comprising aqueous composition, selecting benzalkonium halide as a cationic preservative and adding a nonionic surfactant can unexpectedly make it possible to exhibit a good solution stability.

Furthermore, the inventors have found that the addition of a buffer to a pharmaceutical composition which comprises ursodeoxycholic acid or a salt thereof, a preservative, and water surprisingly improves the preservative efficacy of the pharmaceutical composition. The inventors also have found that the addition of ursodeoxycholic acid or a salt thereof to a pharmaceutical composition comprising a nonionic surfactant and water suppresses the appearance change of the pharmaceutical composition.

[0008]

Specifically, the invention includes the following aspects.

[Item 1]

A pharmaceutical composition comprising ursodeoxycholic acid or a salt thereof, a preservative, and water.

[Item 2]

The pharmaceutical composition according to Item 1, wherein the preservative is selected from benzalkonium halide, boric acid or a salt thereof, and combinations thereof.

[Item 3]

The pharmaceutical composition according to Item 1 or 2, wherein the preservative comprises benzalkonium halide, and optionally comprises boric acid or a salt thereof.

[Item 4]

The pharmaceutical composition according to any one of Items 1 to 3, wherein the preservative comprises benzalkonium halide and boric acid or a salt thereof.

[Item 5]

The pharmaceutical composition according to any one of Items 2 to 4, wherein the benzalkonium halide is selected from benzalkonium chloride, benzalkonium bromide, and a combination thereof.

[Item 32]

Use of the pharmaceutical composition according to any one of Items 1 to 30, in the manufacture of a medicament for treating and/or preventing presbyopia, an eye disease accompanied by a decrease in lens elasticity, or an eye disease accompanied by a decrease in accommodative function of the eye.

[Item 33]

A method for treating and/or preventing presbyopia, an eye disease accompanied by a decrease in lens elasticity, or an eye disease accompanied by a decrease in accommodative function of the eye, comprising administering to a subject in need thereof a therapeutically and/or prophylactically effective amount of the pharmaceutical composition according to any one of Items 1 to 30.

[Item 34]

A method for improving tissue penetration of ursodeoxycholic acid or a salt thereof in a pharmaceutical composition comprising ursodeoxycholic acid or a salt thereof and water, comprising adding a preservative.

[Item 35]

A method for improving solution stability of a pharmaceutical composition comprising ursodeoxycholic acid or a salt thereof, a preservative, and water, comprising adding a nonionic surfactant.

[Item 36]

A method for suppressing an appearance change of a pharmaceutical composition comprising a nonionic surfactant and water, comprising adding ursodeoxycholic acid or a salt thereof.

[Item 37]

A method for suppressing an appearance change of a pharmaceutical composition comprising a nonionic surfactant, a preservative, and water, comprising adding ursodeoxycholic acid or a salt thereof.

[Item 38]

The method according to Item 35 or 37, wherein the preservative comprises benzalkonium halide.

nonionic surfactant in the pharmaceutical composition of the present invention is, relative to 1 part by mass of ursodeoxycholic acid or a salt thereof, for example, 30 parts by mass, preferably 10 parts by mass, more preferably 5 parts by mass, still more preferably 2.5 parts by mass, still more preferably 0.9 parts by mass, particularly preferably 0.8 parts by mass, most preferably 0.75 parts by mass. A preferred range of the content of the nonionic surfactant may be indicated by a combination of the upper and lower limits exemplified above, and is, relative to 1 part by mass of ursodeoxycholic acid or a salt thereof, for example, 0.001 to 30 parts by mass, preferably 0.005 to 10 parts by mass, more preferably 0.01 to 5 parts by mass, still more preferably 0.03 to 2.5 parts by mass, still more preferably 0.05 to 0.9 parts by mass, particularly preferably 0.1 to 0.8 parts by mass, most preferably 0.15 to 0.75 parts by mass. In one embodiment, from a viewpoint of long-term solution stability / suppression of appearance change, the content of the nonionic surfactant in the pharmaceutical composition of the present disclosure is, relative to 1 part by mass of ursodeoxycholic acid or a salt thereof, preferably 0.05 to 5 parts by mass, more preferably 0.1 to 2.5 parts by mass, still more preferably 0.15 to 1 parts by mass, still more preferably 0.15 to 0.75 parts by mass.

[0056]

In one embodiment, in a case where benzalkonium halide is comprised in the pharmaceutical composition of the present disclosure, the lower limit of the content of the nonionic surfactant in the pharmaceutical composition of the present disclosure is, relative to 1 part by mass of benzalkonium halide, for example, 0.1 parts by mass, preferably 1 part by mass, more preferably 3 parts by mass, most preferably 5 parts by mass. The upper limit of the content of the nonionic surfactant in the pharmaceutical composition of the present invention is, relative to 1 part by mass of benzalkonium halide, for example, 30 parts by mass, preferably 15 parts by mass, more preferably 13 parts by mass, most preferably 10 parts by mass. A preferred range of the content of the

[0063]

In one embodiment, this disclosure provides a pharmaceutical composition comprising:

ursodeoxycholic acid or a salt thereof (preferably 0.00001 to 5% (w/v)),

benzalkonium chloride (preferably 0.0001 to 0.05% (w/v)),

boric acid or a salt thereof (preferably 0.001 to 3% (w/v)),

polyoxyethylene sorbitan fatty acid ester (preferably 0.001 to 0.3% (w/v)),

trometamol or a salt thereof (preferably 0.001 to 2% (w/v)), and

water.

[0064]

Other additive(s) may optionally be used in the pharmaceutical composition of the present invention. Examples of additives include tonicity agents, stabilizers, antioxidants, high molecular weight polymers, pH adjusters, bases, etc.

[0065]

The pharmaceutical composition of the present invention may optionally comprise a tonicity agent which is usable as an additive for a pharmaceutical product. Examples of such a tonicity agent include ionic tonicity agents and non-ionic tonicity agents, etc. Examples of the ionic tonicity agents include sodium chloride, potassium chloride, calcium chloride, magnesium chloride, etc.; and examples of the non-ionic tonicity agents include glycerin, propylene glycol, sorbitol, mannitol, etc. From a viewpoint of preservative efficacy of the pharmaceutical composition of the present invention, glycerin is preferred. In a case where tonicity agent(s) is used in the pharmaceutical composition of the present disclosure, the content of tonicity agent(s) may be optionally adjusted according to the type of the tonicity agent(s), and others, and is preferably 0.1 to 5% (w/v), more preferably 0.5 to 4% (w/v), still more preferably 1 to 3% (w/v), particularly preferably 1.2 to 2.5% (w/v), most preferably 1.5 to 2% (w/v).

[0066]

may become in a solution state and the pharmaceutical composition may maintain the solution state. Especially in a case where a cationic preservative is used, white turbidity/precipitation etc. may occur in the composition, but by selecting benzalkonium halide as a cationic preservative and adding a nonionic surfactant, an aqueous solution comprising ursodeoxycholic acid may be obtained. In this case, the composition preferably does not comprise any cationic preservative other than benzalkonium halide, but other cationic preservative(s) may be comprised to the extent permitted from a viewpoint of the solution stability.

[0088]

In this disclosure, "suppressing an appearance change of a pharmaceutical composition" means to suppress changes in appearance such as color of the pharmaceutical composition over time. For example, even if a pharmaceutical composition is a clear, colorless liquid at the time of preparation, it may become turbid or the like over time depending on the conditions, and suppression of such change in appearance such as turbid or the like may be included in "suppressing an appearance change of a pharmaceutical composition." In this disclosure, by further adding ursodeoxycholic acid or a salt thereof to a pharmaceutical composition comprising a nonionic surfactant and water, the change in appearance of a pharmaceutical composition over time, especially white turbidity, may be suppressed and the initial condition at the time of preparation may be maintained. The composition may or may not comprise preservatives such as benzalkonium halide.

[0089]

According to the method of improving solution stability of the pharmaceutical composition of the present disclosure, the pharmaceutical composition may maintain a dissolved state over a long period of time (for example, at room temperature, for 1 month, preferably for 3 months, more preferably for 6 months, even more preferably for 1 year, especially preferably for 2 years, most preferably for 3 years) without having white turbidity or precipitates.

CLAIMS

1. A pharmaceutical composition comprising ursodeoxycholic acid or a salt thereof, a preservative, and water.

2. The pharmaceutical composition according to Claim 1, wherein the preservative is selected from benzalkonium halide, boric acid or a salt thereof, and combinations thereof.

3. The pharmaceutical composition according to Claim 1 or 2, wherein the preservative comprises benzalkonium halide, and optionally comprises boric acid or a salt thereof.

4. The pharmaceutical composition according to any one of Claims 1 to 3, wherein the preservative comprises benzalkonium halide and boric acid or a salt thereof.

5. The pharmaceutical composition according to any one of Claims 2 to 4, wherein the benzalkonium halide is selected from benzalkonium chloride, benzalkonium bromide, and a combination thereof.

6. The pharmaceutical composition according to any one of Claims 2 to 5, wherein the benzalkonium halide is benzalkonium chloride.

7. The pharmaceutical composition according to any one of Claims 2 to 6, wherein the boric acid or a salt thereof is selected from boric acid, borax, and a combination thereof.

8. The pharmaceutical composition according to any one of Claims 1 to 7, wherein the pharmaceutical composition has a pH greater than or equal to 8.0.

9. The pharmaceutical composition according to any one of Claims 1 to 8, wherein the pharmaceutical composition has a

pH of 8.3 to 9.3.

10. The pharmaceutical composition according to any one of Claims 1 to 9, further comprising a nonionic surfactant

11. The pharmaceutical composition according to Claim 10, wherein the nonionic surfactant is polyoxyethylene sorbitan fatty acid ester.

12. The pharmaceutical composition according to Claim 11, wherien the polyoxyethylene sorbitan fatty acid ester is polysorbate 80.

13. The pharmaceutical composition according to any one of Claims 1 to 12, further comprising a buffer.

14. The pharmaceutical composition according to Claim 13, wherein the buffer is selected from phosphoric acid or a salt thereof, citric acid or a salt thereof, acetic acid or a salt thereof, carbonic acid or a salt thereof, tartaric acid or a salt thereof, ε-aminocaproic acid or a salt thereof, trometamol or a salt thereof, and combinations thereof.

15. The pharmaceutical composition according to Claim 13, wherein the buffer is trometamol or a salt thereof.

16. The pharmaceutical composition according to any one of Claims 1 to 15, wherein the content of the ursodeoxycholic acid or a salt thereof in the pharmaceutical composition is 0.00001 to 5% (w/v).

17. The pharmaceutical composition according to any one of Claims 1 to 16, wherein the content of the ursodeoxycholic acid or a salt thereof in the pharmaceutical composition is 0.0003 to 0.9% (w/v).

18. The pharmaceutical composition according to any one of Claims 1 to 17, wherein the content of the preservative in the pharmaceutical composition is 0.0001 to 3.5% (w/v).

19. The pharmaceutical composition according to any one of Claims 2 to 18, wherein the content of the benzalkonium halide in the pharmaceutical composition is 0.0001 to 0.05% (w/v).

20. The pharmaceutical composition according to any one of Claims 2 to 19, wherein the content of the boric acid or a salt thereof in the pharmaceutical composition is 0.001 to 3% (w/v).

21. The pharmaceutical composition according to any one of Claims 10 to 20, wherein the content of the nonionic surfactant in the pharmaceutical composition is 0.001 to 30 parts by mass relative to 1 part by mass of ursodeoxycholic acid or a salt thereof.

22. The pharmaceutical composition according to any one of Claims 10 to 21, wherein the content of the nonionic surfactant in the pharmaceutical composition is 0.001 to 0.3% (w/v).

23. The pharmaceutical composition according to any one of Claims 10 to 22, wherein the content of the nonionic surfactant in the pharmaceutical composition is 0.03 to 0.09% (w/v).

24. The pharmaceutical composition according to any one of Claims 13 to 23, wherein the content of the buffer in the pharmaceutical composition is 0.001 to 5% (w/v).

25. The pharmaceutical composition according to any one of Claims 14 to 24, wherein the content of the trometamol or a salt thereof in the pharmaceutical composition is 0.001 to 2% (w/v).

26. The pharmaceutical composition according to any one of Claims 14 to 25, wherein the content of the trometamol or a

salt thereof in the pharmaceutical composition is 0.05 to 0.9% (w/v).

27. The pharmaceutical composition according to any one of Claims 1 to 26, further comprising glycerin.

28. The pharmaceutical composition according to any one of Claims 1 to 27, which is a solution.

29. The pharmaceutical composition according to any one of Claims 1 to 28, wherein the pharmaceutical composition is administered into eye.

30. The pharmaceutical composition according to any one of Claims 1 to 29, wherein the pharmaceutical composition is an eye drop.

31. The pharmaceutical composition according to any one of Claims 1 to 30, wherein the pharmaceutical composition is for treating and/or preventing presbyopia, an eye disease accompanied by a decrease in lens elasticity, or an eye disease accompanied by a decrease in accommodative function of the eye.

32. Use of the pharmaceutical composition according to any one of Claims 1 to 30, in the manufacture of a medicament for treating and/or preventing presbyopia, an eye disease accompanied by a decrease in lens elasticity, or an eye disease accompanied by a decrease in accommodative function of the eye.

33. A method for treating and/or preventing presbyopia, an eye disease accompanied by a decrease in lens elasticity, or an eye disease accompanied by a decrease in accommodative function of the eye, comprising administering to a subject in need thereof a therapeutically and/or prophylactically effective amount of the pharmaceutical composition according to any one of Claims 1 to 30.

34. A method for improving tissue penetration of ursodeoxycholic acid or a salt thereof in a pharmaceutical composition comprising ursodeoxycholic acid or a salt thereof and water, comprising adding a preservative.

35. A method for improving solution stability of a pharmaceutical composition comprising ursodeoxycholic acid or a salt thereof, a preservative, and water, comprising adding a nonionic surfactant.

36. A method for suppressing an appearance change of a pharmaceutical composition comprising a nonionic surfactant and water, comprising adding ursodeoxycholic acid or a salt thereof.

37. A method for suppressing an appearance change of a pharmaceutical composition comprising a nonionic surfactant, a preservative, and water, comprising adding ursodeoxycholic acid or a salt thereof.

38. The method according to Claim 35 or 37, wherein the preservative comprises benzalkonium halide.

39. A method for improving preservative efficacy of a pharmaceutical composition comprising ursodeoxycholic acid or a salt thereof, a preservative, and water, comprising adding a buffer.