

DESCRIPTION

TITLE OF INVENTION

Aqueous Ophthalmic Composition Comprising Diquafosol or Salt Thereof and
5 Polyvinylpyrrolidone

TECHNICAL FIELD

[0001] The present invention relates to an aqueous ophthalmic composition comprising diquafosol or a salt thereof and polyvinylpyrrolidone.

BACKGROUND ART

10 [0002] The diquafosol is a purinoceptor agonist called P¹,P⁴-di(uridine-5') tetraphosphate or Up4U, having a tear secretion promoting action. Diquafosol sodium, which is a salt thereof, is used for treatment of dry eye as "Diquas (registered trademark) Ophthalmic Solution 3%" (hereinafter, also referred to as "Diquas (registered trademark) Ophthalmic Solution") (Japanese Patent No. 3652707 (PTL 1),
15 Package Insert of Diquas (registered trademark) Ophthalmic Solution 3% (NPL 1)). In accordance with the dosage and administration of Diquas (registered trademark) Ophthalmic Solution, the ophthalmic solution is usually instilled into the eye 6 times a day in a dose of 1 drop each time (NPL 1), but a sufficient therapeutic effect cannot be obtained in some severe dry eye patients even when the ophthalmic solution is used in
20 accordance with the predetermined dosage and administration. Moreover, an expected effect cannot be obtained in some patients due to poor adherence to instillation because of a situation where frequent instillations on a regular and daily basis is difficult in their daily life. Alternatively, some patients have complained about side effects such as eye stimulating sensation due to use of Diquas (registered trademark) Ophthalmic Solution,
25 although at a low frequency (NPL 1).

[0003] As an attempt to explore a novel therapeutic agent for dry eye having a higher tear volume increasing action, it is known that diquafosol or a salt thereof and an existing therapeutic agent for dry eye are used in combination. Japanese Patent Laying Open No. 2012-077080 (PTL 2) discloses that combining diquafosol or a salt

thereof with hyaluronic acid, which is a therapeutic agent for dry eye, allows tear secretion to be promoted synergistically. Japanese Patent Laying Open No. 2015-160826 (PTL 3) discloses that combining diquafosol or a salt thereof with Rebamipide, which is a therapeutic agent for dry eye, allows tear secretion to be promoted synergistically.

CITATION LIST

PATENT LITERATURE

PTL 1: Japanese Patent No. 3652707

PTL 2: Japanese Patent Laying Open No. 2012-077080

PTL 3: Japanese Patent Laying Open No. 2015-160826

NON PATENT LITERATURE

NPL 1: Package Insert of Diquas (registered trademark) Ophthalmic Solution 3%

SUMMARY OF INVENTION

TECHNICAL PROBLEM

[0006] It is an interesting object to provide an aqueous ophthalmic composition that enhances the drug efficacy of diquafosol or a salt thereof as well as that can reduce side effects thereof such as an eye stimulatory property.

SOLUTION TO PROBLEM

[0007] The present inventors have extensively conducted studies, resultantly found that an aqueous ophthalmic composition comprising diquafosol or a salt thereof and polyvinylpyrrolidone (hereinafter, also referred to as "the present composition") exhibits a marked improvement in the fluorescein staining score, that is, a marked improvement action for corneal epithelial disorders, and revealed that polyvinylpyrrolidone allows the drug efficacy of diquafosol or a salt thereof to be enhanced. Additionally, the present inventors have also found that the present composition, which has become to have a certain viscosity due to inclusion of polyvinylpyrrolidone having a certain K value, exhibits a potent therapeutic effect equivalent to or more than that of an existing Diquas (registered trademark) Ophthalmic Solution with a lower instillation frequency than that of the existing Diquas

(registered trademark) Ophthalmic Solution. It has been also found that the present composition exhibits a high cell viability and has high safety to the keratoconjunctival epithelium. It has been also found that the present composition exhibits no neurostimulatory property and may further improve the pouring touch of an ophthalmic solution. Additionally, it has been also found that, even when the present composition is allowed to contain a silver salt, the silver salt is stable and the present composition having the silver salt exhibits excellent preservative effectiveness.

[0008] That is, the present invention relates to the following.

(1) An aqueous ophthalmic composition comprising diquafosol or a salt thereof and polyvinylpyrrolidone.

[0009] (2) The aqueous ophthalmic composition according to (1), further comprising a silver salt.

(3) The aqueous ophthalmic composition according to (2), wherein the silver salt comprises silver nitrate.

[0010] (4) The aqueous ophthalmic composition according to any one of (1) to (3), wherein the aqueous ophthalmic composition is for prevention or treatment of dry eye.

[0011] (5) The aqueous ophthalmic composition according to (4), comprising diquafosol sodium at a concentration of 1 to 5% (w/v) and polyvinylpyrrolidone having a K value of more than 30 and 120 or less.

[0012] (6) The aqueous ophthalmic composition according to (4), comprising diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone having a K value of more than 30 and 120 or less.

[0013] (7) The aqueous ophthalmic composition according to (4), comprising diquafosol sodium at a concentration of 1 to 5% (w/v) and having a viscosity at 25°C of 1.5 to 30 mPa·s.

[0014] (8) The aqueous ophthalmic composition according to (4), comprising diquafosol sodium at a concentration of 3% (w/v) and having a viscosity at 25°C of 1.5 to 30 mPa·s.

[0015] (9) The aqueous ophthalmic composition according to any one of (5) to (8),

wherein the aqueous ophthalmic composition is used so as to be instilled into the eye 2 to 4 times a day.

5 [0016] (10) The aqueous ophthalmic composition according to any one of (5) to (8), wherein the aqueous ophthalmic composition is used so as to be instilled into the eye 3 times a day.

[0017] (11) The aqueous ophthalmic composition according to (9) or (10), wherein the aqueous ophthalmic composition is used so as to be instilled into the eye in a dose of 1 to 2 drops each time.

10 [0018] (12) An ophthalmic medicament product comprising 0.1 to 1 mL of the aqueous ophthalmic composition according to (1) filled in a unit dose-type eye drop container.

[0019] (13) An ophthalmic medicament product comprising 0.3 to 0.5 mL of the aqueous ophthalmic composition according to (1) filled in a unit dose-type eye drop container.

15 [0020] (14) An ophthalmic medicament product comprising 1 to 10 mL of the aqueous ophthalmic composition according to any one of (1) to (3) filled in a multidose-type eye drop container.

[0021] (15) An ophthalmic medicament product comprising 5 mL of the aqueous ophthalmic composition according to any one of (1) to (3) filled in a multidose-type eye drop container.

20 [0022] (16) An ophthalmic medicament product comprising 1 to 10 mL of the aqueous ophthalmic composition according to (1) filled in a PFMD container.

[0023] (17) An ophthalmic medicament product comprising 5 mL of the aqueous ophthalmic composition according to (1) filled in a PFMD container.

25 [0024] (18) The ophthalmic medicament product according to any one of (12) to (17), wherein the ophthalmic medicament product is for prevention or treatment of dry eye.

[0025] (19) The ophthalmic medicament product according to (18), wherein the aqueous ophthalmic composition comprises diquafosol sodium at a concentration of 1 to 5% (w/v) and polyvinylpyrrolidone having a K value of more than 30 and 120 or less.

- [0026] (20) The ophthalmic medicament product according to (18), wherein the aqueous ophthalmic composition comprises diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone having a K value of more than 30 and 120 or less.
- 5 [0027] (21) The ophthalmic medicament product according to (18), wherein the aqueous composition comprises diquafosol sodium at a concentration of 1 to 5% (w/v) and has a viscosity at 25°C of 1.5 to 30 mPa·s.
- [0028] (22) The ophthalmic medicament product according to (18), wherein the aqueous composition comprises diquafosol sodium at a concentration of 3% (w/v) and has a viscosity at 25°C of 1.5 to 30 mPa·s.
- 10 [0029] (23) The ophthalmic medicament product according to any one of (19) to (22), wherein the ophthalmic medicament product is used so as to be instilled into the eye 2 to 4 times a day.
- [0030] (24) The ophthalmic medicament product according to any one of (19) to (22), wherein the ophthalmic medicament product is used so as to be instilled into the eye 3
- 15 times a day.
- [0031] (25) The ophthalmic medicament product according to (23) or (24), wherein the ophthalmic medicament product is used so as to be instilled into the eye in a dose of 1 to 2 drops each time.
- [0032] (26) The aqueous ophthalmic composition according to any one of (1) to (4),
- 20 comprising polyvinylpyrrolidone having a K value of 17 or more.
- [0033] (27) The aqueous ophthalmic composition according to any one of (1) to (4), comprising polyvinylpyrrolidone having a K value of 17 to 120.
- [0034] (28) The aqueous ophthalmic composition according to any one of (1) to (4), comprising polyvinylpyrrolidone having a K value of more than 30 and 120 or less.
- 25 [0035] (29) The aqueous ophthalmic composition according to any one of (1) to (4), comprising polyvinylpyrrolidone having a K value of 90.
- [0036] (30) The aqueous ophthalmic composition according to any one of (1) to (11), wherein the concentration of the polyvinylpyrrolidone is 0.001% (w/v) or more.
- [0037] (31) The aqueous ophthalmic composition according to any one of (1) to (4),

- wherein the concentration of the diquafosol or a salt thereof is 0.0001 to 10% (w/v).
- [0038] (32) The aqueous ophthalmic composition according to any one of (1) to (4), wherein the concentration of the diquafosol or a salt thereof is 0.01 to 5% (w/v).
- [0039] (33) The aqueous ophthalmic composition according to any one of (1) to (4),
- 5 wherein the concentration of the diquafosol or a salt thereof is 1 to 5% (w/v).
- [0040] (34) The aqueous ophthalmic composition according to any one of (1) to (4), wherein the concentration of the diquafosol or a salt thereof is 3% (w/v).
- [0041] (35) The aqueous ophthalmic composition according to any one of (1) to (11), wherein the aqueous ophthalmic composition has a pH in the range of 6 to 8.
- 10 [0042] (36) The aqueous ophthalmic composition according to any one of (1) to (11), wherein the aqueous ophthalmic composition has a pH in the range of 7 to 8.
- [0043] (37) The aqueous ophthalmic composition according to any one of (1) to (11), wherein the aqueous ophthalmic composition is a sterile aqueous ophthalmic solution.
- [0044] (38) The aqueous ophthalmic composition according to any one of (1) to (11),
- 15 wherein the aqueous ophthalmic composition is preservable at room temperature.
- [0045] (39) The aqueous ophthalmic composition according to any one of (1) to (6), wherein the aqueous ophthalmic composition has a viscosity at 25°C of 1.5 to 30 mPa·s.
- [0046] (40) The aqueous ophthalmic composition according to any one of (1) to (4),
- 20 wherein the salt of diquafosol is diquafosol sodium.
- [0047] (41) An aqueous ophthalmic composition for prevention or treatment of dry eye, comprising diquafosol sodium at a concentration of 3% (w/v), polyvinylpyrrolidone having a K value of 90, and silver nitrate, wherein the aqueous ophthalmic composition is used so as to be instilled into the eye 2 to 4 times a day in a
- 25 dose of 1 or 2 drops each time.
- [0048] (42) An aqueous ophthalmic composition for prevention or treatment of dry eye, comprising diquafosol sodium at a concentration of 3% (w/v), polyvinylpyrrolidone, and silver nitrate, wherein the aqueous ophthalmic composition is used so as to be instilled into the eye 2 to 4 times a day in a dose of 1 or 2 drops each

time, having a viscosity at 25°C of 3 to 30 mPa·s.

[0049] (43) The aqueous ophthalmic composition according to (41) or (42), wherein the aqueous ophthalmic composition is used so as to be instilled into the eye 3 times a day.

5 [0050] (44) An ophthalmic medicament product for prevention or treatment of dry eye, comprising 0.1 to 1 mL of an aqueous ophthalmic composition filled in a unit dose-type eye drop container, the aqueous ophthalmic composition comprising diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone having a K value of 90, wherein the aqueous ophthalmic composition is used so as to be instilled into the eye 2
10 to 4 times a day in a dose of 1 or 2 drops each time.

[0051] (45) An ophthalmic medicament product for prevention or treatment of dry eye, comprising 0.1 to 1 mL of an aqueous ophthalmic composition filled in a unit dose-type eye drop container, the aqueous ophthalmic composition comprising diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone, wherein the aqueous
15 ophthalmic composition has a viscosity at 25°C of 3 to 30 mPa·s and is used so as to be instilled into the eye 2 to 4 times a day in a dose of 1 or 2 drops each time.

[0052] (46) An ophthalmic medicament product for prevention or treatment of dry eye, comprising 1 to 10 mL of an aqueous ophthalmic composition filled in a multidose-type eye drop container, the aqueous ophthalmic composition comprising diquafosol
20 sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone having a K value of 90, wherein the aqueous ophthalmic composition is used so as to be instilled into the eye 2 to 4 times a day in a dose of 1 or 2 drops each time.

[0053] (47) An ophthalmic medicament product for prevention or treatment of dry eye, comprising 1 to 10 mL of an aqueous ophthalmic composition filled in a multidose-type eye drop container, the aqueous ophthalmic composition comprising diquafosol
25 sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone, wherein the aqueous ophthalmic composition has a viscosity at 25°C of 3 to 30 mPa·s and is used so as to be instilled into the eye 2 to 4 times a day in a dose of 1 or 2 drops each time.

[0054] (48) An ophthalmic medicament product for prevention or treatment of dry eye,

comprising 1 to 10 mL of an aqueous ophthalmic composition filled in a PFMD container, the aqueous ophthalmic composition comprising diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone having a K value of 90, wherein the aqueous ophthalmic composition is used so as to be instilled into the eye 2 to 4 times a day in a dose of 1 or 2 drops each time.

[0055] (49) An ophthalmic medicament product for prevention or treatment of dry eye, comprising 1 to 10 mL of an aqueous ophthalmic composition filled in a PFMD container, the aqueous ophthalmic composition comprising diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone, wherein the aqueous ophthalmic composition has a viscosity at 25°C of 3 to 30 mPa·s and is used so as to be instilled into the eye 2 to 4 times a day in a dose of 1 or 2 drops each time.

[0056] (50) The ophthalmic medicament product according to any one of (44) to (49), wherein the ophthalmic medicament product is used so as to be instilled into the eye 3 times a day.

[0057] (51) The ophthalmic medicament product according to either one of (46) or (47), further comprising silver nitrate.

[0058] The present invention also relates to the following.

(A-1) A method for treating dry eye, comprising instilling an aqueous ophthalmic composition filled in a unit dose-type eye drop container into the eye(s) of a patient 2 to 4 times a day in a dose of 1 or 2 drops each time, wherein the aqueous ophthalmic composition comprises diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone having a K value of 90, and 0.1 to 1 mL of the aqueous ophthalmic composition is filled in the unit dose-type eye drop container.

[0059] (A-2) A method for treating dry eye, comprising instilling an aqueous ophthalmic composition filled in a unit dose-type eye drop container into the eye(s) of a patient 2 to 4 times a day in a dose of 1 or 2 drops each time, wherein the aqueous ophthalmic composition comprises diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone and has a viscosity at 25°C of 3 to 30 mPa·s, and 0.1 to 1 mL of the aqueous ophthalmic composition is filled in the unit dose-type eye drop

container.

[0060] (A-3) A method for treating dry eye, comprising instilling an aqueous ophthalmic composition filled in a multidose-type eye drop container into the eye(s) of a patient 2 to 4 times a day in a dose of 1 or 2 drops each time, wherein the aqueous ophthalmic composition comprises diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone having a K value of 90, and 1 to 10 mL of the aqueous ophthalmic composition is filled in the multidose-type eye drop container.

[0061] (A-4) A method for treating dry eye, comprising instilling an aqueous ophthalmic composition filled in a multidose-type eye drop container into the eye(s) of a patient 2 to 4 times a day in a dose of 1 or 2 drops each time, wherein the aqueous ophthalmic composition comprises diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone and has a viscosity at 25°C of 3 to 30 mPa·s, and 1 to 10 mL of the aqueous ophthalmic composition is filled in the multidose-type eye drop container.

[0062] (A-5) A method for treating dry eye, comprising instilling an aqueous ophthalmic composition filled in a PFMD container into the eye(s) of a patient 2 to 4 times a day in a dose of 1 or 2 drops each time, wherein the aqueous ophthalmic composition comprises diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone having a K value of 90, and 1 to 10 mL of the aqueous ophthalmic composition is filled in the PFMD container.

[0063] (A-6) A method for treating dry eye, comprising instilling an aqueous ophthalmic composition filled in a PFMD container into the eye(s) of a patient 2 to 4 times a day in a dose of 1 or 2 drops each time, wherein the aqueous ophthalmic composition comprises diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone and has a viscosity at 25°C of 3 to 30 mPa·s, and 1 to 10 mL of the aqueous ophthalmic composition is filled in the PFMD container.

[0064] (A-7) The method for treating dry eye according to any one of (A-1) to (A-6), comprising instilling the aqueous ophthalmic composition into the eye(s) of a patient 3 times a day in a dose of 1 or 2 drops each time.

5 [0065] (B-1) An ophthalmic medicament product comprising 0.1 to 1 mL of an aqueous ophthalmic composition filled in a unit dose-type eye drop container, for use in prevention or treatment of dry eye, wherein the aqueous ophthalmic composition comprises diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone having a K value of 90 and is used so as to be instilled into the eye 2 to 4 times a day in a dose of 1 or 2 drops each time.

10 [0066] (B-2) An ophthalmic medicament product comprising 0.1 to 1 mL of an aqueous ophthalmic composition filled in a unit dose-type eye drop container, for use in prevention or treatment of dry eye, wherein the aqueous ophthalmic composition comprises diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone, has a viscosity at 25°C of 3 to 30 mPa·s, and is used so as to be instilled into the eye 2 to 4 times a day in a dose of 1 or 2 drops each time.

15 [0067] (B-3) An ophthalmic medicament product comprising 1 to 10 mL of an aqueous ophthalmic composition filled in a multidose-type eye drop container, for use in prevention or treatment of dry eye, wherein the aqueous ophthalmic composition comprises diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone having a K value of 90 and is used so as to be instilled into the eye 2 to 4 times a day in a dose of 1 or 2 drops each time.

20 [0068] (B-4) An ophthalmic medicament product comprising 1 to 10 mL of an aqueous ophthalmic composition filled in a multidose-type eye drop container, for use in prevention or treatment of dry eye, wherein the aqueous ophthalmic composition comprises diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone, has a viscosity at 25°C of 3 to 30 mPa·s, and is used so as to be instilled into the eye 2 to 4 times a day in a dose of 1 or 2 drops each time.

25 [0069] (B-5) An ophthalmic medicament product comprising 1 to 10 mL of an aqueous ophthalmic composition filled in a PFMD container, for use in prevention or treatment of dry eye, wherein the aqueous ophthalmic composition comprises diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone having a K value of 90 and is used so as to be instilled into the eye 2 to 4 times a day in a dose of 1 or 2 drops each

time.

5 [0070] (B-6) An ophthalmic medicament product comprising 1 to 10 mL of an aqueous ophthalmic composition filled in a PFMD container, for use in prevention or treatment of dry eye, wherein the aqueous ophthalmic composition comprises diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone, has a viscosity at 25°C of 3 to 30 mPa·s, and is used so as to be instilled into the eye 2 to 4 times a day in a dose of 1 or 2 drops each time.

10 [0071] (B-7) The ophthalmic medicament product according to any one of (B-1) to (B-6), wherein the aqueous ophthalmic composition is used so as to be instilled into the eye 3 times a day in a dose of 1 or 2 drops each time.

15 [0072] (C-1) Use of an aqueous ophthalmic composition for the manufacture of a medicament for preventing or treating dry eye, the aqueous ophthalmic composition comprising diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone having a K value of 90, wherein 0.1 to 1 mL of the aqueous ophthalmic composition is filled in a unit dose-type eye drop container and used so as to be instilled into the eye 2 to 4 times a day in a dose of 1 or 2 drops each time.

20 [0073] (C-2) Use of an aqueous ophthalmic composition for the manufacture of a medicament for preventing or treating dry eye, the aqueous ophthalmic composition comprising diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone and having a viscosity at 25°C of 3 to 30 mPa·s, wherein 0.1 to 1 mL of the aqueous ophthalmic composition is filled in a unit dose-type eye drop container and used so as to be instilled into the eye 2 to 4 times a day in a dose of 1 or 2 drops each time.

25 [0074] (C-3) Use of an aqueous ophthalmic composition for the manufacture of a medicament for preventing or treating dry eye, the aqueous ophthalmic composition comprising diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone having a K value of 90, wherein 1 to 10 mL of the aqueous ophthalmic composition is filled in a multidose-type eye drop container and used so as to be instilled into the eye 2 to 4 times a day in a dose of 1 or 2 drops each time.

[0075] (C-4) Use of an aqueous ophthalmic composition comprising diquafosol sodium

at a concentration of 3% (w/v) and polyvinylpyrrolidone and having a viscosity at 25°C of 3 to 30 mPa·s, for the manufacture of a medicament for preventing or treating dry eye, wherein 1 to 10 mL of the aqueous ophthalmic composition is filled in a multidose-type eye drop container and used so as to be instilled into the eye 2 to 4 times a day in a dose of 1 or 2 drops each time.

[0076] (C-5) Use of an aqueous ophthalmic composition for the manufacture of a medicament for preventing or treating dry eye, the aqueous ophthalmic composition comprising diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone having a K value of 90, wherein 1 to 10 mL of the aqueous ophthalmic composition is filled in a PFMD container and used so as to be instilled to an eye 2 to 4 times a day in a dose of 1 or 2 drops each time.

[0077] (C-6) Use of an aqueous ophthalmic composition comprising diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone and having a viscosity at 25°C of 3 to 30 mPa·s, for the manufacture of a medicament for preventing or treating dry eye, wherein 1 to 10 mL of the aqueous ophthalmic composition is filled in a PFMD container and used so as to be instilled into the eye 2 to 4 times a day in a dose of 1 or 2 drops each time.

[0078] (C-7) Use of aqueous ophthalmic composition according to any one of (C-1) to (C-6), wherein the aqueous ophthalmic composition is used so as to be instilled to an eye 3 times a day in a dose of 1 or 2 drops each time.

[0079] (D-1) A method for imparting preservative effectiveness to an aqueous ophthalmic composition comprising diquafosol or a salt thereof and polyvinylpyrrolidone, the method comprising allowing the aqueous ophthalmic composition to contain silver salt.

[0080] (D-2) A method for maintaining preservative effectiveness of an aqueous ophthalmic composition comprising diquafosol or a salt thereof and polyvinylpyrrolidone, the method comprising allowing the aqueous ophthalmic composition to contain silver salt.

[0081] Two or more of the elements of the present invention may be optionally

selected and combined.

ADVANTAGEOUS EFFECTS OF INVENTION

[0082] The present composition has a high tear volume increasing action and thus is expected to exhibit a more potent therapeutic effect on dry eye as compared to a case where an existing Diquas (registered trademark) Ophthalmic Solution is instilled into the eye. Accordingly, the present composition is expected to exhibit a potent therapeutic effect on dry eye equivalent to or more than that of the existing Diquas (registered trademark) Ophthalmic Solution with a lower concentration than that thereof. The existing Diquas (registered trademark) Ophthalmic Solution is required to be instilled into the eye 6 times a day, and some patients are unable to obtain an expected effect due to poor adherence to instillation. The present composition, which has become to have a certain viscosity due to inclusion of polyvinylpyrrolidone having a certain K value, exhibits a potent therapeutic effect equivalent to or more than that of the existing Diquas (registered trademark) Ophthalmic Solution with a lower instillation frequency than that of the existing Diquas (registered trademark) Ophthalmic Solution, and thus is expected to improve adherence to instillation.

[0083] It is also expected that the present composition exhibits a high cell viability and thus has high safety to the keratoconjunctival epithelium, and exhibits no neurostimulatory property and thus may improve the pouring touch of an ophthalmic solution.

[0084] Additionally, even when the present composition is allowed to contain a silver salt, the silver salt is stable, and the present composition exhibits excellent preservative effectiveness.

BRIEF DESCRIPTION OF DRAWINGS

[0085] FIG. 1 is a graph showing the fluorescein staining score of the cornea.

FIG. 2 is a graph showing the results of the cytotoxicity test of corneal epithelial cells.

FIG. 3 is a graph showing a maximum fluorescence intensity (RFU_{max}) after addition of diquafosol sodium.

[0086] The present invention will be described in more detail.

5 [0087] "PVP" herein denotes polyvinylpyrrolidone.

[0088] "CMC-Na" herein denotes carboxymethyl cellulose sodium.

[0090] "CVP" herein denotes a carboxyvinyl polymer.

[0091] A "diqafosol sodium ophthalmic solution" herein means an aqueous ophthalmic solution containing diqafosol sodium.

15 formula.

- 14 -

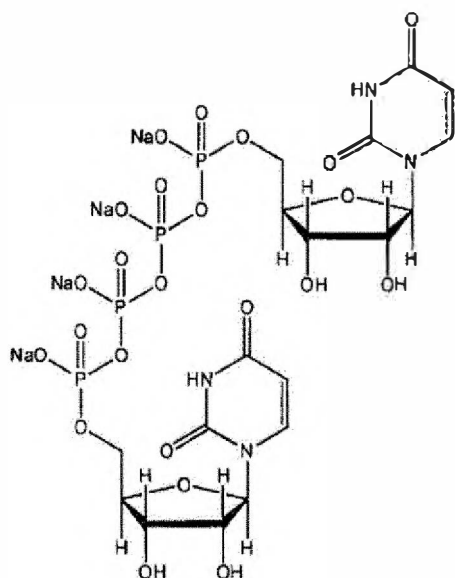
as lithium, sodium, potassium, calcium, magnesium, and zinc; salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, sulfuric acid, and phosphoric acid; salts with organic acids such as acetic acid, fumaric acid, maleic acid, succinic acid, citric acid, tartaric acid, adipic acid, gluconic acid, glucoheptonic acid, glucuronic acid, terephthalic acid, methanesulfonic acid, lactic acid, hippuric acid, 1,2-ethanedithionic acid, isethionic acid, lactobionic acid, oleic acid, pantoic acid, polygalacturonic acid, stearic acid, tannic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, lauryl sulfate, methyl sulfate, naphthalenesulfonic acid, and sulfosalicylic acid; quaternary ammonium salts with methyl bromide, methyl iodide and the like; salts with halogen ions such as bromine ions, chlorine ions, and iodine ions; salts with ammonia; and salts with organic amines such as 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.

[0095] In the present invention, the "diquafosol or a salt thereof" include hydrates and organic solvates of diquafosol (free body) or salts thereof.

[0096] When the "diquafosol or a salt thereof" have crystal polymorphs and crystal polymorph groups (crystal polymorph systems), the crystal polymorphs and crystal polymorph groups (crystal polymorph systems) are also included within the scope of the present invention. Here, the crystal polymorph group (crystal polymorph system) means individual crystal forms in various stages where crystal forms are changed according to the conditions and states of production, crystallization and storage of the crystals, and the entire process of the stages.

[0097] As the "diquafosol or a salt thereof" according to the present invention, a sodium salt of diquafosol is preferable, and a diquafosol tetrasodium salt represented by the following chemical structural formula (herein, also referred to simply as "diquafosol sodium") is especially preferable.

[0098] [Formula 2]



[0099] The diquafosol or a salt thereof can be produced by, for example, the method disclosed in Japanese National Patent Publication No. 2001-510484.

[0100] The present composition may further contain active ingredients other than diquafosol or a salt thereof, or may contain diquafosol or a salt thereof as a single active ingredient.

[0101] The concentration of the diquafosol or a salt thereof in the present composition is not particularly limited, and is, for example, preferably 0.0001 to 10% (w/v), more preferably 0.001 to 5% (w/v), still more preferably 0.01 to 5% (w/v), furthermore preferably 0.1 to 5% (w/v), still furthermore preferably 1 to 5% (w/v), especially preferably 3% (w/v). More specifically, the concentration is preferably 0.001% (w/v), 0.002% (w/v), 0.003% (w/v), 0.004% (w/v), 0.005% (w/v), 0.006% (w/v), 0.007% (w/v), 0.008% (w/v), 0.009% (w/v), 0.01% (w/v), 0.02% (w/v), 0.03% (w/v), 0.04% (w/v), 0.05% (w/v), 0.06% (w/v), 0.07% (w/v), 0.08% (w/v), 0.09% (w/v), 0.1% (w/v), 0.2% (w/v), 0.3% (w/v), 0.4% (w/v), 0.5% (w/v), 0.6% (w/v), 0.7% (w/v), 0.8% (w/v), 0.9% (w/v), 1% (w/v), 1.5% (w/v), 2% (w/v), 2.5% (w/v), 3% (w/v), 3.5% (w/v), 4% (w/v), 4.5% (w/v), or 5% (w/v).

[0102] In the present invention, "polyvinylpyrrolidone" is a polymer compound obtained by polymerizing N-vinyl-2-pyrrolidone and is generally used as a viscosifying

agent. Polyvinylpyrrolidone is also called povidone. The K value of polyvinylpyrrolidone for use in the present invention is preferably 17 or more, more preferably 17 to 120, still more preferably 25 to 120, furthermore preferably 30 to 120, still furthermore preferably more than 30 and 120 or less, even still furthermore preferably 40 to 120, particularly preferably 60 to 120, especially preferably 60 to 90, still especially preferably 90. Examples of the polyvinylpyrrolidone include polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, polyvinylpyrrolidone K30, polyvinylpyrrolidone K40, polyvinylpyrrolidone K50, polyvinylpyrrolidone K60, polyvinylpyrrolidone K70, polyvinylpyrrolidone K80, polyvinylpyrrolidone K85, polyvinylpyrrolidone K90, and polyvinylpyrrolidone K120. The K value of polyvinylpyrrolidone is a viscosity-characteristic value correlated to the molecular weight, and is determined by measuring a relative viscosity (25°C) with a capillary viscometer, and substituting the relative viscosity into the following Fikentscher equation (1).

[0103] [Expression 1]

$$K = \frac{1.5 \log \eta_{\text{rel}} - 1}{0.15 + 0.003c} + \frac{[300c \log \eta_{\text{rel}} + 2(c + 1.5 \log \eta_{\text{rel}})]^{1/2}}{0.15c + 0.003c^2} \quad (1)$$

[0104] In equation (1), η_{rel} is a viscosity of a polyvinylpyrrolidone aqueous solution relative to water, and c is a concentration (%) of polyvinylpyrrolidone in the polyvinylpyrrolidone aqueous solution.

[0105] Here, in accordance with the description of the K value of "Povidone" in The Japanese Pharmacopoeia, 17th Edition, the K value corresponds to 90 to 108% of the K value shown. Thus, for example, "K90" refers to a viscosity-characteristic value (K value), determined by substitution into the above equation (1), in the range of 81 to 97.2.

[0106] In the present invention, one polyvinylpyrrolidone may be used singly, or any combination of two or more polyvinylpyrrolidones each having a different K value may be used.

[0107] The concentration of polyvinylpyrrolidone in the present invention is not particularly limited, and may be, for example, 0.001% (w/v) or more, preferably 0.001 to 10% (w/v), more preferably 0.01 to 10% (w/v), still more preferably 0.05 to 10% (w/v), furthermore preferably 0.1 to 10% (w/v), particularly preferably 0.1 to 5% (w/v), especially preferably 1 to 5% (w/v).

[0108] If necessary, a pharmaceutically acceptable preservative may be further added to the present composition. Examples of the preservative include silver salts such as silver nitrate, benzalkonium chloride, benzalkonium bromide, benzethonium chloride, chlorhexidine gluconate, boric acid, borax, sorbic acid, potassium sorbate, methyl paraoxybenzoate, propyl paraoxybenzoate, chlorobutanol, polidronium chloride, and hydrochloric acid polyhexanide.

[0109] As is evident from the test results described later, the present composition containing a silver salt has excellent preservative effectiveness. Thus, a preferred preservative in the present invention is a silver salt. Examples of the silver salt include silver nitrate, silver sulfate, silver chloride, silver bromide, silver oxide, silver acetate, silver carbonate, silver citrate, silver lactate, silver phosphate, silver oxalate, silver thiosulfate, and silver protein, and preferred is silver nitrate.

[0110] The concentration of the silver salt in the present invention is not particularly limited as long as the concentration is in the range of 0.00000001 to 1% (w/v).

Specifically, the lower limit value is preferably, for example, 0.00000001% (w/v) or more, 0.0000001% (w/v) or more, 0.000001% (w/v) or more, 0.0000025% (w/v) or more, 0.000004% (w/v) or more, 0.000005% (w/v) or more, 0.000008% (w/v) or more, 0.00001% (w/v) or more, 0.000016% (w/v) or more, 0.000025% (w/v) or more, 0.00004% (w/v) or more, 0.00005% (w/v) or more, 0.00008% (w/v) or more, or 0.0001% (w/v) or more. The upper limit value is preferably, for example, 1% (w/v) or less, 0.5% (w/v) or less, 0.1% (w/v) or less, 0.05% (w/v) or less, 0.01% (w/v) or less, 0.005% (w/v) or less, or 0.001% (w/v) or less.

[0111] If necessary, pharmaceutically acceptable additives may be further added to the present composition, in addition to the polyvinylpyrrolidone and preservative

mentioned above. Examples of the additives that may be selected and added if necessary include buffering agents such as sodium phosphate, sodium hydrogen phosphate, sodium hydrogen phosphate hydrate, sodium dihydrogen phosphate, sodium acetate, and epsilon-aminocaproic acid; tonicity agents such as calcium chloride, sodium chloride, potassium chloride, and concentrated glycerin; stabilizing agents such as sodium edetate, sodium edetate hydrate, citric acid hydrate, and sodium citrate hydrate; surfactants such as polysorbate; antioxidants such as ascorbic acid; viscosifying agents (also referred to as thickening agents) such as hydroxyethyl cellulose and hydroxypropylmethyl cellulose; and pH adjusters such as hydrochloric acid and sodium hydroxide. These additives may be used singly, or any combination of two or more thereof may be used. The present composition may not include a cellulose-based polymer as a viscosifying agent, such as hydroxyethyl cellulose and hydroxypropylmethyl cellulose.

[0112] The pH of the present composition is not limited to a specific value as long as the pH is within a range of values that are pharmaceutically acceptable. However, the pH of the present composition is preferably 8 or less, more preferably in the range of 4 to 8, still more preferably in the range of 5 to 8, furthermore preferably in the range of 6 to 8, particularly preferably in the range of 7 to 8, especially preferably about 7. More specifically, for example, pH 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, and 8.0 are preferred, and 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, and 8.0 are more preferred.

[0113] In the present invention, the "ophthalmic composition" refers to a composition for use in prevention and/or treatment of eye diseases. Examples of the dosage form of the present composition include eye drops, eye ointments, injections, and ointments (which can be administered to, for example, the eyelid skin), with eye drops being preferable. Here, the eye drop is synonymous with an ophthalmic solution or an ophthalmic drug, and eye drops for contact lenses are also within the definition of eye drops.

[0114] In the present invention, the "aqueous ophthalmic composition" is an aqueous

ophthalmic composition having water as a solvent (base), more preferably an aqueous eye drop.

[0115] The present composition may be a solution-type eye drop or a suspension-type eye drop depending on the nature, content, and the like of each of active ingredients and additives.

[0116] The present composition is preferably a sterile aqueous ophthalmic solution. Sterile herein means a state where microbes are killed or removed, and specifically means, for example, a state that passes the criterion of the preservative effectiveness test described in The Japanese Pharmacopoeia, 17th Edition.

[0117] The present composition is preferably preservable at room temperature.

The viscosity of the present composition is not particularly limited as long as the viscosity is within a range of values that are pharmaceutically acceptable. The viscosity is adjusted to be, for example, preferably in the range of 1 to 500 mPa·s, more preferably in the range of more than 1.4 and 100 mPa·s or less, still more preferably in the range of 1.5 to 100 mPa·s, furthermore preferably in the range of 1.5 to 50 mPa·s, still furthermore preferably in the range of 1.5 to 30 mPa·s, even still furthermore preferably in the range of 1.5 to 20 mPa·s, particularly preferably in the range of 1.5 to 10 mPa·s, still particularly preferably in the range of 2 to 10 mPa·s, especially preferably in the range of 3 to 10 mPa·s, still especially preferably in the range of 5 to 10 mPa·s, even still especially preferably in the range of 7 to 10 mPa·s. The viscosity of the present composition also may be adjusted to be in the range of 1.5 to 30 mPa·s, preferably in the range of 2 to 30 mPa·s, more preferably in the range of 3 to 30 mPa·s, still more preferably in the range of 5 to 30 mPa·s, especially preferably in the range of 7 to 30 mPa·s. The lower limit value of the viscosity of the present composition is, for example, preferably 1 mPa·s or more, 1.5 mPa·s or more, 2 mPa·s or more, 3 mPa·s or more, 5 mPa·s or more, or 7 mPa·s or more. The upper limit value thereof is, for example, preferably 500 mPa·s or less, 100 mPa·s or less, 50 mPa·s or less, 30 mPa·s or less, 20 mPa·s or less, or 10 mPa·s or less. The viscosity of the present composition is

measured by a rotary viscometer (25°C; shear rate of 50 s⁻¹).

[0118] The osmotic pressure of the present composition is not limited to a specific value as long as the osmotic pressure is within a range of values that are pharmaceutically acceptable. However, the osmotic pressure of the present

5 composition is preferably 2 or less, more preferably in the range of 0.5 to 2, still more preferably in the range of 0.7 to 1.6, furthermore preferably in the range of 0.8 to 1.4, especially preferably in the range of 0.9 to 1.2.

[0119] The present composition can be filled and preserved in an airtight container, specifically in an eye drop container. Examples of the eye drop container in which the

10 present composition is filled include a "multidose-type eye drop container" or a "unit dose-type eye drop container".

[0120] An "ophthalmic medicament product" in the present invention refers to a product for an ophthalmic medicament including the present composition filled in an eye drop container. Examples of the "ophthalmic medicament product" here include

15 products of eye drops. The definition of each term in the "ophthalmic medicament product" of the present invention is the same as the definition of each term in "the present composition".

[0121] In the present invention, the "multidose-type eye drop container" refers to an eye drop container including a container body, and a cap attachable to the container

20 body, the eye drop container allowing the cap to be freely detached and reattached. The multidose-type eye drop container typically contains a plurality of doses of an ophthalmic solution so that the ophthalmic solution is used over a certain period of time. When the present composition does not contain a preservative such as benzalkonium chloride, the present composition may be contained in a PFMD

25 (preservative-free multidose) container. The amount of the present composition to be filled in a multidose-type eye drop container or PFMD container is, for example, preferably 1 to 20 mL, more preferably 1 to 15 mL, still more preferably 1 to 10 mL, furthermore preferably 2.5 to 10 mL, especially preferably 5 mL.

[0122] On the other hand, the "unit dose-type eye drop container" refers to an eye drop

container in which a cap is welded to a bottle mouth portion with the intent of breaking the welded portion of the cap and a bottle-shaped body to detach the cap at the time of use. The unit dose-type eye drop container contains one or several doses of an ophthalmic solution. An ophthalmic solution to be contained in a unit dose-type eye drop container generally contains no preservative such as benzalkonium chloride. The amount of the present composition to be filled in a unit dose-type eye drop container is, for example, preferably 0.1 to 1 mL, more preferably 0.1 to 0.5 mL, still more preferably 0.3 mL to 0.5 mL, especially preferably 0.3 mL or 0.4 mL.

[0123] The dose regimen of the present composition can be appropriately changed according to the dosage form, the severity of a symptom of a patient to be dosed, the age and the body weight of the patient, the doctor's judgment, and the like. For example, when an eye drop is selected as the dosage form, the present composition can be instilled into the eye 1 to 6 times a day, preferably 1 to 4 times a day, more preferably 2 to 4 times a day, still more preferably 3 times a day, at intervals of one day to one week, in a dose of 1 to 5 drops, preferably 1 to 3 drops, more preferably 1 to 2 drops, especially preferably 1 drop each time. Here, more specifically, the instillation frequency is, for example, preferably 6 times a day, 5 times a day, 4 times a day, 3 times a day, 2 times a day or 1 time a day, more preferably 6 times a day, 4 times a day, 3 times a day, or 2 times a day, still more preferably 4 times a day, 3 times a day, or 2 times a day, especially preferably 3 times a day.

[0124] When the concentration of diquafosol or a salt thereof in the present composition is 3% (w/v), the present composition can be instilled into the eye 6 times a day, 5 times a day, 4 times a day, 3 times a day, 2 times a day or 1 time a day, preferably 6 times a day, 4 times a day, 3 times a day or 2 times a day, more preferably 4 times a day or 3 times a day, especially preferably 3 times a day, in a dose of 1 to 5 drops, preferably 1 to 3 drops, more preferably 1 to 2 drops, especially preferably 1 drop each time.

[0125] The amount of a drop is preferably 10 to 50 μ L, more preferably 20 to 50 μ L, especially preferably 40 to 50 μ L.

[0126] The present composition is used for prevention or treatment of dry eye, and effective as a preventive or therapeutic agent for dry eye. The dry eye is defined as a "chronic lacrimal and keratoconjunctival epithelial disease which is attributed to various factors and which involves ocular discomfort or visual abnormality", and the dry eye includes keratoconjunctivitis sicca (KCS). In the present invention, the dry eye also includes development of dry eye symptoms caused by wear of soft contact lenses.

[0127] The dry eye symptoms include subjective symptoms such as a feeling of ocular dryness, ocular discomfort, a feeling of ocular fatigue, a dull feeling, a photophobic feeling, ocular pain, and blurred vision (filmy vision), and objective findings such as bloodshot eyes and keratoconjunctival epithelial disorders. In the present invention, "prevention or treatment of dry eye" also includes improvement of the aforementioned subjective symptoms and/or objective findings.

[0128] While there are many unclear points regarding causal factors of dry eye, the causes of the dry eye have been reported to be Sjogren's syndrome; congenital alacrima; sarcoidosis; graft versus host disease (GVHD) resulting from bone-marrow transplantation; ocular pemphigoid; Stevens-Johnson syndrome; lacrimal occlusion caused by trachoma or the like; diabetes; decreased reflex secretion caused by laser-assisted in situ keratomileusis (LASIK) or the like; meibomian gland dysfunction; oily layer reduction caused by blepharitis or the like; incomplete eyeblinking or incomplete eyelid closure caused by bulging of eyeballs, rabbit eye, or the like; decreased mucin secretion from embryonic cells; operations with visual display terminals (VDTs); and the like.

[0129] The present composition can be instilled into the eye of a dry eye patient wearing soft contact lenses. Here, the instillation to the eye of a dry eye patient wearing soft contact lenses means that the ophthalmic solution is instilled into the eye with a soft contact lens placed on the cornea of the dry eye patient.

Examples

[0130] The results of pharmacological tests and Preparation Examples will be shown

below, and these are intended to provide a better understanding of the present invention and not to limit the scope of the present invention.

[0131] [Test 1]

5 Using normal male white rabbits, a time-dependent change in tear volume after instillation of the present composition was evaluated.

[0132] (Method for preparing sample)

Ophthalmic solution 1:

Ophthalmic solution 1 was prepared in accordance with the formulation table shown in Table 1. That is, diquafosol sodium (9 g), sodium hydrogen phosphate
10 hydrate (0.6 g), sodium edetate hydrate (0.03 g), and sodium chloride (1.35 g) were dissolved in sterile purified water to make the volume of the solution 50 mL to give a 6-fold concentrated solution. 10 mL of the 6-fold concentrated solution and 5 mL of sterile purified water were mixed, a pH adjuster was then appropriately added to adjust the pH to 7, and sterile purified water was added to make the volume 20 mL to give a
15 3-fold concentrated solution. PVP K90 (4 g) was dissolved in sterile purified water, the total amount was adjusted to 100 g, and the solution was then subjected to high-pressure steam sterilization (at 121°C for 20 minutes) to give a 4.00% (w/w) PVP K90 solution. 4 mL of the 3-fold concentrated solution was added to 6.0 g of the 4.00% (w/w) PVP K90 solution, sterile purified water was added to adjust the total volume to
20 12 mL, and a pH adjuster was then appropriately added to adjust the pH to 7, thereby preparing Ophthalmic solution 1.

[0133] Ophthalmic solution 2:

Ophthalmic solution 2 was prepared in accordance with the formulation table shown in Table 1. That is, diquafosol sodium (9 g), sodium hydrogen phosphate
25 hydrate (0.6 g), sodium edetate hydrate (0.03 g), and sodium chloride (1.35 g) were dissolved in sterile purified water to make the volume of the solution 50 mL to give a 6-fold concentrated solution. 10 mL of the 6-fold concentrated solution and 5 mL of sterile purified water were mixed, PVP K30 (1.2 g) was then dissolved, a pH adjuster was then appropriately added to adjust the pH to 7, and sterile purified water was added

to make the volume 20 mL to give a 3-fold concentrated solution. To 4 mL of the 3-fold concentrated solution, sterile purified water was added to adjust the total volume to 12 mL, and a pH adjuster was then appropriately added to adjust the pH to 7, thereby preparing Ophthalmic solution 2.

5 [0134] Ophthalmic solution 3:

Ophthalmic solution 3 was prepared in accordance with the formulation table shown in Table 1. That is, diquafosol sodium (9 g), sodium hydrogen phosphate hydrate (0.6 g), sodium edetate hydrate (0.03 g), and sodium chloride (1.35 g) were dissolved in sterile purified water to make the volume of the solution 50 mL to give a
10 6-fold concentrated solution. 10 mL of the 6-fold concentrated solution and 5 mL of sterile purified water were mixed, a pH adjuster was then appropriately added to adjust the pH to 7, and sterile purified water was added to make the volume 20 mL to give a 3-fold concentrated solution. Hydroxyethyl cellulose (15 g) was dissolved in 1500
15 mL of sterile purified water, and the solution was subjected to high-pressure steam sterilization (at 121°C for 20 minutes) to give a 1.00% (w/w) hydroxyethyl cellulose solution. 4 mL of the 3-fold concentrated solution was added to 3.6 g of the 1.00% (w/w) hydroxyethyl cellulose solution, and sterile purified water was added to adjust the total volume to 12 mL. A pH adjuster was then appropriately added to adjust the pH to 7, thereby preparing Ophthalmic solution 3.

20 [0135] Ophthalmic solution 4:

Ophthalmic solution 4 was prepared in accordance with the formulation table shown in Table 1. That is, diquafosol sodium (9 g), sodium hydrogen phosphate hydrate (0.6 g), sodium edetate hydrate (0.03 g), and sodium chloride (1.35 g) were dissolved in sterile purified water to make the volume of the solution 50 mL to give a
25 6-fold concentrated solution. 10 mL of the 6-fold concentrated solution and 5 mL of sterile purified water were mixed, a pH adjuster was then appropriately added to adjust the pH to 7, and sterile purified water was added to make the volume 20 mL to give a 3-fold concentrated solution. To 4 mL of the 3-fold concentrated solution, sterile purified water was added to adjust the total volume to 12 mL, and a pH adjuster was

then appropriately added to adjust the pH to 7, thereby preparing Ophthalmic solution 4.

[0136] Ophthalmic solution 5:

Ophthalmic solution 5 was prepared in accordance with the formulation table shown in Table 1. That is, diquafosol sodium (18 g), sodium hydrogen phosphate hydrate (1.2 g), and sodium edetate hydrate (0.06 g) were dissolved in sterile purified water to make the volume of the solution 100 mL to give a 6-fold concentrated solution. 2.5 mL of 6-fold concentrated solution and 5 mL of sterile purified water were mixed, a PVP K60 45% aqueous solution (0.67 g) and sodium chloride (0.068 g) were then dissolved, a pH adjuster was then appropriately added to adjust the pH to 7, and sterile purified water was added to make the volume 15 mL to prepare Ophthalmic solution 5.

[0137] The viscosity of Ophthalmic solutions 1 to 5 prepared was measured in accordance with the method described in 2.53 Viscosity Determination, Method II Viscosity measurement by rotational viscometer, 2.1.3. Cone-flat plate-type rotational viscometer (Cone-plate type viscometer) in The Japanese Pharmacopoeia, 17th Edition. Specifically, Kinexuspro+ (manufactured by Malvern Panalytical) was used, and the measurement conditions were set as follows. (Measurement conditions)

Rotor angle: 1°

Rotor diameter: 50 mm

Amount of sample: 0.57 mL

Measurement temperature: 25°C

Shear rate: 50 s⁻¹

Measurement time: the viscosity was measured every 2 seconds, and the average value during 1 minute was taken as the viscosity.

[0138] (Test method and method for administering drug)

Benoxil (registered trademark) Ophthalmic Solution 0.4% (manufactured by Santen Pharmaceutical Co., Ltd.) was instilled into the eye to normal male white rabbits (total 16 rabbits with 32 eyes), and topical anesthesia was applied. After three

minutes, a Schirmer test strip (manufactured by AYUMI Pharmaceutical Corporation) was inserted into the lower eyelid. One minute after the insertion, the test strip was extracted, and the length of a wet portion (tear volume) was read. This value was defined as a pre-instillation value. Subsequently, Ophthalmic solutions 1 to 5 were each instilled into the eye once (4 rabbits with 8 eyes per group with the exception of Ophthalmic solution 4 instilled to 12 rabbits with 24 eyes). Three minutes before a Schirmer test strip (manufactured by AYUMI Pharmaceutical Corporation) was inserted into the lower eyelid, Benoxil (registered trademark) Ophthalmic Solution 0.4% (manufactured by Santen Pharmaceutical Co., Ltd.) was instilled into an eye, and topical anesthesia was applied. 60 minutes after the instillation of the ophthalmic solutions, a Schirmer test strip (manufactured by AYUMI Pharmaceutical Corporation) was inserted into the lower eyelid. One minute after the insertion, the test strip was extracted, and the length of a wet portion (tear volume) was read.

[0139] (Evaluation method)

15 A change between tear volume before and tear volume after instillation of the ophthalmic solution was calculated as Δ tear volume (mm/minute).

[0140] (Test results)

20 Tables 1 and 2 shows Δ tear volume (mm/minute) 60 minutes after instillation (each value is an average value for 8 eyes with the exception of Ophthalmic solution 4 for which average values for 24 eyes are shown). The tear volume increasing action of the present composition was evaluated in accordance with the following criteria.

+++ : Δ tear volume (mm/minute) 60 minutes after instillation is 4 mm/minute or more.

++ : Δ tear volume (mm/minute) 60 minutes after instillation is 1 mm/minute or more and less than 4 mm/minute.

25 + : Δ tear volume (mm/minute) 60 minutes after instillation is more than 0 mm/minute and less than 1 mm/minute.

- : Δ tear volume (mm/minute) 60 minutes after instillation is 0 mm/minute or less.

[0141] [Table 1]

(unit: g/100 mL in Table 1)

Ophthalmic solution	1	2	3	4
Diquafosol sodium	3	3	3	3
PVP K30	-	2	-	-
PVP K90	2	-	-	-
HEC	-	-	0.3	-
Sodium hydrogen phosphate hydrate	0.2	0.2	0.2	0.2
Sodium edetate hydrate	0.01	0.01	0.01	0.01
Sodium chloride	0.45	0.45	0.45	0.45
pH Adjuster	q.s.	q.s.	q.s.	q.s.
pH	7.0	7.0	7.0	7.0
Viscosity (mPa·s)	7.4	1.4	26.9	1.0
Δ tear volume 60 minutes after instillation (mm/minute)	4.4	0.4	-0.6	0.3
Evaluation	+++	+	-	+

[0142] As shown in the results of the above Table 1, with the ophthalmic solution containing PVP K30 (Ophthalmic solution 2), no tear volume increasing action 60 minutes after instillation was observed, similarly to the ophthalmic solution not containing PVP K30 (Ophthalmic solution 4). Although HEC is generally used as a thickening agent, with the ophthalmic solution containing HEC (Ophthalmic solution 3), in spite of having a relatively high viscosity, no tear volume increasing action 60 minutes after instillation was observed, similarly to Ophthalmic solution 4. On the other hand, the ophthalmic solution containing PVP K90 (Ophthalmic solution 1) exhibited an extremely higher tear volume increasing action than that of Ophthalmic solutions 2 to 4.

[0143] [Table 2]

(unit: g/100 mL in Table 2)

Ophthalmic solution	5
Diquafosol sodium	3
PVP K60	2
Sodium hydrogen phosphate hydrate	0.2
Sodium edetate hydrate	0.01
Sodium chloride	0.45
pH Adjuster	q.s.
pH	7.0
Viscosity (mPa·s)	3.0

Δtear volume 60 minutes after instillation (mm/minute)	4.4
Evaluation	+++

[0144] As shown in the results of the above Table 2, the ophthalmic solution containing PVP (Ophthalmic solution 5) had a tear volume increasing action even though the K value of PVP was 60.

5 [0145] (Discussions)

Polyvinylpyrrolidone increased the viscosity of the aqueous compositions containing diquafosol or a salt thereof and allowed the drug efficacy of the diquafosol or a salt thereof to be enhanced. Particularly when polyvinylpyrrolidone having a K value of more than 30 was added or when addition of polyvinylpyrrolidone caused the aqueous composition to have a viscosity of more than 1.4, it was shown that the drug efficacy of the diquafosol or salt thereof was markedly enhanced.

[0146] [Test 2]

A rat exorbital lacrimal gland excision model has been generally used as a model for evaluating therapeutic effects on corneal epithelial disorders induced by dry eye, and has also been used as a model for evaluating therapeutic effects of P2Y₂ receptor agonists (Invest. Ophthalmol. Vis. Sci., 42(1), 96-100 (2001)). Using the dry eye model, it was examined whether or not an improvement effect on corneal epithelial disorders could be achieved by instillation of the present composition into the eye.

[0147] (Method for producing dry eye model)

Using a male SD rat, a rat exorbital lacrimal gland excision model was produced in accordance with the method by Fujihara et al. (Invest. Ophthalmol. Vis. Sci., 42(1), 96-100 (2001)). That is, somnopentyl was administered to the rat to give general anesthesia, an exorbital lacrimal gland was excised from the rat, and a corneal epithelial disorder was induced in the rat.

25 [0148] (Method for preparing sample)

Ophthalmic solution A:

Sodium hydrogen phosphate hydrate (0.2 g), sodium edetate hydrate (0.01 g),

sodium chloride (0.45 g), silver nitrate (0.00004 g), polyvinylpyrrolidone K90 (2 g), and diquafosol sodium (3 g) were dissolved in sterile purified water to make the volume of the solution 100 mL, and a pH adjuster (q.s.) was added to adjust the pH to 7.5.

5 [0149] Ophthalmic solution B:

Sodium hydrogen phosphate hydrate (0.2 g), sodium edetate hydrate (0.01 g), sodium chloride (0.45 g), silver nitrate (0.00004 g), and polyvinylpyrrolidone K90 (4 g) were dissolved in sterile purified water to make the volume of the solution 100 mL, and a pH adjuster (q.s.) was added to adjust the pH to 7.5.

10 [0150] Ophthalmic solution X:

As an ophthalmic solution X, "Diquas (registered trademark) Ophthalmic Solution 3%" (manufactured by Santen Pharmaceutical Co., Ltd.) used as a therapeutic agent for dry eye was used. Ophthalmic solution X contains 30 mg of diquafosol sodium as an active ingredient and potassium chloride, sodium chloride, a
15 chlorhexidine gluconate solution, sodium hydrogenphosphate hydrate, sodium edetate hydrate, and a pH adjuster as additives in 1 mL of water.

[0151] The viscosity of Ophthalmic solutions A, B, and X prepared was measured in accordance with the method described in 2.53 Viscosity Determination, Method II Viscosity measurement by rotational viscometer, 2.1.3. Cone-flat plate-type rotational
20 viscometer (Cone-plate type viscometer) in The Japanese Pharmacopoeia, 17th Edition. Specifically, Kinexuspro+ (manufactured by Malvern Panalytical) was used, and the measurement conditions were set as follows.

(Measurement conditions)

Rotor angle: 1°

25 Rotor diameter: 50 mm

Amount of sample: 0.57 mL

Measurement temperature: 25°C

Shear rate: 50 s⁻¹

Measurement time: the viscosity was measured every 2 seconds, and the average value

during 1 minute was taken as the viscosity.

[0152] The measurement results of each ophthalmic solution were as follows.

Ophthalmic solution A: 7.9 mPa·s

Ophthalmic solution B: 28.0 mPa·s

5 Ophthalmic solution X: 0.9 mPa·s

(Test method and method for administering drug)

To the rats for which a corneal epithelial disorder was induced, Ophthalmic solution A, Ophthalmic solution B, and Ophthalmic solution X were administered in the following manner.

10 • Group to which Ophthalmic solution A was administered 3 times a day: Ophthalmic solution A was instilled into both eyes 3 times a day for 4 weeks (12 eyes of 6 rats per group).

• Group to which Ophthalmic solution B was administered 3 times a day: Ophthalmic solution B was instilled into both eyes 3 times a day for 4 weeks (12 eyes of 6 rats per group).

15 • Group to which Ophthalmic solution X was administered 6 times a day: Ophthalmic solution X was instilled into both eyes 6 times a day for 4 weeks (12 eyes of 6 rats per group).

20 Among the rats for which a corneal epithelial disorder was not induced, those rats to which no drug was administered for 4 weeks were defined as a non-administered group (8 eyes of 4 rats per group).

[0153] Four weeks after the initiation of the instillation into the eyes, an affected part of the cornea was stained with fluorescein, and the occurrence of the corneal epithelial disorder was determined in accordance with the method by Murakami et al. (Journal of the Eye (Atarashii Ganka), 21(1), 87-90 (2004)). That is, with respect to each of an upper part, an intermediate part, and a lower part of the cornea, scores of the degree of staining with fluorescein were determined in accordance with the criteria mentioned below, and the average value of the sum total of the scores was calculated. In each of the scores 0, 1, 2 and 3, an intermediate value 0.5 was set.

[0154] (Determination criteria)

0: not stained

1: sparsely stained, wherein dot-shaped stained parts were distanced from each other

5 2: the degree of staining was moderate, wherein some of dot-shaped stained parts were adjacent to each other

3: densely stained, wherein dot-shaped stained parts were adjacent to one another

[0155] (Results)

10 A graph of calculated fluorescein staining scores for each group is shown in FIG. 1. Each of the scores is an average value + a standard error for 8 or 12 samples.

[0156] As apparent from FIG. 1, in the group to which Ophthalmic solution A was administered 3 times a day, improvement in fluorescein staining scores was observed 2 weeks after the initiation of the instillation into the eyes, in comparison with

15 administration of Ophthalmic solution B 3 times a day. In the group to which Ophthalmic solution X was administered 6 times a day, improvement in fluorescein staining scores was observed 4 weeks after the initiation of the instillation into the eyes, in comparison with administration of Ophthalmic solution B 3 times a day. The group to which Ophthalmic solution A was administered 3 times a day and the group to which
20 Ophthalmic solution X was administered 6 times a day exhibited comparable effects 4 weeks after the instillation into the eyes.

[0157] (Discussions)

25 Ophthalmic solution X is used for treatment of dry eye as "Diquas (registered trademark) Ophthalmic Solution 3%", and the instillation frequency thereof is 6 times a day. It became apparent that instillation of the present composition including polyvinylpyrrolidone K90 added into the eyes 3 times a day has a sufficient therapeutic effect. Particularly, 2 weeks after the initiation of the instillation into the eyes, a therapeutic effect exceeding that of instillation of "Diquas (registered trademark) Ophthalmic Solution 3%" into the eyes 6 times a day was observed. Accordingly, it

was shown that the present composition exhibits a potent therapeutic effect equivalent to or more than that of the existing Diquas (registered trademark) Ophthalmic Solution with a lower instillation frequency than that of the existing Diquas (registered trademark) Ophthalmic Solution. Particularly, in consideration of the test results of

5 Test 1, it was suggested that the instillation of the present composition including polyvinylpyrrolidone having a K value of more than 30 added or the present composition of which the viscosity became more than 1.4 due to addition of polyvinylpyrrolidone into the eyes 2 to 4 times a day exhibits a potent therapeutic effect equivalent to or more than that of the instillation of the existing "Diquas
10 (registered trademark) Ophthalmic Solution 3%" into the eyes 6 times a day.

[0158] [Test 3]

In order to examine effects of the present composition on corneal epithelial cells, a test for cytotoxicity on corneal epithelial cells was conducted.

[0159] (Method for preparing sample)

15 Ophthalmic solutions Y, C, and D were prepared in accordance with the formulation shown in Table 3.

[0160] Ophthalmic solution Y:

An ophthalmic solution of Ophthalmic solution Y was prepared in accordance with the formulation shown in Table 3. Specifically, sodium hydrogen phosphate
20 hydrate (0.2 g), sodium edetate hydrate (0.01 g), sodium chloride (0.45 g), silver nitrate (0.00004 g), and diquafosol sodium (3 g) were dissolved in sterile purified water to make the volume of the solution 100 mL, and a pH adjuster (q.s.) was added to adjust the pH to 7.5.

[0161] Ophthalmic solutions C and D:

25 Ophthalmic solutions of each of Ophthalmic solutions C and D were prepared in the same manner as for Ophthalmic solution Y, in accordance with the formulation shown in Table 3.

[0162] The viscosity of Ophthalmic solutions Y, C, and D prepared was measured in accordance with the method described in 2.53 Viscosity Determination, Method II

Viscosity measurement by rotational viscometer, 2.1.3. Cone-flat plate-type rotational viscometer (Cone-plate type viscometer) in The Japanese Pharmacopoeia, 17th Edition. Specifically, Kinexus pro+ (manufactured by Malvern Panalytical) was used, and the measurement conditions were set as follows.

5 (Measurement conditions)

Rotor angle: 1°

Rotor diameter: 50 mm

Amount of sample: 0.57 mL

Measurement temperature: 25°C

10 Shear rate: 50 s⁻¹

Measurement time: the viscosity was measured every 2 seconds, and the average value during 1 minute was taken as the viscosity.

[0163] [Table 3]

(unit: g/100 mL in Table 3)

Ophthalmic solution	Y	C	D
Diquafosol sodium	3	3	3
PVP K90	-	2	4
Sodium hydrogen phosphate hydrate	0.2	0.2	0.2
Sodium edetate hydrate	0.01	0.01	0.01
Silver nitrate	0.00004	0.00004	0.00004
Sodium chloride	0.45	0.45	0.45
pH Adjuster	q.s.	q.s.	q.s.
pH	7.5	7.5	7.5
Viscosity (mPa·s)	1.0	8.1	27.2

15

[0164] (Test method)

SV40 immortalized human corneal epithelial cells (HCE-T: RIKEN

BioResource Research Center, Cell No.: RCB2280) were plated in a 96-well plate (1 × 10⁴ cells/well) and cultured in a 10% FBS-containing D-MEM/F12 medium for one day. On the following day, the medium was replaced by Ophthalmic solution Y, Ophthalmic solution C, or Ophthalmic solution D, and then the corneal epithelial cells were cultured for 5, 10, and 15 minutes. Using Cell Proliferation Assay Kit

20

(manufactured by Promega Corporation, Catalog No.: G3580), the cell viability (corresponding to the absorbance at 490 nm) was measured.

[0165] (Results)

The test results are shown in FIG. 2.

5 [0166] As apparent from FIG. 2, the diquafosol ophthalmic solutions caused to contain polyvinylpyrrolidone (Ophthalmic solutions C and D) maintained a high viability in the immortalized human corneal epithelial cells even 15 minutes after the culture. On the other hand, with the diquafosol ophthalmic solution not containing polyvinylpyrrolidone (Ophthalmic solution Y), the viability decreased over time.

10 [0167] (Discussions)

The diquafosol ophthalmic solutions caused to contain polyvinylpyrrolidone exhibit a high cell viability in the cultured immortalized human corneal epithelial cells, and thus have higher safety to the keratoconjunctival epithelium and are useful for use in diseases such as dry eye in which the keratoconjunctival epithelium is unstable.

15 [0168] [Test 4]

The stimulatory property of diquafosol sodium to peripheral nerves in the presence of PVP was examined.

[0169] (Method for preparing sample)

Formulation Solution 1:

20 Formulation solution 1 was prepared in accordance with the formulation table shown in Table 4. That is, sodium chloride (8.5 g) and sodium hydrogen phosphate hydrate (2 g) were dissolved in sterile purified water, a pH adjuster was added to adjust the pH to 7.5, and the total volume was then adjusted to 100 mL to give a 10-fold buffer solution. PVP K30 (16 g) was dissolved in sterile purified water, and the total
25 volume was adjusted to 200 mL to give an 8% PVP K30 aqueous solution. 2 mL of the 10-fold buffer solution and 5 mL of the 8% PVP K30 aqueous solution were weighed and taken, the total volume was adjusted to 20 mL with sterile purified water, and the pH was adjusted to 7.5 with a pH adjuster to give Formulation solution 1.

[0170] Formulation Solution 2:

Formulation solution 2 was prepared in accordance with the formulation table shown in Table 4. That is, sodium chloride (8.5 g) and sodium hydrogen phosphate hydrate (2 g) were dissolved in sterile purified water, a pH adjuster was added to adjust the pH to 7.5, and the total volume was then adjusted to 100 mL to give a 10-fold buffer solution. 2 mL of the 10-fold buffer solution and PVP K90 (0.4 g) were dissolved in sterile purified water, the PH was adjusted to 7.5 with a pH adjuster, and the total volume was adjusted to 20 mL to give Formulation solution 2.

[0171] Formulation Solution 3:

Formulation solution 3 was prepared in accordance with the formulation table shown in Table 4. That is, sodium chloride (8.5 g) and sodium hydrogen phosphate hydrate (2 g) were dissolved in sterile purified water, a pH adjuster was added to adjust the pH to 7.5, and the total volume was then adjusted to 100 mL to give a 10-fold buffer solution. 2 mL of the 10-fold buffer solution and sodium chondroitin sulfate (0.06 g) were added to sterile purified water, and the PH was adjusted to 7.5 with a pH adjuster. After making sure that the solid component was dissolved, the total volume was adjusted to 20 mL to give Formulation solution 3.

[0172] Formulation Solutions 4 to 6

Similarly to Formulation solution 3, each of Formulation solutions 4 to 6 was prepared in accordance with the formulation table shown in Table 4.

[0173] [Table 4]

(unit: g/100 mL in Table 4)

Formulation solution	1	2	3	4	5	6
Sodium chloride	0.85	0.85	0.85	0.85	0.80	0.85
Sodium hydrogen phosphate hydrate	0.20	0.20	0.20	0.20	0.20	0.20
PVP K30	2.00	-	-	-	-	-
PVP K90	-	2.00	-	-	-	-
Sodium chondroitin sulfate	-	-	0.30	-	-	-
HPMC	-	-	-	0.30	-	-
CVP	-	-	-	-	0.30	-
CMC-Na	-	-	-	-	-	0.30
pH Adjuster	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

pH	7.5	7.5	7.5	7.5	7.5	7.5
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[0174] (Test method)

Cultured peripheral nerve cells (dorsal neuro ganglion neuron; purchased from Lonza Japan Ltd.) were incubated in a buffer solution containing an intracellular
5 calcium indicator fluorescent dye (FLIPR Calcium 6 Assay Kit; Molecular Devices, LLC). 40% of the total volume of the buffer solution was replaced by each of the above-described formulation solutions. A non-stimulation group and a stimulation control group were similarly treated with the buffer solution instead of the formulation solution. The cells were left standing at room temperature, followed by starting
10 fluorescence measurement over time with the calcium indicator dye using a fluorescence plate reader. 60 seconds after the start of the measurement, diquafosol sodium (final concentration: 0.3%) was added, and the measurement of fluorescence intensity was continued.

[0175] (Evaluation method)

15 The maximum fluorescence intensity (RFU_{max}) after addition of diquafosol sodium was calculated as a relative value against the fluorescence intensity (RFU) immediately before the addition which was defined as 100%.

[0176] (Test results)

20 The results are shown in FIG. 3. For the stimulation control group and each of the groups treated with Formulation solutions 3 to 6, RFU increased after addition of diquafosol sodium, and an RFU_{max} of 103.5% or more was recorded. On the other hand, in each of the groups treated with Formulation solutions 1 and 2 containing PVP, the RFU_{max} was less than 101%.

[0177] (Discussions)

25 Peripheral nerve cells receiving some stimulation generate an action potential to fall into an excited state, and thereafter a stimulation signal converted into the action potential is transmitted to the central nerve system. The action potential is a cell membrane potential change caused by penetration of cations including calcium ions

into cells. Thus, an increase in concentration of calcium ions in nerve cells is widely used experimentally as an indicator of an excited state of nerve cells. When peripheral nerve cells were exposed to diquafosol sodium, an increase in the fluorescence intensity of intracellular calcium ions was quickly observed, and it was shown that the nerve cells received diquafosol sodium as a stimulation to fall into an excited state. In each of the groups of polymer formulation solutions 3 to 6 containing no PVP, which were Comparative Examples, there was a similar stimulation response, and thus the polymers, i.e. sodium chondroitin sulfate, HPMC, CVP, and CMC-Na, each had no effect on the neurostimulatory property of diquafosol sodium. On the other hand, under Formulation solutions 1 and 2 containing PVP, there was no increase in calcium ion signals in nerve cells after addition of diquafosol sodium. That is, diquafosol sodium has no neurostimulatory property in the presence of PVP, and thus addition of PVP improves the pouring touch of diquafosol sodium.

[0178] [Test 5]

Effects of the present composition on the stability of the preservative were examined.

[0179] (Method for preparing sample)

Ophthalmic solution 6:

Ophthalmic solution 6 was prepared in accordance with the formulation shown in Table 5. Specifically, diquafosol sodium (3 g), chlorhexidine gluconate (0.0025 g), hydroxyethyl cellulose (0.2 g), sodium hydrogen phosphate hydrate (0.2 g), sodium edetate hydrate (0.01 g), and sodium chloride (0.45 g) were dissolved in water make the volume of the solution 100 mL, and a pH adjuster (q.s.) was added to adjust the pH to 7.5.

[0180] Ophthalmic solutions 7 to 10:

Similarly to Ophthalmic solution 6, Ophthalmic solutions 7 to 10 were prepared in accordance with the formulations shown in Table 5.

[0181] [Table 5]

(unit: g/100 mL in Table 5)

Ophthalmic solution	6	7	8	9	10
Diquafosol sodium	3	3	3	3	3
Chlorhexidine gluconate (preservative)	0.0025	0.0025	0.0025	0.0025	-
Silver nitrate (preservative)	-	-	-	-	0.00008
PVP K30	-	2	-	-	2
PVP K90	-	-	2	4	-
HEC	0.2	0.2	-	-	0.25
Sodium hydrogen phosphate hydrate	0.2	0.2	0.2	0.2	0.2
Sodium edetate hydrate	0.01	0.01	0.01	0.01	0.01
Sodium chloride	0.45	0.45	0.45	0.45	0.45
Concentrated glycerin	-	-	1.2	1.2	-
pH Adjuster	q.s.	q.s.	q.s.	q.s.	q.s.
pH	7.5	7.5	7.5	7.5	7.5

[0182] (Test method)

After Ophthalmic solutions 6 and 7 each were preserved at 60°C after 4 weeks, the content of chlorhexidine gluconate was determined using high-performance liquid chromatography (HPLC), and the residual ratio (%) thereof was calculated. After Ophthalmic solutions 8 and 9 each were preserved at 60°C for 2 weeks, the content of chlorhexidine gluconate was determined using high-performance liquid chromatography (HPLC), and the residual ratio (%) thereof was calculated. After Ophthalmic solution 10 was preserved at 60°C for 4 weeks, the content of silver nitrate was determined using high-frequency inductively coupled plasma atomic emission spectrometry (ICP-AES), and the residual ratio (%) thereof was calculated.

[0183] (Test results)

The results of the stability test are shown in Table 6.

[0184] [Table 6]

Ophthalmic solution	6	7	8	9	10
Residual ratio (%)	90.1	20.4	26.7	8.0	100

[0185] (Discussions)

When the aqueous ophthalmic composition containing diquafosol or a salt

thereof, and polyvinylpyrrolidone (the present composition) was caused to contain chlorhexidine gluconate as the preservative, the residual ratio remarkably decreased (Ophthalmic solutions 7 to 9). On the other hand, when the composition was caused to contain silver nitrate, which is a silver salt, as the preservative, the residual ratio was high (Ophthalmic solution 10). Those described above have shown that the present composition destabilizes chlorhexidine gluconate whereas stabilizing the silver salt. [0186] [Test 6]

The preservative effectiveness of the present composition containing a silver salt was examined.

[0187] (Method for preparing sample)

Ophthalmic solution 11:

Ophthalmic solution 11 was prepared in accordance with the formulation shown in Table 7. Specifically, diquafosol sodium (3 g), silver nitrate (0.00008 g), sodium hydrogen phosphate hydrate (0.2 g), sodium edetate hydrate (0.01 g), polyvinylpyrrolidone K30 (2 g), concentrated glycerin (1.2 g), and hydroxyethyl cellulose (0.25 g) were dissolved in sterile purified water to make the volume of the solution 100 mL, and a pH adjuster (q.s.) was added to adjust the pH to 7.5.

[0188] Ophthalmic solutions 12 to 15:

Similarly to Ophthalmic solution 11, each of ophthalmic solutions of Ophthalmic solutions 12 to 15 was prepared in accordance with the formulation shown in Table 7.

[0189] [Table 7]

(unit: g/100 mL in Table 7)

Ophthalmic solution	11	12	13	14	15
Diquafosol sodium	3	3	3	3	3
Silver nitrate	0.00008	0.00004	0.000016	0.000008	0.000004
Sodium hydrogen phosphate hydrate	0.2	0.2	0.2	0.2	0.2
Sodium edetate hydrate	0.01	0.01	0.01	0.01	0.01
PVP K30	2	2	2	2	2
Sodium chloride	-	0.45	0.45	0.45	0.45

Concentrated glycerin	1.2	-	-	-	-
HEC	0.25	0.25	0.25	0.25	0.25
pH Adjuster	q.s	q.s	q.s	q.s	q.s
pH	7.5	7.5	7.5	7.5	7.5

[0190] (Test method)

The preservative effectiveness test was conducted in compliance with the preservative effectiveness test method in The Japanese Pharmacopoeia, 17th Edition.

- 5 In the present test, *Escherichia Coli* (*E. coli*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Staphylococcus aureus* (*S. aureus*), *Candida albicans* (*C. albicans*), and *Aspergillus brasiliensis* (*A. brasiliensis*) were used as test microorganisms.

[0191] (Test results)

The test results are shown in FIG. 8.

- 10 [0192] [Table 8]

(unit: Log Reduction)

Ophthalmic solution		11	12	13	14	15
<i>E.coli</i>	Week 1	4.6	4.7	4.7	4.7	4.7
	Week 2	4.6	4.7	4.7	4.7	4.7
	Week 4	4.6	4.7	4.7	4.7	4.7
<i>P.aeruginosa</i>	Week 1	4.7	4.7	4.7	4.7	4.7
	Week 2	4.7	4.7	4.7	4.7	4.7
	Week 4	4.7	4.7	4.7	4.7	4.7
<i>S.aureus</i>	Week 1	4.7	4.6	3.1	2.3	1.8
	Week 2	4.7	4.6	4.6	4.6	4.6
	Week 4	4.7	4.6	4.6	4.6	4.6
<i>C.albicans</i>	Week 1	4.3	3.9	3.1	2.6	2.0
	Week 2	4.6	4.8	4.8	4.8	4.2
	Week 4	4.6	4.8	4.8	4.8	4.8
<i>A.brasiliensis</i>	Week 1	3.2	0.5	0.2	0.2	0.2
	Week 2	4.3	0.7	0.3	0.2	0.2
	Week 4	4.3	1.1	0.4	0.4	0.3
Determination		Pass	Pass	Pass	Pass	Pass

[0193] The test results in Table 8 indicate the extent of decrease in the number of

viable microorganisms in the test relative to the number of inoculated microorganisms, based on log reduction. For example, the log reduction "1" indicates that the number of viable microorganisms in the test has decreased to 10% relative to the number of inoculated microorganisms.

5 [0194] As indicated in Table 8, the present composition containing a silver salt was shown to pass the criterion of the preservative effectiveness test of the Japanese Pharmacopoeia.

[0195] (Discussions)

10 The above-described results have shown that the present composition containing a silver salt has excellent preservative effectiveness.

[0196] [Test 7]

Using normal male white rabbits, a time-dependent change in tear volume 90 minutes after instillation of the present composition was evaluated.

[0197] (Method for preparing sample)

15 Ophthalmic solution 16:

As Ophthalmic solution 16, sodium hydrogen phosphate hydrate (0.2 g), sodium edetate hydrate (0.01 g), sodium chloride (0.45 g), silver nitrate (0.00004 g), polyvinylpyrrolidone K90 (2 g), and diquafosol sodium (3 g) were dissolved in sterile purified water make the volume of the solution 100 mL, and a pH adjuster (q.s.) was added to adjust the pH to 7.5.

20 [0198] Ophthalmic solution 17:

As Ophthalmic solution 17, "Diquas (registered trademark) Ophthalmic Solution 3%" (manufactured by Santen Pharmaceutical Co., Ltd.) used as a therapeutic agent for dry eye was used. Ophthalmic solution 17 contains 30 mg of diquafosol sodium as an active ingredient and potassium chloride, sodium chloride, a chlorhexidine gluconate solution, sodium hydrogen phosphate hydrate, sodium edetate hydrate, and a pH adjuster as additives in 1 mL of water.

25 [0199] (Test method and method for administering drug)

Benoxil (registered trademark) Ophthalmic Solution 0.4% (manufactured by

Santen Pharmaceutical Co., Ltd.) was instilled into the eye to normal male white rabbits (total 12 rabbits with 24 eyes), and topical anesthesia was applied. After three minutes, a Schirmer test strip (manufactured by AYUMI Pharmaceutical Corporation) was inserted into the lower eyelid. One minute after the insertion, the test strip was extracted, and the length of a wet portion (tear volume) was read. This value was defined as a pre-instillation value. Subsequently, Ophthalmic solutions 16 and 17 were each instilled into the eye once (6 rabbits with 12 eyes per group). Three minutes before a Schirmer test strip (manufactured by AYUMI Pharmaceutical Corporation) was inserted into the lower eyelid, Benoxil (registered trademark) Ophthalmic Solution 0.4% (manufactured by Santen Pharmaceutical Co., Ltd.) was instilled into an eye, and topical anesthesia was applied. 90 minutes after the instillation of the ophthalmic solutions, a Schirmer test strip (manufactured by AYUMI Pharmaceutical Corporation) was inserted into the lower eyelid. One minute after the insertion, the test strip was extracted, and the length of a wet portion (tear volume) was read.

[0200] (Evaluation method)

A change between tear volume before and tear volume after instillation of the ophthalmic solution was calculated as Δ tear volume (mm/minute).

[0201] (Test results)

Table 9 shows Δ tear volume (mm/minute) 90 minutes after instillation (each value is an average value for 12 eyes). The tear volume increasing action of the present composition was evaluated in accordance with the following criteria.

+++ : Δ tear volume (mm/minute) 90 minutes after instillation is 4 mm/minute or more.

++ : Δ tear volume (mm/minute) 90 minutes after instillation is 1 mm/minute or more and less than 4 mm/minute.

± : Δ tear volume (mm/minute) 90 minutes after instillation is more than 0 mm/minute and less than 1 mm/minute.

- : Δ tear volume (mm/minute) 90 minutes after instillation is 0 mm/minute or less.

[0202] [Table 9]

Ophthalmic solution	16	17
Δ tear volume 90 minutes after instillation (mm/minute)	2.0	-0.3
Evaluation	++	-

[0203] As shown in the results of the above Table 9, the present composition exhibited a high tear volume increasing action even at 90 minutes after the instillation.

[0204] [Test 8]

- 5 The preservative effectiveness of the present composition containing a silver salt was examined.

[0205] (Method for preparing sample)

Ophthalmic solution 18:

- 10 Ophthalmic solution 18 was prepared in accordance with the formulation shown in Table 10. Specifically, diquafosol sodium (3 g), silver nitrate (0.00003 g), sodium hydrogen phosphate hydrate (0.2 g), sodium edetate hydrate (0.01 g), polyvinylpyrrolidone K90 (2 g), and sodium chloride (0.45 g) were dissolved in sterile purified water to make the volume of the solution 100 mL, and a pH adjuster (q.s.) was added to adjust the pH to 7.0.

- 15 [0206] Ophthalmic solution 19:

Similarly to Ophthalmic solution 18, Ophthalmic solution 19 was prepared in accordance with the formulation shown in Table 10.

[0207] [Table 10]

(unit: g/100 mL in Table 10)

Ophthalmic solution	18	19
Diquafosol sodium	3	3
Sodium edetate hydrate	0.01	-
Sodium hydrogen phosphate hydrate	0.2	0.2
PVP K90	2	2
Silver nitrate	0.00003	0.00003
Sodium chloride	0.45	0.45
pH Adjuster	q.s	q.s

pH	7.0	7.0
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[0208] (Test method)

The preservative effectiveness test was conducted in compliance with the preservative effectiveness test method in The Japanese Pharmacopoeia, 17th Edition.

- 5 In the present test, *Escherichia Coli* (*E. coli*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Staphylococcus aureus* (*S. aureus*), *Candida albicans* (*C. albicans*), and *Aspergillus brasiliensis* (*A. brasiliensis*) were used as test microorganisms.

[0209] (Test results)

The test results are shown in FIG. 11.

- 10 [0210] [Table 11]

(unit: Log Reduction)

Ophthalmic solution		18	19
E.coli	Week 1	4.1	4.1
	Week 2	4.1	4.1
	Week 4	4.1	4.1
P.aeruginosa	Week 1	3.2	4.4
	Week 2	4.4	4.4
	Week 4	4.4	4.4
S.aureus	Week 1	4.4	4.4
	Week 2	4.4	4.4
	Week 4	4.4	4.4
C.albicans	Week 1	4.2	4.2
	Week 2	4.2	4.2
	Week 4	4.2	4.2
A.brasiliensis	Week 1	0.4	0.4
	Week 2	0.3	0.3
	Week 4	0.6	0.8
Determination		Pass	Pass

[0211] The test results in Table 11 indicate the extent of decrease in the number of viable microorganisms in the test relative to the number of inoculated microorganisms, based on log reduction. For example, the log reduction "1" indicates that the number of viable microorganisms in the test has decreased to 10% relative to the number of inoculated microorganisms.

[0212] As indicated in Table 11, with or without EDTA, the present composition containing a silver salt was shown to pass the criterion of the preservative effectiveness test of the Japanese Pharmacopoeia.

[0213] (Discussions)

The above-described results have shown that the present composition containing a silver salt has excellent preservative effectiveness.

[0214] [Test 9]

The preservative effectiveness of the present composition containing a silver salt was examined.

[0215] (Method for preparing sample)

Ophthalmic solution 20:

Ophthalmic solution 20 was prepared in accordance with the formulation shown in Table 12. Specifically, diquafosol sodium (3 g), silver nitrate (0.00004 g), sodium hydrogen phosphate hydrate (0.2 g), sodium edetate hydrate (0.01 g), polyvinylpyrrolidone K90 (2 g), and sodium chloride (0.45 g) were dissolved in sterile purified water to make the volume of the solution 100 mL, and a pH adjuster (q.s.) was added to adjust the pH to 7.5.

[0216] Ophthalmic solutions 21 to 23:

Similarly to Ophthalmic solution 20, each of ophthalmic solutions of Ophthalmic solutions 21 to 23 was prepared in accordance with the formulation shown in Table 12.

[0217] [Table 12]

(unit: g/100 mL in Table 12)

Ophthalmic solution	20	21	22	23
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Diquafosol sodium	3	3	3	3
Sodium edetate hydrate	0.01	-	0.01	0.01
Sodium hydrogen phosphate hydrate	0.2	0.2	0.2	0.2
PVP K90	2	2	2	2
Silver nitrate	0.00004	0.00004	-	-
Silver phosphate	-	-	0.0000328	-
Silver chloride	-	-	-	0.0000337
Sodium chloride	0.45	0.45	0.45	0.45
pH Adjuster	q.s	q.s	q.s	q.s
pH	7.5	7.5	7.5	7.5

[0218] (Test method)

The preservative effectiveness test was conducted in compliance with the preservative effectiveness test method in The Japanese Pharmacopoeia, 17th Edition.

- 5 In the present test, *Escherichia Coli* (*E. coli*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Staphylococcus aureus* (*S. aureus*), *Candida albicans* (*C. albicans*), and *Aspergillus brasiliensis* (*A. brasiliensis*) were used as test microorganisms.

[0219] (Test results)

The test results are shown in FIG. 13.

10 [0220] [Table 13]

(unit: Log Reduction)

Ophthalmic solution		20	21	22	23
E.coli	Week 1	4.9	4.9	4.9	4.9
	Week 2	4.9	4.9	4.9	4.9
	Week 4	4.9	4.9	4.9	4.9
aeruginosa	Week 1	4.8	4.8	4.8	4.8
	Week 2	4.8	4.8	4.8	4.8
	Week 4	4.8	4.8	4.8	4.8
S.aureus	Week 1	4.8	4.8	4.8	4.8
	Week 2	4.8	4.8	4.8	4.8

	Week 4	4.8	4.8	4.8	4.8
C.albicans	Week 1	3.7	3.3	3.6	3.8
	Week 2	4.6	4.6	4.5	4.6
	Week 4	4.6	4.6	4.6	4.6
A.brasiliensis	Week 1	0.4	0.3	0.3	0.5
	Week 2	0.5	0.5	0.6	0.8
	Week 4	0.6	0.7	1.0	1.0
Determination		Pass	Pass	Pass	Pass

[0221] The test results in Table 13 indicate the extent of decrease in the number of viable microorganisms in the test relative to the number of inoculated microorganisms, based on log reduction. For example, the log reduction "1" indicates that the number of viable microorganisms in the test has decreased to 10% relative to the number of inoculated microorganisms.

[0222] As indicated in Table 13, with or without EDTA, the present composition containing a silver salt was shown to pass the criterion of the preservative effectiveness test of the Japanese Pharmacopoeia. The ophthalmic solutions containing silver phosphate or silver chloride as the silver salt, instead of silver nitrate were also shown to pass the criterion of the preservative effectiveness test of the Japanese Pharmacopoeia.

[0223] (Discussions)

The above-described results have shown that the present composition containing a silver salt has excellent preservative effectiveness.

[0224] [Test 10]

Effects of the present composition on the stability of the preservative were examined.

[0225] (Method for preparing sample)

Ophthalmic solution 24:

Diquafosol sodium (3 g), sodium edetate hydrate (0.01 g), sodium hydrogen phosphate hydrate (0.2 g), sodium chloride (0.45 g), polyvinylpyrrolidone K90(2 g),

and silver nitrate (0.00004 g) were dissolved in water to make the volume 100 mL, and a pH adjuster (q.s.) was added to adjust the pH to 7.5 to prepare Ophthalmic solution 24.

[0226] (Test method)

- 5 Six months after Ophthalmic solution 24 was preserved at 40°C, the content of silver nitrate was determined using high-frequency inductively coupled plasma atomic emission spectrometry (ICP-AES), and the residual ratio (%) thereof was calculated.

[0227] (Test results)

The results of the stability test are shown in Table 14.

- 10 [0228] [Table 14]

	Residual ratio (%)
6 month at 40°C	97.0

[0229] (Discussions)

- 15 When silver nitrate, which is a silver salt, was contained as the preservative, the residual ratio was high. From the description above, the silver salt was shown to be stable in the present composition.

[0230] [Preparation Examples]

The pharmaceutical agents of the present invention will be described in further detail by way of Preparation Examples, which should not be construed as limiting the present invention.

- 20 [0231] (Formulation Example 1: sterile aqueous ophthalmic solution (3% (w/v)) in 100 mL:

Diquafosol sodium: 3 g

Sodium hydrogen phosphate hydrate: 0.01 to 0.5 g

Sodium chloride: 0.01 to 1 g

- 25 Sodium edetate hydrate: 0.0001 to 0.1 g

Polyvinylpyrrolidone K90: 0.0001 to 10 g

pH adjuster: q.s.

The above ophthalmic solution can be prepared by adding diquafosol sodium and the other components to the sterile purified water and sufficiently stirring the mixture. An ophthalmic medicament product can be produced by filling 1 to 10 mL of the above ophthalmic solution into a multidose-type eye drop container or a PFMD container. Alternatively, an ophthalmic medicament product can be produced by filling 0.1 to 1 mL of the above ophthalmic solution into a unit dose-type eye drop container. The above ophthalmic solution can be preserved at room temperature. [0232] (Formulation Example 2: sterile aqueous ophthalmic solution (3% (w/v)) in 100 mL:

- 10 Diquafosol sodium: 3 g
- Sodium hydrogen phosphate hydrate: 0.01 to 0.5 g
- Sodium chloride: 0.01 to 1 g
- Sodium edetate hydrate: 0.0001 to 0.1 g
- Polyvinylpyrrolidone K60: 0.0001 to 10 g
- 15 pH adjuster: q.s.

The above ophthalmic solution can be prepared by adding diquafosol sodium and the other components to the sterile purified water and sufficiently stirring the mixture. An ophthalmic medicament product can be produced by filling 1 to 10 mL of the above ophthalmic solution into a multidose-type eye drop container or a PFMD container. Alternatively, an ophthalmic medicament product can be produced by filling 0.1 to 1 mL of the above ophthalmic solution into a unit dose-type eye drop container. The above ophthalmic solution can be preserved at room temperature. [0233] (Formulation Example 3: sterile aqueous ophthalmic solution (3% (w/v)) in 100 mL:

- 25 Diquafosol sodium: 3 g
- Sodium hydrogen phosphate hydrate: 0.01 to 0.5 g
- Sodium chloride: 0.01 to 1 g
- Sodium edetate hydrate: 0.0001 to 0.1 g
- Polyvinylpyrrolidone K40: 0.0001 to 10 g

pH adjuster: q.s.

The above ophthalmic solution can be prepared by adding diquafosol sodium and the other components to the sterile purified water and sufficiently stirring the mixture. An ophthalmic medicament product can be produced by filling 1 to 10 mL of the above ophthalmic solution into a multidose-type eye drop container or a PFMD container. Alternatively, an ophthalmic medicament product can be produced by filling 0.1 to 1 mL of the above ophthalmic solution into a unit dose-type eye drop container. The above ophthalmic solution can be preserved at room temperature.

[0234] (Formulation Example 4: sterile aqueous ophthalmic solution (3% (w/v))

in 100 mL:

Diquafosol sodium: 3 g

Sodium hydrogen phosphate hydrate: 0.01 to 0.5 g

Sodium chloride: 0.01 to 1 g

Sodium edetate hydrate: 0.0001 to 0.1 g

Polyvinylpyrrolidone K90: 0.0001 to 10 g

Silver nitrate: 0.00000001 to 1 g

pH adjuster: q.s.

The above ophthalmic solution can be prepared by adding diquafosol sodium and the other components to the sterile purified water and sufficiently stirring the mixture. An ophthalmic medicament product can be produced by filling 1 to 10 mL of the above ophthalmic solution into a multidose-type eye drop container. The above eye drop can be preserved at room temperature.

[0235] (Formulation Example 5: sterile aqueous ophthalmic solution (3% (w/v))

in 100 mL:

Diquafosol sodium: 3 g

Sodium hydrogen phosphate hydrate: 0.01 to 0.5 g

Sodium chloride: 0.01 to 1 g

Sodium edetate hydrate: 0.0001 to 0.1 g

Polyvinylpyrrolidone K60: 0.0001 to 10 g

Silver nitrate: 0.00000001 to 1 g

pH adjuster: q.s.

5 The above ophthalmic solution can be prepared by adding diquafosol sodium and the other components to the sterile purified water and sufficiently stirring the mixture. An ophthalmic medicament product can be produced by filling 1 to 10 mL of the above ophthalmic solution into a multidose-type eye drop container. The above ophthalmic solution can be preserved at room temperature.

[0236] (Formulation Example 6: sterile aqueous ophthalmic solution (3% (w/v)) in 100 mL:

10 Diquafosol sodium: 3 g

Sodium hydrogen phosphate hydrate: 0.01 to 0.5 g

Sodium chloride: 0.01 to 1 g

Sodium edetate hydrate: 0.0001 to 0.1 g

Polyvinylpyrrolidone K40: 0.0001 to 10 g

15 Silver nitrate: 0.00000001 to 1 g

pH adjuster: q.s.

20 The above ophthalmic solution can be prepared by adding diquafosol sodium and the other components to the sterile purified water and sufficiently stirring the mixture. An ophthalmic medicament product can be produced by filling 1 to 10 mL of the above ophthalmic solution into a multidose-type eye drop container. The above ophthalmic solution can be preserved at room temperature.

[0237] (Formulation Example 7: sterile aqueous ophthalmic solution (3% (w/v)) in 100 mL:

Diquafosol sodium: 3 g

25 Sodium hydrogen phosphate hydrate: 0.01 to 0.5 g

Sodium chloride: 0.01 to 1 g

Polyvinylpyrrolidone K90: 0.0001 to 10 g

pH adjuster: q.s.

The above eye drop can be prepared by adding diquafosol sodium and the other

components to a sterile purified water and sufficiently stirring the mixture. An ophthalmic medicament product can be produced by filling 1 to 10 mL of the above ophthalmic solution into a multidose-type eye drop container or a PFMD container. Alternatively, an ophthalmic medicament product can be produced by filling 0.1 to 1 mL of the above ophthalmic solution into a unit dose-type eye drop container. The above eye drop can be preserved at room temperature.

5

[0238] (Formulation Example 8: sterile aqueous ophthalmic solution (3% (w/v)) in 100 mL:

Diquafosol sodium: 3 g

10

Sodium hydrogen phosphate hydrate: 0.01 to 0.5 g

Sodium chloride: 0.01 to 1 g

Polyvinylpyrrolidone K60: 0.0001 to 10 g

pH adjuster: q.s.

15

The above ophthalmic solution can be prepared by adding diquafosol sodium and the other components to the sterile purified water and sufficiently stirring the mixture. An ophthalmic medicament product can be produced by filling 1 to 10 mL of the above ophthalmic solution into a multidose-type eye drop container or a PFMD container. Alternatively, an ophthalmic medicament product can be produced by filling 0.1 to 1 mL of the above ophthalmic solution into a unit dose-type eye drop container. The above eye drop can be preserved at room temperature.

20

[0239] (Formulation Example 9: sterile aqueous ophthalmic solution (3% (w/v)) in 100 mL:

Diquafosol sodium: 3 g

Sodium hydrogen phosphate hydrate: 0.01 to 0.5 g

25

Sodium chloride: 0.01 to 1 g

Polyvinylpyrrolidone K40: 0.0001 to 10 g

pH adjuster: q.s.

The above ophthalmic solution can be prepared by adding diquafosol sodium and the other components to the sterile purified water and sufficiently stirring the

mixture. An ophthalmic medicament product can be produced by filling 1 to 10 mL of the above ophthalmic solution into a multidose-type eye drop container or a PFMD container. Alternatively, an ophthalmic medicament product can be produced by filling 0.1 to 1 mL of the above ophthalmic solution into a unit dose-type eye drop container. The above eye drop can be preserved at room temperature.

5

[0240] (Formulation Example 10: sterile aqueous ophthalmic solution (3% (w/v)) in 100 mL:

Diquafosol sodium: 3 g

Sodium hydrogen phosphate hydrate: 0.01 to 0.5 g

10

Sodium chloride: 0.01 to 1 g

Polyvinylpyrrolidone K90: 0.0001 to 10 g

Silver nitrate: 0.00000001 to 1 g

pH adjuster: q.s.

15

The above ophthalmic solution can be prepared by adding diquafosol sodium and the other components to the sterile purified water and sufficiently stirring the mixture. An ophthalmic medicament product can be produced by filling 1 to 10 mL of the above ophthalmic solution into a multidose-type eye drop container. The above eye drop can be preserved at room temperature.

[0241] (Formulation Example 11: sterile aqueous ophthalmic solution (3% (w/v)) in 100 mL:

20

Diquafosol sodium: 3 g

Sodium hydrogen phosphate hydrate: 0.01 to 0.5 g

Sodium chloride: 0.01 to 1 g

Polyvinylpyrrolidone K60: 0.0001 to 10 g

25

Silver nitrate: 0.00000001 to 1 g

pH adjuster: q.s.

The above ophthalmic solution can be prepared by adding diquafosol sodium and the other components to the sterile purified water and sufficiently stirring the mixture. An ophthalmic medicament product can be produced by filling 1 to 10 mL

of the above ophthalmic solution into a multidose-type eye drop container. The above eye drop can be preserved at room temperature.

[0242] (Formulation Example 12: sterile aqueous ophthalmic solution (3% (w/v)) in 100 mL:

- 5 Diquafosol sodium: 3 g
 Sodium hydrogen phosphate hydrate: 0.01 to 0.5 g
 Sodium chloride: 0.01 to 1 g
 Polyvinylpyrrolidone K40: 0.0001 to 10 g
 Silver nitrate: 0.00000001 to 1 g
10 pH adjuster: q.s.

The above ophthalmic solution can be prepared by adding diquafosol sodium and the other components to the sterile purified water and sufficiently stirring the mixture. An ophthalmic medicament product can be produced by filling 1 to 10 mL of the above ophthalmic solution into a multidose-type eye drop container. The above eye drop can be preserved at room temperature.

[0243] (Formulation Example 13: sterile aqueous ophthalmic solution (3% (w/v)) in 100 mL:

- Diquafosol sodium: 3 g
 Sodium hydrogen phosphate hydrate: 0.01 to 0.5 g
20 Sodium chloride: 0.01 to 1 g
 Citric acid hydrate: 0.0001 to 0.1 g
 Polyvinylpyrrolidone K90: 0.0001 to 10 g
 pH adjuster: q.s.

- The above ophthalmic solution can be prepared by adding diquafosol sodium
25 and the other components to the sterile purified water and sufficiently stirring the
 mixture. An ophthalmic medicament product can be produced by filling 1 to 10 mL
 of the above ophthalmic solution into a multidose-type eye drop container or a PFMD
 container. Alternatively, an ophthalmic medicament product can be produced by
 filling 0.1 to 1 mL of the above ophthalmic solution into a unit dose-type eye drop

container. The above eye drop can be preserved at room temperature.

[0244] (Formulation Example 14: sterile aqueous ophthalmic solution (3% (w/v)) in 100 mL:

Diquafosol sodium: 3 g

5 Sodium hydrogen phosphate hydrate: 0.01 to 0.5 g

Sodium chloride: 0.01 to 1 g

Citric acid hydrate: 0.0001 to 0.1 g

Polyvinylpyrrolidone K90: 0.0001 to 10 g

Silver nitrate: 0.00000001 to 1 g

10 pH adjuster: q.s.

The above ophthalmic solution can be prepared by adding diquafosol sodium and the other components to the sterile purified water and sufficiently stirring the mixture. An ophthalmic medicament product can be produced by filling 1 to 10 mL of the above ophthalmic solution into a multidose-type eye drop container. The above eye drop can be preserved at room temperature.

INDUSTRIAL APPLICABILITY

[0245] The existing Diquas (registered trademark) Ophthalmic Solution is required to be instilled into the eye 6 times a day, but a sufficient therapeutic effect cannot be obtained in some severe dry eye patients even when the Ophthalmic Solution is used in the predetermined dosage and administration. Moreover, an expected effect cannot be obtained in some patients due to poor adherence to instillation. The present composition exhibits a more potent therapeutic effect on dry eye than the existing Diquas (registered trademark) Ophthalmic Solution and additionally is expected to improve adherence to instillation due to reduced instillation frequency. The present composition is also expected to exhibit a potent therapeutic effect on dry eye equivalent to or more than that of the existing Diquas (registered trademark) Ophthalmic Solution with a lower concentration than that thereof.

[0246] It is also expected that the present composition exhibits a high cell viability and thus has high safety to the keratoconjunctival epithelium, and exhibits no

neurostimulatory property and thus may improve the pouring touch of an ophthalmic solution.

[0247] Additionally, even when the present composition is allowed to contain a silver salt, the silver salt is stable, and the present composition exhibits excellent preservative effectiveness.

5

CLAIMS

1. An aqueous ophthalmic composition for prevention or treatment of dry eye, comprising diquafosol sodium at a concentration of 1 to 5% (w/v) and
5 polyvinylpyrrolidone having a K value of more than 30 and 120 or less filled in a multidose-type eye drop container, wherein the amount of the aqueous ophthalmic composition to be filled is 1 to 10 mL.
2. The aqueous ophthalmic composition according to claim 1, further
10 comprising a silver salt.
3. The aqueous ophthalmic composition according to claim 2, wherein the silver salt comprises silver nitrate.
- 15 4. The aqueous ophthalmic composition according to claim 1, comprising diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone having a K value of more than 30 and 120 or less.
- 20 5. The aqueous ophthalmic composition according to claim 1, comprising diquafosol sodium at a concentration of 1 to 5% (w/v) and having a viscosity at 25°C of 1.5 to 30 mPa·s.
- 25 6. The aqueous ophthalmic composition according to claim 1, comprising diquafosol sodium at a concentration of 3% (w/v) and having a viscosity at 25°C of 1.5 to 30 mPa·s.
7. An ophthalmic medicament product for prevention or treatment of dry eye, comprising 1 to 10 mL of an aqueous ophthalmic composition comprising diquafosol sodium at a concentration of 1 to 5% (w/v) and polyvinylpyrrolidone having a K value

of more than 30 and 120 or less filled in a multidose-type eye drop container.

5 8. An ophthalmic medicament product for prevention or treatment of dry eye, comprising 5 mL of an aqueous ophthalmic composition comprising diquafosol sodium at a concentration of 1 to 5% (w/v) and polyvinylpyrrolidone having a K value of more than 30 and 120 or less filled in a multidose-type eye drop container.

10 9. An ophthalmic medicament product for prevention or treatment of dry eye, comprising 1 to 10 mL of an aqueous ophthalmic composition comprising diquafosol sodium at a concentration of 1 to 5% (w/v) and polyvinylpyrrolidone having a K value of more than 30 and 120 or less filled in a PFMD container.

15 10. An ophthalmic medicament product for prevention or treatment of dry eye, comprising 5 mL of an aqueous ophthalmic composition comprising diquafosol sodium at a concentration of 1 to 5% (w/v) and polyvinylpyrrolidone having a K value of more than 30 and 120 or less filled in a PFMD container.

20 11. The ophthalmic medicament product according to any one of claims 7 to 10, wherein the aqueous ophthalmic composition comprises diquafosol sodium at a concentration of 3% (w/v) and polyvinylpyrrolidone having a K value of more than 30 and 120 or less.

25 12. The ophthalmic medicament product according to any one of claims 7 to 10, wherein the aqueous composition comprises diquafosol sodium at a concentration of 1 to 5% (w/v) and has a viscosity at 25°C of 1.5 to 30 mPa·s.

 13. The ophthalmic medicament product according to any one of claims 7 to 10, wherein the aqueous composition comprises diquafosol sodium at a concentration of 3% (w/v) and has a viscosity at 25°C of 1.5 to 30 mPa·s.

14. The aqueous ophthalmic composition according to any one of claims 1 to 3, comprising polyvinylpyrrolidone having a K value of 90 or more.

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15. The aqueous ophthalmic composition according to any one of claims 1 to 6, wherein the concentration of the polyvinylpyrrolidone is 0.001% (w/v) or more.

16. The aqueous ophthalmic composition according to any one of claims 1 to 3, wherein the concentration of the diquafosol sodium is 3% (w/v).

10

17. The aqueous ophthalmic composition according to any one of claims 1 to 6, wherein the aqueous ophthalmic composition has a pH in the range of 6 to 8.

18. The aqueous ophthalmic composition according to any one of claims 1 to 6, wherein the aqueous ophthalmic composition has a pH in the range of 7 to 8.

15

19. The aqueous ophthalmic composition according to any one of claims 1 to 6, wherein the aqueous ophthalmic composition is a sterile aqueous ophthalmic solution.

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20. The aqueous ophthalmic composition according to any one of claims 1 to 6, wherein the aqueous ophthalmic composition is preservable at room temperature.

21. The aqueous ophthalmic composition according to any one of claims 1 to 4, wherein the aqueous ophthalmic composition has a viscosity at 25°C of 1.5 to 30 mPa·s.

25