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(54) **OPHTHALMIC COMPOSITION**

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(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

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(51) **Int. Cl.**[7] **A61K 31/19**
(52) **U.S. Cl.** **514/570**; 514/912
(58) **Field of Search** ..... 514/91 L, 570

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(57) **ABSTRACT**

An ophthalmic composition containing a divalent salt and a non-steroidal anti-inflammatory agent as a precipitate. The composition reduces or eliminates the risk of stinging and burning the eye from topical application. Additionally a preservative system comprising a perborate salt, a polyphosphonic acid peroxy stabilizer and EDTA provides stable preservation of a variety of aqueous ophthalmic compositions.

31 Claims, 1 Drawing Sheet

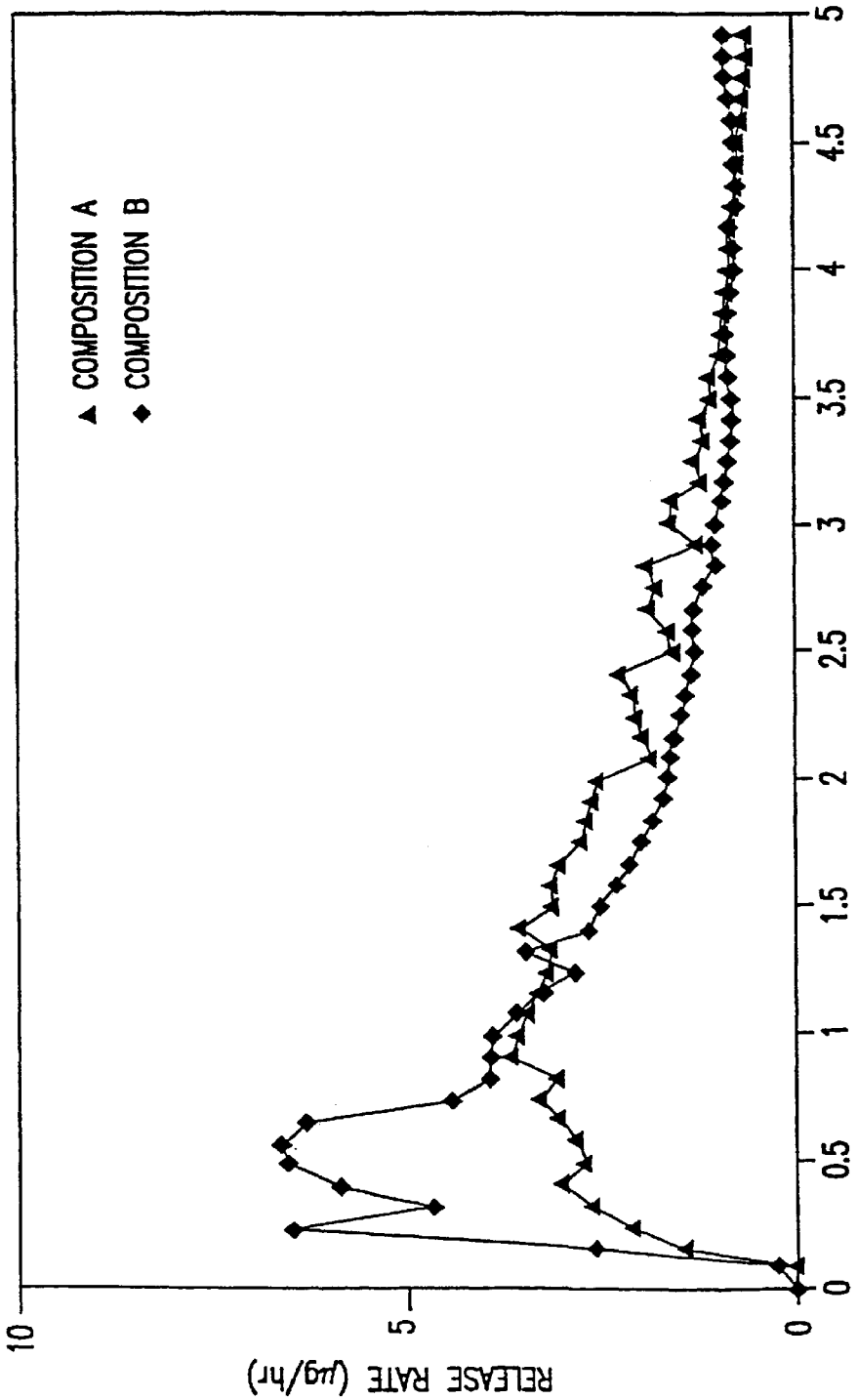

FIG. 1

OPHTHALMIC COMPOSITION

This application is a Continuation-in-Part of prior co-pending application Ser. No. 08/863,015, filed May 23, 1997, the entire contents of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to ophthalmic compositions and more particularly, to ophthalmic compositions containing a divalent cation and a non-steroidal anti-inflammatory agent and/or to ophthalmic compositions containing a preservative system.

2. Description of the Related Art

Non-steroidal anti-inflammatory agents can be used in a variety of ophthalmic treatments such as for treating ocular tissue inflammation and its associated pain. Additional uses include (i) preventing particular side-effects from surgical trauma (e.g., on the pupil preventing surgical meiosis), (ii) preventing fluid accumulation in the back of the eye after cataract surgery (post-surgical macular edema) and (iii) preventing the appearance of inflammatory cells and vessel leakage in the anterior chamber. Diclofenac, suprofen, and flurbiprofin are specific examples of non-steroidal anti-inflammatory agents that have been used for the treatment of postoperative inflammation in patients who have undergone cataract extraction. Topical application of non-steroidal anti-inflammatory agents in the eye also appears to relieve some of the itching due to allergic conjunctivitis.

In the past, anti-inflammatory agents, in general, have been administered in solutions at neutral pH. Injection of anti-inflammatory agents in the form of a suspension has also been proposed. Suspensions have been used for topical ophthalmic applications when the drug is not very soluble. However, when the drug is soluble, at an acceptable pH, solutions are normally used to avoid potential irritation caused by the particles of the suspension. The following patents illustrate ophthalmic solutions containing non-steroidal anti-inflammatory agents, including diclofenac.

U.S. Pat. No. 4,960,799 to Nagy concerns a storage stable aqueous solution of sodium ortho-(2,6-dichlorophenyl) aminophenylacetate acid, which is the chemical name for diclofenac sodium, for topical treatment of ocular inflammation. The solution taught by Nagy has a pH of about 7.0 to 7.8.

U.S. Pat. No. 4,829,088 to Doulakas also relates to an ophthalmic medicament containing diclofenac sodium in aqueous solution. The solution contains 2-amino-2-hydroxymethyl-1,3-propanediol as a preservative.

U.S. Pat. No. 5,110,493 to Cherng-Chyi et al. relates to ophthalmic non-steroidal anti-inflammatory drug formulations containing a quaternary ammonium preservative and a non-ionic surfactant.

Patent Abstracts of Japan, Vol. 8, No. 7, Abs. Gp. C-204, concerning Japanese published application 58-174309 (pub. Oct. 13, 1983) relates to an antiphlogistic eye drop composition containing (1) a non-steroidal antiphlogistic agent having a carboxyl group in its structure and (2) a physiologically permissible calcium or magnesium salt. The salt is described as an irritation mitigating agent and is normally added in an amount of 1–1.5 mol per 1 mol of the non-steroidal agent. Sodium diclofenac is specifically mentioned as the non-steroidal antiphlogistic agent and the pH of the composition is preferably maintained in the 7–8 range.

However, a problem with the use of non-steroidal anti-inflammatory agents, as recognized in the above-mentioned Japanese published application, is that stinging or burning sensations are commonly experienced during the first few minutes after topical administration on the eye. Not only are patients who experience such stinging likely to avoid regularly taking their medication, they also receive less benefit from each application. Specifically, the stinging causes tearing which washes away the drug. Having physically removed a portion of the drug from the eye by tearing, the bioavailability of the drug is reduced.

In addressing the stinging problem, it has been proposed to supply a portion of the non-steroidal anti-inflammatory agent in suspension form, as is described in commonly assigned co-pending application Ser. No. 08/248,500, filed May 24, 1994 (the entire contents of which are hereby incorporated by reference). The particle must dissolve before it can treat the eye. By providing some of the active agent as a particle, the flow of the drug onto the eye is delayed; i.e., providing some of the active agent as a particle reduces the initial concentration of the drug contacting the eye. This delay in drug delivery contrasted with the prior compositions wherein all of the agent was in solution, owing to a pH of 7–8, thereby immediately providing to the cornea a high concentration of the drug. The high concentration of the drug on the eye was believed to aggravate the burning and stinging effects of the drug.

While some improvements have been made with respect to the stinging problem by such a technique, there is still a segment of the population that will experience stinging when topically administering non-steroidal anti-inflammatory ophthalmic compositions. Accordingly, further improvements are desirable.

Additionally, preserving an ophthalmic composition that contains a non-steroidal anti-inflammatory agent can be problematic. Conventional broad spectrum antimicrobial agents like benzalkonium chloride (BAK) tend to interact with the non-steroidal anti-inflammatory agents over time and thereby reduce the efficacy of the medication. Indeed, as a general matter, preservatives in ophthalmic compositions are not entirely satisfactory. Effective, broad spectrum antimicrobials tend to reduce the storage stability of the composition and/or have adverse interactions with other components.

A useful preservative system that seeks to overcome some of these deficiencies is disclosed in U.S. Pat. Nos. 5,576,028 and 5,607,698. These systems use a low amount of hydrogen peroxide, or a hydrogen peroxide source, as a preservative in combination with a peroxy stabilizer. The stabilizer is preferably a phosphonic acid such as diethylene triamine penta (methylene-phosphonic acid) and the like which are commercially available from Monsanto under the DEQUEST brand name. Although this system is quite useful, certain improvements in storage stability would be desirable.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide an ophthalmic composition that contains a topically effective amount of a non-steroidal anti-inflammatory agent and that is no more irritating than conventional eye drops.

It is another object of the present invention to provide a non-steroidal anti-inflammatory agent-containing ophthalmic composition that can be taken by a large segment of the population without experiencing stinging or irritation.

A further object of the present invention is to provide a preserved ophthalmic composition that exhibits good stability during storage.

Another object of the present invention is to provide a method for treating diseases of the eye, including inflammation, by topically applying to eyes in need of such treatment a non-steroidal anti-inflammatory agent-containing ophthalmic composition.

Preferred forms of the invention contemplated accomplish at least some of the above objects. One embodiment of the invention is an ophthalmic composition comprising an aqueous medium containing an effective amount of a non-steroidal anti-inflammatory agent, wherein at least about 80 mol. % of said agent is in the form of a precipitate, and at least about 0.5 equivalents of a pharmacologically acceptable divalent cation per mole of said non-steroidal anti-inflammatory agent; said aqueous medium having a pH of from about 4.0 to 6.7. Another embodiment of the invention relates to a method for treating an eye, which comprises administering to an eye in need thereof an effective amount of such an ophthalmic composition. A further aspect of the present invention relates to a method for making such an ophthalmic composition. Another preferred embodiment of the present invention relates to an ophthalmic composition that is formed by combining at least (1) sodium diclofenac, (2) a divalent metal salt, (3) a water insoluble, water-swellable polymer, and (4) water.

A further embodiment of the invention is an ophthalmic composition which comprises water, about 0.01 to 0.5 wt. % of a perborate salt, about 0.001 to 0.06 wt. % of a polyphosphonic acid peroxy stabilizer, and about 0.01 to 0.1 wt. % of ethylenediaminetetraacetic acid. The composition in this embodiment may further comprise a pharmaceutically active agent such as a non-steroidal anti-inflammatory agent.

BRIEF DESCRIPTION OF THE DRAWING

FIG. **1** shows the illustrious results of Example 21 regarding release rate curves for an inventive and a comparative ophthalmic composition.

DETAILED DESCRIPTION OF THE INVENTION

The present inventors have discovered that by providing the non-steroidal anti-inflammatory (NSAI) agent as a solid and in the presence of a divalent cation, the dissolution of the NSAI agent during the first several minutes at neutral pH is sufficiently slowed so as to further avoid stinging the eye. For reasons that are not entirely clear, stinging and burning irritation are typically only induced during the first minutes after contact with a sufficiently high concentration of NSAI agent. After this initial time period, the eye is apparently no longer sensitive to the NSAI agent, regardless of its concentration level. Thus, by delaying the dissolution of the NSAI agent during the first few minutes, the initial NSAI agent concentration on the eye can be sufficiently low to avoid irritation. Afterward, the high concentration caused by the dissolution of the solid NSAI agent precipitate is too late to cause irritation. In this way the stinging problem is effectively avoided while still providing a topically effective dose of NSAI agent.

In contrast, the typical prior art composition would supply all of the NSAI agent as a solute and thus apply an immediate high concentration to the surface of the eye. Such a technique has the greatest chance of inducing stinging in the patient. While the use of sodium diclofenac in both suspension and solution form, simultaneously, is described in the above-mentioned co-pending application and provides good results, the presence of a divalent cation in accordance with the present invention improves the avoidance of stinging. The divalent cation reduces the solubility of the NSAI agent in the aqueous medium and thus reduces the dissolution rate of the solid NSAI agent precipitate during the first several minutes after administration.

As used in this application, the term "divalent cation" means a cation having a +2 charge. The divalent cation can be in either solid or dissolved form, or both. In solid form, the cation is ionically bonded to an anion thereby making a salt. When in solution, the cation is not required to be directly associated with a specific anion. Typically the cation is, or contains, a metal; i.e., a "metal divalent cation". Examples of suitable divalent cations include Group IIA elements (alkaline earth metals) such as calcium, magnesium, barium, etc. Particularly preferred divalent cations are Ca^{++} and Mg^{++}. The divalent cation and any salts thereof in the composition are pharmacologically acceptable so as to not harm the eye or the patient. Typical anions include chlorides, sulfates, and the NSAI agent.

The divalent cation is only required to be present in the composition and is not necessarily associated or otherwise bonded with the NSAI agent. In one embodiment, all or essentially all of the divalent cation is in solution with no cation present in the solid NSAI agent.

The amount of divalent cation is at least about 0.5 equivalents and generally within the range of from about 0.5 to about 10 equivalents, more preferably 1.0 to about 5.0 equivalents, per mole of NSAI. Note that molar equivalents are specified since NSAI agents may be monovalent and hence stoichiometrically require only half as many moles of the divalent cation. Thus, for example, one mole of Mg^{++} per one mole of diclofenac anion would be 2.0 equivalents of Mg^{++} (twice as much cation as is required).

"Non-steroidal anti-inflammatory agents" as used herein are intended to mean any non-narcotic analgesic/non-steroidal anti-inflammatory compound useful in treating or ameliorating a disease or medical condition. They include drugs intended to therapeutically treat conditions of the eye itself or the tissue surrounding the eye and drugs administered via the ophthalmic route to treat therapeutically a local condition other than that involving the eye. Preferably the NSAI agent is useful as a cyclooxygenase inhibitor. Cyclooxygenase is essential in the biosynthesis of prostaglandins which have been shown in many animal models to be mediators of intraocular inflammation. The NSAI agent typically contains at least one carboxy group in its molecule.

Examples of NSAI agents that are useful in the present invention include aspirin, benoxaprofen, benzofenac, bucloxic acid, butibufen, caiprofen, ciclopROfen, cinmetacin, clidanac, clopirac, diclofenac, etodolac, fenbufen, fenclofenac, fenclorac, fenoprofen, fentiazac, flunoxaprofen, furaprofen, flurbiprofen, furobufen, furofenac, ibuprofen, ibufenac, indomethacin, indoprofen, isoxepac, ketorolac, ketroprofen, lactorolac, lonazolac, metiazinic, miroprofen, naproxen, oxaprozin, oxepinac, phenacetin, pirprofen, pirazolac, protizinic acid, sulindac, suprofen, tiaprofenic acid, tolmetin, and zomepirac. Preferably, the NSAI agent is selected from the group consisting of diclofenac, suprofen, flurbiprofen and mixtures thereof.

The composition of the present invention contains at least 80% of the NSAI agent in precipitate form. This means that 80%, by mole, of the NSAI is in a solid state. The remainder, if any, is in solution. In this regard the term "precipitate" is not meant to require that the solid was formed by a precipitation process, although such is usually the case. Preferably, 85% to 95% of the NSAI agent is in precipitate form. The

precipitate is usually dispersed in the aqueous medium or carried on a dispersed carrier such as a polymer particle, but such a dispersed form is not required.

In one embodiment of the invention, the precipitate is the free-acid form (or free-base form) and not a salt form of the NSAI agent. Generally, the free-acid is almost always formed, even if formed from an NSAI divalent salt solution. For example, originally, a calcium or magnesium salt of diclofenac was believed to have been formed as the precipitate. However, subsequent investigations showed that the precipitate was in fact the free-acid of diclofenac. The divalent cation remained in solution. The presence of this divalent cation serves to reduce the solubility of the NSAI agent; thereby causing the desired delayed release. Alternatively, the precipitate can be a salt of the divalent cation and the NSAI agent or a mixture of salt and the free-acid forms.

The remaining portion, if any, of the NSAI agent is in solution (a solute) and is typically in a salt form such as sodium diclofenac or magnesium diclofenac for example.

The total amount of NSAI agent present in the composition is an amount effective to treat the selected target condition. Generally the concentration will be about 0.001 to about 5.0% by weight of the composition. Preferably, the drug is about 0.005 to about 3.0% by weight of the composition, and more preferably about 0.1 to about 1.0% by weight of the composition. These same ranges of drug concentrations are believed to be appropriate for treating a wide range of conditions, such as those discussed above, in addition to treating inflammation.

The pH of the aqueous medium is set to be within the range of 4.0 to 6.7. Importantly the pH is below that of the pH of the eye. In this way, upon topical application of the composition to the eye, an increase in pH occurs thereby changing the solubility equilibrium of the NSAI agent and causing the precipitate to dissolve. As slow dissolution during the first minutes after administration is desired, the use of a lower pH is preferred, such as from 4.0 to 6.5.

The most preferred composition contains solid diclofenac in free-acid form and all of the divalent cation as well as the remaining diclofenac in solution. The divalent cation is preferably calcium or magnesium. One of the advantages of this composition is the ability to fully (100%) redissolve at pH 7.0 or above with adequate residence time in the eye. This means that all of the diclofenac is recovered and made bioavailable when the composition is placed into the eye.

The aqueous medium used in the present invention is made of water that has no physiologically or ophthalmologically harmful constituents. Typically purified or deionized water is used. The pH is adjusted by adding any physiologically and ophthalmologically acceptable pH adjusting acids, bases or buffers. Examples of acids include acetic, boric, citric, lactic, phosphoric, hydrochloric, and the like, and examples of bases include sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate, tromethamine, THAM (trishydroxymethylamino-methane), and the like. Salts and buffers would include citrate/dextrose, sodium bicarbonate, ammonium chloride and mixtures of the aforementioned acids and bases.

The osmotic pressure (π) of the present composition is preferably from about 10 milliosmolar (mOsM) to about 400 mOsM. If necessary, the osmotic pressure can be adjusted by using appropriate amounts of physiologically and ophthalmologically acceptable salts or excipients. When needed, sodium chloride is preferred to approximate physiologic fluid, and amounts of sodium chloride ranging from about 0.01% to about 1% by weight, and preferably from about 0.05% to about 0.45% by weight, based on the total weight of the composition, are typically used. Equivalent amounts of one or more salts made up of cations such as potassium, ammonium and the like and anions such as chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate, bisulfate, sodium bisulfate, ammonium sulfate, and the like can also be used in addition to or instead of sodium chloride to achieve osmolalities within the above-stated range. Sugars like mannitol, dextrose, glucose or other polyols may be added to adjust osmolarity.

The composition of the present invention may contain water soluble polymers or water insoluble polymers as a suspending agent. Examples of such soluble polymers are dextran, polyethylene glycols, polyvinylpyrolidone, polysaccaride gels, Gelrite®, and cellulosic polymers like hydroxypropyl methylcellulose as well as other polymeric demulcents. Water insoluble polymers are preferably crosslinked carboxy-vinyl polymers.

A preferred embodiment of the invention provides the ophthalmic composition as either gel or liquid drops that contain water insoluble, water-swellable polymers which release the drug over time; i.e., over one or more hours. Preferably, the polymer is contained in an amount of about 0.1 to about 6.5%, more preferably about 0.5 to about 1.3% by weight based on the total weight of the composition. These polymer carriers include lightly crosslinked carboxy-containing polymers (such as polycarbophil (Noveon AA-1) or Carbopol®) which typically have an average dry particle size of not more than about 50 μm in equivalent spherical diameter, more preferably not more than 20μm in equivalent spherical diameter. The crosslinked carboxy-containing polymers can be formed from carboxy-containing monoethylenically unsaturated monomers such as acrylic acid, methacrylic acid, crotonic acid, and the like and from suitable crosslinking agents such as difunctional crosslinkers including divinyl glycol, divinyl benzene, 2,5-dimethyl-1,5-hexadiene, and polyalkenyl polyether compounds. The carboxy-containing polymer backbone can be a homopolymer or a copolymer comprised of two or more monomer species. When two or more monomers are used, non-carboxy-containing monomers may be employed, such as acrylic acid esters and methacrylic acid esters (ethyl acrylate, methyl methacrylate, etc.), vinyl acetate, N-vinylpyrrolidone, and the like. These non-carboxy-containing comonomers are preferably present in an amount of not more than 40 wt. %, more preferably 0 to 20 wt. %, based on the total weight of monomers present. The amount of crosslinker employed is preferably from about 0.01 to 5%, more preferably from 0.1 to 1.0%, based on the total weight of monomers present. Suitable carboxy-containing polymers for use in the present invention and methods for making them are described in U.S. Pat. No. 5,192,535 to Davis et al. which is hereby incorporated by reference. A suitable carboxy-containing polymer system for use in the present composition is known by the tradename DuraSite®, containing polycarbophil, which is a sustained release topical ophthalmic delivery system that releases the drug at a controlled rate.

The ophthalmic compositions of the present invention have a viscosity that is suited for the selected route of administration. A viscosity up to about 30,000 centipoise is useful for a drop. About 30,000 to about 100,000 centipoise is an advantageous viscosity range for ophthalmic administration in ribbon form. The viscosity can be controlled in many ways known to the worker skilled in the art.

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