/v)
5.5
6
6.5
7
7.5
8
8.5
pH

FIG. 1

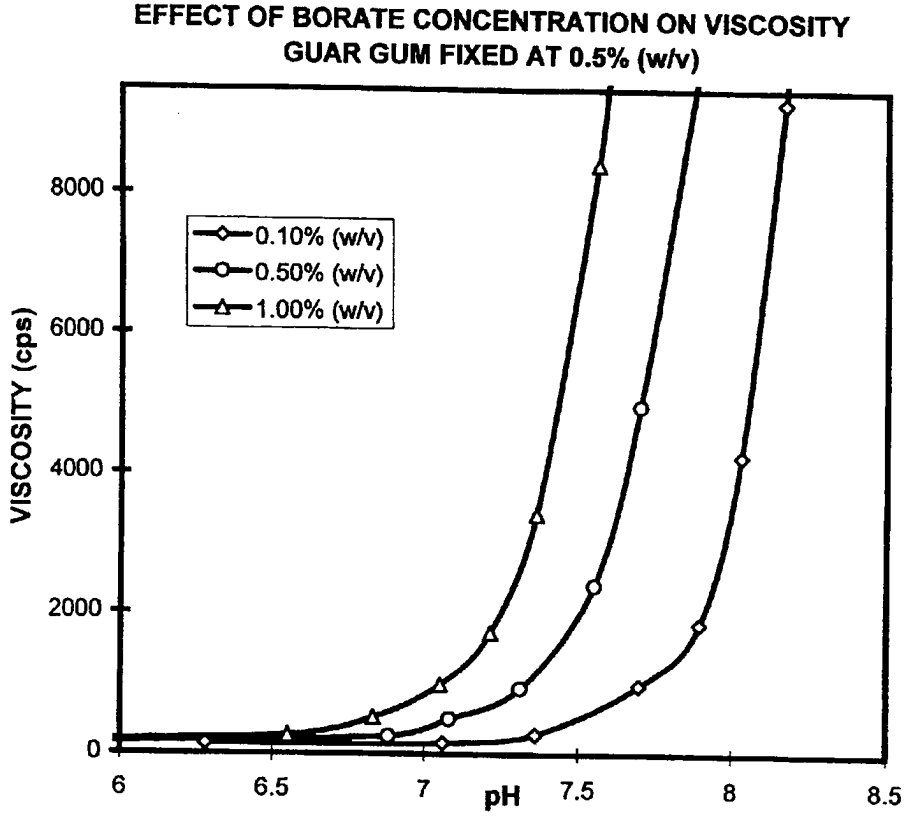
EFFECT OF BORATE CONCENTRATION ON VISCOSITY
GUAR GUM FIXED AT 0.5% (w/v)
VISCOSITY (cps)
8000
6000
4000
2000
0
0.10% (w/v)
0.50% (w/v)
1.00% (w/v)
6
6.5
7
pH
7.5
8
8.5

FIG. 2

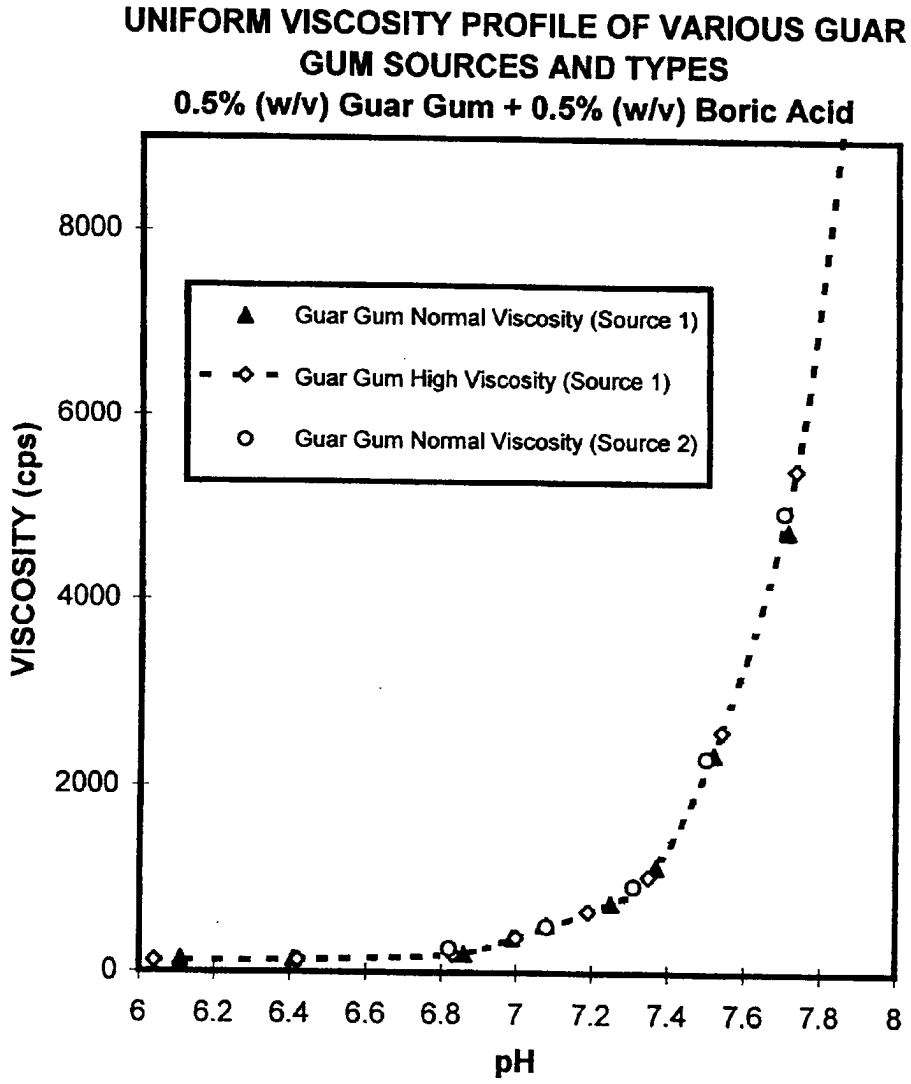
UNIFORM VISCOSITY PROFILE OF VARIOUS GUAR GUM SOURCES AND TYPES
0.5% (w/v) Guar Gum + 0.5% (w/v) Boric Acid
VISCOSITY (cps)
8000
6000
4000
2000
0
Guar Gum Normal Viscosity (Source 1)
Guar Gum High Viscosity (Source 1)
Guar Gum Normal Viscosity (Source 2)
6
6.2
6.4
6.6
6.8
7
7.2
7.4
7.6
7.8
8
pH

FIG. 3

OPHTHALMIC COMPOSITIONS CONTAINING GALACTOMANNAN POLYMERS AND BORATE

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of U.S. patent application Ser. No. 09/423,762 filed Nov. 12, 1999, now U.S. Pat. No. 6,403,609, which claims priority to PCT/US98/14596 filed Jul. 17, 1998 and U.S. Provisional Application Serial No. 60/054,132 filed Jul. 29, 1997.

BACKGROUND OF THE INVENTION

The present invention relates to the use of adjuvants in topical ophthalmic compositions. In particular, the present invention relates to pharmaceutical compositions comprising galactomannan polymers in combination with borates, and methods for the controlled administration of pharmaceutically active agents to patients, wherein the compositions are administered as liquids which thicken to form gels upon instillation into the eye. The transition from liquid to gel is primarily due to the change in pH and ionic strength.

Topical ophthalmic compositions have taken the form of liquids, ointments, gels and inserts. Liquid compositions for drop-wise instillation of pharmaceutically active agents to the eye provide for easy administration, but they do not always provide for an accurate dosage amount, as portions of the liquid are often blinked away during administration or drained down the punctum into the nasal passage. Ointments and gels, which usually reside in the eye longer than a liquid and therefore provide for more accurate administration, often interfere with a patient's vision. Ocular inserts, both bioerodible and non-bioerodible, are also available and allow for less frequent administration of drug. These inserts, however, require complex and detailed preparation and are frequently uncomfortable to the wearer. An additional problem with non-bioerodible inserts is that they must be removed after use.

U.S. Pat. No. 4,136,173 (Pramoda, et al.) discloses the use of therapeutic compositions containing xanthan gum and locust bean gum which are administered in liquid form and gel upon instillation. This reference describes a mechanism for transition from liquid to gel involving pH change. pH sensitive gels such as carbomers, xanthan, gellan, and those described above, need to be formulated at or below the pKa of their acidic groups (typically at a pH of about 2 to 5). Compositions formulated at low pH, however, are irritating to the eye.

The use of locust bean gum to form a gel vehicle for ophthalmic drug delivery is described in U.S. Pat. No. 4,136,177 (Lin, et al.). However, the gels described by Lin, et al. are formed at the time of manufacture, rather than upon application to the eye.

U.S. Pat. No. 4,861,760 (Mazuel, et al.) discloses ophthalmic compositions containing gellan gum which are administered to the eye as non-gelled liquids and gel upon instillation due to a change in ionic strength. These systems do not involve the use of small cross-linking molecules, but instead provide gel characteristics due to self cross-linking during ionic condition changes.

Gels involving the cross-linking of polysaccharides with borates are disclosed for use as well fracturing fluids in U.S. Pat. Nos. 5,082,579 (Dawson), 5,145,590 (Dawson), and 5,160,643 (Dawson). These patents describe the use of borates and polysaccharides for industrial oil well excavation.

The ophthalmic use of current gelling liquid systems have a number of drawbacks. For example, natural polymers such as xanthan gum have the disadvantage of lot to lot variability due to variations in source and/or limited manufacturing controls during processing. These variabilities cause significant undesirable changes in the properties of the compound, such as variable gelling characteristics. Thermogelling systems such as polyethylene oxide/polypropylene oxide block copolymers ("PEO/PPO") lose water in order to form gels, and consequently result in turbid gels. Polyvinyl alcohol ("PVA")-borate combination gelling systems need to be formulated at low pH, and therefore, can cause ocular irritation upon instillation. Other gelling systems have viscosity, rehydration and cloud point instability problems associated with autoclaving.

Polyvinyl alcohol crosslinking with borates have been disclosed in U.S. Pat. No. 4,255,415 (Sukhbir et al.). These compositions are pre-formed gels, and are therefore hard to dispense. WIPO Publication No. WO 94/10976 (Goldenberg et al.) discloses a low pH PVA-borate delivery system that does go through liquid/gel transition. This system has the disadvantage, however, of limited gelling effects, and only at certain concentrations of PVA depending on the molecular weight of the PVA utilized. Furthermore, since the crosslinking cites are unlimited with this system, strong local gelation upon addition of base has limited its manufacturing, and therefore, polyvinyl pyrrolidone presumably has been included in these compositions to overcome the shortcoming. The novel gelling system of the present invention does not have the above limitation.

SUMMARY OF THE INVENTION

The present invention is directed to topical ophthalmic compositions comprising galactomannan polymers and borate compounds which provide controlled administration of a drug to the eye. The invention is based on a new gelling system which comprises a galactomannan polysaccharide and a borate crosslinker which forms a gel upon increases in pH and ionic strength. In this novel system, bisdiol borates crosslink with the cis diol groups of the sugar moieties of the polysaccharide. The compositions are administered as liquids or partially gelled liquids (hereinafter "liquids") which thicken to form gels upon instillation into the eye. Alternatively, the compositions may not contain a pharmaceutically active agent, and can be administered to the eye for lubrication or to supplement tears in the treatment of, for example, dry eye.

The present invention galactomannan-borate gelling system has several advantages over other gelling systems. One advantage is that the compositions of the present invention are clear solutions and the resultant gel is also crystal clear. While other systems may become opaque or cloudy upon instillation, the crystal clear gel of the present invention provides greater clarity of vision to the treated eye. The present invention compositions may be formulated at slightly acidic to neutral pH and require only a minor pH change to activate gelation (i.e., about 0.5 to 1.0 pH unit). This feature minimizes possible irritation of the eye resulting from acidic exposure, such as may result with other pH sensitive systems which require a pH change of about 2.4 to about 4.4 pH units (i.e., are formulated with a pH of about 3–5). Galactomannan polymers are also heat stable and show no cloud point even during autoclaving conditions. As such, viscosity and rehydration problems resulting from batch scale up, such as exist with PVA and carbomer polymer systems, are not present with the galactomannan polymer containing compositions of the present invention.

Galactomannan polysaccharides are non-ionic and, in combination with borates at acidic to neutral pH, are also essentially non-ionic. Thus, the polymer system is completely compatible with anionic, neutral and cationic drugs. Furthermore, the preservative efficacy of the preservatives are not compromised by the presence of the polymer. Typically, the efficacy of benzalkonium chloride or other cationic preservatives are compromised with anionic polymers such as gellan and carageenan, and excess preservative may therefore be needed in those systems. Increases in preservative concentration may also increase irritation and toxicity of the composition.

The galactomannan-borate gelling system of the present invention has other advantages. Galactomannan polymers have a relatively low molecular weight and are therefore easy to manufacture and scale up. Galactomannan polymers are also readily available and have been used in food and personal care products such that the polymers are considered to be safe. Furthermore, control or manipulation of the gelling characteristics of the galactomannan-borate gelling compositions of the present invention is relatively simple as compared with prior art systems. The gelling properties of other single polymer systems, such as ionomers, e.g., gellan and carageenans, and thermogels, e.g., poloxamines and poloxamers, are typically related to the molecular weight and the number of functional groups of the polymers. Thus, in order to change the gel point or degree of gelation of those prior art systems, one would need to modify the base polymer—a labor intensive activity. In contrast, by simply manipulating the borate to galactomannan ratio in the present invention compositions, a wide range of gelling characteristics is available in order to fine tune the compositions to the targeted requirements (see FIGS. **1** and **2**). Moreover, as illustrated in FIG. **3**, the galactomannans of the present invention (e.g., guar gum) demonstrate excellent gelling consistency and reproducibility, though the type or source of the galactomannan is varied.

Still other advantages are present in the compositions of the present invention. The galactomannan polymer and the borate crosslinker compositions of the present invention are liquids and, therefore, easy to dispense. Some gelling systems such as gellan gum, as disclosed in U.S. Pat. No. 4,861,760 (Mazuel et al.), are thixotropic, which may require shaking to increase the fluidity and ease of dispensing. The present invention compositions contain a relatively low concentration of galactomannan (about 0.2 to 0.5%) as compared to some thermogelling systems such as PEO/PPO block copolymers, which require very high concentrations. Lower concentrations of the gelling polymer provide lower potential toxicity and ease of preservation from microbial contamination over higher concentration systems.

The methods of the present invention involve the topical administration of the galactomannan-borate containing compositions of the present invention.

The present invention is also directed to methods of sterilization of the galactomannans involving autoclaving.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a graph illustrating the gelling characteristics of various concentrations of guar gum in the presence of borate, relative to pH.

FIG. **2** is a graph illustrating the gelling characteristics of various concentrations of borate in the presence of guar gum, relative to pH.

FIG. **3** is a graph illustrating the uniformity of the gelling characteristics of three different types/sources of guar gum.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to ophthalmic compositions which comprise one or more galactomannan polysaccharide(s) and one or more borate compound(s). The present invention is also directed to methods of using these compositions to treat various ophthalmic disorders including dry eye, glaucoma, ocular hypertension, infection, allergy and inflammation.

The types of galactomannans that may be used in the present invention are typically derived from guar gum, locust bean gum and tara gum. As used herein, the term "galactomannan" refers to polysaccharides derived from the above natural gums or similar natural or synthetic gums containing mannose or galactose moieties, or both groups, as the main structural components. Preferred galactomannans of the present invention are made up of linear chains of (1–4)-β-D-mannopyranosyl units with α-D-galactopyranosyl units attached by (1–6) linkages. With the preferred galactomannans, the ratio of D-galactose to D-mannose varies, but generally will be from about 1:2 to 1:4. Galactomannans having a D-galactose:D-mannose ratio of about 1:2 are most preferred. Additionally, other chemically modified variations of the polysaccharides are also included in the "galactomannan" definition. For example, hydroxyethyl, hydroxypropyl and carboxymethylhydroxypropyl substitutions may be made to the galactomannans of the present invention. Non-ionic variations to the galactomannans, such as those containing alkoxy and alkyl (C1–C6) groups are particularly preferred when a soft gel is desired (e.g., hydroxylpropyl substitutions). Substitutions in the non-cis hydroxyl positions are most preferred. An example of non-ionic substitution of a galactomannan of the present invention is hydroxypropyl guar, with a molar substitution of about 0.4. Anionic substitutions may also be made to the galactomannans. Anionic substitution is particularly preferred when strongly responsive gels are desired.

The borate compounds which may be used in the compositions of the present invention are boric acid and other pharmaceutically acceptable salts such as sodium borate (borax) and potassium borate. As used herein, the term "borate" refers to all pharmaceutically suitable forms of borates. Borates are common excipients in ophthalmic formulations due to good buffering capacity at physiological pH and well known safety and compatibility with a wide range of drugs and preservatives. Borates also have inherent bacteriostatic and fungistatic properties, and therefore aid in the preservation of the compositions.

The present invention compositions comprise one or more galactomannan(s) in the amount of from about 0.1 to 5% weight/volume ("w/v") and borate in the amount of from about 0.05 to 5% (w/v). Preferably, the compositions will contain 0.2 to 2.0% (w/v) of galactomannan and 0.1 to 2.0% (w/v) of a borate compound. Most preferably, the compositions will contain 0.3 to 0.8% (w/v) of galactomannan and 0.25 to 1.0% (w/v) of a borate compound. The particular amounts will vary, depending on the particular gelling properties desired. In general, the borate or galactomannan concentration may be manipulated in order to arrive at the appropriate viscosity of the composition upon gel activation (i.e., after administration). As shown in FIGS. **1** and **2**, manipulating either the borate or galactomannan concentration provides stronger or weaker gelation at a given pH. If a strongly gelling composition is desired, then the borate or galactomannan concentration may be increased. If a weaker

gelling composition is desired, such as a partially gelling composition, then the borate or galactomannan concentration may be reduced. Other factors may influence the gelling features of the compositions of the present invention, such as the nature and concentration of additional ingredients in the compositions, such as salts, preservatives, chelating agents and so on. Generally, preferred non-gelled compositions of the present invention, i.e., compositions not yet gel-activated by the eye, will have a viscosity of from about 5 to 1000 cps. Generally, preferred gelled compositions of the present invention, i.e., compositions gel-activated by the eye, will have a viscosity of from about 50 to 50,000 cps.

The galactomannans of the present invention may be obtained from numerous sources. Such sources include guar gum, locust bean gum and tara gum, as further described below. Additionally, the galactomannans may also be obtained by classical synthetic routes or may be obtained by chemical modification of naturally occurring galactomannans.

Guar gum is the ground endosperm of *Cyamopisis tetragonolobus* (L) Taub. The water soluble fraction (85%) is called "guaran" (molecular weight of 220,000), which consists of linear chains of (1–4)-β-D mannopyranosyl units with α-D-galactopyranosyl units attached by (1–6) linkages. The ratio of D-galactose to D-mannose in guaran is about 1:2. The gum has been cultivated in Asia for centuries and is primarily used in food and personal care products for its thickening property. It has five to eight times the thickening power of starch. Its derivatives, such as those containing hydroxypropyl or hydroxypropyltrimonium chloride substitutions, have been commercially available for over a decade. Guar gum may be obtained, for example, from Rhone-Polulenc (Cranbury, N.J.), Hercules, Inc. (Wilmington, Del.) and TIC Gum, Inc. (Belcamp, Md.).

Locust bean gum or carob bean gum is the refined endosperm of the seed of the carob tree, ceratonia siliqua. The ratio of galactose to mannose for this type of gum is about 1:4. Cultivation of the carob tree is old and well known in the art. This type of gum is commercially available and may be obtained from TIC Gum, Inc. (Bekamp, Md.) and Rhone-Polulenc (Cranbury, N.J.).

Tara gum is derived from the refined seed gum of the tara tree. The ratio of galactose to mannose is about 1:3. Tara gum is not produced in the United States commercially, but the gum may be obtained from various sources outside the United States.

In order to limit the extent of cross-linking to provide a softer gel characteristic, chemically modified galactomannans such as hydroxypropyl guar may be utilized. Modified galactomannans of various degree of substitution are commercially available from Rhone-Poulenc (Cranbury, N.J.). Hydroxypropyl guar with low molar substitution (e.g., less than 0.6) is particularly preferred.

Other ingredients may be added to the compositions of the present invention. Such ingredients generally include tonicity adjusting agents, chelating agents, active pharmaceutical agent(s), solubilizers, preservatives, pH adjusting agents and carriers. Other polymer or monomeric agents such as polyethylene glycol and glycerol may also be added for special processing. Tonicity agents useful in the compositions of the present invention may include salts such as sodium chloride, potassium chloride and calcium chloride; non-ionic tonicity agents may include propylene glycol and glycerol; chelating agents may include EDTA and its salts; solubilizing agents may include Cremophor EL® and tween 80; other carriers may include amberlite® IRP-69; pH adjusting agents may include hydrochloric acid, Tris, triethanolamine and sodium hydroxide; and suitable preservatives may include benzalkonium chloride, polyquaternium-1 and polyhexamethylene biguanide. The above listing of examples is given for illustrative purposes and is not intended to be exhaustive. Examples of other agents useful for the foregoing purposes are well known in ophthalmic formulation and are contemplated by the present invention.

Combination of the gelling system of the present invention with prior art gelling systems is also contemplated by the present invention. Such systems may include the inclusion of ionomers, such as xanthan, gellan, carageenan and carbomers, and thermogels, such as ethylhydroxyethyl cellulose.

In general, the compositions of the present invention will be used to administer various pharmaceutically active compounds to the eye. Such pharmaceuticals may include, but are not limited to, anti-hypertensive, anti-glaucoma, neuroprotective, anti-allergy, muco-secretagogue, angiostatic, anti-microbial, pain relieving and anti-inflammatory agents.

Examples of pharmaceutically active agents which may be included in the compositions of the present invention, and administered via the methods of the present invention include, but are not limited to: glaucoma agents, such as betaxolol, timolol, pilocarpine, carbonic anhydrase inhibitors and prostglandins; dopaminergic antagonists; post-surgical antihypertensive agents, such as para-amino clonidine (apraclonidine); anti-infectives, such as ciprofloxacin and tobramycin; non-steroidal and steroidal anti-inflammatories, such as naproxen, diclofenac, suprofen, ketorolac, tetrahydrocortisol and dexamethasone; proteins; growth factors, such as epidermal growth factor; and anti-allergics.

Optionally, the compositions of the present invention may be formulated without a pharmaceutically active compound. Such compositions may be used to lubricate the eye or provide artificial tear solutions to treat, for example, dry eye. In general, artificial tear solutions will contain tonicity agents, polymers and preservatives, as described above. The amount of galactomannan and borate contained in the artificial tear solutions will vary, as described above, but will generally be in the amount of from 0.1 to 3.0% (w/v) and 0.1 to 2.0% (w/v), respectively.

In general, the compositions of the present invention are formulated in two parts. The galactomannan polymer is hydrated and sterilized (Part I). Any pharmaceutical agent(s) and/or other ingredients to be included in the composition are then dissolved in water and sterile filtered (Part II). Parts I and II are then combined and the pH of the resultant mixture is adjusted to the target level, generally 6.0 to 7.0. If the pharmaceutical agent(s) to be included have low water solubility, they will generally be added last. In certain cases, it may be preferred to sterilize the pharmaceutical agent(s) separately, and then aspetically add the agent(s) and other ingredients together.

Sterilization of the galactomannan polysaccharide can be accomplished by autoclaving. Since the polymers undergo depolymerization at the extreme conditions of autoclaving, non-aqueous autoclaving is generally preferred. This can be accomplished by dispersing the polymer in a suitable organic liquid such as low molecular weight polyethylene glycols. The resulting suspension may then be autoclaved to sterilize the polymer. The sterilized polymer is then hydrated aseptically, prior to admixture with the other ingredients.

The following example illustrates a novel method of sterilizing a galactomannan polysaccharide of the present invention:

EXAMPLE 1

Preliminarily, a compounding vessel (20 L stainless steel pressure can), a 0.2 micron sterilizing filter, a receiving vessel (20 L carboy), a 4.5 micron polishing filter, a 0.2 micron sterilizing filter, a vent filter, and the filling equipment are sterilized by autoclaving.

In a beaker equipped with an overhead agitator, add the weighed amount of polyethylene glycol 400 (200 g). While mixing slowly disperse the weighed amount of hydroxypropyl ("HP")Guar gum (100 g). Mix until completely homogeneous. In a 500 ml Schott bottle, equipped with a magnetic stir bar, weigh exactly 120.0 g of the HPGuar gum/PEG-400 dispersion. Prepare to sterilize by autoclaving. In a second identical 500 ml Schott bottle weigh exactly 120.0 g of the same dispersion. Prepare to use as a dummy during the autoclaving cycle. To both bottles add 1.3 ml of purified water (amount equivalent, by volume, of the microorganism suspension used to inoculate the bottles during the validation study). Mix both bottles for 10 minutes using a magnetic stir plate. Autoclave the HPGuar gum/PEG-400 dispersion using the validated time-temperature cycle of 80 minutes at 125° C.

The other set of ingredients to be included in the final formulation may be prepared separately by various methods known in the art. The resultant mixture can be added by sterile filtration to the compounding vessel, along with the HPGuar gum/PEG-400 preparation.

Aseptically transfer the sterilized HPGuar gum/PEG-400 dispersion into the pre-sterilized compounding vessel. Rinse the bottle content with sterilized purified water. Bring the content of the compounding vessel to exactly 95% of the theoretical batch weight (19.0 liters or 19.06 Kg) using sterile room temperature purified water. Allow the HPGuar gum/PEG slurry to hydrate while mixing, at moderate speed, in the compounding vessel for a minimum of 2 hours. Transfer the contents of the compounding vessel through a 4.5 micron pre-sterilized polishing filter into the pre-sterilized receiving vessel equipped with a to stir bar. There will be some loss of the contents due to the product held in filter housing and filter cartridge. (If a pressure can is used as compounding vessel, the recommended pressure for clarification filtration is approximately 30 psi.) Check and adjust pH, if necessary, to 6.9–7.1 (target 7.0) using 1N NaOH or 1N HCl. Approximately 3–4 ml of 1N NaOH per 1 liter of final batch weight is needed to achieve the desired pH. QS to final batch weight using sterile purified water. Mix at low speed for a minimum of 30 minutes.

The following examples further illustrate preferred ophthalmic compositions of the present invention:

EXAMPLE 2

The following is an example of a topical ophthalmic composition containing timolol.

Compound	Amount % (w/v)
Timolol Maleate	0.68*
Boric Acid	0.5
Guar Gum	0.5
PEG-400	1.0
Sodium Chloride	0.5
Benzalkonium Chloride	0.01
Sodium Hydroxide/Hydrochloric Acid	QS to pH 6.5
Purified Water	QS

*0.68% Timolol Maleate is equivalent to 0.5% Timolol.

The above formulation is prepared by first preparing a Part I and Part II mixture. The guar gum is first dispersed in PEG-400 and autoclaved as Part I. The other ingredients are dissolved in about 90% of the volume of water and sterile filtered in a receiving vessel as Part II. Part I is then added to Part II aseptically. The pH may then be adjusted aseptically and the batch is then brought to final weight (volume). The combined solution is then passed through a 1.0 μm polish filter, aseptically, to remove the particulates.

EXAMPLE 3

The following is another example of a topical ophthalmic composition containing timolol.

Compound	Amount % (w/v)
Timolol Maleate	0.34*
Boric Acid	0.5
Guar Gum	0.25
Glycerol	1.0
Benzalkonium Chloride	0.005
Sodium Hydroxide/Hydrochloric Acid	QS to pH 7.0
Purified Water	QS

*0.34% Timolol Maleate is equivalent to 0.25% Timolol.

The above composition may be prepared in a similar way as the Example 2 composition.

EXAMPLE 4

The following is an example of an artificial tear solution.

Compound	Amount % (w/v)
Boric Acid	0.5
Hydroxpropyl Guar	0.3
Propylene glycol	1.4
Polyquaternium-1	0.0005
Sodium Hydroxide/Hydrochloric Acid	QS to pH 6.8
Purified Water	QS

The above composition may be prepared in a similar way as the Example 2 composition.

The invention in its broader aspects is not limited to the specific details shown and described above. Departures may be made from such details within the scope of the accompanying claims without departing from the principles of the invention and without sacrificing its advantages.

What is claimed is:

1. An artificial tear solution comprising a galactomannan polymer, a borate compound and water; wherein the solution contains the galactomannan polymer and the borate compound in amounts effective to form a gel or partial gel when the solution is topically administered to the eye, and does not contain a pharmaceutically active agent.

2. An artificial tear solution according to claim 1, wherein the borate compound is selected from the group consisting of boric acid, sodium borate, potassium borate and combinations thereof.

3. An artificial tear solution according to claim 2, wherein the galactomannan is selected from the group consisting of guar gum, locust bean gum, tara gum and chemically modified derivatives thereof.

4. An artificial tear solution according to claim 3, wherein the borate compound comprises boric acid.

5. An artificial tear solution according to claim 1, wherein the galactomannan comprises hydroxypropyl guar and the borate compound comprises boric acid.

6. An artificial tear solution according to any one of claims 1–4, the composition contains the galactomannan polymer in a concentration of 0.1 to 3.0% (w/v) and the borate compound in a concentration of 0.1 to 2.0% (w/v).

7. A method of lubricating or moisturizing an eye, which comprises topically applying to the eye an effective amount of an artificial tear solution according to claim 6.

8. An artificial tear solution according to any one of claims 1–5, wherein the composition has a slightly acidic to neutral pH.

9. An artificial tear solution according to claim 1, wherein the composition has a pH of 6 to 7.

10. A method of lubricating or moisturizing an eye, which comprises topically applying to the eye an effective amount of a composition according to claim 9.

11. A method of lubricating or moisturizing an eye which comprises topically applying to the eye an effective amount of an artificial tear solution according to any one of claims 1–5.

12. A method of lubricating or moisturizing an eye, which comprises topically applying to the eye an effective amount of a composition according to claim 1.

* * * * *

US006838449B2

(12) **United States Patent**
Asgharian

(10) **Patent No.: US 6,838,449 B2**
(45) **Date of Patent: Jan. 4, 2005**

(54) **OPHTHALMIC COMPOSITIONS CONTAINING GALACTOMANNAN POLYMERS AND BORATE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(22) Filed: **May 14, 2003**

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Related U.S. Application Data

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(60) Provisional application No. 60/054,132, filed on Jul. 29, 1997.

(51) **Int. Cl.**[7] **A61K 33/22**; A61K 31/736

(52) **U.S. Cl.** **514/54**; 514/310; 514/839; 514/912; 514/944; 536/123.1; 536/124; 536/128; 424/401; 424/402; 424/427; 424/659; 424/660; 507/209; 507/241; 507/271; 166/300; 166/308.5; 516/107

(58) **Field of Search** 514/54, 310, 839, 514/912, 944; 536/123.1, 124, 128; 424/401, 402, 427, 659, 660; 507/209, 241, 271; 166/300, 308.5; 516/107

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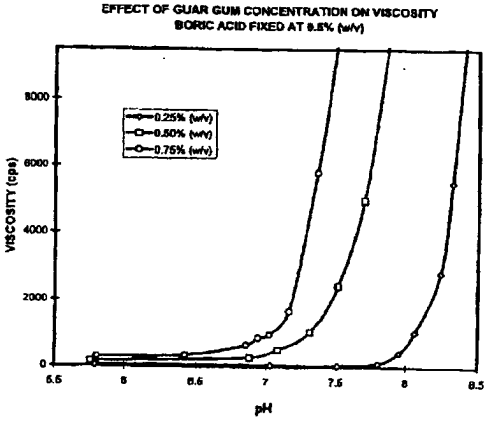
Assistant Examiner—Devesh Khare
(74) *Attorney, Agent, or Firm*—Gregg C. Brown

(57) **ABSTRACT**

The present invention is directed to ophthalmic compositions containing a gelling amount of a combination of galactomannan polysaccharides and borates. The compositions gel or partially gel upon administration to the eye. The present invention also discloses methods of topical ophthalmic administration of the compositions to the eye.

9 Claims, 3 Drawing Sheets



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6,403,609	B1 *	6/2002	Asgharian	514/310
6,583,124	B2 *	6/2003	Asgharian	514/54

* cited by examiner

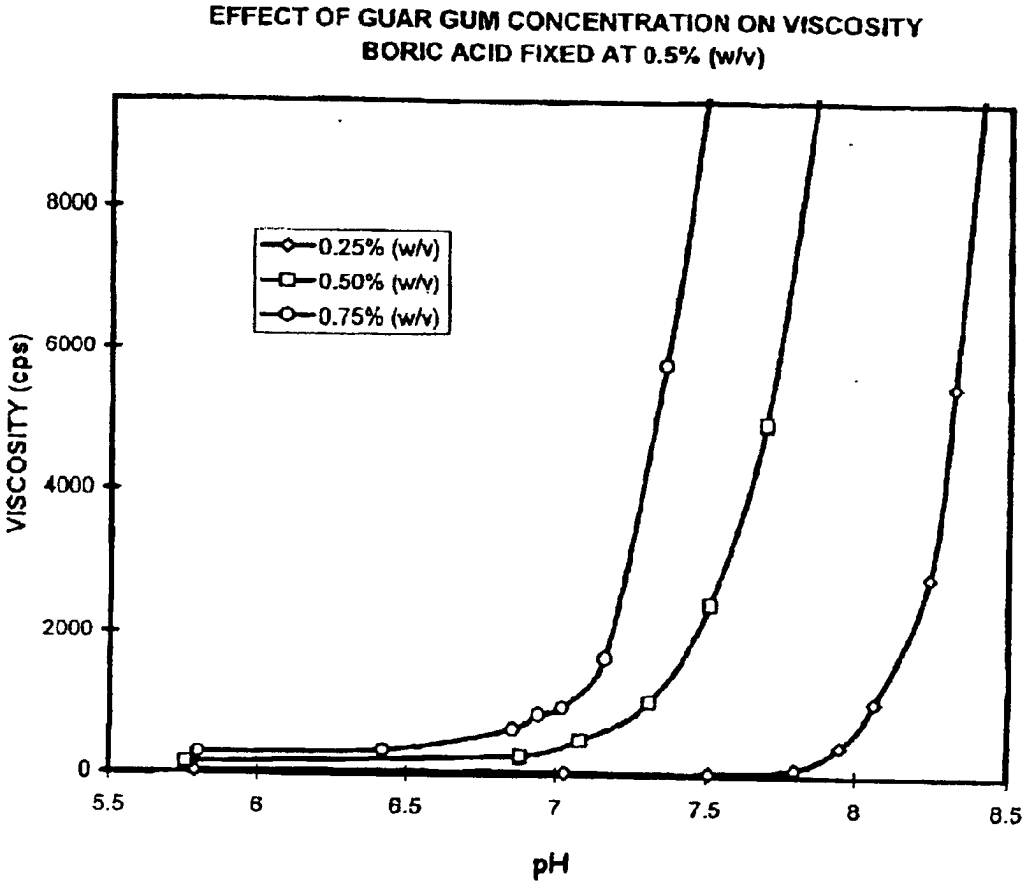
EFFECT OF GUAR GUM CONCENTRATION ON VISCOSITY
BORIC ACID FIXED AT 0.5% (w/v)
0.25% (w/v)
0.50% (w/v)
0.75% (w/v)
VISCOSITY (cps)
8000
6000
4000
2000
0
5.5
6
6.5
7
7.5
8
8.5
pH

FIG. 1

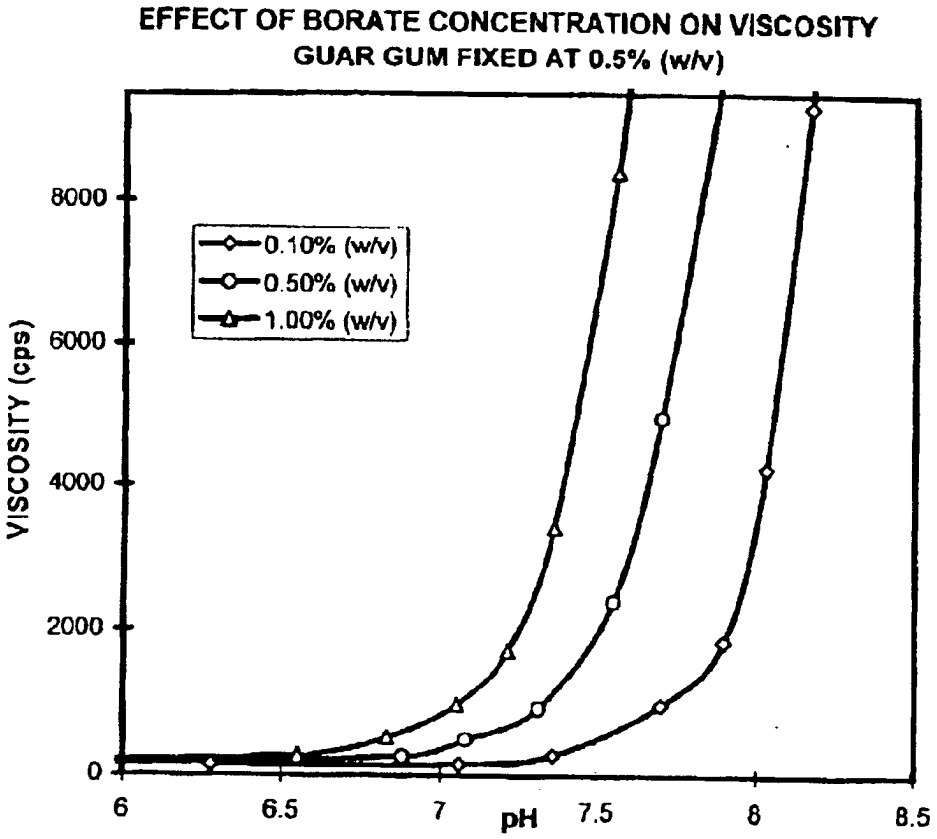
EFFECT OF BORATE CONCENTRATION ON VISCOSITY
GUAR GUM FIXED AT 0.5% (w/v)
VISCOSITY (cps)
8000
6000
4000
2000
0
0.10% (w/v)
0.50% (w/v)
1.00% (w/v)
6
6.5
7
pH
7.5
8
8.5

FIG. 2

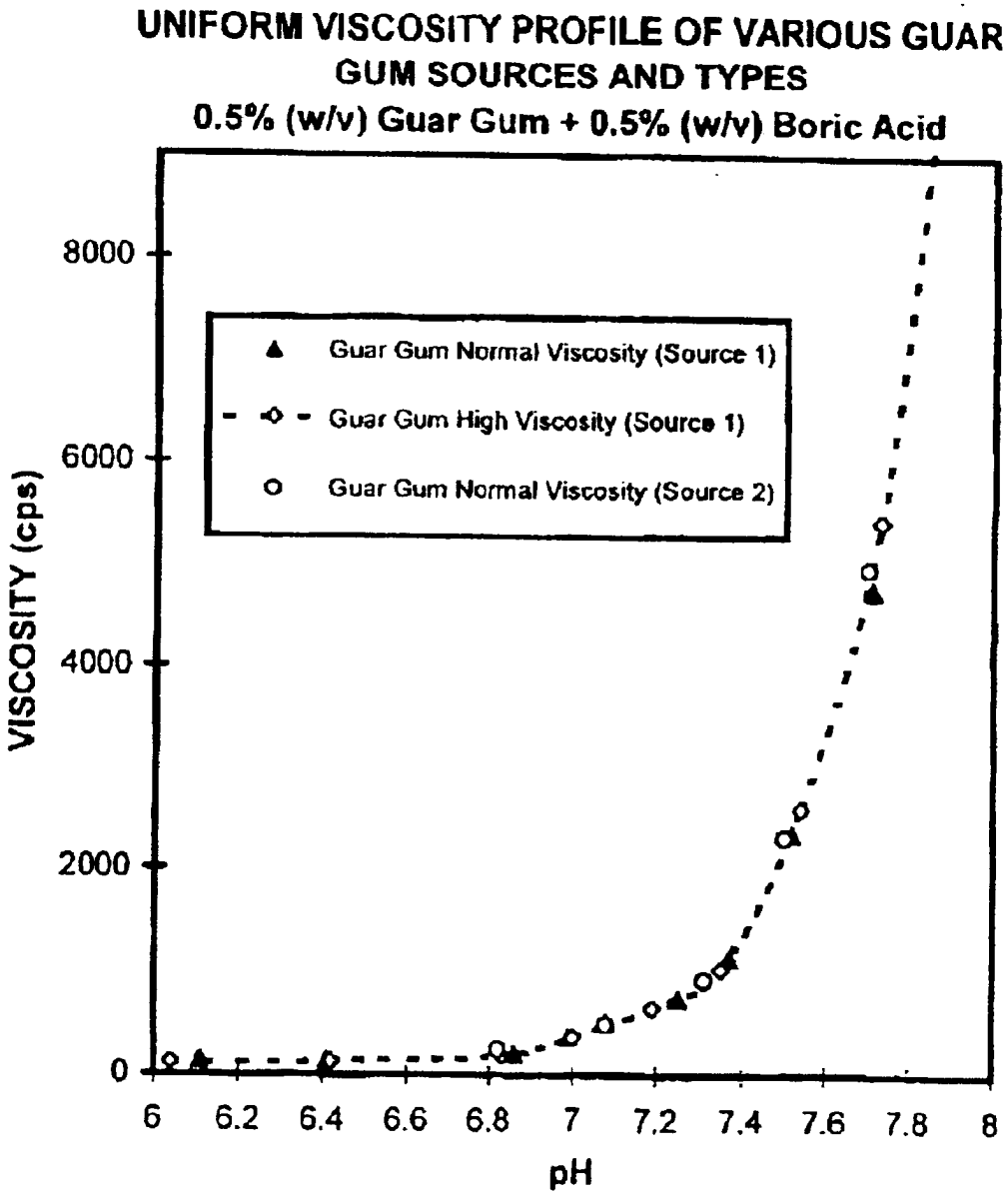
UNIFORM VISCOSITY PROFILE OF VARIOUS GUAR GUM SOURCES AND TYPES
0.5% (w/v) Guar Gum + 0.5% (w/v) Boric Acid
VISCOSITY (cps)
8000
6000
4000
2000
0
Guar Gum Normal Viscosity (Source 1)
Guar Gum High Viscosity (Source 1)
Guar Gum Normal Viscosity (Source 2)
6
6.2
6.4
6.6
6.8
7
7.2
7.4
7.6
7.8
8
pH

FIG. 3

OPHTHALMIC COMPOSITIONS CONTAINING GALACTOMANNAN POLYMERS AND BORATE

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of U.S. patent application Ser. No. 10/128,559 filed Apr. 22, 2002 now U.S. Pat. No. 6,583,124 (now allowed), which is a continuation of U.S. patent application Ser. No. 09/423,762 filed Nov. 12, 1999 (U.S. Pat. No. 6,403,609), which is the National Stage of International Application No. PCT/US98/14596 filed Jul. 17, 1998, which claims benefit of U.S. Provisional Application Ser. No. 60/054,132 filed Jul. 29, 1997.

BACKGROUND OF THE INVENTION

The present invention relates to the use of adjuvants in topical ophthalmic compositions. In particular, the present invention relates to pharmaceutical compositions comprising galactomannan polymers in combination with borates, and methods for the controlled administration of pharmaceutically active agents to patients, wherein the compositions are administered as liquids which thicken to form gels upon instillation into the eye. The transition from liquid to gel is primarily due to the change in pH and ionic strength.

Topical ophthalmic compositions have taken the form of liquids, ointments, gels and inserts. Liquid compositions for drop-wise instillation of pharmaceutically active agents to the eye provide for easy administration, but they do not always provide for an accurate dosage amount, as portions of the liquid are often blinked away during administration or drained down the punctum into the nasal passage. Ointments and gels, which usually reside in the eye longer than a liquid and therefore provide for more accurate administration, often interfere with a patient's vision. Ocular inserts, both bioerodible and non-bioerodible, are also available and allow for less frequent administration of drug. These inserts, however, require complex and detailed preparation and are frequently uncomfortable to the wearer. An additional problem with non-bioerodible inserts is that they must be removed after use.

U.S. Pat. Nos. 4,136,173 (Pramoda, et al.) and 4,136,177 (Lin, et al.) disclose the use of therapeutic compositions containing xanthan gum and locust bean gum which are administered in liquid form and gel upon instillation. These disclosures describe a mechanism for transition from liquid to gel involving pH change. pH sensitive gels such as carbomers, xanthan, gellan, and those described above, need to be formulated at or below the pKa of their acidic groups (typically at a pH of about 2 to 5). Compositions formulated at low pH, however, are irritating to the eye. U.S. Pat. No. 4,861,760 (Mazuel, et al.) discloses ophthalmic compositions containing gellan gum which are administered to the eye as non-gelled liquids and gel upon instillation due to a change in ionic strength. These systems do not involve the use of small cross-linking molecules, but instead provide gel characteristics due to self cross-linking during ionic condition changes. Gels involving the cross-linking of polysaccharides with borates are disclosed for use as well fracturing fluids in U.S. Pat. Nos. 5,082,579, 5,144,590, and 5,160,643. These patents describe the use of borates and polysaccharides for industrial oil well excavation.

The ophthalmic use of current gelling liquid systems have a number of drawbacks. For example, natural polymers such as xanthan gum have the disadvantage of lot to lot variability due to variations in source and/or limited manufacturing controls during processing. These variabilities cause significant undesirable changes in the properties of the compound, such as variable gelling characteristics. Thermogelling systems such as polyethylene oxide/polypropylene oxide block copolymers ("PEO/PPO") lose water in order to form gels, and consequently result in turbid gels. Polyvinyl alcohol ("PVA")-borate combination gelling systems need to be formulated at low pH, and therefore, can cause ocular irritation upon instillation. Other gelling systems have viscosity, rehydration and cloud point instability problems associated with autoclaving.

Polyvinyl alcohol crosslinking with borates have been disclosed in U.S. Pat. No. 4,255,415 (Sukhbir et al.). These compositions are pre-formed gels, and are therefore hard to dispense. WIPO Publication No. WO 94/10976 (Goldenberg et al.) discloses a low pH PVA-borate delivery system that does go through liquid/gel transition. This system has the disadvantage, however, of limited gelling effects, and only at certain concentrations of PVA depending on the molecular weight of the PVA utilized. Furthermore, since the crosslinking cites are unlimited with this system, strong local gelation upon addition of base has limited its manufacturing, and therefore, polyvinyl pyrrolidone presumably has been included in these compositions to overcome the shortcoming. The novel gelling system of the present invention does not have the above limitation.

SUMMARY OF THE INVENTION

The present invention is directed to topical ophthalmic compositions comprising galactomannan polymers and borate compounds which provide controlled administration of a drug to the eye. The invention is based on a new gelling system which comprises a galactomannan polysaccharide and a borate crosslinker which forms a gel upon increases in pH and ionic strength. In this novel system, bisdiol borates crosslink with the cis diol groups of the sugar moieties of the polysaccharide. The compositions are administered as liquids or partially gelled liquids (hereinafter "liquids") which thicken to form gels upon instillation into the eye. Alternatively, the compositions may not contain a pharmaceutically active agent, and can be administered to the eye for lubrication or to supplement tears in the treatment of, for example, dry eye.

The present invention galactomannan-borate gelling system has several advantages over other gelling systems. One advantage is that the compositions of the present invention are clear solutions and the resultant gel is also crystal clear. While other systems may become opaque or cloudy upon instillation, the crystal clear gel of the present invention provides greater clarity of vision to the treated eye. The present invention compositions may be formulated at slightly acidic to neutral pH and require only a minor pH change to activate gelation (i.e., about 0.5 to 1.0 pH unit). This feature minimizes possible irritation of the eye resulting from acidic exposure, such as may result with other pH sensitive systems which require a pH change of about 2.4 to about 4.4 pH units (i.e., are formulated with a pH of about 3–5). Galactomannan polymers are also heat stable and show no cloud point even during autoclaving conditions. As such, viscosity and rehydration problems resulting from batch scale up, such as exist with PVA and carbomer polymer systems, are not present with the galactomannan polymer containing compositions of the present invention.

Galactomannan polysaccharides are non-ionic and, in combination with borates at acidic to neutral pH, are also essentially non-ionic. Thus, the polymer system is com-

pletely compatible with anionic, neutral and cationic drugs. Furthermore, the preservative efficacy of the preservatives are not compromised by the presence of the polymer. Typically, the efficacy of benzalkonium chloride or other cationic preservatives are compromised with anionic polymers such as gellan and carageenan, and excess preservative may therefore be needed in those systems. Increases in preservative concentration may also increase irritation and toxicity of the composition.

The galactomannan-borate gelling system of the present invention has other advantages. Galactomannan polymers have a relatively low molecular weight and are therefore easy to manufacture and scale up. Galactomannan polymers are also readily available and have been used in food and personal care products such that the polymers are considered to be safe. Furthermore, control or manipulation of the gelling characteristics of the galactomannan-borate gelling compositions of the present invention is relatively simple as compared with prior art systems. The gelling properties of other single polymer systems, such as ionomers, e.g., gellan and carageenans, and thermogels, e.g., poloxamines and poloxamers, are typically related to the molecular weight and the number of functional groups of the polymers. Thus, in order to change the gel point or degree of gelation of those prior art systems, one would need to modify the base polymer-a labor intensive activity. In contrast, by simply manipulating the borate to galactomannan ratio in the present invention compositions, a wide range of gelling characteristics is available in order to fine tune the compositions to the targeted requirements (see FIGS. 1 and 2). Moreover, as illustrated in FIG. 3, the galactomannans of the present invention (e.g., guar gum) demonstrate excellent gelling consistency and reproducibility, though the type or source of the galactomannan is varied.

Still other advantages are present in the compositions of the present invention. The galactomannan polymer and the borate crosslinker compositions of the present invention are liquids and, therefore, easy to dispense. Some gelling systems such as gellan gum, as disclosed in U.S. Pat. No. 4,861,760 (Mazuel et al.), are thixotropic, which may require shaking to increase the fluidity and ease of dispensing. The present invention compositions contain a relatively low concentration of galactomannan (about 0.2 to 0.5%) as compared to some thermogelling systems such as PEO/PPO block copolymers, which require very high concentrations. Lower concentrations of the gelling polymer provide lower potential toxicity and ease of preservation from microbial contamination over higher concentration systems.

The methods of the present invention involve the topical administration of the galactomannan-borate containing compositions of the present invention.

The present invention is also directed to methods of sterilization of the galactomannans involving autoclaving.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph illustrating the gelling characteristics of various concentrations of guar gum in the presence of borate, relative to pH.

FIG. 2 is a graph illustrating the gelling characteristics of various concentrations of borate in the presence of guar gum, relative to pH.

FIG. 3 is a graph illustrating the uniformity of the gelling characteristics of three different types/sources of guar gum.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to ophthalmic compositions which comprise one or more galactomannan polysaccharide(s) and one or more borate compound(s). The present invention is also directed to methods of using these compositions to treat various ophthalmic disorders including dry eye, glaucoma, ocular hypertension, infection, allergy and inflammation.

The types of galactomannans that may be used in the present invention are typically derived from guar gum, locust bean gum and tara gum. As used herein, the term "galactomannan" refers to polysaccharides derived from the above natural gums or similar natural or synthetic gums containing mannose or galactose moieties, or both groups, as the main structural components. Preferred galactomannans of the present invention are made up of linear chains of (1–4)-β-D-mannopyranosyl units with α-D-galactopyranosyl units attached by (1–6) linkages. With the preferred galactomannans, the ratio of D-galactose to D-mannose varies, but generally will be from about 1:2 to 1:4. Galactomannans having a D-galactose:D-mannose ratio of about 1:2 are most preferred. Additionally, other chemically modified variations of the polysaccharides are also included in the "galactomannan" definition. For example, hydroxyethyl, hydroxypropyl and carboxymethylhydroxypropyl substitutions may be made to the galactomannans of the present invention. Non-ionic variations to the galactomannans, such as those containing alkoxy and alkyl (C1–C6) groups are particularly preferred when a soft gel is desired (e.g., hydroxylpropyl substitutions). Substitutions in the non-cis hydroxyl positions are most preferred. An example of non-ionic substitution of a galactomannan of the present invention is hydroxypropyl guar, with a molar substitution of about 0.4. Anionic substitutions may also be made to the galactomannans. Anionic substitution is particularly preferred when strongly responsive gels are desired.

The borate compounds which may be used in the compositions of the present invention are boric acid and other pharmaceutically acceptable salts such as sodium borate (borax) and potassium borate. As used herein, the term "borate" refers to all pharmaceutically suitable forms of borates. Borates are common excipients in ophthalmic formulations due to good buffering capacity at physiological pH and well known safety and compatibility with a wide range of drugs and preservatives. Borates also have inherent bacteriostatic and fungistatic properties, and therefore aid in the preservation of the compositions.

The present invention compositions comprise one or more galactomannan(s) in the amount of from about 0.1 to 5% weight/volume ("w/v") and borate in the amount of from about 0.05 to 5% (w/v). Preferably, the compositions will contain 0.2 to 2.0% (w/v) of galactomannan and 0.1 to 2.0% (w/v) of a borate compound. Most preferably, the compositions will contain 0.3 to 0.8% (w/v) of galactomannan and 0.25 to 1.0% (w/v) of a borate compound. The particular amounts will vary, depending on the particular gelling properties desired. In general, the borate or galactomannan concentration may be manipulated in order to arrive at the appropriate viscosity of the composition upon gel activation (i.e., after administration). As shown in FIGS. 1 and 2, manipulating either the borate or galactomannan concentration provides stronger or weaker gelation at a given pH. If a strongly gelling composition is desired, then the borate or galactomannan concentration may be increased. If a weaker gelling composition is desired, such as a partially gelling composition, then the borate or galactomannan concentration may be reduced. Other factors may influence the gelling features of the compositions of the present invention, such as the nature and concentration of additional ingredients in

the compositions, such as salts, preservatives, chelating agents and so on. Generally, preferred non-gelled compositions of the present invention, i.e., compositions not yet gel-activated by the eye, will have a viscosity of from about 5 to 1000 cps. Generally, preferred gelled compositions of the present invention, i.e., compositions gel-activated by the eye, will have a viscosity of from about 50 to 50,000 cps.

The galactomannans of the present invention may be obtained from numerous sources. Such sources include guar gum, locust bean gum and tara gum, as further described below. Additionally, the galactomannans may also be obtained by classical synthetic routes or may be obtained by chemical modification of naturally occurring galactomannans.

Guar gum is the ground endosperm of *Cyamopisis tetragonolobus* (*L.*) *Taub*. The water soluble fraction (85%) is called "guaran" (molecular weight of 220,000), which consists of linear chains of (1–4)-β-D mannopyranosyl units with α-D-galactopyranosyl units attached by (1–6) linkages. The ratio of D-galactose to D-mannose in guaran is about 1:2. The gum has been cultivated in Asia for centuries and is primarily used in food and personal care products for its thickening property. It has five to eight times the thickening power of starch. Its derivatives, such as those containing hydroxypropyl or hydroxypropyltrimonium chloride substitutions, have been commercially available for over a decade. Guar gum may be obtained, for example, from Rhone-Polulenc (Cranbury, N.J.), Hercules, Inc. (Wilmington, Del.) and TIC Gum, Inc. (Belcamp, Md.).

Locust bean gum or carob bean gum is the refined endosperm of the seed of the carob tree, *ceratonia siliqua*. The ratio of galactose to mannose for this type of gum is about 1:4. Cultivation of the carob tree is old and well known in the art. This type of gum is commercially available and may be obtained from TIC Gum, Inc. (Bekamp, Md.) and Rhone-Polulenc (Cranbury, N.J.).

Tara gum is derived from the refined seed gum of the tara tree. The ratio of galactose to mannose is about 1:3. Tara gum is not produced in the United States commercially, but the gum may be obtained from various sources outside the United States.

In order to limit the extent of cross-linking to provide a softer gel characteristic, chemically modified galactomannans such as hydroxypropyl guar may be utilized. Modified galactomannans of various degree of substitution are commercially available from Rhone-Poulenc (Cranbury, N.J.). Hydroxypropyl guar with low molar substitution (e.g., less than 0.6) is particularly preferred.

Other ingredients may be added to the compositions of the present invention. Such ingredients generally include tonicity adjusting agents, chelating agents, active pharmaceutical agent(s), solubilizers, preservatives, pH adjusting agents and carriers. Other polymer or monomeric agents such as polyethylene glycol and glycerol may also be added for special processing. Tonicity agents useful in the compositions of the present invention may include salts such as sodium chloride, potassium chloride and calcium chloride; non-ionic tonicity agents may include propylene glycol and glycerol; chelating agents may include EDTA and its salts; solubilizing agents may include Cremophor EL® and tween 80; other carriers may include amberlite® IRP-69; pH adjusting agents may include hydrochloric acid, Tris, triethanolamine and sodium hydroxide; and suitable preservatives may include benzalkonium chloride, polyquaternium-1 and polyhexamethylene biguanide. The above listing of examples is given for illustrative purposes and is not intended to be exhaustive. Examples of other agents useful for the foregoing purposes are well known in ophthalmic formulation and are contemplated by the present invention.

Combination of the gelling system of the present invention with prior art gelling systems is also contemplated by the present invention. Such systems may include the inclusion of ionomers, such as xanthan, gellan, carageenan and carbomers, and thermogels, such as ethylhydroxyethyl cellulose.

In general, the compositions of the present invention will be used to administer various pharmaceutically active compounds to the eye. Such pharmaceuticals may include, but are not limited to, anti-hypertensive, anti-glaucoma, neuroprotective, anti-allergy, muco-secretagogue, angiostatic, anti-microbial, pain relieving and anti-inflammatory agents.

Examples of pharmaceutically active agents which may be included in the compositions of the present invention, and administered via the methods of the present invention include, but are not limited to: glaucoma agents, such as betaxolol, timolol, pilocarpine, carbonic anhydrase inhibitors and prostglandins; dopaminergic antagonists; post-surgical antihypertensive agents, such as para-amino clonidine (apraclonidine); anti-infectives, such as ciprofloxacin and tobramycin; non-steroidal and steroidal anti-inflammatories, such as naproxen, diclofenac, suprofen, ketorolac, tetrahydrocortisol and dexamethasone; proteins; growth factors, such as epidermal growth factor; and anti-allergics.

Optionally, the compositions of the present invention may be formulated without a pharmaceutically active compound. Such compositions may be used to lubricate the eye or provide artificial tear solutions to treat, for example, dry eye. In general, artificial tear solutions will contain tonicity agents, polymers and preservatives, as described above. The amount of galactomannan and borate contained in the artificial tear solutions will vary, as described above, but will generally be in the amount of from 0.1 to 3.0% (w/v) and 0.1 to 2.0% (w/v), respectively.

In general, the compositions of the present invention are formulated in two parts. The galactomannan polymer is hydrated and sterilized (Part I). Any pharmaceutical agent(s) and/or other ingredients to be included in the composition are then dissolved in water and sterile filtered (Part II). Parts I and II are then combined and the pH of the resultant mixture is adjusted to the target level, generally 6.0 to 7.0. If the pharmaceutical agent(s) to be included have low water solubility, they will generally be added last. In certain cases, it may be preferred to sterilize the pharmaceutical agent(s) separately, and then aspetically add the agent(s) and other ingredients together.

Sterilization of the galactomannan polysaccharide can be accomplished by autoclaving. Since the polymers undergo depolymerization at the extreme conditions of autoclaving, non-aqueous autoclaving is generally preferred. This can be accomplished by dispersing the polymer in a suitable organic liquid such as low molecular weight polyethylene glycols. The resulting suspension may then be autoclaved to sterilize the polymer. The sterilized polymer is then hydrated aseptically, prior to admixture with the other ingredients.

The following example illustrates a novel method of sterilizing a galactomannan polysaccharide of the present invention:

EXAMPLE 1

Preliminarily, a compounding vessel (20 L stainless steel pressure can), a 0.2 micron sterilizing filter, a receiving

vessel (20 L carboy), a 4.5 micron polishing filter, a 0.2 micron sterilizing filter, a vent filter, and the filling equipment are sterilized by autoclaving.

In a beaker equipped with an overhead agitator, add the weighed amount of polyethylene glycol 400 (200 g). While mixing slowly disperse the weighed amount of hydroxypropyl ("HP") Guar gum (100 g). Mix until completely homogeneous. In a 500 ml Schott bottle, equipped with a magnetic stir bar, weigh exactly 120.0 g of the HPGuar gum/PEG-400 dispersion. Prepare to sterilize by autoclaving. In a second identical 500 ml Schott bottle weigh exactly 120.0 g of the same dispersion. Prepare to use as a dummy during the autoclaving cycle. To both bottles add 1.3 ml of purified water (amount equivalent, by volume, of the microorganism suspension used to inoculate the bottles during the validation study). Mix both bottles for 10 minutes using a magnetic stir plate. Autoclave the HPGuar gum/PEG-400 dispersion using the validated time-temperature cycle of 80 minutes at 125° C.

The other set of ingredients to be included in the final formulation may be prepared separately by various methods known in the art. The resultant mixture can be added by sterile filtration to the compounding vessel, along with the HPGuar gum/PEG-400 preparation.

Aseptically transfer the sterilized HPGuar gum/PEG-400 dispersion into the pre-sterilized compounding vessel. Rinse the bottle content with sterilized purified water. Bring the content of the compounding vessel to exactly 95% of the theoretical batch weight (19.0 liters or 19.06 Kg) using sterile room temperature purified water. Allow the HPGuar gum/PEG slurry to hydrate while mixing, at moderate speed, in the compounding vessel for a minimum of 2 hours. Transfer the contents of the compounding vessel through a 4.5 micron pre-sterilized polishing filter into the pre-sterilized receiving vessel equipped with a stir bar. There will be some loss of the contents due to the product held in filter housing and filter cartridge. (If a pressure can is used as compounding vessel, the recommended pressure for clarification filtration is approximately 30 psi.) Check and adjust pH, if necessary, to 6.9–7.1 (target 7.0) using 1N NaOH or 1N HCl. Approximately 3–4 ml of 1N NaOH per 1 liter of final batch weight is needed to achieve the desired pH. QS to final batch weight using sterile purified water. Mix at low speed for a minimum of 30 minutes.

The following examples further illustrate preferred ophthalmic compositions of the present invention:

EXAMPLE 2

The following is an example of a topical ophthalmic composition containing timolol.

Compound	Amount % (w/v)
Timolol Maleate	0.68*
Boric Acid	0.5
Guar Gum	0.5
PEG-400	1.0
Sodium Chloride	0.5
Benzalkonium Chloride	0.01
Sodium Hydroxide/Hydrochloric Acid	QS to pH 6.5
Purified Water	QS

*0.68% Timolol Maleate is equivalent to 0.5% Timolol.

The above formulation is prepared by first preparing a Part I and Part II mixture. The guar gum is first dispersed in PEG-400 and autoclaved as Part I. The other ingredients are dissolved in about 90% of the volume of water and sterile filtered in a receiving vessel as Part II. Part I is then added to Part II aseptically. The pH may then be adjusted aseptically and the batch is then brought to final weight (volume). The combined solution is then passed through a 1.0 μm polish filter, aseptically, to remove the particulates.

EXAMPLE 3

The following is another example of a topical ophthalmic composition containing timolol.

Compound	Amount % (w/v)
Timolol Maleate	0.34*
Boric Acid	0.5
Guar Gum	0.25
Glycerol	1.0
Benzalkonium Chloride	0.005
Sodium Hydroxide/Hydrochloric Acid	QS to pH 7.0
Purified Water	QS

*0.34% Timolol Maleate is equivalent to 0.25% Timolol.

The above composition may be prepared in a similar way as the Example 2 composition.

EXAMPLE 4

The following is an example of an artificial tear solution.

Compound	Amount % (w/v)
Boric Acid	0.5
Hydroxpropyl Guar	0.3
Propylene glycol	1.4
Polyquaternium-1	0.0005
Sodium Hydroxide/Hydrochloric Acid	QS to pH 6.8
Purified Water	QS

The above composition may be prepared in a similar way as the Example 2 composition.

The invention in its broader aspects is not limited to the specific details shown and described above. Departures may be made from such details within the scope of the accompanying claims without departing from the principles of the invention and without sacrificing its advantages.

What is claimed is:

1. An ocular lubricant composition, comprising:

0.1 to 5% (w/v) of one or more borate compounds selected from the group consisting of boric acid and pharmaceutically acceptable salts thereof;

0.05 to 5% (w/v) of one or more galactomannan polysaccharides having linear chains of (1–4)-β-D-mannopyranosyl units with α-D-galactopyranosyl units attached by (1–6) linkages; and

water;

wherein the composition does not contain a pharmaceutically active agent.

2. An ocular lubricant composition according to claim 1, wherein the ratio of D-galactose to D-mannose in the galactomannan polysaccharide is from 1:2 to 1:4.

3. An ocular lubricant composition according to claim 2, wherein the ratio of D-galactose to D-mannose is 1:2.

4. An ocular lubricant composition according to claim **1**, wherein the concentration of the one or more galactomannan polysaccharides is 0.1 to 3.0% (w/v), and the concentration of the one or more borate compounds is 0.1 to 2.0% (w/v).

5. An ocular lubricant composition according to any one of claims **1–4**, wherein the composition is a solution having a slightly acidic to neutral pH.

6. An ocular lubricant composition according to any one of claims **1–4**, wherein the composition is a solution having a pH of 6 to 7.

7. A method of lubricating or moisturizing an eye, which comprises topically applying to the eye an effective amount of an ocular lubricant composition according to any one of claims **1–4**.

8. A method according to claim **7**, wherein the composition is a solution and has a slightly acidic to neutral pH.

9. A method according to claim **7**, wherein the composition is a solution and has a pH of 6 to 7.

* * * * *