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**Sawa et al.**

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(54) **AQUEOUS LIQUID PREPARATION  
CONTAINING  
2-AMINO-3-(4-BROMOBENZOYL)  
PHENYLACETIC ACID**

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8,129,431.

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USPC ..... **514/619**; 514/535; 514/570; 514/618

(58) **Field of Classification Search**  
USPC ..... 514/619, 535, 570  
See application file for complete search history.

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(57) **ABSTRACT**

An aqueous liquid preparation of the present invention con-  
taining 2-amino-3-(4-bromobenzoyl)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 is stable. Since even in the case where a  
preservative is incorporated into said aqueous liquid prepa-  
ration, the preservative exhibits a sufficient preservative  
effect for a long time, said aqueous liquid preparation in the  
form of an eye drop is useful for the treatment of blepharitis,  
conjunctivitis, scleritis, and postoperative inflammation.  
Also, the aqueous liquid preparation of the present invention  
in the form of a nasal drop is useful for the treatment of  
allergic rhinitis and inflammatory rhinitis (e.g. chronic rhini-  
tis, hypertrophic rhinitis, nasal polyp, etc.).

**30 Claims, No Drawings**

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**AQUEOUS LIQUID PREPARATION  
CONTAINING  
2-AMINO-3-(4-BROMOBENZOYL)  
PHENYLACETIC ACID**

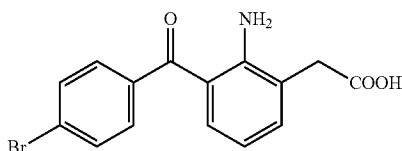
This is a divisional of Ser. No. 13/353,653 filed Jan. 19, 2012, which is a divisional of Ser. No. 10/525,006, filed Mar. 28, 2005, now issued as U.S. Pat. No. 8,129,431, which is a U.S. national stage of International Application No. PCT/JP2004/000350 filed Jan. 16, 2004.

TECHNICAL FIELD

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.

BACKGROUND ART

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



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).

The eye drop as mentioned above is 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).

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.

Further, in Japanese patent No. 2,954,356, there is the following description—"Benzalkonium chloride is a widely

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pounds are generally considered to be incompatible with ophthalmic compositions of drugs with acidic groups, such as nonsteroidal anti-inflammatory drugs. These preservatives lose their ability to function as they form complexes with the charged drug compounds".

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 decrease in preservative effect of benzalkonium chloride and other quaternary ammonium compounds.

DISCLOSURE OF THE INVENTION

It is 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 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.

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.

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 preservative effect of said preservative is inhibited.

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 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.

Namely, the present invention relates to:

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

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

(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 %,

(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 %,

(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 %,

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

(10) The aqueous liquid preparation according to anyone of the above (1) to (9), wherein the pharmacologically acceptable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt,

(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,

(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,

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

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

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

(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,

(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

(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.

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

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taining 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.

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.).

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.

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 1/2 hydrate, 1 hydrate, and 3/2 hydrate, among which 3/2 hydrate is preferable.

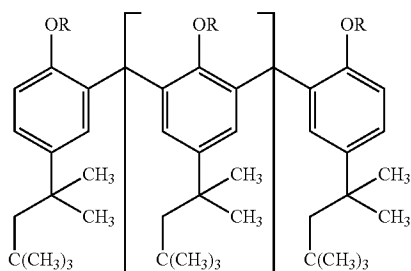
In the aqueous liquid preparation of the present invention, the content (concentration range) of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a pharmacologically acceptable salt thereof or a hydrate thereof is usually about 0.01 to 0.5 w/v %, preferably about 0.05 to 0.2 w/v %, especially about 0.1 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.

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, isoocetyl, nonyl, isononyl, decyl, isodecyl, undecyl, isoundecyl, dodecyl, isododecyl, tridecyl, isotridecyl, tetradecyl, isotetradecyl, pentadecyl, isopentadecyl, hexadecyl, isohexadecyl, heptadecyl, isoheptadecyl, octadecyl, isoocetadecyl, and isomers thereof, among which octyl and its isomer (e.g. isoocetyl, 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.

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.

Among the above-mentioned alkyl aryl polyether alcohol

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R = (CH<sub>2</sub>CH<sub>2</sub>O)<sup>x</sup>H  
 x = 8-10  
 m < 6

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<sub>17</sub>H<sub>35</sub>COO(CH<sub>2</sub>CH<sub>2</sub>O)<sub>n</sub>H which is a non-ionic surfactant and n is about 40.

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 %.

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.

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.

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

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mobenzoyl)phenylacetic acid or its pharmacologically acceptable salt or a hydrate thereof.

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.

Further, so long as the purpose of the present invention is achieved, conventional various additives such as isotonic 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 isotonic 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.

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.

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.

So long as the purpose of the present invention is achieved, other same or different kind of active ingredients may be appropriately added.

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, 14<sup>th</sup> Edition, General Rules for Preparations, Solutions or Ophthalmic solutions.

The aqueous liquid preparation of the present invention can be applied to warm-blooded animals such as human, rat, mouse, rabbit, cow, pig, dog, cat, and the like.

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

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