OPHTHALMIC COMPOSITION

TECHNICAL FIELD

[0001]

The present invention relates to an ophthalmic composition and a method of reducing a temporal change in the kinetic viscosity of the ophthalmic composition and/or maintaining the antiseptic or preservative effect of the ophthalmic composition at a high level.

BACKGROUND ART

[0002]

Hyaluronic acid or a salt thereof is commonly known as a therapeutic agent for dry eye, and for example, widely used in eye drops in Japan. As eye drops, a multi-dose type, which is designed for using multiple times, and can be freely opened and closed with a cap, is widely used. In order to use multi-dose type eye drops for a long time, an antiseptic agent needs to be included therein.

[0003]

Conventionally, benzalkonium chloride is widely known as an ophthalmic antiseptic agent. Alternatively, use of chlorhexidine has been recently proposed (for example, Patent Document 1). Further, ethylenediaminetetraacetate is commonly included as a stabilizing agent for eye drops (for example, Patent Document 2).

[0004]

Patent Document 1: PCT International Publication No. WO2008/050776

Patent Document 2: Japanese Unexamined Patent Application, Publication No. 2003-327530

DISCLOSURE OF THE INVENTION

Problems to be Solved by the Invention

[0005]

Studies conducted by the present inventors, however, have revealed that an eye drop including hyaluronic acid or a salt thereof and chlorhexidine may suffer from a decreased kinetic viscosity of the eye drop over time.

[0006]

An object of the present invention is to maintain the retention percentage of the kinetic viscosity of an ophthalmic composition such as an eye drop containing hyaluronic acid or a salt thereof at a high level.

Means for Solving the Problems

[0007]

The present inventors found that the kinetic viscosity of an ophthalmic composition such as an eye drop containing hyaluronic acid or a salt thereof and chlorhexidine can be stably maintained for a long time when propylene glycol is added to the ophthalmic composition, and the blending concentration of ethylenediaminetetraacetate is 0.015% (w/v) or less. Then the present invention has been completed. Specifically, the present invention can provide the

followings.

[0008]

[1] An ophthalmic composition comprising 0.001 to 0.5% (w/v) of hyaluronic acid or a salt thereof, 0.0005 to 0.02% (w/v) of chlorhexidine, 0.03 to 1.5% (w/v) of propylene glycol, and 0.015% (w/v) or less of ethylenediaminetetraacetate.

[2] The ophthalmic composition according to [1], wherein the concentration of hyaluronic acid or a salt thereof is 0.01 to 0.3% (w/v).

[3] The ophthalmic composition according to [1], wherein the concentration of chlorhexidine is 0.0007 to 0.008% (w/v).

[4] The ophthalmic composition according to [1], wherein the concentration of propylene glycol is 0.05 to 1.0% (w/v).

[5] The ophthalmic composition according to [1], wherein the concentration of ethylenediaminetetraacetate is 0.01% (w/v) or less.

[6] The ophthalmic composition according to any one of [1] to [5], wherein the value of pH is 5.5 to 8.

[7] The ophthalmic composition according to any one of [1] to [6], wherein the osmotic pressure is 0.4 to 1.1.

[8] The ophthalmic composition according to any one of [1] to [7], which is an eye drop for medical purposes, an eye drop for soft contact lenses, or a wearing agent for soft contact lenses. It is noted that the above configurations of [1] to [8] may be used in any combinations of two or more.

[0009]

[9] A method of reducing a temporal change in the kinetic viscosity of an ophthalmic composition comprising hyaluronic acid or a salt thereof and chlorhexidine, the method comprising allowing propylene glycol and ethylenediaminetetraacetate to be comprised of the ophthalmic composition.

[10] A method of reducing a temporal change in the kinetic viscosity of an ophthalmic composition comprising hyaluronic acid or a salt thereof and chlorhexidine, the method comprising allowing 0.03 to 1.5% (w/v) of propylene glycol and 0.015% (w/v) or less of ethylenediaminetetraacetate to be comprised of the ophthalmic composition.

[11] A method of maintaining the antiseptic or preservative effect of an ophthalmic composition comprising hyaluronic acid or a salt thereof and chlorhexidine at a high level, the method comprising allowing propylene glycol and ethylenediaminetetraacetate to be comprised of the ophthalmic composition.

[12] A method of maintaining the antiseptic or preservative effect of an ophthalmic composition comprising hyaluronic acid or a salt thereof and chlorhexidine at a high level, the method comprising allowing 0.03 to 1.5% (w/v) of propylene glycol and 0.015% (w/v) or less of ethylenediaminetetraacetate to be comprised of the ophthalmic composition.

[13] A method of reducing a temporal change in the kinetic viscosity of an ophthalmic composition comprising hyaluronic acid or a salt thereof and chlorhexidine and maintaining the

antiseptic or preservative effect of the ophthalmic composition at a high level, the method comprising allowing propylene glycol and ethylenediaminetetraacetate to be comprised of the ophthalmic composition.

[14] A method of reducing a temporal change in the kinetic viscosity of an ophthalmic composition comprising hyaluronic acid or a salt thereof and chlorhexidine and maintaining the antiseptic or preservative effect of the ophthalmic composition at a high level, the method comprising allowing 0.03 to 1.5% (w/v) of propylene glycol and 0.015% (w/v) or less of ethylenediaminetetraacetate to be comprised of the ophthalmic composition.

[15] A suppressing agent for suppressing a temporal change in the kinetic viscosity of an ophthalmic composition comprising hyaluronic acid or a salt thereof and chlorhexidine, the suppressing agent comprising propylene glycol and ethylenediaminetetraacetate.

[16] A composition used for reducing a temporal change in the kinetic viscosity of an ophthalmic composition comprising hyaluronic acid or a salt thereof and chlorhexidine, the composition comprising propylene glycol and ethylenediaminetetraacetate.

[17] An antiseptic or preservative agent for maintaining the antiseptic or preservative effect of an ophthalmic composition comprising hyaluronic acid or a salt thereof and chlorhexidine at a high level, the antiseptic or preservative agent comprising propylene glycol and ethylenediaminetetraacetate.

[18] A composition used for maintaining the antiseptic or preservative effect of an ophthalmic composition comprising hyaluronic acid or a salt thereof and chlorhexidine at a high level, the composition comprising propylene glycol and ethylenediaminetetraacetate.

[19] A composition used for reducing a temporal change in the kinetic viscosity of an ophthalmic composition comprising hyaluronic acid or a salt thereof and chlorhexidine and maintaining the antiseptic or preservative effect of the ophthalmic composition at a high level, the composition comprising propylene glycol and ethylenediaminetetraacetate.

It is noted that the concentrations of components of the configurations [9] to [19] can be appropriately selected so that they fall in preferred ranges and combinations according to the embodiments of the present invention.

Effects of the Invention

[0010]

According to the present invention, a temporal change in the kinetic viscosity of an ophthalmic composition such as an eye drop containing hyaluronic acid or a salt thereof and chlorhexidine can be reduced, and the antiseptic or preservative effect can be maintained at a high level.

PREFERRED MODE FOR CARRYING OUT THE INVENTION

[0011]

Below, the embodiments of the present invention will be described in detail.

[0012]

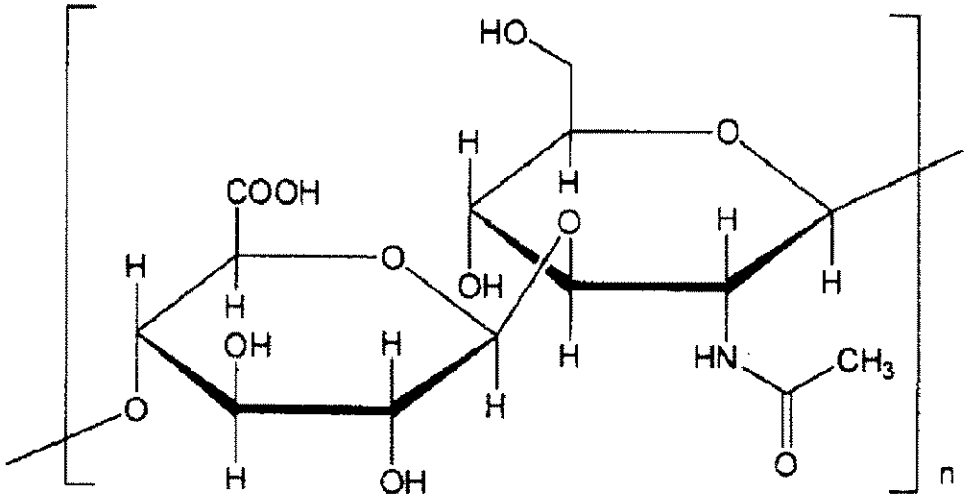
The ophthalmic composition according to the present embodiment contains hyaluronic acid or a salt thereof, chlorhexidine, and propylene glycol, and also contains 0.015% (w/v) or less of ethylenediaminetetraacetate. The present embodiment is based on a finding that the kinetic viscosity of an eye drop can be stably maintained when the blending amount of ethylenediaminetetraacetate, which is conventionally and widely blended as a stabilizing agent for ophthalmic compositions, is very small (0.015% or less). That is, the ophthalmic composition according to the present embodiment may include 0.001 to 0.5% (w/v) of hyaluronic acid or a salt thereof, 0.0005% to 0.02% (w/v) of chlorhexidine, 0.03 to 1.5% (w/v) of propylene glycol, and 0.015% (w/v) or less of ethylenediaminetetraacetate. Below, these components will be each described.

[0013]

Hyaluronic acid or a salt thereof

Hyaluronic acid used in the present embodiment is a compound represented by the following general formula (1).

[Chem. 1]



(1)

wherein n represents a natural number.

[0014]

The "hyaluronic acid" used in the present embodiment preferably has an average molecular weight of 500,000 to 3,900,000, more preferably 500,000 to 1,200,000.

[0015]

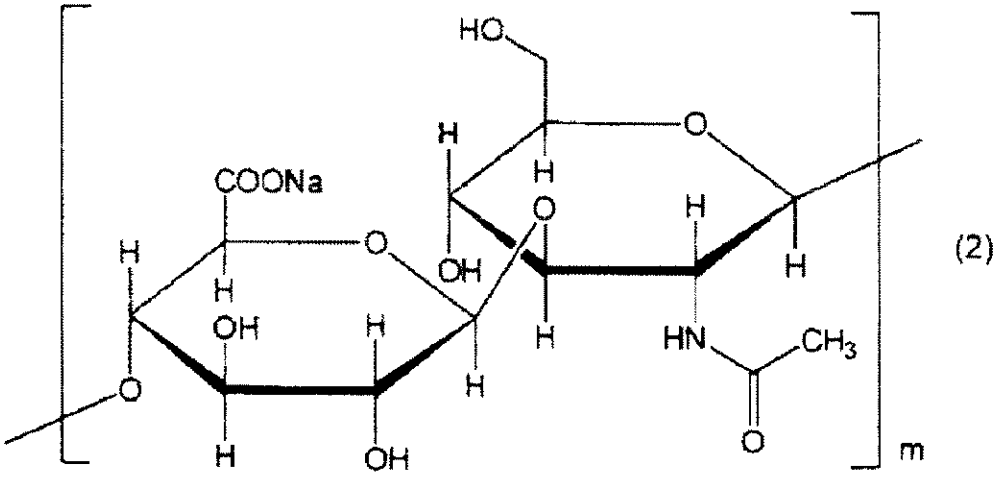
There is no particular limitation for a salt of hyaluronic acid as long as it is a pharmaceutically acceptable salt. Examples thereof include a salt with an inorganic acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, sulfuric acid, and phosphoric acid; a salt with an organic acid 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-ethanedisulfonic acid, isethionic acid, lactobionic acid, oleic acid, pamoic acid, polygalacturonic acid, stearic acid, tannic acid, trifluoromethanesulfonic acid,

benzenesulfonic acid, p-toluenesulfonic acid, lauryl sulfuric acid ester, methyl sulfate, naphthalenesulfonic acid, and sulfosalicylic acid; a quarternary ammonium salt with a methyl bromide, methyl iodide, and the like; a salt with a halogen ion such as a bromine ion, a chlorine ion, and an iodine ion; a salt with an alkaline metal such as lithium, sodium, and potassium; a salt with alkaline earth metal such as calcium and magnesium; a metal salt with iron, zinc, and the like; a salt with ammonia; a salt with an organic amine 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; and the like.

[0016]

The "salt of hyaluronic acid" used in the present embodiment is preferably a sodium salt (hereinafter, may also be referred to as a "sodium hyaluronate") represented by the following general formula (2).

[Chem. 2]



(2)

wherein m represents a natural number. The "hyaluronic acid or a salt thereof" used in the present embodiment may be in a form of a hydrate or solvate.

[0017]

When a geometrical isomer or an optical isomer is present in hyaluronic acid, these isomers or salts thereof are also within the scope of the present invention. Further, when a proton tautomer is present in hyaluronic acid, the proton tautomer or a salt thereof is also within the scope of the present invention.

[0018]

When a polymorphous crystal and a polymorphous crystal group (polymorphous crystal system) are present in hyaluronic acid or a salt, hydrate, or solvate thereof, they are also within the scope of the present invention. Here, the above polymorphous crystal group (polymorphous crystal system) means individual polymorphous crystals at each stage and the entire process thereof when crystal forms differ depending on conditions and states of production, crystallization, storage, and the like of crystals (it is noted that the above states include a state after formulation).

[0019]

The "hyaluronic acid or a salt thereof" can be manufactured in accordance with a conventional method in the field of synthetic organic chemistry, or can be manufactured in accordance with the method described in Japanese Unexamined Patent Application, Publication No. H1-115902. Further, those

commercially available from Sigma and others can also be used as the "hyaluronic acid or a salt thereof." For example, "sodium hyaluronate" is commercially available from Sigma (Catalog number: H5388).

[0020]

The ophthalmic composition according to the present embodiment may include the "hyaluronic acid or a salt thereof" as the sole active ingredient, or may include an active ingredient other than the "hyaluronic acid or a salt thereof." The ophthalmic composition according to the present embodiment may not necessarily include, for example, cromoglycic acid or a salt thereof or pranoprofen as active ingredients other than the "hyaluronic acid or a salt thereof." The term "active ingredient" as used in the present invention means a component having a pharmacological effect.

[0021]

With regard to the concentration of the "hyaluronic acid or a salt thereof" in the ophthalmic composition according to the present embodiment, the lower limit is preferably 0.001% (w/v), more preferably 0.01% (w/v), and even more preferably 0.05% (w/v), and the upper limit is preferably 0.5% (w/v), more preferably 0.3% (w/v).

[0022]

Chlorhexidine

Examples of chlorhexidine include chlorhexidine gluconate, chlorhexidine acetate, chlorhexidine hydrochloride, and the like. It is preferably chlorhexidine gluconate. With

regard to the concentration of chlorhexidine, the lower limit is preferably 0.0005% (w/v), more preferably 0.0007, and even more preferably 0.0008% (w/v), and the upper limit is preferably 0.02% (w/v), more preferably 0.01% (w/v), and even more preferably 0.008% (w/v).

[0023]

The ophthalmic composition according to the present embodiment may include an antiseptic agent other than chlorhexidine such as benzalkonium chloride in a concentration of preferably 0.002% (w/v) or less, more preferably 0.0015% (w/v) or less. However, the ophthalmic composition according to the present embodiment preferably does not include benzalkonium chloride, and more preferably includes chlorhexidine as the sole antiseptic agent.

[0024]

Propylene glycol

With regard to the concentration of propylene glycol in the ophthalmic composition according to the present embodiment, the lower limit is preferably 0.03% (w/v), more preferably 0.05% (w/v), and the upper limit is preferably 1.5% (w/v), more preferably 1.0% (w/v).

[0025]

Ethylenediaminetetraacetate

Ethylenediaminetetraacetate in the ophthalmic composition according to the present embodiment is edetic acid or a salt thereof, and may be in a form of hydrate, or may be used as an acid-salt mixture. Salts of edetic acid include, for example,

alkaline metal such as sodium edetate, disodium edetate, and tetrasodium edetate. Hydrates thereof include, for example, sodium edetate hydrate such as disodium edetate dihydrate.

[0026]

The concentration of ethylenediaminetetraacetate in the ophthalmic composition according to the present embodiment is 0.015% (w/v) or less and preferably 0.01% (w/v) or less, and may be 0.003% (w/v) or less, or 0.001% (w/v) or less. Further, the ophthalmic composition according to the present embodiment may not necessarily include any ethylenediaminetetraacetate.

[0027]

With regard to the value of pH of the ophthalmic composition according to the present embodiment, the lower limit is preferably 5.5, more preferably 6, and even more preferably more than 6, and the upper limit is preferably 8, more preferably 7.5, and even more preferably 7. An ophthalmic composition in the above pH ranges can be suitably used because hyaluronic acid or a salt thereof in the ophthalmic composition can be stabilized, and the ophthalmic composition is less irritating.

[0028]

Buffer agent

Preferably, the ophthalmic composition according to the present embodiment further includes a buffer agent for adjusting pH to the above preferred ranges. Buffer agents can include epsilon-aminocaproic acid, sodium phosphate, sodium hydrogen phosphate, sodium dihydrogen phosphate, sodium

acetate, and the like. There is no particular limitation for the addition amount (concentration) of a buffer agent as long as the value of pH of the ophthalmic composition according to the present embodiment can be adjusted to the above preferred ranges.

[0029]

Other additives

The ophthalmic composition according to the present embodiment may further include a pH regulator for adjusting pH to the above preferred ranges. There is no particular limitation for the pH regulator as long as the pH of the ophthalmic composition according to the present embodiment can be adjusted. Specific examples thereof include dilute hydrochloric acid, sodium hydroxide, and the like. There is no particular limitation for the addition amount (concentration) of the pH regulator as long as the value of pH of the ophthalmic composition according to the present embodiment can be adjusted to the above preferred ranges.

[0030]

There is no particular limitation for the osmotic pressure of the ophthalmic composition according to the present embodiment as long as it is within a range acceptable for ophthalmic compositions, but the lower limit is preferably 0.4, more preferably 0.6, and even more preferably more than 0.9, and the upper limit is preferably 1.3, more preferably 1.2, and even more preferably 1.1 or less. The term "osmotic pressure" as used herein refers to a value as measured in

accordance with a method described in Osmotic pressure determination (Osmolarity Determination) in the Japanese Pharmacopoeia 16th edition.

[0031]

The ophthalmic composition according to the present embodiment is preferably an aqueous composition. The term "aqueous composition" as used in the present invention means a composition including water as a base material. The ophthalmic composition according to the present embodiment as an aqueous composition is preferably an aqueous solution containing at least hyaluronic acid or a salt thereof, chlorhexidine, and propylene glycol as described above, and can be, for example, an ophthalmic liquid as an eye drop as described below.

[0032]

A pharmaceutically acceptable additive may be added to the ophthalmic composition according to the present embodiment, if desired.

[0033]

The ophthalmic composition according to the present embodiment can be prepared, for example, by the conventional method. For example, hyaluronic acid or a salt thereof, chlorhexidine, and propylene glycol as well as ethylenediaminetetraacetate, a buffer agent, a pH regulator, and the like, which may be added if desired, may be dissolved in water, and a pH regulator may be further added, if necessary, to obtain an ophthalmic composition.

[0034]

The ophthalmic composition according to the present embodiment can be suitably used as an eye drop for medical purposes, for contact lenses, and other purposes, and can also be used as a wearing agent for contact lenses. In particular, it can be suitably used as an eye drop or wearing agent for soft contact lenses when benzalkonium chloride is not contained. In the case of medical purposes, for example, it can be used for treating not only corneal and conjunctival epithelium disorders associated with endogenous diseases such as dry eye (xerophthalmia syndromes), Sjoegren's syndromes, and Stevens-Johnson syndromes but also exogenous diseases due to surgery, chemicals, injury, wearing of contact lens, and the like.

[0035]

The ophthalmic composition according to the present embodiment can reduce a temporal change in the kinetic viscosity to a low level. For example, it can reduce a temporal change in the kinetic viscosity to a low level even under severe test conditions where a sample is allowed to stand for two weeks at 50 to 70°C, typically at 60°C. Specifically, the kinetic viscosity of the ophthalmic composition according to the present embodiment is measured in accordance with the kinetic-viscosity measurement test described below, for example, before and after allowed to stand for two weeks at 60°C. The lower limit of the retention percentage of kinetic viscosity determined as described above is preferably 70%, more preferably 75%, and even more

preferably 77%. The upper limit is preferably 100%, but, for example, even 95%, 90%, 85%, and so on may also be suitable.

[0036]

The ophthalmic composition according to the present embodiment has a high retention percentage of kinetic viscosity as described above. This is likely because stabilization, preferably long-term stabilization of hyaluronic acid or a salt thereof as an active ingredient can be achieved. Stabilization of hyaluronic acid or a salt thereof in the ophthalmic composition according to the present embodiment appears to be achieved by rather reducing the blending amount of ethylenediaminetetraacetate to 0.015% (w/v) or less although it is conventionally and widely blended as a stabilizing agent for ophthalmic compositions.

[0037]

The ophthalmic composition according to the present embodiment can maintain an outstanding antiseptic effect by virtue of chlorhexidine added. Specifically, the preservative effect (as used herein, may also be referred to as an "antiseptic effect") of the ophthalmic composition according to the present embodiment as measured in accordance with the preservatives-effectiveness tests described below means that it is 3.0 or more after stored for 2 or 4 weeks for E. coli, P. aeruginosa, or S. aureus, and no bacterial growth is observed after stored for 2 or 4 weeks for C. albicans or A. brasiliensis.

[0038]

The ophthalmic composition according to the present invention has a high retention percentage of kinetic viscosity as described above, and also can maintain an antiseptic or preservative effect at a high level. This allows the ophthalmic composition according to the present invention to stably show an effect such as drug efficacy required for various uses, for example, for medical purposes, for contact lenses, and the like as described above as an ophthalmic composition, for example, as a multi-dose type ophthalmic composition.

[0039]

When an ophthalmic composition containing hyaluronic acid or a salt thereof and chlorhexidine (hereinafter as used herein, may also be referred to as an "target ophthalmic composition") includes propylene glycol and ethylenediaminetetraacetate, a temporal change in the kinetic viscosity of the target ophthalmic composition can be reduced, and the antiseptic or preservative effect of the target ophthalmic composition can be maintained at a high level. In addition, the temporal change in the kinetic viscosity of the target ophthalmic composition can be reduced, and simultaneously the antiseptic or preservative effect can be maintained at a high level. As described above, a method of reducing a temporal change in the kinetic viscosity of a target ophthalmic composition, a method of maintaining the antiseptic or preservative effect of a target ophthalmic composition, and a method of reducing a temporal change in the

kinetic viscosity of a target ophthalmic composition and simultaneously maintaining the antiseptic or preservative effect at a high level are also within the scope of the present invention. Each of the above methods preferably includes allowing propylene glycol and ethylenediaminetetraacetate to be comprised of a target ophthalmic composition so that the concentration of propylene glycol is 0.03 to 1.5% (w/v) relative to the total of the target ophthalmic composition, propylene glycol, and ethylenediaminetetraacetate, and so that the concentration of ethylenediaminetetraacetate is 0.015% (w/v) or less relative to the total of the target ophthalmic composition, propylene glycol, and ethylenediaminetetraacetate.

[0040]

A composition including propylene glycol and ethylenediaminetetraacetate can be used to reduce a temporal change in the kinetic viscosity of an ophthalmic composition (a target ophthalmic composition) containing hyaluronic acid or a salt thereof and chlorhexidine, and can also be used to maintain the antiseptic or preservative effect of a target ophthalmic composition at a high level, and further can be used to reduce a temporal change in the kinetic viscosity of a target ophthalmic composition and to simultaneously maintain the antiseptic or preservative effect at a high level. The aforementioned composition including propylene glycol and ethylenediaminetetraacetate preferably includes 0.03 to 1.5% (w/v) of propylene glycol and 0.015% (w/v) or less of

ethylenediaminetetraacetate relative to the total of the above composition and a target ophthalmic composition to which the above composition is to be added.

[0041]

The composition including propylene glycol and ethylenediaminetetraacetate can serve as a suppressing agent for suppressing a temporal change in the kinetic viscosity of an ophthalmic composition (a target ophthalmic composition) containing hyaluronic acid or a salt thereof and chlorhexidine, and can also serve as an antiseptic or preservative agent for maintaining the antiseptic or preservative effect of an ophthalmic composition containing hyaluronic acid or a salt thereof and chlorhexidine at a high level. The suppressing agent and the antiseptic or preservative agent described above including propylene glycol and ethylenediaminetetraacetate are also within the scope of the present invention. The above suppressing agent and the above antiseptic or preservative agent preferably include propylene glycol and ethylenediaminetetraacetate so that the concentration of propylene glycol is 0.03 to 1.5% (w/v) relative to the total of the suppressing agent or the antiseptic or preservative agent and an target ophthalmic composition to which the suppressing agent or the above antiseptic or preservative agent is to be added, and so that the concentration of ethylenediaminetetraacetate is 0.015% (w/v) or less relative to the total of the suppressing agent or the antiseptic or preservative agent and the target

ophthalmic composition.

EXAMPLES

[0042]

Below, an eye drop as an embodiment of the ophthalmic composition according to the present invention will be described more specifically with reference to Formation Examples and Sample Preparation Examples, but the present invention shall not be limited to these only.

[0043]

[Formation Examples]

Formation Example 1

Eye drop (0.3% (w/v)) in 100 mL

Sodium hyaluronate 0.3 g

Chlorhexidine gluconate 0.005 g

Disodium hydrogen phosphate 0.2 g

Sodium dihydrogen phosphate 0.04 g

Sodium chloride 0.6 g

Propylene glycol 0.4 g

Dilute hydrochloric acid q.s. Sodium hydroxide q.s.

Sterile purified water q.s. A 0.3% (w/v) sodium-hyaluronate eye drop can be prepared by adding sodium hyaluronate and the other components described above to sterile purified water and thoroughly mixing these.

[0044]

Formation Example 2

Eye drop (0.1% (w/v)) in 100 mL

Sodium hyaluronate 0.1 g

Chlorhexidine gluconate 0.002 g

Disodium hydrogen phosphate 0.2 g

Sodium dihydrogen phosphate 0.04 g

Sodium chloride 0.5 g

Propylene glycol 0.75 g

Sodium edetate hydrate 0.001 g

Dilute hydrochloric acid q.s. Sodium hydroxide q.s.

Sterile purified water q.s. A 0.1% (w/v) sodium-hyaluronate eye drop can be prepared by adding sodium hyaluronate and the other components described above to sterile purified water and thoroughly mixing these.

[0045]

Formation Example 3

Eye drop (0.3% (w/v)) in 100 mL

Sodium hyaluronate 0.3 g

Chlorhexidine gluconate 0.001 g

Epsilon-aminocaproic acid 0.2 g

Sodium chloride 0.6 g

Propylene glycol 0.5 g

Dilute hydrochloric acid q.s. Sodium hydroxide q.s.

Sterile purified water q.s. A 0.3% (w/v) sodium-hyaluronate eye drop can be prepared by adding sodium hyaluronate and the other components described above to sterile purified water and thoroughly mixing these.

[0046]

Formation Example 4

Eye drop (0.2% (w/v)) in 100 mL

Sodium hyaluronate 0.2 g

Chlorhexidine gluconate 0.0025 g

Epsilon-aminocaproic acid 0.2 g

Sodium chloride 0.7 g

Propylene glycol 0.25 g

Sodium edetate hydrate 0.002 g

Dilute hydrochloric acid q.s. Sodium hydroxide q.s.

Sterile purified water q.s. A 0.2% (w/v) sodium-hyaluronate eye drop can be prepared by adding sodium hyaluronate and the other components described above to sterile purified water and thoroughly mixing these.

[0047]

Formation Example 5

Eye drop (0.005% (w/v)) in 100 mL

Sodium hyaluronate 0.005 g

Chlorhexidine gluconate 0.001 g

Epsilon-aminocaproic acid 0.1 g

Sodium chloride 0.7 g

Propylene glycol 0.3 g

Dilute hydrochloric acid q.s. Sodium hydroxide q.s.

Sterile purified water q.s. A 0.005% (w/v) sodium-hyaluronate eye drop can be prepared by adding sodium hyaluronate and the other components described above to sterile purified water and thoroughly mixing these, but may further include other active ingredients.

[0048]

Formation Example 6

Eye drop (0.05% (w/v)) in 100 mL

Sodium hyaluronate 0.05 g

Chlorhexidine gluconate 0.001 g

Epsilon-aminocaproic acid 0.1 g

Sodium chloride 0.7 g

Propylene glycol 0.3 g

Sodium edetate hydrate 0.015 g

Dilute hydrochloric acid q.s. Sodium hydroxide q.s.

Sterile purified water q.s. A 0.05% (w/v) sodium-hyaluronate eye drop can be prepared by adding sodium hyaluronate and the other components described above to sterile purified water and thoroughly mixing these, but may further include other active ingredients.

[0049]

Formation Example 7

Eye drop (0.1% (w/v)) in 100 mL

Sodium hyaluronate 0.1 g

Chlorhexidine gluconate 0.001 g

Epsilon-aminocaproic acid 0.1 g

Sodium chloride 0.7 g

Propylene glycol 0.3 g

Sodium edetate hydrate 0.01 g

Dilute hydrochloric acid q.s. Sodium hydroxide q.s.

Sterile purified water q.s. A 0.1% (w/v) sodium-hyaluronate eye drop can be prepared by adding sodium hyaluronate and the other components described above to sterile purified water and

thoroughly mixing these, but may further include other active ingredients.

[0050]

Formation Example 8

Eye drop (0.3% (w/v)) in 100 mL

Sodium hyaluronate 0.3 g

Chlorhexidine gluconate 0.001 g

Epsilon-aminocaproic acid 0.1 g

Sodium chloride 0.7 g

Propylene glycol 0.3 g

Sodium edetate hydrate 0.015 g

Dilute hydrochloric acid q.s. Sodium hydroxide q.s.

Sterile purified water q.s. A 0.3% (w/v) sodium-hyaluronate eye drop can be prepared by adding sodium hyaluronate and the other components described above to sterile purified water and thoroughly mixing these, but may further include other active ingredients.

[0051]

[Sample preparation examples]

Examples 1 to 3

Sodium hyaluronate 0.3 g, chlorhexidine gluconate 0.005 g, propylene glycol 0.25 g, sodium chloride 0.7 g, disodium hydrogen phosphate 0.2 g, and sodium dihydrogen phosphate 0.04 g were dissolved in water to obtain 100 mL of an eye drop. Dilute hydrochloric acid and/or sodium hydroxide were/was added to the above eye drop to obtain Example 1 of pH 6.5, Example 2 of pH 7.0, and Example 3 of pH 7.5.

[0052]

Examples 4 to 6

Sodium hyaluronate 0.3 g, chlorhexidine gluconate 0.005 g, propylene glycol 0.25 g, sodium edetate hydrate 0.001 g, sodium chloride 0.7 g, disodium hydrogen phosphate 0.2 g, and sodium dihydrogen phosphate 0.04 g were dissolved in water to obtain 100 mL of an eye drop. Dilute hydrochloric acid and/or sodium hydroxide were/was added to the above eye drop to obtain Example 4 of pH 6.5, Example 5 of pH 7.0, and Example 6 of pH 7.5.

[0053]

Examples 7 to 9

Sodium hyaluronate 0.3 g, chlorhexidine gluconate 0.0008 g, propylene glycol 0.25 g, sodium chloride 0.7 g, disodium hydrogen phosphate 0.2 g, and sodium dihydrogen phosphate 0.04 g were dissolved in water to obtain 100 mL of an eye drop. Dilute hydrochloric acid and/or sodium hydroxide were/was added to the above eye drop to obtain Example 7 of pH 6.5, Example 8 of pH 7.0, and Example 9 of pH 7.5.

[0054]

Examples 10 to 12

Sodium hyaluronate 0.3 g, chlorhexidine gluconate 0.0008 g, propylene glycol 0.25 g, sodium edetate hydrate 0.001 g, sodium chloride 0.7 g, disodium hydrogen phosphate 0.2 g, and sodium dihydrogen phosphate 0.04 g were dissolved in water to obtain 100 mL of an eye drop. Dilute hydrochloric acid and/or sodium hydroxide were/was added to the above eye drop to

obtain Example 10 of pH 6.5, Example 11 of pH 7.0, and Example 12 of pH 7.5.

[0055]

Comparative Examples 1 to 3

Sodium hyaluronate 0.3 g, chlorhexidine gluconate 0.005 g, sodium edetate hydrate 0.1 g, potassium chloride 0.15 g, sodium chloride 0.7 g, disodium hydrogen phosphate 0.2 g, and sodium dihydrogen phosphate 0.04 g were dissolved in water to obtain 100 mL of an eye drop. Dilute hydrochloric acid and/or sodium hydroxide were/was added to the above eye drop to obtain Comparative Example 1 of pH 6.5, Comparative Example 2 of pH 7.0, and Comparative Example 3 of pH 7.5.

[0056]

Comparative Example 4

Sodium hyaluronate 0.3 g, chlorhexidine gluconate 0.005 g, propylene glycol 0.25 g, sodium edetate hydrate 0.1 g, sodium chloride 0.7 g, disodium hydrogen phosphate 0.2 g, and sodium dihydrogen phosphate 0.04 g were dissolved in water to obtain 100 mL of an eye drop. Dilute hydrochloric acid and/or sodium hydroxide were/was added to the above eye drop to obtain Comparative Example 4 of pH 7.5.

[0057]

<Test methods>

Each of the hyaluronic acid-containing eye drops prepared in Examples 1 to 12 and Comparative Examples 1 to 4 were tested as follows.

[0058]

[Kinetic-viscosity measurement test]

Kinetic-viscosity measurement tests were performed in accordance with "Method I Viscosity measurement by capillary tube viscometer, Viscosity Determination, General Test Procedures in the Japanese Pharmacopoeia 16th edition" by measuring kinetic viscosity at a measurement temperature of 30°C to evaluate a kinetic-viscosity stabilization effect of each eye drop. Results are shown in Tables 1 to 3. It is noted that the unit for each of the added components in Tables 1 to 3 is % (w/v), and the unit of the kinetic viscosity for each of the eye drops is mm^2/s, and the unit of the kinetic-viscosity retention percentage is %.

[0059]

[Preservatives-effectiveness tests]

Each of the hyaluronic acid-containing eye drops prepared in Examples 7 to 12 was subjected to preservatives-effectiveness tests to evaluate an effect of propylene glycol on the preservative effect of the hyaluronic acid-containing eye drops. Preservatives-effectiveness tests were performed in accordance with the preservatives-effectiveness tests in the Japanese Pharmacopoeia 16th edition (hereinafter may also simply be referred to the "Japanese pharmacopoeia"). In the tests, the follows were used as test bacteria: Esherichia Coli (E. coli; designated as "EC" in Table 2), Pseudomonas aeruginosa (P. aeruginosa; designated as "PA" in Table 2), Staphylococcus aureus (S. aureus; designated as "SA" in Table 2), Candida albicans (C. albicans; designated as "CA" in Table

2), and Aspergillus brasiliensis (A. niger; designated as "AB" in Table 2). Results are shown in Table 2. In Table 2, "ND" means that no bacterium was detected.

[0060]

[Table 1]

Components to be blended	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6
Sodium hyaluronate	0.3	0.3	0.3	0.3	0.3	0.3
Chlorhexidine gluconate	0.005	0.005	0.005	0.005	0.005	0.005
Propylene glycol	0.25	0.25	0.25	0.25	0.25	0.25
Sodium edetate hydrate				0.001	0.001	0.001
Sodium chloride	0.7	0.7	0.7	0.7	0.7	0.7
Disodium hydrogen phosphate	0.2	0.2	0.2	0.2	0.2	0.2
Sodium dihydrogen phosphate	0.04	0.04	0.04	0.04	0.04	0.04
pH	6.5	7.0	7.5	6.5	7.0	7.5
Kinetic viscosity (At start of test)	24.8	25.4	24.6	24.2	25.4	24.5
Kinetic viscosity (at 60°C after two weeks)	20.2	21.2	20.0	19.3	20.6	18.9
Retention percentage (at 60°C after two weeks)	81.4	83.5	81.3	79.7	81.2	77.5

[0061]

[Table 2]

Components to be blended			Example 7	Example 8	Example 9	Example 10	Example 11	Example 12
Sodium hyaluronate			0.3	0.3	0.3	0.3	0.3	0.3
Chlorhexidine gluconate			0.0008	0.0008	0.0008	0.0008	0.0008	0.0008
Propylene glycol			0.25	0.25	0.25	0.25	0.25	0.25
Sodium edetate hydrate						0.001	0.001	0.001
Sodium chloride			0.7	0.7	0.7	0.7	0.7	0.7
Disodium hydrogen phosphate			0.2	0.2	0.2	0.2	0.2	0.2
Sodium dihydrogen phosphate			0.04	0.04	0.04	0.04	0.04	0.04
pH			6.5	7.0	7.5	6.5	7.0	7.5
Kinetic viscosity (At start of test)			28.0	28.2	28.5	28.5	29.4	28.1
Kinetic viscosity (at 60°C after two weeks)			22.1	22.8	22.4	22.2	22.7	21.6
Retention percentage (at 60°C after two weeks)			78.8	80.8	78.6	78.0	77.4	77.0
Preservative effect (Log reduction)	EC	After stored for one week	ND	ND	ND	ND	ND	ND
		After stored for two weeks	ND	ND	ND	ND	ND	ND
		After stored for 4 weeks	ND	ND	ND	ND	ND	ND
	PA	After stored for one week	ND	ND	ND	ND	ND	ND
		After stored for two weeks	ND	ND	ND	ND	ND	ND
		After stored for 4 weeks	ND	ND	ND	ND	ND	ND
	SA	After stored for one week	3.4	ND	ND	2.6	3.5	4.7
		After stored for two weeks	ND	ND	ND	ND	ND	ND
		After stored for 4 weeks	ND	ND	ND	ND	ND	ND
	CA	After stored for one week	4.8	4.5	ND	4.8	ND	3.8
		After stored for two weeks	ND	ND	ND	ND	ND	ND
		After stored for 4 weeks	ND	ND	ND	ND	ND	ND
	AB	After stored for one week	0.3	0.4	0.6	0.1	0.2	0.2
		After stored for two weeks	0.6	0.3	0.7	0.3	0.0	0.2
		After stored for 4 weeks	0.3	0.4	0.4	0.6	0.3	0.4
Result			Suitable	Suitable	Suitable	Suitable	Suitable	Suitable

[0062]

[Table 3]

Components to be blended	Comparative Example 1	Comparative Example 2	Comparative Example 3	Comparative Example 4
Sodium hyaluronate	0.3	0.3	0.3	0.3
Chlorhexidine gluconate	0.005	0.005	0.005	0.005
Propylene glycol				0.25
Sodium edetate hydrate	0.1	0.1	0.1	0.1
Potassium chloride	0.15	0.15	0.15	
Sodium chloride	0.7	0.7	0.7	0.7
Disodium hydrogen phosphate	0.2	0.2	0.2	0.2
Sodium dihydrogen phosphate	0.04	0.04	0.04	0.04
pH	6.5	7.0	7.5	7.5
Kinetic viscosity (At start of test)	23.5	23.8	23.1	23.6
Kinetic viscosity (at 60°C after two weeks)	12.4	10.2	10.3	16.5
Retention percentage (at 60°C after two weeks)	52.6	43.0	44.5	69.7

[0063]

(Discussion)

As shown in Tables 1 and 2, chlorhexidine-containing hyaluronic-acid eye drops including propylene glycol and 0.015% (w/v) or less, specifically 0.001% (w/v) or less of sodium edetate hydrate all showed a kinetic-viscosity retention percentage of 77.0 % or more after stored for two weeks at 60°C. In contrast, as shown in Table 3, when propylene glycol was not blended, or when 0.1% (w/v) of sodium edetate hydrate was blended, the kinetic viscosity retention percentages were all 69.7% or less after stored for two weeks at 60°C. Therefore, a chlorhexidine-containing hyaluronic-acid eye drop in which propylene glycol is included, and the blending concentration of edetate is 0.015% (w/v) or less (including a case where edetate is not included) shows an

effect for improving the stability of the kinetic viscosity of the eye drop as compared with a case where propylene glycol is not included or a case where propylene glycol and 0.1% (w/v) or more of sodium edetate hydrate are included.

[0064]

Further, as shown in Table 2, for chlorhexidine-containing hyaluronic-acid eye drops including propylene glycol and 0.015% (w/v) or less, specifically 0.001% (w/v) or less of sodium edetate hydrate, the preservative effect was ND after stored for one week and later for E. coli and P. aeruginosa, 2.6 or more after stored for one week and ND after stored for two weeks for S. aureus, 3.8 or more after stored for one week and ND after stored for two weeks for C. albicans, and 0.0 or more both after stored for one week and two weeks for A. brasiliensis, showing no apparent increase. Therefore, a chlorhexidine-containing hyaluronic-acid eye drop in which propylene glycol is included, and the blending concentration of edetate is 0.015% (w/v) or less shows an effect for maintaining the preservative effect of the eye drop at a high level. This showed that for chlorhexidine-containing hyaluronic-acid eye drops, propylene glycol had essentially no or negligible effect on the preservative effect of the hyaluronic-acid eye drops.

CLAIMS

1. An ophthalmic composition comprising 0.001 to 0.5% (w/v) of hyaluronic acid or a salt thereof, 0.0005 to 0.02% (w/v) of chlorhexidine, 0.03 to 1.5% (w/v) of propylene glycol, and 0.015% (w/v) or less of ethylenediaminetetraacetate.

2. The ophthalmic composition according to claim 1, wherein the concentration of hyaluronic acid or a salt thereof is 0.01 to 0.3% (w/v).

3. The ophthalmic composition according to claim 1, wherein the concentration of chlorhexidine is 0.0007 to 0.008% (w/v).

4. The ophthalmic composition according to claim 1, wherein the concentration of propylene glycol is 0.05 to 1.0% (w/v).

5. The ophthalmic composition according to claim 1, wherein the concentration of ethylenediaminetetraacetate is 0.01% (w/v) or less.

6. The ophthalmic composition according to any one of claims 1 to 5, wherein the value of pH is 5.5 to 8.

7. The ophthalmic composition according to any one of claims 1 to 6, which is an eye drop for medical purposes, an eye drop for soft contact lenses, or a wearing agent for soft contact

lenses.

8. A method of suppressing a temporal change in the kinetic viscosity of an ophthalmic composition comprising hyaluronic acid or a salt thereof and chlorhexidine, the method comprising allowing propylene glycol and ethylenediaminetetraacetate to be comprised of the ophthalmic composition.

9. A method of maintaining the antiseptic or preservative effect of an ophthalmic composition comprising hyaluronic acid or a salt thereof and chlorhexidine at a high level, the method comprising allowing propylene glycol and ethylenediaminetetraacetate to be comprised of the ophthalmic composition.

10. A method of suppressing a temporal change in the kinetic viscosity of an ophthalmic composition comprising hyaluronic acid or a salt thereof and chlorhexidine and maintaining the antiseptic or preservative effect of the ophthalmic composition at a high level, the method comprising allowing propylene glycol and ethylenediaminetetraacetate to be comprised of the ophthalmic composition.

11. A suppressing agent for suppressing a temporal change in the kinetic viscosity of an ophthalmic composition comprising hyaluronic acid or a salt thereof and chlorhexidine, the

suppressing agent comprising propylene glycol and ethylenediaminetetraacetate.

12. An antiseptic or preservative agent for maintaining the antiseptic or preservative effect of an ophthalmic composition comprising hyaluronic acid or a salt thereof and chlorhexidine at a high level, the antiseptic or preservative agent comprising propylene glycol and ethylenediaminetetraacetate.