



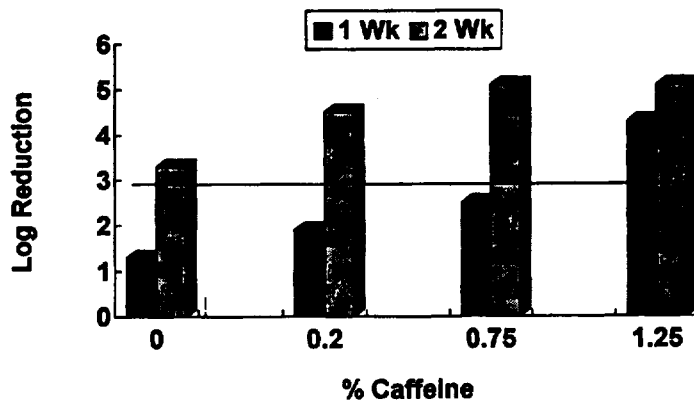
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(54) Title: TOPICAL OPHTHALMIC FORMULATIONS COMPRISING AN ACIDIC DRUG, VITAMIN E TPGS, BENZALKONIUM CHLORIDE AND CAFFEINE

0.1% Diclofenac, 0.01% BAC, 1.5% TPGS

▷ *S. aureus* PET screen



(57) Abstract

Stable, comfortable, preserved, topical, ophthalmic compositions of acid drugs and their use for treating inflammation of the eye are disclosed. The compositions contain an acidic drug (e.g. a NSAID, preferably diclofenac, or a prostaglandin), Vitamin E, TPGS, Benzalkonium chloride or homologues thereof and caffeine.

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Field of the Invention

This application is directed to stable and comfortable preserved ophthalmic formulations containing an acidic drug.

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Background of the Invention

Carboxyl containing compounds, including most non-steroidal antiinflammatory drugs (NSAIDs), are difficult to formulate into stable, preserved, comfortable, ophthalmic compositions. Acidic drugs with carboxyl groups are inherently irritating to the eye. In addition, the drugs tend to form insoluble complexes with quaternary ammonium preservatives, such as benzalkonium chloride (BAC). Many NSAIDs have been formulated with other than desirable preservatives (e.g. sorbic acid, thimerosol) because the compounds complex with desired preservatives, such as, quaternary ammonium compounds, particularly BAC. In addition, it has proved difficult to formulate carboxyl containing compounds that are comfortable when applied topically to the eye.

There are ophthalmic products containing acidic drugs. Commonly, these drugs are NSAIDs containing a carboxyl group. Examples of these products are suprofen (Profenal[®], Alcon Laboratories, Inc. which is preserved with thimerosol); diclofenac sodium (Voltaren Ophthalmic[™], Ciba Vision Ophthalmics which is preserved with sorbic acid); flurbiprofen sodium (Ocufer[®], Allergan Medical Optics which is preserved with thimerosol); and ketorolac tromethamine (Acular[®], Allergan, Inc. which is preserved with BAC and Octoxynol 40).

U. S. Patent No. 5,110,493 discloses aqueous, ophthalmic, non-steroidal anti-inflammatory formulations which include a preservative system formed of a quaternary ammonium compound and a nonionic surfactant which is an ethoxylated alkyl phenol, such as Octoxynol 10 or 40.

WO 94/15597 discloses the use of lauralkonium chloride, a C₁₂ homologue of BAC, which is compatible with acidic drug entities in ophthalmic formulations.

U. S. Patent No. 4,960,799 discloses an ophthalmic formulation of a salt of ortho-
5 (2,6-dichlorophenyl) aminophenylacetic acid, EDTA, a solubilizer, and a bacteriostat.

EP 0,621,036-A1 discloses ophthalmic formulations of particular arginine amides
and either cyclodextrin or caffeine. The application discloses that the use of cyclodextrin
or caffeine improves the arginine amide solubility in water and that the caffeine can
10 stabilize the compound in water.

U. S. Patent No. 4,559,343 discloses ophthalmic formulations containing NSAIDs
and a xanthine derivative to reduce ocular discomfort.

15 The compositions of the present invention are stable, yet they contain an acidic
drug and the desired preservative, BAC, or mixtures of at least two homologues of BAC.
In addition, the compositions are comfortable upon topical instillation in the eye.

Summary of the Invention

20 The present invention is directed to stable, comfortable, and preserved topical
ophthalmic formulations comprising an acidic drug, Vitamin E Tocopherol Polyethylene
Glycol 1000 Succinate (TPGS) (Eastman Chemical Co., Kingsport, TN), BAC, or mixtures
of at least two homologues of BAC, and caffeine. Types of acidic drugs can include
25 NSAIDs, antibacterials, diagnostic agents, antiinfective agents, and prostaglandins.
Methods for the compositions' use are also disclosed.

PC1/0390/01970

Brief Description of the Drawing

Figure 1 shows the effect of caffeine concentration on the preservative efficacy of BAC.

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Detailed Description of Preferred Embodiments

The compositions of the present invention comprise an acidic drug, Vitamin E TPGS, BAC, or mixtures of BAC homologues, such as C₁₂ and C₁₄ and caffeine. As used herein the term "acidic" means the drug contains a carboxyl moiety or a salt thereof and/or a sulfamide group or a salt thereof.

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Acidic drugs which can be formulated according to the present invention include NSAIDs, including, but not limited to, diclofenac, bromfenac, flurbiprofen, naproxen, ketorolac, suprofen, ibuprofen, and tolmetin, including their pharmaceutically acceptable salts, esters, and prodrugs; prostaglandins; antibacterial and antiinfective agents; and diagnostic agents. BAC is used to preserve the formulations. The Vitamin E TPGS is used to solubilize the acidic drug and reduce ocular discomfort in aqueous conditions. The caffeine is added to reduce ocular discomfort, but surprisingly, it was found that it acts synergistically with Vitamin E TPGS to reduce discomfort and it also potentiates the preservative efficacy of BAC.

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In the formulations, the acidic drug is present at concentrations from 0.001 weight percent (wt. %) to 2.5 wt. %, preferably 0.01 to 1.0 wt. %. The Vitamin E TPGS concentration is 0.0001 to 30 wt. %, preferably 0.01 to 10 wt. %. BAC or its homologue mixtures are present at concentrations from 0.00001 to 0.02 wt. %, preferably .0001 to 0.01 wt. %; and the caffeine concentration is from 0.001 to 5.0 wt. %, preferably 0.01 to 1.0 wt. %.

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The compositions of the invention may also contain other components such as, but not limited to, those listed below:

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