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(54) Title: OPHTHALMIC PHARMACEUTICAL COMPOSITION WITH IMPROVED PRESERVATIVE EFFECTIVENESS OR LIGHT STABILITY

(57) Abstract: A problem to be solved by the present invention is the provision of an ophthalmic pharmaceutical composition with enhanced preservative effectiveness and/or improved light stability of carteolol. The problem may be solved by combining carteolol or a pharmaceutically acceptable salt thereof with edetic acid or a pharmaceutically acceptable salt thereof.

Description

Title of Invention: OPHTHALMIC PHARMACEUTICAL COMPOSITION WITH IMPROVED PRESERVATIVE EFFECTIVENESS OR LIGHT STABILITY

Technical Field

[0001] The present invention relates to ophthalmic pharmaceutical compositions comprising carteolol, which is a β blocker, processes for preparing the same, and medical uses of the same. The present invention also relates to methods for enhancing preservative effectiveness, improving light stability, and/or reducing decomposition of carteolol.

Background Art

[0002] Carteolol is known as a β blocker with its chemical name of 5-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-3,4-dihydroquinolin-2(1H)-one, and is known to be therapeutically effective against glaucoma and ocular hypertension for ophthalmic use. Eye drops are usually required to contain a preserving agent or a preservative to avoid contamination by incorporation of microorganisms in use. Such a preserving agent or preservative usually includes benzalkonium chloride, benzethonium chloride, chlorhexidine gluconate, parabens, chlorobutanol, and sorbate. These preserving agents and preservatives may, however, negatively affect human tissues such as cornea.

[0003] Instead of using preserving agents or preservatives, it has been known a method of imparting preservative effectiveness to eye drops by addition of boric acid or a salt thereof, etc. Use of boric acid, etc., however, may cause hypersensitive symptoms such as blepharitis as side effects (see PTL 1).

[0004] Eye drops without a preserving agent or a preservative include a single-dose packaged and single-use disposable eye drop, i.e., a unit-dose eye drop, of which a single dose is individually packaged. For example, PTL 2 discloses bacteriostatic-agent-free eye drops comprising carteolol hydrochloride of which a single dose is individually packaged. Such a unit-dose eye drop, however, requires a disposable individual container for each administration, and may not be suitable for long-term continuous administration in terms of costs and securement of storage facilities, etc.

[0005] Treatment of eye diseases that require long-term continuous administration of drugs, such as glaucoma and ocular hypertension, has required stable eye drops with high preservative effectiveness.

[0006] Some β blockers decompose under light irradiation, and carteolol is one of such β blockers. Thus, it has been generally necessary to prevent eye drops comprising carteolol from light during storage and in use.

Citation List

Patent Literature

[0007] [PTL 1] WO2011/013794 pamphlet

[PTL 2] CN101461780A

Summary of Invention

Technical Problem

[0008] One of the problems to be solved by the present invention is the provision of an ophthalmic pharmaceutical composition with enhanced preservative effectiveness and/or improved light stability of carteolol. Another problem is the provision of a method for enhancing preservative effectiveness, improving light stability, and/or reducing decomposition of carteolol.

Solution to Problem

[0009] The inventors have found through extensive studies that the problems may be solved by combining carteolol or a pharmaceutically acceptable salt thereof with edetic acid or a pharmaceutically acceptable salt thereof, and achieved the present invention.

[0010] One embodiment of the present invention provides an ophthalmic pharmaceutical composition comprising carteolol or a pharmaceutically acceptable salt thereof and edetic acid or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention also provides a method for enhancing preservative effectiveness of carteolol or a pharmaceutically acceptable salt thereof with edetic acid or a pharmaceutically acceptable salt thereof, comprising combining carteolol or a pharmaceutically acceptable salt thereof with edetic acid or a pharmaceutically acceptable salt thereof.

Still another embodiment of the present invention also provides a method for improving light stability or reducing decomposition of carteolol or a pharmaceutically acceptable salt thereof with edetic acid or a pharmaceutically acceptable salt thereof and/or a sustaining agent, comprising combining carteolol or a pharmaceutically acceptable salt thereof with edetic acid or a pharmaceutically acceptable salt thereof and/or the sustaining agent.

Still another embodiment of the present invention also provides a process for preparing an ophthalmic pharmaceutical composition comprising carteolol or a pharmaceutically acceptable salt thereof and edetic acid or a pharmaceutically acceptable salt thereof, comprising mixing carteolol or a pharmaceutically acceptable salt thereof with edetic acid or a pharmaceutically acceptable salt thereof.

Effects of Invention

[0011] A pharmaceutical composition of the present invention may have preservative effectiveness or control microbe growth without a preserving agent or a preservative. A

pharmaceutical composition of the present invention may also improve light stability. A pharmaceutical composition of the present invention may have enhanced preservative effectiveness and/or improved light stability, and it may also be useful for treatment of eye diseases that require long-term continuous administration of drugs, such as glaucoma and ocular hypertension.

In the present invention, adding edetic acid or a pharmaceutically acceptable salt thereof to carteolol or a pharmaceutically acceptable salt thereof, which can intrinsically, though weakly, control microbe growth, may enhance preservative effectiveness or antibacterial effect of carteolol or a pharmaceutically acceptable salt thereof and permit the provision of an eye drop without a preserving agent or a preservative, resulting in improvement of light stability of carteolol which has low light stability. In addition, addition of a tonicity agent, e.g., propylene glycol, and/or a sustaining agent, e.g., alginic acid, may enhance preservative effectiveness or antibacterial effect or improve light stability of carteolol or a pharmaceutically acceptable salt thereof.

Description of Embodiments

[0012] The present invention may include the embodiments illustrated as follows.

Item 1. An ophthalmic pharmaceutical composition, comprising carteolol or a pharmaceutically acceptable salt thereof and edetic acid or a pharmaceutically acceptable salt thereof.

Item 2. An ophthalmic pharmaceutical composition for improving preservative effectiveness and/or light stability of carteolol or a pharmaceutically acceptable salt thereof, comprising edetic acid or a pharmaceutically acceptable salt thereof.

Item 3. The composition of Item 1 or 2, further comprising a tonicity agent. Examples of the tonicity agent include propylene glycol, glycerin, polyethylene glycol, trehalose, maltose, sucrose, glucose, sorbitol, mannitol, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, and a combination thereof.

Item 4. The composition of any one of Items 1 to 3, further comprising a sustaining agent. Examples of the sustaining agent include hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinyl alcohol, carboxyvinyl polymer, polyvinylpyrrolidone, carboxymethyl cellulose, polyacrylic acid, sodium polyacrylate, alginic acid, sodium alginate, and a combination thereof.

Item 5. The composition of any one of Items 1 to 4, further comprising a buffering agent and a pH adjusting agent.

Item 6. The composition of any one of Items 1 to 5, further comprising a prostaglandin F2α derivative. Examples of the prostaglandin F2α derivative include latanoprost, bimatoprost, travoprost, and tafluprost.

Item 7. The composition of any one of Items 1 to 6, further comprising a carbonic

anhydrase inhibitor. Examples of the carbonic anhydrase inhibitor include dorzolamide, brinzolamide, acetazolamide, and a pharmaceutically acceptable salt thereof.

Item 8. The composition of any one of Items 1 to 7, further comprising another agent having ocular hypotensive effect such as an adrenaline α2 agonist and a ROCK (Rho kinase) inhibitor. Examples of the adrenaline α2 agonist include brimonidine tartrate, dipivefrin hydrochloride, and clonidine. Examples of the ROCK inhibitor include ripasudil hydrochloride hydrate and netarsudil mesylate.

Item 9. The composition of any one of Items 1 to 8, wherein carteolol or a pharmaceutically acceptable salt thereof is comprised in an amount ranging from 0.1 to 5 w/v% to the total amount of the composition.

Item 10. The composition of any one of Items 1 to 9, wherein edetic acid or a pharmaceutically acceptable salt thereof is comprised in an amount ranging from 0.01 to 0.2 w/v% to the total amount of the composition.

Item 11. The composition of any one of Items 1 to 10, wherein edetic acid or a pharmaceutically acceptable salt thereof is comprised in a ratio ranging from 0.002 to 2.0 w/w to the amount of carteolol or a pharmaceutically acceptable salt thereof comprised in the composition.

Item 12. The composition of any one of Items 1 to 11, wherein pH ranges from 5.0 to 8.0.

Item 13. The composition of any one of Items 1 to 12 in the form of an eye drop.

Item 14. The composition of any one of Items 1 to 13 in the form of an aqueous eye drop or suspended eye drop.

Item 15. The composition of any one of Items 1 to 14 for use as a multiple-dose-type eye drop.

Item 16. The composition of any one of Items 1 to 15 for the treatment of glaucoma or ocular hypertension.

Item 17. The composition of any one of Items 1 to 16 for use in combination with a prostaglandin formulation. The prostaglandin formulation refers to a formulation comprising a prostaglandin F2α derivative.

[0013] Item 18. A method for enhancing preservative effectiveness of carteolol or a pharmaceutically acceptable salt thereof with edetic acid or a pharmaceutically acceptable salt thereof, comprising combining carteolol or a pharmaceutically acceptable salt thereof with edetic acid or a pharmaceutically acceptable salt thereof.

Item 19. Use of edetic acid or a pharmaceutically acceptable salt thereof for enhancing preservative effectiveness of carteolol or a pharmaceutically acceptable salt thereof.

Item 20. A method for enhancing preservative effectiveness of carteolol or a pharmaceutically acceptable salt thereof with propylene glycol, comprising combining

carteolol or a pharmaceutically acceptable salt thereof with propylene glycol.

Item 21. Use of propylene glycol for enhancing preservative effectiveness of carteolol or a pharmaceutically acceptable salt thereof.

Item 22. Use of a combination of edetic acid or a pharmaceutically acceptable salt thereof and propylene glycol for enhancing preservative effectiveness of carteolol or a pharmaceutically acceptable salt thereof.

Item 23. A method for improving light stability of carteolol or a pharmaceutically acceptable salt thereof with edetic acid or a pharmaceutically acceptable salt thereof, comprising combining carteolol or a pharmaceutically acceptable salt thereof with edetic acid or a pharmaceutically acceptable salt thereof.

Item 24. Use of edetic acid or a pharmaceutically acceptable salt thereof for improving light stability of carteolol or a pharmaceutically acceptable salt thereof.

Item 25. A method for improving light stability of carteolol or a pharmaceutically acceptable salt thereof with alginic acid, comprising combining carteolol or a pharmaceutically acceptable salt thereof with alginic acid.

Item 26. Use of alginic acid for improving light stability of carteolol or a pharmaceutically acceptable salt thereof.

Item 27. Use of a combination of edetic acid or a pharmaceutically acceptable salt thereof and alginic acid for improving light stability of carteolol or a pharmaceutically acceptable salt thereof.

[0014] Item 28. A process for preparing an ophthalmic pharmaceutical composition, comprising the step of mixing carteolol or a pharmaceutically acceptable salt thereof with edetic acid or a pharmaceutically acceptable salt thereof, optionally together with a pH adjusting agent, or propylene glycol, alginic acid or a combination thereof, wherein the pH adjusting agent is mixed so that pH of the resulted composition ranges from 5.0 to 8.0, and propylene glycol, alginic acid, or a combination thereof is mixed so that the osmotic pressure ratio of the resulted composition ranges from 0.8 to 1.2.

[0015] The present invention includes the embodiments illustrated as follows as well as any combinations thereof. Starting materials for the ingredients used herein may be in the form of a solvate such as a hydrate or an anhydrate as long as pharmaceutically applicable.

[0016] A pharmaceutical composition of the present invention comprises carteolol or a pharmaceutically acceptable salt thereof and edetic acid or a pharmaceutically acceptable salt thereof.

A pharmaceutical composition of the present invention can exert preservative effectiveness without a preserving agent or a preservative. Such a preserving agent or preservative includes, but is not limited thereto, benzalkonium chloride, benzethonium chloride, chlorhexidine gluconate, parabens, chlorobutanol, and sorbate. One em-

bodiment of a pharmaceutical composition in the present invention may not comprise a preserving agent or a preservative. Another embodiment of a pharmaceutical composition in the present invention may not comprise boric acid or a salt thereof. Still another embodiment of a pharmaceutical composition in the present invention may comprise boric acid or a salt thereof.

[0017] In one embodiment, a pharmaceutical composition of the present invention may comprise carteolol or a pharmaceutically acceptable salt thereof in an amount ranging from 0.1 to 5 w/v% to the total amount of the composition. A preferable amount (concentration) of carteolol or a pharmaceutically acceptable salt thereof includes the range of 0.5 and 2.5 w/v% to the total amount of the composition. A more preferable one ranges from 1 to 2 w/v%.

A pharmaceutically acceptable salt of carteolol includes a salt of carteolol with an inorganic acid. A preferable one is carteolol hydrochloride.

[0018] A pharmaceutical composition of the present invention may further comprise edetic acid or a pharmaceutically acceptable salt thereof in an amount ranging from 0.01 to 0.2 w/v% to the total amount of the composition. A preferable amount (concentration) of edetic acid or a pharmaceutically acceptable salt thereof includes the range of 0.01 and 0.15 w/v% to the total amount of the composition. A more preferable one ranges from 0.02 to 0.1 w/v%, further preferably from 0.03 to 0.07 w/v%.

Edetic acid or a pharmaceutically acceptable salt thereof may be comprised in the composition in a ratio ranging from 0.002 to 2.0 w/w to the amount of carteolol or a pharmaceutically acceptable salt thereof comprised in the composition. A preferable ratio ranges from 0.004 to 0.3 w/w, more preferably from 0.008 to 0.2 w/w, further preferably from 0.015 to 0.07 w/w, particularly preferably from 0.025 to 0.06 w/w.

A pharmaceutically acceptable salt of edetic acid includes a salt of edetic acid (ethylenediamine tetracetate; EDTA) with an inorganic base. A preferable one is disodium edetate hydrate.

Edetic acid or a pharmaceutically acceptable salt thereof may enhance preservative effectiveness that carteolol or a pharmaceutically acceptable salt thereof itself has, improve light stability, and/or reduce decomposition of carteolol.

[0019] A pharmaceutical composition of the present invention may optionally further comprise an additive ingredient such as a tonicity agent, a sustaining agent, a buffering agent, a pH adjusting agent, a solubilizing agent, and a solvent.

[0020] Such a tonicity agent includes, but is not limited thereto, propylene glycol, glycerin, polyethylene glycol, trehalose, maltose, sucrose, glucose, sorbitol, mannitol, sodium chloride, potassium chloride, calcium chloride, magnesium chloride, and a combination thereof. A preferable one is propylene glycol or sodium chloride.

The amount (concentration) of a tonicity agent comprised in the composition

includes, but is not limited thereto, such an amount that the osmotic pressure ratio of the composition is in the range of 0.8 and 1.2, preferably the range of 0.9 and 1.1. Such an amount specifically ranges from 0.5 to 2.0 w/v%, preferably 1.0 to 1.6 w/v%.
A tonicity agent may be comprised in the composition in a ratio ranging from 0.08 to 20 w/w to the amount of carteolol or a pharmaceutically acceptable salt thereof comprised in the composition, preferably 0.16 to 4 w/w, more preferably 0.2 to 2 w/w.
A tonicity agent may be comprised in the composition in a ratio ranging from 3 to 200 w/w to the amount of edetic acid or a pharmaceutically acceptable salt thereof, preferably 4 to 100 w/w, more preferably 6 to 70 w/w.

[0021] Such a sustaining agent includes, but is not limited thereto, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinyl alcohol, carboxyvinyl polymer, polyvinylpyrrolidone, carboxymethyl cellulose, polyacrylic acid, sodium polyacrylate, alginic acid, sodium alginate, and a combination thereof. A preferable one is alginic acid.

The amount (concentration) of a sustaining agent comprised in the composition includes, but is not limited thereto, an amount ranging from 0.1 to 5 w/v%. A preferable one is an amount ranging from 0.5 to 2 w/v%, more preferably from 0.8 to 1.2 w/v%.

A sustaining agent may be comprised in the composition in a ratio ranging from 0.25 to 2 w/w to the amount of carteolol or a pharmaceutically acceptable salt thereof comprised in the composition, preferably from 0.4 to 1.2 w/w.

A sustaining agent may be comprised in the composition in a ratio ranging from 5 to 100 w/w to the amount of edetic acid or a pharmaceutically acceptable salt thereof comprised in the composition, preferably from 10 to 40 w/w.

[0022] Such a buffering agent includes, but is not limited thereto, phosphate such as sodium phosphate, sodium dihydrogen phosphate, disodium hydrogen phosphate, potassium phosphate, potassium dihydrogen phosphate, and dipotassium hydrogen phosphate, boric acid and borate such as sodium borate and potassium borate, citric acid and citrate such as sodium citrate and disodium citrate, acetic acid and acetate such as sodium acetate, potassium acetate, carbonate such as sodium carbonate and sodium hydrogencarbonate, and a combination thereof. A preferable one is phosphate. A more preferable one is sodium dihydrogen phosphate and disodium hydrogen phosphate.

The amount (concentration) of a buffering agent comprised in the composition includes, but is not limited thereto, an amount ranging from 0.01 to 1 w/v%, preferably from 0.04 to 0.4 w/v%.

[0023] Such a pH adjusting agent includes, but is not limited thereto, an acid such as hydrochloric acid, lactic acid, citric acid, phosphoric acid, and acetic acid, and an alkali base such as sodium hydroxide, potassium hydroxide, sodium carbonate, and sodium

hydrogencarbonate. A preferable one is hydrochloric acid or sodium hydroxide. The amount (concentration) of a pH adjusting agent comprised in the composition includes, but is not limited thereto, such an amount that a pH value of the composition is adjusted to be in the range of 5.0 and 8.5. Preferably, a pH value is adjusted to be in the range of 5.0 and 8.0. More preferably, a pH value is adjusted to be in the range of 6.0 to 8.0, further preferably in the range of 6.2 and 7.2.

[0024] Such a solubilizing agent includes, but is not limited thereto, vegetable fat and oil such as polysorbate 80, polyoxyethylene hydrogenated castor oil 60, macrogol 4000, polyvinyl alcohol, tyloxapol, polyoxyethylene polyoxypropylene glycol, polyoxyl stearate, and soy oil. A preferable one is polysorbate 80.

The amount (concentration) of a solubilizing agent comprised in the composition includes, but is not limited thereto, an amount ranging from 0.05 to 5 w/v%, preferably from 0.1 to 3 w/v%, more preferably from 0.1 to 2 w/v%.

[0025] Such a solvent includes, but is not limited thereto, purified water, sterile purified water, and water for injection. A preferable one is sterile purified water or water for injection.

[0026] A pharmaceutical composition of the present invention may further comprise a prostaglandin F2α derivative. A prostaglandin F2α derivative may be comprised in the composition in an amount ranging from 0.0005 to 0.1 w/v% to the total amount of the composition. A preferable amount (concentration) of a prostaglandin F2α derivative comprised in the composition includes an amount ranging from 0.001 to 0.05 w/v% to the total amount of the composition, more preferably from 0.0015 to 0.03 w/v%.

A prostaglandin F2α derivative includes, but is not limited thereto, latanoprost, bimatoprost, travoprost, and tafluprost.

[0027] In another embodiment, the present invention may be a pharmaceutical composition for use in combination with a formulation comprising a prostaglandin F2α derivative (hereinafter also referred to as a "prostaglandin formulation"). A pharmaceutical composition of the present invention may be administered to a subject simultaneously with or at a certain time before or after administration of a prostaglandin F2α derivative.

[0028] A pharmaceutical composition of the present invention may further comprise a carbonic anhydrase inhibitor. A carbonic anhydrase inhibitor may be comprised in the composition in an amount ranging from 0.1 to 5 w/v% to the total amount of the composition. A preferable amount (concentration) of a carbonic anhydrase inhibitor comprised in the composition includes an amount ranging from 0.5 to 2.5 w/v% to the total amount of the composition, more preferably from 1 to 2 w/v%.

A carbonic anhydrase inhibitor includes, but is not limited thereto, dorzolamide, brinzolamide, acetazolamide, and a pharmaceutically acceptable salt thereof.

[0029] A pharmaceutical composition of the present invention may further comprise another

agent having ocular hypotensive effect. The agent having ocular hypotensive effect may be comprised in the composition in an amount ranging from 0.1 to 5 w/v% to the total amount of the composition. A preferable amount (concentration) of the agent having ocular hypotensive effect comprised in the composition includes an amount ranging from 0.5 to 2.5 w/v% to the total amount of the composition, more preferably from 1 to 2 w/v%.

The agent having ocular hypotensive effect includes, but is not limited thereto, an adrenaline α2 agonist and a ROCK (Rho kinase) inhibitor. Examples of the adrenaline α2 agonist include brimonidine tartrate, dipivefrin hydrochloride, and clonidine. Examples of the ROCK inhibitor include ripasudil hydrochloride hydrate, and netarsudil mesylate.

[0030] A pharmaceutical composition of the present invention may be preferably in the form of an ophthalmic solution. A more preferable one is an aqueous eye drop or suspended eye drop comprising aqueous solvent such as purified water, sterile purified water or water for injection. A pharmaceutical composition of the present invention may be also a unit-dose-type eye drop wherein a single dose is individually packaged, or a multiple-dose-type eye drop that can be repeatedly used. A preferable one is a multiple-dose-type eye drop.

[0031] A pharmaceutical composition of the present invention may be useful for the treatment of glaucoma such as primary open-angle glaucoma, primary closed-angle glaucoma, developmental glaucoma, secondary glaucoma, normal tension glaucoma, and eye diseases such as ocular hypertension. Carteolol can reduce intraocular pressure, and a pharmaceutical composition of the present invention may also be useful for the treatment of glaucoma such as primary open-angle glaucoma, primary closed-angle glaucoma, developmental glaucoma, and secondary glaucoma, and eye diseases such as ocular hypertension.

[0032] One embodiment of the present invention provides a pharmaceutical composition comprising carteolol or a pharmaceutically acceptable salt thereof and edetic acid or a pharmaceutically acceptable salt thereof, wherein weak preservative effectiveness which carteolol or a pharmaceutically acceptable salt thereof has in addition to its main effect is enhanced.

In another embodiment, edetic acid or a pharmaceutically acceptable salt thereof may enhance preservative effectiveness of carteolol or a pharmaceutically acceptable salt thereof in a mixed solution with carteolol or a pharmaceutically acceptable salt thereof. Preservative effectiveness of carteolol or a pharmaceutically acceptable salt thereof may be further enhanced by adding a tonicity agent to the mixed solution.

[0033] Another embodiment of the present invention provides a pharmaceutical composition comprising carteolol or a pharmaceutically acceptable salt thereof and edetic acid or a

pharmaceutically acceptable salt thereof, wherein low light stability of carteolol or a pharmaceutically acceptable salt thereof is improved or its decomposition is reduced. In another embodiment, edetic acid or a pharmaceutically acceptable salt thereof may improve light stability of or reduce decomposition of carteolol or a pharmaceutically acceptable salt thereof in a mixed solution with carteolol or a pharmaceutically acceptable salt thereof. Adding a sustaining agent to the mixed solution may further improve light stability of or further reduce decomposition of carteolol or a pharmaceutically acceptable salt thereof.

[0034] Another embodiment of the present invention provides a process for preparing an ophthalmic pharmaceutical composition. A process for preparation in the present invention comprises the step of mixing carteolol or a pharmaceutically acceptable salt thereof with edetic acid or a pharmaceutically acceptable salt thereof. Carteolol or a pharmaceutically acceptable salt thereof and edetic acid or a pharmaceutically acceptable salt thereof may be optionally mixed with the pH adjusting agent mentioned above so that pH of the resulted pharmaceutical composition is adjusted in the range of 5.0 and 8.5, preferably 5.0 and 8.0, more preferably 6.0 and 8.0, further preferably 6.0 and 7.2. Carteolol or a pharmaceutically acceptable salt thereof and edetic acid or a pharmaceutically acceptable salt thereof may also be optionally mixed with the tonicity agent, the sustaining agent mentioned above or a combination thereof. Such a tonicity agent may be added so that the osmotic pressure ratio of the resulted pharmaceutical composition is adjusted in the range of 0.8 and 1.2, preferably 0.9 and 1.1.

Examples

[0035] The present invention is, but is not limited thereto, illustrated with the following experiments and examples in more detail. Unless otherwise specified, concentrations herein refer to weight per volume %, i.e., "w/v%", which is synonymous with "g/100 mL".

[0036] <Preservative Effectiveness Test>

Preservative effectiveness was assessed for the test solutions in the following Experiments in accordance with the test method of preservative effectiveness described in The Japanese Pharmacopoeia 17th edition, Reference information.

Specifically, bacteria such as Escherichia coli ATCC 8739, Pseudomonas aeruginosa ATCC 9027, and Staphylococcus aureus ATCC 6538, and/or fungi such as Candida albicans ATCC 10231 and Aspergillus brasiliensis ATCC 16404 were used to prepare corresponding bacterial liquids. Each bacterial liquid was inoculated into a test solution so as to comprise 10^5 to 10^6 CFU (colony forming unit)/mL, and the resultant was stored at 20 to 25°C. Viable bacterial counts were measured 7, 14, and 28 days after inoculation. Preservative effectiveness was determined on the basis of the change of

bacterial counts to the counts of bacteria inoculated. As for bacteria such as Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus, the case was determined as "adequate" where the bacterial counts were reduced in 1.0 log or more 7 days after inoculation and in 3.0 log or more 14 days after inoculation, and where the reduction of the bacterial counts 28 days after inoculation was equal to or less than that 14 days after inoculation. As for fungi such as Candida albicans and Aspergillus brasiliensis, the case was determined as "adequate" where the bacterial counts 7 days after inoculation was equal to or less than the counts of bacteria inoculated and those 14 and 28 days after inoculation were equal to or less than the counts of bacteria inoculated.

[0037] <Experiment 1>: Preservative effectiveness test for carteolol

Preservative effectiveness was assessed for carteolol in accordance with the following method.

<Preparation of the test solutions of Examples 1 to 10>

The components in the test solutions of Examples 1 to 10 were shown in Table 1. Carteolol hydrochloride, anhydrous disodium hydrogen phosphate, sodium dihydrogen phosphate dihydrate, and NaCl, which was added in such an amount that the osmotic pressure ratio of the solution was adjusted to 0.9 to 1.1, were measured, and sterile purified water was added to the mixture to be dissolved. The pH values of the solutions were adjusted to 5.0, 6.0, 7.0, 8.0, or 8.5 by addition of 5N sodium hydroxide or 1% hydrochloric acid, and sterile purified water was added to the solutions to obtain prescribed volumes. The solutions were filtered through a 0.22-μm-membrane filter, and 5 mL each of the solutions was loaded to a sterile glass vessel for a test solution.

[0038] <Preparation for Comparative examples 1 to 4: test solutions without carteolol hydrochloride>

The components in the test solutions of Comparative examples 1 to 4 were shown in Table 1. Anhydrous disodium hydrogen phosphate, sodium dihydrogen phosphate dihydrate, and NaCl, which was added in such an amount that the osmotic pressure ratio of the solution was adjusted to 0.9 to 1.1, were measured, and sterile purified water was added to the mixture to be dissolved. The pH values of the solutions were adjusted to 5.0, 6.0, 7.0, or 8.0 by addition of 5N sodium hydroxide or 1% hydrochloric acid, and sterile purified water was added to the solutions to obtain prescribed volumes. The solutions were filtered through a 0.22-μm-membrane filter, and 5 mL each of the solutions was loaded to a sterile glass vessel for a test solution.

[0039]

[Table 1-1]

Amounts (g/100 mL)	Example 1	Example 2	Example 3	Example 4	Example 5
Carteolol hydrochloride	1.0	1.0	1.0	1.0	1.0
Na_2HPO_4	0.04	0.04	0.04	0.04	0.04
$NaH_2PO_4.2H_2O$	0.04	0.04	0.04	0.04	0.04
NaOH or HCl	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
NaCl	0.674	0.674	0.674	0.674	0.674
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100	100
pH	5.0	6.0	7.0	8.0	8.5
Osmotic pressure ratio	1.0	1.0	1.0	1.0	1.0

[Table 1-2]

Amounts (g/100 mL)	Example 6	Example 7	Example 8	Example 9	Example 10
Carteolol hydrochloride	2.0	2.0	2.0	2.0	2.0
Na_2HPO_4	0.04	0.04	0.04	0.04	0.04
$NaH_2PO_4.2H_2O$	0.04	0.04	0.04	0.04	0.04
NaOH or HCl	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
NaCl	0.564	0.564	0.564	0.564	0.564
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100	100
pH	5.0	6.0	7.0	8.0	8.5
Osmotic pressure ratio	1.0	1.0	1.0	1.0	1.1

[Table 1-3]

Amounts (g/100 mL)	Comparative example 1	Comparative example 2	Comparative example 3	Comparative example 4
Carteolol hydrochloride	-	-	-	-
Na_2HPO_4	0.04	0.04	0.04	0.04
$NaH_2PO_4.2H_2O$	0.04	0.04	0.04	0.04
NaOH or HCl	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
NaCl	0.843	0.843	0.843	0.843
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100
pH	5.0	6.0	7.0	8.0
Osmotic pressure ratio	1.0	1.0	1.0	1.0

[0040] Preservative effectiveness was measured for the test solutions of Examples 1 to 10 and Comparative examples 1 to 4. The test results of preservative effectiveness were shown in Table 2 for each of Examples and Comparative examples.

In view of the test results of preservative effectiveness for each bacterium, it was demonstrated that Examples 1 to 10 were adequate for fungi in the preservative effectiveness test and basically showed preservative effectiveness against bacteria as well. All of Comparative examples 1 to 4 which did not contain carteolol hydrochloride were inadequate in the preservative effectiveness test. The results showed that carteolol hydrochloride has preservative effectiveness.

[0041]

[Table 2-1]

Test strains	*Escherichia coli*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*
Example 1	X	X	O
Example 2	X	X	O
Example 3	O	X	O
Example 4	O	O	O
Example 5	O	O	O
Example 6	X	X	O
Example 7	X	X	O
Example 8	O	O	O
Example 9	O	O	O
Example 10	O	O	O
Comparative example 1	X	X	O
Comparative example 2	X	X	X
Comparative example 3	X	X	X
Comparative example 4	X	X	X

[Table 2-2]

Test strains	*Candida albicans*	*Aspergillus brasiliensis*	Overall assessment of preservative effectiveness
Example 1	O	O	Inadequate
Example 2	O	O	Inadequate
Example 3	O	O	Inadequate
Example 4	O	O	Adequate
Example 5	O	O	Adequate
Example 6	O	O	Inadequate
Example 7	O	O	Inadequate
Example 8	O	O	Adequate
Example 9	O	O	Adequate
Example 10	O	O	Adequate
Comparative example 1	O	O	Inadequate
Comparative example 2	O	O	Inadequate
Comparative example 3	O	O	Inadequate
Comparative example 4	O	O	Inadequate

O means that a test strain was adequate in the assessment criterion of each bacterium

X means that a test strain was inadequate in the assessment criterion of each bacterium

[0042] <Experiment 2>: Effect of addition of disodium edetate hydrate on preservative effectiveness

Enhancement in preservative effectiveness of carteolol hydrochloride by disodium edetate hydrate was demonstrated according to the following method.

<Preparation of the test solutions of Examples 11 to 15>

The components in the test solutions of Examples 11 to 15 were shown in Table 3. Carteolol hydrochloride, anhydrous disodium hydrogen phosphate, sodium dihydrogen phosphate dihydrate, disodium edetate hydrate, and NaCl, which was added in such an amount that the osmotic pressure ratio of the solution was adjusted to 0.9 to 1.1, were measured, and sterile purified water was added to the mixture to be dissolved. The pH values of the solutions were adjusted to 5.0, 6.0, or 7.0 by addition of 5N sodium hydroxide or 1% hydrochloric acid, and sterile purified water was added to the solutions to obtain prescribed volumes. The solutions were filtered through a

0.22-μm-membrane filter, and 5 mL each of the solutions was loaded to a sterile glass vessel for a test solution.

[0043] <Preparation for Comparative examples 5 to 8: test solutions without carteolol hydrochloride>

The components in the test solutions of Comparative examples 5 to 8 were shown in Table 4. Disodium edetate hydrate, anhydrous disodium hydrogen phosphate, sodium dihydrogen phosphate dihydrate, and NaCl, which was added in such an amount that the osmotic pressure ratio of the solution was adjusted to 0.9 to 1.1, were measured, and prescribed volumes of sterile purified water was added to the mixture. The pH values of the solutions were adjusted to 5.0, 6.0, 7.0, or 8.0 by addition of 5N sodium hydroxide or 1% hydrochloric acid, and sterile purified water was added to the solutions to obtain prescribed volumes. The solutions were filtered through a 0.22-μm-membrane filter, and 5 mL each of the solutions was loaded to a sterile glass vessel for a test solution.

[0044] [Table 3]

Amounts (g/100 mL)	Example 11	Example 12	Example 13	Example 14	Example 15
Carteolol hydrochloride	1.0	1.0	1.0	2.0	2.0
Disodium edetate hydrate	0.05	0.05	0.05	0.05	0.05
Na_2HPO_4	0.04	0.04	0.04	0.04	0.04
$NaH_2PO_4.2H_2O$	0.04	0.04	0.04	0.04	0.04
NaOH or HCl	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
NaCl	0.660	0.660	0.660	0.553	0.553
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100	100
pH	5.0	6.0	7.0	5.0	6.0
Osmotic pressure ratio	1.0	1.0	1.0	1.0	1.0

[Table 4]

Amounts (g/100 mL)	Comparative example 5	Comparative example 6	Comparative example 7	Comparative example 8
Carteolol hydrochloride	-	-	-	-
Disodium edetate hydrate	0.05	0.05	0.05	0.05
Na_2HPO_4	0.04	0.04	0.04	0.04
$NaH_2PO_4.2H_2O$	0.04	0.04	0.04	0.04
NaOH or HCl	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
NaCl	0.830	0.830	0.830	0.830
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100
pH	5.0	6.0	7.0	8.0
Osmotic pressure ratio	1.0	1.0	1.0	1.0

[0045] Preservative effectiveness was measured for the test solutions of Examples 11 to 15 and Comparative examples 5 to 8 against bacteria such as Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus. The test results of preservative effectiveness were shown in Table 5 for each of Examples and Comparative examples.

Examples 11 to 15 basically showed preservative effectiveness against bacteria, but Comparative examples 5 to 8 were inadequate in the preservative effectiveness test. The results showed that a combination of carteolol hydrochloride and disodium edetate hydrate enhanced preservative effectiveness.

[0046]

[Table 5]

Test strains	*Escherichia coli*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	Overall assessment of preservative effectiveness against bacteria
Example 11	X	O	O	Inadequate
Example 12	X	O	O	Inadequate
Example 13	O	O	O	Adequate
Example 14	X	O	O	Inadequate
Example 15	X	O	O	Inadequate
Comparative example 5	X	X	O	Inadequate
Comparative example 6	X	X	X	Inadequate
Comparative example 7	X	X	X	Inadequate
Comparative example 8	O	X	X	Inadequate

O means that a test strain was adequate in the assessment criterion of each bacterium

X means that a test strain was inadequate in the assessment criterion of each bacterium

[0047] <Experiment 3>: Effect of addition of propylene glycol on preservative effectiveness

Effect of addition of propylene glycol on preservative effectiveness of carteolol hydrochloride was demonstrated at pH 5.0 and 6.0 according to the following method.

<Test solutions of Examples 16 to 19>

The components in the test solutions of Examples 16 to 19 were shown in Table 6. Carteolol hydrochloride, anhydrous disodium hydrogen phosphate, sodium dihydrogen phosphate dihydrate, disodium edetate hydrate, and propylene glycol were measured so that the compositions shown in Table 6 were prepared. Sterile purified water was added to the mixture to be dissolved. The pH values of the solutions were adjusted to 5.0 or 6.0 by addition of 1% hydrochloric acid, and sterile purified water was added to the solutions to obtain prescribed volumes. The solutions were filtered through a 0.22-μm-membrane filter, and 5 mL each of the solutions was loaded to a sterile glass vessel for a test solution.

[0048] <Preparation of the test solutions of Comparative examples 9 to 16>

The components in the test solutions of Comparative example 9 to 16 were shown in Table 7. Carteolol hydrochloride, anhydrous disodium hydrogen phosphate, sodium di-

hydrogen phosphate dihydrate, and propylene glycol (for Comparative examples 9 to 12), anhydrous disodium hydrogen phosphate, sodium dihydrogen phosphate dihydrate, propylene glycol, and NaCl, which was added in such an amount that the osmotic pressure ratio of the solution was adjusted to 0.9 to 1.1 (for Comparative examples 13 and 14), or disodium edetate hydrate, anhydrous disodium hydrogen phosphate, sodium dihydrogen phosphate dihydrate, propylene glycol, and NaCl, which was added in such an amount that the osmotic pressure ratio of the solution was adjusted to 0.9 to 1.1 (for Comparative examples 15 and 16) were mixed to be dissolved. The pH values of the solutions were adjusted to 5.0 or 6.0 by addition of 1% hydrochloric acid, and sterile purified water was added to the solutions to obtain prescribed volumes. The solutions were filtered through a 0.22-μm-membrane filter, and 5 mL each of the solutions was loaded to a sterile glass vessel for a test solution.

[0049] [Table 6]

Amounts (g/100 mL)	Example 16	Example 17	Example 18	Example 19
Carteolol hydrochloride	1.0	1.0	2.0	2.0
Disodium edetate hydrate	0.05	0.05	0.05	0.05
Propylene glycol	1.55	1.55	1.3	1.3
Na_2HPO_4	0.04	0.04	0.04	0.04
$NaH_2PO_4.2H_2O$	0.04	0.04	0.04	0.04
HCl	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100
pH	5.0	6.0	5.0	6.0
Osmotic pressure ratio	1.0	1.0	1.1	1.0

[0050]

[Table 7-1]

Amounts (g/100 mL)	Comparative example 9	Comparative example 10	Comparative example 11	Comparative example 12
Carteolol hydrochloride	1.0	1.0	2.0	2.0
Disodium edetate hydrate	-	-	-	-
Propylene glycol	1.55	1.55	1.3	1.3
Na_2HPO_4	0.04	0.04	0.04	0.04
$NaH_2PO_4.2H_2O$	0.04	0.04	0.04	0.04
HCl	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100
pH	5.0	6.0	5.0	6.0
Osmotic pressure ratio	1.0	1.0	1.0	1.0

[Table 7-2]

Amounts (g/100 mL)	Comparative example 13	Comparative example 14	Comparative example 15	Comparative example 16
Carteolol hydrochloride	-	-	-	-
Disodium edetate hydrate	-	-	0.05	0.05
Propylene glycol	1.55	1.55	1.55	1.55
Na_2HPO_4	0.04	0.04	0.04	0.04
$NaH_2PO_4.2H_2O$	0.04	0.04	0.04	0.04
HCl	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
NaCl	0.217	0.217	0.205	0.205
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100
pH	5.0	6.0	5.0	6.0
Osmotic pressure ratio	1.0	1.0	1.0	1.0

[0051] Preservative effectiveness was measured for the test solutions of Examples 16 to 19 and Comparative examples 9 to 16 against bacteria such as Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus. The test results of preservative effectiveness were shown in Table 8 for each of Examples and Comparative examples.

Examples 16 to 19 wherein propylene glycol was added to the composition comprising carteolol hydrochloride and disodium edetate hydrate met the criteria against all of the three bacteria of Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus to be adequate in the preservative effectiveness test. Comparative examples 9 to 12 which contained carteolol hydrochloride but did not contain disodium edetate hydrate did not meet the criteria against Escherichia coli or Pseudomonas aeruginosa to be inadequate. Comparative examples 13 and 14 which did not contain carteolol hydrochloride or disodium edetate hydrate but contained propylene glycol only were inadequate in the preservative effectiveness test. Comparative examples 15 and 16 which did not contain carteolol hydrochloride but contained propylene glycol and disodium edetate hydrate did not meet the criteria to be inadequate in the preservative effectiveness test. The results revealed that good preservative effectiveness was shown in a combination of carteolol hydrochloride,

disodium edetate hydrate, and propylene glycol.

[0052] [Table 8]

Test strains	*Escherichia coli*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	Overall assessment of preservative effectiveness against bacteria
Example 16	O	O	O	Adequate
Example 17	O	O	O	Adequate
Example 18	O	O	O	Adequate
Example 19	O	O	O	Adequate
Comparative example 9	X	X	O	Inadequate
Comparative example 10	X	X	O	Inadequate
Comparative example 11	X	O	O	Inadequate
Comparative example 12	O	X	O	Inadequate
Comparative example 13	X	X	O	Inadequate
Comparative example 14	X	X	X	Inadequate
Comparative example 15	X	X	O	Inadequate
Comparative example 16	X	X	X	Inadequate

O means that a test strain was adequate in the assessment criterion of each bacterium

X means that a test strain was inadequate in the assessment criterion of each bacterium

[0053] <Experiment 4>: Effect of addition of alginic acid on preservative effectiveness

Enhancement in preservative effectiveness of carteolol hydrochloride by alginic acid was demonstrated according to the following method.

<Preparation of the test solutions of Examples 20 and 21>

The components in the test solutions of Examples 20 and 21 were shown in Table 9. Carteolol hydrochloride, anhydrous disodium hydrogen phosphate, sodium dihydrogen phosphate dihydrate, disodium edetate hydrate, propylene glycol, and alginic acid were measured so that the compositions shown in Table 9 were prepared, and sterile purified water and 5N sodium hydroxide were added to the mixture to be dissolved. The pH values of the solutions were adjusted to 6.7 by addition of 5N sodium hydroxide, and sterile purified water was added to the solutions to obtain prescribed volumes. The solutions were filtered through a 0.22-μm-membrane filter, and 5 mL each of the solutions was loaded to a sterile glass vessel for a test solution.

[0054] <Preparation of the test solutions of Comparative examples 17 and 18: test solutions without alginic acid>

The components in the test solutions of Comparative examples 17 and 18 were shown in Table 9. Carteolol hydrochloride, anhydrous disodium hydrogen phosphate, sodium dihydrogen phosphate dihydrate, disodium edetate hydrate, and propylene glycol were measured so that the compositions shown in Table 9 were prepared. Sterile purified water was added to the mixture to be dissolved. The pH values of the solutions were adjusted to 6.7 by addition of 5N sodium hydroxide, and sterile purified water was added to the solutions to obtain prescribed volumes. The solutions were filtered through a 0.22-μm-membrane filter, and 5 mL each of the solutions was loaded to a sterile glass vessel for a test solution.

[0055] [Table 9]

Amounts (g/100 mL)	Example 20	Example 21	Comparative example 17	Comparative example 18
Carteolol hydrochloride	1.0	1.0	1.0	1.0
Alginic acid	1.0	1.0	-	-
Disodium edetate hydrate	0.05	0.1	0.05	0.1
Propylene glycol	1.30	1.30	1.55	1.55
Na_2HPO_4	0.04	0.04	0.04	0.04
$NaH_2PO_4.2H_2O$	0.04	0.04	0.04	0.04
NaOH	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100
pH	6.7	6.7	6.7	6.7
Osmotic pressure ratio	1.0	1.0	1.0	1.0

[0056] Preservative effectiveness was measured for the test solutions of Examples 20 and 21 and Comparative examples 17 and 18 against bacteria such as Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus. The test results of preservative

effectiveness were shown in Table 10 for each of Examples and Comparative examples.

[0057] [Table 10]

Test strains	*Escherichia coli*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	Overall assessment of preservative effectiveness against bacteria
Example 20	O	O	O	Adequate
Example 21	O	O	O	Adequate
Comparative example 17	O	O	O	Adequate
Comparative example 18	O	O	O	Adequate

O means that a test strain was adequate in the assessment criterion of each bacterium

X means that a test strain was inadequate in the assessment criterion of each bacterium

[0058] <Experiment 5>: Effect of addition of disodium edetate hydrate on light stability

Improvement in light stability of carteolol hydrochloride by disodium edetate hydrate was demonstrated according to the following method.

<The test solutions of Examples 22 to 25>

The components in the test solutions of Examples 22 to 25 were shown in Table 11. Carteolol hydrochloride, anhydrous disodium hydrogen phosphate, sodium dihydrogen phosphate dihydrate, and disodium edetate hydrate were mixed so that the compositions shown in Table 11 were prepared. Sterile purified water was added to the mixture to be dissolved. The pH values of the solutions were adjusted to 6.7 by addition of 5N sodium hydroxide, and sterile purified water was added to the solutions to obtain prescribed volumes. The solutions were filtered through a 0.22-μm-membrane filter, and 5 mL each of the solutions was loaded to a sterile glass vessel for a test solution.

[0059] <Preparation of the test solutions of Comparative examples 19 and 20: test solutions without disodium edetate hydrate>

The components in the test solutions of Comparative examples 19 and 20 were shown in Table 12. Carteolol hydrochloride, anhydrous disodium hydrogen phosphate, and sodium dihydrogen phosphate dihydrate were mixed so that the compositions shown in Table 12 were prepared. Sterile purified water was added to the mixture to be dissolved. The pH values of the solutions were adjusted to 6.7 by addition of 5N

sodium hydroxide, and sterile purified water was added to the solutions to obtain prescribed volumes. The solutions were filtered through a 0.22-μm-membrane filter, and 5 mL each of the solutions was loaded to a sterile glass vessel for a test solution.

[0060] [Table 11]

Amounts (g/100 mL)	Example 22	Example 23	Example 24	Example 25
Carteolol hydrochloride	1.0	1.0	2.0	2.0
Disodium edetate hydrate	0.05	0.10	0.05	0.10
Na_2HPO_4	0.04	0.04	0.04	0.04
$NaH_2PO_4.2H_2O$	0.04	0.04	0.04	0.04
NaOH	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100
pH	6.7	6.7	6.7	6.7

[0061] [Table 12]

Amounts (g/100 mL)	Comparative example 19	Comparative example 20
Carteolol hydrochloride	1.0	2.0
Disodium edetate hydrate	-	-
Na_2HPO_4	0.04	0.04
$NaH_2PO_4.2H_2O$	0.04	0.04
NaOH	Appropriate amount	Appropriate amount
Purified water	Appropriate amount	Appropriate amount
Total amount (mL)	100	100
pH	6.7	6.7

[0062] Light stability was measured for the test solutions of Examples 22 to 25 and Comparative examples 19 and 20. White light with the illuminance of 3000 Lx from a white

lamp and ultraviolet light with the light intensity of 50 μW/cm^2 from a chemical lamp were irradiated for 400 hours. Each sample solution after light irradiation was compared with a sample solution which was stored in a dark place at 4°C without light irradiation, and in each sample solution, the amount of 3,4-dehydrocarteolol among the decomposed products that were generated under photolysis of carteolol hydrochloride and the total amount of the decomposed products were measured. These are shown in Table 13. The decomposed products of carteolol hydrochloride were analyzed in high performance liquid chromatograph (HPLC).

[0063] (HPLC condition for measurement of the amount of 3,4-dehydrocarteolol)

Column: 5 μm of octadecylsilylated silica gel for liquid chromatography was loaded in a stainless tube with the inner diameter of 4.6 mm and the length of 15 cm.

Mobile phase: To sodium 1-hexane sulfonate (1.51 g) were added acetic acid (100; 3 mL) and water (1000 mL), and the mixture was dissolved. To the solution (830 mL) was added acetonitrile (170 mL).

Detector: Ultraviolet absorptiometer

[0064] [Table 13]

	Decomposed product (%)	Total amount of decomposed products (%)
Example 22	1.369	3.31
Example 23	0.939	2.48
Example 24	1.605	3.62
Example 25	1.451	3.28
Comparative example 19	1.720	3.97
Comparative example 20	1.841	4.34

[0065] The amount of 3,4-dehydrocarteolol which was a photolysis product of carteolol hydrochloride and the total amount of the decomposed products were concentration-dependently decreased by addition of disodium edetate hydrate to a carteolol solution. The results showed that disodium edetate hydrate improved light stability of carteolol hydrochloride.

[0066] <Experiment 6>: Effect of addition of alginic acid on light stability

Improvement in light stability of carteolol hydrochloride by alginic acid was demonstrated according to the following method.

<Test solutions of Examples 26 to 29, 60, and 61>

The components in the test solutions of Examples 26 to 29, 60, and 61 were shown in Table 14. Carteolol hydrochloride, anhydrous disodium hydrogen phosphate, sodium dihydrogen phosphate dihydrate, disodium edetate hydrate, propylene glycol, and alginic acid were measured so that the compositions shown in Table 14 were prepared. Sterile purified water was added to the mixture. 5N sodium hydroxide was added to the mixture with being stirred to be dissolved. The pH values of the solutions were adjusted to 6.7 by addition of 5N sodium hydroxide, and sterile purified water was added to the solutions to obtain prescribed volumes. The solutions were filtered through a 0.22-μm-membrane filter, and 5 mL each of the solutions was loaded to a sterile glass vessel for a test solution.

[0067] <Preparation of the test solutions of Comparative examples 21 to 28: test solutions without disodium edetate hydrate and/or alginic acid>

The components in the test solutions of Comparative examples 21 to 28 were shown in Table 15. Carteolol hydrochloride, anhydrous disodium hydrogen phosphate, sodium dihydrogen phosphate dihydrate, disodium edetate hydrate, propylene glycol, and NaCl, which was added in such an amount that the osmotic pressure ratio of the solution was adjusted to 0.9 to 1.1, were measured so that the compositions shown in Table 15 were prepared, and sterile purified water was added to the mixture to be dissolved. Then, for Comparative examples 21 and 25, alginic acid was added to the solutions with being stirred, and 5N sodium hydroxide was added to the mixture to dissolve alginic acid. The pH values of the solutions were adjusted to 6.7 by addition of 5N sodium hydroxide, and sterile purified water was added to the solutions to obtain prescribed volumes. The solutions were filtered through a 0.22-μm-membrane filter, and 5 mL each of the solutions was loaded to a sterile glass vessel for a test solution.

[0068]

[Table 14]

Amounts (g/100 mL)	Example 26	Example 27	Example 28	Example 29	Example 60	Example 61
Carteolol hydrochloride	1.0	1.0	2.0	2.0	1.0	2.0
Alginic acid	1.0	1.0	1.0	1.0	2.0	2.0
Disodium edetate hydrate	0.05	0.1	0.05	0.1	0.1	0.1
Propylene glycol	1.3	1.3	1.0	1.0	1.0	0.7
Na_2HPO_4	0.04	0.04	0.04	0.04	0.04	0.04
$NaH_2PO_4.2H_2O$	0.04	0.04	0.04	0.04	0.04	0.04
NaOH	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100	100	100
pH	6.7	6.7	6.7	6.7	6.7	6.7
Osmotic pressure ratio	1.0	1.0	1.0	1.0	1.0	1.0

[0069]

[Table 15-1]

Amounts (g/100 mL)	Comparative example 21	Comparative example 22	Comparative example 23	Comparative example 24
Carteolol hydrochloride	1.0	1.0	1.0	1.0
Alginic acid	1.0	-	-	-
Disodium edetate hydrate	-	-	0.05	0.10
Propylene glycol	1.3	1.3	1.3	1.3
Na_2HPO_4	0.04	0.04	0.04	0.04
$NaH_2PO_4.2H_2O$	0.04	0.04	0.04	0.04
NaOH	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100
pH	6.7	6.7	6.7	6.7
Osmotic pressure ratio	1.0	1.0	1.0	1.0

[Table 15-2]

Amounts (g/100 mL)	Comparative example 25	Comparative example 26	Comparative example 27	Comparative example 28
Carteolol hydrochloride	2.0	2.0	2.0	2.0
Alginic acid	1.0	-	-	-
Disodium edetate hydrate	-	-	0.05	0.10
Propylene glycol	1.0	1.3	1.3	1.3
Na_2HPO_4	0.04	0.04	0.04	0.04
$NaH_2PO_4.2H_2O$	0.04	0.04	0.04	0.04
NaOH	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100
pH	6.7	6.7	6.7	6.7
Osmotic pressure ratio	1.0	1.0	1.0	1.0

[0070] Light stability was measured for the test solutions of Examples 26 to 29, 60, and 61 and Comparative examples 21 to 28. White light with the illuminance of 3000 Lx from a white lamp and ultraviolet light with the light intensity of 50 $\mu W/cm^2$ from a chemical lamp were irradiated for 400 hours. In each sample solution after light irradiation, the amount of 3,4-dehydrocarteolol among the decomposed products that were generated under photolysis of carteolol hydrochloride and the total amount of the decomposed products were measured. These are shown in Table 16. The decomposed products of carteolol hydrochloride under photolysis were analyzed in high performance liquid chromatograph (HPLC).

[0071] (HPLC condition for measurement of the amount of 3,4-dehydrocarteolol)

Column: 5 μm of octadecylsilylated silica gel for liquid chromatography was loaded in a stainless tube with the inner diameter of 4.6 mm and the length of 15 cm.

Mobile phase: To sodium 1-hexane sulfonate (1.51 g) were added acetic acid (100; 3 mL) and water (1000 mL), and the mixture was dissolved. To the solution (830 mL) was added acetonitrile (170 mL).

Detector: Ultraviolet absorptiometer

[0072] [Table 16]

	Decomposed product (%)	Total amount of decomposed products (%)
Example 26	0.038	0.53
Example 27	0.043	0.57
Example 28	0.050	0.52
Example 29	0.055	0.65
Example 60	0.009	0.61
Example 61	0.018	0.50
Comparative example 21	0.836	2.57
Comparative example 22	1.838	4.01
Comparative example 23	1.554	3.48
Comparative example 24	1.129	2.57
Comparative example 25	1.233	2.28
Comparative example 26	1.989	4.54
Comparative example 27	1.813	3.95
Comparative example 28	1.501	3.24

[0073] Addition of alginic acid to a sample solution comprising carteolol hydrochloride and disodium edetate hydrate significantly reduced photolysis of carteolol hydrochloride, and the amount of 3,4-dehydrocarteolol which was a decomposed product under photolysis of carteolol hydrochloride increased when either of alginic acid or disodium edetate hydrate or both of them were not added. The amount of 3,4-dehydrocarteolol and the total amount of the decomposed products significantly increased in Comparative examples 22 and 26 where neither alginic acid or disodium edetate hydrate was contained, compared to those in the samples where either of alginic acid

(Comparative examples 21 and 25) or disodium edetate hydrate (Comparative examples 23, 24, 27, and 28) only was added. The results suggested that alginic acid and disodium edetate hydrate reduced photolysis of carteolol hydrochloride and improved its light stability. It was also suggested that a combination of alginic acid and disodium edetate hydrate improved light stability of carteolol hydrochloride.

[0074] <Assessment of test results>

The results revealed that a pharmaceutical composition in the present invention was adequate in the preservative effectiveness test described in The Japanese Pharmacopoeia 17th edition, Reference information, and reduced photolysis of carteolol hydrochloride, resulting in stabilization under light.

In the present invention, it was revealed that addition of disodium edetate hydrate, optionally a tonicity agent, e.g. propylene glycol, and/or a sustaining agent, e.g. alginic acid, to a β blocker allows to keep preservative effectiveness of the β blocker without a preservative such as benzalkonium chloride and boric acid that causes a concern about side effects even in the case where a conventional eye-drop bottle that allows for multiple doses is used. It was also revealed that a pharmaceutical composition in the present invention has so good light stability that the active ingredient may not be decomposed under light even when the composition is stored without protection from light.

[0075] <Formulation example 1>: Formulation examples of formulations comprising prostaglandin F2α derivatives

Examples 30 to 39 and Comparative example 29 were prepared according to the following methods.

<Example 30>

Latanoprost (0.005 g), polysorbate 80 (0.1 g), and purified water (80 g) were measured to be mixed, and the mixture was warmed to 60°C to be dissolved. Then, the mixture was cooled to room temperature. To this solution were added carteolol hydrochloride (2.0 g), alginic acid (1.0 g), boric acid (1.0 g), and disodium edetate hydrate (0.1 g). The mixture was dissolved by addition of sodium hydroxide, and the pH value of the mixture was adjusted to 6.5. Then, to the mixture was added purified water so as to be the total amount of 100 g. The solution was filtered through a membrane filter with the pore diameter of 0.2 μm to prepare Example 30.

[0076] <Example 31>

Latanoprost (0.005 g), polysorbate 80 (0.1 g), and purified water (80 g) were measured to be mixed, and the mixture was warmed to 60°C to be dissolved. Then, the mixture was cooled to room temperature. To this solution were added carteolol hydrochloride (2.0 g), alginic acid (1.0 g), sodium chloride (0.4 g), sodium dihydrogen phosphate dihydrate (0.04 g), anhydrous disodium hydrogen phosphate (0.04 g), and

disodium edetate hydrate (0.1 g). The mixture was dissolved by addition of sodium hydroxide, and the pH value of the mixture was adjusted to 6.5. Then, to the mixture was added purified water so as to be the total amount of 100 g. The solution was filtered through a membrane filter with the pore diameter of 0.2 μm to prepare Example 31.

[0077] <Example 32>

Latanoprost (0.005 g) and purified water (80 g) were measured to be mixed, and the mixture was warmed to 60°C to be dissolved. Then, the mixture was cooled to room temperature. To this solution were added carteolol hydrochloride (2.0 g), alginic acid (1.0 g), sodium chloride (0.4 g), sodium dihydrogen phosphate dihydrate (0.04 g), anhydrous disodium hydrogen phosphate (0.04 g), and disodium edetate hydrate (0.1 g). The mixture was dissolved by addition of sodium hydroxide, and the pH value of the mixture was adjusted to 6.5. Then, to the mixture was added purified water so as to be the total amount of 100 g. The solution was filtered through a membrane filter with the pore diameter of 0.2 μm to prepare Example 32.

[0078] <Examples 33, 36, and 39>

Examples 33, 36, and 39 were prepared according to the method described in Example 30.

[0079] <Examples 34, 35, 37, and 38>

Examples 34, 35, 37, and 38 were prepared according to the method described in Example 31.

[0080] <Comparative example 29>

Latanoprost (0.005 g), polysorbate 80 (0.2 g), and purified water (80 g) were measured to be mixed, and the mixture was warmed to 60°C to be dissolved. Then, the mixture was cooled to room temperature. To this solution were added alginic acid (1.0 g), boric acid (1.5 g), and disodium edetate hydrate (0.2 g). The mixture was dissolved by addition of sodium hydroxide, and the pH value of the mixture was adjusted to 6.5. Then, to the mixture was added purified water so as to be the total amount of 100 g. The solution was filtered through a membrane filter with the pore diameter of 0.2 μm for Comparative example 29.

[0081]

[Table 17-1]

Amounts (g/100 mL)	Example 30	Example 31	Example 32	Example 33	Example 34
Carteolol hydrochloride	2.0	2.0	2.0	2.0	2.0
Latanoprost	0.005	0.005	0.005	0.005	0.005
Alginic acid	1.0	1.0	1.0	1.0	1.0
Boric acid	1.0	-	-	1.0	-
NaCl	-	0.4	0.4	-	0.4
$NaH_2PO_4.2H_2O$	-	0.04	0.04	-	0.04
Na_2HPO_4	-	0.04	0.04	-	0.04
Disodium edetate hydrate	0.1	0.1	0.1	0.05	0.03
Polysorbate 80	0.1	0.1	-	0.1	0.2
NaOH	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
pH	6.5	6.5	6.5	6.5	6.5

[Table 17-2]

Amounts (g/100 mL)	Example 35	Example 36	Example 37	Example 38	Example 39
Carteolol hydrochloride	2.0	2.0	2.0	2.0	2.0
Latanoprost	0.005	0.005	0.005	0.005	0.005
Alginic acid	1.0	1.0	1.0	1.0	1.0
Boric acid	-	-	1.0	-	1.0
NaCl	0.4	0.4	-	0.4	-
$NaH_2PO_4.2H_2O$	0.04	0.04	-	0.04	-
Na_2HPO_4	0.04	0.04	-	0.04	-
Disodium edetate hydrate	0.02	0.07	0.1	0.15	0.2
Polysorbate 80	0.2	0.2	0.2	0.1	0.1
NaOH	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
pH	6.5	6.5	6.5	6.5	6.5

[Table 17-3]

Amounts (g/100 mL)	Comparative example 29
Carteolol hydrochloride	-
Latanoprost	0.005
Alginic acid	1.0
Boric acid	1.5
NaCl	-
$NaH_2PO_4.2H_2O$	-
Na_2HPO_4	-
Disodium edetate hydrate	0.2
Polysorbate 80	0.2
NaOH	Appropriate amount
Purified water	Appropriate amount
pH	6.5

[0082] <Formulation example 2>

Examples 40 to 47 which did not contain benzalkonium chloride were prepared according to the following methods.

<Example 40>

Purified water (80 g), carteolol hydrochloride (1.0 g), alginic acid (1.0 g), propylene glycol (1.3 g), sodium dihydrogen phosphate dihydrate (0.04 g), anhydrous disodium hydrogen phosphate (0.04 g), and disodium edetate hydrate (0.01 g) were measured to be mixed. The mixture was dissolved by addition of sodium hydroxide while being stirred and the pH value of the mixture was adjusted to 6.7. Then, to the mixture was added purified water so as to be the total amount of 100 g. The solution was stirred and filtered through a membrane filter with the pore diameter of 0.2 μm to prepare Example 40.

[0083] <Examples 41 to 47>

Examples 41 to 47 were prepared according to the method described in Example 40.

[0084] [Table 18-1]

Amounts (g/100 mL)	Example 40	Example 41	Example 42	Example 43
Carteolol hydrochloride	1.0	1.0	1.0	2.0
Alginic acid	1.0	1.0	1.0	1.0
Disodium edetate hydrate	0.01	0.03	0.2	0.01
Propylene glycol	1.3	1.3	1.3	1.0
Na_2HPO_4	0.04	0.04	0.04	0.04
$NaH_2PO_4.2H_2O$	0.04	0.04	0.04	0.04
NaOH	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100
pH	6.7	6.7	6.7	6.7

[Table 18-2]

Amounts (g/100 mL)	Example 44	Example 45	Example 46	Example 47
Carteolol hydrochloride	2.0	2.0	2.0	2.0
Alginic acid	1.0	1.0	1.0	1.0
Disodium edetate hydrate	0.03	0.05	0.1	0.2
Propylene glycol	1.0	1.0	1.0	1.0
Na_2HPO_4	0.04	0.04	0.04	0.04
$NaH_2PO_4.2H_2O$	0.04	0.04	0.04	0.04
NaOH	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100
pH	6.7	6.7	6.7	6.7

[0085] <Formulation example 3>: Formulation examples of formulations comprising carbonic anhydrase inhibitors

Examples 48 to 59 were prepared according to the following methods.

<Example 48>

Carteolol hydrochloride (2.0 g), dorzolamide hydrochloride (1.113 g), disodium edetate hydrate (0.01 g), D-mannitol (2.0 g), and sodium citrate hydrate (0.3 g) were measured and dissolved in water. The resulted solution was sterilized by filtration through a membrane filter with the pore diameter of 0.2 μm. The solution was combined with a solution obtained by the steps of dissolving hydroxyethyl cellulose (0.5 g) in water and being sterilized by steam under high pressure. The pH value of the combined solution was adjusted to 5.7 by addition of sodium hydroxide. Then, purified water was added to the solution to prepare Example 48 with the total amount of 100 g.

[0086] <Examples 49 to 51>

Examples 49 to 51 were prepared according to the method described in Example 48.

[0087] <Example 52>

Purified water (80 g), carteolol hydrochloride (2.0 g), dorzolamide hydrochloride (1.113 g), disodium edetate hydrate (0.01 g), propylene glycol (0.7 g), and sodium citrate hydrate (0.3 g) were measured to be dissolved. The pH value of the solution was adjusted to 5.7 by addition of sodium hydroxide. Then, purified water was added to the solution so as to be the total amount of 100 g. The solution was stirred and filtered through a membrane filter with the pore diameter of 0.2 μm to prepare Example 52.

[0088] <Examples 53 to 55>

Examples 53 to 55 were prepared according to the method described in Example 52.

[0089] <Example 56>

Tyloxapol (0.025 g) was measured to be loaded to a cylindrical glass vessel and dissolved by addition of purified water (6 g) heated to 60°C. To the solution were added brinzolamide (1.0 g) and zirconia yttria beads (12 g), and the vessel was sealed and heated at 121°C for 20 minutes. The mixture was cooled, and then, rotated at 50 rpm for 20 hours to be a brinzolamide suspension. Carteolol hydrochloride (2.0 g), disodium edetate hydrate (0.01 g), and propylene glycol (1.0 g) were separately measured and dissolved in purified water (50 g). To the solution was added a solution wherein carbopol (0.4 g) was homogeneously dispersed in purified water (25 g) at 60°C. The resulted solution was heated at 121°C for 20 minutes, and then, the pH value of the solution was adjusted to 7.2 by addition of sodium hydroxide to be used as a solvent. The brinzolamide suspension was filtered to remove zirconia yttria beads and combined with the solvent, and purified water was added to the mixture so as to be 100 g to prepare Example 56.

[0090] <Examples 57 to 59>

Examples 57 to 59 were prepared according to the method described in Example 56.

[0091] [Table 19-1]

Amounts (g/100 mL)	Example 48	Example 49	Example 50	Example 51
Carteolol hydrochloride	2.0	2.0	2.0	2.0
Dorzolamide hydrochloride	1.113	1.113	1.113	1.113
Hydroxyethyl cellulose	0.5	0.5	0.5	0.5
Disodium edetate hydrate	0.01	0.03	0.05	0.1
D-mannitol	2.0	2.0	2.0	2.0
Propylene glycol	-	-	-	-
Sodium citrate hydrate	0.3	0.3	0.3	0.3
NaOH	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100
pH	5.7	5.7	5.7	5.7

[Table 19-2]

Amounts (g/100 mL)	Example 52	Example 53	Example 54	Example 55
Carteolol hydrochloride	2.0	2.0	2.0	2.0
Dorzolamide hydrochloride	1.113	1.113	1.113	1.113
Hydroxyethyl cellulose	-	-	-	-
Disodium edetate hydrate	0.01	0.03	0.05	0.1
D-mannitol	-	-	-	-
Propylene glycol	0.7	0.7	0.7	0.7
Sodium citrate hydrate	0.3	0.3	0.3	0.3
NaOH	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100
pH	5.7	5.7	5.7	5.7

[Table 19-3]

Amounts (g/100 mL)	Example 56	Example 57	Example 58	Example 59
Carteolol hydrochloride	2.0	2.0	2.0	2.0
Brinzolamide	1.0	1.0	1.0	1.0
Carbopol	0.4	0.4	0.4	0.4
Disodium edetate hydrate	0.01	0.03	0.05	0.1
Tyloxapol	0.025	0.025	0.025	0.025
Propylene glycol	1.0	1.0	1.0	1.0
NaOH	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Total amount (mL)	100	100	100	100
pH	7.2	7.2	7.2	7.2

[0092] <Experiment 7>: Preservative effectiveness tests for the formulations of Examples 30 to 39 and Comparative example 29

According to the Preservative Effectiveness Test, preservative effectiveness was assessed for the formulations of Examples 30 to 39 and Comparative example 29. The results are shown below.

[Table 20]

	Overall assessment of preservative effectiveness
Example 30	Adequate
Example 31	Adequate
Example 32	Adequate
Example 33	Adequate
Example 34	Adequate
Example 35	Adequate
Example 36	Adequate
Example 37	Adequate
Example 38	Adequate
Example 39	Adequate
Comparative example 29	Inadequate

Industrial Applicability

[0093] A pharmaceutical composition in the present invention may have enhanced preservative effectiveness and/or improved light stability, and it may be useful for treatment of eye diseases such as glaucoma and ocular hypertension.

Claims

[Claim 1] An ophthalmic pharmaceutical composition, comprising carteolol or a pharmaceutically acceptable salt thereof and edetic acid or a pharmaceutically acceptable salt thereof.

[Claim 2] The composition of claim 1, further comprising a tonicity agent.

[Claim 3] The composition of claim 1 or 2, further comprising a sustaining agent.

[Claim 4] The composition of any one of claims 1 to 3, further comprising a buffering agent and a pH adjusting agent.

[Claim 5] The composition of any one of claims 1 to 4, further comprising a prostaglandin F2α derivative.

[Claim 6] The composition of any one of claims 1 to 5, further comprising a carbonic anhydrase inhibitor.

[Claim 7] The composition of any one of claims 1 to 6, further comprising another agent having ocular hypotensive effect.

[Claim 8] The composition of any one of claims 1 to 7, wherein carteolol or a pharmaceutically acceptable salt thereof is comprised in an amount ranging from 0.1 to 5 w/v% to the total amount of the composition.

[Claim 9] The composition of any one of claims 1 to 8, wherein edetic acid or a pharmaceutically acceptable salt thereof is comprised in an amount ranging from 0.01 to 0.2 w/v% to the total amount of the composition.

[Claim 10] The composition of any one of claims 1 to 9, wherein pH ranges from 5.0 to 8.0.

[Claim 11] The composition of any one of claims 1 to 10 in the form of an eye drop.

[Claim 12] The composition of any one of claims 1 to 11 in the form of an aqueous eye drop or suspended eye drop.

[Claim 13] The composition of any one of claims 1 to 12 for use as a multiple-dose-type eye drop.

[Claim 14] The composition of any one of claims 1 to 13 for the treatment of glaucoma or ocular hypertension.

[Claim 15] A method for enhancing preservative effectiveness of carteolol or a pharmaceutically acceptable salt thereof with edetic acid or a pharmaceutically acceptable salt thereof, comprising combining carteolol or a pharmaceutically acceptable salt thereof with edetic acid or a pharmaceutically acceptable salt thereof.

[Claim 16] A method for improving light stability of carteolol or a pharmaceutically acceptable salt thereof with edetic acid, alginic acid or a

pharmaceutically acceptable salt thereof, comprising combining carteolol or a pharmaceutically acceptable salt thereof with edetic acid or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
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ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	CN 101 461 780 A (UNIV HEBEI SCIENCE & TECH [CN]) 24 June 2009 (2009-06-24) claims 1,2	1-16
Y	EP 2 269 612 A1 (OTSUKA PHARMA CO LTD [JP]) 5 January 2011 (2011-01-05) page 3; claims 1,2,6	1-16
Y	EP 2 609 933 A1 (WAKAMOTO PHARMA CO LTD [JP]) 3 July 2013 (2013-07-03) claims 1-13	1-16

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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