US006770675B2

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

(10) **Patent No.: US 6,770,675 B2**
(45) **Date of Patent: Aug. 3, 2004**

(54) **COMPOSITIONS AND METHODS FOR REDUCING OCULAR HYPERTENSION**

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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 252 days.

(21) Appl. No.: **09/812,162**

(22) Filed: **Mar. 19, 2001**

(65) **Prior Publication Data**

US 2002/0002185 A1 Jan. 3, 2002

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/042,817, filed on Mar. 17, 1998, now abandoned.
(60) Provisional application No. 60/093,065, filed on Mar. 17, 1997.

(51) **Int. Cl.**[7] **A61K 31/215**
(52) **U.S. Cl.** **514/530**; 514/573; 514/912; 514/913
(58) **Field of Search** 514/530, 575, 514/912, 913

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5,212,200	A	5/1993	Ueno et al.	514/530
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(57) **ABSTRACT**

An improved ophthalmic composition, including docosanoid active agents, which is especially useful in lowering intraocular pressure associated with glaucoma. Improvements in IOP reduction efficacy, preservative efficacy and reduced additive concentrations are achieved by utilizing the disclosed compositions which include a docosanoid active agent (e.g., isopropyl unoprostone), in conjunction with selected non-ionic surfactants, preservatives, and non-ionic tonicity adjusting agents.

9 Claims, 1 Drawing Sheet

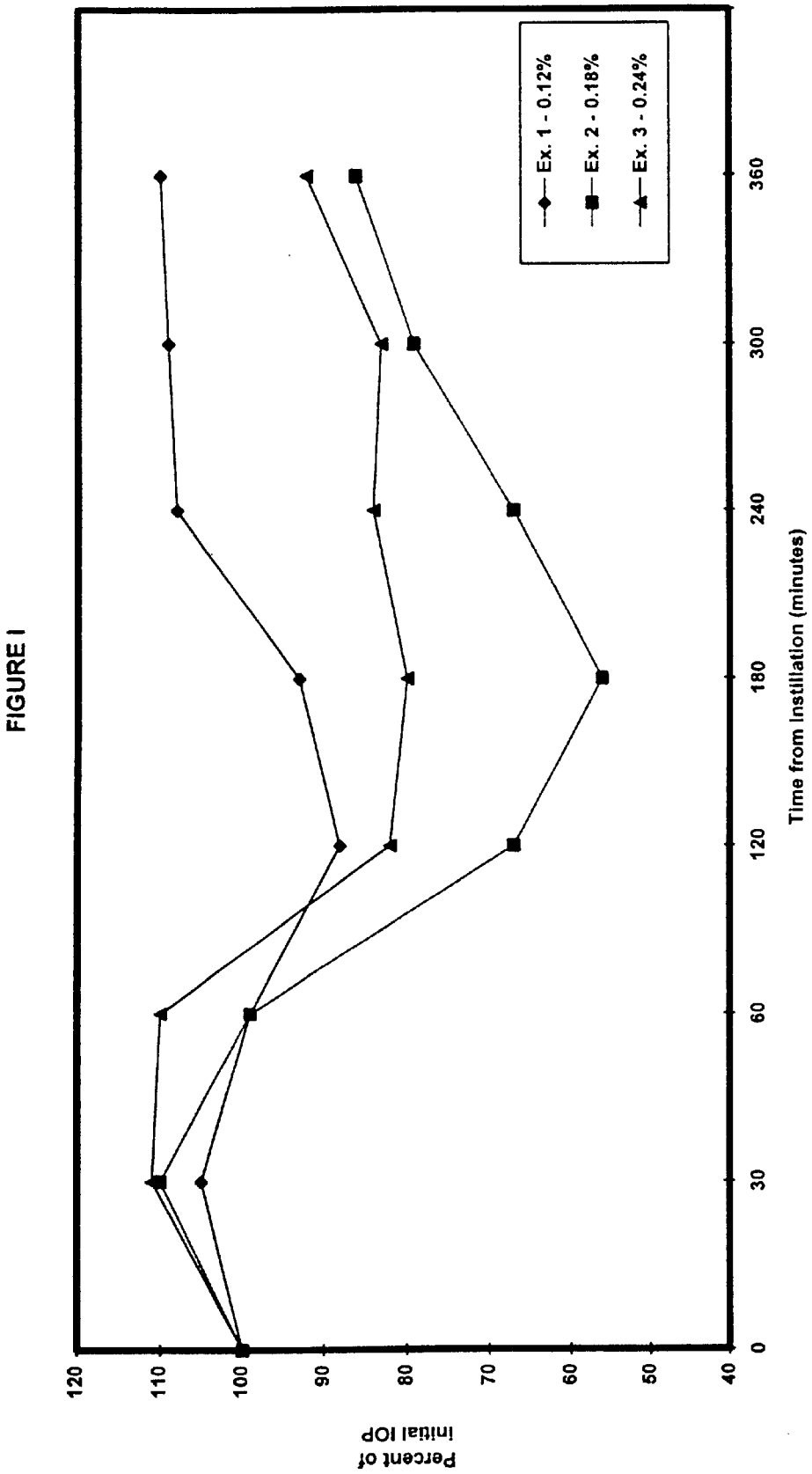


FIGURE I

COMPOSITIONS AND METHODS FOR REDUCING OCULAR HYPERTENSION

This application is a continuation-in-part of U.S. patent application Ser. No. 09/042,817, filed Mar. 17, 1998, abandoned, which claimed priority under 35 U.S.C. §119(e) from U.S. Provisional Patent application Serial No. 60/093,065, abandoned, which was converted from U.S. patent application Ser. No. 08/819,221, filed Mar. 17, 1997, abandoned.

FIELD OF THE INVENTION

The invention relates broadly to ophthalmic technology. More specifically, this invention relates to the therapeutic treatment of the eye to reduce elevated intraocular pressure, for example, the elevated intraocular pressure which is associated with glaucoma.

BACKGROUND OF THE INVENTION

U.S. Pat. No. 5,208,256 teaches a method of treating ocular hyertension by ocularly administering a combination of a docosanoid compound, e.g., [1R-[1α(Z),2β,3α,5α]]-7-[3,5-Dihydroxy-2-(3-oxodecyl)cyclopentenyl]-5-heptenoic acid or a salt or ester thereof and a polyoxyethylenesorbitan unsaturated higher aliphatic acid monoester. Preferred examples of the latter includes myristoleic acid, palmitoleic acid, oleic acid, gadoleic acid and linoleic acid. Polyoxyethylene (20) sorbitan monooleate is also known as Polysorbate 80 and sold, inter alia, under the names SORLATE, CRILLET, TWEEN 80, MONITAN and OLOTHORB.

CREMOPHOR has been used as a surfactant in eye drops (See Japanese Patent 07316060, filed on Dec. 16, 1994). CREMOPHOR is an ethoxylated, hydrogenated castor oil, which is also referred to as a polyoxyethylene hardened castor oil. However, the use of CREMOPHOR with docosanoids in an ophthamic delivery system has not been disclosed or suggested.

While docosanoids are useful for reducing intraocular pressure, there is a need to improve the efficacy of medicaments containing them. In addition, there is a need for improvement in the preservative effectiveness of ophthalmic docosanoid compositions which include surfactants, while maintaining good efficacy and good ocular tolerance. Furthermore, improvements in the shelf life of ophthalmic docosanoid compositions are desirable. Also, it is always desirable to reduce manufacturing difficulties. Thus, there is a need for a docosanoid-containing ophthalmic composition that can be manufactured with a minimum of complexity and which exhibits a balance of efficacy, preservative effectiveness, ocular tolerance, and a long shelf life.

SUMMARY OF THE INVENTION

An object of the invention is to improve the efficacy of docosanoid-containing ophthalmic compositions.

Another object of the invention is to improve the preservative effectiveness of docosanoid-containing ophthalmic compositions.

Still another object of the invention is to improve shelf life of docosanoid-containing ophthalmic compositions.

Yet another object of the invention is to reduce the complexity of manufacturing a docosanoid-containing ophthalmic composition.

A further object of the invention is to produce a docosanoid-containing ophthalmic composition with a

These and other objects and advantages of the invention are achieved with the various embodiments of the present docosanoid-containing ophthalmic compositions, methods of use and methods of manufacture. One embodiment of the invention is an ophthalmic composition which includes a docosanoid, a non-ionic surfactant (e.g. a CREMOPHOR) and a preservative (e.g. benzalkonium chloride). Another embodiment is an ophthalmic composition which includes a docosanoid, a surfactant, a non-ionic tonicity adjusting agent (e.g. mannitol) and a preservative. Still another embodiment is an ophthalmic composition which includes a docosanoid, one or more surfactants, a strong preservative (e.g. BAK) and a preservative enhancer (e.g., EDTA). Yet another embodiment of the invention relates to adding a buffer to improve product shelf life and reduce production complexity.

BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** is a graph showing the time-course changes in the intraocular pressure of a rabbit eye, which received instillation of a 0.12%, 0.18% or 0.24% isaprapyl unaprostone ophthalmic formulation.

DETAILED DESCRIPTION OF THE INVENTION

The various embodiments of the invention offer a number of improvements in docosanoid compositions which are useful, inter alia, for reducing intraocular pressure. The compositions are especially useful in treating elevated intraocular pressure associated with glaucoma. Accordingly, all of the components of the compositions are preferably ophthalmically acceptable, at the concentrations of use and under the conditions in which they are applied. An "ophthalmically acceptable" component, as used herein, refers to a component which will not cause any significant ocular damage or ocular discomfort at the intended concentration and over the time of intended use.

The invention embraces several embodiments, some of which are outlined below to improve the reader's understanding. One group of embodiments of the invention are ophthalmic compositions which are useful in reducing intraocular pressure, especially intraocular pressure which is associated with glaucoma. The ophthalmic compositions include an amount of a docosanoid active agent selected from the group of docosanoids, analogs thereof, derivatives thereof, metabolites thereof, salts thereof, or combinations thereof, which are effective to treat elevated intraocular pressures. Another group of embodiments are methods of reducing intraocular pressure and treating glaucoma by topical application of the aforementioned ophthalmic compositions. However, a person having ordinary skill in the art may vary some of the elements of the embodiments without departing from the spirit and scope of the invention.

One embodiment of the invention is a composition which has a reduced concentration of strong preservative, and correspondingly, generates less ocular irritation. Unexpectedly, it has been found that the use of certain non-ionic tonicity adjusting agents enhances the preservative effectiveness of strong preservatives in compositions containing docosanoid active agents. This allows for a reduced concentration of strong preservatives in the composition. In addition, chelating agents may be added to further boost preservative efficacy and reduce the required concentration of strong preservative. Thus, one embodiment

strong preservative (e.g., benzalkonium chloride), and (3) a non-ionic tonicity enhancing agent (e.g., a simple sugar such as mannitol) effective in increasing the preservative efficacy relative to a composition including solely a strong preservative.

In particular, the complete eradication of *Psuedomonas Aeriginosa* is desired. While benzalkonium chloride (BAK) kills nearly all Psuedomonas, there may remain some which are resistant to BAK. Over time, the BAK-resistant Psuedomonas may propagate to a concentration which is unacceptable. Thus, it is preferable to include a preservative efficacy enhancer to eliminate BAK-resistant Psuedomonas.

It is preferable that the preservative efficacy enhancer or second preservative be a well tolerated component which acts via a mechanism which differs from BAK. The strong preservative (e.g., BAK) will handle the bulk of the bioburden. The use of the second well tolerated preservative or enhancer insures complete kill of contaminating microbes and yet minimizes ophthalmic irritation as compared to using abnormally high concentrations of BAK.

A preferred class of preservative efficacy enhancers are chelating agents, such as calcium chelating agents. A preferred calcium chelating agent is ethylene diamine tetraacetate (EDTA). EDTA has been shown to assist in the eradication of BAK-resistant Psuedomonas without substantially altering ophthalmic compatibility or docosanoid efficacy. In addition, EDTA offers the advantage of simultaneously acting as a buffer.

Thus, in a preferred embodiment, the composition includes (1) a docosanoid active agent, (2) a strong preservative, and (3) a non-ionic tonicity enhancing agent, (4) a chelating agent (e.g., edetate sodium). These compositions are especially advantageous in that preservative effectiveness is improved relative to a composition containing a strong preservative alone. This allows for a reduction in the required concentration of the strong preservative, and accordingly less ophthalmic irritation.

Another embodiment of the invention is a composition containing a docosanoid active agent which has an advantageously reduced total surfactant concentration. It is generally desirable to minimize the concentration additives to an ophthalmic formulation in order to minimize potential ocular irritation associated with the additives. However, in order to solubilize docosanoid active agents, a surfactant is typically required. It has been unexpectedly discovered that the combination of two or more non-ionic surfactants, as opposed to a single surfactant, can reduce the total concentration of surfactant required to achieve a given level of solubility of the docosanoid active agent. Thus, this embodiment of the invention relates to a composition which includes (1) a docosanoid active agent, (2) a first non-ionic surfactant (e.g., Polysorbate 80), (3) a second non-ionic surfactant (e.g., a BRIJ surfactant) and (4) an ophthalmically acceptable carrier. This embodiment of the invention offers advantages in reduced ocular irritation and reduced raw material (surfactant) requirements.

Yet another embodiment of the invention relates to the difficulties in achieving solubility of docosanoid active agents. In order to solubilize the active agent, a non-ionic surfactant, preferably Polysorbate 80, is added to the formulation. Thus, increasing the docosanoid concentration to the preferred ranges described herein requires a corresponding increase in the surfactant concentration, in order to maintain the docosanoid in solution. However, the Polysorbate 80 surfactant also acts as a preservative enhancer, thus an increase in surfactant reduces the preservative effectiveness. In sum, an increase in therapeutic efficacy which is achieved by increasing active agent concentration results in the need for an increase in Polysorbate 80 concentration and therefore a decrease in preservative effectiveness. Accordingly, improvements in both preservative effectiveness and efficacy of the cited formulations are difficult to achieve.

However, it has been unexpectedly found that the use of non-ionic tonicity adjusting agents appreciably improves the action of the preservative in the presence of surfactant. Thus, in order to minimize the aforementioned preservative deactivation problem, a preferred composition includes (1) a docosanoid active agent, (2) a strong preservative (e.g., BAK), (3) a non-ionic surfactant which increases solubility of the docosanoid active agent but decreases the preservative effectiveness of the strong preservative (e.g., Polysorbate 80), and (4) a preservative enhancer which increases the effectiveness of the strong preservative (e.g., mannitol or EDTA), and (5) an ophthalmically acceptable carrier. Thus, the efficacy and preservative effectiveness may be simultaneously improved in the present formulations, while maintaining a solution form, by optimizing the concentrations of active agent, surfactant, non-ionic tonicity adjusting agent, and preservative.

Some prior art anti-glaucoma pharmaceutical formulations have used salts such as sodium chloride to adjust tonicity to ophthalmically acceptable levels (e.g., about 0.8 to about 1.0 mg/ml NaCl equivalents). However, ionic tonicity adjusting agents have been found by the present inventors to reduce the solubility of the docosanoid active agents. Thus, another advantage of the use of non-ionic tonicity adjusting agents (e.g., mannitol) in the present invention is the increased solubility of salts of the active agent.

In accordance with several preferred inventive embodiments disclosed herein, a preferred composition includes:

(a) about 0.06 to about 0.24 weight percent isopropyl unoprostone;

(b) about 0.3 to about 2 weight percent of two non-ionic surfactant selected from the group consisting of CREMOPHOR RH, BRIJ 97, BRIJ 98, CREMOPHOR EL, Polysorbate 80 and mixtures thereof;

(c) about 0.01 to about 0.20 weight percent benzalkonium chloride;

(d) about 0.01 to about 0.1 weight percent EDTA;

(e) about 0.10 to about 10.0 weight percent mannitol;

(f) about 0.01 to about 0.05 molar of an ophthalmically acceptable buffer;

(g) an ophthalmically acceptable carrier;

in which the pH is adjusted to about 4.5 to about 8.0.

The active agents useful in accordance with the invention may be selected from the group consisting of docosanoids, metabolites thereof, analogs thereof, derivatives thereof, salts thereof, docosanoid prodrugs, and mixtures thereof, referred to herein as "docosanoid active agent" or merely "active agent". Thus, the active agent is not limited by the specific form of the active, i.e., whether in free acid or salt form. Rather, the docosanoid active agent is active in that the agent causes a reduction of intraocular pressure (IOP) when applied to the ocular environment of a patient in need of reduction of intraocular pressure.

A docosanoid, as used herein, refers to a group of com-

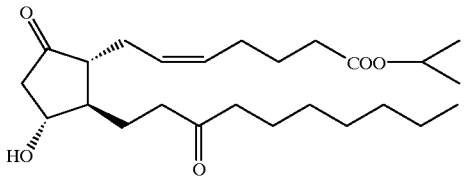
synthetically produced. The preferred docosanoids are those which are useful in therapeutic ophthalmic applications, especially those which reduce intraocular pressure.

A group of docosanoids which have been found to be useful in decreasing intraocular pressure are disclosed in U.S. Pat. Nos. 4,599,353; 5,296,504; 5,422,368; and 5,578,618. These patents are incorporated herein by reference for the teaching and examples of docosanoid active agents which are useful in reducing intraocular pressure.

A particularly preferred group of active agents are described more fully in U.S. Pat. Nos. 5,106,869; 5,221,763 5,208,256; 5,001,153; 5,151,444; 5,166,178 and 5,212,200, each of which is incorporated herein by reference for the disclosure of compounds useful in the present invention.

Docosanoids of the present invention may be docosanoid salts, or those docosanoids with an esterified carboxyl group. Suitable docosanoid salts are ophthalmically acceptable salts, including without limitation thereto, salts of alkali metals such as sodium or potassium; salts of an alkaline earth metal such as calcium or magnesium; salts of ammonia, methylamine, dimethylamine, cyclopentylamine, benzylamine, piperidine, monoethanolamine, diethanolamine, monomethylmonoethanolamine, tromethamine, lysine and tetralkylammonia; and the like and mixtures thereof Suitable docosanoid esters are ophthalmically acceptable esters, including without limitation thereto, methyl, ethyl, propyl, butyl, isopropyl, t-butyl, 2-ethylhexyl, straight or branched-chain alkyl esters which may contain an unsaturated bond. Suitable esters include an ester having an alicyclic group such as a cyclopropyl, cyclopentyl, olr cyclohexyl group; an ester containing an aromatic group such as a benzyl or phenyl group (wherein the aromatic group may contain one or more substituents); a hydroxyalkyl or alkoxyalkyl ester such as hydroxyethyl, hydroxyisopropyl, polyhydroxyisopropyl, methoxyethyl, ethaoxyethyl or methoxyisopropyl groups; an alkysilyl ester (e.g., a trimethylsilyl or triethylsilyl ester); and a tetrahydropyranyl ester.

Most preferred are docosanoids as disclosed in U.S. Pat. No. 5,208,256, which is incorporated herein by reference for its disclosure of docosanoid compounds. A particularly preferred docosanoid is isopropyl unoprostone. The structure of isopropyl unoprostone is given below and a method of preparation is outlined in U.S. Pat. No. 5,212,200, which is incorporated by reference.



The preferred docosanoid concentration is an amount which will substantially reduce intraocular pressure (IOP) of an eye which has elevated IOP, especially in a patient suffering from glaucoma. Clearly the required concentration depends on a number of factors, including the efficacy of the docosanoid in the presence of the other components, the volumetric amount of medicament applied, and the frequency and duration of application.

It has been determined that concentrations of active agents within the range of about 0.001 to about 0.30 weight percent are more efficacious for reducing intraocular pressure percent active agent is preferred, while a concentration of about 0.10 to about 0.20 is more preferred. However, the preferred concentration in any specific application depends on a number of factors, such as the concentrations and chemical nature of other ingredients as well as the delivery method and conditions. Moreover, quite unexpectedly, further increases in active agent concentrations outside these preferred ranges may actually cause less of the desired decrease in intraocular pressure than the concentrations in the preferred ranges.

A surfactant, as used herein, refers to a surface active agent which improves the solubility of a substance, e.g. an active or drug, in a solvent. A non-ionic surfactant, as used herein, refers to a surfactant which possesses no easily ionizable groups.

U.S. Pat. No. 5,208,256 discloses the use of Polysorbate 80 as a surfactant for docosanoid-containing ophthalmic compositions. Polysorbate 80 improves the solubility of isopropyl unoprostone, so that a higher concentration of isopropyl unoprostone can be used in a solution form.

However, it has been discovered that while increasing the Polysorbate 80 concentration allows for increases in the docosanoid concentration in solution, the preservative effectiveness decreases with increasing Polysorbate 80 concentrations. Moreover, it is desired to increase both the efficacy (e.g., by increasing the docosanoid concentration) and preservative effectiveness of the known docosanoid-containing ophthalmic formulations. Thus, it has been determined that use of more Polysorbate 80 has the disadvantage of decreasing preservative effectiveness, while less Polysorbate 80 has the disadvantage of reducing prostaglanin in solution and thereby reducing efficacy.

One embodiment of the present invention offers a solution to these problems by using a combination of two or more non-ionic surfactants. Certain combinations of non-ionic surfactants have been found to increase docosanoid active agent solubility without reducing preservative effectiveness as much as Polysorbate 80 alone in the same concentration.

A preferred group of non-ionic surfactants are those which exhibit better ophthalmic tolerance than Polysorbate 80 alone and/or which do not reduce preservative effectiveness or reduce preservative effectiveness less than Polysorbate 80 alone in the same concentration.

The first and second non-ionic surfactants may be selected from a group of non-ionic surfactants including, without limitation thereto, polyoxyethylene sorbitan fatty acid esters such as Polysorbates 20, 60 and 80; polyoxyethylene alkyl ethers such as Brij's (e.g., BRIJ 97 or BRIJ 98 from ICI Surfactants, Wilmington, Del.), Cremophors (such as Cremophor RH or Cremophor EL), Volpo (e.g., VOLPO 10 and VOLPO 20 from Croda, Inc., Parsippany, N.J.) and equivalents thereof. A preferred group includes polyoxyethylene 20 oleate (e.g., Polysorbate 80), Polyoxyl 10 oleyl ethers (e.g., Brij 97) and Polyoxyl 20 oleyl ethers (e.g., Brij 98).

A particularly preferred combination of surfactants is the combinations of a polyoxyethylene sorbitan fatty acid ester (especially Polysorbate 80) with a polyoxyethylene alkyl ethers (especially BRIJ 97 or BRIJ 98).

Thus, use of at least two surfactants together provides an unexpected synergistic result in that the total concentration of surfactant required to achieve a desired docosanoid active agent solubility is less that the concentration required for an individual surfactant. In addition, certain combinations of surfactants actually improve the preservative effectiveness. Specifically, the combination of Polysorbate 80 with a BRIJ

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