[DESCRIPTION]

[Title of Invention]

HETEROCYCLIDENE-ACETAMIDE-DERIVATIVE-CONTAINING COMPOSITION SUBJECTED TO ELECTRON BEAM STERILIZATION TREATMENT

[Technical Field]

[0001]

The present disclosure relates to the fields of pharmaceuticals, health care, biology, biotechnology, or the like. In particular, the present disclosure relates to improvement of stability of an aqueous liquid formulation containing a heterocyclidene acetamide derivative; and a formulation technique based thereon.

[Background Art]

[0002]

The number of dry eye patients in Japan is estimated to be at least about 8 million, or about 22 million including potential patients who use over-the-counter ophthalmic solutions without visiting a medical institution. It is said that there are 1 billion or more dry eye patients worldwide. It has been widely known that in modern society, use of televisions, computers, mobile terminals, etc. causes people to stare at screens more frequently to thereby reduce eye blink frequency, and use of air conditioners, etc. dries out the air, resulting in increased evaporation of tear fluid and thus causing dry eye. Refractive surgery and the use of contact lenses also result in dry eye. Symptoms associated with dry eye include, for example, ocular discomfort, dryness, burning, and irritation of the ocular surface.

[0003]

When dry eye occurs, the above-mentioned symptoms appear as subjective symptoms, and treatment of dry eye requires regular instillation of eye drops over a long period of time. For this reason, in general, many of the dry eye therapeutic drugs currently on the market require frequent administration. For example, DIQUAS (registered trademark) ophthalmic solution is normally required to be instilled 6 times a day, HYALEIN (registered trademark) ophthalmic solution is required to be instilled 5 to 6 times a day, and MUCOSTA (registered trademark) ophthalmic solution is normally required to be

instilled 4 times a day.

[0004]

A composition including (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof for treating dry eye, or use of the composition for treating dry eye, has been disclosed (PTL 1).

[0005]

An aqueous suspension liquid formulation including (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof; a cellulose-based polymer; and a non-ionic surfactant has been disclosed (PTL 2).

[Citation List]

[Patent Literature]

[0006]

[PTL 1]

PCT International Publication No. WO 2021/066144

[PTL 2]

PCT International Publication No. WO 2022/210784

[Summary of Invention]

[Solution to Problem]

[0007]

(Item 1)

An aqueous liquid formulation including a compound (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the compound, the salt, or the solvate having been subjected to an electron beam treatment.

(Item 2)

The aqueous liquid formulation according to the above item, in which the electron beam treatment is a treatment in a sterilization step.

(Item 3)

The aqueous liquid formulation according to any one of the above items, further including a non-ionic surfactant.

(Item 4)

An aqueous liquid formulation including:

a compound (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the compound, the salt, or the solvate having been subjected to an electron beam treatment; and

a non-ionic surfactant.

(Item 5)

The aqueous liquid formulation according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 10 kGy to about 60 kGy.

(Item 6)

The aqueous liquid formulation according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 15 kGy to about 45 kGy.

(Item 7)

The aqueous liquid formulation according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 20 kGy to about 30 kGy.

(Item 8)

The aqueous liquid formulation according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 10 kGy or more.

(Item 9)

The aqueous liquid formulation according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 15 kGy or more.

(Item 10)

The aqueous liquid formulation according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 20 kGy or more.

(Item 11)

The aqueous liquid formulation according to any one of the above items, in which the electron beam treatment includes

a treatment with an electron beam at an irradiation dose of about 60 kGy or less.

(Item 12)

The aqueous liquid formulation according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 50 kGy or less.

(Item 13)

The aqueous liquid formulation according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 40 kGy or less.

(Item 14)

The aqueous liquid formulation according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 30 kGy or less.

(Item 15)

The aqueous liquid formulation according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 25 kGy.

(Item 16)

The aqueous liquid formulation according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an intensity of about 100 keV to about 5 MeV.

(Item 17)

The aqueous liquid formulation according to any one of the above items, in which the non-ionic surfactant has a concentration of about 0.0001 w/v% to about 1 w/v% in the aqueous liquid formulation.

(Item 18)

The aqueous liquid formulation according to any one of the above items, in which the non-ionic surfactant has a concentration of about 0.001 w/v% to about 0.5 w/v% in the aqueous liquid formulation.

(Item 19)

The aqueous liquid formulation according to any one of

the above items, in which the non-ionic surfactant has a concentration of about 0.01 w/v% to about 0.05 w/v% in the aqueous liquid formulation.

(Item 20)

The aqueous liquid formulation according to any one of the above items, in which the non-ionic surfactant is at least one selected from the group consisting of tyloxapol, polysorbate, polyethylene glycol monostearate, and a polyoxyethylene hydrogenated castor oil.

(Item 21)

The aqueous liquid formulation according to any one of the above items, in which the non-ionic surfactant is tyloxapol.

(Item 22)

An aqueous liquid formulation including:

a compound (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the compound, the salt, or the solvate having been subjected to an electron beam treatment; and

tyloxapol.

(Item 23)

The aqueous liquid formulation according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof has a concentration of about 0.001 w/v% to about 5 w/v% in the aqueous liquid formulation.

(Item 24)

The aqueous liquid formulation according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof has a concentration of about 0.3 w/v% to about 1 w/v% in the aqueous liquid formulation.

(Item 25)

An aqueous liquid formulation including:

a compound (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a

pharmaceutically acceptable salt or solvate thereof, the compound, the salt, or the solvate having been subjected to an electron beam treatment; and

a non-ionic surfactant,

the electron beam treatment including a treatment with an electron beam at an irradiation dose of about 10 kGy to about 60 kGy;

the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof having a concentration of about 0.001 w/v% to about 5 w/v% in the aqueous liquid formulation; and

the non-ionic surfactant having a concentration of about 0.01 w/v% to about 0.05 w/v% in the aqueous liquid formulation.

(Item 26)

The aqueous liquid formulation according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide is (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-((7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide.

(Item 27)

The aqueous liquid formulation according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in a dissolved state has a concentration of about 0.01 w/v% or less in the aqueous liquid formulation.

(Item 28)

The aqueous liquid formulation according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the dissolved state has a concentration of more than 0 w/v% and about 0.01 w/v% or less in the aqueous liquid formulation.

(Item 29)

The aqueous liquid formulation according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-

yl)acetamide or the pharmaceutically acceptable salt or solvate thereof has improved stability in the aqueous liquid formulation.

(Item 30)

The aqueous liquid formulation according to any one of the above items, in which the improved stability is denoted as a residual ratio of the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof of about 90% or more when the aqueous liquid formulation is stored at about 60°C for 2 weeks.

(Item 31)

The aqueous liquid formulation according to any one of the above items, in which the residual ratio is about 95% or more.

(Item 32)

The aqueous liquid formulation according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the dissolved state has improved stability in the aqueous liquid formulation.

(Item 33)

The aqueous liquid formulation according to any one of the above items, in which the improved stability is denoted as a residual ratio of the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the dissolved state of about 90% or more when the aqueous liquid formulation is stored at about 60°C for 2 weeks.

(Item 34)

The aqueous liquid formulation according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the dissolved state has the residual ratio of about 95% or more.

(Item 35)

The aqueous liquid formulation according to any one of

the above items, in which the aqueous liquid formulation has a pH of about 4 to about 8.

(Item 36)

The aqueous liquid formulation according to any one of the above items, in which the aqueous liquid formulation is contained in a plastic container.

(Item 37)

The aqueous liquid formulation according to any one of the above items, in which the plastic container is made of polyethylene or polypropylene.

(Item 38)

The aqueous liquid formulation according to any one of the above items, in which the aqueous liquid formulation is an ophthalmic solution.

(Item 39)

The aqueous liquid formulation according to any one of the above items, in which the aqueous liquid formulation is an aqueous suspension liquid formulation.

(Item 40)

The aqueous liquid formulation according to any one of the above items, in which the aqueous liquid formulation is an ophthalmic suspension.

(Item 41)

A method for producing an aqueous liquid formulation including (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the method including:

treating the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with an electron beam; and

mixing the thus-electron beam-treated (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with a solvent.

(Item 42)

A method for stabilizing an aqueous liquid formulation including (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-

hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the method including:

treating the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with an electron beam; and

mixing the thus-electron beam-treated (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with a solvent.

(Item 43)

A method for producing stabilized (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the method including

treating the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with an electron beam.

(Item 44)

A method for stabilizing (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof in an aqueous liquid formulation, the method including:

treating the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with an electron beam; and

mixing the thus-electron beam-treated (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with a solvent.

(Item 45)

A method for sterilizing (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with an electron beam.

(Item 46)

The method according to the above item, further including adding a non-ionic surfactant.

(Item 47)

The method according to the above item, in which the solvent includes a non-ionic surfactant.

(Item 48)

The method according to the above item, in which the solvent has been subjected to sterile filtration.

(Item 49)

The method according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 10 kGy to about 60 kGy.

(Item 50)

The method according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 15 kGy to about 45 kGy.

(Item 51)

The method according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 20 kGy to about 30 kGy.

(Item 52)

The method according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 25 kGy.

(Item 52-1)

The method according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 10 kGy or more.

(Item 52-2)

The method according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 15 kGy or more.

(Item 52-3)

The method according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 20 kGy or more.

(Item 52-4)

The method according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 60 kGy or less.

(Item 52-5)

The method according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 50 kGy or less.

(Item 52-6)

The method according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 40 kGy or less.

(Item 52-7)

The method according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 30 kGy or less.

(Item 52-8)

The method according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 25 kGy.

(Item 52-9)

The method according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an intensity of about 100 keV to about 5 MeV.

(Item 53)

The method according to any one of the above items, in which the non-ionic surfactant has a concentration of about 0.0001 w/v% to about 1 w/v% in the aqueous liquid formulation.

(Item 54)

The method according to any one of the above items, in which the non-ionic surfactant has a concentration of about 0.001 w/v% to about 0.5 w/v% in the aqueous liquid formulation.

(Item 55)

The method according to any one of the above items, in which the non-ionic surfactant has a concentration of about 0.01 w/v% to about 0.05 w/v% in the aqueous liquid formulation.

(Item 56)

The method according to any one of the above items, in which the non-ionic surfactant is at least one selected from

the group consisting of tyloxapol, polysorbate, polyethylene glycol monostearate, and polyoxyethylene hydrogenated castor oil.

(Item 57)

The method according to any one of the above items, in which the non-ionic surfactant is tyloxapol.

(Item 58)

The method according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof has a concentration of about 0.001 w/v% to about 5 w/v% in the aqueous liquid formulation.

(Item 59)

The method according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof has a concentration of about 0.3 w/v% to about 1 w/v% in the aqueous liquid formulation.

(Item 60)

The method according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in a dissolved state has a concentration of about 0.01 w/v% or less in the aqueous liquid formulation.

(Item 61)

The method according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the dissolved state has a concentration of more than 0 w/v% and about 0.01 w/v% or less in the aqueous liquid formulation.

(Item 62)

The method according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide is (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-((7R)-7-hydroxy-5,6,7,8-

tetrahydronaphthalen-1-yl)acetamide.

(Item 63)

The method according to any one of the above items, in which the aqueous liquid formulation is an ophthalmic solution.

(Item 64)

The method according to any one of the above items, in which the aqueous liquid formulation is an aqueous suspension liquid formulation.

(Item 65)

The method according to any one of the above items, in which the aqueous liquid formulation is an ophthalmic suspension.

(Item 66)

A compound (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the compound, the salt, or the solvate having been subjected to an electron beam treatment.

(Item 67)

A compound (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-((7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the compound, the salt, or the solvate having been subjected to an electron beam treatment.

(Item 68)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 10 kGy to about 60 kGy.

(Item 69)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 15 kGy to about 45 kGy.

(Item 70)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in

which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 20 kGy to about 30 kGy.

(Item 71)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 10 kGy or more.

(Item 72)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 15 kGy or more.

(Item 73)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 20 kGy or more.

(Item 74)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 60 kGy or less.

(Item 75)

The compound or a pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 50 kGy or less.

(Item 76)

The compound or a pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 40 kGy or less.

(Item 77)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 30 kGy or less.

(Item 78)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 25 kGy.

(Item 79)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an intensity of about 100 keV to about 5 MeV.

(Item 80)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items for use in stabilization of an aqueous liquid formulation.

(Item 81)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the aqueous liquid formulation further includes a non-ionic surfactant.

(Item 82)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the non-ionic surfactant has a concentration of about 0.0001 w/v% to about 1 w/v% in the aqueous liquid formulation.

(Item 83)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the non-ionic surfactant has a concentration of about 0.001 w/v% to about 0.5 w/v% in the aqueous liquid formulation.

(Item 84)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the non-ionic surfactant has a concentration of about 0.01 w/v% to about 0.05 w/v% in the aqueous liquid formulation.

(Item 85)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the non-ionic surfactant is at least one selected from the group consisting of tyloxapol, polysorbate, polyethylene glycol monostearate, and polyoxyethylene hydrogenated castor

oil.

(Item 86)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the non-ionic surfactant is tyloxapol.

(Item 87)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof has a concentration of about 0.001 w/v% to about 5 w/v% in the aqueous liquid formulation.

(Item 88)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof has a concentration of about 0.3 w/v% to about 1 w/v% in the aqueous liquid formulation.

(Item 89)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in a dissolved state has a concentration of about 0.01 w/v% or less in the aqueous liquid formulation.

(Item 90)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the dissolved state has a concentration of more than 0 w/v% and about 0.01 w/v% or less in the aqueous liquid formulation.

(Item 91)

The compound or the pharmaceutically acceptable salt or

solvate thereof according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof has improved stability in the aqueous liquid formulation.

(Item 92)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the improved stability is denoted as a residual ratio of the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof of about 90% or more when the aqueous liquid formulation is stored at about 60°C for 2 weeks.

(Item 93)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the residual ratio is about 95% or more.

(Item 94)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the dissolved state has improved stability in the aqueous liquid formulation.

(Item 95)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the improved stability is denoted as a residual ratio of the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the dissolved state of about 90% or more when the aqueous liquid formulation is stored at about 60°C for 2 weeks.

(Item 96)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-

hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the dissolved state has the residual ratio of about 95% or more.

(Item 97)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the aqueous liquid formulation has a pH of about 4 to about 8.

(Item 98)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the aqueous liquid formulation is contained in a plastic container.

(Item 99)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the plastic container is made of polyethylene or polypropylene.

(Item 100)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the aqueous liquid formulation is an ophthalmic solution.

(Item 101)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the aqueous liquid formulation is an aqueous suspension liquid formulation.

(Item 102)

The compound or the pharmaceutically acceptable salt or solvate thereof according to any one of the above items, in which the aqueous liquid formulation is an ophthalmic suspension.

(Item 103)

Use of a compound (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof for producing a medicament, the compound, the salt, or the solvate having been subjected to an electron beam treatment.

(Item 104)

Use of a compound (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-((7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof for producing a medicament, the compound, the salt, or the solvate having been subjected to an electron beam treatment.

(Item 105)

The use according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 10 kGy to about 60 kGy.

(Item 106)

The use according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 15 kGy to about 45 kGy.

(Item 107)

The use according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 20 kGy to about 30 kGy.

(Item 108)

The use according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 10 kGy or more.

(Item 109)

The use according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 15 kGy or more.

(Item 110)

The use according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 20 kGy or more.

(Item 111)

The use according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 60 kGy or less.

(Item 112)

The use according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 50 kGy or less.
(Item 113)

The use according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 40 kGy or less.
(Item 114)

The use according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 30 kGy or less.
(Item 115)

The use according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an irradiation dose of about 25 kGy.
(Item 116)

The use according to any one of the above items, in which the electron beam treatment includes a treatment with an electron beam at an intensity of about 100 keV to about 5 MeV.
(Item 117)

The use according to any one of the above items for use in stabilization of an aqueous liquid formulation.
(Item 118)

The use according to any one of the above items, in which the aqueous liquid formulation further includes a non-ionic surfactant.
(Item 119)

The use according to any one of the above items, in which the non-ionic surfactant has a concentration of about 0.0001 w/v% to about 1 w/v% in the aqueous liquid formulation.
(Item 120)

The use according to any one of the above items, in which the non-ionic surfactant has a concentration of about 0.001 w/v% to about 0.5 w/v% in the aqueous liquid formulation.
(Item 121)

The use according to any one of the above items, in which the non-ionic surfactant has a concentration of about 0.01 w/v% to about 0.05 w/v% in the aqueous liquid formulation.
(Item 122)

The use according to any one of the above items, in which the non-ionic surfactant is at least one selected from the group consisting of tyloxapol, polysorbate, polyethylene glycol monostearate, and a polyoxyethylene hydrogenated castor oil.

(Item 123)

The use according to any one of the above items, in which the non-ionic surfactant is tyloxapol.

(Item 124)

The use according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof has a concentration of about 0.001 w/v% to about 5 w/v% in the aqueous liquid formulation.

(Item 125)

The use according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof has a concentration of about 0.3 w/v% to about 1 w/v% in the aqueous liquid formulation.

(Item 126)

The use according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in a dissolved state has a concentration of about 0.01 w/v% or less in the aqueous liquid formulation.

(Item 127)

The use according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the dissolved state has a concentration of more than 0 w/v% and about 0.01 w/v% or less in the aqueous liquid formulation.

(Item 128)

The use according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the

pharmaceutically acceptable salt or solvate thereof has improved stability in the aqueous liquid formulation.

(Item 129)

The use according to any one of the above items, in which the improved stability is denoted as a residual ratio of the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof of about 90% or more when the aqueous liquid formulation is stored at about 60°C for 2 weeks.

(Item 130)

The use according to any one of the above items, in which the residual ratio is about 95% or more.

(Item 131)

The use according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the dissolved state has improved stability in the aqueous liquid formulation.

(Item 132)

The use according to any one of the above items, in which the improved stability is denoted as a residual ratio of the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the dissolved state of about 90% or more when the aqueous liquid formulation is stored at about 60°C for 2 weeks.

(Item 133)

The use according to any one of the above items, in which the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the dissolved state has the residual ratio of about 95% or more.

(Item 134)

The use according to any one of the above items, in which the aqueous liquid formulation has a pH of about 4 to about 8.

(Item 135)

The use according to any one of the above items, in which

the aqueous liquid formulation is contained in a plastic container.

(Item 136)

The use according to any one of the above items, in which the plastic container is made of polyethylene or polypropylene.

(Item 137)

The use according to any one of the above items, in which the aqueous liquid formulation is an ophthalmic solution.

(Item 138)

The use according to any one of the above items, in which the aqueous liquid formulation is an aqueous suspension liquid formulation.

(Item 139)

The use according to any one of the above items, in which the aqueous liquid formulation is an ophthalmic suspension.

[0008]

In the present disclosure, it is intended that the above-mentioned one or more features may be provided in further combinations in addition to the explicit combinations. Note that, those skilled in the art will recognize further embodiments and advantages of the present disclosure upon reading and understanding the following detailed description, if necessary. Note that, features and significant actions and effects of the present disclosure other than those described above will become clear to those skilled in the art by referring to the following embodiments of the invention and drawings.

[Advantageous Effects of Invention]

[0009]

The present disclosure can provide an aqueous liquid formulation with excellent stability.

[Description of Embodiments]

[0010]

The present disclosure will be described. It should be understood that throughout this specification, singular expressions also include the concept of their plural forms, unless otherwise noted. Thus, it should be understood that singular articles (e.g., “a”, “an”, “the”, etc. in English) also include the concept of their plural forms, unless

otherwise noted. It should also be understood that terms used herein are to be used in the sense normally used in the art, unless otherwise noted. Therefore, unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by those skilled in the art to which the present disclosure pertains. In the event of a conflict, this specification (including definitions) shall prevail.

[0011]

(Definitions)

As used herein, the term "about" means ± 10% of the numeral value that follows, unless otherwise noted.

[0012]

As used herein, the term "or" is used when "at least one or more" of matters enumerated in a text can be employed. The same applies to "alternatively". When the phrase "within a range" of "two values" is specified herein, the range includes the two values themselves.

[0013]

As used herein, the phrase "aqueous liquid formulation" is used with the same meaning as the phrase commonly used in the art and refers to any liquid formulation that contains water in at least a portion thereof. The aqueous liquid formulation encompasses a solution in which components to be mixed are in a dissolved state, one in which components to be mixed are in a suspended state, and one in which components to be mixed are partially dissolved and partially suspended.

[0014]

As used herein, the phrase "aqueous suspension liquid formulation" is used with the same meaning as the phrase commonly used in the art and refers to a liquid formulation that contains water in at least a portion thereof, in which components to be mixed are in a suspended state and in which solid particles are present in the liquid. Since (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof is extremely poorly soluble in water, it is present as suspended particles in the aqueous suspension liquid formulation of the present disclosure,

although a portion thereof is dissolved.

[0015]

As used herein, the phrase “pharmaceutically acceptable salt” means a relatively non-toxic, inorganic or organic acid addition salt or inorganic or organic base addition salt of a compound of the present disclosure.

[0016]

As used herein, the term “stability” refers to a degree to which (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof dissolved and/or suspended in an aqueous liquid formulation retains its original content without undergoing deterioration by, for example, degradation when stored under certain conditions for a certain period of time. As used herein, the “stability” uses, as an index, a content retention rate, in other words, a ratio of a content of the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in an aqueous liquid formulation after storage under certain conditions for a certain period of time to a content of the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the same formulation immediately after preparation. A content retention rate of the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in a dissolved state in the aqueous liquid formulation can also be used as the index. The phrase “storage under certain conditions for a certain period of time” refers, for example, to storage of the aqueous liquid formulation at about 60°C for two weeks.

[0017]

As used herein, the phrase “improved stability” means that, in a comparison between formulations, stability is considered to be improved when (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate

thereof has a higher content retention rate.

[0018]

As used herein, the term “solvate” means one aggregate formed by an interaction of a compound of the present disclosure or a pharmaceutically acceptable salt thereof with any solvent, and encompasses, for example, a solvate with an organic solvent (e.g., an alcoholate (ethanolate, etc.)) and a hydrate. When the hydrate is formed, the compound of the present disclosure or the pharmaceutically acceptable salt thereof may be coordinated with any number of water molecules. The hydrate may include a monohydrate and a dihydrate.

[0019]

As used herein, the term “non-ionic surfactant,” also referred to as a “nonionic surfactant,” means a surfactant whose hydrophilic group is nonionic. Those skilled in the art can easily determine whether a compound is a non-ionic surfactant or not by checking that the compound does not ionize (show ionicity) when dissolved in water. Examples of the non-ionic surfactant include tyloxapol, polyoxyl stearates (polyethylene glycol monostearate, polyethylene glycol monostearate 40 (MYS-40), polyethylene glycol monostearate 400, etc.), polyoxyethylene sorbitan fatty acid esters (polyoxyethylene sorbitan monooleate (polysorbate 80), polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan tristearate, etc.), and polyoxyethylene hydrogenated castor oils (polyoxyethylene hydrogenated castor oil 10, polyoxyethylene hydrogenated castor oil 40, polyoxyethylene hydrogenated castor oil 50, polyoxyethylene hydrogenated castor oil 60 (HCO-60), etc.).

[0020]

As used herein, the phrase “electron beam treatment” refers to application of an electron beam to a solid or liquid object and substantially means irradiation of the object with an electron beam. When the electron beam treatment is performed as a sterilization step, it may also be referred to as “electron beam sterilization”. Alternatively, if the electron beam treatment is a treatment in a sterilization step, it may also be referred to as electron beam treatment in the

sterilization step. In this case, sterilization is achieved through the electron beam treatment, and it is understood that the electron beam treatment is performed under such conditions. An intensity of an electron beam in the electron beam treatment may mean an absorbed dose (Gy) into an object, or it may mean an intensity set on a device to be used for application of an electron beam or an intensity shown on a display of the device. A period of time for which the treatment is performed at an intensity may mean a period of time taken to achieve a predetermined intensity (for example, about 10 kGy to about 60 kGy, about 15 kGy to about 45 kGy, about 20 kGy to about 30 kGy, about 35 kGy to about 45 kGy, about 30 kGy to about 40 kGy, or about 25 kGy, etc.) when an object is irradiated with an electron beam, or it may refer to a period of time set on a device to be used for irradiation of an electron beam or a period of time shown on a display of the device. In the present disclosure, the electron beam treatment can be performed with an electron beam at an intensity of about 100 keV to about 5 MeV. The electron beam treatment may be performed on (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof in a solid form. More specifically, the electron beam treatment may be performed on (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof in a powder form. The term “powder" means a powdery or granular material composed of solid particles having any particle size distribution, in which interactions, such as electrostatic forces or van der Waals forces, act between individual particles.

[0021]

As used herein, the term “sterilization” or the phrase “sterilization treatment” means substantial removal, disinfection, or deactivation, etc., of a virus, a microorganism, etc., present in a solid or liquid object. The sterilization may include, for example, an electron beam sterilization, a gamma sterilization treatment, a dry heat sterilization, and an autoclave sterilization. Thus, as used

herein, the phrase “electron beam sterilization treatment” refers to sterilization of a substance or molecule by irradiating the substance or molecule with an electron beam. In the present disclosure, the sterilization or the sterilization treatment is performed on (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof itself. The electron beam sterilization treatment may be performed on (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof in a solid form. More specifically, the electron beam sterilization treatment may be performed on (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof in a powder form.

[0022]

As used herein, the term “solvent” is used to encompass water, an organic solvent, and a mixture of water and an organic solvent, which may be filter-sterilized or otherwise sterilized. The thus-sterilized solvent is also included in the “solvent” herein. In addition to the water, the organic solvent, or the mixture of water and an organic solvent, the solvent may also contain any additive such as a viscous agent, a stabilizer, a pH adjuster, a buffer, and a preservative (antimicrobial preservative) dissolved therein. Such an additive-containing solvent is also included in the “solvent” herein.

[0023]

(Preferred Embodiment)

Preferred embodiments of the present disclosure will be described. Embodiments provided below are given for a better understanding of the present disclosure, and the scope of the present disclosure should not be limited to the following description. Therefore, it is clear that those skilled in the art may make modifications as appropriate within the scope of the present disclosure, taking into account the description herein. The following embodiments of the present disclosure

may also be used alone or in combination.

[0024]

((E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide having been subjected to electron beam treatment)

In one aspect of the present disclosure, an aqueous liquid formulation including a compound (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the compound, the salt, or the solvate having been subjected to an electron beam treatment can be provided.

[0025]

In another aspect of the present disclosure, an aqueous liquid formulation including a compound (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the compound, the salt, or the solvate having been subjected to an electron beam treatment; and a non-ionic surfactant can be provided.

[0026]

In one aspect of the present disclosure, an aqueous suspension liquid formulation including a compound (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the compound, the salt, or the solvate having been subjected to an electron beam treatment can be provided.

[0027]

In another aspect of the present disclosure, an aqueous suspension liquid formulation including a compound (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the compound, the salt, or the solvate having been subjected to an electron beam treatment; and a non-ionic surfactant can be provided.

[0028]

In another aspect, the present disclosure provides (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-

tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the compound, the salt, or the solvate having been subjected to an electron beam treatment.

[0029]

In one aspect of the present disclosure, a method for producing an aqueous liquid formulation including (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the method including: treating the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with an electron beam; and mixing the thus-electron beam-treated (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with a solvent can be provided.

[0030]

In one aspect of the present disclosure, a method for producing an aqueous suspension liquid formulation including (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the method including: treating the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with an electron beam; and mixing the thus-electron beam-treated (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with a solvent can be provided.

[0031]

In another aspect, the present disclosure provides a method for stabilizing an aqueous liquid formulation including (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the method including: treating the (E)-2-(7-trifluoromethylchroman-4-

ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with an electron beam; and mixing the thus-electron beam-treated (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with a solvent.

[0032]

In another aspect, the present disclosure provides a method for stabilizing an aqueous suspension liquid formulation including (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the method including: treating the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with an electron beam; and mixing the thus-electron beam-treated (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with a solvent.

[0033]

In one embodiment, an aqueous liquid formulation of the present disclosure may be an aqueous suspension liquid formulation, an emulsion formulation, an ophthalmic solution, or the like. Preferably, it is an aqueous suspension liquid formulation or an ophthalmic solution and more preferably an aqueous suspension liquid formulation.

[0034]

In one embodiment, an aqueous liquid formulation of the present disclosure may further include a non-ionic surfactant.

[0035]

In another embodiment, a solvent of the present disclosure includes a non-ionic surfactant.

[0036]

In another embodiment, a solvent for use in an aqueous liquid formulation of the present disclosure is filter-sterilized or otherwise sterilized.

[0037]

The (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide includes an R isomer thereof (CAS. No. 920332-28-1), an S isomer thereof (CAS. No. 920332-29-2), or a racemate thereof (CAS. No. 920332-27-0), and more preferably is the R isomer thereof ((E)-2-(7-trifluoromethylchroman-4-ylidene)-N-((7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide (herein also referred to as Compound (1)).

[0038]

A pharmaceutically acceptable salt of the compound of the present disclosure is not particularly limited as long as it is a pharmaceutically acceptable salt. Specific examples thereof include acid addition salts with mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid; acid addition salts with organic carboxylic acids, including aliphatic monocarboxylic acids such as formic acid, acetic acid, propionic acid, butyric acid, valeric acid, enanthic acid, capric acid, myristic acid, palmitic acid, stearic acid, lactic acid, sorbic acid, and mandelic acid, aromatic monocarboxylic acids such as benzoic acid and salicylic acid, aliphatic dicarboxylic acids such as oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, malic acid, and tartaric acid, and aliphatic tricarboxylic acids such as citric acid; acid addition salts with organic sulfonic acids, including aliphatic sulfonic acids such as methanesulfonic acid, ethanesulfonic acid, and 2-hydroxyethanesulfonic acid and aromatic sulfonic acids such as benzenesulfonic acid and p-toluenesulfonic acid; inorganic base addition salts with metals such as alkali metals or alkaline earth metals, including sodium, potassium, magnesium, and calcium; and organic base addition salts with methylamine, ethylamine, ethanolamine, pyridine, lysine, arginine, ornithine, or the like.

[0039]

These salts can be obtained by a routine procedure, e.g., by mixing equivalent amounts of the compound of the present disclosure with a solution containing a desired acid or base, and then filtering out a desired salt or collecting the desired salt by distilling a solvent off. The compound of the present

disclosure or a salt thereof can also form a solvate with water or a solvent such as ethanol.

[0040]

(E)-2-(7-Trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide has excellent transient receptor potential vanilloid 1 (hereinafter referred to as "TRPV1"; also referred to as "vanilloid receptor 1 (VR1)") antagonistic activity.

[0041]

The R isomer (Compound (1)), the S isomer, or the racemate of the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide is described in PCT International Publication No. WO2007/010383, Japanese Patent No. 4754566, Japanese Patent No. 6230743, PCT International Publication No. WO2018/221543, Japanese Patent No. 6830569, PCT International Publication No. WO2021/038889, and PCT International Publication No. WO2021/039023. The R isomer (Compound (1)), the S isomer, or the racemate can be produced by the production methods described in the above-mentioned patent documents. The contents of the above-mentioned patent documents are incorporated herein by reference in their entirety.

[0042]

The TRPV1 is a TRP channel cloned from the dorsal root ganglion (DRG) as a cation channel responsive to capsaicin, is sensitive to heat of 43°C or more and protons, and has been studied as a key nociceptive molecule (SEIKAGAKU Vol. 85, No. 7: 561-565). The TRPV1 is known to have increased activity and induce hyperalgesia upon inflammation and tissue injury. Therefore, the TRPV1 has attracted attention as a drug target candidate for use in a treatment of pain.

[0043]

A TRPV1 antagonist has previously been reported to be effective in various pain models, including inflammatory pain, neuropathic pain, and osteoarthritis (SEIKAGAKU Vol. 85, No. 7: 561-565).

[0044]

In one embodiment of the present disclosure, (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-

tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof is treated with an electron beam, and the thus-electron beam-treated (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof is then mixed with a solvent to form an aqueous liquid formulation (e.g., aqueous suspension liquid formulation). Thus, the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the aqueous liquid formulation can have improved stability.

[0045]

In one embodiment of the present disclosure, (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof can be present in an aqueous liquid formulation of the present disclosure (e.g., aqueous suspension liquid formulation) at a concentration of typically about 0.001 w/v% to about 5 w/v%, preferably about 0.1 w/v% to about 3 w/v%, more preferably about 0.2 w/v% to about 2 w/v%, particularly preferably about 0.2 w/v% to about 1.5 w/v%, and further preferably about 0.3 w/v% to about 1.0 w/v%.

[0046]

In one embodiment of the present disclosure, when (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-((7R)-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof is used, it can be present in an aqueous liquid formulation of the present disclosure (e.g., aqueous suspension liquid formulation) at a concentration of typically about 0.001 w/v% to about 5 w/v%, preferably about 0.1 w/v% to about 3 w/v%, more preferably about 0.2 w/v% to about 2 w/v%, particularly preferably about 0.2 w/v% to about 1.5 w/v%, and further preferably about 0.3 w/v% to about 1.0 w/v%.

[0047]

In one embodiment of the present disclosure, (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically

acceptable salt or solvate thereof can be treated with an electron beam as a treatment in a sterilization step for the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof. The intensity of the electron beam in the electron beam treatment is not limited as long as the sterilization effect can be observed, and is typically about 100 keV to about 5 MeV. For example, an upper limit thereof may be about 5 MeV, about 4 MeV, about 3 MeV, about 2 MeV, or about 1 MeV, and a lower limit thereof may be about 100 keV, about 110 keV, about 120 keV, about 130 keV, about 140 keV, about 150 keV, about 200 keV, about 300 keV, about 400 keV, or about 500 keV.

[0048]

In one embodiment of the present disclosure, a period of time for which (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof is treated with an electron beam is not limited as long as the sterilization effect can be observed and is typically about 10 minutes to about 24 hours, more preferably about 30 minutes to about 12 hours, particularly preferably about 30 minutes to about 8 hours, and further preferably about 30 minutes to about 5 hours. An irradiation time is selected as appropriate based on an intensity of the selected electron beam.

[0049]

In one embodiment of the present disclosure, (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof can be subjected to electron beam sterilization treatment as a treatment in a sterilization step for the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof, and the irradiation dose of the electron beam in the electron beam sterilization treatment may be any dose as long as a sterilization effect can be confirmed, and may typically be about 10 kGy to about 60 kGy. From the viewpoint of achieving sterilization, the irradiation dose of the electron beam is

preferably about 15 kGy or more and further preferably about 20 kGy or more. From the viewpoint of stability, the irradiation dose is preferably about 50 kGy or less and further preferably about 40 kGy or less. From the viewpoints of sterilization and stability, the irradiation dose is particularly preferably about 25 kGy.

[0050]

In one embodiment of the present disclosure, the non-ionic surfactant is not particularly limited as long as it is pharmaceutically acceptable. Examples thereof include tyloxapol, polyoxyl stearates (polyethylene glycol monostearate, polyethylene glycol monostearate 40 (MYS-40), polyethylene glycol monostearate 400, etc.), polyoxyethylene sorbitan fatty acid esters (polyoxyethylene sorbitan monooleate (polysorbate 80), polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monopalmitate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan tristearate, etc.), and polyoxyethylene hydrogenated castor oils (polyoxyethylene hydrogenated castor oil 10, polyoxyethylene hydrogenated castor oil 40, polyoxyethylene hydrogenated castor oil 50, polyoxyethylene hydrogenated castor oil 60 (HCO-60), etc.). The non-ionic surfactant may be used alone, or two or more thereof may be used in combination. When the aqueous liquid formulation is an aqueous suspension liquid formulation, the non-ionic surfactant is preferably tyloxapol, polysorbate, polyethylene glycol monostearate, or a polyoxyethylene hydrogenated castor oil, more preferably tyloxapol, polysorbate, or polyethylene glycol monostearate, and further preferably tyloxapol from the viewpoint of redispersibility or stability of the aqueous suspension liquid formulation.

[0051]

In one embodiment of the present disclosure, the non-ionic surfactant can be present in the aqueous liquid formulation of the present disclosure at a concentration of about 0.0001 w/v% to about 1 w/v%, preferably about 0.0005 w/v% to about 0.5 w/v%, more preferably about 0.001 w/v% to about 0.5 w/v%, particularly preferably about 0.005 w/v% to about 0.1 w/v%, and further preferably about 0.01 w/v% to about 0.05 w/v%.

[0052]

In one embodiment, a concentration of (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof in a dissolved state in the aqueous liquid formulation of the present disclosure is typically about 0.01 w/v% or less, and preferably, for example, less than about 0.01 w/v%, about 0.009 w/v% or less, less than about 0.009 w/v%, about 0.008 w/v% or less, less than about 0.008 w/v%, about 0.007 w/v% or less, less than about 0.007 w/v%, about 0.006 w/v% or less, less than about 0.006 w/v%, about 0.005 w/v% or less, less than about 0.005 w/v%, about 0.004 w/v% or less, less than about 0.004 w/v%, about 0.003 w/v% or less, less than about 0.003 w/v%, about 0.002 w/v% or less, less than about 0.002 w/v%, about 0.001 w/v% or less, less than about 0.001 w/v%, about 0.0009 w/v% or less, less than about 0.0009 w/v%, about 0.0008 w/v% or less, less than about 0.0008 w/v%, about 0.0007 w/v% or less, less than about 0.0007 w/v%, about 0.0006 w/v% or less, less than about 0.0006 w/v%, about 0.0005 w/v% or less, less than about 0.0005 w/v%, about 0.0001 w/v% or less, less than about 0.0001 w/v%, about 0.00009 w/v% or less, less than about 0.00009 w/v%, about 0.00008 w/v% or less, less than about 0.00008 w/v%, about 0.00007 w/v% or less, less than about 0.00007 w/v%, about 0.00006 w/v% or less, less than about 0.00006 w/v%, about 0.00005 w/v% or less, less than about 0.00005 w/v%, about 0.00001 w/v% or less, less than about 0.00001 w/v%, or more than 0 w/v%.

[0053]

In the case of an aqueous liquid formulation including (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide at a concentration of 0.3 w/v%, the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide is typically dissolved at about 0.01 w/v% or less and the remaining (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide is present as suspension particles. A concentration of (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-

tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof in a dissolved state in the aqueous liquid formulation of the present disclosure is more than 0 w/v% and typically about 0.01 w/v% or less, and preferably, for example, less than about 0.01 w/v%, about 0.009 w/v% or less, less than about 0.009 w/v%, about 0.008 w/v% or less, less than about 0.008 w/v%, about 0.007 w/v% or less, less than about 0.007 w/v%, about 0.006 w/v% or less, less than about 0.006 w/v%, about 0.005 w/v% or less, less than about 0.005 w/v%, about 0.004 w/v% or less, less than about 0.004 w/v%, about 0.003 w/v% or less, less than about 0.003 w/v%, about 0.002 w/v% or less, less than about 0.002 w/v%, about 0.001 w/v% or less, less than about 0.001 w/v%, about 0.0009 w/v% or less, less than about 0.0009 w/v%, about 0.0008 w/v% or less, less than about 0.0008 w/v%, about 0.0007 w/v% or less, less than about 0.0007 w/v%, about 0.0006 w/v% or less, less than about 0.0006 w/v%, about 0.0005 w/v% or less, less than about 0.0005 w/v%, about 0.0001 w/v% or less, less than about 0.0001 w/v%, about 0.00009 w/v% or less, less than about 0.00009 w/v%, about 0.00008 w/v% or less, less than about 0.00008 w/v%, about 0.00007 w/v% or less, less than about 0.00007 w/v%, about 0.00006 w/v% or less, less than about 0.00006 w/v%, about 0.00005 w/v% or less, less than about 0.00005 w/v%, about 0.00001 w/v% or less, less than about 0.00001 w/v%.

[0054]

In one embodiment, (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof has improved stability in the aqueous liquid formulation of the present disclosure. In another embodiment, (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof in a dissolved state has improved stability in the aqueous liquid formulation of the present disclosure.

[0055]

As used herein, improved stability of a compound ((E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-

tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof that is followed by the phrase “in a dissolved state” means that the compound in a dissolved state in an aqueous liquid formulation is stable. On the other hand, in the specification, when the phrase “in a dissolved state” is not added, it is intended that the aqueous liquid formulation is stable as a whole, unless otherwise stated.

[0056]

As used herein, the term “stable” refers to a state in which a compound of interest or the like is retained without degradation, and stability can be verified using the methods exemplified in Examples and the like. A method for verifying stability can be appropriately selected depending on whether the compound is in a dissolved state or not. For example, the compound can be determined as stable if (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof has a residual ratio of about 90% or more and more preferably about 95% or more when stored at about 60°C for 2 weeks.

[0057]

In one embodiment, (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof in a dissolved state may have a concentration of about 0.01 w/v% or less in the aqueous liquid formulation of the present disclosure.

[0058]

In another embodiment, (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof in a dissolved state has improved stability in the aqueous liquid formulation of the present disclosure. In this case, it can be determined as stable if the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the dissolved state has a residual ratio of about 90% or more and preferably about 95% or

more when the aqueous liquid formulation is stored at about 60°C for 2 weeks. A substance in a dissolved state is generally less stable than the substance in a solid state. For the aqueous liquid formulation including the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide, the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the dissolved state is typically degraded, leading to a decrease in its content retention rate over time. For the aqueous liquid formulation of the present disclosure, the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in the dissolved state has improved stability, which generally contributes to improvement of stability of the aqueous liquid formulation as a whole. For example, such stability can be verified by filtering the liquid portion of a suspension liquid formulation, extracting the portion in a dissolved state, and examining an indicator of stability, although the method for verifying stability is not limited thereto.

[0059]

In one particular embodiment, the present disclosure provides an aqueous liquid formulation including a compound (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the compound, the salt, or the solvate having been subjected to an electron beam treatment; and a non-ionic surfactant, the electron beam treatment including a treatment with an electron beam at an irradiation dose of about 10 kGy to about 60 kGy; the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof having a concentration of about 0.01 w/v% to about 5 w/v% in the aqueous liquid formulation, and the non-ionic surfactant having a concentration of about 0.01 w/v% to about 0.05 w/v% in the aqueous liquid formulation. Preferably, the aqueous liquid

formulation is an aqueous suspension liquid formulation.

[0060]

In one embodiment, (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof in the aqueous liquid of the present disclosure can be used in a crystalline form, which is not particularly limited as long as it does not affect stability. For example, in the present disclosure, a type I crystal, a type II crystal, or a type III crystal of (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-((7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide, or a mixture thereof disclosed in PCT International Publication No. WO 2018/221543, Japanese Patent No. 6230743, etc., can be used. The type I crystal is preferably used.

[0061]

(Dosage form)

In one embodiment of the present disclosure, the aqueous liquid formulation can be an ophthalmic solution. For example, the ophthalmic solution can be provided in a form of a suspension of an active ingredient in an aqueous solvent (e.g., phosphate-buffered saline) or in a form of a solution of an active ingredient in an aqueous solvent.

[0062]

In one embodiment of the present disclosure, the aqueous liquid formulation can be an aqueous suspension liquid formulation. For example, the aqueous suspension liquid formulation can be provided in a form of a suspension of an active ingredient in an aqueous solvent (e.g., phosphate-buffered saline) or in a form of a solution of an active ingredient in an aqueous solvent.

[0063]

In one embodiment of the present disclosure, the aqueous liquid formulation is an ophthalmic suspension liquid formulation, which may also be referred to as an ophthalmic suspension, and can be provided as an ocular injection solution, an ophthalmic preparation, or an ocular perfusion solution. For example, the ophthalmic suspension liquid formulation can be provided in a form of a suspension of an active ingredient in an aqueous solvent (e.g., phosphate-

buffered saline) or in a form of a solution of an active ingredient in an aqueous solvent.

[0064]

The aqueous liquid formulation of the present disclosure can be administered by any suitable route determined by those skilled in the art and can be formulated to be suitable for administration via an administration route selected from, but not limited to, ocular injection, topical application (including application to the eye), ocular instillation, intravenous injection, infusion, oral, parenteral, transdermal, etc.

[0065]

(Additive and/or excipient)

The aqueous liquid formulation of the present disclosure may include any pharmaceutically acceptable additive and/or excipient known in the art. Examples of the additive include, but are not limited to, a viscous agent, a stabilizer, a pH adjuster, a buffer, and a preservative (antimicrobial preservative).

[0066]

The viscous agent is not particularly limited to the extent that it is pharmaceutically acceptable. Examples thereof include a water-soluble polymer such as a carboxy vinyl polymer, polyvinyl pyrrolidone, polyethylene glycol, polyvinyl alcohol, xanthan gum, sodium chondroitin sulfate, or sodium hyaluronate; and a cellulosic polymer such as hydroxyethyl cellulose, methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, or sodium carboxymethyl cellulose. The viscous agent may be used alone, or two or more thereof may be used in combination.

[0067]

The stabilizer is not particularly limited to the extent that it is pharmaceutically acceptable. Examples thereof include polyvinyl pyrrolidone, monoethanolamine, cyclodextrin, dextran, ascorbic acid, tocopherol, dibutylhydroxytoluene, a sulfite, and sodium edetate. A content thereof is preferably about 0.001 w/v% to about 1 w/v% relative to a total amount of the aqueous liquid formulation.

[0068]

The pH adjuster is not particularly limited to the extent that it is pharmaceutically acceptable. Examples thereof include an acid such as hydrochloric acid, acetic acid, boric acid, aminoethyl sulfonic acid, or epsilon-aminocaproic acid; and an alkali such as sodium hydroxide, potassium hydroxide, borax, triethanolamine, monoethanolamine, sodium hydrogen carbonate, or sodium carbonate. A content thereof is, for example, 0 w/v% to about 20 w/v% relative to a total amount of the aqueous liquid formulation.

[0069]

In one embodiment of the present disclosure, the aqueous liquid formulation of the present disclosure may be mixed with the above-mentioned pH adjuster, if necessary, so as to have a pH of typically about 4 to about 8, preferably about 5.0 to about 8.0, more preferably about 6.0 to about 8.0, particularly preferably about 7.0 to about 8.0, and further preferably about 7.2 to about 7.8.

[0070]

The buffer for use in the aqueous liquid formulation of the present disclosure is not particularly limited to the extent that it is pharmaceutically acceptable. Examples thereof include a borate buffer, a phosphate buffer, a Tris buffer, a citrate buffer, a tartrate buffer, an acetate buffer, and an amino acid buffer. When the aqueous liquid formulation is a suspension liquid formulation, a borate buffer or a phosphate buffer is preferred, and a borate buffer is particularly preferred, from the viewpoint of stability.

[0071]

A concentration of the buffer may be appropriately set within a range that can impart the desired buffering capacity to an aqueous liquid formulation and may be, for example, about 0.1 w/v% to about 10 w/v%, preferably about 1 w/v% to about 5 w/v%, and more preferably about 1 w/v% to about 3 w/v% from the viewpoint of improvement of redispersibility or stability.

[0072]

The borate buffer is not particularly limited as long as it is pharmaceutically acceptable. For example, boric acid and/or a salt thereof may be used. The boric acid is not particularly limited as long as it is pharmaceutically

acceptable. Examples thereof include orthoboric acid, metaboric acid, tetraboric acid, and the like. The salt of boric acid is not particularly limited as long as it is pharmaceutically acceptable. Examples thereof include a metal salt such as a sodium salt, a potassium salt, a calcium salt, a magnesium salt, or an aluminum salt; and an organic amine salt such as triethylamine, triethanolamine, morpholine, piperazine, or pyrrolidine. The boric acid or the salt thereof may be used alone or two or more thereof may be used in combination. One suitable aspect of the borate buffer includes a combination of boric acid and borax.

[0073]

When boric acid and borax are used in combination, a ratio of the boric acid and the borax is not particularly limited and may be, for example, about 10 to about 300 parts by mass, preferably about 10 to about 250 parts by mass, more preferably about 30 to about 100 parts by mass, and particularly preferably about 40 to about 60 parts by mass of the borax per about 100 parts by mass of the boric acid.

[0074]

Specifically, the phosphate buffer may be phosphoric acid and/or a salt thereof. The salt of phosphoric acid is not particularly limited to the extent that it is pharmaceutically acceptable. Examples thereof include a hydrogen phosphate dialkali metal salt such as disodium hydrogen phosphate or dipotassium hydrogen phosphate; a dihydrogen phosphate alkali metal salt such as sodium dihydrogen phosphate or potassium dihydrogen phosphate; and a trialkali metal phosphate such as trisodium phosphate or tripotassium phosphate, and the like. The salt of phosphoric acid may also be in a form of a solvate such as a hydrate. For example, disodium hydrogen phosphate may be in a form of a dodecahydrate, or sodium dihydrogen phosphate may be in a form of a dihydrate. One selected from the phosphoric acid and the salt thereof may be used alone, or two or more thereof may be used in combination as the phosphate buffer. Among the phosphoric acid and the salt thereof, a phosphate is preferred, at least one of a hydrogen phosphate dialkali metal salt and a dihydrogen phosphate alkali metal salt is more preferred, and at least one of disodium hydrogen

phosphate and sodium dihydrogen phosphate is particularly preferred.

[0075]

The Tris buffer may be Tris (also known as tris(hydroxymethyl)aminomethane) and/or a salt thereof. The salt of Tris is not particularly limited as long as it is pharmaceutically acceptable. For example, a salt such as an acetate, a hydrochloride, a maleate, or a sulfonate may be used. One selected from the Tris and the salt thereof may be used alone, or two or more thereof may be used in combination as the Tris buffer. In another embodiment, the Tris buffer may be specifically trometamol and/or a salt thereof. The salt of trometamol is not particularly limited to the extent that it is pharmaceutically acceptable. For example, an organic acid salt such as an acetate; an inorganic acid salt such as a hydrochloride or a sulfonate, etc., may be used. One selected from the trometamol and the salt thereof may be used alone, or two or more thereof may be used in combination as the Tris buffer. Among the trometamol and the salt thereof, trometamol is preferred.

[0076]

Specifically, the citrate buffer may be citric acid and/or a salt thereof. The salt of citric acid is not particularly limited to the extent that it is pharmaceutically acceptable. Examples thereof include an alkali metal salt such as a sodium salt or a potassium salt; an alkaline earth metal salt such as a calcium salt or a magnesium salt, etc. The salt of citric acid may also be in a form of a solvate such as a hydrate. One selected from the citric acid and the salt thereof may be used alone, or two or more thereof may be used in combination as the citrate buffer. Among the citric acid and the salt thereof, a salt of citric acid is preferred, an alkali metal salt of citric acid is more preferred, and sodium citrate is particularly preferred.

[0077]

Specifically, the tartrate buffer may be tartaric acid and/or a salt thereof. The salt of tartaric acid is not particularly limited to the extent that it is pharmaceutically acceptable. Examples thereof include an alkali metal salt such

as a sodium salt or a potassium salt; an alkaline earth metal salt such as a calcium salt or a magnesium salt, etc. The salt of tartaric acid may also be in a form of a solvate such as a hydrate. One selected from the tartaric acid and the salt thereof may be used alone, or two or more thereof may be used in combination as the tartrate buffer.

[0078]

Specifically, the acetate buffer may be acetic acid and/or a salt thereof. The salt of acetic acid is not particularly limited to the extent that it is pharmaceutically acceptable. Examples thereof include an alkali metal salt such as a sodium salt or a potassium salt; an alkaline earth metal salt such as a calcium salt or a magnesium salt; an ammonium salt, etc. The salt of acetic acid may also be in a form of a solvate such as a hydrate. One selected from the acetic acid and the salt thereof may be used alone, or two or more thereof may be used in combination as the acetate buffer.

[0079]

Specifically, the amino acid buffer may be an acidic amino acid and/or a salt thereof. Specific examples of the acidic amino acid include aspartic acid and glutamic acid. The salt of acidic amino acid is not particularly limited to the extent that it is pharmaceutically acceptable. For example, an alkali metal salt such as a sodium salt and a potassium salt may be used. One selected from the acidic amino acid and the salt thereof may be used alone, or two or more thereof may be used in combination as the amino acid buffer.

[0080]

The preservative is not particularly limited as long as it is pharmaceutically acceptable. Examples thereof include sorbic acid, potassium sorbate, a paraoxybenzoate ester such as methyl paraoxybenzoate, ethyl paraoxybenzoate, propyl paraoxybenzoate, or butyl paraoxybenzoate, a quaternary ammonium salt such as chlorhexidine gluconate, benzalkonium chloride, benzethonium chloride, or cetylpyridinium chloride, alkyl polyaminoethylglycine, chlorobutanol, polyquad, polyhexamethylene biguanide, chlorhexidine, etc. A content thereof can be appropriately varied according to the type and may be, for example, about 0.0001 w/v% to about 0.2 w/v%

relative to a total amount of the aqueous liquid formulation.

[0081]

An ophthalmic solution can be prepared, for example, by dissolving or suspending the desired components as described above in an aqueous solvent such as sterile purified water, a saline solution, a buffer solution (e.g., phosphate buffer, citrate buffer, acetate buffer, etc.) or a non-aqueous solvent such as a vegetable oil, for example, a cottonseed oil, a soybean oil, a sesame oil, a peanut oil, etc.; adjusting the resulting solution or suspension to a predetermined osmotic pressure; and subjecting the resultant to a sterilization treatment such as filtration sterilization.

[0082]

(Container)

A container for containing the aqueous liquid formulation of the present disclosure is not particularly limited, and includes, for example, a glass container, a plastic container, etc. The plastic container can be formed of any material such as polyester (polyethylene terephthalate, polyarylate), polycarbonate, polyethylene, or polypropylene, a mixture thereof, or a mixture with another material. A container for use in the present disclosure may or may not be one for use in the medical field.

[0083]

The container to be used may have any shape, and, typically, any shape may be used as long as it is suitable for the application of the present disclosure (e.g., for eye drops).

[0084]

In a certain embodiment, the aqueous liquid formulation of the present disclosure can be filled into any container for eye drops commonly used in the medical field. The container for eye drops is exemplified by a plastic container. For example, the aqueous liquid formulation can be filled into the plastic container such as a polyethylene (preferably low-density polyethylene) container or a polypropylene container, preferably a colorless polypropylene container. In one embodiment, the ophthalmic container can be formed of any material that complies with the Japanese “Standard for Plastic

Containers for Eye Drops" or any other equivalent standards.

[0085]

(General technologies)

Molecular biological, biochemical, and microbiological procedures used herein are well known and common in the art, and are described in, for example, Sambrook J. et al. (1989). Molecular Cloning: A Laboratory Manual, Cold Spring Harbor and its 3rd Ed. (2001); Ausubel, F. M. (1987). Current Protocols in Molecular Biology, Greene Pub. Associates and Wiley-Interscience; Ausubel, F. M. (1989). Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology, Greene Pub. Associates and Wiley-Interscience; Innis, M. A. (1990). PCR Protocols: A Guide to Methods and Applications, Academic Press; Ausubel, F. M. (1992). Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology, Greene Pub. Associates; Ausubel, F. M. (1995). Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology, Greene Pub. Associates; Innis, M. A. et al. (1995). PCR Strategies, Academic Press; Ausubel, F. M. (1999). Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology, Wiley, and annual updates; Sninsky, J. J. et al. (1999). PCR Applications: Protocols for Functional Genomics, Academic Press, Gait, M. J. (1985). Oligonucleotide Synthesis: A Practical Approach, IRL Press; Gait, M. J. (1990). Oligonucleotide Synthesis: A Practical Approach, IRL Press; Eckstein, F. (1991). Oligonucleotides and Analogues: A Practical Approach, IRL Press; Adams, R. L. et al. (1992). The Biochemistry of the Nucleic Acids, Chapman & Hall; Shabarova, Z. et al. (1994). Advanced Organic Chemistry of Nucleic Acids, Weinheim; Blackburn, G. M. et al. (1996). Nucleic Acids in Chemistry and Biology, Oxford University Press; Hermanson, G. T. (1996). Bioconjugate Techniques, Academic Press, and Bessatsu Jikken Igaku "Experimental Methods for Gene Transfer & Expression Analysis", Yodosha, 1997, etc., each of which is incorporated herein by reference with respect to its relevant portions, which may be the entirety thereof.

[0086]

References cited herein such as scientific literature, patents, and patent applications are incorporated herein by reference in their entirety as if specifically set forth herein.

[0087]

The present disclosure has been described with reference to preferred embodiments for ease of understanding. Hereinafter, the present disclosure will be described with reference to Examples, but the above description and Examples below are provided for illustrative purposes only and are not intended to limit the present disclosure. Accordingly, the scope of the present disclosure is not limited to embodiments or Examples specifically described herein, but is limited only by claims.

[Examples]

[0088]

(Test Example 1: Stability of electron-beam-treated Compound (1) in dissolved state)

[0089]

Sterilization (electron beam sterilization) of Compound (1)

Compound (1) was placed in a colorless, transparent bag and irradiated with an electron beam. Irradiation was stopped when an irradiation dose reached 25 kGy. Thus, a sterilized Compound (1) was obtained.

[0090]

Preparation of aqueous solution

Base solutions were prepared according to compositions shown in Table 1, into which Compound (1) was dissolved with stirring. Thus, aqueous solutions were obtained. Tyloxapol from AMRI Rensselaer (Curia Global, Inc.) and boric acid and borax from Merck KGaA were used. Compound (1) was in a form of the type I crystal. Compound (1), which had been irradiated with gamma rays (cobalt-60) at about 25 kGy, was used for Comparative Example 2.

[0091]

Containerization

Each of the thus-prepared aqueous liquids was collected in 5 mL portions and filled into eye drop containers. Each of the eye drop containers was a colorless container made of

polyethylene (container used for GATIFLO ophthalmic solution 0.3% (manufactured and sold by Senju Pharmaceutical Co., Ltd.)).

[0092]

Stability evaluation

Each of the aqueous solutions was placed in a temperature test chamber (NAGANO SCIENCE CO., LTD., Model Number: CH24-12M), stored at 60°C for 2 weeks (2 W), and measured for a content of Compound (1) in the solution using a liquid chromatographic system (manufactured by SHIMADZU CORPORATION) under the below-described conditions. A content retention rate was calculated as a percentage of the content measured after storage relative to the amount of Compound (1) used in the preparation.

[0093]

(Measurement conditions)

- Column: InertSustain C18 5 μm, 4.6 x 150 mm (GL Sciences Inc.)
- Detector: UV-Vis spectrophotometric detector
- Detection wavelength: 250 nm
- Column temperature: 40°C
- Mobile phase: A mixture of acetonitrile and an aqueous sodium dihydrogen phosphate solution (2:3)

[0094]

Measurement results

The results are shown in Table 1. After storage at 60°C for 2 W, the content retention rate of the electron-beam-treated Compound (1) was 100%, indicating that it was stable.

[0095]

[Table 1]

	Component		Comparative Example 1	Comparative Example 2	Example 1
Formulation	Compound (1)	Sterilization method	Unsterilized	Gamma rays	Electron beams
		Amount	0.001 g	0.001 g	0.001 g
	Boric acid		1.2 g	1.2 g	1.2 g
	Borax		0.4 g	0.4 g	0.4 g
	Tyloxapol		0.5 g	0.5 g	0.5 g
	Purified water		q.s.	q.s.	q.s.
	Total amount		100 mL	100 mL	100 mL
Result	Content retention rate		85%	80%	100%

[0096]

(Test Example 2: Stability of aqueous liquid formulation including electron-beam-treated Compound (1))

[0097]

Sterilization (electron beam sterilization) of Compound (1)

Compound (1) was sterilized in the same manner as in Test Example 1.

[0098]

Preparation of aqueous solution

A base solution was prepared according to the composition shown in Table 2, and Compound (1) was dispersed therein with stirring to obtain a suspension liquid. A concentration of Compound (1) in a dissolved state in the suspension liquid was 0.00101%. Tyloxapol from AMRI Rensselaer (Curia Global, Inc.) and boric acid and borax from Merck KGaA were used. Compound (1) was in a form of the type I crystal.

[0099]

Containerization

The suspension liquid was filled into containers in the same manner as in Test Example 1.

[0100]

Stability evaluation

The suspension liquid was stored at 60°C for 2 weeks (2

W), and the content of Compound (1) in the suspension liquid was measured using a liquid chromatographic system manufactured by SHIMADZU CORPORATION under the conditions described below. A content retention rate was calculated as a percentage of the content measured after storage relative to the amount of Compound (1) used in the preparation.

[0101]

(Measurement conditions)

- Column: InertSustain C18 5 μm, 4.6 x 150 mm (GL Sciences Inc.)
- Detector: UV-Vis spectrophotometric detector
- Detection wavelength: 250 nm
- Column temperature: 40°C
- Mobile phase: A mixture of acetonitrile and an aqueous sodium dihydrogen phosphate solution (2:3)

[0102]

Measurement results

The results are shown in Table 2. After storage at 60°C for 2 W, the content retention rate of the aqueous liquid formulation including electron-beam-treated Compound (1) was 100%, and the aqueous liquid formulation was stable.

[0103]

[Table 2]

	Component		Example 2
Formulation	Compound (1)	Sterilization method	Electron beam
		Amount	0.3 g
	Boric acid		1.2 g
	Borax		0.4 g
	Tyloxapol		0.5 g
	Purified water		q.s.
	Total amount		100 mL
Result	Content retention rate		100%

[0104]

(Notes)

Although the present disclosure has been illustrated with reference to preferred embodiments of the present disclosure, it is understood that the scope of the present disclosure should be construed only by the claims. It is understood that patents, patent applications, and other references cited herein should be incorporated herein by reference in their entirety as if the contents themselves are specifically set forth herein.

This application claims priority to Japanese Patent Application No. 2024-054893 filed with the Japan Patent Office on March 28, 2024, and it is understood that the entire content described in the specification and claims thereof should be incorporated herein by reference.

[Industrial Applicability]

[0105]

The present disclosure can be utilized in the fields of medical care, pharmaceuticals, healthcare, biology, biochemistry, and the like.

[CLAIMS]

[Claim 1]

An aqueous liquid formulation comprising (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof having been subjected to an electron beam treatment.

[Claim 2]

The aqueous liquid formulation according to claim 1, wherein the electron beam treatment is a treatment in a sterilization step.

[Claim 3]

The aqueous liquid formulation according to claim 1 or 2, further comprising a non-ionic surfactant.

[Claim 4]

The aqueous liquid formulation according to any one of claims 1 to 3, wherein the electron beam treatment comprises a treatment at an irradiation dose of about 10 kGy to about 60 kGy.

[Claim 5]

The aqueous liquid formulation according to claim 3 or 4, wherein the non-ionic surfactant has a concentration of about 0.0001 w/v% to about 1 w/v% in the aqueous liquid formulation.

[Claim 6]

The aqueous liquid formulation according to any one of claims 3 to 5, wherein the non-ionic surfactant is tyloxapol.

[Claim 7]

The aqueous liquid formulation according to any one of claims 1 to 6, wherein the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof has a concentration of about 0.001 w/v% to about 5 w/v% in the aqueous liquid formulation.

[Claim 8]

The aqueous liquid formulation according to any one of claims 1 to 7, wherein the (E)-2-(7-trifluoromethylchroman-4-

ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide is (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-((7R)-7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide.

[Claim 9]

An aqueous liquid formulation comprising (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof having been subjected to an electron beam treatment and having improved stability in the aqueous liquid formulation.

[Claim 10]

The aqueous liquid formulation according to any one of claims 1 to 9, wherein the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof in a dissolved state has a concentration of about 0.01 w/v% or less in the aqueous liquid formulation.

[Claim 11]

An aqueous liquid formulation comprising (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof having been subjected to an electron beam treatment and having improved stability in a dissolved state in the aqueous liquid formulation.

[Claim 12]

The aqueous liquid formulation according to any one of claims 1 to 11, wherein the aqueous liquid formulation is an aqueous suspension liquid formulation.

[Claim 13]

A method for producing an aqueous liquid formulation comprising (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or a pharmaceutically acceptable salt or solvate thereof, the method

comprising:

treating the (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with an electron beam; and

mixing the thus-electron beam-treated (E)-2-(7-trifluoromethylchroman-4-ylidene)-N-(7-hydroxy-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide or the pharmaceutically acceptable salt or solvate thereof with a solvent.