and (b). Also provided is a method for treating an ophthalmic disease or disorder that involves tear production in a subject and/or treating or reducing a sign or symptom of such an ophthalmic disease or disorder.

[00012] Broadly, the present disclosure extends to ophthalmic pharmaceutical compositions, comprising about 0.0005% w/v to about 0.01 % w/v (1R,2S,5R)-2-isopropyl-N-(4-methoxyphenyl)-5-methylcyclohexane-1-carboxamide (WS-12) or a pharmaceutically acceptable salt thereof, about 0.1 % w/v to about 5 % w/v of a solubilizing agent, about 0.1 % w/v to about 0.5 % w/v of a viscosity modifier, about 0.3 % w/v to about 1 % w/v of a buffer, and about 0.1 % w/v to about 1.0 % w/v of a tonicity agent.

[00013] The pH of an ophthalmic pharmaceutical composition of the present disclosure can range from about pH 5.0 to about 8.5. More particularly, the pH of an ophthalmic pharmaceutical composition of the present disclosure can range from about 6.7 to about 7.3. In a particular example, the pH of an ophthalmic pharmaceutical composition of the present disclosure is about 7. An ophthalmic pharmaceutical composition of the present disclosure can further comprise a pH adjuster in order to obtain the desired pH. Numerous pH adjusters have applications, including a pH adjuster in an ophthalmic pharmaceutical composition of the present disclosure. A particular example of a pH adjuster having applications in an ophthalmic pharmaceutical composition of the present disclosure is sodium hydroxide (e.g., 1N sodium hydroxide). In order to adjust the pH to about 7 a sufficient quantity of 1N sodium hydroxide is added.

[00014] Moreover, solubilizers having applications in ophthalmic pharmaceutical compositions of the present disclosure include polyethylene glycol (PEG) 400, castor oil, polyoxyethylene (20) sorbitan mono-oleate (TWEEN 80), polyoxyl 35 castor oil (KOLLIPHOR® EL), and purified polyoxyl 35 castor oil (KOLLIPHOR® ELP), as well as any combination thereof. In a particular example, the solubilizer is polyoxyl 35 castor oil (KOLLIPHOR® EL).

[00015] According to the Joint FAO/WHO Expert Committee on Food Additives (JECFA), WS-12 is insoluble in water, and only sparingly soluble in avocado oil or ethanol. Unpredictably, certain excipients failed to satisfactorily solubilize the active agent WS-12, including polyvinylpyrrolidone (PVP), propylene glycol, and ethylene oxide-formaldehyde-para-octylphenol copolymer (Tyloxapol), whereas others satisfactorily solubilized the active agent WS-12, including polyethylene glycol (PEG) 400, castor oil, polyoxyethylene (20) sorbitan mono-oleate (TWEEN 80), polyoxyl 35 castor oil (KOLLIPHOR® EL or KOLLIPHOR® ELP). In some examples, the compositions provided herein comprise about 1.5 to about 5 w/v% polyethylene glycol 400. In some examples, the compositions provided herein comprise about 1 w/v% castor oil. In some examples, the compositions provided herein comprise about 0.1 to about 4 w/v% polyoxyethylene

(20) sorbitan mono-oleate. In some examples, the compositions provided herein comprise about 1 to about 5 w/v% of a polyoxyl 35 castor oil.

[00016] What is more, a variety of viscosity modifiers can readily be used in an ophthalmic pharmaceutical composition of the present disclosure, such as a cellulose derivative, a clay, aluminum or magnesium silicate, a natural gum, a synthetic polymer; colloidal silicon dioxide, a silicate, to name only a few, as well as any combination thereof. Particular examples of a cellulose derivative having applications in an ophthalmic pharmaceutical composition of the present disclosure include, but certainly are not limited to methylcellulose, microcrystalline cellulose, carboxymethylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, and hydroxypropyl methylcellulose. Likewise, several clays can also be used, such as hectorite, bentonite, aluminum and/or magnesium silicate, and kaolin. Natural gums that have applications in an ophthalmic pharmaceutical composition of the present disclosure comprise acacia, guar gum, tragacanth, xanthan gum, alginate, carrageenan, locust bean gum, or any combination thereof. In a particular example of an ophthalmic pharmaceutical composition of the present disclosure, the viscosity modifier is hydroxypropyl methylcellulose (hypromellose).

[00017] Moreover, in an ophthalmic pharmaceutical composition of the present disclosure, a particular tonicity agent having applications is sodium chloride.

[00018] Numerous buffers have applications in an ophthalmic pharmaceutical composition of the present disclosure. Examples include, but certainly are not limited to phosphate buffers, citrate buffers, TRIS Base, TRIS HCl, PBS, HEPES, MES, PIPES, and TES. Other buffer examples include boric acid. In some examples, the buffer comprises a phosphate.

[00019] An ophthalmic pharmaceutical composition of the present disclosure further comprises purified water.

[00020] Similarly, a particular example of an ophthalmic pharmaceutical composition of the present disclosure comprises:

(a) about 0.003 % w/v (1R,2S,5R)-2-isopropyl-N-(4-methoxyphenyl)-5-methylcyclohexane-1-carboxamide;

(b) about 0.14 % w/v hypromellose;

(c) about 3.0 % w/v polyoxyl 35 castor oil;

(d) about 0.78 % w/v a phosphate buffer (e.g., a sodium phosphate buffer, e.g., monosodium phosphate or sodium dihydrogen phosphate dihydrate)

(e) about 0.55 % w/v NaCl;

(f) a sufficient amount of NaOH (e.g., 1 N NaOH) to provide an ophthalmic pharmaceutical composition with a pH of about 7; and

(g) purified water.

(a) about 0.0014 ±15 % w/v (1R,2S,5R)-2-isopropyl-N-(4-methoxyphenyl)-5-methylcyclohexane-1-carboxamide;

(b) about 0.14 ±15 % w/v hypromellose;

(c) about 3.0 ±15 % w/v polyoxyl 35 castor oil;

(d) about 0.78 ±15 % w/v a phosphate buffer (e.g., a sodium phosphate buffer, e.g., monosodium phosphate or sodium dihydrogen phosphate dihydrate)

(e) about 0.55 ±15 % w/v NaCl;

(f) a sufficient amount of NaOH (e.g., 1 N NaOH) to provide an ophthalmic pharmaceutical composition with a pH of about 7; and

(g) purified water.

[00025] Another example of an ophthalmic pharmaceutical composition of the present disclosure comprises:

(a) about 0.0014 ±10 % w/v (1R,2S,5R)-2-isopropyl-N-(4-methoxyphenyl)-5-methylcyclohexane-1-carboxamide;

(b) about 0.14 ±10 % w/v hypromellose;

(c) about 3.0 ±10 % w/v polyoxyl 35 castor oil;

(d) about 0.78 ±10 % w/v a phosphate buffer (e.g., a sodium phosphate buffer, e.g., monosodium phosphate or sodium dihydrogen phosphate dihydrate)

(e) about 0.55 ±10 % w/v NaCl;

(f) a sufficient amount of NaOH (e.g., 1 N NaOH) to provide an ophthalmic pharmaceutical composition with a pH of about 7; and

(g) purified water.

[00026] In addition, the present disclosure further extends to various methods for treating various ophthalmic diseases or disorders, and/or signs or symptoms associated with such diseases or disorders, with an ophthalmic pharmaceutical composition disclosed herein.

[00027] In particular, the present disclosure extends to a method for treating an ophthalmic disease or disorder involving tear production and/or reducing the signs or symptoms thereof, comprising administering a therapeutically effective amount of an ophthalmic pharmaceutical composition of the present disclosure. In a specific example, the ophthalmic disease or disorder is dry eye.

[00028] The present disclosure further extends to a method for treating or reducing ocular irritation involving tear production in a subject in need thereof, comprising administering a therapeutically effective amount of an ophthalmic pharmaceutical composition of the present disclosure

[00029] Also provided is a method for treating or reducing a sign or symptom of an ophthalmic disease or disorder in a subject in need thereof, comprising administering a therapeutically effective amount of an ophthalmic pharmaceutical composition of the

present disclosure. Thus, a method of the present disclosure readily has applications in treating or reducing a sign or symptom of an ophthalmic disease or disorder such as dry eye. Examples of such symptoms of dry eye that can be readily treated or reduced with a therapeutically effective amount of an ophthalmic pharmaceutical composition of the present disclosure include a decrease in visual analog scale (VAS) symptom score (ocular discomfort score [ODS], eye dryness score or ocular pain score) or a decrease in scores obtained from the "Symptom Assessment In Dry Eye" questionnaire disclosed and validated in Schaumberg *et al*., "Global Dry Eye Symptom Index", The Ocular Surface, 5(1):50-57 (2007), and which was designed to quantify the frequency and severity of symptoms of dry eye syndrome based upon a visual analog scale (the SANDE questionnaire), eye dryness, and ocular pain or irritation, to name only a few. Likewise, signs of dry eye that can be treated or reduced with an ophthalmic pharmaceutical composition of the present disclosure include, but are not limited to, Schirmer Score (unanesthetized and anesthetized), ocular surface staining, conjunctival redness, tear film break-up time, and tear production. The Schirmer test, first disclosed in 1903 by Otto Schirmer, is designed to test whether a subject's eye produces sufficient tears to keep the eye moist (Schirmer O, Studien zur Physiologie und Pathologie der Tranenabsonderung und Tranenbfuhr (Arch. Klin. Opthalmol. 56:197-291 (1903)). Thus, this test is concerned with determining whether the subject produces a sufficient amount of tears to lubricate the eye. Ocular staining is also used as a sign for dry eye disease or disorder. In ocular surface staining, a dye is placed on the surface of the eye in order to uncover abnormalities on the surface of the eye. Once a dye is placed upon the eye, the pattern of staining observed using the dye is recorded, usually via imaging. The imaged staining pattern can then be used to diagnose the presence and severity of dry eye. Numerous dyes have applications in ocular surface staining, including but not limited to Rose Bengal, lissamine green, and fluorescein, to name only a few.

[00029a] In an aspect, the present disclosure provides an ophthalmic pharmaceutical composition, comprising:

about 0.003 % w/v (1R,2S,5R)-2-isopropyl-N-(4-methoxyphenyl)-5-methylcyclohexane-1-carboxamide;

about 0.14 % w/v hypromellose;

about 3.0 % w/v polyoxyl 35 castor oil;

about 0.78 % w/v sodium dihydrogen phosphate dihydrate buffer;

about 0.55 % w/v NaCl;

a sufficient amount of NaOH to provide an ophthalmic pharmaceutical composition with a pH of about 7;

purified water; and

a viscosity of less than 5 centipoise.

[0029b] In another aspect, the present disclosure provides an ophthalmic pharmaceutical composition, comprising:

about 0.0014 % w/v (1R,2S,5R)-2-isopropyl-N-(4-methoxyphenyl)-5-methylcyclohexane-1-carboxamide;

about 0.14 % w/v hypromellose;

about 3.0 % w/v polyoxyl 35 castor oil;

about 0.78 % w/v sodium dihydrogen phosphate dihydrate buffer;

about 0.55 % w/v NaCl;

a sufficient amount of NaOH in order to provide an ophthalmic pharmaceutical composition with a pH of about 7;

purified water; and

a viscosity of less than 5 centipoise.

[0029c] In another aspect, the present disclosure provides an ophthalmic pharmaceutical composition comprising:

about 0.003 % w/v (1R,2S,5R)-2-isopropyl-N-(4-methoxyphenyl)-5-methylcyclohexane-1-carboxamide;

about 0.14 % w/v hypromellose;

about 3.0 % w/v polyoxyl 35 castor oil;

about 0.78 % w/v sodium dihydrogen phosphate dihydrate buffer;

about 0.55 % w/v NaCl;

a sufficient amount of NaOH to provide an ophthalmic pharmaceutical composition with a pH of about 7.0;

purified water q.s to about 1.0 mL; and

a viscosity of less than 5 centipoise.

[0029d] In another aspect, the present disclosure provides an ophthalmic pharmaceutical composition comprising:

about 0.0014 % w/v (1R,2S,5R)-2-isopropyl-N-(4-methoxyphenyl)-5-methylcyclohexane-1-carboxamide;

about 0.14 % w/v hypromellose;

about 3.0 % w/v polyoxyl 35 castor oil;

about 0.78 % w/v sodium dihydrogen phosphate dihydrate buffer;

about 0.55 % w/v NaCl;

a sufficient amount of NaOH to provide an ophthalmic pharmaceutical composition with a pH of about 7.0;

purified water q.s to about 1.0 mL; and

a viscosity of less than 5 centipoise.

[0029e] In another aspect, the present disclosure provides use of the ophthalmic pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of dry eye in a subject in need thereof; wherein a therapeutically effective amount of the ophthalmic pharmaceutical composition is to be administered to the subject.

[0029f] In another aspect, the present disclosure provides use of the ophthalmic pharmaceutical composition as defined herein in the manufacture of a medicament for reducing the likelihood of dry eye in a subject in need thereof; wherein a therapeutically effective amount of the ophthalmic pharmaceutical composition is to be administered to the subject.

[0029g] In another aspect, the present disclosure provides use of the ophthalmic pharmaceutical composition as defined herein in the manufacture of a medicament for the treatment of an ophthalmic disease or disorder that involves tear production in a subject in need thereof; wherein a therapeutically effective amount of the ophthalmic pharmaceutical composition is to be administered to the subject.

[0029h] In another aspect, the present disclosure provides use of the ophthalmic pharmaceutical composition as defined herein in the manufacture of a medicament for reducing the signs or symptoms of the ophthalmic disease or disorder that involves tear production in a subject in need thereof; wherein a therapeutically effective amount of the ophthalmic pharmaceutical composition is to be administered to the subject.

[0029i] In another aspect, the present disclosure provides use of the ophthalmic pharmaceutical composition as defined herein in the manufacture of a medicament for reducing the signs or symptoms of dry eye in a subject in need thereof; wherein a therapeutically effective amount of the ophthalmic pharmaceutical composition is to be administered to the subject.

[0029j] In another aspect, the present disclosure provides use of the ophthalmic pharmaceutical composition as defined herein in the manufacture of a medicament for treating ocular irritation involving tear production in a subject in need thereof; wherein a therapeutically effective amount of the ophthalmic pharmaceutical composition is to be administered to the subject.

[0029k] In another aspect, the present disclosure provides use of the ophthalmic pharmaceutical composition as defined herein in the manufacture of a medicament for reducing ocular irritation involving tear production in a subject in need thereof; wherein a therapeutically effective amount of the ophthalmic pharmaceutical composition is to be administered to the subject.

[0029l] In another aspect, the present disclosure provides the ophthalmic pharmaceutical composition as defined herein for use as a medicament.

[00030] These and other aspects of the present disclosure will be better appreciated by reference to the following drawings and Detailed Description.

BRIEF DESCRIPTION OF THE DRAWINGS

[00031] Fig. 1 is a bar graph setting forth changes reported in ocular discomfort (ODS-VAS) of subjects administered a therapeutically effective amount of an ophthalmic pharmaceutical composition of the instant disclosure (* = $p<0.05$).

[00032] Fig. 2 is a bar graph setting forth the changes in SANDE score observed in subjects administered ophthalmic pharmaceutical composition of the instant disclosure.

[00033] Fig. 3 is a bar graph setting forth the changes in the dry eye disease symptom VAS scores eye dryness (EDS-VAS) observed in subjects administered an ophthalmic pharmaceutical composition of the instant disclosure as compared to eye dryness observed before such administration.

CLAIMS

What is claimed is:

1. An ophthalmic pharmaceutical composition, comprising:

about 0.003 % w/v (1R,2S,5R)-2-isopropyl-N-(4-methoxyphenyl)-5-methylcyclohexane-1-carboxamide;

about 0.14 % w/v hypromellose;

about 3.0 % w/v polyoxyl 35 castor oil;

about 0.78 % w/v sodium dihydrogen phosphate dihydrate buffer;

about 0.55 % w/v NaCl;

a sufficient amount of NaOH to provide an ophthalmic pharmaceutical composition with a pH of about 7;

purified water; and

a viscosity of less than 5 centipoise.

2. An ophthalmic pharmaceutical composition, comprising:

about 0.0014 % w/v (1R,2S,5R)-2-isopropyl-N-(4-methoxyphenyl)-5-methylcyclohexane-1-carboxamide;

about 0.14 % w/v hypromellose;

about 3.0 % w/v polyoxyl 35 castor oil;

about 0.78 % w/v sodium dihydrogen phosphate dihydrate buffer;

about 0.55 % w/v NaCl;

a sufficient amount of NaOH in order to provide an ophthalmic pharmaceutical composition with a pH of about 7;

purified water; and

a viscosity of less than 5 centipoise.

3. An ophthalmic pharmaceutical composition comprising:

about 0.003 % w/v (1R,2S,5R)-2-isopropyl-N-(4-methoxyphenyl)-5-methylcyclohexane-1-carboxamide;

about 0.14 % w/v hypromellose;

about 3.0 % w/v polyoxyl 35 castor oil;

about 0.78 % w/v sodium dihydrogen phosphate dihydrate buffer;

about 0.55 % w/v NaCl;

a sufficient amount of NaOH to provide an ophthalmic pharmaceutical composition with a pH of about 7.0;

purified water q.s to about 1.0 mL; and

a viscosity of less than 5 centipoise.

4. An ophthalmic pharmaceutical composition comprising:

about 0.0014 % w/v (1R,2S,5R)-2-isopropyl-N-(4-methoxyphenyl)-5-methylcyclohexane-1-carboxamide;

about 0.14 % w/v hypromellose;

about 3.0 % w/v polyoxyl 35 castor oil;

about 0.78 % w/v sodium dihydrogen phosphate dihydrate buffer;

about 0.55 % w/v NaCl;

a sufficient amount of NaOH to provide an ophthalmic pharmaceutical composition with a pH of about 7.0;

purified water q.s to about 1.0 mL; and

a viscosity of less than 5 centipoise.

5. The ophthalmic pharmaceutical composition of any one of claims 1–4 wherein the sufficient amount of NaOH is 1 N NaOH.

6. The ophthalmic pharmaceutical composition of any one of claims 1–5, wherein the ophthalmic pharmaceutical composition is stored in a polyolefin container.

7. Use of the ophthalmic pharmaceutical composition of any one of claims 1–6 in the manufacture of a medicament for the treatment of dry eye in a subject in need thereof; wherein a therapeutically effective amount of the ophthalmic pharmaceutical composition is to be administered to the subject.

8. Use of the ophthalmic pharmaceutical composition of any one of claims 1–6 in the manufacture of a medicament for reducing the likelihood of dry eye in a subject in need thereof; wherein a therapeutically effective amount of the ophthalmic pharmaceutical composition is to be administered to the subject.

9. Use of the ophthalmic pharmaceutical composition of any one of claims 1–6 in the manufacture of a medicament for the treatment of an ophthalmic disease or disorder that involves tear production in a subject in need thereof; wherein a therapeutically effective amount of the ophthalmic pharmaceutical composition is to be administered to the subject.

10. Use of the ophthalmic pharmaceutical composition of any one of claims 1–6 in the manufacture of a medicament for reducing the signs or symptoms of the ophthalmic disease or disorder that involves tear production in a subject in need thereof; wherein a therapeutically effective amount of the ophthalmic pharmaceutical composition is to be administered to the subject.

11. Use of the ophthalmic pharmaceutical composition of any one of claims 1–6 in the manufacture of a medicament for reducing the signs or symptoms of dry eye in a subject in need thereof; wherein a therapeutically effective amount of the ophthalmic pharmaceutical composition is to be administered to the subject.

12. Use of the ophthalmic pharmaceutical composition of any one of claims 1–6 in the manufacture of a medicament for treating ocular irritation involving tear production in a subject in need thereof; wherein a therapeutically effective amount

of the ophthalmic pharmaceutical composition is to be administered to the subject.

13. Use of the ophthalmic pharmaceutical composition of any one of claims 1–6 in the manufacture of a medicament for reducing ocular irritation involving tear production in a subject in need thereof; wherein a therapeutically effective amount of the ophthalmic pharmaceutical composition is to be administered to the subject.

14. The use of any one of claims 7–13, wherein the ophthalmic pharmaceutical composition is to be administered topically to the subject.

15. The ophthalmic pharmaceutical composition of any one of claims 1–6 for use as a medicament.