DESCRIPTION

AQUEOUS COMPOSITION CONTAINING 2-AMINO-3-(4-BROMOBENZOYL) PHENYLACETIC ACID

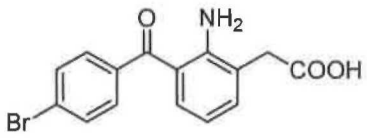
TECHNICAL FIELD

[0001] The present invention relates to an aqueous composition containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof and a method for producing the same.

BACKGROUND ART

[0002] 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a compound represented by formula (1) indicated below.

[Chemical formula 1]



(1)

The generic name of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is bromfenac, which is known as a non-steroidal anti-inflammatory agent that is used as an ophthalmic solution for the treatment of inflammation of the outer ocular area and anterior ocular area in the field of ophthalmology.

[0003] 2-amino-3-(4-bromobenzoyl)phenylacetic acid is known to lack stability in an aqueous solution, resulting in the formation of red insoluble foreign matter during storage. Consequently, in Patent Document 1, 2-amino-3-(4-bromobenzoyl)phenylacetic acid is attempted to be stabilized by incorporating a water-soluble polymer (such as polyvinylpyrrolidone) and a sulfite (such as sodium sulfite) in an ophthalmic solution containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid.

[0004] Patent Document 2 reports the providing of a composition that remains stable during storage by using the combination of an antimicrobial macromolecular quaternary ammonium compound and boric acid in an ophthalmic composition of an acidic drug, and lists bromfenac as an example of an acidic drug.

[0005] Patent Document 3 reports an attempt to stabilize 2-amino-3-(4-bromobenzoyl)phenylacetic acid by adding an alkylaryl polyether alcohol polymer or polyethylene glycol fatty acid ester to an aqueous liquid agent containing

2-amino-3-(4-bromobenzoyl)phenylacetic acid.

[0006] Patent Document 4 discloses an aqueous liquid bromfenac composition that contains a low concentration of benzalkonium chloride and demonstrates storage efficacy and stability.

However, there have been no studies or reports on the stabilization of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof by restricting the contents of benzalkonium chloride and a polyoxyethylene sorbitan fatty acid ester to within specific ranges in an aqueous composition containing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof.

In the meantime, during the manufacturing process of ophthalmic solutions, the risk of contamination of the resulting ophthalmic solution by iron components from the production tank has been previously indicated.

PRIOR ART DOCUMENTS

Patent Documents

[0007] Patent Document 1: U.S. Patent No. 4910225

Patent Document 2: International Publication No. WO 96/14829

Patent Document 3: U.S. Published Patent Application No. 2005/0239895

Patent Document 4: International Publication No. WO 2012/99142

DISCLOSURE OF THE INVENTION

Problems to be Solved by the Invention

[0008] As was previously described, any person has been unable to stabilize an aqueous solution of 2-amino-3-(4-bromobenzoyl)phenylacetic acid by restricting the contents of benzalkonium chloride and a polyoxyethylene sorbitan fatty acid ester to specific ranges in conventional aqueous compositions comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid.

An object of the present invention is to provide an aqueous composition comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid that demonstrates adequate stability during long-term storage by improving the stability of 2-amino-3-(4-bromobenzoyl)phenylacetic acid in an aqueous composition. In addition, the stability of 2-amino-3-(4-bromobenzoyl)phenylacetic acid in an aqueous composition is adequately maintained even in the presence of an iron component that has the potential to contaminate the aqueous composition from a production tank in the manufacturing process thereof.

Means for Solving the Problems

[0009] As a result of conducting extensive studies to improve the stability of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof in an aqueous composition comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof, the inventors of the present invention found that, in the case the content A (parts by mass) of benzalkonium chloride and the content B (parts by mass) of the polyoxyethylene sorbitan fatty acid ester based on 100 parts by mass of 2-amino-3-(4-bromobenzoyl)phenylacetic acid are within the following ranges:

$0 \leq B < 96A + 5$ when $0 \leq A < 1$,

$1 < B \leq 100$ when $A = 1$,

$5 < B \leq 100$ when $1 < A < 3$, and

$20 < B \leq 100$ when $3 \leq A \leq 10$,

the stability of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof improves, a high residual ratio is maintained even when stored for a long period of time, and there is no formation of red insoluble foreign matter, thereby leading to completion of the present invention.

The aqueous composition of the present invention had superior preservative efficacy.

[0010] Namely, the present invention relates to that indicated below.

(1) An aqueous compositioncomprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof, and optionally benzalkonium chloride and/or a polyoxyethylene sorbitan fatty acid ester; wherein, the content A (parts by mass) of benzalkonium chloride and the content B (parts by mass) of the polyoxyethylene sorbitan fatty acid ester based on 100 parts by mass of 2-amino-3-(4-bromobenzoyl)phenylacetic acid are within the following ranges:

$0 \leq B < 96A + 5$ when $0 \leq A < 1$,

$1 < B \leq 100$ when $A = 1$,

$5 < B \leq 100$ when $1 < A < 3$, and

$20 < B \leq 100$ when $3 \leq A \leq 10$.

(2) The aqueous composition described in (1) above, wherein the content A of benzalkonium chloride and the content B of the polyoxyethylene sorbitan fatty acid ester are within the following ranges:

$0 \leq B < 26A + 5$ when $0 \leq A < 1$,

$2 \leq B \leq 30$ when $A = 1$,

$5 < B \leq 30$ when $1 < A < 3$, and

$20 < B \leq 30$ when $3 \leq A \leq 5$.

(3) The aqueous composition described in (1) above, wherein the content A of

benzalkonium chloride and the content B of the polyoxyethylene sorbitan fatty acid ester are within the following ranges:

$1 < A < 3$, and

$5 < B \leq 30$.

(4) The aqueous composition described in (1) above, wherein the content A of benzalkonium chloride and the content B of the polyoxyethylene sorbitan fatty acid ester are within the following ranges:

$1.2 \leq A \leq 2.5$, and

$7 \leq B \leq 20$.

(5) An aqueous composition comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof, and optionally benzalkonium chloride and/or a polyoxyethylene sorbitan fatty acid ester; wherein, the concentration X (w/v%) of benzalkonium chloride and the concentration Y (w/v%) of the polyoxyethylene sorbitan fatty acid are within the following ranges:

$0 \leq Y < 96X + 0.005$ when $0 \leq X < 0.001$,

$0.001 < Y \leq 0.1$ when $X = 0.001$,

$0.005 < Y \leq 0.1$ when $0.001 < X < 0.003$, and

$0.02 < Y \leq 0.1$ when $0.003 \leq X \leq 0.01$.

(6) The aqueous composition described in (5) above, wherein the concentration X of benzalkonium chloride and the concentration Y of the polyoxyethylene sorbitan fatty acid are within the following ranges:

$0 \leq Y < 26X + 0.005$ when $0 \leq X < 0.001$,

$0.002 \leq Y \leq 0.03$ when $X = 0.001$,

$0.005 < Y \leq 0.03$ when $0.001 < X < 0.003$, and

$0.02 < Y \leq 0.03$ when $0.003 \leq X \leq 0.005$.

(7) The aqueous composition described in (5) above, wherein the concentration X of benzalkonium chloride and the concentration Y of the polyoxyethylene sorbitan fatty acid are within the following ranges:

$0.001 < X < 0.003$, and

$0.005 < Y \leq 0.03$.

(8) The aqueous composition described in (5) above, wherein the concentration X of benzalkonium chloride and the concentration Y of the polyoxyethylene sorbitan fatty acid are within the following ranges:

$0.0012 \leq X \leq 0.0025$, and

$0.008 \leq Y \leq 0.02$.

(9) The aqueous composition described in any of (1) to (8) above, wherein the

polyoxyethylene sorbitan fatty acid ester is polysorbate 80.

(10) The aqueous composition described in any of (1) to (9) above, wherein the concentration of 2-amino-3-(4-bromobenzoyl)phenylacetic acid in the aqueous composition is 0.01% (w/v) to 1.0% (w/v).

(11) The aqueous composition described in any of (1) to (10) above, further comprising 0.01% (w/v) to 3.0% (w/v) of sodium chloride.

(12) The aqueous composition described in any of (1) to (8) above, wherein the pH of the aqueous composition is higher than 7.0 to 9.5.

(13) The aqueous composition described in any of (1) to (12) above, wherein the aqueous composition is an injection preparation, an infusion fluid, nasal drops, ear drops or ophthalmic solution.

(14) The aqueous composition described in (13) above, which is an ophthalmic injection preparation.

(15) The aqueous composition described in (13) above, which is an ophthalmic solution.

(16) A method for producing the aqueous composition described in any of (1) to (15) above, comprising: dissolving 2-amino-3-(4-bromobenzoyl)phenylacetic acid, a salt thereof or a hydrate thereof, and optionally benzalkonium chloride and/or a polyoxyethylene sorbitan fatty acid ester in an aqueous solvent.

Furthermore, two or more each of the compositions of (1) to (16) above can be arbitrarily selected and combined.

The present invention also relates to that indicated below.

(17) A method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof in an aqueous composition, comprising: adding 0 parts by mass to 10 parts by mass of benzalkonium chloride (content A (parts by mass)) and a polyoxyethylene sorbitan fatty acid ester represented by content B (parts by mass) to the aqueous medium within the following ranges based on 100 parts by mass of 2-amino-3-(4-bromobenzoyl)phenylacetic acid:

$0 \leq B < 96A + 5$ when $0 \leq A < 1$,

$1 < B \leq 100$ when $A = 1$,

$5 < B \leq 100$ when $1 < A < 3$, and

$20 < B \leq 100$ when $3 \leq A \leq 10$.

Effects of the Invention

[0011] According to the present invention, since 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof present in an aqueous

composition is stabilized over a long period of time, an aqueous composition comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof is provided that can be stably stored for two years or more. In addition, the aqueous composition of the present invention maintains adequate stability of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof even in the presence of an iron component having the potential to contaminate the aqueous composition from a production tank in the manufacturing process thereof.

BEST MODE FOR CARRYING OUT THE INVENTION

[0012] The following provides a detailed explanation of the present invention.

[0013] In the present description, an "aqueous solvent" refers to water or a solvent that contains water (such as a mixture of a water-soluble solvent such as alcohol and water). Although there are no particular limitations on the aqueous solvent provided it is water or a solvent that contains water, it is preferably purified water.

[0014] In a preferred embodiment thereof, the present invention is an aqueous composition comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof, wherein the aqueous composition contains 0 parts by mass to 10 parts by mass of benzalkonium chloride (content A (parts by mass)) and a polyoxyethylene sorbitan fatty acid ester represented by content B (parts by mass) within the following ranges based on 100 parts by mass of 2-amino-3-(4-bromobenzoyl)phenylacetic acid:

$0 \leq B < 96A + 5$ when $0 \leq A < 1$,

$1 < B \leq 100$ when $A = 1$,

$5 < B \leq 100$ when $1 < A < 3$, and

$20 < B \leq 100$ when $3 \leq A \leq 10$.

In the present aqueous composition, the 2-amino-3-(4-bromobenzoyl)phenylacetic acid or salt thereof is present in the form of being uniformly dissolved in an aqueous solvent.

[0015] In the aqueous composition of the present invention, the 2-amino-3-(4-bromobenzoyl)phenylacetic acid can be present in the form of being dissolved as nonionic 2-amino-3-(4-bromobenzoyl)phenylacetic acid per se, a salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid, a zwitter ionic form (in which a carboxyl group forms a carboxylate ionic and an amino group forms an ammonium ion), a cationic form (in which only the amino group forms an ammonium ion) or an anionic form (in which only a carboxyl group forms a carboxylate ion).

[0016] In the aqueous composition of the present invention, there are no particular limitations on the salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid provided it is a

pharmacologically acceptable salt, and examples of salts include salts of inorganic acids, salts of organic acids, quaternary ammonium salts, salts of halogen ions, salts of alkaline metals, salts of alkaline earth metals, metal salts and salts of organic amines. Examples of salts of inorganic acids include salts of hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, sulfuric acid and phosphoric acid. Examples of salts of organic acids include salts of acetic acid, oxalic acid, fumaric acid, maleic acid, succinic acid, citric acid, tartaric acid, adipic acid, gluconic acid, glucoheptonic acid, glucuronic acid, terephthalic acid, methanesulfonic acid, lactic acid, hippuric acid, 1,2-ethanedisulfonic acid, isethionic acid, lactobionic acid, oleic acid, pamoic acid, polygalacturonic acid, stearic acid, tannic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, lauryl sulfate, methyl sulfate, naphthalenesulfonic acid and sulfosalicylic acid. Examples of quaternary ammonium salts include salts of methyl bromide and methyl iodide. Examples of salts of halogen ions include salts of chloride ions, bromide ions and iodide ions, examples of salts of alkaline metals include salts of lithium, sodium and potassium, examples of salts of alkaline earth metals include salts of calcium and magnesium, and examples of metal salts include salts of iron and zinc. Examples of salts of organic amines include salts of triethylenediamine, 2-aminoethanol, 2,2-iminobis(ethanol), 1-deoxy-1-(methylamino)-2-D-sorbitol, 2-amino-2-(hydroxymethyl)-1,3-propanediol, procaine and N,N-bis(phenylmethyl)-1,2-ethanediamine. In the aqueous composition of the present invention, a preferable salt of 2-amino-3-(4-bromobenzoyl)phenylacetic acid is a sodium salt.

[0017] In the aqueous composition of the present invention, although there are no particular limitations on the concentration of 2-amino-3-(4-bromobenzoyl)phenylacetic acid provided it is an adequate amount for demonstrating desired effects, it is preferably 0.01% (w/v) to 1.0% (w/v), more preferably 0.03% (w/v) to 0.5% (w/v), even more preferably 0.05% (w/v) to 0.2% (w/v), and most preferably 0.08% (w/v) to 0.1% (w/v). Furthermore, these concentrations are calculated using the weight as 2-amino-3-(4-bromobenzoyl)phenylacetic acid in the case of using a salt or hydrate of 2-amino-3-(4-bromobenzoyl)phenylacetic acid.

[0018] In the aqueous composition of the present invention, the benzalkonium chloride (to be referred to as BAK) has a chemical structure represented by $[C_6H_5CH_2N(CH_3)_2R]Cl$, where R represents C_8H_{17} to $C_{18}H_{37}$ or a mixture thereof. Preferable examples thereof include N-benzyl-N,N-dimethyl lauryl ammonium chloride in which R is $C_{12}H_{25}$ (to also be referred to as BAK C12), N-benzyl-N,N-dimethyl myristyl ammonium chloride in which R is $C_{14}H_{29}$ (to also be referred to as BAK C14),

N-benzyl-N-cetyl dimethyl ammonium chloride in which R is $C_{16}H_{35}$ (to also be referred to as BAK C16), and mixtures thereof. In the present invention, benzalkonium chloride is preferably BAK C12.

[0019] In the aqueous composition of the present invention, there are no particular limitations on the polyoxyethylene sorbitan fatty acid ester, examples of polyoxyethylene sorbitan fatty acid esters include polysorbate 80, polysorbate 65, polysorbate 60, polysorbate 40, polyoxyethylene sorbitan monolaurate and polyoxyethylene sorbitan trioleate, and polysorbate 80 is preferable.

[0020] In the aqueous composition of the present invention, the contents of benzalkonium chloride and the polyoxyethylene sorbitan fatty acid ester are such that the content A (parts by mass) of benzalkonium chloride and the content B (parts by mass) of the polyoxyethylene sorbitan fatty acid ester based on 100 parts by mass of 2-amino-3-(4-bromobenzoyl)phenylacetic acid are within the following ranges:

$0 \leq B < 96A + 5$ when $0 \leq A < 1$,

$1 < B \leq 100$ when $A = 1$,

$5 < B \leq 100$ when $1 < A < 3$, and

$20 < B \leq 100$ when $3 \leq A \leq 10$,

preferably within the following ranges:

$0 \leq B < 26A + 5$ when $0 \leq A < 1$,

$2 \leq B \leq 30$ when $A = 1$,

$5 < B \leq 30$ when $1 < A < 3$, and

$20 < B \leq 30$ when $3 \leq A \leq 5$,

more preferably within the following ranges:

$1 < A < 3$, and

$5 < B \leq 30$, and

most preferably within the following ranges:

$1.2 \leq A \leq 2.5$, and

$7 \leq B \leq 20$.

[0021] The upper limit of the content of benzalkonium chloride in the aqueous composition of the present invention is preferably 10 parts by mass, more preferably 6 parts by mass, even more preferably 5 parts by mass, still more preferably 4 parts by mass, particularly preferably 3 parts by mass, more particularly preferably 2.5 parts by mass, and most preferably 2 parts by mass based on 100 parts by mass of 2-amino-3-(4-bromobenzoyl)phenylacetic acid. On the other hand, the lower limit of the content of benzalkonium chloride is preferably 0 parts by mass, more preferably 0.2 parts by mass, even more preferably 0.5 parts by mass, still more preferably 0.8 parts by

mass, particularly preferably 1 part by weight and most preferably 1.2 parts by mass. The range of the content of benzalkonium chloride is preferably 0 parts by mass to 10 parts by mass, more preferably 0.2 parts by mass to 5 parts by mass, even more preferably 0.5 parts by mass to 3 parts by mass, particularly preferably 1 part by weight to 2.5 parts by mass and most preferably 1.2 parts by mass to 2 parts by mass.

[0022] The upper limit of the content of the polyoxyethylene sorbitan fatty acid in the aqueous composition of the present invention is preferably 100 parts by mass, more preferably 50 parts by mass, even more preferably 40 parts by mass, still more preferably 30 parts by mass, particularly preferably 25 parts by mass and most preferably 20 parts by mass based on 100 parts by mass of 2-amino-3-(4-bromobenzoyl)phenylacetic acid. On the other hand, the lower limit of the content thereof is preferably 0 parts by mass, more preferably 2 parts by mass, even more preferably 5 parts by mass, still more preferably 6 parts by mass, particularly preferably 7 parts by mass and most preferably 9 parts by mass. The range of the content of the polyoxyethylene sorbitan fatty acid ester is preferably 0 parts by mass to 100 parts by mass, more preferably 0 parts by mass to 50 parts by mass, even more preferably 2 parts by mass to 40 parts by mass, still more preferably 5 parts by mass to 30 parts by mass, particularly preferably 7 parts by mass to 25 parts by mass, and most preferably 9 parts by mass to 20 parts by mass.

[0023] The concentrations of benzalkonium chloride and the polyoxyethylene sorbitan fatty acid ester in the aqueous composition of the present invention are such that the concentration X (w/v%) of benzalkonium chloride and the concentration Y (w/v%) polyoxyethylene sorbitan fatty acid ester are preferably within the following ranges:

$0 \leq Y < 96X + 0.005$ when $0 \leq X < 0.001$,

$0.001 < Y \leq 0.1$ when $X = 0.001$,

$0.005 < Y \leq 0.1$ when $0.001 < X < 0.003$, and

$0.02 < Y \leq 0.1$ when $0.003 \leq X \leq 0.01$,

more preferably within the following ranges:

$0 \leq Y < 26X + 0.005$ when $0 \leq X < 0.001$,

$0.002 \leq Y \leq 0.03$ when $X = 0.001$,

$0.005 < Y \leq 0.03$ when $0.001 < X < 0.003$, and

$0.02 < Y \leq 0.03$ when $0.003 \leq X \leq 0.005$,

even more preferably within the following ranges:

$0001 < X < 0.003$, and

$0.005 < Y \leq 0.03$, and

most preferably within the following ranges:

$0.0012 \leq X \leq 0.0025$, and

$0.008 \leq Y \leq 0.02$.

[0024] The upper limit of the concentration of benzalkonium chloride in the aqueous composition of the present invention is preferably 0.01% (w/v), more preferably 0.006% (w/v), even more preferably 0.005% (w/v), still more preferably 0.004% (w/v), particularly preferably 0.003% (w/v), more particularly preferably 0.025% (w/v), and most preferably 0.002% (w/v). On the other hand, the lower limit of the concentration thereof is preferably 0% (w/v), more preferably 0.0002% (w/v), even more preferably 0.0005% (w/v), still more preferably 0.0008% (w/v), particularly preferably 0.001% (w/v) and most preferably 0.0012% (w/v). The range of the concentration thereof is preferably 0% (w/v) to 0.01% (w/v), more preferably 0.0002% (w/v) to 0.005% (w/v), still more preferably 0.0005% (w/v) to 0.003% (w/v), particularly preferably 0.001% (w/v) to 0.0025% (w/v) and most preferably 0.0012% (w/v) to 0.002% (w/v).

[0025] The upper limit of the concentration of the polyoxyethylene sorbitan fatty acid ester in the aqueous composition of the present invention is preferably 0.1% (w/v), more preferably 0.05% (w/v), even more preferably 0.04% (w/v), still more preferably 0.03% (w/v), particularly preferably 0.025% (w/v) and most preferably 0.02% (w/v). On the other hand, the lower limit of the concentration thereof is preferably 0% (w/v), more preferably 0.002% (w/v), even more preferably 0.005% (w/v), still more preferably 0.008% (w/v), particularly preferably 0.009% (w/v) and most preferably 0.01% (w/v). The range of the concentration thereof is preferably 0% (w/v) to 0.1% (w/v), preferably 0% (w/v) to 0.05% (w/v), even more preferably 0.002% (w/v) to 0.04% (w/v), still more preferably 0.005% (w/v) to 0.03% (w/v), particularly preferably 0.008% (w/v) to 0.025% (w/v) and most preferably 0.01% (w/v) to 0.02% (w/v).

[0026] An aqueous composition comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof that contains neither benzalkonium chloride nor a polyoxyethylene sorbitan fatty acid ester is also included within the scope of the present invention.

[0027] An additive such as a buffer, tonicity agent, pH adjuster, stabilizing agent, preservative, solubilizing agent or thickening agent can be added to the aqueous composition of the present invention.

[0028] A buffer able to be used as an additive of a pharmaceutical can be incorporated in the aqueous composition of the present invention. Examples of buffers include phosphoric acid or salts thereof, boric acid or salts thereof, citric acid or salts thereof, acetic acid or salts thereof, carbonic acid or salts thereof, tartaric acid or salts thereof, ε-aminocaproic acid and trometamol. Examples of phosphates include sodium phosphate, sodium dihydrogen phosphate, disodium hydrogen phosphate, potassium

phosphate, potassium dihydrogen phosphate and dipotassium hydrogen phosphate, examples of borates include borax, sodium borate and potassium borate, examples of citrates include sodium citrate and disodium citrate, examples of acetates include sodium acetate and potassium acetate, examples of carbonates include sodium carbonate and sodium bicarbonate, and examples of tartrates include sodium tartrate and potassium tartrate. In the present invention, the buffer is preferably boric acid or a salt thereof, examples of which include boric acid and borax.

[0029] Although suitably adjusted in consideration of the effects on the drug, other additives and/or osmotic pressure ratio, the concentration of buffer in the aqueous composition of the present invention in terms of the total amount thereof is preferably 0.01% (w/v) to 15% (w/v), more preferably 0.05% (w/v) to 10% (w/v), even more preferably 0.1% (w/v) to 5% (w/v), particularly preferably 0.25% (w/v) to 4% (w/v) and most preferably 0.5% (w/v) to 3% (w/v).

[0030] An tonicity agent able to be used as an additive of a pharmaceutical can be incorporated in the aqueous composition of the present invention. Examples of tonicity agents include ionic tonicity agents and nonionic tonicity agents. Examples of ionic tonicity agents include sodium chloride, potassium chloride, calcium chloride and magnesium chloride, while examples of nonionic tonicity agents include glycerin, propylene glycol, sorbitol and mannitol. The tonicity agent is preferably sodium chloride since the stability of 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof is maintained and a composition free of changes in appearance is obtained.

[0031] A pH adjuster able to be used as an additive of a pharmaceutical can be incorporated in the aqueous composition of the present invention. Examples of pH adjusters include hydrochloric acid, phosphoric acid, citric acid, acetic acid, sodium hydroxide, potassium hydroxide, sodium carbonate and sodium bicarbonate. In the present invention, the pH adjuster is preferably hydrochloric acid or sodium hydroxide.

[0032] The pH of the aqueous composition of the present invention is preferably 7.0 to 9.5, more preferably 7.5 to 9.0, even more preferably 8.0 to 8.6 and most preferably 8.2 to 8.4.

[0033] A stabilizing agent able to be used as an additive of a pharmaceutical can be incorporated in the aqueous composition of the present invention. Examples of stabilizing agents include edetic acid, sodium edetate, sulfites and water-soluble polymers. Examples of sulfites include sodium sulfite, potassium sulfite, magnesium sulfite and calcium sulfite. Examples of water-soluble polymers include polyvinylpyrrolidone, polyvinyl alcohol, carboxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose and sodium polyacrylate.

[0034] The concentration of all stabilizing agents in the aqueous composition of the present invention can be suitably adjusted in consideration of the effects on the drug, other additives and/or osmotic pressure ratio.

[0035] A preservative able to be used as an additive in pharmaceuticals can be incorporated in the aqueous composition of the present invention. Examples of preservatives include benzethonium hydrochloride, sorbic acid, potassium sorbate, methyl parahydroxybenzoate, propyl parahydroxybenzoate and chlorobutanol.

[0036] Although suitably adjusted in consideration of the effects on the drug, other additives and/or osmotic pressure ratio, the concentration of preservative in the aqueous composition of the present invention in terms of the total amount thereof is preferably 0.00005% (w/v) to 0.01% (w/v), more preferably 0.0001% (w/v) to 0.005% (w/v), even more preferably 0.0002% (w/v) to 0.004% (w/v), particularly preferably 0.0005% (w/v) to 0.003% (w/v) and most preferably 0.001% (w/v) to 0.002% (w/v).

[0037] There are no particular limitations on the drug form of the aqueous composition of the present invention provided it is that which can be used as a pharmaceutical. Examples of drug forms include injection preparations, infusion liquids, nose drops, ear drops and ophthalmic solutions. The drug form is preferably an ophthalmic injection preparation or ophthalmic solution, and particularly preferably an ophthalmic solution.

[0038] The aqueous composition of the present invention can be produced by dissolving 2-amino-3-(4-bromobenzoyl)phenylacetic acid, a salt thereof or a hydrate thereof, benzalkonium chloride and a polyoxyethylene sorbitan fatty acid ester in an aqueous solvent.

[0039] When preparing the aqueous composition of the present invention, 2-amino-3-(4-bromobenzoyl)phenylacetic acid, a salt thereof or a hydrate thereof can be used. Specific examples of hydrates include sodium 2-amino-3-(4-bromobenzoyl)phenylacetate hemihydrate, sodium 2-amino-3-(4-bromobenzoyl)phenylacetate monohydrate and sodium 2-amino-3-(4-bromobenzoyl)phenylacetate sesquihydrate, and a preferable example of a hydrate is sodium 2-amino-3-(4-bromobenzoyl)phenylacetate sesquihydrate.

A solvent previously described as an example of an aqueous solvent can be used for the aqueous solvent.

Accordingly, the present invention also relates to a method for producing an aqueous composition comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof, and optionally benzalkonium chloride and/or a polyoxyethylene sorbitan fatty acid ester, wherein the content A (parts by mass) of benzalkonium chloride and the

content B (parts by mass) of the polyoxyethylene sorbitan fatty acid ester based on 100 parts by mass of sodium 2-amino-3-(4-bromobenzoyl)phenylacetic acid are within the following ranges:

$0 \leq B < 96A + 5$ when $0 \leq A < 1$,

$1 < B \leq 100$ when $A = 1$,

$5 < B \leq 100$ when $1 < A < 3$, and

$20 < B \leq 100$ when $3 \leq A \leq 10$; comprising:

dissolving 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof or a hydrate thereof, and optionally benzalkonium chloride and/or a polyoxyethylene sorbitan fatty acid ester, in an aqueous solvent.

[0040] Moreover, the present invention also relates to a method for stabilizing 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof in an aqueous composition, comprising: adding 0 parts by mass to 10 parts by mass of benzalkonium chloride (content A (parts by mass)) and a polyoxyethylene sorbitan fatty acid ester represented by content B (parts by mass) to the aqueous medium within the following ranges based on 100 parts by mass of 2-amino-3-(4-bromobenzoyl)phenylacetic acid:

$0 \leq B < 96A + 5$ when $0 \leq A < 1$,

$1 < B \leq 100$ when $A = 1$,

$5 < B \leq 100$ when $1 < A < 3$, and

$20 < B \leq 100$ when $3 \leq A \leq 10$.

[0041] Although the following indicates test results and preparation examples, these are indicated to further facilitate understanding of the present invention, and are not intended to limit the scope of the present invention.

[0042] 1. Stability Evaluation Test (1)

The stability of the aqueous composition of the present invention was examined.

1-1. Preparation of Test Preparations

Example 1

0.1 g of sodium 2-amino-3-(4-bromobenzoyl)phenylacetate sesquihydrate (to also be referred to as the present compound) 1.25 g of boric acid, 1.0 g of borax, 0.02 g of edetate disodium hydrate, 0.005 g of polysorbate 80 and 0.001 g of benzalkonium chloride were added to 90 mL of purified water and stirred well. After adjusting pH to ca. 8.3 by adding 1 N aqueous sodium hydroxide solution and diluted hydrochloric acid (10%), quantum sufficit (q.s.)of purified water was added to bring to a total volume of 100 mL.

[0043] The preparation of Comparative Example 1 shown in Table 1 was prepared

using the same method as the preparation method of Example 1.

[0044] 1-2. Test Method

The content of 2-amino-3-(4-bromobenzoyl)phenylacetic acid after storing the test preparations for up to six months at 25°C and 40°C was assayed using high-performance liquid chromatography (HPLC) followed by calculation of the residual ratio (%) thereof. In addition, changes in appearance were observed visually.

[0045] 1-3. Test Results and Discussion

The test results are shown in Table 1.

[0046] [Table 1]

			Example 1		Comparative example 1	
Present Compound			0.1g		0.1g	
Boric acid			1.25g		1.25g	
Borax			1.0g		1.0g	
Dried sodium sulfite			-		0.1g	
Edetate disodium hydrate			0.02g		0.02g	
Polyvinylpyrrolidone			-		2g	
Polysorbate 80			0.005g		0.15g	
BAK			0.001g		0.005g	
HCl/NaOH			q.s.		q.s.	
pH			8.3		8.3	
Total volume			100mL		100mL	
Container			PE	PP	PE	PP
Residual ratio (%)/ appearance	25°C	3 months	99.2/-	99.5/-	96.5/-	96.4/-
		6 months	99.7/-	98.9/-	95.2/-	94.8/-
	40°C	1 month	98.9/-	98.8/-	96.9/-	97.2/-
		3 months	100.3/-	99.9/-	94.9/-	94.6/-
		6 months	101.6/-	100.1/-	92.9/-	91.3/-

PE: Polyethylene, PP: Polypropylene

"-" indicates that changes in appearance were not observed.

[0047] As is clear from Table 1, in the case of the preparation of Example 1, a high residual ratio was maintained for six months at 25°C and 40°C in comparison with the preparation of Comparative Example 1, and the preparation remained clear, yellow and free of sediment. On the basis of the above, the aqueous composition of the present invention in the form of the preparation of Example 1 was confirmed to have superior stability.

[0048] 2. Stability Evaluation Test (2)

The stability of the aqueous composition of the present invention was examined when changing the contents of benzalkonium chloride and the polyoxyethylene sorbitan fatty acid ester.

[0049] 2-1. Preparation of Test Preparations

The preparations of Examples 2 to 15 and Comparative Examples 2 to 8 shown in Tables 2 to 4 were prepared using the same method as the preparation method of Example 1.

[0050] 2-2. Test Method

The content of 2-amino-3-(4-bromobenzoyl)phenylacetic acid after having stored the test preparations for up to six months at 40°C or up to one month at 60°C was quantified using high-performance liquid chromatography (HPLC) followed by calculation of the residual ratio (%) thereof. In addition, changes in appearance were observed visually.

[0051] 2-3. Test Results and Discussion

The test results are shown in Tables 2 to 4.

[0052] [Table 2]

		Example 2	Example 3	Example 4	Example 5	Example 6	Example 7	Example 8
Present Compound		0.1g	0.1g	0.1g	0.1g	0.1g	0.1g	0.1g
Boric acid		1.25g	1.25g	1.25g	1.25g	1.25g	1.25g	1.25g
Borax		1.0g	1g	1g	1g	1g	1g	1g
Edetate disodium hydrate		0.02g	0.02g	0.02g	0.02g	0.02g	0.02g	0.02g
Polysorbate 80		0.005g	0.03g	0.01g	0.01g	0.02g	0.02g	0.03g
BAK		0.001g	0.003g	0.0012g	0.002g	0.0012g	0.002g	0.001g
Sodium chloride		0.1g	0.1g	0.1g	0.1g	0.1g	0.1g	0.1g
HCl/NaOH		q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
pH		8.3	8.3	8.3	8.3	8.3	8.3	8.3
Total volume		100mL	100mL	100mL	100mL	100mL	100mL	100mL
Residual ratio (%)/ appearance	40°C, 6 months	101.7/-	100.1/-	NA	NA	NA	NA	103/-
	60°C, 1 month	101.6/-	100.4/-	102.6/-	102.4/-	101.1/-	102/-	NA/-

"-" indicates that changes in appearance were not observed.

[0053] [Table 3]

		Example 9	Example 10	Example 11	Example 12	Example 13	Example 14	Example 15
Present Compound		0.1g	0.1g	0.1g	0.1g	0.1g	0.108g	0.108g
Boric acid		1.25g	1.25g	1.25g	1.25g	1.25g	0.85g	0.85g
Borax		1g	1g	1g	1g	1g	1g	1g
Edetate sodium hydrate		0.02g	0.02g	0.02g	0.02g	0.02g	0.02g	0.02g
Polysorbate 80		0.01g	0.02g	0.03g	0.01g	-	0.01g	0.008g
BAK		0.0015g	0.0025g	0.0015g	0.0025g	-	0.0015g	0.0015g
Sodium chloride		0.1g	0.1g	0.1g	0.1g	0.1g	0.23g	0.23g
HCl/NaOH		q.s.	q.s.	q.s.	q.s.	q.s.	-	-
pH		8.3	8.3	8.3	8.3	8.3	8.3	8.3
Total volume		100mL	100mL	100mL	100mL	100mL	100mL	100mL
Residual ratio (%)/ appearance	40°C, 6 months	104.2/-	101.1/-	NA	NA	NA	NA	NA
	60°C, 1 month	102.5/-	101.6/-	100.4/-	95.5/-	100.6/-	103.8/-	NA/-

"-" indicates that changes in appearance were not observed.

[0054] [Table 4]

		Comparative example 2	Comparative example 3	Comparative example 4	Comparative example 5	Comparative example 6	Comparative example 7	Comparative example 8
Present Compound		0.1g	0.1g	0.1g	0.1g	0.1g	0.1g	0.108g
Boric acid		1.25g	1.25g	1.25g	1.25g	1.25g	1.25g	0.85g
Borax		1g	1g	1g	1g	1g	1g	1g
Edetate disodium hydrate		0.02g	0.02g	0.02g	0.02g	0.02g	0.02g	0.02g
Polysorbate 80		0.005g	0.005g	0.005g	0.02g	0.005g	0.005g	0.15g
BAK		0.003g	0.0012g	0.002g	0.003g	-	0.0015g	0.0015g
Sodium chloride		0.1g	0.1g	0.1g	0.1g	0.1g	0.1g	0.23g
HCl/NaOH		q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	-
pH		8.3	8.3	8.3	8.3	8.3	8.3	8.3
Total volume		100mL	100mL	100mL	100mL	100mL	100mL	100mL
Residual ratio (%)/ appearance	40°C, 6 months	101.5/+	NA	NA	NA	101.7/+	NA	NA
	60°C, 1 month	100.4/+	102.4/+	101.9/+	101.5/+	104/-	100.4/+	NA/+

"-" indicates that changes in appearance were not observed.

"+" indicates that changes in appearance were observed.

[0055] As is clear from Tables 2 to 4, in the case of the preparations of Examples 2 to 15, high residual ratios were maintained for six months at 40°C or for one month at 60°C, and the preparations remained clear, yellow and free of sediment. On the basis of the above, aqueous compositions of the present invention in the form of the preparations of Examples 2 to 15 were confirmed to have superior stability.

[0056] 3. Stability Evaluation Test (3)

The stability of the aqueous composition of the present invention was examined when changing the pH thereof.

[0057] 3-1. Preparation of Test Preparations

The preparations of Examples 16 to 19 shown in Table 5 were prepared using the same method as the preparation method of Example 1.

[0058] 3-2. Test Method

Changes in the appearance of the test preparations after having stored for up to one month at 60°C were visually observed.

[0059] 3-3. Test Results and Discussion

The test results are shown in Table 5.

[0060] [Table 5]

		Example 16	Example 17	Example 18	Example 19
Present Compound		0.1g	0.1g	0.1g	0.1g
Boric acid		0.85g	0.85g	0.85g	0.85g
Borax		1g	1g	1g	1g
Edetate disodium hydrate		0.02g	0.02g	0.02g	0.02g
Polysorbate 80		0.01g	0.01g	0.01g	0.01g
BAK		0.0015g	0.0015g	0.0015g	0.0015g
Sodium chloride		0.23g	0.23g	0.23g	0.23g
pH		7.5	8.0	8.6	9.0
Total volume		100mL	100mL	100mL	100mL
Appearance	60°C/1 month	-	-	-	-

"-" indicates that changes in appearance were not observed.

[0061] As is clear from Table 5, the preparations of Examples 16 to 19 remained clear, yellow and free of sediment after storing for one month at 60°C. On the basis of the above, aqueous compositions of the present invention in the form of the preparations of Examples 16 to 19 were confirmed to have superior stability.

[0062] 4. Stability Evaluation Test (4)

The stability of the aqueous composition of the present invention was examined in the presence of iron.

[0063] 4-1. Preparation of Test Preparations

The preparations of Examples 20 to 23 and Comparative Example 9 shown in Table 6 were prepared using the same method as the preparation method of Example 1.

[0064] 4-2. Test Method

5 μg aliquots of iron (III) chloride were added to each test preparation. The content of 2-amino-3-(4-bromobenzoyl)phenylacetic acid after having stored the test preparations for up to two weeks at 60°C was quantified using high-performance liquid chromatography (HPLC) followed by calculation of the residual ratio (%) thereof after correcting for the amount of moisture that evaporated from the container. In addition, changes in appearance were observed visually.

[0065] 4-3. Test Results and Discussion

The test results are shown in Table 6.

[0066] [Table 6]

			Example 20	Example 21	Example 22	Example 23	Comparative example 9
Present Compound			0.1g	0.1g	0.1g	0.1g	0.1g
Boric acid			1.25g	1.25g	1.25g	1.25g	1.25g
Borax			1g	1g	1g	1g	1g
Dried sodium sulfite			0.1g	0.1g	0.1g	-	0.1g
Edetate disodium hydrate			0.02g	0.02g	-	0.02g	0.02g
Polyvinylpyrrolidone			2g	-	-	-	2g
Polysorbate 80			0.03g	0.03g	0.03g	0.03g	0.15g
BAK			0.005g	0.005g	0.005g	0.005g	0.005g
HCl/NaOH			q.s.	q.s.	q.s.	q.s.	q.s.
pH			8.3	8.3	8.3	8.3	8.3
Total volume			100mL	100mL	100mL	100mL	100mL
Residual ratio (%)/appearance	60°C	1 week	93.2/-	97.9/-	98.2/-	99.8/-	90.0/-
		2 weeks	90.1/-	97.8/-	100.2/-	99.0/-	82.5/-

"-" indicates that changes in appearance were not observed.

[0067] As is clear from Table 6, the preparations of Examples 20 to 23 were stable for 2 weeks at 60°C and remained clear, yellow and free of sediment. On the basis of the above, aqueous compositions of the present invention in the form of the preparations of Examples 20 to 23 were confirmed to have superior stability.

[0068] 3. Preparation Examples

The following indicates typical preparation examples prepared using the present compound. Furthermore, the incorporated amounts of each component in the following preparation examples indicate the content thereof in 100 mL.

[0069] Preparation Example 1

Present Compound	0.1 g
Polysorbate 80	0.005 g
Boric acid	1.25 g
Borax	1.0 g
Sodium edetate	0.02 g
Benzalkonium chloride	0.001 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Purified water	q.s.
pH	8.3

[0070] Preparation Example 2

Present Compound	0.1 g
Polysorbate 80	0.03 g
Boric acid	1.25 g
Borax	1.0 g
Sodium edetate	0.02 g
Benzalkonium chloride	0.01 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Purified water	q.s.
pH	8.3

[0071] Preparation Example 3

Present Compound	0.01 g
Polysorbate 80	0.005 g
Sodium edetate	0.05 g
Benzalkonium chloride	0.001 g
Hydrochloric acid	q.s.
Sodium hydroxide	q.s.
Purified water	q.s.
pH	8.3

[0072] Furthermore, the incorporated amounts and formulation ratios of each component in the aforementioned Preparation Examples 1 to 3, namely the present compound, polysorbate 80, benzalkonium chloride and other additives, can be suitably adjusted.

CLAIMS

1. An aqueous composition comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof, and optionally benzalkonium chloride and/or a polyoxyethylene sorbitan fatty acid ester;

wherein, the content A (parts by mass) of benzalkonium chloride and the content B (parts by mass) of the polyoxyethylene sorbitan fatty acid ester based on 100 parts by mass of 2-amino-3-(4-bromobenzoyl)phenylacetic acid are within the following ranges:

$0 \leq B < 96A + 5$ when $0 \leq A < 1$,

$1 < B \leq 100$ when $A = 1$,

$5 < B \leq 100$ when $1 < A < 3$, and

$20 < B \leq 100$ when $3 \leq A \leq 10$.

2. The aqueous composition according to claim 1, wherein the content A of benzalkonium chloride and the content B of the polyoxyethylene sorbitan fatty acid ester are within the following ranges:

$0 \leq B < 26A + 5$ when $0 \leq A < 1$,

$2 \leq B \leq 30$ when $A = 1$,

$5 < B \leq 30$ when $1 < A < 3$, and

$20 < B \leq 30$ when $3 \leq A \leq 5$.

3. The aqueous composition according to claim 1, wherein the content A of benzalkonium chloride and the content B of the polyoxyethylene sorbitan fatty acid ester are within the following ranges:

$1 < A < 3$, and

$5 < B \leq 30$.

4. The aqueous composition according to claim 1, wherein the content A of benzalkonium chloride and the content B of the polyoxyethylene sorbitan fatty acid ester are within the following ranges:

$1.2 \leq A \leq 2.5$, and

$7 \leq B \leq 20$.

5. An aqueous composition comprising 2-amino-3-(4-bromobenzoyl)phenylacetic acid or a salt thereof, and optionally benzalkonium chloride and/or a polyoxyethylene sorbitan fatty acid ester;

wherein, the concentration X (w/v%) of benzalkonium chloride and the concentration Y (w/v%) of the polyoxyethylene sorbitan fatty acid are within the following ranges:

$0 \leq Y < 96X + 0.005$ when $0 \leq X < 0.001$,

$0.001 < Y \leq 0.1$ when $X = 0.001$,

$0.005 < Y \leq 0.1$ when $0.001 < X < 0.003$, and

$0.02 < Y \leq 0.1$ when $0.003 \leq X \leq 0.01$.

6. The aqueous composition according to claim 5, wherein the concentration X of benzalkonium chloride and the concentration Y of the polyoxyethylene sorbitan fatty acid are within the following ranges:

$0 \leq Y < 26X + 0.005$ when $0 \leq X < 0.001$,

$0.002 \leq Y \leq 0.03$ when $X = 0.001$,

$0.005 < Y \leq 0.03$ when $0.001 < X < 0.003$, and

$0.02 < Y \leq 0.03$ when $0.003 \leq X \leq 0.005$.

7. The aqueous composition according to claim 5, wherein the concentration X of benzalkonium chloride and the concentration Y of the polyoxyethylene sorbitan fatty acid are within the following ranges:

$0.001 < X < 0.003$, and

$0.005 < Y \leq 0.03$.

8. The aqueous composition according to claim 5, wherein the concentration X of benzalkonium chloride and the concentration Y of the polyoxyethylene sorbitan fatty acid are within the following ranges:

$0.0012 \leq X \leq 0.0025$, and

$0.008 \leq Y \leq 0.02$.

9. The aqueous composition according to any of claims 1 to 8, wherein the polyoxyethylene sorbitan fatty acid ester is polysorbate 80.

10. The aqueous composition according to any of claims 1 to 9, wherein the concentration of 2-amino-3-(4-bromobenzoyl)phenylacetic acid in the aqueous composition is 0.01% (w/v) to 1.0% (w/v).

11. The aqueous composition according to any of claims 1 to 10, further comprising 0.01% (w/v) to 3.0% (w/v) of sodium chloride.

12. The aqueous composition according to any of claims 1 to 11, wherein the pH of the aqueous composition is higher than 7.0 to 9.5.

13. The aqueous composition according to any of claims 1 to 12, wherein the aqueous composition is an injection preparation, infusion fluid, nasal drops, ear drops or ophthalmic solution.

14. The aqueous composition according to claim 13, which is an ophthalmic injection preparation.

15. The aqueous composition according to claim 13, which is an ophthalmic

solution.

16. A method for producing the aqueous composition according to any of claims 1 to 15, comprising: dissolving 2-amino-3-(4-bromobenzoyl)phenylacetic acid, a salt thereof or a hydrate thereof, and optionally benzalkonium chloride and/or a polyoxyethylene sorbitan fatty acid ester in an aqueous solvent.