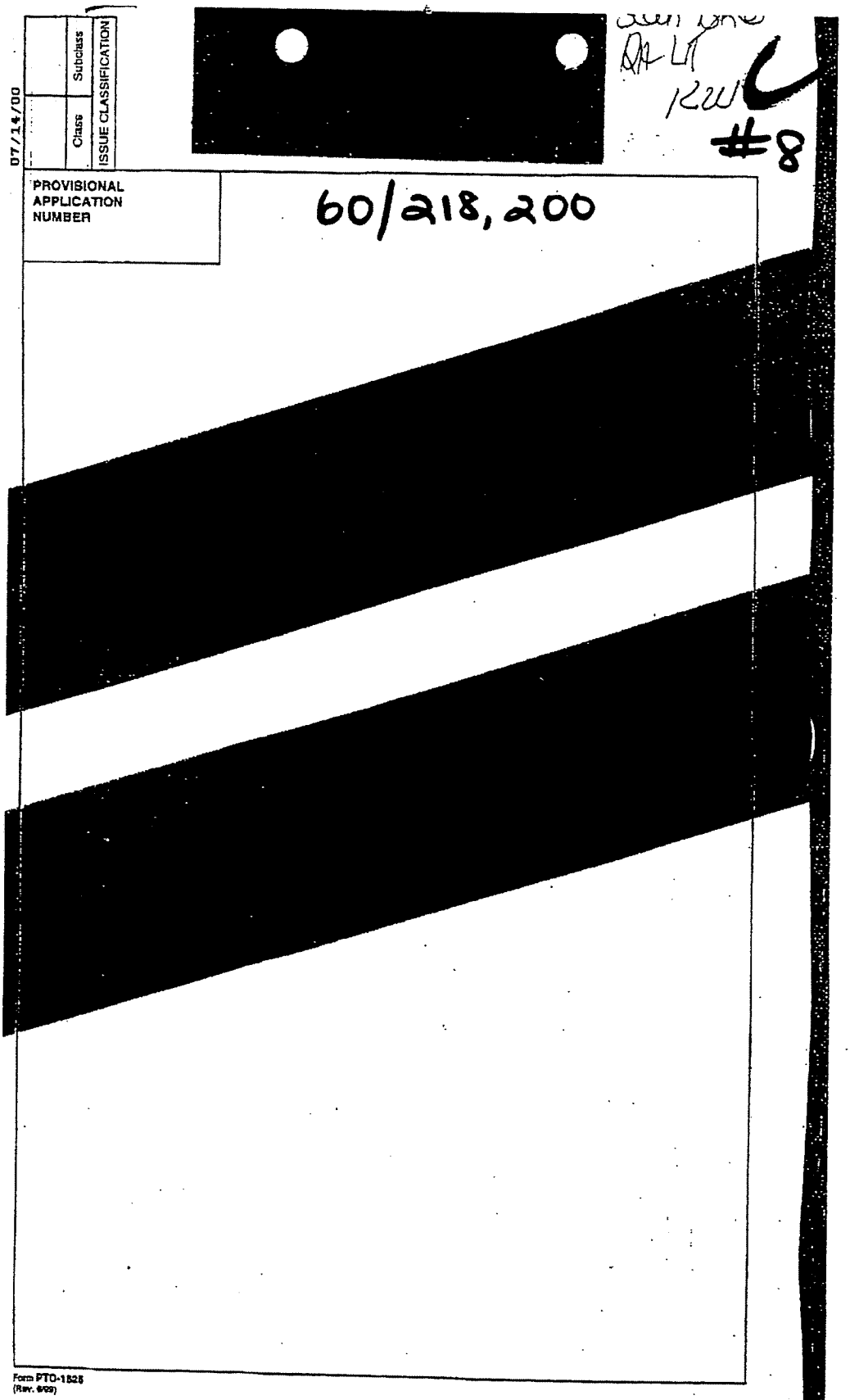
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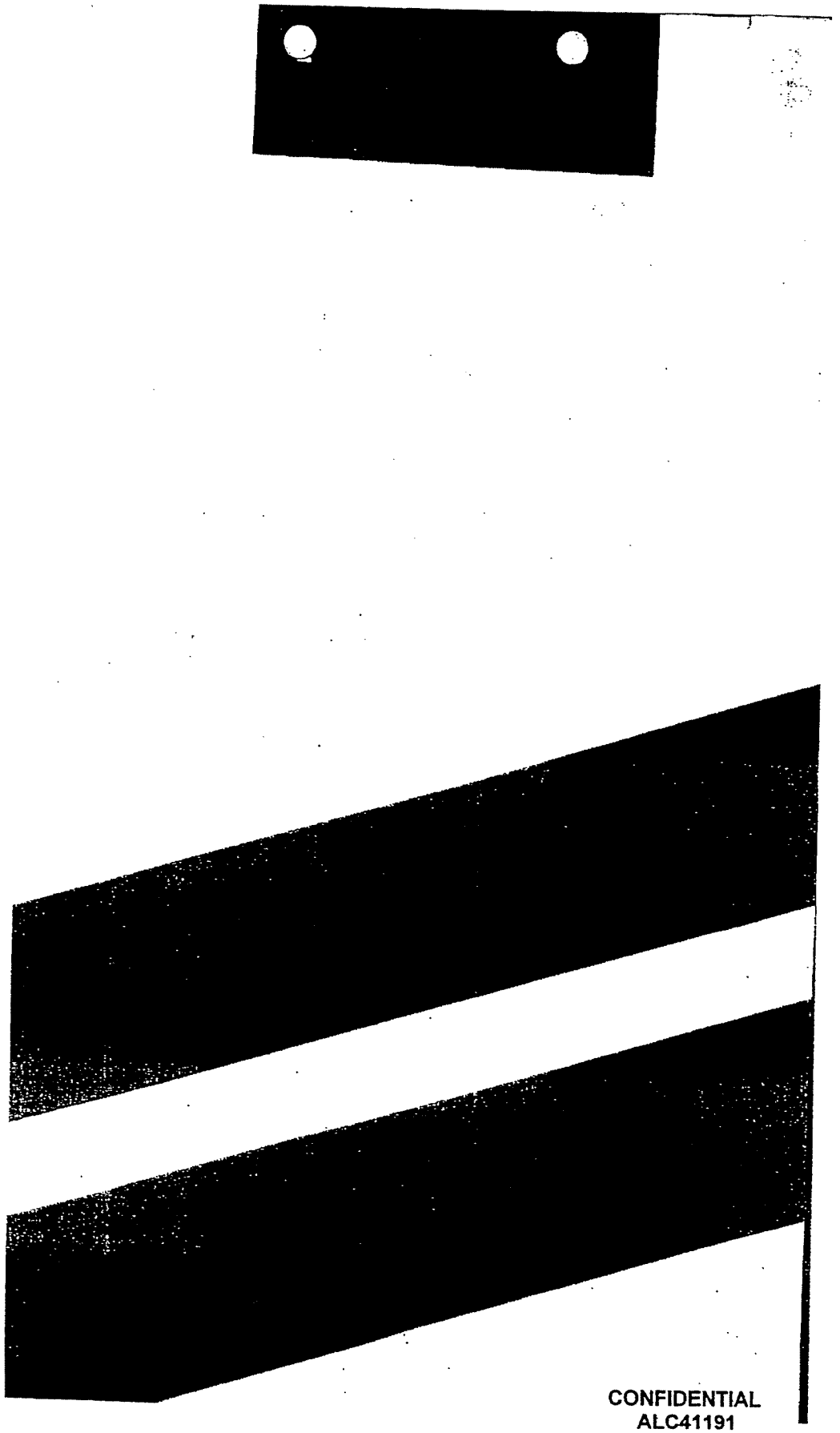
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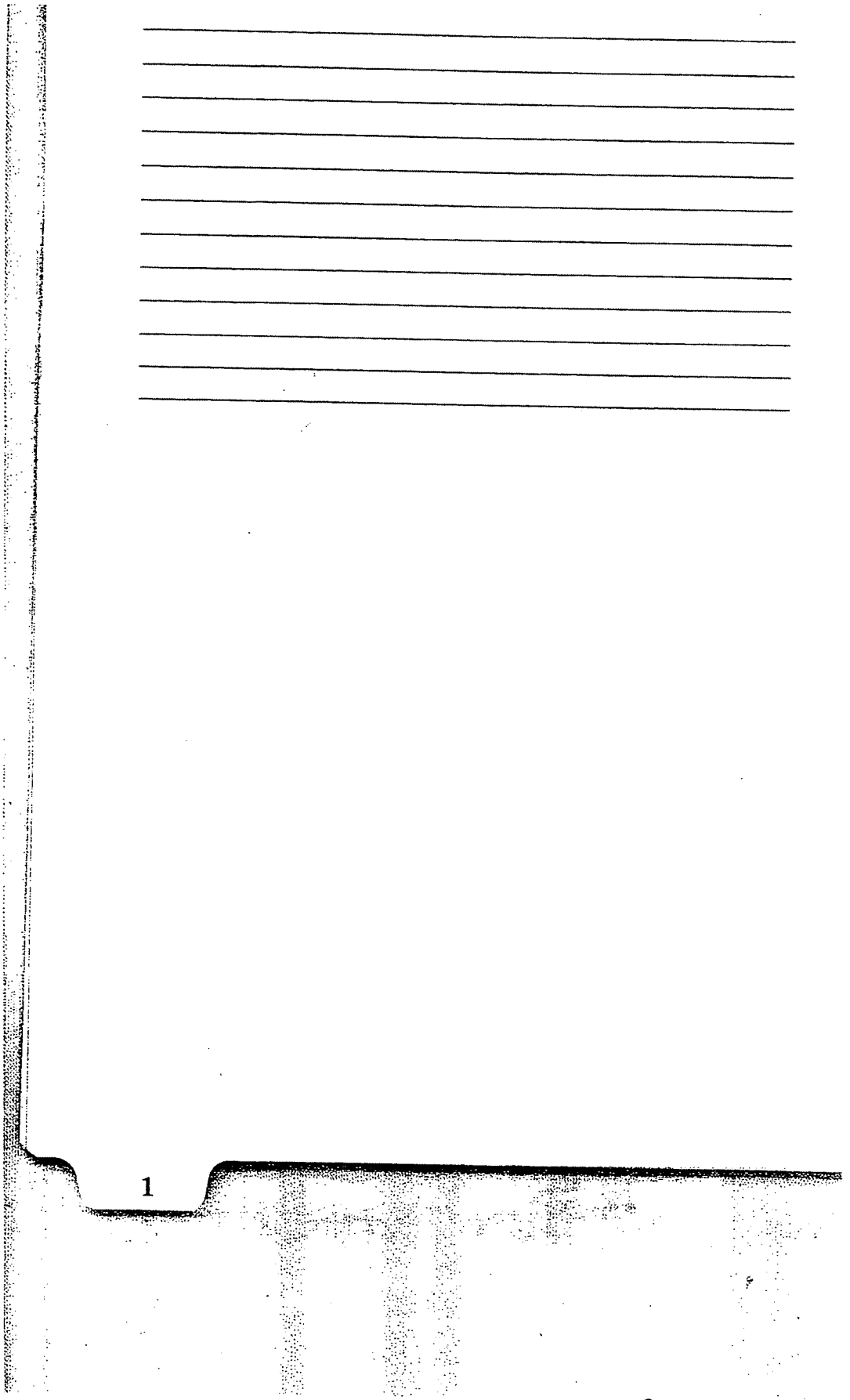
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APPLICANTS

Orest Olejnik, Coto De Caza, CA ;
Edward D.S. Kerslake, Charlestown, MA ;

** CONTINUING DATA **********

** FOREIGN APPLICATIONS **********

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ADDRESS

Stout Uxa Buyan & Mullins LLP
Suite 300
4 Venture
Irvine , CA 92618

TITLE

Compositions containing alpha-2-adrenergic agonist components

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07/14/00 jc674 U.S. PTO

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (b)(2).

jc674 U.S. PTO 60/218200 07/14/00

Docket Number	D-2892 P	Type a plus sign (+) inside this box →	+

INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
OLEJNIK KERSLAKE	OREST EDWARD	D.S.	COTO DE CAZA, CA CHARLESTOWN, MA

TITLE OF THE INVENTION (280 characters max)

COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

CORRESPONDENCE ADDRESS

STOUT, UXA, BUYAN & MULLINS, LLP
4 VENTURE
SUITE 300
IRVINE, CA 92618

STATE	CA	ZIP CODE	92618	COUNTRY	USA

ENCLOSED APPLICATION PARTS *(check all that apply)*

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X	Drawing(s)	*Number of Sheets*	1			Other(specify)	

METHOD OF PAYMENT *(check one)*

	A check or money order is enclosed to cover the Provisional filing fee	PROVISIONAL FILING FEE AMOUNT ($)	$150.00
X	The Commissioner is hereby authorized to charge filing fees and credit deposit Account Number: 01-0885		

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.
■ No.
□ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE _____ Date 7/14/00
FRANK J. UXA, Reg. No. 34,610

□ Additional inventors are being named on separately numbered sheets attached hereto

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Docket: D-2892P

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application:
Olejnik et al

Filed: Herewith

For: **COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS**

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1. Provisional Application Cover Sheet;
2. Specification forty-one (41) pages;
3. One (1) sheet of informal drawings; and a
4. Return Receipt postcard to verify receipt.

The four (4) above-identified documents are enclosed herewith.

Respectfully submitted,

Lynette L. Gascoigne
Office of Frank J. Uxa
Attorney for Applicant
Registration No. 25,612
4 Venture, Suite 300
Irvine, CA 92618
(949) 450-1750
Facsimile (949) 450-1764

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THE ENCLOSED PATENT APPLICATION OF OLEJNIK, ET AL IS BEING FILED IN ACCORDANCE WITH SECTION 37 C.F.R. §1.10 BY EXPRESS MAIL AND SHOULD BE ACCORDED A FILING DATE OF

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COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

ABSTRACT OF THE DISCLOSURE

Compositions useful for improving effectiveness of alpha-2-adrenergic agonist components include carrier components, alpha-2-adrenergic agonist components, solubility enhancing components which aid in solubilizing the alpha-2-adrenergic agonist components. In one embodiment, the alpha-2-adrenergic agonist components include alpha-2-adrenergic agonists. In another embodiment, the solubility enhancing components include carboxymethylcellulose.

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COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

BACKGROUND OF THE INVENTION

The present invention relates to compositions containing alpha-2-adrenergic agonist components. More particularly, the invention relates to such compositions in which the alpha-2-adrenergic agonist components have enhanced solubility at the therapeutically effective concentrations.

Alpha-2-adrenergic agonist components include chemical entities, such as compounds, ions, complexes and the like, which are effective to act on or bind to Alpha-2-adrenergic receptors and provide a therapeutic effect. Alpha-2-adrenergic agonist components means the agonists themselves and any and all precursors thereof, metabolites thereof and combinations thereof. One of the continuing challenges of formulating compositions having alpha-2-adrenergic agonist components is to render such components more effective. For example, alpha-2-adrenergic agonist components in liquid compositions often benefit from being soluble in the liquid carriers of such compositions. Such solubility promotes uniform and accurate administration.

Additionally, the dispensed or administered alpha-2-adrenergic agonist components should advantageously be soluble in biological systems or environments, for example, for effective or enhanced in vivo diffusion through cell membranes or lipid bilayers. Some alpha-2-adrenergic agonist components with higher pKa's, for example, greater than about 7, tend to diffuse very well through lipid membranes at pH valves near their pka, because in such circumstances they are predominantly unionized in neutral to alkaline biological environments.

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However, some of these alpha-2-adrenergic agonist components become insoluble at neutral to alkaline biological pH's. Such insolubility may decrease membrane diffusion capabilities, rendering the alpha-2-adrenergic agonist components less effective and/or their therapeutic effects more variable at a given dosage. Furthermore, solubilized alpha-2-adrenergic agonist components provide other benefits, for example, reduced irritation to tissues that interact with alpha-2-adrenergic agonist components.

There continues to be a need for new compositions containing alpha-2-adrenergic agonist components.

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SUMMARY OF THE INVENTION

New alpha-2-adrenergic agonist component-containing compositions have been discovered. The present compositions contain certain materials which are effective in at least aiding or assisting in solubilizing the alpha-2-adrenergic agonist components in the compositions, and preferably in environments to which the compositions are administered or introduced, for example, biological environments, such as the human eye. Preferably, solubilization of the alpha-2-adrenergic agonist components in accordance with the present invention facilitates transport of such components across lipid membranes. Also, preferably such solubilization allows the provision of more reliable and reproducible dosage forms of the drug. In addition, alpha-2-adrenergic agonist component-containing compositions have been discovered which include preservatives which provide substantial advantages, for example, reduced adverse interactions with the alpha-2-adrenergic agonist components and/or with the patients to whom the compositions are administered, while maintaining preservative effectiveness.

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The present compositions preferably enhance the effectiveness of alpha-2-adrenergic agonist components by increasing the apparent water solubility of the alpha-2-adrenergic agonist components, preferably at pH's higher than neutral. The present compositions include, in addition to the adrenergic agonist components, solubility enhancing components (SECs) in amounts effective to enhance the solubility of the alpha-2-adrenergic agonist components. Preferably, the alpha-2-adrenergic agonist components are more soluble in the present compositions having, for example, pH's of about 7 or greater, relative to similar compositions without the SECs. In another embodiment, the alpha-2-adrenergic agonist components of the present compositions are more soluble in neutral, preferably alkaline, biological environments into which the compositions are administered relative to alpha-2-adrenergic agonist components in similar compositions without the SECs.

In one embodiment, the alpha-2-adrenergic agonist components include imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, biologically compatible salts and esters and mixtures thereof. Preferably, the alpha-2-adrenergic agonist components include quinoxaline components. Quinoxaline components include quinoxaline, biologically compatible salts thereof, esters thereof, other derivatives thereof and the like, and mixtures thereof. Non-limiting examples of quinoxaline derivatives include (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and biologically compatible salts thereof and esters thereof, preferably the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and the like and mixtures thereof. Hereinafter, the tartrate of 5-bromo-6-(2-imidozolin-2-

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ylamino) quinoxaline is referred to as "Brimonidine tartrate."

In a preferred embodiment, the alpha-2-adrenergic agonist components, such as those listed above, are specific for the alpha-2A-adrenergic receptors, alpha-2B-adrenergic receptors and/or alpha-2D-adrenergic receptors.

In one embodiment, the alpha-2-adrenergic agonist components are unionized in the compositions. Preferably, the alpha-2-adrenergic agonist components are also unionized in the biological environment into which the compositions are administered.

In a useful embodiment, the SEC includes a polyanionic component. As used herein, the term "polyanionic component" refers to a chemical entity, for example, an ionically charged species, such as an ionically charged polymeric material, which includes more than one discrete anionic charge, that is multiple discrete anionic charges. Preferably, the polyanionic component is selected from polymeric materials having multiple anionic charges, and mixtures thereof.

Particularly useful polyanionic components are selected from anionic polymers derived from acrylic acid (meaning to include polymers from acrylic acid, acrylates and the like and mixtures thereof), anionic polymers derived from methacrylic acid (meaning to include polymers from methacrylic acid, methacrylates, and the like and mixtures thereof), anionic polymers derived from alginic acid (meaning to include alginic acid, alginates, and the like and mixtures thereof), anionic polymers of amino acids (meaning to include polymers of amino acids, amino acid salts, and the like and mixtures thereof), and the like, and mixtures thereof. Very useful polyanionic components are those selected from anionic cellulose

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derivatives and mixtures thereof, especially carboxymethylcelluloses.

The polyanionic component preferably is sufficiently anionic to interact with or otherwise affect, in particular increase, the solubility of the alpha-2-adrenergic components. This interaction preferably is sufficient to render the alpha-2-adrenergic components substantially completely soluble at therapeutically effective concentrations. The amount of SEC in the composition preferably is in the range of about 0.1% (w/v) to about 30% (w/v), more preferably about 0.2% (w/v) to about 10% (w/v), and even more preferably about 0.2% (w/v) to about 0.6% (w/v).

The compositions include carrier components, for example, aqueous liquid carrier components. In one embodiment, the compositions have pH's of about 7 or greater, preferably about 7 to about 9, and are ophthalmically acceptable.

In a preferred embodiment, a composition is provided which includes an alpha-2-adrenergic agonist component in an amount effective to provide at least one therapeutic benefit to a patient to whom the composition is administered, an anionic cellulose derivative in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component and an aqueous liquid carrier component. The alpha-2-adrenergic agonist component preferably comprises a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline. The anionic cellulose derivative preferably comprises a carboxymethylcellulose. The concentration of the anionic cellulose derivative in the composition should be about 0.2% (w/v) to about 0.6% (w/v).

In a preferred embodiment, the present compositions are ophthalmically acceptable, e.g. the compositions do

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not have deleterious or toxic properties which could harm the eye of the human or animal to whom the compositions are administered.

In one broad aspect of the invention, complexes are formed in the compositions. In one embodiment, the complexes include monomer units derived from at least one quinoxaline component. In a preferred embodiment, the complexes of the present invention are dimers. In a particularly preferred embodiment, the complexes are complexes, especially dimers, of Bromodidine tartrate.

In another broad aspect of the present invention, compositions are provided which comprise an alpha-2-adrenergic agonist component and a preservative component in an effective amount to at least aid in preserving the compositions. Preferably, the preservative components include oxy-chloro components, such as compounds, ions, complexes and the like which are biologically acceptable, chemically stable and do not substantially or significantly detrimentally affect the an alpha-2-adrenergic agonist component in the compositions or the patients to whom the compositions are administered. Such compositions preferably are substantially free of cyclodextrins in the compositions or the patients to whom the compositions are administered.

Any feature or combination of features described herein are included within the scope of the present invention provided that the features included in any such combination are not mutually inconsistent as will be apparent from the context, this specification, and the knowledge of one of ordinary skill in the art.

Additional advantages and aspects of the present invention are apparent in the following detailed description and claims.

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BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 is a graph of soluble Brimonidine tartrate verses pH at various carboxymethylcellulose concentrations.

DETAILED DESCRIPTION OF THE INVENTION

Compositions comprising alpha-2-adrenergic agonist components and SECs are provided. The alpha-2-adrenergic agonist components in the present compositions are made more soluble and may be more effectively utilized as therapeutic agents. The SECs employed in the present compositions may be effective in the solubilization of ionized alpha-2-adrenergic agonist components, unionized alpha-2-adrenergic agonist components or both. The present compositions include liquid carrier components and have the characteristics of liquid, for example, aqueous liquid, solutions.

Preferably, the alpha-2-adrenergic agonist components have increased solubility in the present compositions at pH's greater than 7, as compared to identical alpha-2-adrenergic agonist components, at comparable concentrations, in similar compositions without the SECs. More preferably, the alpha-2-adrenergic agonist components have increased solubility in the present compositions at pH's in the range of about 7 to about 10 and, as compared to identical alpha-2-adrenergic agonist components in similar compositions, at comparable concentrations, without the SECs.

Without wishing to be limited by any theory or mechanism of operation, it is believed that solubilized alpha-2-adrenergic agonist components are better able to cross the lipid membranes relative to unsolubilized alpha-2-adrenergic agonist components. It is further believed that the solubilized alpha-2-adrenergic agonist components

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are physically smaller and are therefore more able to physically permeate or diffuse through the lipid membranes.

In one embodiment, the SECs of this invention are capable of solubilizing the alpha-2-adrenergic agonist components in the biological environments into which they are introduced at therapeutically effective concentrations. Preferably, the biological environments into which the present compositions are introduced have pH's ranging from about 7 to about 9. For example, a composition comprising a SEC and an alpha-2-adrenergic agonist component may be administered to the cornea of an eye, which has a pH of about 7, wherein the alpha-2-adrenergic agonist component is substantially solubilized at the administered area. Furthermore, in one embodiment, the alpha-2-adrenergic agonist components solubilized by SECs at the administered area diffuse through biological lipid membranes more readily than alpha-2-adrenergic agonist components which are not solubilized by SECs. The solubilization of alpha-2-adrenergic agonist components preferably reduces irritation to sensitive tissues in contact or interacting with the alpha-2-adrenergic agonist components.

The presently useful alpha-2-adrenergic agonist components preferably are chosen to benefit from the presence of the SECs. In general, the alpha-2-adrenergic agonist components are provided with increased apparent solubility, preferably increased apparent water solubility, by the presence of the SECs.

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

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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,

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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. Patent No. 5,703,077. See also Danielwicz et al 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

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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

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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
  - metal p-styrenesulfonate
  - 2-methacryloyloxyethylsulfonic acids

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metal 2-methacryloyloxethylsulfonates
3-methacryloyloxy-2-hydroxypropylsulonic acids
metal 3-methacryloyloxy-2-hydroxypropylsulfonates
2-acrylamido-2-methylpropanesulfonic acids
metal 2-acrylamido-2-methylpropanesulfonates
allylsulfonic acid
metal allylsulfonate and the like.

In another embodiment, the polyanionic components include anionic polysaccharides which tend to exist in ionized forms at higher pH's, for example, pH's of about 7 or higher. The following are some examples of anionic polysaccharides which may be employed in accordance with this invention.

Polydextrose is a randomly bonded condensation polymer of dextrose which is only partially metabolized by mammals. The polymer can contain a minor amount of bound sorbitol, citric acid, and glucose.

Chondroitin sulfate also known as sodium chondroitin sulfate is a mucopolysaccharide found in every part of human tissue, specifically cartilage, bones, tendons, ligaments, and vascular walls. This polysaccharide has been extracted and purified from the cartilage of sharks.

Carrageenan is a linear polysaccharide having repeating galactose units and 3,6 anhydrogalactose units, both of which can be sulfated or nonsulfated, joined by alternating 1-3 and beta 1-4 glycosidic linkages. Carrageenan is a hydrocolloid which is heat extracted from several species of red seaweed and irish moss.

Maltodextrins are water soluble glucose polymers which are formed by the reaction of starch with an acid and/or enzymes in the presence of water.

Other anionic polysaccharides found useful in the

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