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Huth

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(54) **COMPOSITIONS FOR TREATING HYPEREMIA**

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A61K 47/30 (2006.01)

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(58) **Field of Classification Search** 424/78.04, 424/427, 400, 401, 466, 422; 514/772.3, 514/781, 784, 785, 772.4, 772.6, 249
See application file for complete search history.

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(57) **ABSTRACT**

The present compositions advantageously treat hyperemia with substantially no added irritation to the eye. In one embodiment, the compositions include an ophthalmically acceptable carrier component, a vasoconstrictor component in an amount effective to treat hyperemia when the composition is administered to an eye, and a polyanionic component in an amount effective to provide lubrication to an eye when the compositions are administered to the eye.

17 Claims, 2 Drawing Sheets

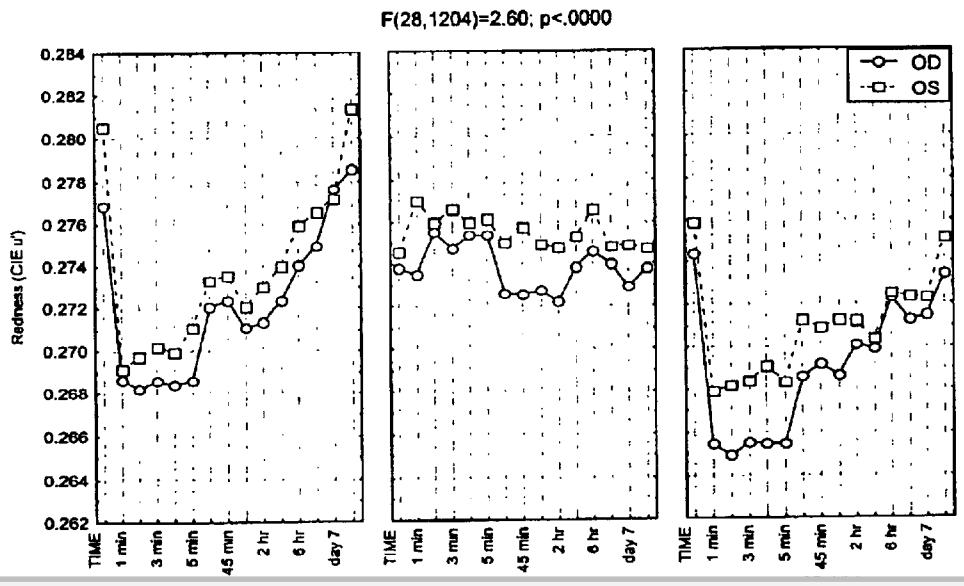


Figure 1
F(28,1204)=2.60; p<.0000

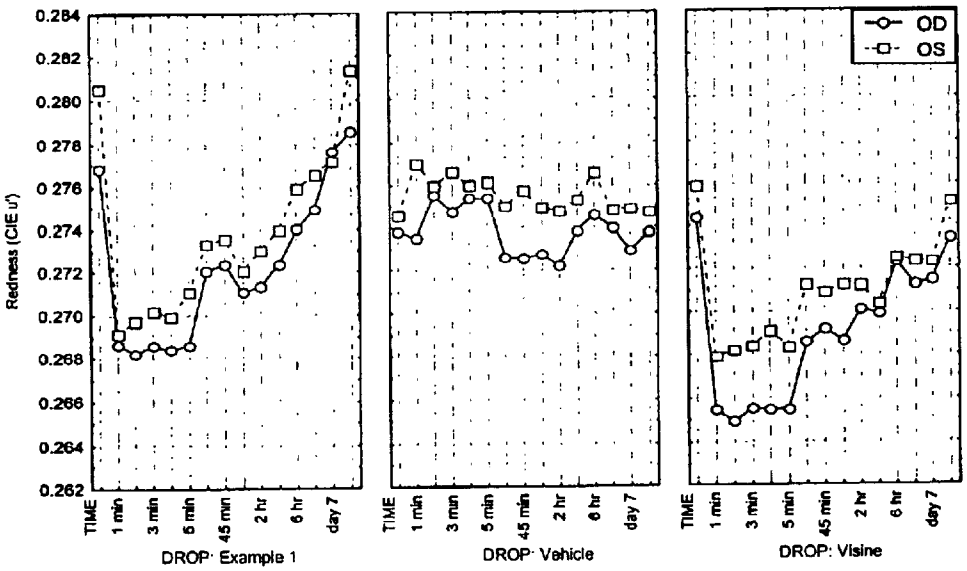


Figure 2a
F(26,1118)=18 76, p<0.000

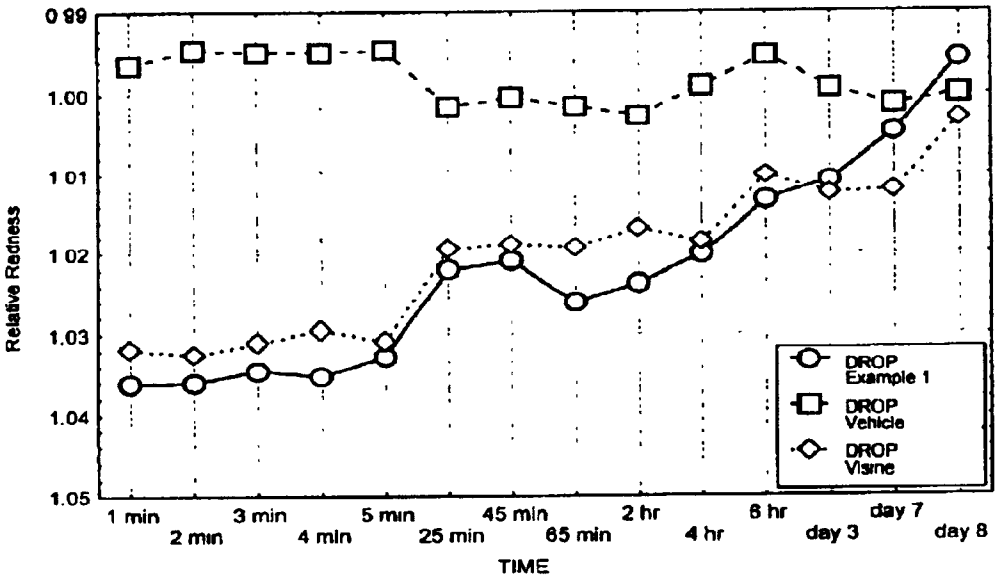
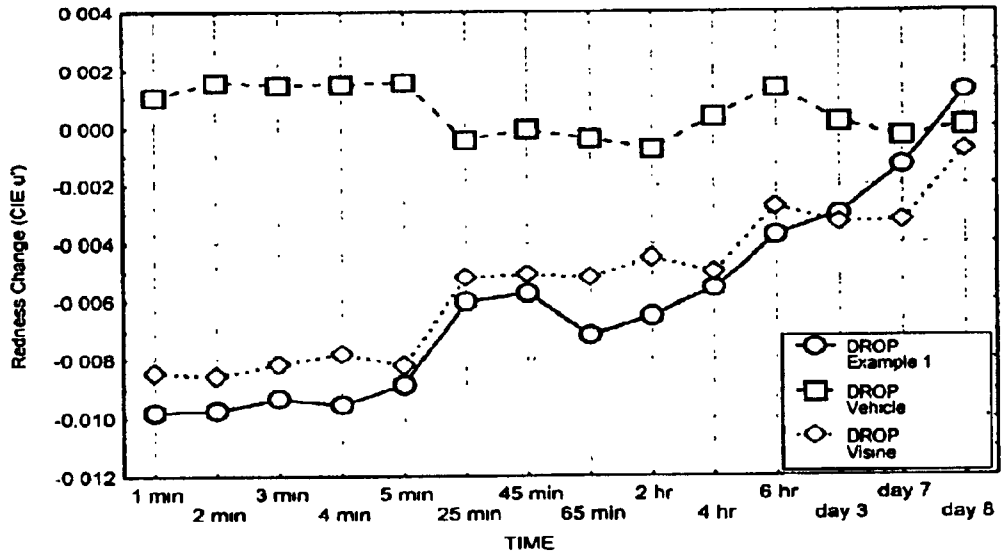


Figure 2b
F(26,1118)=17.93, p<0 000



COMPOSITIONS FOR TREATING HYPEREMIA

BACKGROUND OF THE INVENTION

The present invention relates to compositions including vasoconstrictor components for treating ocular hyperemia, preferably without resulting in significant eye irritation, and to methods for making and using such compositions. In one embodiment, the present invention relates to compositions effective to provide dual treatments for eye conditions, for example a dual treatment of hyperemia and dry eye.

Reddening or inflammation of the superficial tissues of the eye is a relatively common affliction since it usually accompanies various allergic reactions, such as hay fever allergies and the like, foreign body irritation in the eye, or eye fatigue. Such superficial conjunctival redness, often referred to as hyperemia or ocular hyperemia, can be the result of ciliary flush, dilation of the deep straight vessels of the episclera, and/or dilation of the superficial vessels of the conjunctiva.

Various types of palliative treatments have been used to treat this condition. The most common treatment includes the administration of eye drops which contain emollients and other ingredients designed to ease the discomfort due to the inflammation and to eliminate the redness associated with the condition. These treatments have not been entirely satisfactory, however.

For example, many commercially available eye drops include preservatives, an ingredient which may be quite harmful to the eye. Furthermore, many of the commercially available eye drops include ethylenediaminetetraacetic acid and/or salts thereof (EDTA), which may produce substantial discomfort when the eye drops are administered to the eye.

Also, these commercially available products often have pHs which are relatively acidic and can result in ocular irritation and/or discomfort.

Thus, there is a continued need to have improved compositions and methods for treating hyperemia.

SUMMARY OF THE INVENTION

New ophthalmic compositions useful for the treatment of hyperemia, and methods of making and using such compositions, have been discovered. The present compositions advantageously treat hyperemia with substantially no added irritation to the eye. These compositions are relatively straightforward, can be easily and cost effectively manufactured and can be used much like conventional eye drops. In one embodiment, the present compositions are effective to provide dual treatments for eye conditions, for example a dual treatment of hyperemia and dry eye.

In accordance with one broad aspect of the present invention, compositions are provided comprising an ophthalmically acceptable carrier component, preferably an aqueous carrier component, a vasoconstrictor component in an amount effective to treat hyperemia when the composition is administered to an eye, and a demulcent component, preferably a polyanionic component, in an amount effective to provide lubrication to an eye when the composition is administered to the eye. Advantageously, the present compositions are solutions, more preferably, liquid solutions, to facilitate convenient, consistent and effective use of the compositions.

In another broad aspect of the present invention, compositions are provided comprising an ophthalmically acceptable carrier component, a chlorine dioxide precursor component in an amount effective in preserving the composition, and a vasoconstrictor component in an amount effective to treat hyperemia when the composition is administered to an eye.

In a further broad aspect of the invention, compositions are provided comprising an ophthalmically acceptable, aqueous carrier component including at least one of a potassium component and an alkaline earth metal component, and a vasoconstrictor component in an amount effective to treat hyperemia when the composition is administered to an eye.

In an additional broad aspect of the invention, compositions are provided comprising an ophthalmically acceptable aqueous carrier component and a vasoconstrictor component in an amount effective to treat hyperemia when the composition is administered to an eye, the component having a pH in a range of about 6.7 to about 7.2 or about 7.4 or about 8.0.

Any suitable vasoconstrictor component may be employed in the present invention provided it is effective to treat ocular hyperemia. Advantageously, the vasoconstrictor is compatible with the other components of the composition, for example, is stable in the presence of the other components of the composition, for example for at least about 6 months or at least about 12 months, during storage. In one embodiment, the compositions are stable for about 36 months.

In a very useful embodiment, the vasoconstrictor component comprises at least one alpha-1-adrenergic agonist. For example, the vasoconstrictor component may be selected from the group consisting of tetrahydrozoline, ephedrine, naphazoline, phenylephrine, salts thereof and mixtures thereof. More preferably, the vasoconstrictor component is selected from tetrahydrozoline, salts thereof and mixtures thereof. In one useful embodiment, the present composition comprises about 0.001% or about 0.005% to about 0.15% or about 0.5% (w/v), more preferably about 0.01% to about 0.05% (w/v), of the vasoconstrictor component.

Any suitable demulcent may be employed in accordance with the invention, as long as it is compatible with other components in the composition. In one embodiment, the demulcent provides for lubrication to the eye. Non-limiting examples of demulcents include polyanionic components, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, dextran, gelatin, glycerin, polyethylene glycols, for example, polyethylene glycol 300, polyethylene glycol 400 and the like, polysorbate, propylene glycol, polyvinyl alcohol, polyvinyl pyrrolidone and the like and mixtures thereof. In one embodiment, the polyanionic component is selected from the group consisting of anionic cellulosic derivatives and mixtures thereof. In one embodiment, the polyanionic component is selected from the group consisting of carboxy methyl celluloses and mixtures thereof. Preferably, the present compositions comprise about 0.05% or about 0.1% to about 5% (w/v), more preferably about 0.15% or about 0.3% to about 2%, of a polyanionic component.

Still further in accordance with the present invention, the compositions comprise a carrier component. In one embodiment, the carrier component comprises water and has a pH in a range of about 6.7 to about 8.0, more preferably about 6.8 to about 7.2. In one embodiment, the carrier component comprises an electrolyte component. In one embodiment, the carrier component includes an alkaline earth metal component, for example, calcium components,

in an amount in a range of about 0.001% to about 0.05% (w/v), preferably about 0.005% to about 0.2% (w/v). In one embodiment, the carrier component comprises an electrolyte component. In one embodiment, the present compositions are free of an ethylenediaminetetraacetic acid (EDTA) component, for example, EDTA, salts of EDTA, and the like and mixtures thereof.

In one embodiment, the chlorine dioxide precursor component is present in an amount in a range of about 10 ppm to about 200 ppm. Preferably, the chlorine dioxide precursor component is the sole material effective as a preservative in the composition. In one embodiment, the chlorine dioxide precursor component includes at least one chlorite component. In one embodiment, the chlorine dioxide precursor component includes stabilized chlorine dioxide.

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.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a presentation of eye redness data from a comparative study of a composition, in accordance with the present invention and Visine® eye drops.

FIG. **2***a* shows another presentation of these redness data.

FIG. **2***b* shows a further presentation of these redness data.

DETAILED DESCRIPTION OF THE INVENTION

The present invention involves ophthalmic compositions, which are advantageously ophthalmically acceptable, comprising an ophthalmically acceptable carrier component, a vasoconstrictor component and, optionally, a demulcent component, for example a polyanionic component.

A composition, carrier component or other material is "ophthalmically acceptable" when it is compatible with ocular tissue, that is, it does not cause significant or undue detrimental effects when brought into contact with ocular tissue. Preferably, the ophthalmically acceptable material is also compatible with other components of the present compositions.

The present compositions treat hyperemia advantageously with substantially no added irritation to the eye. In one embodiment, the present compositions treat hyperemia and dry eye syndrome advantageously with substantially no added irritation to the eye.

The present compositions preferably are solutions, although other forms, such as ointments, gels, and the like, may be employed.

Preferably, the present compositions meet, and pass, the EP-B antimicrobial preservative effectiveness criteria.

The present compositions include a vasoconstrictor component. In one embodiment, the vasoconstrictor component comprises an agent, for example a compound, which is effective in constricting a blood vessel of an eye, preferably a blood vessel on or near the ocular surface of the eye. In one

1-adrenergic agonists include tetrahydrozoline, ephedrine, naphazoline, phenylephrine, salts thereof and mixtures thereof. Preferably, the vasoconstrictor component is stable in the composition. For example, it is preferred that the vasoconstrictor component is not degraded, is soluble in the compositions and/or is therapeutically effective when the compositions are administered to the eye. Also, it is preferable that the vasoconstrictor component is stable in the compositions for more than about 10 months, preferably about 18 months, more preferably about 36 months or more, at storage conditions. In a preferred embodiment, the vasoconstrictor component comprises a tetrahydrozoline and/or a salt thereof.

The compositions comprise an amount of vasoconstrictor component effective to treat hyperemia when the compositions are administered to the eye. In one embodiment, the compositions comprise about 0.005% to about 0.15% (w/v) of the vasoconstrictor component. In one embodiment, the compositions comprise about 0.01% to about 0.10%, preferably 0.01% to about 0.05% of the vasoconstrictor component.

In one embodiment, the present compositions comprise a demulcent component. Without wishing to limit the invention to any theory or mechanism of operation, it is believed that the demulcent component is believed to be effective in lubricating an eye, for example, an eye which has, or has a propensity for having, dry eye syndrome. Non-limiting examples of demulcent components include polyanionic components, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose, dextran, gelatin, glycerin, polyethylene glycols, for example, polyethylene glycol 300, polyethylene glycol 400 and the like, polysorbates, propylene glycol, polyvinyl alcohol, polyvinyl pyrrolidone and the like and mixtures thereof. See U.S. Pat. Nos. 4,421,748 and 5,474,979, the disclosure of each of which is incorporated in its entirety herein by reference. The demulcent component preferably is present, if at all, in a range of about 0.1% to about 5 (w/v).

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 the group consisting of polymeric materials having multiple anionic charges and mixtures thereof.

Any suitable polyanionic component may be employed in accordance with the present invention provided that it functions as described herein and has no substantial detrimental effect on the compositions as a whole or on the eye to which the compositions are administered. The polyanionic component is preferably ophthalmically acceptable at the concentrations used. 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 present compositions at ambient (room) temperature.

Examples of suitable polyanionic components useful in the present compositions include, without limitation, anionic cellulose derivatives, anionic acrylic acid-containing

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