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3. The English translation attached to this declaration is an accurate and correct translation of the following document, attached hereto:
   JP H02-124817 A (225 counterpart application)

I declare that the foregoing is true and correct to the best of my knowledge.

Executed on October 26, 2015

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COMM. #2019014
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Commission Expires APR 11, 2017

(19) Japan Patent Office (JP)

(11) Unexamined Patent Application Publication Number

(12) Kokai Patent Gazette (A) H2-124817

(51) Int. Cl.[5]	ID Symbol	JPO File Nos.
A61K 31/195	ABM	7330-4C
	ABE	7330-4C
// C07C 229/40		

(43) Publication Date: May 14, 1990

Request for examination: Not yet requested Number of claims: 6 (Total of 11 pages)

(54) Title of Invention: Locally Administrable Therapeutic Composition for Inflammatory Disease

(21) Application No.: H1-18549

(22) Filing Date: January 27, 1989

Claim of Priority (32) January 27, 1988; (33) Japan (JP); (31) Application No. S63-16683

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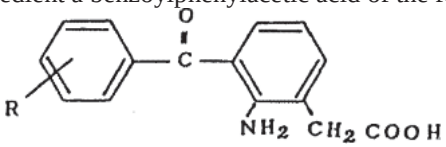
Specification

1. Title of the Invention

Locally Administrable Therapeutic Composition for Inflammatory Disease

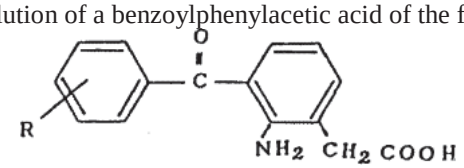
2. Claims

1) A locally administrable ophthalmic, otic or nasal therapeutic composition for the treatment of inflammatory disease which includes as its active ingredient a benzoylphenylacetic acid of the formula:



(wherein R is hydrogen atom or a halogen atom), or a salt thereof or the hydrate of said acid or salt.

2) An aqueous locally administrable therapeutic composition for the treatment of inflammatory disease which includes as its active ingredient an aqueous solution of a benzoylphenylacetic acid of the formula:



(wherein R is hydrogen atom or a halogen atom), or a salt thereof or the hydrate of said acid or salt, wherein: the aqueous solution contains a water-soluble polymer and a sulfite salt and is stable at a pH of 6–9.

3) The locally administrable therapeutic composition for the treatment of inflammatory disease according to claim 2 wherein the water-soluble polymer is polyvinylpyrrolidone, polyvinyl alcohol, carboxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose or sodium polyacrylate.

4) The locally administrable therapeutic composition for the treatment of inflammatory disease according to claim 2 wherein the concentration of the water-soluble polymer is in the range of about 0.1–10 W/W %.

5) The locally administrable therapeutic composition for the treatment of inflammatory disease according to claim 2 wherein the sulfite salt is in the form of sodium, potassium, calcium or magnesium.

6) The locally administrable therapeutic composition for the treatment of inflammatory disease according to claim 2 wherein the concentration of the sulfite salt is in the range of about 0.1–1 W/W %.

3. Detailed Description of the Invention

(Industrial Field of Utility)

This invention relates to a locally administrable ophthalmic, otic or nasal therapeutic composition for inflammatory disease. More particularly, it relates to a locally administrable ophthalmic, otic or nasal therapeutic composition for inflammatory disease, which contains as its active ingredient a benzoylphenylacetic acid derivative, a salt thereof or the hydrate of said acid or salt.

Another object of the present invention is to provide a stable locally administrable aqueous composition such as eye drops, otic composition and nasal composition containing the above compounds.

(Prior Art)

That certain benzoylphenylacetic acid derivatives, when orally administered, exhibit anti-inflammatory activity has been reported in detail in Journal of Medicinal Chemistry, Volume 27, pages 1370–88 (1984), among others. Furthermore, Japanese Unexamined Patent Application Publication No. JP S62-126124 A describes pharmaceutical compositions for percutaneous administration which contain these compounds. However, none of the published literature – inclusive of the specification of the abovementioned patent application – contains any description indicating or suggesting that these medicinal substances are effective against inflammatory disease of the eye, nose or ear when they are administered topically.

For the treatment, with topical application of drugs, of inflammatory ophthalmopathy such as uveitis and conjunctivitis which are most frequently observed in the ophthalmological field, steroidal drugs such as dexamethasone have so far been employed. Topical application of steroidal drugs to the eye has some apprehension of increasing intraocular pressure to cause glaucoma. And, there is a fear not only of causing corneal perforation when such steroidal drugs are applied to patients suffered from corneal herpes, corneal ulcer or the like, but also of induction of corneal herpes, keratomycosis, *Pseudomonas* infections and the like by the topical application of steroidal drugs. As there has been known such side effects as above, steroidal anti-inflammatory agents must be applied with particular care. In spite of such a situation, there is no known non-steroidal anti-inflammatory agent comparable with steroidal anti-inflammatory drugs in effectiveness for the treatment of inflammatory ophthalmopathy such as uveitis. Thus, in the present stage in this technical field, for the treatment of inflammatory ophthalmopathy, it is hardly possible not to use steroidal anti-inflammatory agents with particular care to avoid the side effects as abovementioned. Under such circumstances, it is natural that ophthalmological experts are awaiting the appearance of non-steroidal drugs which are effectively usable against uveitis or the like.

(Problems the Invention is Intended to Solve)

The present inventors investigated to find topically applicable drugs with lesser side effects and with superior effectiveness by which the topically applicable drugs that have been employed in the treatment of inflammatory ophthalmopathy, i.e. steroidal anti-inflammatory agents, can be replaced. As a result, the present inventors unexpectedly found that certain derivatives of benzoylphenylacetic acid are very effective in the treatment of inflammatory ophthalmopathy, especially of uveitis, by topical application, and that the effectiveness of such drugs is compatible with that of conventional steroidal anti-inflammatory drugs.

Furthermore, since the inventors obtained the finding that there are some problems that the above-mentioned benzoylphenylacetic acid derivatives are unstable in an aqueous solution with the optimal pH range for a locally administrable therapeutic composition, they extensively investigated in search of the method for the preparation of a stable aqueous solution. As a result, we have succeeded in preparing a stable aqueous composition. Thus, the stable aqueous composition according to the invention is achieved based on the above finding.

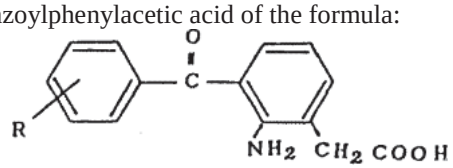
While a number of compounds falling under the category of non-steroidal anti-inflammatory agents are known, not all of them are effective in treating inflammatory eye diseases when topically administered to the eye. This is because there are several problems with them. First, when topically administered to the eye, a medicinal agent has to pass through the cornea so that it can reach the site of inflammation. Even when it has succeeded in arriving at the site of inflammation, it must remain there at a necessary concentration for a necessary period of time. If it fails to meet these requirements, it will be unable to produce the expected therapeutic effects. Furthermore, in case it is irritating to the eye, it is rather possible that the topical administration of the medicinal agent to the eye would cause exacerbation of symptoms. Therefore, great caution and much care are necessary in selecting a medicinal agent for topical administration to the eye. Furthermore, in case of administration in the form of eye drops, it goes without saying that it is desirable that the eye drop be stable for a long period of time in an aqueous solution without decomposition or forming foreign insoluble matter.

Accordingly, it is an object of the invention to solve the above problems and provide a novel and useful agent for ophthalmic use or for otic or nasal therapeutic use.

Moreover, another object of the invention is to provide a sufficiently stable aqueous solution such as eye drops, otic solution and nasal solution which contains the above compounds when stored for a long period of time.

(Means of Solving the Problem)

Based on the above findings, the present invention solves the aforementioned problems, being a locally administrable ophthalmic, otic or nasal therapeutic composition for the treatment of inflammatory disease characterized in that it includes as its active ingredient a benzoylphenylacetic acid of the formula:



(wherein R is hydrogen atom or a halogen atom), or a salt thereof or the hydrate of said acid or salt. In the formula, the halogen atom represented by R is, for example, fluorine, chlorine, bromine or iodine. The above compound to be used in accordance with the invention may be in a salt form. The salt includes alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as calcium salt and magnesium salt, among others, and any salt may suitably be used provided that it can attain the object of the invention. The compounds defined above may be obtained in the form of a hydrate depending on the conditions of synthesis, recrystallization and so forth, and such form may be used in practicing the invention without any inconvenience or trouble.

Further, the above compounds may be unstable when stored in an aqueous solution for long periods of time, and there are some problems in the stability of an aqueous solution containing the compounds. Therefore the inventors extensively investigated stabilizing methods in order to enhance the stability. As a result, unexpectedly, they have succeeded in stabilizing the solution by incorporating a water-soluble polymer and sulfite and adjusting the pH to about 6–9.

The compounds to be used as active ingredients in the topically administrable therapeutic compositions for inflammatory eye disease as well as nasal or otic disease in accordance with the invention (although such compositions are occasionally hereinafter referred to as “ophthalmic composition according to the present invention,” use of this abbreviation does not exclude the application of the composition in the nasal or otic fields) can be produced as described in the above-cited report in the Journal of Medicinal Chemistry, Volume 27, pages 1370–88 (1984) or U.S. Pat. No. 1,136,375, for instance, or by a modification of the method described therein. The ophthalmic compositions according to the invention can be prepared in the form of eye drops, eye ointments and so on in the same manner as various known compositions for topical administration to the eye. Thus, a compound of the above formula or a mixture of two or more compounds of the above formula is preferably made up into an aqueous or non-aqueous solution or mixed with an ointment base suited for ophthalmic use. In this case, an aqueous base generally used in the production of ophthalmic preparations, for example sterile distilled water, is suitably used as the aqueous base and the solution state (pH) thereof is adjusted to a level suited for topical administration to the eye. It is desirable that an appropriate buffer should be added in adjusting the pH. The pH of the ophthalmic compositions according to the invention is selected with due consideration paid to the stability and topical eye irritation of the active ingredient, among others. According to the present invention, the stability of an aqueous composition containing the above compounds is remarkably so enhanced by incorporating a water-soluble polymer and sulfite, and adjusting the pH to 6–9, preferably about 7.5–8.5. The eye irritation of the solution is not observed. A water-soluble polymer includes polyvinylpyrrolidone, carboxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl alcohol, sodium polyacrylate and so on. Polyvinylpyrrolidone is preferred among them. The concentration of the water-soluble polymer is in the range of about 0.1 to 10 wt.%. The sulfite salt includes sodium sulfite, potassium sulfite, magnesium sulfite, calcium sulfite and so on. The concentration of sulfite is in the range of about 0.1 to 1.0 wt.%. The pH adjustment is generally conducted with sodium hydroxide or hydrochloric acid, for instance, and it is typical to form a buffer solution by combined use of, for example, sodium acetate, sodium borate or sodium phosphate and acetic acid, boric acid or phosphoric acid, respectively. The ophthalmic compositions according to the invention may further contain pharmaceutically active ingredients, such as an anti-inflammatory agent of another kind, an analgesic and an antimicrobial, unless they are unfit for the purpose of attaining the object of the invention. Examples of such anti-inflammatory agents are indomethacin and pranoprofen. Usable examples of the anti-microbial agents are the penicillins, cephalosporins, and synthetic antimicrobial agents of the quinolone-carboxylic acid series. Among these active ingredients for combined use with the active ingredient according to the invention, the anti-inflammatory agent is expected to be synergistic with said active ingredient in the ophthalmic compositions according to the invention. The analgesic is suited for the purpose of alleviating inflammation-associated pain, and the antimicrobial agent is suited for the purpose of preventing secondary infection. It is of course possible to incorporate active agents other than those mentioned

above in the ophthalmic compositions according to the invention unless the object of the invention cannot be attained due to the presence thereof.

In preparing the ophthalmic compositions according to the invention as mentioned above, an isotonizing agent, a microbicidal agent or preservative, a chelating agent, a thickening agent and so forth may be added to the compositions in accordance with the general practice of ophthalmic preparation manufacture. The isotonizing agent includes, among others, sorbitol, glycerin, polyethylene glycol, propylene glycol, glucose and sodium chloride. The preservative includes para-oxybenzoic acid esters, benzyl alcohol, para-chloro-meta-xylenol, chlorocresol, phenethyl alcohol, sorbic acid and salts thereof, thimerosal, chlorobutanol, and the like. The chelating agent is, for example, sodium edetate, sodium citrate or sodium salt of condensed phosphoric acid. In preparing the ophthalmic compositions according to the invention in the form of eye ointments, the ointment base can be selected from among petrolatum, Macrogol, carboxymethylcellulose sodium, etc.

The ophthalmic composition according to this invention is prepared by incorporating the active compound in a base or vehicle for topical application to the eye. To prepare a liquid preparation, the content of the active ingredient may range from about 0.001 to about 10% and is preferably in the range of about 0.01 to about 5%. An ointment may be prepared by using the active compound in a concentration from about 0.001 to about 10%, preferably about 0.01 to about 5%. The ophthalmic composition of this invention may be administered in accordance with the following schedules. In the form of eye drops, one to several drops per dose are instilled with a frequency of once to 4 times a day according to the clinical condition. In the form of eye ointment, about 0.1 g to 0.2 g per dose is applied to the corneal surface with a frequency of once to 4 times a day according to the clinical condition. Of course, the dosage may be adjusted according to symptoms.

According to this invention, there can be obtained a stable aqueous composition such as otic composition or nasal composition. Other conventional methods can be used unless unsuitable for the object of this invention. Among others, an isotonizing agent, buffer solution and preservatives can be used. The concentrations of the compounds of the invention varies depending on symptoms and so on, and usually may be in the range of about 0.001 to about 10%, preferably about 0.01 to about 5%.

The following experimental examples are given to demonstrate the efficacy of the ophthalmic composition of this invention and the stability of the aqueous compositions of the invention.

Experimental Example 1

Anti-inflammatory effect of the ophthalmic agent according to this invention on experimental ophthalmitis induced by bovine serum albumin in white rabbits

[Animals]

Seventeen male white rabbits weighing about 2 kg were used. They were fed 80 g of Labo RG-RO (Nosan Corporation) daily and had free access to tap water.

[Test drug]

Sodium 3-(4-bromobenzoyl)-2-aminophenylacetate monohydrate (hereafter referred to as Compound [I]) was used as 0.5% and 0.1% ophthalmic solutions. These ophthalmic solutions had a pH value of 8.11 and osmotic pressures of 310 mOsm/kg·H_2O and 325 mOsm/kg·H_2O, respectively. Bovine serum albumin (hereafter referred to as "BSA") was dissolved in physiological saline to a concentration of 5% and sterilized by filtration. A 0.1 ml portion of the solution was injected into the central part of the vitreous body of both eyes using a 27G needle under anesthesia with 0.4% oxybuprocaine hydrochloride to induce ophthalmitis (ophthalmitis I). After 28 days when the ophthalmitis I had nearly recovered, 2.5% BSA solution was administered in a dose of 25 mg/ml/kg into the auricular vein to cause ophthalmitis again (ophthalmitis II). The severity of ophthalmitis was rated according to the rating scale [1)] of Yamauchi et al., based on the Draize Test in which an increased weight given to the internal segment of the eye. Observation was made with a frequency of once every one or two days during the peak period of inflammation and once every three or four days before and after the peak period for ophthalmitis I and 3, 6, 12 and 24 hours after intravenous injection of BSA for ophthalmitis II.

[Results]

Anti-inflammatory effect on ophthalmitis I

Table 1 shows the sum of scores for respective parameters during a peak inflammatory period of 3 days after aseptic injection of 5% BSA into the central part of the vitreous body.

Table 2 shows the amount of protein, white blood cell count and the concentration of prostaglandins in the anterior chamber aqueous humor.

Anti-inflammatory effect on ophthalmitis II

The administration of 2.5 ml/kg of 2.5% BSA solution into the auricular vein after 29 days when the inflammatory symptoms of ophthalmitis I had substantially subsided resulted in a relapse of inflammation after 3 hours in the physiological saline group, where both the external and internal segment of

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1) Hideyasu YAMAUCHI, Makoto INGU, Tadashi ISO and Kozo UDA: Anti-inflammatory effect of fluorometholone ophthalmic solution in experimental uveitis in rabbits, Folia Ophthalmologica Japonica, 24: 969-79 (1973).

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