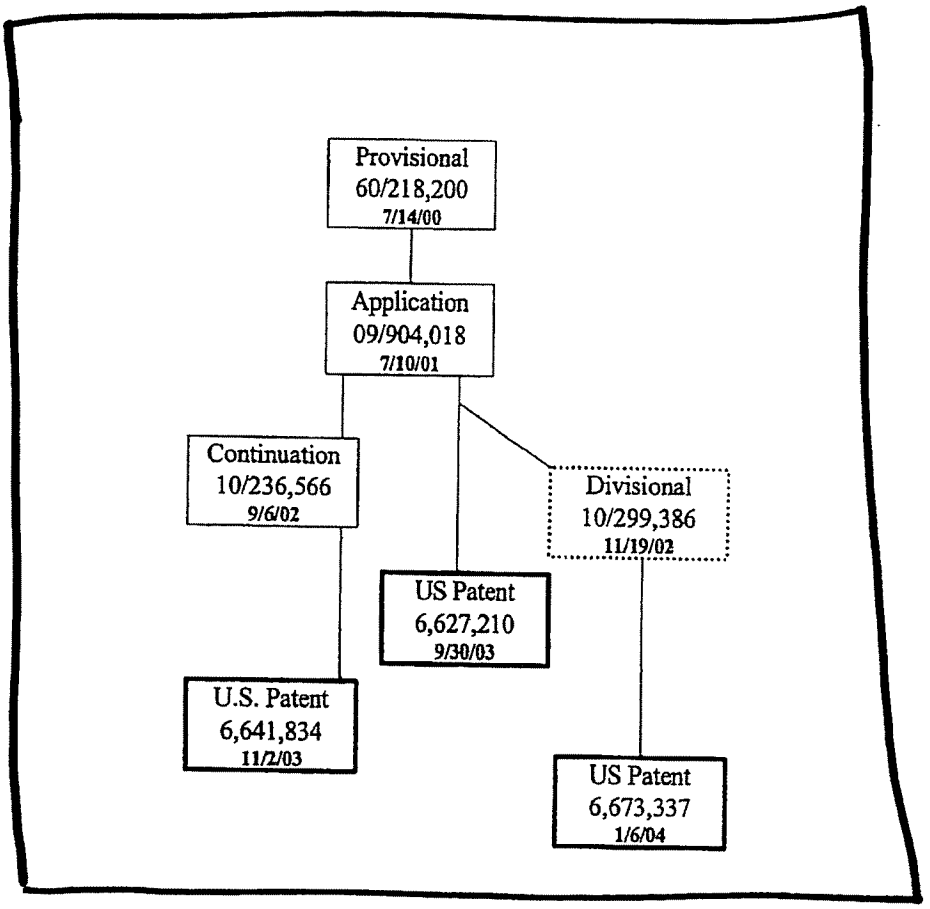

Allergan claims a July 14, 2000 priority date for the '337 patent based on the provisional application that preceded the Parent Application. Although the '210 patent is not asserted here, its prosecution history is particularly relevant to interpreting the scope of the claims of the '337 patent. See Microsoft Corp v. Multi-Tech Sys., Inc., 357 F.3d 1340, 1350 (Fed. Cir. 2004).

a. **The Prosecution History Of The '210 Patent**

The '210 patent issued on September 30, 2003 directly from the Parent Application, which was filed on July 10, 2001.[8] In the first Office Action during its prosecution, the Examiner concluded that the original 46 claims covered four separate and distinct inventions and entered a restriction requirement that compelled the applicants to pursue prosecution of each

[8] The prosecution history ("PH") of the '210 patent is attached as Exhibit D ("Ex. D").

WHAT IS CLAIMED IS:

Sub A1

1. A composition comprising:

an alpha-2-adrenergic agonist component in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered;

a solubility enhancing component in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component in the composition relative to the solubility of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component; and

a liquid carrier component.

2. The composition of claim 1 wherein the alpha-2-adrenergic agonist component is selected from the group consisting of imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, derivatives thereof and mixtures thereof.

3. The composition of claim 1 wherein the therapeutically active component includes a quinoxaline component.

4. The composition of claim 3 wherein the quinoxaline component is selected from the group consisting of quinoxaline, derivatives thereof, and mixtures thereof.

5. The composition of claim 3 wherein the quinoxaline component is selected from the group consisting of quinoxaline, (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and tartrate of 5-bromo-6-(2-imidozolin-2-

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1-30, drawn to composition, classified in class 424, subclass 455.

   II. Claims 31-33, drawn to complex, classified in class 514, subclass 249.

   III. Claims 34-39, drawn to oligmer comprising monomer units, classified in class 514, subclass 1.

   IV. Claims 40-46, drawn to a composition comprising oxychloro, classified in class 424, subclass 400.

The inventions are distinct, each from the other because of the following reasons:

The inventions of Group I and Groups II & III are independent and distinct because the complex and oligomer of Groups II & III do not require a solubility enhancing component or an aqueous liquid carrier component as required by Group I.

The inventions of Group I and Group IV are independent and distinct because the composition of Group I does not require the preserving agent as required by Group IV.

The inventions of Group II and III are independent and distinct because the complex of Group II is not a dimmer as required by the oligomer of Group III.

The inventions of Group IV and Groups II & III are independent and distinct because the complex and oligmer of Groups II & III do not require an oxy-chloro component and a liquid carrier as required by the composition of Group IV.

comprising 5-bromo-6-(2-imidozolin-2-ylamino) quinozaline tartate and 5-bromo-6-(2-imidozolin-2-ylamino) quinozaline in an ophthalmically acceptable formulation while Application 10/236566 claims a composition comprising a tartate of 5-bromo-6-(2-imidozolin-2-ylamino) quinozaline in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered and an aqueous liquid carrier component.

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

Specification

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1,7-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 7-8 are indefinite because Applicants do not clearly define "substantially unionized". Clarification is request.

Claim Rejections - 35 USC § 103

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

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

6. Claims 1-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burke (US 5215991) and in further view of Remington's Pharmaceutical Sciences.

Burke discloses pharmaceutical compositions of alpha 2 agonists and Na+/H+ exchange inhibitors which are useful in lowering intraocular pressure (IOP) and treatment of intraocular hypertension (see abstract). Preferred imidazoline-derived alpha 2 agonists or pharmaceutically acceptable salts thereof are disclosed in col. 3 (see formula). The most preferred imidazoline-derived alpha 2 agonist compounds include 5-bromo-6-(2-imidazolidine-2-ylamino) quinoaxaline. Doses of alpha 2 agonist in an ophthalmic preparation effective, non-toxic amount of the agonist in a pharmaceutically acceptable liquid, gel, cream or aqueous or nonaqueous liquid suspension or solution are preferably from about 0.001% to about 1.0% weight/volume. Regardless of the preferred range stated herein, one can determine the most efficacious dose for a particular alpha 2 agonist by carrying out a dose response curve as is well known in the art (see col. 4 lines 34-44). Various buffers and means for adjusting pH may be used as long as the resulting preparation is ophthalmically acceptable. Burke does not disclose the solubility enhancing agent to be carboxymethylcellulose or the pH of the composition.

Remington discloses carboxymethylcellulose sodium as a known pharmaceutic aid for use as a suspending agent or viscosity-increasing agent (see page 1305).

Absent unexpected results, it is the position of the examiner it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the composition of Burke by adding carboxymethylcellulose in order to achieve the desired viscosity as taught by Remington. Burke teaches topical ophthalmic preparations, for example ocular drops, gels or creams, are preferred because of ease of application, ease of dose delivery and fewer systemic side effects. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add a suitable amount of

US005215991A

United States Patent [19]

Burke

[11] Patent Number: 5,215,991

[45] Date of Patent: Jun. 1, 1993

[54] COMBINATION OF SELECTIVE ALPHA-ADRENERGIC AGONISTS AND NA+/H+ EXCHANGE INHIBITORS USEFUL IN LOWERING INTRAOCULAR PRESSURE

[75] Inventor: James A. Burke, Tustin, Calif.

[73] Assignee: Allergan, Inc., Irvine, Calif.

[21] Appl. No.: 633,103

[22] Filed: Dec. 20, 1990

Related U.S. Application Data

[63] Continuation of Ser. No. 470,848, Jan. 26, 1990, abandoned.

[51] Int. Cl.[5] A61K 31/495; A61K 31/415

[52] U.S. Cl. 514/255; 514/392; 514/913

[58] Field of Search 514/255, 913, 392

[56] References Cited

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3,890,319	6/1975	Danielewicz et al.	424/250
4,400,378	8/1983	Immemee et al.	424/244
4,515,800	5/1985	Cavero et al.	514/392

FOREIGN PATENT DOCUMENTS

2127167 12/1972 Fed. Rep. of Germany .

OTHER PUBLICATIONS

Rouot et al., *J. Med. Chemistry* 19(8), 1049 (1976).
Simchowitz and Cragoe, *Molecular Pharmacology* 30, 112 (1986).
Chem. Abst. 109: 32089w (1988).
Chem. Abst. 103: 68755a (1985).

Primary Examiner—Frederick E. Waddell
Assistant Examiner—Zohreh A. Fay

[57] ABSTRACT

Methods and pharmaceutical compositions of alpha$_2$ agonists and Na+/H+ exchange inhibitors which are useful in lowering intraocular pressure (IOP) and treatment of intraocular hypertension are disclosed. Co-administration of a therapeutic amount of alpha$_2$ agonist with a potentiating amount of Na+/H+ exchange inhibitor is effective in lowering IOP and treatment of intraocular hypertension.

12 Claims, 7 Drawing Sheets

dose ranges may be prepared. However, it is preferred to make ophthalmic preparations having both an alpha$_2$ agonist and a Na^+/H^+ exchange inhibitor for the convenience of the patient.

Topical ophthalmic preparations, for example ocular drops, gels or creams, are preferred because of ease of application, ease of dose delivery, and fewer systemic side effects, such as hypotension. An exemplary topical ophthalmic formulation is shown below in Table I. The abbreviation q.s. means a quality sufficient to effect the result or make volume.

TABLE I

Ingredient	Amount (% w/v)
alpha$_2$ agonist	about 0.00001 to about 1.0
Na^+/H^+ exchange inhibitor	about 0.01 to about 2.0
Preservative	0-0.10
Vehicle	0-40
Tonicity Adjustor	1-10
Buffer	0.01-10
pH Adjustor	q.s. pH 4.5-7.5
Antioxidant	as needed
Purified Water	as needed to make 100%

Various preservatives may be used in the ophthalmic preparation described in Table I, above. Preferred preservatives include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, and phenylmercuric nitrate. Likewise, various preferred vehicles may be used in the ophthalmic preparation of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose, and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol, and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include, but are not limited to, acetate buffers, citrate buffers, phosphate buffers, and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

An ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole, and butylated hydroxytoluene.

Other excipient components which may be included in the exemplary ophthalmic preparation described in Table I are chelating agents which may be added as needed. The preferred chelating agent is edetate disodium, although other chelating agents may also be used in place of or in conjunction with it.

A useful formulation for an ophthalmic preparation comprising the present invention is shown below in Table II.

TABLE II

Ingredient	Amount (% w/v)
alpha$_2$ agonist	about 0.0001
Na^+/H^+ exchange inhibitor	about 0.01 to about 2.0
Benzalkonium Chloride	0-0.10
Polyvinyl Alcohol (Grade 20-90)	0-40
Sodium Chloride	1-10
Sodium Citrate, Dihydrate	0.01-10
Citric Acid, Monohydrate	0.01-2
Purified Water	q.s. to make 100%

EXPERIMENTAL

Ocular co-administration of an alpha$_2$ agonist and a Na^+/H^+ exchange inhibitor to effect lowering of IOP was experimentally tested in the New Zealand White rabbit. In the experimental model, co-administrating an alpha$_2$ agonist and a Na^+/H^+ exchange inhibitor demonstrated significant potentiation of the ocular hypotensive effect of the alpha$_2$ agonist.

The effect of co-administrating of alpha$_2$ agonists and a Na^+/H^+ exchange inhibitor on lowering IOP was testing in New Zealand White rabbits with normotensive IOP and weighing 3–4 kg. Topical anesthesia was produced by instillation of about 5 µl of 0.05%.

Separate solution of various alpha$_2$ agonists and a Na^+/H^+ exchange inhibitor were prepared by dissolving the specified quantity of agonists or the Na^+/H^+ exchange inhibitor in distilled water to obtain the concentrations shown below in Table III. The pH of the final solutions ranged from about 4 to about 7.5 as indicated by the characteristics of the individual drugs.

TABLE III

	Concentration (% w/v)
Alpha Agonist	
Clonidine	0.1
p-aminoclonidine	0.1
5-bromo-6-(2-imidazolidine-2-ylamino)quinoxaline	0.1; 0.01; 0.001
Na^+/H^+ exchange inhibitor 5(N-ethyl-N-isopropyl) amiloride	0.1; 0.3; 1

The animals were divided into 2 groups. One group was treated with the Na^+/H^+ exchange inhibitor followed by an alpha$_2$ agonist and the other group received vehicle followed by the alpha$_2$ agonist. Intraocular pressure (IOP) was measured in both eyes for each animal using a calibrated DIGILAB® pneumatonograph. Immediately following the baseline reading for each animal, 50 µl of the Na^+/H^+ exchange inhibitor solution or vehicle was instilled into the lower conjunctival sac of the test eye of the animal, with the contralateral eye receiving 50 µl of saline in the lower conjunctival sac as a control. Thirty minutes after application of the Na^+/H^+ exchange inhibitor or vehicle, IOP was again measured for the eye. Immediately following these measurements, 50 µl of one of the alpha$_2$ agonists solution given in Table III was administered to the test eye in the same manner described above. Thereafter, IOP measurements for each eye of each animal were made at 30 minutes after administration of the alpha$_2$ agonist, then hourly for 6 hours. In separate experiments, the IOP response to the Na^+/H^+ exchange inhibitor alone was determined.

The experimental results are illustrated in FIGS. 1–4. Administration of three concentrations (0.1, 0.3, 1%) of the Na^+/H^+ exchange inhibitor did not significantly alter IOP (FIG. 1). Pretreatment with the Na^+/H^+ exchange inhibitor (1%) augmented the ocular hypotensive response to 5-bromo-6-(2-imidazolidine-2-ylamino) quinoxaline (FIG. 2A, B, C), clonidine (FIG.

Interview Summary	Application No. 09/904,018	Applicant(s) OLEJNIK ET AL.	
	Examiner Rachel M. Bennett	Art Unit 1615	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Rachel M. Bennett*. (3)_____.

(2) *Carlos A. Fisher*. (4)_____.

Date of Interview: *25 February 2003*.

Type: a)☒ Telephonic b)☐ Video Conference
c)☐ Personal [copy given to: 1)☐ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: _____.

Claim(s) discussed: *all pending claims*.

Identification of prior art discussed: *Burke (US 5215991)*.

Agreement with respect to the claims f)☒ somewhat was reached. g)☐ was not reached. h)☐ N/A.

Substance of interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *The attorney explained the instant invention was an invention of selection. The attorney agreed to file a declaration showing unexpected results with regards to the anionic solubility enhancing agent. The attorney also indicated support for "substantially unionized" is found on pages 1-2 of the specification. It was agreed upon that a terminal disclaimer would be filed when allowable subject matter was indicated in the instant application.*

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

i)☒ It is not necessary for applicant to provide a separate record of the substance of the interview(if box is checked).

Unless the paragraph above has been checked, THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

Rachel Bennett
Examiner's signature, if required

Examiner Note: You must sign this form unless it is an Attachment to a signed Office action.

U.S. Patent and Trademark Office
PTO-413 (Rev. 03-98) Interview Summary Paper No. 8.

Secondly, the specification at e.g., page 11 lines 13-21 makes clear that in a preferred embodiment of disclosed invention the alpha 2 adrenergic agonist (such as brimonidine (5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline), as now claimed) is substantially unionized (i.e., formulated at a pH approaching or at its pK_a) to facilitate permeation of the compound across membrane lipid bilayers, such as, for example, the cell membranes of corneal cells. In this context, the word "substantially" would be understood by the person of skill in the art to refer to the fact that the alpha agonist is present in the claimed composition as a population of molecules; when substantially unionized at a given pH the majority of the molecules will be electronically neutral, but perhaps not every molecule will be uncharged.

Foe this reason Applicants believe that the term "substantially unionized" is not indefinite, and request reconsideration of the rejection.

35 USC §103

The Examiner has rejected claims 1-30 over Burke (US 5,215,991) in view of Remington Pharmaceutical Sciences. The Examiner has stated that Burke discloses brimonidine in various formulations; including an aqueous formulation; at column 5 it also discloses "vehicles" which could be used in such a formulation; these include polyvinyl alcohol, povidone (polyvinylpyrrolidone), hydroxypropylcellulose, poloxamers, carboxymethylcellulose, hydroxyethylcellulose. Remington is said to teach the desirability of increasing viscosity. Applicants respectfully traverse this rejection for the following reasons.

The current claims are directed to compositions comprising brimonidine and salts and esters thereof in combination with an anionic polymeric solubility enhancing component. The specification (at page 12, lines 13-19) discloses that in preferred embodiments of the invention, the solubility enhancing components are sufficiently anionic to interact with and solubilize the brimonidine.

Of the "vehicles" specifically disclosed by the Burke patent, all will function to increase viscosity of a liquid aqueous composition. However, of these vehicles only carboxymethylcellulose (CMC) is an anionic polymer. All of the other polymers are non-ionic. They may act to increase the solution's viscosity, but they do not have the same characteristics as an anionic polymer such as CMC.

Attached to this communication is a Declaration of Orest Olejnik, Ph.D., Principal Scientist, Pharmaceutical Sciences Department, Allergan Inc. Dr. Graham states in this declaration that anionic solubility enhancing components such as CMC have surprising and beneficial properties in the solubilization of brimonidine as compared to non-ionic or cationic polymers. In particular, the use of an anionic polymer solubility enhancing

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component such as CMC (as compared to, for example, hydroxypropyl methyl cellulose) has the advantage of adsorbing to cellular surfaces, such as the cornea of the eye, in a manner that retains any drug in solution with the CMC to be retained at the ocular surface far longer (and in a larger volume) than viscous formulations made with other, non-anionic polymers, while simultaneously increasing solubility.

In light of Dr. Olejnik's Declaration, the patent specification and the state of the art, the Applicants therefore submit that, alone or in combination with Remington, Burke contains no disclosure that would direct or motivate the person of ordinary skill in the art to select or want to select an anionic polymeric solubility enhancing component such as CMC from the list of optional viscous "vehicles" contained in the '991 patent.

Only the present patent application provides the necessary direction; and to pick and choose elements from lists within the prior art to "create" a claimed invention based in whole or in part on the patent application within which it is first disclosed is clearly impermissible hindsight reconstruction of the invention. Yet, the Applicants respectfully believe that this must be the conclusion of the current rejection.

For these reasons, the Applicants respectfully request reconsideration and withdrawal of the pending rejection.

Date: 8/11/03 By: _____

Carlos A. Fisher
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ALLERGAN SALES, INC.

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O I P E JC54
MAR 17 2003
PATENT & TRADEMARK OFFICE

DOCKET NO. 17361 (AP)
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Olejnik, et al.

Serial No: 09/904,018

Filed: July 10, 2001

For: COMPOSITIONS CONTAINING ALPHA-2-ADRNERGIC AGONIST COMPONENTS

Group Art Unit: 1626

Examiner: Bennett, R.

RECEIVED
MAR 24 2003
TECH CENTER 1600/2900

DECLARATION OF OREST OLEJNIK, Ph.D.

Dear Sir,

I, Orest Olejnik, Ph.D., hereby declare as follows:

1. I received a B.Sc. degree in Pharmacy, with honors, from the Sunderland School of Pharmacy, England in 1977. In 1981 I was awarded a Ph.D. in Pharmaceutics by the University of Nottingham, Nottingham, England.

2. I have worked in the pharmaceutical development field as a pharmacist and in various managerial capacities since 1977. From 1991-1999 I was Director of Pharmaceutical Development at Allergan, Inc., in Irvine, California. I presently hold the position of Vice President of Pharmaceutical Sciences at Allergan.

3. I am a co-inventor of the present patent application 09/904,018, entitled "Compositions Containing Alpha-2-Adrenergic Agonist Components". I understand that the formerly pending claims were rejected under 35 USC 103 as obvious over US Patent 5,215,991 (the "Burke" patent) in view of Remington's Pharmaceutical Sciences, cited in the Form PTO-892 as part of Paper No. 7. I have reviewed each of these references.

4. The Burke patent references the presently claimed alpha-2-agonist 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline ("brimonidine"). The Burke patent discloses a multitude of different ingredients that may be contained in formulations containing brimonidine; among these are mentioned optional "vehicles" which may include, without limitation, polyvinyl alcohol, povidone (polyvinylpyrrolidone), hydroxypropylcellulose, poloxamers, carboxymethylcellulose (CMC), and

hydroxyethylcellulose. See Burke, column 5, line 28-34. Burke is silent concerning the purpose of these prospective vehicles.

5. Remington discloses that these listed polymers, including CMC, may be used as viscosity increasing agents.

6. Neither Burke nor Remington discloses that CMC would have any characteristics that would motivate a person of ordinary skill in the art to choose it over other polymers in formulating a brimonidine solution.

7. Unlike the other listed polymers (polyvinyl alcohol, povidone (polyvinylpyrrolidone), hydroxypropylcellulose, poloxamers, and hydroxyethylcellulose), CMC is anionic at pH 7 or greater. The other listed polymers are non-ionic polymers. I have discovered as a result of work done and/or directed by me at Allergan that CMC possesses the surprising advantages of both increasing the solubility of brimonidine in solution, as shown in Table 1, and causing such solutions to have superior adherence to cell surfaces, including ocular surfaces such as the cornea. Polyvinyl alcohol was found not to possess both of these properties. Increased adherence of the CMC solution is particularly surprising given the fact that the corneal surface is negatively charged; one would expect less adherence in such a solution due to electrostatic repulsion, rather than increased adherence. This surprising result may be due to repulsive forces between the polymer and the cornea orienting the hydrophilic portions of the molecule away from the cornea, thus permitting the hydrophobic domains of these polymers to form an interaction with the lipid portion of the cell surface. With such increased adherence, the active ingredient in solution is placed in contact with the cell surface longer than would otherwise be the case.

8. It is also my belief that brimonidine solutions made using the other "vehicles" mentioned in the Burke patent would not possess this surprising combination of advantages. Therefore, the disclosures of Burke and Remington's in no way would render the presently claimed compositions obvious to the worker of ordinary (or even extraordinary) skill in the art.

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

Sincerely yours,

Orest Olejnik, Ph.D.

10299386.111902

D-2892DIV

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT

2

In re application of:
OLEJNIK ET AL

Serial No. N/A

Dated: Submitted herewith

For: COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

Group Art Unit: N/A
(Prior: 1615)

Examiner: N/A
(Prior: Bennett, R.)

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, DC 20231

Sir:

Please amend the above-identified application as follows:

IN THE SPECIFICATION:

On page 1, before the first sentence, add the following paragraph:

A1

--This application is a division of application Serial No. 09/904,018, filed July 10, 2001, which application claims the benefit of U.S. Provisional Application Serial No. 60/218,200 filed July 14, 2000, the disclosure of each of these applications is hereby incorporated herein in its entirety by reference.--

IN THE CLAIMS:

Cancel claims 1 to 39, without prejudice.

Add new claims 40 to 46 as follows.

B1
A2

40. (New Claim) A composition comprising:
an alpha-2-adrenergic agonist component in an amount effective to provide a therapeutic benefit to a patient to whom the

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a composition is administered;

an oxy-chloro component in an effective amount to at least aid in preserving the composition; and

a liquid carrier component,

wherein the composition is substantially free of cyclodextrins.

41. (New claim) The composition of claim 40 wherein the alpha-2-adrenergic agonist component is selected from the group consisting of imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, derivatives thereof and mixtures thereof.

A2 cont.

42. (New claim) The composition of claim 40 wherein the therapeutically active component includes a quinoxaline component.

43. (New claim) The composition of claim 42 wherein the quinoxaline component is selected from the group consisting of quinoxaline, derivatives thereof, and mixtures thereof.

44. (New claim) The composition of claim 40 which further includes a solubility enhancing component in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component in the composition relative to the solubility of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component.

45. (New claim) The composition of claim 44 wherein the solubility enhancing component is effective to increase the solubility in a biological environment of the alpha-2-adrenergic agonist component relative to the solubility in a biological environment of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component.

patentably distinct from each other because both applications claim an alpha –2-adrenergic agonist with an oxy-cholo component.

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

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 40-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants do not clearly define "substantially free of cyclodextrins" in the claims or the specification. Clarification is requested.

Claim Rejections - 35 USC § 103

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

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

7. Claims 40-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burke (US 5215991) in further view of Beck et al. (US .6358935).

Burke discloses pharmaceutical compositions of alpha 2 agonists and Na+/H+ exchange inhibitors which are useful in lowering intraocular pressure (IOP) and treatment of intraocular hypertension (see abstract). Preferred imidazoline-derived alpha-2 agonists or pharmaceutically acceptable salts thereof are disclosed in col. 3 (see formula). The most preferred imidazoline-

derived alpha 2-agonist compounds include 5-bromo-6-(2-imidazalidine-2-ylamino)quinoxaline. Doses of alpha 2-agonist in an ophthalmic preparation effective, non-toxic amount of the agonist in a pharmaceutically acceptable liquid, gel, cream or aqueous or nonaqueous liquid suspension or solution are preferably from about 0.001% to about 1.0% weight/volume. Regardless of the preferred range stated herein, one can determine the most efficacious dose for a particular alpha-2-agonist by carrying out a dose response curve as is well known in the art (see col. 4 lines 34-44). Various buffers and means for adjusting pH may be used as long as the resulting preparation is ophthalmically acceptable. Benzalkonium chorlide may be used as a preservative. Vehicles include carboxy methyl cellulose. Burke does not disclose the preservative to be a chlorite component.

Beck discloses compositions including a liquid medium, a cylodextrin component and a preservative component which has a reduced tendency of being complexed with the cyclodextrin component. The clycodextrin component can be in an amount as little as 0.1%. In one embodiment, the preservative component is a chlorite component. Active compounds, such as pharmaceutically active components or drugs, preferably are included in the compositions (see abstracts). For example, the present compositions may include a pharmaceutically effective in providing a therapeutic effect when administered to the eyes of a human or animal. The preservative employed is preferably ophthalmically acceptable at the concentration employed so that the human or animal is effectively treated without significant harm caused by the presence of the preservative (see col. 1). Preferably, the preservative component has in increased or greater preservative efficacy in the composition relative to an identical amount (w/v) of benzalkonium chloride.

The claims have now been amended to set forth the invention in a preferred embodiment thereof. Thus, as now claimed, the invention comprises a therapeutically effective ophthalmic composition containing an alpha -2- adrenergic receptor agonist and a solubility enhancing component.

The Examiner points out that Burke discloses compositions comprising a combination of alpha 2 agonists and Na+/H+ exchanges inhibitors for the treatment of high IOP. These combinations may be in liquid form, either suspensions or solutions. Burke discloses that the combinations claimed may optionally be formulated using various vehicles, including carboxymethyl cellulose, various tonicity agents, and various preservatives, including benzalkonium chloride.

The Examiner also cites Beck for the proposition that an oxychoro component may be used in an ophthalmic formulation. Applicants have amended the claims to remove the necessity for a preservative, this reference is no longer thought to be applicable.

Applicants respectfully maintain that for all its discussion of possible formulations, nothing in Burke discloses or suggests the use of a solubility enhancing component in combination with an alpha adrenergic agonist. The present application, which also discloses the advantages of using such a component (such as greater flexilibity with the concentration and pH at which such composition is formlated, is, to the Applicants' knowledge, the first reference to do so.

For these reasons, the Applicants respectfully request reconsideration and withdrawal of the pending rejections.

If there is a fee, please charge deposit account 01-0885.

Date: 12/13/03 By: Carlos A. Fisher

Carlos A. Fisher
Reg. No. 36,510
ALLERGAN SALES, INC.

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Telephone: 714/246-4920
Fax: 714/246-4249

dihydrate, and magnesium chloride hexahydrate were USP grade. Boric acid and sodium borate decahydrate were NF grade.

TABLE III

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	
Brimonidine tartrate	0.2%	0.2%	0.2%	0.2%	0.2%	(w/v)
CMC	0.0%	0.056%	0.17%	0.5%	1.5%	(w/v)
Stabilized chlorine dioxide*	0.005%	0.005%	0.005%	0.005%	0.005%	(w/v)
Sodium chloride	0.58%	0.58%	0.58%	0.58%	0.58%	(w/v)
Potassium chloride	0.14%	0.14%	0.14%	0.14%	0.14%	(w/v)
Calcium chloride, dihydrate	0.02%	0.02%	0.02%	0.02%	0.02%	(w/v)
magnesium chloride, hexahydrate	0.006%	0.006%	0.006%	0.006%	0.006%	(w/v)
boric acid	0.2%	0.2%	0.2%	0.2%	0.2%	(w/v)
sodium tetraborate, decahydrate	0.14%	0.14%	0.14%	0.14%	0.14%	(w/v)

*Sold under the trademark Purite ™ by Allergan, Inc.

Each sample (1 through 5) was subjected to a range of pH's from about 7 to about 10. The vials containing the sample solutions were placed on a laboratory rotator and left for equilibration for fifteen days at room temperature (~21° C.). The sample solutions were filtered using a 25 mm diameter polysulfone cellulose acetate syringe type filter with 0.45 μm pore size. The filtered solutions were assayed for Brimonidine.

Conventional HPLC and detection techniques were used to detect and determine the concentrations of soluble Brimonidine tartrate. Table IV. The solubility is plotted against pH for each CMC concentration. The experimental data points were fitted to a modified Henderson-Hasselbalch equation using a nonlinear least squares routine (Deltagraph version 4.0 DeltaPoint, Inc.), FIG. 1. The R^2 values show the goodness of fit between the experimental values and the theoretical equation to be better than 0.991.

TABLE IV

	Solubility of Brimonidine tartrate (%)				
	0% CMC	0.056% CMC	0.17% CMC	0.5% CMC	1.5% CMC
pH					
6.67		0.9302		1.4464	
6.68	1.4256		1.4200		
6.93			0.7302		
7.10				0.3693	
7.11	0.2064	0.2828			
7.35					0.1904
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8.50	0.0286				
8.55			0.0328		
8.67					0.0311
9.93		0.0234			
9.94				0.0250	
10.05			0.0241		
10.09	0.0218				
10.11					0.0222

FIG. 1 clearly shows that the solubility of Brimonidine tartrate tends to increase with increasing CMC concentrations. For example, at pH 7.5, the sample with 0% CMC resulted in 1000 ppm of Brimonidine tartrate; 0.0560% CMC, 1300 ppm; 0.17% CMC, 1300 ppm; and 0.50%, 1600 ppm. At pH 7.5, the sample with 1.5% CMC resulted in about 1400 ppm, which is less than that of a similar solution with CMC at 0.5%. It is unclear at this point what the cause of this observation may be. Nonetheless, Brimonidine tartrate is more soluble in solution with a 1.5% CMC than with no CMC.

CMC is also effective to solubilize Brimonidine tartrate in a biological environment, for example the biological environment of the cornea.

EXAMPLE 3

Brimonidine Tartrate Dimers

Brimonidine tartrate is added to a test tube containing a composition including chlorite. The test tube was allowed to equilibrate for ten days. Samples obtained from the test tube is analyzed. It is observed that a portion of the Brimonidine tartrate monomer units conjugated to form dimers.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced with the scope of the following claims.

What is claimed is:

1. A therapeutically effective ophthalmic composition comprising:

an alpha-2-adrenergic agonist component in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered; and

a solubility enhancing component other than a cyclodextrin in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component in the composition relative to the solubility of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component.

2. The composition of claim 1 wherein the alpha-2-adrenergic component is selected from the group consisting of imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, derivatives thereof, and mixtures thereof.

3. The composition of claim 1 wherein the therapeutically active component includes a quinoxaline component.

4. The composition of claim 3 wherein the quinoxaline component is selected from the group consisting of quinoxaline, derivatives thereof, and mixtures thereof.

5. The composition of claim 1 wherein said solubility enhancing component comprises an anionic polymer.

6. The composition of claim 1 wherein the solubility enhancing component is effective to increase the solubility in a biological environment of the alpha-2-adrenergic ago

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5. The composition of claim 1 wherein said solubility enhancing component comprises an anionic polymer.

6. The composition of claim 1 wherein the solubility enhancing component is effective to increase the solubility in a biological environment of the alpha-2-adrenergic ago

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description).[3] While not case dispositive, the basis for Alcon's claim construction positions on '834 patent is also rooted in representations by Allergan to the PTO. During prosecution of the '834 patent, Allergan argued that it had discovered that a specific concentration of brimonidine tartrate (0.15% (w/v)) had "unexpected" properties at a particular pH (7.0 or greater) and temperature (21° C). Having so argued, and having failed to claim any range of values or measurements, Allergan cannot now materially broaden the scope of the asserted claims by relying on an undefined meaning of the term "about." Given the absence of any clear definition in the specification, Alcon contends that accepted scientific practice would be to define the values at issue in the most straightforward way possible – the range of values would be rounded to the values claimed in the patent.

Thus, in the event that the Court reaches the '834 claim construction issues, Alcon respectfully requests the following constructions:

The term "about 0.15% (w/v)" in the '834 patent means 0.15% ± 0.005% (w/v) (likewise, "up to about 0.15% (w/v)" means up to 0.155% (w/v) (the upper limit of 0.15 ± 0.005% (w/v)).

The term "pH of about 7.0 or greater" in the '834 patent means pH of 6.95 (the lower limit of 7.0 ± 0.05) or greater.

The term "about 21° C" in the '834 patent means 21° C ± 0.5° C.

II. BACKGROUND

It was well known in the art that alpha-2-adrenergic agonists, including brimonidine tartrate, could be used to treat ophthalmic disorders such as elevated intraocular pressure. In fact, Allergan had marketed a product (Alphagan®) containing 0.2% brimonidine tartrate for

[3] While the '834 patent is invalid for inadequate written description of the claimed invention of a therapeutically effective ophthalmic composition containing up to "about 0.15% (w/v)" brimonidine tartrate, the summary judgment motion does not depend on any particular definition or range of values being ascribed to the term "about 0.15% (w/v)," as the specification

The current claims are directed to therapeutically effective aqueous ophthalmic compositions comprising brimonidine and salts and esters thereof at a pH of up to about 7.0, and in a concentration of about 0.15% or less. Other claims indicate that the composition is preserved using a quaternary ammonium preservative or an oxychloro preservative.

To appreciate the surprising aspects of the present invention it is important to understand that previous brimonidine solutions for ophthalmic use have been formulated at a pH of about 6.3 – 6.5 and a concentration of 0.2% (w/v). This formulation was approved for marketing in the United States and foreign countries under the trade name Alphagan®.

The present invention is the result of the surprising finding that increasing the pH of a brimonidine solution to a pH of greater than about 7.0 leads to similar efficacy at a 25% lower concentration (from 0.2% (w/v) to about 0.15% (w/v) or less) than is seen in a brimonidine solution at a pH of about 6.6-6.8. This appears to be due to the fact that at a pH closer to the pKa of brimonidine (which has a pKa of about 7.4) than pH 6.3-6.5, a larger proportion of the molecules are electrostatically neutral, and thus less lipophobic than the polarized molecule. As such, a greater amount of the active drug is able to enter the cornea of the eye at a given solution concentration; this effect counters the effects of decreased brimonidine solubility at the higher pH. See specification at e.g., paragraph bridging pages 1 and 2.

However, it is particularly surprising that such a therapeutically effective dosage of brimonidine could be formulated in aqueous solution at a pH greater than about 7.0. Figure 1 of the present specification shows that brimonidine's solubility decreases precipitously at pH values above 7.0. The fact that a therapeutically effective dosage could be provided by a composition containing about 0.15% or less of brimonidine at such pH values is truly unexpected.

For the Examiner's convenience, Applicants hereby attach a copy of an article Katz, et al., *J. Glaucoma* 11:119 (April 2002) which shows the comparison of the 0.2% brimonidine formulation having a pH 6.3-6.5 (the "0.2% formulation") with 0.15% brimonidine solution at pH 7.2 (the 0.15% formulation).

Although the Katz paper does not disclose the pH of either solution, Applicants hereby enclose a Declaration of Amy Batoosingh, Director of Ophthalmological Clinical Research at Allergan, Inc. Ms. Batoosingh, whose work is contained within and acknowledged on page 126 of Katz, indicates in her Declaration that the formulation called "brimonidine 0.2%" in the Katz paper, which used benzalkonium chloride as a preservative, comprised 0.2% brimonidine at pH 6.3-6.5, and that the formulation termed "brimonidine-Purite 0.15%" in Katz, (which used oxy-chloro as a preservative) comprised 0.15% brimonidine at pH 7.2.

As can be seen in Figure 1 on page 122 of Katz, topical application of the 0.15% formulation resulted in no statistically significant differences in its ability to lower intraocular pressure (IOP) compared to the 0.2% formulation, despite 25% less active agent in the former formulation. Thus,

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of Olejnik, et al.	Group Art Unit: 1626
Serial No: 10/236,566	Examiner: Bennett, R.
Filed: September 6, 2002	
For: COMPOSITIONS CONTAINING ALPHA-2-ADRNERGIC AGONIST COMPONENTS	

RD 4-10-03

DECLARATION OF AMY BATOOSINGH

Dear Sir,

I, Amy Batoosingh, B.A., hereby declare as follows:

1. I hold the title of Director, Ophthalmological Clinical Research at Allergan, Inc. I have worked in the Department of Clinical Research at Allergan for over 20 years.

2. I am a co-author of the article, Katz, et al., *J. Glaucoma* 11:119 (April 2002), entitled *Twelve-Month Evaluation of Brimonidine Purite Versus Brimonidine in Patients with Glaucoma or Ocular Hypertension*, and am familiar with the studies referenced therein.

3. The compositions called "brimonidine 0.2%" and "brimonidine-Purite 0.15%" in the Katz article comprised 0.2% (w/v) brimonidine at pH 6.3-6.5, and 0.15% brimonidine at pH 7.1-7.3, respectively.

4. The conclusion reached as a result of the studies referenced in the Katz et al., article was that brimonidine 0.2% and brimonidine-Purite 0.15% showed comparable efficacy when each was used for the treatment of ocular hypertension in glaucoma and/or ocular hypertensive human patients over a 12 month period of time, despite a significant reduction in the concentration of the active ingredient in the latter formulation.

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

Sincerely yours,

Amy Batoosingh, B.A.

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2-adrenergic agonist components are amine-containing molecules with pKa's of greater than about 7, more preferably about 7 to about 9.

Alpha-2-adrenergic agonist components include alpha-2-adrenergic agonists. As used herein, the term alpha-2 adrenergic agonist includes chemical entities, such as compounds, ions, complexes and the like, that produce a net sympatholytic response, resulting in increased accommodation, for example, by binding to presynaptic alpha-2 receptors on sympathetic postganglionic nerve endings or for example, to postsynaptic alpha-2 receptors on smooth muscle cells. A sympatholytic response is characterized by the inhibition, diminishment, or prevention of the effects of impulses conveyed by the sympathetic nervous system. The alpha-2 adrenergic agonists of the invention bind to the alpha-2 adrenergic receptors presynaptically, causing negative feedback to decrease the release of neuronal norepinephrine. Additionally, they also work on alpha-2 adrenergic receptors postsynaptically, inhibiting beta-adrenergic receptor-stimulated formation of cyclic AMP, which contributes to the relaxation of the ciliary muscle, in addition to the effects of postsynaptic alpha-2 adrenergic receptors on other intracellular pathways. Activity at either pre- or postsynaptic alpha-2 adrenergic receptors will result in a decreased adrenergic influence. Decreased adrenergic influence results in increased contraction resulting from cholinergic innervations. Alpha-2 adrenergic agonists also include compounds that have neuroprotective activity. For example, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline is an alpha-2-adrenergic agonist which has a neuroprotective activity through an unknown mechanism.

Without limiting the invention to the specific groups and compounds listed, the following is a list of representative alpha-2 adrenergic agonists useful in this invention: imino-imidazolines, including clonidine, apraclonidine; imidazolines, including naphazoline, xymetazoline, tetrahydrozoline, and tramazoline; imidazoles, including detomidine, medetomidine, and dexmedetomidine; azepines, including B-HT 920 (6-allyl-2-amino-5,6,7,8 tetrahydro-4H-thiazolo[4,5-d]-azepine and B-HT 933; thiazines, including xylazine; oxazolines, including rilmenidine; guanidines, including guanabenz and guanfacine; catecholamines; and the like and derivatives thereof.

Particularly useful alpha-2-adrenergic agonists include quinoxaline components. In one embodiment, the quinoxaline components include quinoxaline, derivatives thereof and mixtures thereof. Preferably, the derivatives of quinoxaline include (2-imidozolin-2-ylamino) quinoxaline. More preferably, the derivatives of quinoxaline include 5-halide-6-(2-imidozolin-2-ylamino) quinoxaline The "halide" of the 5-halide-6-(2-imidozolin-2-ylamino) quinoxaline may be a fluorine, a chlorine, an iodine, or preferably, a bromine, to form 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline . Even more preferably, the derivatives of quinoxaline to be used in accordance with this invention include a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline , or Brimonidine tartrate.

Other useful quinoxaline derivatives are well known. For example, useful derivatives of a quinoxaline include the ones disclose by Burke et al U.S. Pat. No. 5,703,077. See also Danielwicz et al U.S. Pat. No. 3,890,319. Each of the disclosures of Burke et al and Danielwicz et al is incorporated in its entirety by reference herein.

The quinoxaline and derivatives thereof, for example Brimonidine tartrate, are amine-containing and preferably have pKa's of greater than 7, preferably about 7.5 to 9.

Analogs of the foregoing compounds that function as alpha-2 adrenergic agonists also are specifically intended to be embraced by the invention.

Preferably, the alpha-2-adrenergic agonists, for example the ones listed above, are effective toward activating alpha-2A-adrenergic receptors, alpha-2B-adrenergic receptors and alpha-2D-adrenergic receptors.

In one embodiment, the alpha-2-adrenergic agonists, for example Brimonidine tartrate, are substantially unionized in the compositions. In another embodiment, the adrenergic compounds are substantially unionized in the environment to which they are administered, for example the cornea. Without wishing to be limited by any theory or mechanism of action, it is believed that the unionized forms of the adrenergic compounds facilitate their permeation across membrane lipid bilayers.

Any suitable SEC may be employed in accordance with the present invention. In one embodiment, the SECs include pyrrolinidone components. Examples of pyrrolinidone components are polyvinylpyrrolinidones and derivatives thereof. In a preferred embodiment, the SECs include polyanionic components. The useful polyanionic components include, but are not limited to, those materials which are effective in increasing the apparent solubility, preferably water solubility, of poorly soluble alpha-2-adrenergic agonist components and/or enhance the stability of the alpha-2-adrenergic agonist components and/or reduce unwanted side effects of the alpha-2-adrenergic agonist components. Furthermore, the polyanionic component is preferably ophthalmically acceptable at the concentrations used. Additionally, the polyanionic component preferably includes three (3) or more anionic (or negative) charges. In the event that the polyanionic component is a polymeric material, it is preferred that each of the repeating units of the polymeric material include a discrete anionic charge. Particularly useful anionic components are those which are water soluble, for example, soluble at the concentrations used in the presently useful liquid aqueous media, such as a liquid aqueous medium containing the alpha-2-adrenergic components.

The polyanionic component is preferably sufficiently anionic to interact with the alpha-2-adrenergic agonist component. Such interaction is believed to be desirable to solubilize the alpha-2-adrenergic agonist component and/or to maintain such alpha-2-adrenergic agonist component soluble in the carrier component, for example a liquid medium.

Polyanionic components also include one or more polymeric materials having multiple anionic charges. Examples include:

- metal carboxymethylstarchs
- metal carboxymethylhydroxyethylstarchs
- hydrolyzed polyacrylamides and polyacrylonitriles
- heparin
- homopolymers and copolymers of one or more of:
  - acrylic and methacrylic acids
  - metal acrylates and methacrylates
  - alginic acid
  - metal alginates
  - vinylsulfonic acid
  - metal vinylsulfonate
  - amino acids, such as aspartic acid, glutamic acid and the like
  - metal salts of amino acids
  - p-styrenesulfonic acid

dihydrate, and magnesium chloride hexahydrate were USP grade. Boric acid and sodium borate decahydrate were NF grade.

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Potassium chloride	0.14%	0.14%	0.14%	0.14%	0.14%	(w/v)
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10.09	0.0218				
10.31					0.0222

FIG. 1 clearly shows that the solubility of Brimonidine tartrate tends to increase with increasing CMC concentrations. For example, at pH 7.5, the sample with 0% CMC resulted in 1000 ppm of Brimonidine tartrate; 0.056% CMC, 1300 ppm; 0.17% CMC, 1300 ppm; and 0.5%, 1600 ppm. At pH 7.5, the sample with 1.5% CMC resulted in about 1400 ppm, which is less than that of a similar solution with CMC at 0.5%. It is unclear at this point what the cause of this observation may be. Nonetheless, Brimonidine tartrate is more soluble in solution with a 1.5% CMC than with no CMC.

CMC is also effective to solubilize Brimonidine tartrate in a biological environment, for example the biological environment of the cornea.

EXAMPLE 3

Brimonidine Tartrate Dimers.

Brimonidine tartrate is added to a test tube containing a composition including chlorite. The test tube was allowed to equilibrate for ten days. Samples obtained from the test tube is analyzed. It is observed that a portion of the Brimonidine tartrate monomer units conjugated to form dimers.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced with the scope of the following claims.

What is claimed is:

1. A therapeutically effective aqueous ophthalmic composition comprising:

up to about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate, the composition having a pH of about 7.0 or greater, and the 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate being soluble in the composition at about 21° C.

2. The composition of claim 1 which includes up to 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate.

3. The composition of claim 1 which includes about 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate.

4. The composition of claim 1 which includes 0.15% (w/v) of 5-bromo-6-(2-imidozolin-2-ylamino)quinoxaline tartrate.

5. The composition of claim 1 having a pH of 7.0 or greater.

6. The composition of claim 1 which further comprises a preservative selected from the group consisting of an oxychloro component and a quaternary ammonium compound in an amount effective to at least assist in preserving the composition.

DRAFT CLAIMS: FOR DISCUSSION PURPOSES ONLY
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Group Art Unit 1615 Examiner BENNETT

1. (Amended) A therapeutically effective aqueous composition comprising:

~~an alpha-2-adrenergic agonist component~~ a therapeutically active component selected from the group consisting of 5-bromo-6-(2-imidazolin-2-ylamino) quinoxaline, a salt thereof, and an ester thereof in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered; and

an anionic solubility enhancing component in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component in the composition relative to the solubility of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component; ~~and~~

~~a liquid carrier component.~~

2. Cancel

3. Cancel

4. Cancel

5. Cancel

6. Original claim

7. Original claim

8. Original claim

9. (Amended) The composition of claim 1 wherein the ~~therapeutically active alpha-2-adrenergic agonist~~ component has increased diffusion through a lipid membrane relative to an identical therapeutically active ~~alpha-2-adrenergic agonist~~ component in a similar composition without the solubility enhancing component.

10. Cancel

11. Original claim

12. Cancel

13. (Amended) The composition of claim ~~12~~ 1 wherein said polyanionic component is selected from the group consisting of anionic cellulose derivatives, anionic polymers derived from acrylic acid, anionic polymers derived from

DRAFT claims
DO NOT ENTER

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CERTIFICATE OF SERVICE

I, Karen E. Keller, Esquire hereby certify that on July 6, 2005, I caused to be electronically filed a true and correct copy of the foregoing document with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

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I further certify that on July 6, 2005, I caused a copy of the foregoing document to be served on the following non-registered participants in the manner indicated:

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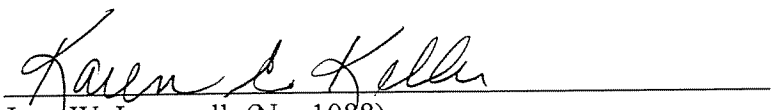

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