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(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2007/0287749 A1****Sawa et al.**(43) **Pub. Date: Dec. 13, 2007**(54) **BROMFENAC OPHTHALMIC
FORMULATIONS AND METHODS OF USE****Publication Classification**(75) Inventors: **Shirou Sawa**, Kobe-shi (JP); **Shuhei Fujita**, Kakogawa-shi (JP); **Lisa R. Grillone**, Carlsbad, CA (US)(51) **Int. Cl.**
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SAN FRANCISCO, CA 94111-3834 (US)**(57) **ABSTRACT**(73) Assignee: **ISTA Pharmaceuticals, Inc.**, Irvine, CA(21) Appl. No.: **11/755,662**(22) Filed: **May 30, 2007****Related U.S. Application Data**(63) Continuation-in-part of application No. 10/525,006,
filed on Mar. 28, 2005.(30) **Foreign Application Priority Data**

Jan. 21, 2003 (JP) 12427/2003

The present invention discloses a stability enhanced aqueous liquid preparation containing 2-amino-3-(4-bromobenzo-
zoyl)phenylacetic acid or its pharmacologically acceptable
salt or a hydrate thereof, an alkyl aryl polyether alcohol type
polymer such as tyloxapol, or a polyethylene glycol fatty
acid ester such as polyethylene glycol monostearate. The
present invention further discloses new bromfenac oph-
thalmic compositions which can potentially treat a broader
patient population, and have greater stability properties, and
may require a lower concentration or less doses of bro-
mfenac then previously known bromfenac compositions.
The present invention further comprises a method for treat-
ing inflammation and/or pain of the eye in a patient which
method comprises topical application to the eye of a patient
in need thereof of a therapeutically effective amount of a
topical ophthalmic composition comprising bromfenac at a
concentration of about 0.05% w/v to about 0.24% w/v.

BROMFENAC OPHTHALMIC FORMULATIONS AND METHODS OF USE

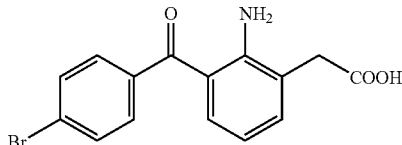
CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 10/525,006 filed Jan. 16, 2004, which claims priority to Japanese Patent Application No. 12427/2003 filed on Jan. 21, 2003 in Japan. This application also claims the benefit of priority from U.S. Provisional Patent Application 60/803,621, and 60/803,618 both filed May 31, 2006. All four of the listed applications are hereby incorporated in their entirety as if fully set forth.

BACKGROUND OF THE INVENTION

[0002] The present invention relates to an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof. More particularly, the present invention relates to an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

[0003] Benzoylphenylacetic acid derivatives including bromfenac (generic name) of formula (I):



[0004] of which chemical name is 2-amino-3-(4-bromobenzoyl)phenylacetic acid are known as disclosed in JP-A-23052/1977 and its corresponding U.S. Pat. No. 4,045, 576. 2-Amino-3-(4-bromobenzoyl)phenylacetic acid, its pharmacologically acceptable salt and a hydrate thereof are known as a non-steroidal anti-inflammatory agent, and they are effective against inflammatory diseases of anterior or posterior segment of the eye, such as blepharitis, conjunctivitis, scleritis, and postoperative inflammation in the field of ophthalmology, and its sodium salt has been practically used in the form of eye drops ("New Drugs in Japan, 2001", 2001 Edition, Published by Yakuji Nippo Ltd., May 11, 2001, p. 27-29).

[0005] The eye drop as mentioned above was designed to stabilize 2-amino-3-(4-bromobenzoyl)phenylacetic acid by means of addition of a water-soluble polymer (e.g. polyvinylpyrrolidone, polyvinyl alcohol, etc.) and a sulfite (e.g. sodium sulfite, potassium sulfite, etc.) (Japanese patent No. 2,683,676 and its corresponding U.S. Pat. No. 4,910,225).

[0006] In addition, as an eye drop other than the above-mentioned one, Japanese patent No. 2,954,356 (corresponding to U.S. Pat. Nos. 5,603,929 and 5,653,972) discloses a stable ophthalmic composition which comprises incorporating an antibacterial quaternary ammonium polymer and boric acid into an acidic ophthalmic agent. The acidic agent described therein includes, for example, 2-amino-3-(4-bromobenzoyl)phenylacetic acid.

[0007] Further, in Japanese patent No. 2,954,356, there is the following description—"Benzalkonium chloride is a widely used preservative in ophthalmic solutions. However, benzalkonium chloride and other quaternary ammonium compounds are generally considered to be incompatible with ophthalmic compositions of drugs with acidic groups, such as nonsteroidal anti-inflammatory drugs (NSAIDs). These preservatives lose their ability to function as they form complexes with the charged drug compounds".

[0008] In these prior art references, there is no disclosure that alkyl aryl polyether alcohol type polymers or polyethylene glycol fatty acid esters are able to stabilize an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt, and inhibit the decrease in preservative effect of benzalkonium chloride and other quaternary ammonium compounds.

[0009] The present invention further relates to ophthalmic formulations, kits and uses thereof, wherein the formulations utilize a stability enhanced bromfenac formulation for the treatment of ocular disorders, diseases or injuries.

[0010] The primary active ingredient contemplated in the present invention is bromfenac. Bromfenac is an anti-inflammatory compound classified as a Non-Steroidal Anti-Inflammatory Drug (NSAID).

[0011] The product inserts for many ophthalmic medications including an NSAID includes at least in part the following warnings.

[0012] All topical NSAIDs may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

[0013] Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health. Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight-threatening. Topical NSAIDs should be used with caution in these patients.

[0014] The literature is also filled with references to hazards related to prolonged NSAID use or deleterious effects associated with NSAID exposure in the eye. Therefore, any product that can decrease overall exposure while attaining equivalent results would be very useful in the treatment of many ophthalmic diseases, disorders or conditions. Moreover, any product that can be more efficacious even with a decreased concentration of an active agent and still achieve equal or better treatment results due to an enhanced stability, distribution, or metabolism of the active agent is in great demand.

BRIEF SUMMARY OF THE INVENTION

[0015] The present invention comprises a novel formulation of bromfenac or its derivative for the treatment of

various ophthalmic injuries, diseases or disorders. This novel formulation is chemically stable, and may be equally or more effective than the current bromfenac (Xibrom™ ophthalmic solution) on the market yet uses a lower concentration of the active ingredient, or enables the treatment to comprise only once a day administration of Bromfenac with a higher concentration of the active ingredient.

[0016] The present invention may also include a novel formulation of bromfenac which does not utilize sulfites (e.g. sodium sulfite) in the final formulation. Therefore, there should be no patient restrictions regarding those with allergic susceptibilities to sodium sulfite.

[0017] The formulation of the present invention may also be used for the treatment of pain and/or inflammation for patients who have recently undergone or are about to undergo ophthalmic surgery. The most prevalent surgeries contemplated are cataract surgery and any of the various corneal refractive eye surgeries, such as photorefractive keratectomy (PRK) and Laser epithelial keratomileusis (LASEK).

[0018] The invention also includes methods of treating patients having an ophthalmic disease, injury or disorder, utilizing the compositions or formulations described herein. Further, the compositions or formulations can be utilized to treat the inflammation and/or pain associated with disruptions or changes of the normal condition of the eye. Also provided are kits comprising the compositions or formulations and a means of applying the compositions or formulations to the patients' eyes.

[0019] Another aspect of the invention is a method for treating inflammation and/or pain of the eye in a patient which method comprises a twice a day topical application to the eye of a patient in need thereof of a therapeutically effective amount of a topical ophthalmic composition comprising bromfenac at a lower concentration of about 0.08% w/v.

[0020] Yet another aspect of the invention is a method for treating inflammation and/or pain of the eye in a patient which method comprises a once a day topical application to the eye of a patient in need thereof of a therapeutically effective amount of a topical ophthalmic composition comprising bromfenac at a higher concentration of about 0.18% w/v.

[0021] It is also an object of the present invention to provide an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which is stable within a pH range giving minimal or no irritation to eyes and in which, when a preservative such as benzalkonium chloride is incorporated therein, preservative effect of the preservative does not substantially deteriorate.

[0022] Another object of the invention is to provide a method for stabilizing an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof.

[0023] A further object of the invention is to provide an aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative, wherein, when specifically a quaternary ammonium salt

such as benzalkonium chloride is incorporated as a preservative, decrease in the preservative effect of said preservative is inhibited.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0024] "Antimicrobial compound" includes those that effectively kill or mitigate the activity of a microbe. Antimicrobial includes antibacterial, bacteriostatic, and the like. These agents include, but are not limited to: azithromycin, tobramycin, gentamicin, ciprofloxacin, norfloxacin, ofloxacin, and sparfloxacin.

[0025] "Astigmatic Keratotomy" (AK) is a refractive surgery useful for correcting astigmatism. AK is a simple (non-excimer laser) procedure where the surgeon places incisions in the cornea to change its curvature in a controlled fashion. It is often a useful enhancement procedure following previous LASIK or PRK.

[0026] "Cataract surgery" is a surgical procedure designed to remove or repair the cloudiness or opacity of the normally clear lens of the eye. All surgical work is done through a self-sealing opening into the eye that is about the size of a pen tip. The cloudy lens is removed with an instrument that loosens the cloudy lens protein (emulsifies) and gently vacuums it out of the eye. The instrument is called a phacoemulsifier and is not a laser. Once the cloudy lens is removed, a lens implant is necessary to restore the focus of the eye. The lens implant is folded and inserted through the same tiny opening into the eye. The lens is placed through the pupil, behind the colored iris to replace the natural human lens. The lens is typically permanent and restores the ability of the eye to focus.

[0027] "Conductive keratoplasty" (CK) is a procedure indicated for the temporary reduction of farsightedness in those 40 years of age or older. Similar to LTK, CK steepens the central cornea by thermal contraction of the peripheral cornea. Unlike LTK, heat is applied through a radio frequency probe instead of a laser.

[0028] "Conjunctivitis", or "pink eye", is the name given to the inflammation of the conjunctiva of the eye when exposed to bacteria, viruses, allergens or other irritants. Conjunctivitis is the most common eye disease in the developed world and can vary in severity from a mild inflammation with tearing to a severe inflammation that causes tissue injury. The most common cause of conjunctivitis is viral infection, caused mainly by adenovirus. Other types of conjunctivitis include bacterial and fungal disease, caused mainly by *Haemophilus influenzae* and *Streptococcus pneumoniae*. Non-infective, or allergic, conjunctivitis is characterized by ocular redness and itching and may involve mucus production in the eye. Other clinical manifestations are tearing (clear tears), crusting of the eyelids and photophobia. This condition is normally seasonal and is very frequent in patients that suffer from allergic rhinitis. Pediatric allergic conjunctivitis is a commonly occurring often contagious conjunctivitis condition found in children.

[0029] "Corneal opacification" consists of a clouding or scarring of the normally transparent cornea, that diminishes the amount of light entering the eye, impairing vision.

Corneal opacification can occur as a result of bacterial, fungal or viral infections, or from trauma to the eye.

[0030] “Derivative” means any analog, salt, ester, amine, amide, acid and/or alcohol derived from an active agent of the invention which may be used in place of that active agent.

[0031] “Diabetic retinopathy” is a complication of diabetes typically classified into two stages, Non-Proliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR).

[0032] “Dose” means the concentration of the active ingredient bromfenac or a derivative thereof which may be comprised of an analog, salt, ester, amine, amide, alcohol or acid of bromfenac and may be used in place of bromfenac used in the present invention. Wherein, the “Lower Dose” formulation of the present invention comprises bromfenac at a concentration of about 0.05% w/v to about 0.1% w/v with a preferred bromfenac concentration of about 0.08% w/v, and the “Higher Dose” formulation of the present invention comprises bromfenac at a concentration about 0.12% w/v to about 0.24% w/v with a preferred bromfenac concentration of about 0.18% w/v.

[0033] “Eye surface inflammation” includes any inflammatory disorder involving the ocular surface. The eye surface includes the eye lids, conjunctiva and cornea. “Inflammation” refers to white blood cell or leukocytic infiltration associated with cellular injury. Eye surface inflammatory disorders treatable by the ophthalmic preparations of the invention are typically manifested by signs and symptoms such as increased cells and flare in the anterior chamber, eye redness, and/or eye irritation. These diseases include, for example, meibomianitis, blepharitis, uveitis, iritis, conjunctival hyperemia, eyelid hyperemia, keratitis and ocular rosacea. The inflammation of tissue associated with the eye can be the result of a number of different causes. Whether the cause is bacterial, viral, traumatic, iatrogenic or environmental, inflammation can be painful, damaging to tissues and requires special care.

[0034] “Laser in-situ keratomileusis” (LASIK) represents the combination of two separate procedures: 1) making a corneal flap, and 2) sculpting the cornea under the flap with a laser. In the first step, the surgeon uses an instrument called a microkeratome to make a hinged corneal flap. The flap is folded back exposing the bed of the cornea. In the second step, a cool laser beam sculpts the curvature of the exposed cornea by evaporating tissue. Then the corneal flap is repositioned and it adheres without the need for stitches.

[0035] “Laser epithelial keratomileusis” (LASEK) is a modified form of photorefractive keratectomy (PRK); this procedure requires the surgeon to loosen the outer layer of the cornea, called the epithelium. Unlike in PRK, the epithelium is not removed in LASEK. The surgeon instead folds back the loosened epithelium so that the laser can reshape the exposed cornea. After laser application, the surgeon replaces the “flap” of epithelium over the corneal bed and places a bandage soft contact lens on top. Visual recovery after LASEK is generally faster than in PRK but slower than in LASIK.

[0036] “Laser thermal keratoplasty” (LTK) is a procedure designed for the temporary reduction of hyperopia for patients 40 years and older with astigmatism and refractive

stability for the previous 6 months. Unlike most refractive surgery, LTK is not performed in an operating suite but in an ordinary exam room. It involves the strategic placement of 16 laser spots onto the peripheral cornea. In LTK, the eye is numbed with anesthetic drops and held open with an eyelid holder. The tear film is allowed to dry for 3 minutes before the laser is applied. The laser application itself takes less than 3 seconds per eye. The treatment thermally contracts the tissue, causing the central cornea to steepen. A bandage soft contact lens is usually placed on the eye until the following day. The eye may have some irritation for the first few days.

[0037] “Non-Proliferative Diabetic Retinopathy” (NPDR) is a complication of diabetes in the early stage of diabetic retinopathy that occurs when normal blood vessels in the retina are damaged due to diabetes and swell and begin to leak fluid and small amounts of blood into the eye.

[0038] “Ocular infection” is an abnormal condition caused by bacteria, fungi and viruses. Infections, if not treated, can lead to more severe ocular disorders.

[0039] “Ocular inflammation” includes, but is not limited to: inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, anterior segment of the globe, and posterior segments of the globe including but not limited to uveitis, scleritis, inflammatory conditions of the retina and macula including but not limited to macular edema.

[0040] “Ophthalmically-acceptable” means that the formulation, active agent, excipient or other material is compatible with ocular tissue; that is, it does not cause significant or undue detrimental effects when brought into contact with ocular tissue. In some instances, actives and/or excipients of the formulation may cause some discomfort or stinging in the eye; however, those excipients are still considered ophthalmically-acceptable for the purposes of this application. In many instances, these irritating components are removed from the formulations for comfort of the patient. For example, polyvinyl alcohol (PVA) can be eliminated from the formulation ingredients.

[0041] A “patient” is a vertebrate, preferably mammal, more preferably a human. Mammals include, but are not limited to: humans, rodents, sport animals and pets, such as rats, dogs, and horses.

[0042] “Photorefractive Keratectomy” (PRK) uses a laser to sculpt the surface of the cornea. This contrasts with LASIK, which sculpts inside the cornea. PRK is useful for treating low to moderate levels of myopia or hyperopia with and without astigmatism. It is the procedure of choice if the patient has certain corneal dystrophies, certain corneal scars, or a condition called “recurrent corneal erosion”. PRK involves first removing the epithelium of the cornea. A cool laser beam is then applied to the cornea, and a soft contact lens is placed over the eye as a bandage to help the outer layer to grow back. It usually takes 3-5 days for the outer layer to re-grow over the cornea. During that period, the patient may experience mild to marked discomfort with blurry vision. Unlike with LASIK, it takes longer to achieve the final result in PRK since a greater amount of tissue healing takes place. Because no corneal flap is created and manipulated during PRK, it is technically easier for a surgeon to perform PRK than LASIK.

[0043] "Photo Therapeutic Keratectomy" (PTK) uses a "cold" laser removal of surface tissue of the cornea such as scar tissue for medical or optical treatment reasons.

[0044] "Radial Keratotomy" (RK) is described as a surgical operation to improve myopia by changing the curve of the cornea over the pupil. The surgeon makes several deep incisions in the cornea in a radial or spoke-like pattern. The incisions are intended to flatten out the central cornea to correct the patient's vision.

[0045] "Refractive surgery" is an eye care specialty for reducing refractive error (i.e., reduction of myopia (nearsightedness), hyperopia (farsightedness), and astigmatism) and presbyopia without using glasses or contact lenses. The term, "refractive surgery" refers to several procedures, including LASIK, PRK, LASEK, Intacs, LTK, CK, AK, RK, and several emerging techniques. Also included is the term, "laser vision correction". LASIK is the most widely performed of all refractive surgery procedures.

[0046] "Therapeutically-active agent" means any agent capable of having a therapeutic effect.

[0047] "Therapeutically-effective amount" means an amount of active sufficient to prevent, inhibit, or reduce the level of inflammation, irritation or other abnormal conditions in the eye.

Bromfenac

[0048] The active ingredient of the present invention includes bromfenac or a derivative thereof which may be comprised of an analog, salt, ester, amine, amide, alcohol or acid of bromfenac and may be used in place of bromfenac.

[0049] Bromfenac has been shown to be an effective active ingredient in combating various eye conditions. The present invention comprises a safe, stable and effective alternative bromfenac formulation to the current Xibrom™ ophthalmic 0.09% bromfenac solution on the market. The present bromfenac formulations include a lower dose formulation and a higher dose formulation.

[0050] The present bromfenac lower dose formulation is formulated so that it is more generally acceptable to the patient population and may also decrease the total concentration of bromfenac necessary to treat the ophthalmic condition when given the lower concentration formulation as compared to the formulations in the art. By decreasing the overall exposure to bromfenac and attaining the same or better clinical results, one may be able to further reduce the incidents of adverse effects, and decrease overall exposure to this NSAID.

[0051] Whereas, the present bromfenac higher dose formulation is formulated so that it is also more generally acceptable to the patient population yet may also decrease the total number of doses necessary to treat the ophthalmic condition as compared to the formulations in the art. By decreasing the number of overall doses of bromfenac and attaining the same or better clinical results, greater patient compliance is expected and incidents of adverse effects will be reduced, and there will be a decrease in the prolonged exposure to this NSAID. By decreasing the number of overall doses of bromfenac and attaining the same or better clinical results, greater patient compliance is expected and

incidents of adverse effects will be reduced, and there will be a decrease in the prolonged exposure to this NSAID.

[0052] The lower dose ophthalmic formulation of the present invention comprises bromfenac or a derivative thereof at a concentration ranging from about 0.05% w/v to about 0.1% w/v. A further embodiment of the present invention utilizes bromfenac at a preferred lower dose concentration as a free acid of about 0.08% w/v. Furthermore a further embodiment utilizes the salt form of bromfenac as bromfenac sodium.

[0053] The higher dose ophthalmic formulation of the present invention comprises bromfenac or a derivative thereof at a concentration ranging from about 0.12% w/v to about 0.24% w/v. A further embodiment of the present invention utilizes bromfenac at a preferred higher dose concentration as a free acid of about 0.18% w/v. Furthermore a further embodiment utilizes the salt form of bromfenac as bromfenac sodium.

Enhanced Stability of Bromfenac Formulations

[0054] As a result of various studies, the inventors of the present invention have found that, by adding, for example, an alkyl aryl polyether alcohol type polymer such as tyloxapol, or a polyethylene glycol fatty acid ester such as polyethylene glycol monostearate to an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, the aqueous solution becomes stable within a pH range giving minimal or no irritation to eyes, and change of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid over time can be inhibited, and furthermore, when the aqueous solution contains a preservative, deterioration in the preservative effect of said preservative can be inhibited for a long period of time. The inventors of the present invention have further studied extensively and completed the present invention.

[0055] Namely, the present invention relates to:

[0056] (1) An aqueous liquid preparation comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester,

[0057] (2) The aqueous liquid preparation according to the above (1), wherein the alkyl aryl polyether alcohol type polymer has a polymerization degree of 3 to 10, the alkyl contains 1 to 18 carbon atoms, the aryl is a phenyl residue, and the polyether alcohol is represented by the formula $O(CH_2CH_2O)_xH$ in which X is an integer of 5 to 100,

[0058] (3) The aqueous liquid preparation according to the above (1) or (2), wherein the alkyl aryl polyether alcohol type polymer is tyloxapol,

[0059] (4) The aqueous liquid preparation according to the above (1), wherein the carbon number of the fatty acid in the polyethylene glycol fatty acid ester is 12 to 18,

[0060] (5) The aqueous liquid preparation according to the above (1) or (4), wherein the polyethylene glycol fatty acid ester is polyethylene glycol monostearate,

[0061] (6) The aqueous liquid preparation according to any one of the above (1) to (3), wherein the concentration of

the alkyl aryl polyether alcohol type polymer is selected from a range of minimum concentration of 0.01% w/v to maximum concentration of 0.5% w/v,

[0062] (7) The aqueous liquid preparation according to any one of the above (1), (2) or (4), wherein the concentration of the polyethylene glycol fatty acid ester is selected from a range of minimum concentration of 0.02% w/v to maximum concentration of 0.1% w/v,

[0063] (8) The aqueous liquid preparation according to any one of the above (1) to (7), wherein the concentration of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is 0.01 to 0.5% w/v,

[0064] (9) The aqueous liquid preparation according to any one of the above (1) to (8), wherein benzalkonium chloride is contained as a preservative,

[0065] (10) The aqueous liquid preparation according to anyone of the above (1) to (9),

[0066] wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt,

[0067] (11) The aqueous liquid preparation according to any one of the above (1) to (10), wherein the pH of the aqueous liquid preparation is within a range of 7 to 9,

[0068] (12) The aqueous liquid preparation according to the above (11), wherein the pH of the aqueous liquid preparation is within a range of 7.5 to 8.5,

[0069] (13) The aqueous liquid preparation according to any one of the above (1) to (12), wherein the aqueous liquid preparation is an eye drop,

[0070] (14) The aqueous liquid preparation according to any one of the above (1) to (12), wherein the aqueous liquid preparation is a nasal drop,

[0071] (15) An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.01 to 0.5% w/v of tyloxapol,

[0072] (16) An eye drop comprising sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate and 0.02 to 0.1% w/v of polyethylene glycol monostearate,

[0073] (17) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof in an aqueous liquid preparation, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, and

[0074] (18) A method for inhibiting decrease in preservative effect of a preservative in an aqueous liquid preparation of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof, which comprises incorporating tyloxapol or polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof and a preservative.

[0075] According to the present invention, a stable aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof can be prepared by incorporating an alkyl aryl polyether alcohol type polymer such as tyloxapol, or a polyethylene glycol fatty acid ester such as polyethylene glycol monostearate into an aqueous liquid preparation containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof. Also, an aqueous liquid preparation of the present invention, wherein a preservative is incorporated, has a sufficient preservative effect.

[0076] Therefore, the aqueous liquid preparation of the present invention is advantageously used as an eye drop for the treatment of, for example, blepharitis, conjunctivitis, scleritis, and postoperative inflammation. In addition, such aqueous liquid preparation can be used as a nasal drop for the treatment of, for example, allergic rhinitis and inflammatory rhinitis (e.g. chronic rhinitis, hypertrophic rhinitis, nasal polyp, etc.).

[0077] The pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid includes, for example, an alkali metal salt such as sodium salt and potassium salt, and an alkaline earth metal salt such as calcium salt and magnesium salt, among which sodium salt is especially preferable.

[0078] 2-Amino-3-(4-bromobenzoyl)phenylacetic acid and its pharmacologically acceptable salt can be prepared according to the method as described in JP-A-23052/1977 (corresponding to U.S. Pat. No. 4,045,576) or by a similar method thereof. These compounds can be obtained as their hydrate depending on synthetic conditions and recrystallization conditions. The hydrate includes $\frac{1}{2}$ hydrate, 1 hydrate, and {fraction ($\frac{3}{2}$)} hydrate, among which {fraction ($\frac{3}{2}$)} hydrate is preferable.

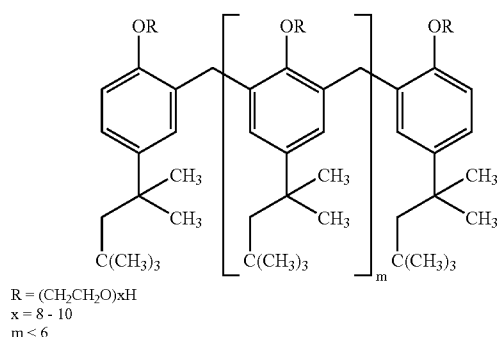
[0079] In the aqueous liquid preparation of the present invention, the content (concentration range) of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is usually about 0.01 to 0.5% w/v, preferably about 0.05 to 0.2% w/v, especially about 0.1% w/v, and it is preferable to appropriately vary the content depending on the purpose of use and the degree of disease to be treated.

[0080] The carbon number of the alkyl in the an alkyl aryl polyether alcohol type polymer which is a non-ionic surfactant used as a stabilizer for 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is approximately 1 to 18. Specifically, the alkyl group includes, for example, methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, sec-butyl, tert-butyl, cyclobutyl, pentyl, isopentyl, neopentyl, tert-pentyl, 1-ethylpropyl, 4-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 1,2-dimethylbutyl, 2-ethylbutyl, cyclopentyl, hexyl, cyclohexyl, heptyl, isoheptyl, octyl, isooctyl, nonyl, isononyl, decyl, isodecyl, undecyl, isoundecyl, dodecyl, isododecyl, tridecyl, isotridecyl, tetradecyl, isotetradecyl, pentadecyl, isopentadecyl, hexadecyl, isohexadecyl, heptadecyl, isoheptadecyl, octadecyl, isooctadecyl, and isomers thereof, among which octyl and its isomer (e.g. isooctyl, sec-octyl, 1-methylheptyl, 1-ethylhexyl, 2-ethylhexyl, 1-propylpentyl, 1,5-dimethylhexyl, 1,1,3,3-

tetramethylbutyl-, etc.) are preferable, and 1,1,3,3-tetramethylbutyl which is an isomer of octyl groups is especially preferable.

[0081] The aryl in the alkyl aryl polyether alcohol type polymer can be preferably a phenyl residue. The polyether alcohol can be represented by the formula $O(CH_2CH_2O)_xH$ in which x is an integer of 5 to 100, preferably 5 to 30, more preferably 8 to 10. The average polymerization degree is preferably about 3 to 10.

[0082] Among the above-mentioned alkyl aryl polyether alcohol type polymers, tyloxapol having the following formula is especially preferable.



[0083] The fatty acid of the polyethylene glycol fatty acid ester which is a non-ionic surfactant used as a stabilizer for 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof can be preferably a fatty acid having the carbon number of 12 to 18. Specific examples of such polyethylene glycol fatty acid esters are polyethylene glycol monostearate (e.g. polyoxyl 8 stearate, polyoxyl 40 stearate, etc.), polyethylene glycol monolaurate, polyethylene glycol monooleate, polyethylene glycol diisostearate, polyethylene glycol dilaurate, polyethylene glycol dioleate, and the like. Among these compounds, polyethylene glycol monostearate is preferable, and polyoxyl 40 stearate is especially preferable. The polyoxyl 40 stearate is a monostearic acid ester of an ethylene oxide condensed polymer, and can be represented by the formula $C_{17}H_{35}COO(CH_2CH_2O)_nH$ which is a non-ionic surfactant and n is about 40.

[0084] Although the content (concentration range) of the alkyl aryl polyether alcohol type polymer in the aqueous liquid preparation of the present invention depends on the kind of compounds used, the minimum concentration is about 0.01% w/v and the maximum concentration is about 0.5% w/v. With respect to the tyloxapol content (concentration range), for example, the minimum content is about 0.01% w/v, 0.02% w/v or 0.03% w/v, and the maximum content is about 0.05% w/v, 0.1% w/v, 0.3% w/v or 0.5% w/v, and preferably the minimum content is about 0.02% w/v and the maximum content is about 0.05% w/v.

[0085] Although the content (concentration range) of the polyethylene glycol fatty acid ester in the aqueous liquid preparation of the present invention depends on the kind of compounds used, it is within a range of about 0.02% w/v of minimum concentration to about 0.1% w/v of maximum

concentration. For example, the content (concentration range) of polyethylene glycol monostearate is within a range of about 0.02% w/v of minimum content to about 0.1 w/v of maximum content, and preferably within a range of about 0.02% w/v of the minimum content to about 0.05% w/v of the maximum content.

[0086] The incorporation ratio of tyloxapol in the aqueous liquid preparation of the invention is within a range of the minimum content of about 0.1 or 0.2 part by weight to the maximum content of about 0.5, 1, 3 or 5 parts by weight, relative to 1 part by weight of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt or a hydrate thereof.

[0087] The incorporation ratio of polyethylene glycol monostearate in the aqueous liquid preparation of the present invention is within a range of the minimum content of about 0.2 part by weight to the maximum content of about 0.5 or 1 part by weight, relative to 1 part by weight of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or its pharmacologically acceptable salt or a hydrate thereof.

[0088] The preservative used in the present invention includes, for example, quaternary ammonium salts (e.g. benzalkonium chloride, benzethonium chloride, etc.), chlorhexidine gluconate, and the like, among which benzalkonium chloride is especially preferable.

[0089] Further, so long as the purpose of stabilizing the bromfenac formulation of the present invention is achieved, conventional various additives such as isotonicity, buffers, thickeners, stabilizers, chelating agents, pH controlling agents, perfumes and the like may be appropriately added to the aqueous liquid preparation of the present invention. The isotonicity include sodium chloride, potassium chloride, glycerine, mannitol, sorbitol, boric acid, glucose, propylene glycol and the like. The buffers include, for example, phosphate buffer, borate buffer, citrate buffer, tartarate buffer, acetate buffer, boric acid, borax, amino acids, and the like. The thickeners include polyvinylpyrrolidone, carboxymethylcellulose, carboxypropylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinyl alcohol, sodium polyacrylate, and the like. The stabilizers include sulfites such as sodium sulfite and the like. The chelating agents include sodium edetate, sodium citrate, condensed sodium phosphate and the like. The pH controlling agents include hydrochloric acid, sodium hydroxide, phosphoric acid, acetic acid and the like. The perfumes include 1-menthol, borneol, camphor, Eucalyptus oil, and the like.

[0090] With respect to the concentrations of the above various additives in the aqueous liquid preparation of the present invention, the isotonic is incorporated into an osmotic pressure ratio of about 0.8 to 1.2, and the concentrations of the buffer and the thickener to be added are about 0.01 to 2% w/v and 0.1 to 10% w/v, respectively.

[0091] The pH of the aqueous liquid preparation of the present invention is adjusted to about 6 to 9, preferably about 7 to 9, especially about 7.5 to 8.5.

[0092] The aqueous liquid preparation of the present invention can be prepared by per se known method or according to the method as described in the Japanese Pharmacopoeia, 14th Edition, General Rules for Preparations, Solutions or Ophthalmic solutions.

[0093] The aqueous liquid preparation of the present invention can be prepared easily by dissolving the above-mentioned components in, for example, distilled water or sterile purified water. For example, the aqueous liquid preparation in the form of an eye drop can be used for the treatment of inflammatory diseases in anterior or posterior segment of the eye such as blepharitis, conjunctivitis, scleritis, postoperative inflammation, and the like. The dose of the aqueous liquid preparation containing 0.1% w/v of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hydrate is, for example, administered to an adult 3 to 6 times daily in an amount of 1 to 2 drops per one time. Depending on the degree of diseases, frequency of dosing is appropriately controlled.

Ophthalmic Formulations

[0094] The ophthalmic formulations of the present invention include bromfenac or a derivative thereof as an active agent, a stabilizing agent (such as polyvinylpyrrolidone), a solubilizing agent (such as tyloxapol), a chelating agent (such as ethylenediaminetetraacetic acid (EDTA)), a preservative (such as benzalkonium chloride), a buffer (such as boric acid and sodium borate), a tonicity agent (such as sodium chloride) and optional additional active agents, viscosity/osmolality/pH enhancing agents, and various excipients.

[0095] A preferred lower dose formulation of the present invention comprises bromfenac or a derivative thereof at a concentration of about 0.05% w/v to about 0.1% w/v; polyvinylpyrrolidone at a concentration of about 0.35% w/v to about 3.00% w/v; a solubilizing agent at a concentration of about 0.002% w/v to about 0.2% w/v; a chelating agent at a concentration of about 0.005%, 10 w/v to about 0.1% w/v; a preservative at a concentration of about 0.0025% w/v to about 0.02% w/v; a tonicity agent at a concentration of about 0.08% w/v to about 0.14% w/v; wherein the final osmolality is about 250 to about 350 mOsm; and a buffering agent; wherein the final pH of the formulation is about 8.0 to about 8.5. A further embodiment of the present invention utilizes an alkyl aryl polyether alcohol type polymer as the solubilizer, EDTA as the chelating agent at a concentration of about 0.005% w/v to about 0.1% w/v, and/or benzalkonium chloride (BAK) as the preservative at a concentration of about 0.0025% w/v to about 0.02% w/v. A further embodiment includes tyloxapol as the preferred alkyl aryl polyether alcohol type polymer as the solubilizer in the formulation.

[0096] Another embodiment of the present invention is a lower dose topical ophthalmic formulation comprising bromfenac or a derivative thereof at a concentration of about 0.05% w/v to about 0.1% w/v; boric acid at a concentration of about 0.8% w/v to about 1.4% w/v; sodium borate at a concentration of about 0.8% w/v to about 1.4% w/v; benzalkonium chloride at a concentration of about 0.0025% w/v to about 0.02% w/v; polyvinylpyrrolidone at a concentration of about 0.35% w/v to about 3.00% w/v; EDTA at a concentration of about 0.005% w/v to about 0.1% w/v; tyloxapol at a concentration of about 0.002% w/v to about 0.2% w/v; sodium chloride at a concentration of about 0.08% w/v to about 0.14% w/v; wherein the final pH of the formulation is about 8.0 to about 8.5. A further embodiment of the present formulation would have a final pH of about 8.3. A further embodiment of the present formulation comprises the final formulation in an aqueous formulation.

[0097] Another embodiment of the present invention is a lower dose topical ophthalmic formulation comprising bromfenac or a derivative thereof at a concentration of about 0.08% w/v; boric acid at a concentration of about 1.1% w/v; sodium borate at a concentration of about 1.1% w/v; benzalkonium chloride at a concentration of about 0.005% w/v; polyvinylpyrrolidone at a concentration of about 2.00% w/v; EDTA at a concentration of about 0.02% w/v; tyloxapol at a concentration of about 0.02% w/v; sodium chloride at a concentration of about 0.109% w/v; and wherein the final pH of the formulation is about 8.3.

[0098] A preferred higher dose formulation of the present invention comprises bromfenac or a derivative thereof at a concentration of about 0.12% w/v to about 0.24% w/v; polyvinylpyrrolidone at a concentration of about 0.35% w/v to about 3.00% w/v; a solubilizing agent at a concentration of about 0.002% w/v to about 0.2% w/v; a chelating agent at a concentration of about 0.005% w/v to about 0.1% w/v; a preservative at a concentration of about 0.0025% w/v to about 0.02% w/v; a tonicity agent at a concentration of about 0.04% w/v to about 0.14% w/v; wherein the final osmolality is about 250 to about 350 mOsm; and a buffering agent; wherein the final pH of the formulation is about 7.6 to about 8.0. A further embodiment of the present invention utilizes an alkyl aryl polyether alcohol type polymer as the solubilizer, EDTA as the chelating agent at a concentration of about 0.005% w/v to about 0.1% w/v, and/or benzalkonium chloride (BAK) as the preservative at a concentration of about 0.0025% w/v to about 0.02% w/v. A further embodiment includes tyloxapol as the preferred alkyl aryl polyether alcohol type polymer as the solubilizer in the formulation.

[0099] Another embodiment of the present invention is a higher dose topical ophthalmic formulation comprising bromfenac or a derivative thereof at a concentration of about 0.12% w/v to about 0.24% w/v; boric acid at a concentration of about 0.9% w/v to about 1.7% w/v; sodium borate at a concentration of about 0.4% w/v to about 1.0% w/v; benzalkonium chloride at a concentration of about 0.0025% w/v to about 0.02% w/v; polyvinylpyrrolidone at a concentration of about 0.35% w/v to about 3.00% w/v; EDTA at a concentration of about 0.005% w/v to about 0.1% w/v; tyloxapol at a concentration of about 0.002% w/v to about 0.5% w/v; sodium chloride at a concentration of about 0.04% w/v to about 0.14% w/v; wherein the final pH of the formulation is about 7.6 to about 8.0. A further embodiment of the present formulation would have a final pH of about 7.8. A further embodiment of the present formulation comprises the final formulation in an aqueous formulation.

[0100] Another embodiment of the present invention is a higher dose topical ophthalmic formulation comprising bromfenac or a derivative thereof at a concentration of about 0.18% w/v; boric acid at a concentration of about 1.30% w/v; sodium borate at a concentration of about 0.74% w/v; benzalkonium chloride at a concentration of about 0.005% w/v; polyvinylpyrrolidone at a concentration of about 2.00% w/v; EDTA at a concentration of about 0.02% w/v; tyloxapol at a concentration of about 0.02% w/v; sodium chloride at a concentration of about 0.087% w/v; and wherein the final pH of the formulation is about 7.8.

[0101] Tyloxapol is an example of an isotonic surfactant which may function as a stabilizing, solubilizing or dispersing agent in the present formulation. The formulation may

contain an alkyl aryl polyether alcohol type polymer such as tyloxapol which serves as a solubilizer in the formulation. Some of the properties related to alkyl aryl polyether alcohol type polymers, such as tyloxapol, in relation to stabilizing ophthalmic compositions is described in U.S. Patent Application Publication Number 2005/0239895, and is herein incorporated by reference. The formulation of the present invention may include an alkyl aryl polyether alcohol type polymer at a concentration of about 0.002% w/v to about 0.5% w/v. Another embodiment of the present invention comprises tyloxapol at a concentration of about 0.002% w/v to about 0.2% w/v, and most preferably at a concentration of about 0.02% w/v.

[0102] Additional ophthalmic formulations of the present invention include bromfenac or a derivative thereof as an active agent, a stabilizing agent (such as polyvinylpyrrolidone), a solubilizing agent (such as tyloxapol), a chelating agent (such as ethylenediaminetetraacetic acid (EDTA)), a preservative (such as benzalkonium chloride), a buffer (such as boric acid and sodium borate), sodium sulfite and optional additional active agents, viscosity/osmolality/pH enhancing agents, and various excipients.

[0103] A preferred lower dose formulation of the present invention comprises bromfenac or a derivative thereof at a concentration of about 0.05% w/v to about 0.1% w/v; polyvinylpyrrolidone at a concentration of about 0.35% w/v to about 3.00% w/v; a solubilizing agent at a concentration of about 0.002% w/v to about 0.2% w/v; a chelating agent at a concentration of about 0.005% w/v to about 0.1% w/v; a preservative at a concentration of about 0.0025% w/v to about 0.02% w/v; sodium sulfite at a concentration of about 0.02% w/v to about 0.5% w/v; wherein the final osmolality is about 250 to about 350 mOsm; and a buffering agent; wherein the final pH of the formulation is about 8.0 to about 8.5. A further embodiment of the present invention utilizes an alkyl aryl polyether alcohol type polymer as the solubilizer, EDTA as the chelating agent at a concentration of about 0.005% w/v to about 0.1% w/v, and/or benzalkonium chloride (BAK) as the preservative at a concentration of about 0.0025% w/v to about 0.02% w/v. A further embodiment includes tyloxapol as the preferred alkyl aryl polyether alcohol type polymer as the solubilizer in the formulation.

[0104] Another embodiment of the present invention is a lower dose topical ophthalmic formulation comprising bromfenac or a derivative thereof at a concentration of about 0.05% w/v to about 0.1% w/v; boric acid at a concentration of about 0.8% w/v to about 1.4% w/v; sodium borate at a concentration of about 0.8% w/v to about 1.4% w/v; benzalkonium chloride at a concentration of about 0.0025% w/v to about 0.02% w/v; polyvinylpyrrolidone at a concentration of about 0.35% w/v to about 3.00% w/v; EDTA at a concentration of about 0.005% w/v to about 0.1% w/v; tyloxapol at a concentration of about 0.002% w/v to about 0.2% w/v; sodium sulfite at a concentration of about 0.02% w/v to about 0.5% w/v; wherein the final pH of the formulation is about 8.0 to about 8.5. A further embodiment of the present formulation would have a final pH of about 8.3. A further embodiment of the present formulation comprises the final formulation in an aqueous formulation.

[0105] Another embodiment of the present invention is a lower dose topical ophthalmic formulation comprising bromfenac or a derivative thereof at a concentration of about

0.08% w/v; boric acid at a concentration of about 1.1% w/v; sodium borate at a concentration of about 1.1% w/v; benzalkonium chloride at a concentration of about 0.005% w/v; polyvinylpyrrolidone at a concentration of about 2.00% w/v; EDTA at a concentration of about 0.02% w/v; tyloxapol at a concentration of about 0.02% w/v; sodium sulfite at a concentration of about 0.2% w/v; and wherein the final pH of the formulation is about 8.3.

[0106] A preferred higher dose formulation of the present invention comprises bromfenac or a derivative thereof at a concentration of about 0.12% w/v to about 0.24% w/v; polyvinylpyrrolidone at a concentration of about 0.35% w/v to about 3.00% w/v; a solubilizing agent at a concentration of about 0.002% w/v to about 0.5% w/v; a chelating agent at a concentration of about 0.005% w/v to about 0.1% w/v; a preservative at a concentration of about 0.0025% w/v to about 0.02% w/v; sodium sulfite at a concentration of about 0.02% w/v to about 0.4% w/v; wherein the final osmolality is about 250 to about 350 mOsm; and a buffering agent; wherein the final pH of the formulation is about 7.6 to about 8.0. A further embodiment of the present invention utilizes an alkyl aryl polyether alcohol type polymer as the solubilizer, EDTA as the chelating agent at a concentration of about 0.005% w/v to about 0.1% w/v, and/or benzalkonium chloride (BAK) as the preservative at a concentration of about 0.0025% w/v to about 0.02% w/v. A further embodiment includes tyloxapol as the preferred alkyl aryl polyether alcohol type polymer as the solubilizer in the formulation.

[0107] Another embodiment of the present invention is a higher dose topical ophthalmic formulation comprising bromfenac or a derivative thereof at a concentration of about 0.12% w/v to about 0.24% w/v; boric acid at a concentration of about 0.9% w/v to about 1.7% w/v; sodium borate at a concentration of about 0.4% w/v to about 1.0% w/v; benzalkonium chloride at a concentration of about 0.0025% w/v to about 0.02% w/v; polyvinylpyrrolidone at a concentration of about 0.35% w/v to about 3.00% w/v; EDTA at a concentration of about 0.005% w/v to about 0.1% w/v; tyloxapol at a concentration of about 0.002% w/v to about 0.5% w/v; sodium sulfite at a concentration of about 0.02% w/v to about 0.4% w/v; wherein the final pH of the formulation is about 7.6 to about 8.0. A further embodiment of the present formulation would have a final pH of about 7.8. A further embodiment of the present formulation comprises the final formulation in an aqueous formulation.

[0108] Another embodiment of the present invention is a higher dose topical ophthalmic formulation comprising bromfenac or a derivative thereof at a concentration of about 0.18% w/v; boric acid at a concentration of about 1.30% w/v; sodium borate at a concentration of about 0.74% w/v; benzalkonium chloride at a concentration of about 0.005% w/v; polyvinylpyrrolidone at a concentration of about 2.00% w/v; EDTA at a concentration of about 0.02% w/v; tyloxapol at a concentration of about 0.3% w/v; sodium sulfite at a concentration of about 0.2% w/v; and wherein the final pH of the formulation is about 7.8.

[0109] The high dose formulation containing sodium sulfite may also contain an alkyl aryl polyether alcohol type polymer such as tyloxapol which serves as a solubilizer in the formulation. The high dose formulation containing sodium sulfite may include an alkyl aryl polyether alcohol type polymer at a concentration of about 0.002% w/v to

about 0.5% w/v. Another embodiment of the present invention comprises tyloxapol at a concentration of about 0.002% w/v to about 0.5% w/v, and most preferably at a concentration of about 0.3% w/v.

Excipients

[0110] The formulation may contain various excipients incorporated ordinarily, such as buffering agents (e.g., phosphate buffers, borate buffers, citrate buffers, tartarate buffers, acetate buffers, amino acids, boric acid, borax, sodium acetate, sodium citrate and the like), isotonicity agents (e.g., saccharides such as sorbitol, glucose and mannitol, polyhydric alcohols such as glycerin, concentrated glycerin, polyethylene glycol and propylene glycol, salts such as sodium chloride and potassium chloride, boric acid), preservatives or antiseptics (e.g., benzalkonium chloride, benzethonium chloride, p-oxybenzoates such as methyl p-oxybenzoate or ethyl p-oxybenzoate, benzyl alcohol, phenethyl alcohol, sorbic acid or its salt, thimerosal, chlorobutanol, other quaternary amines and the like, chlorhexidine gluconate), solubilizing aids or stabilizing agents (e.g., cyclodextrins and their derivatives, water-soluble polymers such as polyvinylpyrrolidone, or carbomer, surfactants such as polysorbate 80 (Tween 80)), pH modifiers (e.g., hydrochloric acid, acetic acid, phosphoric acid, sodium hydroxide, potassium hydroxide, ammonium hydroxide and the like), thickening agents (e.g., polyvinylpyrrolidone, polyvinyl alcohol, sodium polyacrylate, hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxypropylmethyl cellulose, carboxypropyl cellulose, carboxymethyl cellulose, and their salts), chelating agents (e.g., sodium edetate, sodium citrate, condensed sodium phosphate), antioxidant or radical scavenging agents (e.g., ascorbic acid (vitamin C) and its salts, tocopherol (vitamin E), and its derivatives, butylated hydroxy benzoic acids and their salts, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, gallic acid and its alkyl esters, uric acid and its salts and alkyl esters, sorbic acid and its salts, the ascorbyl esters of fatty acids, amines, sulfhydryl compounds (e.g., glutathione), and dihydroxy fumaric acid and its salts may be used, as well as EDTA (edetate, sodium edetate) BHT and the like. Descriptions of compounds used in standard ophthalmic formulations may be found in, for example, *Remington's Pharmaceutical Sciences*, latest edition, Mack Publishing Co. Easton, Pa.

[0111] Non-limiting examples of the contemplated excipients include a buffer, osmotic agent, demulcent, surfactant, emollient, tonicity agent, antioxidant and/or a preservative component.

Viscosity/osmolality/pH

[0112] The ophthalmic formulation when in an aqueous or non-aqueous form may also contain, but is not limited to: suspending agents (e.g., polyvinyl pyrrolidone, glycerin monostearate, sorbitan esters, lanolin alcohols) and dispersing agents (e.g., surfactants such as tyloxapol and polysorbate 80, ionic polymers such as sodium alginate) in addition to the agents listed above, to ensure that the ophthalmic formulation is satisfactorily dispersed in a uniform micro-particulate suspension.

[0113] When the lower dose ophthalmic formulation is in the form of an aqueous suspension or solution, a non-aqueous suspension or solution, or a gel or ointment, it is

preferable to use a pH modifier to give the formulation a pH between about 8.0 to 8.5, more preferably about 8.3. A preferred pH modifier is hydrochloric acid, sulfuric acid, boric acid, sodium borate, sodium hydroxide or any other ophthalmically-acceptable pH modifier.

[0114] When the higher dose ophthalmic formulation is in the form of an aqueous suspension or solution, a non-aqueous suspension or solution, or a gel or ointment, it is preferable to use a pH modifier to give the formulation a pH between about 7.6 to 8.0, more preferably about 7.8. A preferred pH modifier is hydrochloric acid, sulfuric acid, boric acid, sodium borate, sodium hydroxide or any other ophthalmically-acceptable pH modifier.

Additional Actives

[0115] Unless the intended purpose of use is affected adversely, the ophthalmic formulation of the present invention may further comprise one or more additional therapeutically-active agents. Specific therapeutically-active agents include, but are not limited to: antibacterial antibiotics, synthetic antibacterials, antifungal antibiotics, synthetic antifungals, antineoplastic agents, steroidal anti-inflammatory agents, non-steroidal anti-inflammatory agents, anti-allergic agents, glaucoma-treating agents, antiviral agents, and anti-mycotic agents. Further contemplated are any derivatives of the therapeutically-active agents which may include, but not be limited to: analogs, salts, esters, amines, amides, alcohols and acids derived from an agent of the invention and may be used in place of an agent itself.

[0116] Examples of the antibacterial antibiotics include, but are not limited to: aminoglycosides (e.g., amikacin, apramycin, arbekacin, bambarmycins, butirosin, dibekacin, dihydrostreptomycin, fortimicin(s), gentamicin, isepamicin, kanamycin, micromomicin, neomycin, neomycin undecylate, netilmicin, paromomycin, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, trospectomycin), amphenicols (e.g., azidamfenicol, chloramphenicol, florfenicol, thiamphenicol), ansamycins (e.g., rifamide, rifampin, rifamycin sv, rifapentine, rifaximin), β -lactams (e.g., carbacephems (e.g., loracarbef), carbapenems (e.g., biapenem, imipenem, meropenem, panipenem), cephalosporins (e.g., cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefcapene pivoxil, cefclidin, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, cefozopran, cefpimizole, cefpiramide, cefpirome, cefpodoxime proxetil, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteteram, ceftazole, ceftibuten, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephaetrile sodium, cephalixin, cephaloglycin, cephaloridine, cephalosporin, cephalothin, cepiparin sodium, cephradine, pivcefalexin), cephamycins (e.g., cefbuperazone, cefmetazole, cefiniox, cefotetan, cefoxitin), monobactams (e.g., aztreonam, carumonam, tigemonam), oxacephems, flomoxef, moxalactam), penicillins (e.g., amdinocillin, amdinocillin pivoxil, amoxicillin, ampicillin, apalcillin, aspoxicillin, azidocillin, azlocillin, bacampicillin, benzylpenicillinic acid, benzylpenicillin sodium, carbenicillin, carindacillin, clometocillin, cloxacillin, cyclacillin, dicloxacillin, epicillin, fenbenicillin, floxacillin, hetacillin, lenampicillin, metampicillin, methicillin sodium, mezlocillin, nafcillin sodium, oxacillin, penamecillin, penethamate hydriodide, penicillin g benethamine, penicillin g benza-

thine, penicillin g benzhydrylamine, penicillin g calcium, penicillin g hydrabamine, penicillin g potassium, penicillin g procaine, penicillin n, penicillin o, penicillin v, penicillin v benzathine, penicillin v hydrabamine, penimepicycline, phenethicillin potassium, piperacillin, pivampicillin, propicillin, quinacillin, sulbenicillin, sultamicillin, talampicillin, temocillin, ticarcillin), other (e.g., ritipenem), lincosamides (e.g., clindamycin, lincomycin), macrolides (e.g., azithromycin, carbomycin, clarithromycin, dirithromycin, erythromycin, erythromycin acistrate, erythromycin estolate, erythromycin glucoheptonate, erythromycin lactobionate, erythromycin propionate, erythromycin stearate, josamycin, leucomycins, midecamycins, miokamycin, oleandomycin, primycin, rokitamycin, rosaramicin, roxithromycin, spiramycin, troleandomycin), polypeptides (e.g., amphomycin, bacitracin, capreomycin, colistin, enduracidin, enviomycin, fusafungine, gramicidin s, gramicidin(s), mikamycin, polymyxin, pristnamycin, ristocetin, teicoplanin, thiostrepton, tuberactinomycin, tyrocidine, tyrothricin, vancomycin, viomycin, virginiamycin, zinc bacitracin), tetracyclines (e.g., apicycline, chlortetracycline, clomocycline, demeclocycline, doxycycline, guamecycline, lymecycline, meclocycline, methacycline, minocycline, oxytetracycline, penimepicycline, pipacycline, rolitetracycline, sancycline, tetracycline), and others (e.g., cycloserine, mupirocin, tuberin).

[0117] Examples of the synthetic antibacterials include, but are not limited to: 2,4-diaminopyrimidines (e.g., brodimoprim, tetraoxoprim, trimethoprim), nitrofurans (e.g., furaltadone, furazolidone, chloride, nifuratel, nifurfoline, nifurpirinol, nifurprazine, nifurtinol, nitrofurantoin), quinolones and analogs (e.g., cinoxacin, ciprofloxacin, cinafloxacin, difloxacin, enoxacin, fleroxacin, flumequine, grepafloxacin, lomefloxacin, miloxacin, nadifloxacin, nalidixic acid, norfloxacin, ofloxacin, oxolinic acid, pazufloxacin, pefloxacin, pefloxacin, pipemidic acid, piromidic acid, roxoxacin, rifloxacin, sparfloxacin, temafloxacin, tosufloxacin, trovafloxacin), sulfonamides (e.g., acetyl sulfamethoxy-pyrazine, benzylsulfamide, chloramine-b, chloramine-t, dichloramine t, n²-formylsulfisomidine, n⁴-β-d-glucosylsulfanilamide, mafenide, 4'-(methylsulfamoyl)sulfanilamide, noprilsulfamide, phthalylsulfacetamide, phthalylsulfathiazole, salazosulfadimidine, succinylsulfathiazole, sulfabenzamide, sulfacetamide, sulfachlorpyridazine, sulfachrysoidine, sulfacytine, sulfadiazine, sulfadiazine, sulfadimethoxine, sulfadoxine, sulfaethidole, sulfaguandine, sulfaguanol, sulfalene, sulfaloxacin, sulfamerazine, sulfameter, sulfamethazine, sulfamethazole, sulfamethomidine, sulfamethoxazole, sulfamethoxy-pyridazine, sulfametrole, sulfamidochrysoidine, sulfamoxole, sulfanilamide, 4-sulfanilamidosalicylic acid, n⁴-sulfanilylsulfanilamide, sulfanilylurea, n-sulfanilyl-3,4-xylamide, sulfanitrin, sulfaperine, sulfaphenazole, sulfaproxyline, sulfapyrazine, sulfapyridine, sulfasomizole, sulfasymazine, sulfathiazole, sulfathiazurea, sulfatolamide, sulfisomidine, sulfisoxazole) sulfones (e.g., acedapsone, acediasulfone, acetosulfone sodium, dapson, diathymosulfone, glucosulfone sodium, solasulfone, succinylsulfone, sulfanilic acid, p-sulfanilylbenzylamine, sulfonoxone sodium, thiazolsulfone), and others (e.g., clofoctol, hexedine, methenamine, methenamine anhydromethylencitrate, methenamine hippurate, methenamine mandelate, methenamine sulfosalicylate, nitroxoline, taurolidine, xibornol).

[0118] Examples of the antifungal antibiotics include, but are not limited to: polyenes (e.g., amphotericin b, candicidin, dennostatin, filipin, fungichromin, hachimycin, hamycin, lucensomycin, mepartricin, natamycin, nystatin, pecilocin, perimycin), others (e.g., azaserine, griseofulvin, oligomycins, neomycin undecylenate, pyrrolnitrin, siccanin, tubercidin, viridin).

[0119] Examples of the synthetic antifungals include, but are not limited to: allylamines (e.g., butenafine, naftifine, terbinafine), imidazoles (e.g., bifonazole, butoconazole, chlordanol, chlormidazole, clotrimazole, econazole, enilconazole, fenticonazole, flutrimazole, isoconazole, ketoconazole, lanoconazole, miconazole, omoconazole, oxiconazole nitrate, sertaconazole, sulconazole, tioconazole), thiocarbamates (e.g., tolclate, tolindate, tolinafate), triazoles (e.g., fluconazole, itraconazole, saperconazole, terconazole) others (e.g., acrisorcin, amorolfine, biphenamine, bromosalicylchloranilide, buclosamide, calcium propionate, chlorphenesin, ciclopirox, cloxyquin, coparaffinate, diamthazole dihydrochloride, exalamide, flucytosine, haletazole, hexetidine, loflucarban, nifuratel, potassium iodide, propionic acid, pyriithione, salicylanilide, sodium propionate, sulbentine, tenonitroazole, triacetin, ujothion, undecylenic acid, zinc propionate).

[0120] Examples of the antineoplastic agents include, but are not limited to: antineoplastic antibiotics and analogs (e.g., aclacinomycins, actinomycin f₁, anthramycin, azaserine, bleomycins, cactinomycin, carubicin, carzinophilin, chromomycins, dactinomycin, daunorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, idarubicin, menogaril, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, pirarubicin, plicamycin, porfirimycin, puromycin, streptonigrin, streptozocin, tubercidin, zinostatin, zorubicin), antimetabolites exemplified by folic acid analogs (e.g., denopterin, edatrexate, methotrexate, piritrexim, pteropterin, Tomudex®, trimetrexate), purine analogs (e.g., cladribine, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine), pyrimidine analogs (e.g., ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, doxifluridine, emitefur, enocitabine, floxuridine, fluorouracil, gemcitabine, tagafur).

[0121] Examples of the steroidal anti-inflammatory agents include, but are not limited to: 21-acetoxypregnenolone, alclometasone, algestone, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, dexamethasone, diflorasone, diflucortolone, difluprednate, enoxolone, fluazacort, flucoronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednidene acetate, fluprednisolone, flurandrenolide, fluticasone propionate, formocortol, halcinonide, halobetasol propionate, halometasone, halopredone acetate, hydrocortamate, hydrocortisone, loteprednol etabonate, mazipredone, medrysone, meprednisone, methylprednisolone, mometasone furoate, paramethasone, prednicarbate, prednisolone, prednisolone 25-diethylaminoacetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, rimexolone, tixocortol, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, and triamcinolone hexacetone.

[0122] Examples of the non-steroidal anti-inflammatory agents include, but are not limited to: aminoarylcarboxylic acid derivatives (e.g., enfenamic acid, etofenamate, flufenamic acid, isonixin, meclofenamic acid, mefenamic acid, niflumic acid, talniflumate, terofenamate, tolfenamic acid), arylacetic acid derivatives (e.g., aceclofenac, acetaminacin, alclofenac, amfenac, amtolmetin guacil, bufexamac, cinmetacin, clopirac, diclofenac sodium, etodolac, felbinac, fenclozic acid, fentiazac, glucametacin, ibufenac, indomethacin, isofezolac, isoxepac, lonazolac, metiazinic acid, mofezolac, oxametacine, pirazolac, proglumetacin, sulindac, tiaramide, tolmetin, tropesin, zomepirac), arylbutyric acid derivatives (e.g., bumadizon, butibufen, fenbuten, xenbucin), arylcarboxylic acids (e.g., clidanac, ketorolac, tinoridine), arylpropionic acid derivatives (e.g., alminoprofen, benoxaprofen, bermoprofen, bucloxic acid, carprofen, fenoprofen, flunoxaprofen, flurbiprofen, ibuprofen, ibuprofen, indoprofen, ketoprofen, loxoprofen, naproxen, oxaprozin, piketoprofen, pirprofen, pranoprofen, protizinic acid, suprofen, tiaprofenic acid, ximoprofen, zaltoprofen), pyrazoles (e.g., difenamizole, epirizole), pyrazolones (e.g., apazone, benzpiperylon, feprazone, mofebutazone, morazone, oxyphenbutazone, phenylbutazone, pipebutazone, propyphenazone, ramifenazone, suxibuzone, thiazolinobutazone), salicylic acid derivatives (e.g., acetaminosalol, aspirin, benorylate, bromosaligenin, calcium acetylsalicylate, diflunisal, etersalate, fendosal, gentisic acid, glycol salicylate, imidazole salicylate, lysine acetylsalicylate, mesalamine, morpholine salicylate, 1-naphthyl salicylate, olsalazine, parsalimide, phenyl acetylsalicylate, phenyl salicylate, salacetamide, salicylamide o-acetic acid, salicylsulfuric acid, salsalate, sulfasalazine), thiazinecarboxamides (e.g., ampiroxicam, droxicam, isoxicam, lornoxicam, piroxicam, tenoxicam), E-acetamidocaproic acid, s-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, α -bisabolol, bucolome, difenpiramide, ditazol, emorfazone, fepradinol, guaiazulene, nabumetone, nimesulide, oxaceprol, paranyline, perisoxal, proquazone, superoxide dismutase, tenidap, and zileuton.

[0123] Examples of anti-allergic agents include, but are not limited to: tranilast, ketotifen fumarate, pheniramine, diphenhydramine hydrochloride, sodium cromoglicate, bepotastine and bepotastine besilate.

[0124] Examples of glaucoma-treating agents include, but are not limited to: pilocarpine hydrochloride, latanoprost, timolol, iganipidine and isopropylunoprostone.

[0125] Examples of antiviral agents include, but are not limited to: idoxuridine, acyclovir, and trifluorouridine.

[0126] Examples of anti-mycotic agents include, but are not limited to: pimarinic, fluconazole, miconazole, amphotericin B, flucytosine, and itraconazole.

Preparations

[0127] The active agent of the present invention can be mixed with an ophthalmically acceptable carrier, excipient or diluent and formulated by a known method into a composition or formulation in various dosage forms such as injection solutions, eye drops, and ophthalmic gels or ointments. It is especially preferred that the formulation is in a topical dosage form, preferably an eye drop formulation in solution, or suspension form or an ophthalmic gel or ointment.

[0128] The ophthalmic formulations may, for example, be aqueous based such as aqueous eye drops, aqueous suspension eye drops, viscous eye drops and solubilized eye drops as well as non-aqueous based such as non-aqueous eye drops and non-aqueous suspension eye drops, or an ophthalmic gel or ointment.

[0129] An aqueous suspension preferably contains sodium borate and boric acid as buffering agents, an alkyl aryl polyether alcohol type polymer such as tyloxapol as a stabilizing, solubilizing, dispersing or isotonicity agent, and polyvinyl pyrrolidone as a stabilizing agent.

[0130] An ophthalmic ointment may employ an ointment base known per se, such as purified lanolin, petrolatum, plastibase, liquid paraffin, polyethylene glycol and the like.

[0131] The present invention also provides for an ophthalmic kit comprising the formulation disclosed herein and a means to apply the formulation to the eye. The ophthalmic kits may contain an application means which is an eye dropper, an eye cup, an eye spray or gel ointment tube and can comprise a single dose or a multi dose of the formulation in a single container.

Conditions/Diseases

[0132] According to one aspect of the present invention there is provided a method of treating an ocular disease, injury or disorder in a patient by administering a topical ophthalmic formulation described above.

[0133] Furthermore the method may include a dosing regime of once, twice, or up to six times daily administration into said eye to treat the pain and/or inflammation associated with said ocular disease, injury or disorder. With the preferred dosing being once a day with a higher dose bromfenac formulation and twice a day with a lower dose bromfenac formulation.

[0134] A further aspect of the present invention is a therapeutic method wherein said ocular disease, injury or disorder is caused by surgery, physical damage to the eye, glaucoma, macular degeneration, or diabetic retinopathy. A still further aspect of the present invention is wherein the ocular disease, injury or disorder is one caused by vascular leakage in the eye or by inflammation in the eye.

[0135] Examples of conditions related to inflammation in the eye include, but are not limited to the following: surgical trauma, dry eye, allergic conjunctivitis, viral conjunctivitis, bacterial conjunctivitis, blepharitis, anterior uveitis, injury from a chemical, radiation or thermal burn, or penetration of a foreign body.

[0136] An embodiment of the present invention includes the method of treating ocular inflammation and/or pain in a patient in need with one of the ophthalmic formulations described above, wherein said inflammation and/or pain is caused by surgical trauma, and wherein said treatment comprises treating the patient once, twice, or up to six times daily with any of the formulations disclosed herein.

[0137] An additional embodiment of the present invention includes the method of treating ocular pain and/or inflammation in a patient in need thereof, wherein said inflammation and accompanying pain is the result of cataract surgery or one of many refractive eye surgical techniques, and

wherein said treatment comprises treating the patient once or twice daily with a formulation herein.

[0138] An additional embodiment of the present invention includes the method of treating ocular pain and/or inflammation in a patient in need thereof, wherein said inflammation and accompanying pain is the result of allergic, viral or bacterial conjunctivitis, and wherein said treatment comprises treating the patient with any of the disclosed formulations.

[0139] An additional embodiment of the present invention includes a method treating ocular pain and/or inflammation associated with allergic, viral or bacterial conjunctivitis with one of the topical ophthalmic formulations. An additional embodiment may include one or more additional active ingredients as part of the formulation, such additional actives may include, but are not limited to, antihistamines and/or antibacterials and/or antimicrobial compounds, to further assist with the treatment of the conjunctivitis condition.

[0140] An additional embodiment of the present invention includes a method for treating an eye wherein its normal condition has been disrupted or changed comprising administering to said eye one to six times daily the selected formulation.

[0141] An additional embodiment of the present invention includes a method for treating postoperative inflammation and/or pain in patients who have undergone cataract extraction comprising the once, twice or up to six times daily administration of a selected formulation into the effected eye.

Administration

[0142] The bromfenac ophthalmic composition or formulation of the present invention may be administered to a patient which is or may be suffering from an ophthalmic injury, surgery, disease or disorder (e.g., human, rat, mouse, rabbit, dog, cat, cattle, horse, monkey). The composition or formulation is given in an amount sufficient to cure, treat, or at least partially arrest the symptoms or complications of the ocular surgery, injury, disease or disorder. Amounts effective for this use will depend on the severity and course of the surgery, injury, disease or disorder, the patient's health status and response to the composition or formulation, and the judgment of the treating physician.

[0143] The formulation of the present invention and its subsequent administration is within the skill of those in the art. Dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from one day to several months, or until a cure is effected or a diminution of the disease state is achieved. Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient.

[0144] An exemplary dosing schedule would comprise pretreating a patient from 48 hours to immediately before a scheduled ophthalmic procedure (such as cataract surgery), and then continuing treatment one or two times daily for approximately 14 days after surgery or until a physician is satisfied that the condition has been sufficiently corrected and no longer requires external intervention.

[0145] In cases where the formulation is used to treat a condition that is unscheduled, treatment may begin immediately from onset of any symptoms of whatever condition, disease or disorder is to be treated, and treated once or twice

daily for approximately 14 days afterwards or until a physician is satisfied that the condition has been sufficiently corrected.

EXAMPLES

[0146] Having now generally described the invention, the same will be more readily understood through reference to the following examples which are provided by way of illustration, and are not intended to be limiting of the present invention, unless specified. The present invention is illustrated by way of the following Experimental Examples and Working Examples, but it is not restricted by these Examples.

Experimental Example 1

Stability Test of Sodium

2-amino-3-(4-bromobenzoyl)phenylacetate

[0147] Four eye drops of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate comprising the components as shown in Table 1 were prepared, filled respectively into a polypropylene container and subjected to stability test at 60.degree. C.

TABLE 1

Component	Comparison Example 1	A-01	A-02	A-03
Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate	0.1 g	0.1 g	0.1 g	0.1 g
Boric acid	1.5 g	1.5 g	1.5 g	1.5 g
Benzalkonium chloride	0.005 g	0.005 g	0.005 g	0.005 g
Polysorbate 80	0.15 g	—	—	—
Polyoxyl 40 stearate	—	0.15 g	—	—
Tyloxapol	—	—	0.15 g	0.02 g
Sterile purified water	q.s.	q.s.	q.s.	q.s.
Total volume	100 mL	100 mL	100 mL	100 mL
pH	7.0	7.0	7.0	7.0
Remaining rate (%) at 60° C. after 4 weeks	51.3	63.7	73.8	89.6

[0148] The remaining rate (%) in the above Table 1 indicates values obtained by correcting moisture vaporization from the container. As is apparent from the Table 1, stability test was carried out under the conditions of pH 7.0 at 60° C. for 4 weeks, and sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in each eye drop was stable in the order of tyloxapol-containing preparation>polyoxyl 40 stearate-containing preparation>polysorbate 80-containing preparation.

[0149] Further, with respect to eye drops containing tyloxapol (compositions A-02 and A-03), sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in composition A-03 containing 0.02% w/v of tyloxapol is more stable than that in composition A-02 containing 0.15% w/v of tyloxapol.

Experimental Example 2

Stability Test of Sodium

2-amino-3-(4-bromobenzoyl)phenylacetate

[0150] Five eye drops of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate comprising the components as shown in Table 2 were prepared, filled respectively into a polypropylene container and preserved at 60.degree. C. for 4 weeks, and then the content of 2-amino-3-(4-bromobenzoyl)phenylacetic acid and the pH in each eye drop were measured.

TABLE 2

Components	A-04	A-05	A-06	A-07	A-08
Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate	0.1 g	0.1 g	0.1 g	0.1 g	0.1 g
Boric acid	1.1 g	1.1 g	1.1 g	1.1 g	1.1 g
Borax	1.1 g	1.1 g	1.1 g	1.1 g	1.1 g
Benzalkonium chloride	0.005 g	0.005 g	0.005 g	0.005 g	0.005 g
Polysorbate 80	—	—	—	—	—
Tyloxapol	0.02 g	0.05 g	0.03 g	—	—
Polyoxyl 40 stearate	—	—	—	0.02 g	0.05 g
Polyvinylpyrrolidone (K-30)	2.0 g	2.0 g	2.0 g	2.0 g	1.0 g
Sodium edetate	0.02 g	0.02 g	0.02 g	0.02 g	0.02 g
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.
Sterile purified water	q.s.	q.s.	q.s.	q.s.	q.s.
Total volume	100 mL	100 mL	100 mL	100 mL	100 mL
pH	8.17	8.16	8.15	8.19	8.19
60° C., Remaining rate (%)	92.6	90.9	92.0	93.4	93.1
4 weeks pH	8.15	8.16	8.15	8.13	8.14

[0151] Table 2 shows the remaining rate and the pH of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate after storage at 60° C. for 4 weeks, when the remaining rate of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate at the time of production of eye drops is set to 100%. The remaining rate is a value obtained by correcting moisture vaporization from the container. As is apparent from Table 2, the remaining rate of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate in the compositions A-04, A-05, A-06, A-07 and A-08 containing 0.02% w/v, 0.03% w/v and 0.05% w/v of tyloxapol or 0.02% w/v and 0.05% w/v of polyoxyl 40 stearate is not less than 90% after storage at 60° C. for 4 weeks, which indicates that those compositions have sufficient stability for eye drops.

Experimental Example 3

Preservative Effect Test of Aqueous Liquid Preparation Containing Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate

[0152] Preservative effect test of compositions A-04, A-05 and A-07 of Experimental Example 2 was carried out against *Staphylococcus aureus* (hereinafter referred to as *S. aureus*), *Escherichia Coli* (hereinafter referred to as *E. coli*), *Pseudomonas aeruginosa* (hereinafter referred to as *P. aeruginosa*), *Candida albicans* (hereinafter referred to as *C. albicans*) and *Aspergillus niger* (hereinafter referred to as *A. niger*).

[0153] The results are shown in Tables 3-1, 3-2 and 3-3.

TABLE 3-1

Cell count (CFU/mL)							
	Inoculum count	6 hours	24 hours	7 days	14 days	21 days	28 days
		after inoculation	after inoculation	after inoculation	after inoculation	after inoculation	after inoculation
A-04							
<i>S. aureus</i>	2.1×10^6	3.0×10^1	0	0	0	0	0
<i>E. coli</i>	6.5×10^6	0	0	0	0	0	0
<i>P. aeruginosa</i>	5.8×10^6	0	0	0	0	0	0
<i>C. albicans</i>	3.2×10^5	—	—	0	0	0	0
<i>A. niger</i>	1.8×10^5	—	—	0	0	0	0

TABLE 3-2

Cell count (CFU/mL)							
	Inoculum count	6 hours	24 hours	7 days	14 days	21 days	28 days
		after inoculation	after inoculation	after inoculation	after inoculation	after inoculation	after inoculation
A-05							
<i>S. aureus</i>	2.1×10^6	1.7×10^5	2.0×10^1	0	0	0	0
<i>E. coli</i>	6.5×10^6	0	0	0	0	0	0
<i>P. aeruginosa</i>	5.8×10^6	0	0	0	0	0	0
<i>C. albicans</i>	3.2×10^5	—	—	0	0	0	0
<i>A. niger</i>	1.8×10^5	—	—	0	0	0	0

TABLE 3-3

	Cell count (CFU/mL)						
	Inoculum count	6 hours after inoculation	24 hours after inoculation	7 days after inoculation	14 days after inoculation	21 days after inoculation	28 days after inoculation
A-07							
<i>S. aureus</i>	2.7×10^6	3.1×10^4	0	0	0	0	0
<i>E. coli</i>	7.4×10^6	0	0	0	0	0	0
<i>P. aeruginosa</i>	8.8×10^6	0	0	0	0	0	0
<i>C. albicans</i>	4.6×10^5	—	—	0	0	0	0
<i>A. niger</i>	1.0×10^5	—	—	0	0	0	0

[0157] As is apparent from Tables 3-1, 3-2 and 3-3, the preservative effect of composition A-04 was found to be compatible with EP-criteria A in European Pharmacopoeia (EP), and those of compositions A-05 and A-07 were found to be compatible with EP-criteria B.

The EP-criteria A and EP-criteria B are given in the following.

EP-Criteria A:

[0158] Viable cell counts of bacteria (*S. aureus*, *P. aeruginosa*) 6 hours, 24 hours, and 28 days after inoculation decrease to not more than {fraction ($1/100$)}, not more than {fraction ($1/1000$)}, and undetectable, respectively.

[0159] Viable cell count of fungi (*C. albicans*, *A. niger*) 7 hours after inoculation decreases to not more than {fraction ($1/100$)}, and thereafter, the cell count levels off or decreases.

EP-Criteria B

[0160] Viable cell counts of bacteria (*S. aureus*, *P. aeruginosa*) 24 hours and 7 days after inoculation decrease to not more than {fraction ($1/10$)} and not more than {fraction ($1/1000$)}, respectively, and thereafter, the cell count levels off or decreases.

[0161] Viable cell count of fungi (*C. albicans*, *A. niger*) 14 days after inoculation decreases to not more than {fraction ($1/10$)}, and thereafter, the cell count keeps the same level as that of 14 days after inoculation.

General Ophthalmic Formulation Example 1

[0162] Eye prop

Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate 3/2 hydrate	0.1 g
Boric acid	1.1 g
Borax	1.1 g
Benzalkonium chloride	0.005 g
Tyloxapol	0.02 g
Polyvinylpyrrolidone (K-30)	2.0 g
Sodium edetate	0.02 g
Sodium hydroxide	q.s.
Sterile purified water	to make total volume of 100 mL pH 8.17

An eye drop is prepared using the above components in a conventional manner.

General Ophthalmic Formulation Example 2

[0163] Eye Drop

Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate 3/2 hydrate	0.1 g
Boric acid	1.1 g
Borax	1.1 g
Benzalkonium chloride	0.005 g
Tyloxapol	0.05 g
Polyvinylpyrrolidone (K-30)	2.0 g
Sodium edetate	0.02 g
Sodium hydroxide	q.s.
Sterile purified water	to make total volume of 100 mL pH 8.16

An eye drop is prepared using the above components in a conventional manner.

General Ophthalmic Formulation Example 3

[0164] Eye prop

Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate 3/2 hydrate	0.1 g
Boric acid	1.1 g
Borax	1.1 g
Benzalkonium chloride	0.005 g
Polyoxyl 40 stearate	0.02 g
Polyvinylpyrrolidone (K-30)	2.0 g
Sodium edetate	0.02 g
Sodium hydroxide	q.s.
Sterile purified water	to make total volume of 100 mL pH 8.19

[0165] An eye drop is prepared using the above components in a conventional manner.

[0166] Prospective Lower Dose Ophthalmic Formulation 1:

Bromfenac or a derivative thereof	about 0.05% w/v to about 0.1% w/v;
a stabilizing agent	about 0.35% w/v to about 3.00% w/v;
a solubilizing agent	about 0.002% w/v to about 0.2% w/v;
a chelating agent	about 0.005% w/v to about 0.1% w/v;
a tonicity agent	about 0.08% w/v to about 0.14% w/v;
a preservative	about 0.0025% w/v to about 0.02% w/v;

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a buffering agent,	Q.S. sufficient to bring final pH of the composition to about 8.0 to about 8.5.
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[0167] Prospective Lower Dose Ophthalmic Formulation 2:

bromfenac sodium	about 0.05% w/v to about 0.1% w/v;
polyvinylpyrrolidone	about 0.35% w/v to about 3.00% w/v;
tyloxapol	about 0.002% w/v to about 0.2% w/v;
a chelating agent	about 0.005% w/v to about 0.1% w/v;
a tonicity agent	about 0.08% w/v to about 0.14% w/v;
a preservative	about 0.0025% w/v to about 0.02% w/v;
buffering agents,	Q.S. sufficient to bring final pH of the composition to about 8.0 to about 8.5.

[0168] Prospective Lower Dose Ophthalmic Formulation 3:

bromfenac or a derivative thereof	about 0.08% w/v;
polyvinylpyrrolidone	about 2.00% w/v;
tyloxapol	about 0.02% w/v;
a chelating agent	about 0.02% w/v;
a tonicity agent	about 0.11% w/v;
a preservative	about 0.005% w/v;
a buffering agent,	Q.S. sufficient to bring final pH of the composition to about 8.0 to about 8.5.

[0169] Prospective Lower Dose Ophthalmic Formulation 4 (to be formulated in purified water):

bromfenac sodium	about 0.08% w/v;
boric acid	about 1.10% w/v;
sodium borate	about 1.10% w/v;
benzalkonium chloride	about 0.005% w/v;
polyvinylpyrrolidone	about 2.00% w/v;
EDTA	about 0.02% w/v;
sodium chloride	about 0.109% w/v;
tyloxapol	about 0.02% w/v;
pH	about 8.3.

[0170] Exemplary Quantities for Formulating Prospective Lower Dose Ophthalmic Formulation 4

Ingredient	Theoretical Quantity
Bromfenac sodium	0.092 g (equal to 0.08 g as a free acid)
Boric acid	1.1 g
Sodium borate	1.1 g
Benzalkonium chloride	0.005 g
PVP	2.0 g
EDTA	0.02 g

-continued

Ingredient	Theoretical Quantity
Sodium chloride	0.1085 g
Tyloxapol	0.02 g
2 N NaOH	q.s.
1 N HCl	q.s.
Purified Water	100 mL

Prospective Instructions for Formulating Prospective Lower Dose Ophthalmic Formulation 4

Step:

- 1). Place 50 mL of purified water in a 250 mL graduated glass beaker with a stir bar;
- 2). add 2.0 g of PVP to the beaker and stir until it dissolves;
- 3). add 1.1 g of boric acid to the beaker and stir until it dissolves;
- 4). add 1.1 g of sodium borate to the beaker and stir until it dissolves;
- 5). add 0.02 g of EDTA to the beaker and stir until it dissolves;
- 6). add 0.1085 g of sodium chloride to the beaker and stir until it dissolves;
- 7). add 0.02 g of tyloxapol to the beaker and stir until it dissolves;
- 8). add 0.092 g as bromfenac sodium (equal to 0.08 g of bromfenac as a free acid) to the beaker and stir until it dissolves;
- 9). add 0.05 mL of 10% BAK to the beaker and stir until it dissolves;
- 10). add about 40 mL of purified sterile water to the beaker;
- 11). adjust the pH to 8.3 using 2 N NaOH and 1 N HCl (when necessary);
- 12). make up the volume to 100 mL; and
- 13). filter the solution using a sterile filtration assembly.

[0171] The following formulation below has been formulated as follows:

[0172] Aqueous Lower Dose Ophthalmic Formulation 1 (Formulated in Purified Water):

bromfenac	about 0.08% (as a free acid) w/v;
boric acid	about 1.10% w/v;
sodium borate	about 1.10% w/v;
benzalkonium chloride	about 0.005% w/v;
polyvinylpyrrolidone	about 2.00% w/v;
EDTA	about 0.02% w/v;
sodium chloride	about 0.109% w/v;
tyloxapol	about 0.02% w/v;
pH	about 8.3.

[0173] Measured Quantities for Formulating Aqueous Ophthalmic Lower Dose Formulation 1

Ingredient	Theoretical Quantity
Bromfenac sodium	0.092 g (equal to 0.08 g of bromfenac as a free acid)
Boric acid	1.1 g
Sodium borate	1.1 g
Benzalkonium chloride	0.005 g
PVP	2.0 g
EDTA	0.02 g
Sodium chloride	0.1085 g
Tyloxapol	0.02 g
2 N NaOH	q.s.
1 N HCl	q.s.
Purified Water	100 mL

Instructions Followed for Formulating Aqueous Ophthalmic Lower Dose Formulation 1**Step:**

- 1). About 50 mL of purified water was placed in a 250 mL graduated glass beaker with a stir bar;
- 2). 2.0 g of PVP was added to the beaker and stirred until it dissolved;
- 3). 1.1 g of boric acid was added to the beaker and stirred until it dissolved;
- 4). 1.1 g of sodium borate was added to the beaker and stirred until it dissolved;
- 5). 0.02 g of EDTA was added to the beaker and stirred until it dissolved;
- 6) 0.1085 g of sodium chloride was added to the beaker and stirred until dissolved;
- 7). 0.02 g of tyloxapol was added to the beaker and stirred until it dissolved;
- 8). 0.092 g bromfenac sodium (equal to 0.08 g of bromfenac as a free acid) was added to the beaker and stirred until it dissolved;
- 9). 0.05 mL of 10% BAK was added to the beaker and stirred until it dissolved;
- 10). about 40 mL of purified water was added to the beaker;
- 11). the pH was adjusted to 8.3 using 2 N NaOH and 1 N HCl (when necessary);
- 12). the volume was made up to 100 mL; and
- 13). the solution was filtered using a sterile filtration assembly.

[0174] Prospective Lower Dose Ophthalmic Formulation 5:

Bromfenac or a derivative thereof	about 0.05% w/v to about 0.1% w/v;
sodium sulfite	about 0.02% w/v to about 0.5% w/v;
a stabilizing agent	about 0.35% w/v to about 3.00% w/v;
a solubilizing agent	about 0.002% w/v to about 0.2% w/v;
a chelating agent	about 0.005% w/v to about 0.1% w/v;

-continued

a preservative	about 0.0025% w/v to about 0.02% w/v;
a buffering agent,	Q.S. sufficient to bring final pH of the composition to about 8.0 to about 8.5.

[0175] Prospective Lower Dose Ophthalmic Formulation 6:

bromfenac sodium	about 0.05% w/v to about 0.1% w/v;
sodium sulfite	about 0.02% w/v to about 0.5% w/v;
polyvinylpyrrolidone	about 0.35% w/v to about 3.00% w/v;
tyloxapol	about 0.002% w/v to about 0.2% w/v;
a chelating agent	about 0.005% w/v to about 0.1% w/v;
a preservative	about 0.0025% w/v to about 0.02% w/v;
buffering agents,	Q.S. sufficient to bring final pH of the composition to about 8.0 to about 8.5.

[0176] Prospective Lower Dose Ophthalmic Formulation 7:

bromfenac or a derivative thereof	about 0.08% (as a free acid) w/v;
sodium sulfite	about 0.2% w/v;
polyvinylpyrrolidone	about 2.00% w/v;
tyloxapol	about 0.02% w/v;
a chelating agent	about 0.02% w/v;
a preservative	about 0.005% w/v;
a buffering agent,	Q.S. sufficient to bring final pH of the composition to about 8.0 to about 8.5.

[0177] The following formulation below has been formulated as follows:**[0178] Aqueous Lower Dose Ophthalmic Formulation 2 (Formulated in Purified Water):**

bromfenac sodium	about 0.08% (as a free acid) w/v;
boric acid	about 1.10% w/v;
sodium borate	about 1.10% w/v;
sodium sulfite	about 0.2% w/v;
benzalkonium chloride	about 0.005% w/v;
polyvinylpyrrolidone	about 2.00% w/v;
EDTA	about 0.02% w/v;
tyloxapol	about 0.02% w/v;
pH	about 8.3.

[0179] Measured Quantities for Formulating Aqueous Ophthalmic Lower Dose Formulation 2

Ingredient	Theoretical Quantity
Bromfenac sodium	0.092 g (equal to 0.08 g of bromfenac as a free acid)
Boric acid	1.1 g
Sodium borate	1.1 g
Benzalkonium chloride	0.005 g
PVP	2.0 g
EDTA	0.02 g
Sodium sulfite	0.2 g
Tyloxapol	0.02 g
2 N NaOH	q.s.

-continued

Ingredient	Theoretical Quantity
Purified Water	100 mL

Instructions Followed for Formulating Aqueous Ophthalmic Lower Dose Formulation 2

Step:

- 1). About 50 mL of purified water was placed in a 250 mL graduated glass beaker with a stir bar;
- 2). 2.0 g of PVP was added to the beaker and stirred until it dissolved;
- 3). 1.1 g of boric acid was added to the beaker and stirred until it dissolved;
- 4). 1.1 g of sodium borate was added to the beaker and stirred until it dissolved;
- 5). 0.02 g of EDTA was added to the beaker and stirred until it dissolved;
- 6). 0.2 g of sodium sulfite was added to the beaker and stirred until dissolved;
- 7). 0.02 g of tyloxapol was added to the beaker and stirred until it dissolved;
- 8). 0.092 g of bromfenac sodium (equal to 0.08 g of bromfenac as free acid) was added to the beaker and stirred until it dissolved;
- 9). 0.05 mL of 10% BAK was added to the beaker and stirred until it dissolved;
- 10). about 40 mL of purified water was added to the beaker;
- 11). the pH was adjusted to 8.3 using 2 N NaOH and 1 N HCl (when necessary);
- 12). the volume was made up to 100 mL; and
- 13). the solution was filtered using a sterile filtration assembly.

[0180] The Lower Dose formulations may be used to pretreat a patient by administering the formulation to the patient twice daily from 48 hours to immediately before a scheduled ophthalmic procedure (such as cataract surgery). Post-surgical care then requires continued treatment two times daily for approximately 14 days or until a physician is satisfied that the condition has been sufficiently corrected no longer requires external intervention.

[0181] The formulations may be used to treat a condition that is unscheduled, by starting treatment upon onset of any symptoms of the condition, disease or disorder. The formulation is administered twice daily for approximately 14 days or until a physician is satisfied that the condition has been sufficiently corrected.

[0182] Prospective Higher Dose Ophthalmic Formulation 1

Bromfenac or a derivative thereof	about 0.12% w/v to about 0.24% w/v;
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a stabilizing agent	about 0.35% w/v to about 3.00% w/v;
a solubilizing agent	about 0.002% w/v to about 0.5% w/v;
a chelating agent	about 0.005% w/v to about 0.1% w/v;
a tonicity agent	about 0.04% w/v to about 0.14% w/v;
a preservative	about 0.0025% w/v to about 0.02% w/v;
a buffering agent,	Q.S. sufficient to bring final pH of the composition to about 7.6 to about 8.0.

[0183] Prospective Higher Dose Ophthalmic Formulation 2:

bromfenac sodium	about 0.12% w/v to about 0.24% w/v;
polyvinylpyrrolidone	about 0.35% w/v to about 3.00% w/v;
tyloxapol	about 0.002% w/v to about 0.5% w/v;
a chelating agent	about 0.005% w/v to about 0.1% w/v;
a tonicity agent	about 0.04% w/v to about 0.14% w/v;
a preservative	about 0.0025% w/v to about 0.02% w/v;
buffering agents,	Q.S. sufficient to bring final pH of the composition to about 7.6 to about 8.0.

[0184] Prospective Higher Dose Ophthalmic Formulation 3:

bromfenac or a derivative thereof	about 0.18% (as a free acid) w/v;
polyvinylpyrrolidone	about 2.00% w/v;
tyloxapol	about 0.02% w/v;
a chelating agent	about 0.02% w/v;
a tonicity agent	about 0.087% w/v;
a preservative	about 0.005% w/v;
a buffering agent,	Q.S. sufficient to bring final pH of the composition to about 7.6 to about 8.0.

[0185] Prospective Higher Dose Ophthalmic Formulation 4

bromfenac sodium	about 0.12% w/v to about 0.24% w/v;
polyvinylpyrrolidone	about 0.35% w/v to about 3.00% w/v;
tyloxapol	about 0.002% w/v to about 0.5% w/v;
sodium sulfite	about 0.02% w/v to about 0.4% w/v;
a chelating agent	about 0.005% w/v to about 0.1% w/v;
a preservative	about 0.0025% w/v to about 0.02% w/v;
buffering agents,	Q.S. sufficient to bring final pH of the composition to about 7.6 to about 8.0.

[0186] Prospective Higher Dose Ophthalmic Formulation 5:

bromfenac or a derivative thereof	about 0.18% (as a free acid) w/v;
polyvinylpyrrolidone	about 2.00% w/v;
tyloxapol	about 0.3% w/v;
sodium sulfite	about 0.2% w/v;
a chelating agent	about 0.02% w/v;
a preservative	about 0.005% w/v;
a buffering agent,	Q.S. sufficient to bring final pH of the composition to about 7.6 to about 8.0.

[0187] Prospective Higher Dose Ophthalmic Formulation 6:

bromfenac or a derivative thereof	about 0.18% (as a free acid) w/v;
polyvinylpyrrolidone	about 2.00% w/v;
tyloxapol	about 0.3% w/v;
sodium sulfite	about 0.2% w/v;
disodium edetate	about 0.02% w/v;
benzalkonium chloride	about 0.005% w/v;
a buffering agent,	Q.S. sufficient to bring final pH of the composition to about 7.6 to about 8.0.

[0188] The following formulation below has been formulated as follows:

[0189] Aqueous Higher Dose Ophthalmic Formulation 1 (was Formulated in Purified Water):

bromfenac sodium	about 0.206% (equal to 0.18% of bromfenac as a free acid) w/v;
boric acid	about 1.30% w/v;
sodium borate	about 0.74% w/v;
benzalkonium chloride	about 0.005% w/v;
polyvinylpyrrolidone	about 2.00% w/v;
EDTA	about 0.02% w/v;
sodium chloride	about 0.087% w/v;
tyloxapol	about 0.02% w/v;
pH	about 7.8.

[0190] Measured Quantities Used for Formulating Aqueous Higher Dose Ophthalmic Formulation 1

Ingredient	Theoretical Quantity
Bromfenac sodium	0.2064 g (equal to about 0.18 g of bromfenac as a free acid)
Boric acid	1.30 g
Sodium borate	0.74 g
Benzalkonium chloride	0.005 g
PVP	2.0 g
EDTA	0.02 g
Sodium chloride	0.087 g
Tyloxapol	0.02 g
2 N NaOH	q.s. to pH 7.8
1 N HCl	q.s. to pH 7.8
Purified Water	100 mL

Instructions for formulating Aqueous Higher Dose Ophthalmic Once Daily Formulation 1

Step:

- 1). About 50 mL of purified water was placed in a 250 mL graduated glass beaker with a stir bar;
- 2). 2.0 g of PVP was added to the beaker and stirred until it dissolved;
- 3). 1.30 g of boric acid was added to the beaker and stirred until it dissolved;
- 4). 0.74 g of sodium borate was added to the beaker and stirred until it dissolved;
- 5). 0.02 g of EDTA was added to the beaker and stirred until it dissolved;

6) 0.087 g of sodium chloride was added to the beaker and stirred until dissolved;

7). 0.02 g of tyloxapol was added to the beaker and stirred until it dissolved;

8). 0.2064 g of bromfenac sodium (equal to about 0.18% bromfenac as free acid) was added to the beaker and stirred until it dissolved;

9). 0.05 mL of 10% BAK was added to the beaker and stirred until it dissolved;

10). about 40 mL of purified water was added to the beaker;

11). the pH was adjusted to 7.8 using 2 N NaOH and 1 N HCl (when necessary);

12). the volume was made up to 100 mL; and

13). the solution was filtered using a sterile filtration assembly.

[0191] The following formulation below has been formulated as follows:

[0192] Aqueous Higher Dose Ophthalmic Formulation 2 (was Formulated in Purified Water):

bromfenac sodium	about 0.2064% w/v (which equals 0.18% bromfenac as free acid);
boric acid	about 1.30% w/v;
sodium borate	about 0.74% w/v;
benzalkonium chloride	about 0.005% w/v;
polyvinylpyrrolidone	about 2.00% w/v;
sodium sulfite	about 0.2% w/v;
EDTA	about 0.02% w/v;
tyloxapol	about 0.3% w/v;
pH	about 7.8.

[0193] Measured Quantities Used for Formulating Aqueous Higher Dose Ophthalmic Formulation 2

Ingredient	Theoretical Quantity
Bromfenac sodium	0.2064 g (equal to about 0.18 g of bromfenac as a free acid)
Boric acid	1.30 g
Sodium borate (Sodium tetraborate)	0.74 g
Benzalkonium chloride	0.005 g
PVP	2.0 g
EDTA	0.02 g
Sodium sulfite	0.2 g
Tyloxapol	0.3 g
2 N NaOH	q.s. to pH 7.8
Purified Water	100 mL

Instructions for Formulating Aqueous Higher Dose Ophthalmic Once Daily Formulation 2

Step:

- 1). About 50 mL of purified water was placed in a 250 mL graduated glass beaker with a stir bar;
- 2). 2.0 g of PVP was added to the beaker and stirred until it dissolved;
- 3). 1.30 g of boric acid was added to the beaker and stirred until it dissolved;

- 4). 0.74 g of sodium borate was added to the beaker and stirred until it dissolved;
- 5). 0.02 g of EDTA was added to the beaker and stirred until it dissolved;
- 6) 0.2 g of sodium sulfite was added to the beaker and stirred until dissolved;
- 7). 0.3 g of tyloxapol was added to the beaker and stirred until it dissolved;
- 8). 0.2064 g of bromfenac sodium (which equals 0.18% bromfenac as free acid) was added to the beaker and stirred until it dissolved;
- 9). 0.05 mL of 10% BAK was added to the beaker and stirred until it dissolved;
- 10). about 40 mL of purified water was added to the beaker;
- 11). the pH was adjusted to 7.8 using 2 N NaOH and 1 N HCl (when necessary);
- 12). the volume was made up to 100 mL; and
- 13). the solution was filtered using a sterile filtration assembly.

[0194] The Higher Dose formulations may be used to pretreat a patient by administering the formulation to the patient once daily from 48 hours to immediately before a scheduled ophthalmic procedure (such as cataract surgery). Post-surgical care then requires continued treatment once daily for approximately 14 days or until a physician is satisfied that the condition has been sufficiently corrected no longer requires external intervention.

[0195] The formulations may be used to treat a condition that is unscheduled, by starting treatment upon onset of any symptoms of the condition, disease or disorder. The formulations may be administered once daily for approximately 14 days or until a physician is satisfied that the condition has been sufficiently corrected.

[0196] All references cited herein, including patents, patent applications, and publications, are hereby incorporated by reference in their entireties, whether previously specifically incorporated or not.

[0197] Having now fully described this invention, it will be appreciated by those skilled in the art that the same can be performed within a wide range of equivalent parameters, concentrations, and conditions without departing from the spirit and scope of the invention and without undue experimentation.

[0198] While this invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications. This application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth.

What is claimed is:

1. A method of treating pain and/or inflammation associated with an ocular disease, injury or disorder comprising administering to a patient, in need of such treatment, an aqueous liquid preparation comprising 2-amino-3-(4-bro-

mobenzoyl)phenylacetic acid or a pharmaceutically acceptable salt thereof or a hydrate thereof, and an alkyl aryl polyether alcohol type polymer or a polyethylene glycol fatty acid ester.

2. The method of claim 1, wherein the alkyl aryl polyether alcohol type polymer is tyloxapol.

3. The method of claim 2, wherein the concentration of tyloxapol is selected from a range of about 0.01% w/v to about 0.5% w/v.

4. The method of claim 3, wherein the concentration of tyloxapol is about 0.02 to about 0.3% w/v.

5. The method of claim 4, wherein the pharmacologically acceptable salt of the 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt.

6. The method of claim 5, wherein the concentration of the salt is about 0.05 to about 0.2% w/v.

7. The method of claim 6, wherein the concentration of the salt is about 0.09 to about 0.21% w/v.

8. The method of claim 7, wherein the pH of the aqueous liquid preparation is from about 7 to about 9.

9. The method of claim 8, wherein the pH is from about 7.5 to about 8.5.

10. The method of claim 9, wherein said formulation is administered once per day.

11. The method of claim 10, wherein the ocular disease, injury, or disorder is caused by surgery, physical damage to the eye, glaucoma, diabetic retinopathy, and/or macular degeneration.

12. The method of claim 11, wherein the ocular disease, injury, or disorder is one which results in vascular leakage in the eye or inflammation in the eye.

13. The method of claim 12, wherein the inflammation in the eye is caused by surgical trauma; dry eye; allergic, viral, or bacterial conjunctivitis; injury from a chemical, radiation, or thermal burn; and/or penetration of a foreign body.

14. The method of claim 13, wherein said inflammation in the eye is caused by allergic, viral, or bacterial conjunctivitis.

15. The method of claim 13, wherein said inflammation in the eye is caused by surgical trauma.

16. The method of claim 15, wherein said surgical trauma is the result of cataract surgery.

17. The method of claim 15, wherein said surgical trauma is the result of a refractive eye surgery.

18. The method of claim 17, wherein said refractive eye surgery is photorefractive keratectomy (PRK) or laser epithelial keratomileusis (LASEK) refractive eye surgery.

19. A method of treating an eye wherein its normal condition has been disrupted or changed comprising:

administering the formulation of claim 1 to said eye one time daily.

20. The method of claim 19, wherein the disruption or change is due to blepharitis, conjunctivitis, scleritis, or postoperative inflammation.

21. The method of claim 19, wherein said formulation is administered to treat or alleviate pain and/or inflammation associated with said disrupted or changed condition of the eye.

22. A method for treating a patient for pain and/or inflammation associated with eye surgery comprising:

pre-dosing the patient for up to 48 hours before the eye surgery with the formulation of claim 1;

wherein the formulation is applied once daily; and

applying said formulation once daily post surgery for about 14 days or until condition has been alleviated.

23. The method of claim 22, wherein said eye surgery is cataract surgery.

24. The method of claim 22, wherein said eye surgery is any refractive eye surgery.

25. The method of claim 24, wherein said refractive surgery is photorefractive keratectomy (PRK) surgery or laser epithelial keratomileusis (LASEK) refractive eye surgery.

26. The method of claim 22, wherein the pain and/or inflammation is due to postoperative eye surgery.

27. The method of claim 9, wherein said formulation is administered twice per day.

28. The method of claim 27, wherein the ocular disease, injury, or disorder is caused by surgery, physical damage to the eye, glaucoma, diabetic retinopathy, and/or macular degeneration.

29. The method of claim 27, wherein the ocular disease, injury, or disorder is one which results in vascular leakage in the eye or inflammation in the eye.

30. The method of claim 29, wherein the inflammation in the eye is caused by surgical trauma; dry eye; allergic, viral, or bacterial conjunctivitis; injury from a chemical, radiation, or thermal burn; and/or penetration of a foreign body.

31. The method of claim 30, wherein the inflammation in the eye is caused by allergic, viral, or bacterial conjunctivitis.

32. The method of claim 30, wherein the inflammation in the eye is caused by surgical trauma.

33. The method of claim 32, wherein said surgical trauma is the result of cataract surgery.

34. The method of claim 32, wherein said surgical trauma is the result of refractive eye surgery.

35. The method of claim 34, wherein said refractive eye surgery is photorefractive keratectomy (PRK) or laser epithelial keratomileusis (LASEK) refractive eye surgery.

36. A method of treating an eye wherein its normal condition has been disrupted or changed comprising:

administering the formulation of claim 1 to said eye two times daily.

37. The method of claim 36, wherein the disruption or change is due to blepharitis, conjunctivitis, scleritis, or postoperative inflammation.

38. The method of claim 36, wherein said formulation is administered to treat or alleviate pain and/or inflammation associated with said disrupted or changed condition of the eye.

39. A method for treating a patient for pain and/or inflammation associated with eye surgery comprising:

pre-dosing the patient for up to 48 hours before the eye surgery with the formulation of claim 1;

wherein the formulation is applied two times daily; and

applying said formulation two times daily post surgery for about 14 days or until condition has been alleviated.

40. The method of claim 39, wherein said eye surgery is cataract surgery.

41. The method of claim 39, wherein said eye surgery is any refractive eye surgery.

42. The method of claim 41, wherein said refractive eye surgery is photorefractive keratectomy (PRK) surgery or laser epithelial keratomileusis (LASEK) refractive eye surgery.

43. The method of claim 39, wherein the pain and/or inflammation is due to postoperative eye surgery.

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