

PHARMACEUTICAL COMPOSITION

TECHNICAL FIELD

[0001]

The present invention relates to a pharmaceutical composition excellent in storage stability.

BACKGROUND ART

[0002]

Various ophthalmic pharmaceutical compositions to complement tears have been sought in order to reduce discomfort, dryness of the eye, eyestrain, blurred vision or the like in wearing a soft contact lens or a hard contact lens.

[0003]

Tears means a mixture of a lacrimal gland secretion secreted by a main lacrimal gland and substances secreted by four or more accessory lacrimal glands, and contain inorganic components such as Na, K, Ca and Cl and organic components such as glucose, ascorbic acid, citric acid, urea, ammonia, amino acid and protein.

[0004]

Although there are individual differences of the glucose concentration in tears, the concentration is approximately 0.001 to 0.01 w/v%. The concentration of glucose in an ophthalmic pharmaceutical composition is preferably high, since glucose is contained as a nutrient component. When an ophthalmic pharmaceutical composition contains glucose, the glucose concentration is generally 0.1 w/v% or 0.2 w/v% (Patent documents 1 to 8).

PRIOR ART DOCUMENT

PATENT DOCUMENT

[0005]

Patent document 1: JP 2005-336153 A

Patent document 2: JP 2007-99643 A

Patent document 3: JP 2009-46480 A

Patent document 4: JP 2011-93888 A

Patent document 5: JP 2011-213729 A

Patent document 6: JP 2014-5417 A

Patent document 7: JP 2015-78248 A

Patent document 8: JP 2017-178880 A

SUMMARY

PROBLEMS TO BE SOLVED BY THE DISCLOSURE

[0006]

The objective of the present disclosure is to provide a pharmaceutical composition excellent in storage stability.

MEANS FOR SOLVING THE PROBLEMS

[0007]

The inventor of the present disclosure made extensive studies. As a result, the inventor found that while a residual ratio of glucose in a pharmaceutical composition having a low concentration of glucose is decreased with time, a non-ionic surfactant is very effective in stabilizing glucose. The inventor completed the present disclosure by finding that a pharmaceutical composition mixed with a non-ionic surfactant becomes cloudy during storage but such white turbidity can be suppressed by mixing an alkyldiaminoethylglycine

hydrochloride.

Hereinafter, the embodiment of the present disclosure is described.

[0007a]

In one aspect, the present disclosure refers to a pharmaceutical composition comprising 0.0005 w/v% or more and 0.05 w/v% or less of glucose, a non-ionic surfactant and 0.0005 w/v% or more and 0.01 w/v% or less of an alkyldiaminoethylglycine hydrochloride.

[0007b]

In another aspect, the present disclosure refers to a pharmaceutical composition comprising:

0.005 w/v% of glucose,

0.01 w/v% of a non-ionic surfactant, and

0.0025 w/v% of an alkyldiaminoethylglycine hydrochloride.

[0008]

[1] A pharmaceutical composition comprising 0.0005 w/v% or more and 0.05 w/v% or less of glucose, a non-ionic surfactant and an alkyldiaminoethylglycine hydrochloride.

[2] The pharmaceutical composition according to the above [1], comprising 0.0005 w/v% or more and 0.01 w/v% or less of the glucose.

[3] The pharmaceutical composition according to the above [1] or [2], comprising 0.002 w/v% or more and 0.01 w/v% or less of the glucose.

[4] The pharmaceutical composition according to any one of the above [1] to [3], wherein the non-ionic surfactant is one or more non-ionic surfactants selected from the group consisting of polyoxyethylene hydrogenated castor oil, polyoxyethylene sorbitan long-chain fatty acid monoester,

polyethylene glycol long-chain fatty acid monoester and polyoxyethylene-polyoxypropylene block copolymer.

[5] The pharmaceutical composition according to any one of the above [1] to [4], comprising 0.001 w/v% or more and 0.5 w/v% or less of the non-ionic surfactant.

[6] The pharmaceutical composition according to any one of the above [1] to [4], wherein a concentration of the non-ionic surfactant is 0.005 w/v% or more and 0.3 w/v% or less.

[7] The pharmaceutical composition according to the above [4], wherein the polyoxyethylene hydrogenated castor oil is polyoxyethylene hydrogenated castor oil 60.

[8] The pharmaceutical composition according to any one of

the above [1] to [7], comprising 0.0005 w/v% or more and 0.05 w/v% or less of the alkyldiaminoethylglycine hydrochloride.

[9] The pharmaceutical composition according to any one of the above [1] to [7], comprising 0.001 w/v% or more and 0.01 w/v% or less of the alkyldiaminoethylglycine hydrochloride.

[10] The pharmaceutical composition according to any one of the above [1] to [9], comprising:

0.002 w/v% or more and 0.01 w/v% or less of the glucose,
0.005 w/v% or more and 0.3 w/v% or less of the non-ionic surfactant, and

0.001 w/v% or more and 0.01 w/v% or less of the alkyldiaminoethylglycine hydrochloride.

[11] The pharmaceutical composition according to any one of the above [1] to [10], further comprising an inorganic salt.

[12] The pharmaceutical composition according to the above [11], wherein the inorganic salt is sodium chloride and/or potassium chloride.

[13] The pharmaceutical composition according to the above [11] or [12], comprising 0.05 w/v% or more and 5.0 w/v% or less of the inorganic salt.

[14] The pharmaceutical composition according to the above [11] or [12], comprising 0.1 w/v% or more and 2.0 w/v% or less of the inorganic salt.

[15] The pharmaceutical composition according to any one of the above [1] to [14], further comprising a buffering agent.

[16] The pharmaceutical composition according to the above [15], wherein the buffering agent is one or more buffering agents selected from the group consisting of a borate buffering agent, a phosphate buffering agent, a carbonate buffering agent, a citrate buffering agent, an acetate

buffering agent, a HEPES buffering agent and a MOPS buffering agent.

[17] The pharmaceutical composition according to the above [15], wherein the buffering agent is boric acid and/or borax.

[18] The pharmaceutical composition according to any one of the above [15] to [17], comprising 0.05 w/v% or more and 5.0 w/v% or less of the buffering agent.

[19] The pharmaceutical composition according to any one of the above [15] to [17], comprising 0.1 w/v% or more and 2.0 w/v% or less of the buffering agent.

[20] The pharmaceutical composition according to any one of the above [1] to [19], further comprising a thickening agent.

[21] The pharmaceutical composition according to the above [20], wherein the thickening agent is hydroxypropyl methylcellulose.

[22] The pharmaceutical composition according to the above [20] or [21], comprising 0.01 w/v% or more and 3.0 w/v% or less of the thickening agent.

[23] The pharmaceutical composition according to the above [20] or [21], comprising 0.05 w/v% or more and 2.0 w/v% or less of the thickening agent.

[24] The pharmaceutical composition according to any one of the above [1] to [23], further comprising an amino acid.

[25] The pharmaceutical composition according to the above [24], wherein the amino acid is one or more amino acids selected from the group consisting of taurine, glutamic acid, aspartic acid, glycine, alanine, arginine, lysine, γ -aminobutyric acid, γ -aminovaleric acid, chondroitin sulfate ester and salts thereof.

[26] The pharmaceutical composition according to the above

[24], wherein the amino acid is taurine.

[27] The pharmaceutical composition according to any one of the above [24] to [26], comprising 0.01 w/v% or more and 1.0 w/v% or less of the amino acid.

[28] The pharmaceutical composition according to any one of the above [24] to [26], comprising 0.05 w/v% or more and 0.5 w/v% or less of the amino acid.

[29] The pharmaceutical composition according to any one of the above [1] to [28], comprising:

0.002 w/v% or more and 0.01 w/v% or less of the glucose,
0.005 w/v% or more and 0.3 w/v% or less of the non-ionic surfactant,

0.001 w/v% or more and 0.01 w/v% or less of the alkyldiaminoethylglycine hydrochloride,

0.1 w/v% or more and 2.0 w/v% or less of the inorganic salt,

0.1 w/v% or more and 2.0 w/v% or less of the buffering agent,

0.05 w/v% or more and 2.0 w/v% or less of the thickening agent, and

0.05 w/v% or more and 0.5 w/v% or less of the amino acid.

[30] The pharmaceutical composition according to any one of the above [1] to [29], further comprising a pH adjuster.

[31] The pharmaceutical composition according to any one of the above [1] to [30], wherein pH is 5.0 or more and 8.5 or less.

[32] The pharmaceutical composition according to any one of the above [1] to [30], wherein pH is 5.5 or more and 8.0 or less.

[33] The pharmaceutical composition according to any one of the above [1] to [32], further comprising a monoterpene.

[34] The pharmaceutical composition according to the above [33], wherein the monoterpene is one or more monoterpenes selected from the group consisting of menthol, camphor and borneol.

[35] The pharmaceutical composition according to the above [33], wherein the monoterpene is l-menthol.

[36] The pharmaceutical composition according to any one of the above [33] to [35], comprising 0.0005 w/v% or more and 0.1 w/v% or less of the monoterpene.

[37] The pharmaceutical composition according to any one of the above [33] to [35], comprising 0.001 w/v% or more and 0.05 w/v% or less of the monoterpene.

[38] The pharmaceutical composition according to any one of the above [1] to [37], further comprising a chelating agent.

[39] The pharmaceutical composition according to the above [38], wherein the chelating agent is ethylenediaminetetraacetic acid or a salt thereof.

[40] The pharmaceutical composition according to the above [38] or [39], comprising 0.001 w/v% or more and 0.15 w/v% or less of the chelating agent.

[41] The pharmaceutical composition according to the above [38] or [39], comprising 0.002 w/v% or more and 0.1 w/v% or less of the chelating agent.

[42] The pharmaceutical composition according to any one of the above [1] to [41], comprising:

0.002 w/v% or more and 0.01 w/v% or less of the glucose,
0.005 w/v% or more and 0.3 w/v% or less of the non-ionic surfactant,

0.001 w/v% or more and 0.01 w/v% or less of the
alkyldiaminoethylglycine hydrochloride,

0.1 w/v% or more and 2.0 w/v% or less of the inorganic
salt,

0.1 w/v% or more and 2.0 w/v% or less of the buffering
agent,

0.05 w/v% or more and 2.0 w/v% or less of the thickening
agent,

0.05 w/v% or more and 0.5 w/v% or less of the amino acid,

0.001 w/v% or more and 0.05 w/v% or less of the
monoterpene, and

0.002 w/v% or more and 0.1 w/v% or less of the chelating
agent.

[43] The pharmaceutical composition according to any one of
the above [1] to [42], comprising:

0.002 w/v% or more and 0.01 w/v% or less of the glucose,

0.005 w/v% or more and 0.1 w/v% or less of the non-ionic
surfactant,

0.001 w/v% or more and 0.005 w/v% or less of the
alkyldiaminoethylglycine hydrochloride,

0.1 w/v% or more and 2.0 w/v% or less of the inorganic
salt,

0.1 w/v% or more and 2.0 w/v% or less of the buffering
agent,

0.05 w/v% or more and 0.5 w/v% or less of the thickening
agent,

0.05 w/v% or more and 0.5 w/v% or less of the amino acid,

0.001 w/v% or more and 0.05 w/v% or less of the
monoterpene, and

0.005 w/v% or more and 0.05 w/v% or less of the chelating

agent,

wherein pH is 6.5 or more and 8.0 or less.

[44] A pharmaceutical composition comprising:

0.005 w/v% of glucose,

0.01 w/v% of a non-ionic surfactant, and

0.0025 w/v% of an alkyldiaminoethylglycine hydrochloride.

[45] The pharmaceutical composition according to any one of the above [1] to [44], wherein the pharmaceutical composition is ophthalmic.

[46] The pharmaceutical composition according to any one of the above [1] to [45], wherein the pharmaceutical composition is an aqueous liquid composition.

[47] The pharmaceutical composition according to any one of the above [1] to [46], wherein the pharmaceutical composition is an ophthalmic solution.

[48] Use of 0.0005 w/v% or more and 0.05 w/v% or less of glucose, a non-ionic surfactant and an alkyldiaminoethylglycine hydrochloride for improving storage of a pharmaceutical composition.

[49] Use of 0.0005 w/v% or more and 0.05 w/v% or less of glucose, a non-ionic surfactant and an alkyldiaminoethylglycine hydrochloride for producing a pharmaceutical composition excellent in storage stability.

[50] A method for improving storage stability of a pharmaceutical composition,

wherein the pharmaceutical composition comprises 0.0005 w/v% or more and 0.01 w/v% or less of glucose,

the method comprising the step of mixing a non-ionic surfactant and an alkyldiaminoethylglycine hydrochloride in the pharmaceutical composition.

The matters specified in the above [1] to [47] can be applied to the above-described use and method.

EFFECT OF THE DISCLOSURE

[0009]

The pharmaceutical composition of the present disclosure is excellent in storage stability.

MODE FOR CARRYING OUT THE INVENTION

[0010]

Various ophthalmic pharmaceutical compositions to complement tears have been developed as described above, and the glucose concentration in an ophthalmic pharmaceutical composition is generally adjusted to be higher than the concentration in actual tears.

[0011]

The present inventor found that when the glucose concentration in a composition is adjusted to be low similarly to the concentration in tears, the glucose concentration cannot be maintained during storage. Thus, the present inventor investigated a component to stabilize glucose and found that a non-ionic surfactant is effective. On the one hand, the present inventor found that when a non-ionic surfactant is mixed in a composition containing low concentration glucose, the composition becomes cloudy during storage. The present inventor investigated a component to prevent such white turbidity; and as a result, found that an alkylldiaminoethylglycine hydrochloride is effective.

[0012]

The pharmaceutical composition of the present invention

comprises 0.0005 w/v% or more and 0.05 w/v% or less of glucose, a non-ionic surfactant, and an alkyldiaminoethylglycine hydrochloride.

[0013]

The term "pharmaceutical composition" means a composition for medicinal use. The pharmaceutical composition can be produced in accordance with an ordinary method. In particular, the pharmaceutical composition of the present invention is useful as an ophthalmic pharmaceutical composition.

[0014]

The "glucose" is represented by the formula of $C_6H_{12}O_6$ and is one of aldohexoses. Natural glucose is D-glucose and is conjugated to an electron transport system to produce a large amount of ATP in an animal having a respiratory system. There is approximately 0.001 w/v% or more and 0.01 w/v% or less of glucose in tears. Glucose is also mixed in a pharmaceutical composition as a tonicity agent and a thickening agent.

[0015]

The pharmaceutical composition of the present invention comprises 0.0005 w/v% or more and 0.05 w/v% or less of glucose. When the concentration is 0.0005 w/v% or more, glucose can sufficiently exert the function effect thereof as a tear component. The concentration is preferably 0.001 w/v% or more or 0.002 w/v% or more, more preferably 0.003 w/v% or more, and even more preferably 0.004 w/v% or more with respect to the lower limit of the concentration. In addition, when the concentration of glucose is lower, the stability tends to be lower. When the concentration is 0.05 w/v% or less, the pharmaceutical composition of the present invention may not remarkably become cloudy and the storage stability is

sufficient. The concentration is preferably 0.01 w/v% or less, more preferably 0.008 w/v% or less, and even more preferably 0.006 w/v% or less with respect to the upper limit of the concentration.

[0016]

The "non-ionic surfactant" means a surfactant that does not dissociate into an ion even when the surfactant is dissolved in water. In general, the polyoxyethylene chain and the hydroxy group thereof act as a hydrophilic group, and the long-chain alkyl group thereof acts as a hydrophobic group. An example of the non-ionic surfactant includes a non-ionic surfactant such as polyoxyethylene hydrogenated castor oil, polyoxyethylene sorbitan long-chain fatty acid monoester, polyethylene glycol long-chain fatty acid monoester and polyoxyethylene-polyoxypropylene block copolymer. Only one of the non-ionic surfactant may be used, or two or more of the non-ionic surfactants may be used in combination.

[0017]

The polyoxyethylene hydrogenated castor oil means a compound obtained by etherifying hydrogenated castor oil with a polyoxyethylene chain. The addition mole number of the ethylene oxide of the polyoxyethylene chain in the polyoxyethylene hydrogenated castor oil may be adjusted to, for example, 5 or more and 100 or less. The addition mole number is preferably 10 or more, more preferably 20 or more, even more preferably 30 or more, and particularly preferably 40 or more with respect to the lower limit of the addition mole number from the viewpoint of the improved solubility. The addition mole number is preferably 90 or less, more preferably 80 or less, even more preferably 70 or less with respect to

the upper limit of the addition mole number from the viewpoint of the lower toxicity. An example of the polyoxyethylene hydrogenated castor oil includes polyoxyethylene hydrogenated castor oil 5, polyoxyethylene hydrogenated castor oil 10 and polyoxyethylene hydrogenated castor oil 60. Polyoxyethylene hydrogenated castor oil 60, which is widely used in an ophthalmic solution, is preferred as the polyoxyethylene hydrogenated castor oil.

[0018]

The polyoxyethylene sorbitan long-chain fatty acid monoester is also called as polysorbate and is a polyoxyethylene ether of a sorbitan fatty acid ester. The polyoxyethylene sorbitan long-chain fatty acid monoester can be obtained by reacting sorbitol with a long-chain fatty acid with heating in the presence of an alkali catalyst to produce a sorbitan long-chain fatty acid ester and condensing the sorbitan long-chain fatty acid ester with ethylene oxide. For example, totally about 18 molecules or more and about 22 molecules or less of ethylene oxide is generally bound to one molecule of the polyoxyethylene sorbitan long-chain fatty acid monoester. The carbon number of the long-chain fatty acid is generally about 10 or more and about 20 or less, and an example of the long-chain fatty acid includes lauric acid, palmitic acid, stearic acid and oleic acid. For example, polysorbate 20, polysorbate 60, polysorbate 65 and polysorbate 80 can be used as the polyoxyethylene sorbitan long-chain fatty acid monoester. Polysorbate 80, which is widely used in an ophthalmic solution, is preferred as the polyoxyethylene sorbitan long-chain fatty acid monoester.

[0019]

The polyethylene glycol long-chain fatty acid monoester means an ester of a long-chain fatty acid and polyethylene glycol. An example of the long-chain fatty acid includes stearic acid. For example, the polymerization degree of the polyethylene glycol is about 10 or more and about 60 or less. The polyethylene glycol long-chain fatty acid monoester is preferably polyoxyl 40 stearate.

[0020]

The polyoxyethylene-polyoxypropylene block copolymer means a copolymer of propylene oxide and ethylene oxide. An example of the polyoxyethylene-polyoxypropylene block copolymer includes polyoxyethylene (160) polyoxypropylene (30) glycol (Poloxamer 188), polyoxyethylene (196) polyoxypropylene (67) glycol (Poloxamer 407) and Poloxamer 235.

[0021]

The inventor of the present invention found that when the concentration of glucose in a pharmaceutical composition is low, the concentration is decreased during storage. In addition, the present inventor found that the glucose concentration can be prevented from being decreased by mixing the non-ionic surfactant. The concentration of the non-ionic surfactant in the pharmaceutical composition can be appropriately adjusted. The concentration can be adjusted to, for example, 0.001 w/v% or more and 0.5 w/v% or less. When the concentration is 0.001 w/v% or more, the concentration of glucose can be sufficiently maintained. The concentration is preferably 0.005 w/v% or more, more preferably 0.008 w/v% or more, and even more preferably 0.01 w/v% or more with respect to the lower limit of the concentration. When the concentration is 0.5 w/v% or less, the pharmaceutical

composition does not remarkably become cloudy and the storage stability can be sufficiently exerted. The concentration is preferably 0.3 w/v% or less, more preferably 0.1 w/v% or less, and even more preferably 0.05 w/v% or less with respect to the upper limit of the concentration.

[0022]

Also, the ratio of the non-ionic surfactant to glucose may be appropriately adjusted. For example, the ratio of the non-ionic surfactant to 1 part by mass of glucose may be adjusted to 0.02 parts or more by mass and 1000 parts or less by mass. When the parts by mass of the non-ionic surfactant is 0.02 parts or more by mass, the concentration of glucose can be maintained more effectively. The parts by mass is preferably 0.5 parts or more by mass, more preferably 1.0 part or more by mass, and even more preferably 1.7 parts or more by mass with respect to the lower limit of the parts by mass. When the parts by mass of the non-ionic surfactant is 1000 parts or less by mass, the pharmaceutical composition of the present invention may not remarkably become cloudy and the storage stability is sufficient. The parts by mass is more preferably 500 parts or less by mass or 150 parts or less by mass, even more preferably 33 parts or less by mass, and particularly preferably 13 parts or less by mass with respect to the upper limit of the parts by mass.

[0023]

The "alkyldiaminoethylglycine hydrochloride" means a compound having the following chemical structure and in general, is conventionally used as a component having an bactericidal activity.



wherein R is an alkyl group of C₈H₁₇ to C₁₆H₃₃ and is mainly C₁₂H₂₅ and C₁₄H₂₉.

[0024]

The inventor of the present invention found that white turbidity of a pharmaceutical composition caused by low concentration glucose and a non-ionic surfactant can be reduced by mixing the alkyldiaminoethylglycine hydrochloride. The concentration of the alkyldiaminoethylglycine hydrochloride in the pharmaceutical composition may be appropriately adjusted. For example, the concentration can be adjusted to 0.0005 w/v% or more and 0.05 w/v% or less. When the concentration is 0.0005 w/v% or more, white turbidity of the pharmaceutical composition can be sufficiently suppressed. The concentration is preferably 0.001 w/v% or more, more preferably 0.0015 w/v% or more, and even more preferably 0.002 w/v% or more with respect to the lower limit of the concentration. When the concentration is 0.05 w/v% or less, the irritation that occurs when the pharmaceutical composition is administered to the eye can be sufficiently suppressed. The concentration is preferably 0.01 w/v% or less, more preferably 0.005 w/v% or less, and even more preferably 0.003 w/v% or less with respect to the upper limit of the concentration.

[0025]

The ratio of the alkyldiaminoethylglycine hydrochloride to glucose may be also appropriately adjusted. For example, the parts by mass of the alkyldiaminoethylglycine hydrochloride to 1 part by mass of glucose can be adjusted to 0.01 parts or more by mass and 100 parts or less by mass. When the parts by mass of the alkyldiaminoethylglycine hydrochloride is 0.01 parts or more by mass, white turbidity of the pharmaceutical

composition can be sufficiently suppressed. The parts by mass is preferably 0.1 parts or more by mass, more preferably 0.2 parts or more by mass, and even more preferably 0.33 parts or more by mass with respect to the lower limit of the parts by mass. When the parts by mass of the alkyldiaminoethylglycine hydrochloride is 100 parts or less by mass, the irritation that occurs when the pharmaceutical composition is administered to the eye can be sufficiently suppressed. The parts by mass is preferably 50 parts or less by mass or 5.0 parts or less by mass, more preferably 1.7 parts or less by mass, and even more preferably 0.8 parts or less by mass with respect to the upper limit of the parts by mass.

[0026]

The ratio of the alkyldiaminoethylglycine hydrochloride to the non-ionic surfactant may be also appropriately adjusted. For example, the parts by mass of the alkyldiaminoethylglycine hydrochloride to 1 part by mass of the non-ionic surfactant can be adjusted to 0.001 parts or more by mass and 50 parts or less by mass. When the parts by mass of the alkyldiaminoethylglycine hydrochloride is 0.001 parts or more by mass, white turbidity of the pharmaceutical composition can be sufficiently suppressed. The parts by mass is preferably 0.003 parts or more by mass, more preferably 0.015 parts or more by mass, and even more preferably 0.04 parts or more by mass with respect to the lower limit of the parts by mass. When the parts by mass of the alkyldiaminoethylglycine hydrochloride is 50 parts or less by mass, the irritation that occurs when the pharmaceutical composition is administered to the eye can be sufficiently suppressed. The parts by mass is preferably 2.0 parts or less by mass, more preferably 0.6

parts or less by mass, and even more preferably 0.3 parts or less by mass with respect to the upper limit of the parts by mass.

[0027]

The "inorganic salt" means an inorganic compound corresponding to an inorganic acid of which hydrogen atom is substituted by a metal and is mainly mixed as a tonicity agent. An inorganic salt that can be dissolved in water, which is a solvent of the pharmaceutical composition, is preferred. The phrase "can be dissolved in water" means that a material to be tested is powderized so that the material can pass Sieve No. 100 having a mesh size of 150 μm , 1 g of the powderized material is added in water, the mixture is vigorously shaken at 20°C for 30 seconds every 5 minutes, and an amount of water required for dissolution of the material within 30 minutes is less than 10 mL.

[0028]

An example of the inorganic salt includes an alkali metal chloride such as sodium chloride and potassium chloride; a group 2 metal chloride such as calcium chloride and magnesium chloride; an alkali metal carbonate such as sodium carbonate; an alkali metal hydrogencarbonate such as sodium hydrogencarbonate; a group 2 metal sulfate such as magnesium sulfate; an alkali metal sulfite such as sodium sulfite; an alkali metal hydrogensulfite such as sodium hydrogensulfite; an alkali metal thiosulfate such as sodium thiosulfate; an alkali metal hydrogenphosphate such as disodium hydrogenphosphate; and an alkali metal dihydrogenphosphate such as sodium dihydrogenphosphate and potassium dihydrogenphosphate. Sodium chloride and/or potassium chloride

is preferably used. A group 2 metal is preferably an alkaline earth metal such as calcium. Only one inorganic salt may be used, or two or more inorganic salts may be used in combination.

[0029]

The concentration of the inorganic salt in the pharmaceutical composition may be appropriately adjusted. For example, the concentration may be adjusted to 0.05 w/v% or more and 5.0 w/v% or less from the viewpoint of the tonicity action of the inorganic salt. The concentration is preferably 0.1 w/v% or more, more preferably 0.5 w/v% or more, and even more preferably 0.55 w/v% or more with respect to the lower limit of the concentration. The concentration is preferably 2.0 w/v% or less, more preferably 1.0 w/v% or less, and even more preferably 0.9 w/v% or less with respect to the upper limit of the concentration.

[0030]

The "buffering agent" mainly means a component to ease the change of pH due to a foreign substance and exemplified by borate buffering agent, phosphate buffering agent, carbonate buffering agent, citrate buffering agent, acetate buffering agent, HEPES buffering agent and MOPS buffering agent. Only one buffering agent may be used, or two or more buffering agents may be used in combination. The buffering agent is preferably borate buffering agent and more preferably boric acid and/or borax. Boric acid and borax are also used as a preserving agent and have a disinfecting effect on the conjunctival sac.

[0031]

The concentration of the buffering agent in the

pharmaceutical composition may be appropriately adjusted. For example, the concentration may be adjusted to 0.05 w/v% or more and 5.0 w/v% or less from the viewpoint of the buffering action of the buffering agent. The concentration is preferably 0.1 w/v% or more, more preferably 0.25 w/v% or more, and even more preferably 0.4 w/v% or more with respect to the lower limit of the concentration. The concentration is preferably 2.0 w/v% or less, more preferably 1.0 w/v% or less, and even more preferably 0.6 w/v% or less with respect to the upper limit of the concentration.

[0032]

The "thickening agent" means a component to increase the viscosity of the pharmaceutical composition and to contribute to the suppression of the rapid evaporation of the pharmaceutical composition, the improvement of the dripping performance, the suppression of the variation of the dropping quantity and the improvement of the use feeling. Glucose is also used as a thickening agent; but glucose is excluded from the category of the thickening agent for the sake of convenience in the present invention, since the pharmaceutical composition of the present invention comprises glucose as an essential component.

[0033]

The viscosity of the pharmaceutical composition of the present invention may be appropriately adjusted. For example, the viscosity may be adjusted to 1 mPa·s or more and 100 mPa·s or less. The viscosity is preferably 1.2 mPa·s or more, more preferably 1.5 mPa·s or more, and even more preferably 2.0 mPa·s or more with respect to the lower limit of the viscosity in order to sufficiently suppress the hasty evaporation of the

pharmaceutical composition. The viscosity is preferably 30 mPa·s or less, more preferably 10 mPa·s or less, and even more preferably 5.0 mPa·s or less with respect to the upper limit of the viscosity in order to sufficiently ensure the use feeling.

[0034]

An example of the thickening agent includes hydroxypropyl methylcellulose, carboxyvinyl polymer, hydroxyethyl cellulose, methylcellulose, alginic acid, polyvinyl alcohol and polyvinylpyrrolidone, and hydroxypropyl methylcellulose is preferred. Only one thickening agent may be used, or two or more thickening agents may be used in combination.

[0035]

The concentration of the thickening agent in the pharmaceutical composition may be appropriately adjusted. For example, the concentration may be adjusted to 0.01 w/v% or more and 3.0 w/v% or less from the viewpoint of the above-described effects. The concentration is preferably 0.05 w/v% or more, more preferably 0.08 w/v% or more, and even more preferably 0.1 w/v% or more with respect to the lower limit of the concentration in order to sufficiently suppress the hasty evaporation of the pharmaceutical composition. The concentration is preferably 2.0 w/v% or less, more preferably 0.5 w/v% or less, and even more preferably 0.2 w/v% or less with respect to the upper limit of the concentration in order to ensure the use feeling.

[0036]

The "amino acid" means a compound having an amino group and an acidic group such as a carboxy group and a sulfonic acid group in one molecule, and is not restricted to 20 kinds of so-called protein-constituting amino acids. The amino acid

mainly plays a role of a nutrient component for the eye and contributes to reduction of eye fatigue. An example of the amino acid includes taurine, glutamic acid, aspartic acid, glycine, alanine, arginine, lysine, γ -aminobutyric acid, γ -aminovaleric acid, chondroitin sulfate ester and salts thereof. An example of the amino acid salt includes an alkali metal salt such as sodium salt and potassium salt. Only one of the amino acid may be used, or two or more of the amino acids may be used in combination. The amino acid is preferably taurine. Taurine is a nutrient component and also has a metabolism promoting action.

[0037]

The concentration of the amino acid in the pharmaceutical composition may be appropriately adjusted. For example, the concentration may be adjusted to 0.01 w/v% or more and 1.0 w/v% or less from the viewpoint of nutritional support. The concentration is preferably 0.03 w/v% or more and more preferably 0.05 w/v% or more with respect to the lower limit of the concentration. The concentration is preferably 0.5 w/v% or less and 0.2 w/v% or less with respect to the upper limit of the concentration.

[0038]

The pH of the pharmaceutical composition according to the present invention is adjusted to the range applicable to a living body, especially the eyes. For example, the pH may be adjusted to 5.0 or more and 8.5 or less and is preferably 5.5 or more and 8.0 or less. The pH of the pharmaceutical composition may be adjusted by the above-described buffering agent or a pH adjuster. The pH is preferably 6.0 or more, more preferably 6.5 or more, and even more preferably 6.7 or more

with respect to the lower limit of the pH in order to sufficiently ensure the use feeling. The pH is preferably 7.7 or less, more preferably 7.5 or less, and even more preferably 7.2 or less with respect to the upper limit of the pH in order to sufficiently maintain the glucose concentration.

[0039]

The pH adjuster is not particularly restricted as long as the pH adjuster is applicable to a living body, especially the eyes. An example of the pH adjuster includes an inorganic acid such as hydrochloric acid and boric acid; an organic acid such as acetic acid, glutamic acid and aspartic acid; an inorganic base such as sodium hydroxide, sodium carbonate and sodium hydrogencarbonate; and an organic base such as triethanolamine and monoethanolamine. The kind and additive amount of the pH adjuster may be adjusted depending on the pH to be adjusted of the pharmaceutical composition.

[0040]

The "monoterpene" means a compound composed of two isoprene units and having a molecular formula of $C_{10}H_{16}$. A monocyclic monoterpene, which has a cooling action, is mainly used in the present invention. An example of the monoterpene includes menthol, camphor and borneol. Any of l-menthol and dl-menthol may be used as menthol, and l-menthol is preferred. Any one of d-body and dl-body of camphor and borneol may be used, and d-body is preferred. Only one of the monoterpene may be used, or two or more of the monoterpenes may be used in combination.

[0041]

The concentration of the monoterpene in the pharmaceutical composition may be appropriately adjusted and for example, may be adjusted to 0.0005 w/v% or more and 0.1 w/v% or less from

the viewpoint of the moderate cooling sensation. The concentration is preferably 0.001 w/v% or more, more preferably 0.0015 w/v% or more, and even more preferably 0.002 w/v% or more with respect to the lower limit of the concentration. The concentration is preferably 0.05 w/v% or less, more preferably 0.015 w/v% or less, and even more preferably 0.01 w/v% or less with respect to the upper limit of the concentration.

[0042]

The "chelating agent" means a compound to improve the storage stability of the composition by sequestering a metal ion such as calcium ion to prevent an insoluble metal salt from being produced. The chelating agent is not particularly restricted as long as the chelating agent is applicable to a living body, especially the eyes, and has the above-described action. An example of the chelating agent includes ethylenediaminetetraacetic acid (edetic acid), ascorbic acid, citric acid and salts thereof. An example of the ethylenediaminetetraacetate salt includes ethylenediaminetetraacetic acid tetrasodium salt and ethylenediaminetetraacetic acid disodium salt. Only one of the chelating agent may be used, or two or more of the chelating agents may be used in combination.

[0043]

The concentration of the chelating agent in the pharmaceutical composition may be appropriately adjusted. For example, the concentration may be adjusted to 0.001 w/v% or more and 0.15 w/v% or less in order to sufficiently ensure the stabilizing effect by the chelating agent. When the concentration is adjusted within the range, the stabilizing

effect by the chelating agent can be sufficiently obtained. The concentration is preferably 0.002 w/v% or more, more preferably 0.005 w/v% or more, and even more preferably 0.007 w/v% or more with respect to the lower limit of the concentration. The concentration is preferably 0.1 w/v% or less, more preferably 0.05 w/v% or less, and even more preferably 0.03 w/v% or less with respect to the upper limit of the concentration.

[0044]

A preserving agent or an antiseptic agent may be added in the pharmaceutical composition of the present invention in addition to the alkylldiaminoethylglycine hydrochloride without particular restriction as long as the effect of the present invention is not impaired. An example of the preserving agent or antiseptic agent includes benzalkonium chloride, benzalkonium bromide, benzethonium chloride, chlorhexidine hydrochloride, chlorhexidine gluconate, chlorhexidine acetate, chlorobutanol, benzyl alcohol, phenethyl alcohol, sorbic acid or a salt thereof, methyl parahydroxybenzoate, ethyl parahydroxybenzoate, propyl parahydroxybenzoate, dehydroacetic acid or a salt thereof, zinc chloride, polidronium chloride, thimerosal, dibutylhydroxytoluene, sodium chlorite, polyhexamethylene biguanide, boric acid and borax. Only one of the preserving agent or antiseptic agent may be used alone, or two or more of the preserving agents or antiseptic agents may be used in combination.

[0045]

The pharmaceutical composition of the present invention can be produced by an ordinary method. For example, each component may be dissolved in water as a solvent. For example, water

that is so clear that an amount of an impurity, a bacterium, a virus, a fungus or the like is lower than the detection limit or sufficiently small, such as distilled water, purified water and sterile water, is used as a solvent.

[0046]

The container for the pharmacological composition of the present invention is not particularly restricted and may be a container that has been conventionally used as an eyedropper container. The container may be made of glass or plastic. When the container for the pharmacological composition of the present invention is made of plastic, the material of the plastic container is not particularly restricted and for example, is exemplified by any one kind or two or more kinds mixture of polyethylene naphthalate, polyacrylate, polyethylene terephthalate, polybutylene terephthalate, polypropylene, polyethylene and polyimide. The material of the container main body, in other words, the part in which the pharmaceutical composition is contained, is preferably polyethylene terephthalate, polyethylene and polypropylene and more preferably polyethylene terephthalate from the viewpoint to ensure the storage stability of the pharmaceutical composition.

[0047]

The "storage stability" of the pharmaceutical composition according to the present invention means that a degree to maintain the concentration of glucose and suppress white turbidity even after the aqueous composition is stored for a predetermined period. The phrase "the concentration of glucose is maintained" in the pharmaceutical composition of the present invention means that the concentration of glucose in

the aqueous composition is maintained or is not significantly decreased after the aqueous composition is stored for a predetermined period in comparison with the concentration of glucose in the aqueous composition before the storage. The degree to which "the concentration of glucose is maintained" can be demonstrated as a glucose residual ratio. For example, the phrase means that the glucose residual ratio after the pharmaceutical composition of the present invention is stored at 80°C for 2 weeks is 75% or more to the initial concentration. The glucose residual ratio is preferably 80% or more.

[0048]

The phrase "white turbidity is suppressed" in the pharmaceutical composition of the present invention means that white turbidity cannot be found to the naked eye in the appearance of the pharmaceutical composition after the aqueous composition is stored in a predetermined period. For example, the phrase means that white turbidity cannot be found to the naked eye after the pharmaceutical composition of the present invention is stored at 80°C for 2 weeks.

[0049]

The phrase "storage stability is improved" of the pharmaceutical composition according to the present invention means that the concentration of glucose is maintained and white turbidity is suppressed after the aqueous composition is stored in a predetermined period. For example, the phrase means that the glucose residual ratio is equal or higher, the degree of white turbidity is equal or lower and the glucose residual ratio is higher, and/or the degree of white turbidity is lower in the pharmaceutical composition of the present

invention after the composition is stored at 80°C for 2 weeks in composition with the pharmaceutical composition that does not contain one or more of 0.0005 w/v% or more and 0.05 w/v% or less of glucose, the non-ionic surfactant and the alkylldiaminoethylglycine hydrochloride or of which concentration of glucose is outside the range. The glucose, non-ionic surfactant and alkylldiaminoethylglycine hydrochloride are the essential components of the pharmaceutical composition according to the present invention.

[0050]

The pharmaceutical composition of the present invention complements tears and is effective in relieving discomfort, dryness of eyes, eye fatigue and blurred vision in wearing a soft contact lens or a hard contact lens. In particular, the composition is effective in relieving discomfort in wearing a soft contact lens.

[0051]

The pharmaceutical composition of the present invention can be used in either an internal form or an external form depending on the purpose. The composition can be provided as a local administration liquid medicinal agent for various application. For example, the composition can be provided for medical application in an internal form and for ophthalmic, dental, ontological and dermatologic applications in an external form. In particular, the composition can be provided for ophthalmic application.

[0052]

The term "ophthalmic pharmaceutical composition" means a pharmaceutical composition for ophthalmic application. An example of the pharmaceutical composition particularly

includes an aqueous liquid composition containing water as a solvent. The term "aqueous liquid composition" particularly means a liquid pharmaceutical composition containing water as a solvent. The aqueous liquid composition can be produced by an ordinary method. For example, the aqueous liquid composition can be produced by dissolving or dispersing each component in water as a solvent.

[0053]

An example of the ophthalmic pharmaceutical composition includes an ophthalmic solution, an eye wash, an eye ointment, a contact lens fitting liquid and a contact lens care liquid. An ophthalmic solution is exemplified by an ophthalmic solution usable while wearing a contact lens and is also called as an eye-drop and an ophthalmic agent. An eye wash is exemplified by an eye wash usable while wearing a contact lens and is also called as an eye lotion and an eye wash agent. An example of a contact lens care liquid includes a cleaning liquid, a preservative solution, a sterilizing liquid and an antiseptic solution such as a multi-purpose solution. The ophthalmic pharmaceutical composition is preferably an ophthalmic solution, a contact lens fitting liquid, an eye wash and a contact lens care liquid, and particularly preferably an ophthalmic solution.

[0054]

The pharmaceutical composition of the present invention is exemplified by an ophthalmic solution usable with wearing a contact lens. An example of a contact lens includes any types of a contact lens such as a soft contact lens and a hard contact lens such as an oxygen permeable hard contact lens in this disclosure. The kind of a soft contact lens is not

particularly restricted, and the composition can be used for any one of a disposable soft contact lens, a periodic replacement soft contact lens, a conventional soft contact lens, a silicone hydrogel soft contact lens and a color soft contact lens. A silicone hydrogel soft contact lens is made of a silicone hydrogel material.

[0055]

The administration and dosage of the ophthalmic solution according to the present invention is adjusted depending on the symptom, age or the like of a patient, and one drop or more and 3 drops or less of the ophthalmic solution may be generally instilled into an eye one time or more and 6 times or less per one day.

[0056]

The container used for the pharmaceutical composition of the present invention is sterilized by an ordinary method. The sterilization method is not particularly restricted as long as the method is generally used and is exemplified by dry heat sterilization, electron beam sterilization, gamma sterilization, ethylene gas sterilization and hydrogen peroxide sterilization. Electron beam sterilization is used as a sterilization method in one embodiment.

[0057]

The present invention relates to a method for improving storage stability of a pharmaceutical composition comprising glucose, the method comprising the step of mixing a non-ionic surfactant and an alkylldiaminoethylglycine hydrochloride in the pharmaceutical composition, wherein the pharmaceutical composition comprises 0.0005 w/v% or more and 0.05 w/v% or less of glucose.

[0058]

In particular, when the concentration of glucose in the pharmaceutical composition comprising glucose is adjusted to 0.0005 w/v% or more and 0.05 w/v% in the method for improving storage stability according to the present invention, more excellent effect of the present invention can be exerted.

[0059]

The kind and the concentration with respect to the above-described pharmaceutical composition may be applied alone or in combination to the kind and the concentration of glucose, the non-ionic surfactant, the alkyldiaminoethylglycine hydrochloride and other optional component to be used in the above-described method for improving storage stability of the pharmaceutical composition comprising glucose. The pH, container or the like of the pharmaceutical composition can be also similarly applied to the method.

[0060]

The present application claims the benefit of the priority date of Japanese patent application No. 2019-217421 filed on November 29, 2019. All of the contents of the Japanese patent application No. 2019-217421 filed on November 29, 2019, are incorporated by reference herein.

EXAMPLES

[0061]

Hereinafter, the present invention is described in more detail with Examples. The present invention is however not restricted to the following Examples in any way, and it is possible to work the present invention in accordance with the Examples with an additional appropriate change within the

range of the above descriptions and the following descriptions. Such a changed embodiment is also included in the technical scope of the present invention.

[0062]

Test example 1: Storage stability test - appearance evaluation

Each component was dissolved in purified water in accordance with the compositions shown in Table 1. The unit of the numerical values in Table 1 is w/v%. Glass ampoules were filled with each of the prepared aqueous liquid composition (5 mL) and stored at 80°C for 2 weeks.

After the storage, the appearance was evaluated in accordance with Procedure of property described in General Notices of The Japanese Pharmacopoeia 17th edition. Specifically, the glass ampoule filled with each aqueous liquid composition was placed in front of a black background, and it was observed whether the aqueous liquid composition was colorless and clear or a white insoluble component was deposited and the aqueous liquid composition became cloudy. The evaluation result is shown in Table 1.

[0063]

Test example 2: Storage stability test - glucose residual ratio measurement

The glucose residual ratio after the composition was stored at 80°C for 2 weeks was determined using a glucose quantity determination kit ("Glucose CII Test Wako" manufactured by FUJIFILM Wako Pure Chemical Corporation) in accordance with Ultraviolet-visible Spectrophotometry of The Japanese Pharmacopoeia 17th edition. Specifically, the aqueous liquid composition having the glucose concentration of 0.1 w/v% among

the aqueous liquid compositions prepared in Test example 1 was diluted so that the glucose concentration was adjusted to 0.005 w/v%. A coloring reagent (3 mL) was mixed into the aqueous liquid composition having the glucose concentration of 0.005 w/v% directly and the diluted aqueous composition (2 mL). The mixture was heated at 37°C for 5 minutes. An absorbance of 505 nm was measured using water heated similarly as a control. In addition, a glucose standard solution was separately prepared by dissolving glucose (50 mg) in water to obtain totally 100 mL solution and adding water to the solution (2 mL) so that the total amount was adjusted to 20 mL, and the absorbance of the glucose standard solution of which glucose concentration was preliminarily determined was similarly measured. The glucose content amount (%) and the glucose residual ratio (%) were calculated from the measurement result in accordance with the following formulas. The result is shown in Table 1.

Glucose content amount (%) = [weighing amount of standard solution (mg) × absorbance of sample / absorbance of standard solution] × 2

Glucose residual ratio (%) = [glucose content amount after storage / glucose content amount before storage] × 100

[0064]

Table 1

	Comparative example 1	Comparative example 2	Comparative example 3	Example 1
Glucose	0.1	0.005	0.005	0.005
Alkyldiaminoethylglycine hydrochloride	—	—	—	0.0025
Polyoxyethylene hydrogenated castor oil 60	—	—	0.01	0.01
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Appearance	Colorless and clear	Colorless and clear	Slightly white turbidity	Colorless and clear
Glucose residual ratio	86.8%	70.2%	79.7%	76.8%

[0065]

Used product

Glucose: product name "Glucose" manufactured by San-ei

Sucrochemical

Alkyldiaminoethylglycine hydrochloride: product name "LEBON
LAG-40" manufactured by Sanyo Chemical Industries

Polyoxyethylene hydrogenated castor oil 60: product name
"HCO-60 (for medicinal purposes)" manufactured by Nikko
Chemicals

[0066]

The appearance and the glucose residual ratio of the 0.1 w/v% glucose aqueous solution were not significantly changed even after the storage but the glucose residual ratio of the glucose aqueous solution having the low concentration of 0.005 w/v% was significantly decreased as the result shown in Table 1. It is not clarified what kind of compound glucose was changed to, but the decrease of the residual ratio clearly demonstrated quality loss.

On the one hand, when polyoxyethylene hydrogenated castor oil 60 was mixed, the decrease of the residual ratio of low concentration glucose was suppressed. Instead, white turbidity

occurred over time.

The inventor of the present invention therefore mixed an alkyldiaminoethylglycine hydrochloride in addition to polyoxyethylene hydrogenated castor oil 60; as a result, it was found that an aqueous liquid composition remarkably excellent in storage stability could be obtained as not only the decrease of the residual ratio of low concentration glucose but also white turbidity were suppressed.

[0067]

Test example 3: Storage stability test - appearance evaluation and glucose residual ratio measurement

Aqueous liquid compositions were prepared by dissolving each component in purified water in accordance with the compositions shown in Table 2. The unit of the numerical values in Table 2 is w/v%.

The appearance was evaluated and the glucose residual ratio was measured after each aqueous liquid composition of Example 2 was stored in the same conditions of Test example 1 and Test example 2. The result is shown in Table 2.

[0068]

Table 2

	Comparative example 4	Example 2	Comparative example 5	Example 3
Glucose	0.005	0.005	0.005	0.005
Alkyldiaminoethylglycine hydrochloride	—	0.0025	—	0.0025
Polysorbate 80	0.01	0.01	—	—
Polyoxyl 40 stearate	—	—	0.01	0.01
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Appearance	Slightly white turbidity	Colorless and clear	Slightly white turbidity	Colorless and clear
Glucose residual ratio	89.0%	80.7%	84.9%	83.4%

[0069]

Used product

Polysorbate 80: product name "Polysorbate 80 (SS)"
manufactured by NOF CORPORATION

Polyoxyl 40 stearate: product name "MYS-40MV" manufactured by
NIPPON SURFACTANT INDUSTRIES

[0070]

When polysorbate 80 (polyoxyethylene sorbitan long-chain fatty acid monoester) as a non-ionic surfactant was mixed in 0.005 w/v% glucose aqueous solution, the decrease of the glucose residual ratio was suppressed but white turbidity occurred depending on storage condition (Comparative example 4) as the result shown in Table 2. When the non-ionic surfactant was changed to polyoxyl 40 stearate as a polyethylene glycol long-chain fatty acid monoester (Comparative example 5), the result was similar.

On the one hand, it was demonstrated that an aqueous liquid composition remarkably excellent in storage stability could be obtained as not only the decrease of the residual ratio of low concentration glucose but also white turbidity were suppressed by mixing an alkyl diaminoethylglycine hydrochloride in addition to a non-ionic surfactant (Example 2 and Example 3).

[0071]

Production example

Production example is hereinafter described as specific embodiments of the aqueous liquid composition according to the present invention. The unit of the numerical values other than pH in Tables is w/v%. When the non-ionic surfactant and the alkyl diaminoethylglycine hydrochloride were mixed in the aqueous liquid composition also in the case of Production examples, remarkably excellent storage stability could be obtained as not only the decrease of the residual ratio of low

concentration glucose but also white turbidity were suppressed.

[0072]

Table 3

	Production example 1	Production example 2	Production example 3	Production example 4	Production example 5	Production example 6	Production example 7	Production example 8
Glucose	0.001	0.003	0.01	0.05	0.005	0.005	0.005	0.005
Alkyldiaminoethylglycine hydrochloride	0.0025	0.0025	0.0025	0.0025	0.0005	0.001	0.01	0.05
Polyoxyethylene hydrogenated castor oil	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
pH	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0

Table 4

	Production example 9	Production example 10	Production example 11	Production example 12	Production example 13	Production example 14	Production example 15	Production example 16
Glucose	0.005	0.005	0.005	0.001	0.005	0.005	0.005	0.005
Alkyldiaminoethylglycine hydrochloride	0.0025	0.0025	0.0025	0.0025	0.0025	0.0025	0.0025	0.0025
Polyoxyethylene hydrogenated castor oil	0.001	0.01	0.005	0.5	0.01	0.01	0.01	0.01
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
pH	7.0	7.0	7.0	7.0	5.0	5.5	8.0	8.5

[0074]

Test example 4 - Study of glucose concentration

The glucose aqueous solutions having the concentrations shown in Table 5 were prepared, and the glucose residual ratio after the solution was stored at 80°C for 2 weeks was determined similarly to Test example 1. The result is shown in Table 5.

[0075]

Table 5

	Rerference example 1	Rerference example 2	Rerference example 3	Rerference example 4
Glucose	0.0005%	0.005%	0.01%	0.1%
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Glucose residual ratio	51.3%	70.2%	73.3%	88.2%

[0076]

It was found as the result shown in Table 5 that the stability of glucose in the glucose aqueous solution having relatively high concentration as 0.1 mass% is relatively high, but the stability tends to be lower in the case of lower glucose concentration, and the stability of glucose is not sufficient at least in the range of 0.0005 mass% or more and 0.01 mass% or less.

[0077]

Test example 5 - Study of non-ionic surfactant concentration

The glucose - non-ionic surfactant aqueous solutions having the concentrations shown in Table 6 were prepared, and the glucose residual ratio was determined and the appearance was evaluated similarly to Test example 1 after the solution was stored at 80°C for 2 weeks. Polyethylene glycol monostearate (40E.O.) ("NIKKOL MYS-40" manufactured by Nikko Chemicals) was

used as a non-ionic surfactant. The result is shown in Table 6.

[0078]

Table 6

	Rerference example 5	Rerference example 6	Rerference example 7	Rerference example 8	Rerference example 9
Glucose	0.005%	0.005%	0.005%	0.005%	0.005%
PEG monostearate (40)	—	0.001%	0.005%	0.01%	0.05%
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Appearance	Colorless and clear	Colorless and clear	Slightly white turbidity	Slightly white turbidity	Slightly white turbidity
Glucose residual ratio	72.5%	74.7%	89.8%	86.1%	85.1%

[0079]

It was found as the result shown in Table 6 that the stability of low concentration glucose can be improved by mixing 0.005 mass% or more and 0.05 mass% or less of a non-ionic surfactant but the mixture becomes cloudy.

[0080]

Test example 6 - Study of alkyldiaminoethylglycine hydrochloride concentration

The mixture liquid having the composition shown in Table 7 was prepared, and the glucose residual ratio after the mixture liquid was stored at 80°C for 2 weeks was determined and the appearance was evaluated similarly to Test example 1. The result is shown in Table 7.

[0081]

Table 7

	Comparative example 6	Example 4	Example 5	Example 6	Comparative example 7
Glucose	0.005%	0.005%	0.005%	0.005%	0.005%
Polyoxyethylene hydrogenated castor oil 60	0.01%	0.01%	0.01%	0.01%	0.01%
Alkyldiaminoethylglycine hydrochloride	—	0.001%	0.0025%	0.005%	0.05%
Purified water	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount	Appropriate amount
Appearance	Slightly white turbidity	Colorless and clear	Colorless and clear	Colorless and clear	Slightly yellow white turbidity
Glucose residual ratio	81.0%	84.9%	79.0%	84.4%	82.4%

[0082]

It was experimentally demonstrated as the result shown in Table 7 that the white turbidity of the mixture liquid of which low concentration glucose becomes stable by mixing a non-ionic surfactant is not improved even by mixing an excess alkyldiaminoethylglycine hydrochloride but the white turbidity can be resolved by mixing 0.001 mass% or more and 0.005 mass% or less of an alkyldiaminoethylglycine hydrochloride.

CLAIMS

1. A pharmaceutical composition comprising 0.0005 w/v% or more and 0.05 w/v% or less of glucose, a non-ionic surfactant and 0.0005 w/v% or more and 0.01 w/v% or less of an alkyldiaminoethylglycine hydrochloride.

2. The pharmaceutical composition according to claim 1, comprising 0.0005 w/v% or more and 0.01 w/v% or less of the glucose.

3. The pharmaceutical composition according to claim 1 or 2, wherein the non-ionic surfactant is one or more non-ionic surfactants selected from the group consisting of polyoxyethylene hydrogenated castor oil, polyoxyethylene sorbitan long-chain fatty acid monoester, polyethylene glycol long-chain fatty acid monoester and polyoxyethylene-polyoxypropylene block copolymer.

4. The pharmaceutical composition according to any one of claims 1 to 3, comprising 0.001 w/v% or more and 0.5 w/v% or less of the non-ionic surfactant.

5. The pharmaceutical composition according to any one of claims 1 to 4, comprising:

0.002 w/v% or more and 0.01 w/v% or less of the glucose,
0.005 w/v% or more and 0.05 w/v% or less of the non-ionic surfactant, and

0.001 w/v% or more and 0.005 w/v% or less of the alkyldiaminoethylglycine hydrochloride.

6. The pharmaceutical composition according to any one of claims 1 to 5, further comprising an amino acid.
7. The pharmaceutical composition according to claim 6, wherein the amino acid is taurine.
8. The pharmaceutical composition according to claim 6 or 7, comprising 0.01 w/v% or more and 1.0 w/v% or less of the amino acid.
9. The pharmaceutical composition according to any one of claims 1 to 8, wherein pH is 5.0 or more and 8.5 or less.
10. A pharmaceutical composition comprising:
 - 0.005 w/v% of glucose,
 - 0.01 w/v% of a non-ionic surfactant, and
 - 0.0025 w/v% of an alkyldiaminoethylglycine hydrochloride.

Abstract

PHARMACEUTICAL COMPOSITION

The objective of the present invention is to provide a pharmaceutical composition excellent in storage stability. The pharmaceutical composition of the present invention comprises 0.0005 w/v% or more and 0.05 or w/v% less of glucose, a non-ionic surfactant and an alkylidiaminoethylglycine hydrochloride.

[No Suitable Figure]