

CONTACT LENS WITH TRPM8 AGONIST IS RELEASABLY ADHERED TO THE POLYMERIC LENS BODY

FIELD OF THE INVENTION

[001] The field of the invention relates to contact lenses, and particularly, to contact lenses that provide a pleasant cooling sensation when worn.

BACKGROUND

[002] The cornea is the most densely innervated tissue in the body and is exclusively innervated by A-delta and C primary afferent fibers. The C nerve fibers are nonmyelinated; and while the A-delta fibers are slightly myelinated, they lose their myelin sheath after they enter the cornea to keep the cornea transparent. Thus, both types of nerve fibers have their nerve terminals exposed when they reach the squamous layer of the cornea. Located on these nerve terminals are receptors for sensing temperature, chemical, pain, and touch.

[003] The transient receptor potential cation channel subfamily M member 8 (TRPM8) is a protein channel that is the primary molecular transducer of cold somatosensation in humans. Therapeutic compositions comprising TRPM8 agonists in amounts effective to increase tearing have been proposed for the treatment of dry eye syndrome (Belmonte et al. US Pat No 10,028,920).

[004] N-(4-Methoxyphenyl)-5-methyl-2-(1-methylethyl)cyclohexanecarboxamide (CAS No. 68489-09-8), known as WS12, is a synthetic menthol derivative that acts as a selective TRPM8 agonist. WS12 can be incorporated into silicone hydrogel contact lenses and withstand autoclave sterilization without degradation or leaching into the packaging solution. Such lenses can impart a cooling sensation, reduce sensations of lens dryness and improve comfortable lens wearing time in contact lens wearers. However, for some lens wearers there is a stinging/burning sensation upon initial insertion of the lens (U.S. Pat. Publ. No. 2022/0350163). This stinging/burning sensation can cause a wearer not to use the contact lens at all even though stinging/burning sensation is temporary.

[005] There is a desire to provide a contact lens that can impart a pleasant, cooling sensation for contact lens wearers without causing stinging or burning upon insertion.

SUMMARY

[006] A feature of the present invention is to provide a contact lens that can release a TRPM8 agonist when worn to impart a pleasant, cooling sensation without causing insertion stinging or burning.

[007] An additional feature of the present invention is to provide a cooling contact lens comprising a TRPM8 agonist that a majority of contact lens wearers find more comfortable to wear than a lens made of the same material but lacking the TRPM8 antagonist, regardless of whether they experience symptoms of discomfort or dryness with their habitual contact lenses.

[008] Additional features and advantages of the present invention will be set forth in part in the description that follows, and in part will be apparent from the description, or may be learned by practice of the present invention. The objectives and other advantages of the present invention will be realized and attained by means of the elements and combinations particularly pointed out in the description and appended claims.

[009] To achieve these and other advantages, and in accordance with the purposes of the present invention, as embodied and broadly described herein, the present invention, in part relates to a contact lens containing an amount of a TRPM8 agonist releasably adhered to the lens that enhances the comfort or desirability of the contact lens and an amount of a TRPM8 antagonist that is delivered to the eye upon initial insertion of the contact lens to attenuate the activity of the TRPM8 agonist during the initial wear period.

BRIEF DESCRIPTION OF THE DRAWING

[010] **FIG. 1** is a box plot showing symptomatic and asymptomatic contact lens wearers preference for either a WS12-releasing contact lens or a control lens after 30 days of lens wear.

DETAILED DESCRIPTION

[011] It was discovered that a TRPM8 agonist when embedded in and released from contact lenses, improves end-of day dryness and/or reduces CLDEQ-8 score after 30 days of wear. However, for some subjects there is an initial stinging/burning sensation at insertion that decreases but may not disappear at the end of the 30-day period (see U.S. Pat. Appln. Publ. No. 2022/0350163).

[012] A TRPM8 agonist-releasing contact lens that additionally delivers a fast-acting TRPM8 antagonist to the eye upon initial insertion reduces or eliminates the stinging/burning sensation caused by release of the TRPM8 agonist. Thus, by using a TRPM8 antagonist in combination with a TRPM8 agonist and leveraging their different solubility and/or release characteristics, a TRPM8 agonist-releasing contact lens is provided that is comfortable to wear from initial insertion to the end of the day.

[013] The present invention, in part, relates to contact lenses (e.g., hydrogel contact lenses), uses for the contact lenses, and methods of making the contact lenses. A TRPM8 agonist is present in and/or on the lenses that is released from the lens during wear in amounts that improve the comfort of contact lens wear. A TRPM8 antagonist is additionally present in and/or on the lenses such that the TRPM8 antagonist is released from the lens during wear and/or upon initial insertion in amounts that can prevent or reduce any stinging/burning sensation that the wearer may experience during initial contact lens wear, for example, within the first 30 minutes of the contact lens being initially inserted in the eye.

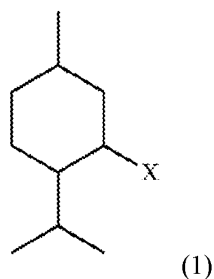
[014] The present invention, in part, relates to an unworn sterile contact lens immersed in a packaging solution and sealed in a package (e.g., blister package). The preferred contact lens, namely, a hydrogel contact lens is discussed hereafter, but it is to be understood that the present invention can be applicable to other contact lens types.

[015] The unworn hydrogel contact lens can comprise, consist essentially of, consists of, or include a) a polymeric lens body; b) an amount of at least one TRPM8 agonist releasably adhered to the polymeric lens body; and c) an amount of at least one TRPM8 antagonist either releasably adhered to the polymeric lens body or present in the packaging solution or both.

[016] As used herein, the term “TRPM8 agonist” refers to a compound that acts as a physiological coolant agent by activating TRPM8. The term “a TRPM8 agonist” or “the TRPM8 agonist” encompasses one or more such cooling agents.

[017] Some examples of TRPM8 agonists that may be loaded into the polymeric lens body include, but are not limited to, 1,8-cineol (CAS No. 470-82-6), D-3263 (CAS No. 1008763-54-9), ethyl menthane carboxamide (CAS No. 39711-79-0), Evercool 180 (CAS No. 1187627-98-0), Evercool 190 (CAS No. 926913-58-8), Frescolat MGA (CAS No. 63187-91-7), Frescolat ML (CAS No. 59236-38-0), icilin (CAS No. 36945-98-9), isopulegol (CAS No. 7786-67-6), menthoxypropanediol (CAS No. 87061-04-9), menthyl diisopropyl propionamide (CAS No 5115-67-4), menthyl lactate (CAS No. 59259-38-0), piperitenone oxide (CAS No. 3564-96-3), p-menthane-3,8-diol (CAS No. 42822-86-6), WS12 (CAS No. 68489-09-8), WS-3 (CAS No. 39711-79-0), WS-5 (CAS No. 68489-14-5), or any mixture or combinations thereof. These and other TRPM8 agonists are well known in the field (see e.g., Leffingwell & Rowsell, *Perfumer & Flavorist*, Vol. 39, Mar. 2014, p. 34-44).

[018] In some examples, the TRPM8 agonist is a menthol compound. As used herein, the term “menthol compound” refers to a compound of formula 1:



where X denotes OH (and thus formula 1 is menthol) or a substituent that results in a menthol derivative that is a TRPM8 agonist and thus acts as a physiological coolant. Examples of menthol compounds include, but are not limited to, menthol, 1-menthol, menthoxypropanediol, WS-3, and WS12. Additional menthol compounds are well-known and commercially available (see, e.g., US Pat. No. 10,028,920 and González-Muñiz et al, *Int. J. Mol. Sci.* (2019) 20, 2618). References herein to a specific compound are intended to encompass all enantiomeric forms and pharmaceutically-acceptable salts of the compound unless context dictates otherwise.

[019] A TRPM8 agonist can be releasably adhered to a contact lens so that when the lens is worn the TRPM8 agonist is released from the lens to provide a cool pleasant sensation to the lens wearer and/or increase wearer comfort. Various methods are well-known in the ophthalmic field for determining improvement in contact lens wear comfort (e.g., reducing symptoms of dryness in the contact lens wearer, and/or increasing comfortable lens wearing time by the contact lens wearer, and/or increasing tear meniscus height of the contact lens wearer, and/or lowering CLDEQ-8 scores in the contact lens wearer, and/or lowering VAS scores in the contact lens wearer), as described further below.

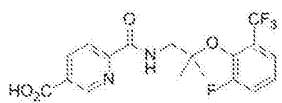
[020] As used herein, an amount of a compound “releasably adhered” to a polymeric lens body refers to the amount of the compound that can be extracted from the contact lens using the ethanol extraction method described in Example 1 below. The amount of TRPM8 agonist releasably adhered to the polymeric lens body may be from about 0.10 µg to 100 µg or more, or from about 0.25 µg to 50 µg or more, or from about 0.5 µg to 25 µg, or other amounts above or below any of the ranges presented here. In a specific example, the TRPM8 agonist is a menthol compound. In a further specific example, the TRPM8 agonist present in the polymeric lens body is WS12 and the amount of WS12 releasably adhered to the polymeric lens body is from about 0.25 µg to about 10.0 µg, and preferably from about 0.5 µg to 5 µg.

[021] The TRPM8 agonist can be present in the polymeric lens body in an amount such that it has an *in vitro* release of 0.01 µg to 10 µg or more of the TRPM8 agonist after 1 hour. As used herein, the amount of TRPM8 agonist released from a polymeric lens body *in vitro* at a given time point or over a series of time points (i.e., a “release profile”) is determined using a release media consisting of 25 vol.% ethanol (EtOH) in phosphate buffered saline (PBS) (hereinafter “*in vitro* release media”) and the method described in Example 3 (hereinafter “*in vitro* release method”). The *in vitro* release of the TRPM8 agonist after 1 hour can be from 0.01 µg to 10 µg, or 0.02 µg to 10 µg, or 0.05 µg to 10 µg, or 0.075 µg to 10 µg, or 0.1 µg to 10 µg, or 0.5 µg to 10 µg, or 0.75 µg to 10 µg, or 1 µg to 10 µg, or 2 µg to 10 µg, or 3 µg to 10 µg, or 5 µg to 10 µg.

[022] The TRPM8 agonist can be present in the polymeric lens body in an amount to provide sustained release of the TRPM8 agonist from the contact lens for at least 9 hours. Sustained release for 9 hours is demonstrated by the *in vitro* release method when the cumulative amount of TRPM8 agonist released from the polymeric lens body at the 12-hour time point is greater than the cumulative amount of TRPM8 agonist released from the polymeric lens body at the 9-hour time point. Similarly, sustained release of the TRPM8 agonist for at least 12 hours is demonstrated by having a greater cumulative amount of TRPM8 agonist released from the polymeric lens body at the 16-hour time point than the 12-hour time point. In one example, the TRPM8 agonist present in the polymeric lens body is WS12 and the amount of WS12 released *in vitro* after 1 hour is from 0.01 µg to 0.20 µg. In another example, the TRPM8 agonist present in the polymeric lens body is WS12 and release of the WS12 is sustained for at least 6 hours, preferably at least 9 hours, and more preferably at least 12 hours.

[023] The contact lens further comprises at least one TRPM8 antagonist either releasably adhered to the polymeric lens body or present in the packaging solution or both releasably adhered to the polymeric lens body and present in the packaging solution. The TRPM8 is capable of attenuating the activity of the TRPM8 agonist that is released from the lens during the initial wear period. As

used herein, the term “a TRPM8 antagonist” or “the TRPM8 antagonist” encompasses one TRPM8 antagonist or encompasses more than one TRPM8 antagonist used together. Exemplary TRPM8 antagonists include AMG-333 (CAS No. 1416799-28-4), AMG-2850 (CAS No. 1470018-52-0), AMG-8788 (CAS No. 1159996-43-6), AMG-9090 (CAS No. 118215-82-0), AMG-9678 (CAS No. 1159997-27-9), AMTB: *N*-(3-aminopropyl)-2-[(3-methylphenyl)methoxy]-*N*-(2-thienylmethyl) benzamide hydrochloride (CAS No. 926023-82-7), BCTC (CAS No. 393514-24-4),

Cannabidivarin (CAS No. 24274-48-4), M8-An:  (see Patel et al., J Pharmacol Exp Ther. 2014 Apr; 349(1):47-55), M8-B (CAS No. 883976-12-3), PF 05105679 (CAS No. 1398583-31-7), RN-1747 (CAS No. 1024448-59-6), RQ 00203078 (CAS No. 1254205-52-1), TC-I 2000 (CAS No. 1159996-20-9), TC-I 2014 (CAS No. 1221349-53-6) or any mixture or combination thereof. These and other TRPM8 antagonists are well known in the field (see e.g., Gavva et al., Mol Pain, 2012 May 9:8:36; and Beccari et al., Nature.com, Scientific Reports, 2017, 7:10999).

[024] The amount of TRPM8 antagonist that is used in the contact lens and/or packaging solution is effective to provide a decrease in stinging or discomfort during the first 30 minutes of wearing a TRPM8 agonist-releasing lens compared to a control lens that lacks the TRPM8 antagonist but is otherwise identical. This “effective amount” of the TRPM8 antagonist can be determined by a routine clinical study in which test lenses (i.e., lenses containing both the TRPM8 agonist and the TRPM8 antagonist) and control lenses are worn by subjects contralaterally for 30 minutes. A reduction in initial unpleasant sensations, such as within 30 minutes of lens insertion, may be demonstrated using a validated visual analog scale (VAS) in which a lens wearer records perceived discomfort on a linear scale with the left end of the scale representing “no discomfort” and the right end of the scale represent “most uncomfortable” (see Delgado et al. J Am Acad Orthop Surg Glob Res Rev. 2018 Mar; 2(3): e088). An improvement of at least 1 on a scale of 1 to 10 (i.e.,

equivalent to 1 cm on a traditional paper-based 10-cm line scale) when wearing the lens containing both the TRPM8 agonist and the TRPM8 antagonist compared to a lens not containing the TRPM8 antagonist but otherwise identical demonstrates a significant reduction in discomfort. In some examples, the improvement in VAS score is at least 2, at least 3, or at least 4 or more.

[025] In some examples the TRPM8 antagonist is releasably adhered to the polymeric lens body in amounts of about 0.10 μg to 100 μg or more, or from about 0.25 μg to 50 μg or more, or from about 0.5 μg to 25 μg , or other amounts above or below any of the ranges presented here. In some examples the TRPM8 antagonist may additionally or alternatively be present in the packaging solution in amounts of about 0.1 $\mu\text{g/ml}$ up to about 100 $\mu\text{g/ml}$, or from about 1 $\mu\text{g/ml}$ to about 10 $\mu\text{g/ml}$.

[026] As an option, the TRPM8 antagonist can be loaded onto or into the contact lens after the TRPM8 agonist is loaded onto or into the same lens. As an example, the TRPM8 agonist can be loaded into a contact lens during a solvent extraction step and subsequently the TRPM8 antagonist is loaded into the contact lens during a hydration step. As an option, the TRPM8 antagonist is at least partially soluble in the packaging solution such that if a contact lens is loaded with a TRPM8 antagonist and then subsequently placed in a packaging solution at least some of TRPM8 antagonist leaches from the lens into the packaging solution.

[027] As an option, the TRPM8 antagonist can be dissolved in the packaging solution. As an option, when a lens is placed in a packaging solution containing a TRPM8 antagonist at least some of the TRPM8 antagonist partitions into the lens and becomes releasably adhered to the polymeric lens body. Thus, in some examples both the contact lens and the packaging solution contain the TRPM8 antagonist.

[028] In examples where at least some of the TRPM8 antagonist is present in the contact lens packaging solution, the contact lens can carry over some of the packaging solution when the lens is removed from the package and placed on the eye. In this way the TRPM8 antagonist present in

the packaging solution is immediately available to block TRPM8 and attenuate the action of the TRPM8 agonist during the initial contact lens wearing period. In some examples, the TRPM8 antagonist is releasably adhered to the lens and releases from the contact lens prior to or simultaneously with release of the TRPM8 agonist. In some examples, a TRPM8 antagonist is both present in the packaging solution and releasably adhered to the contact lens.

[029] In some examples, the TRPM8 antagonist is at least minimally soluble in water at room temperature (herein after “water soluble”) and has a water solubility that is greater than the TRPM8 agonist. In one example, the TRPM8 antagonist is water-soluble and the TRPM8 agonist is insoluble in water. In one example, the TRPM8 antagonist is at least partially soluble in the packaging solution and the TRPM8 agonist is insoluble in the packaging solution.

[030] In one example, the amount of TRPM8 antagonist released from the lens at the 2-hour time point, as determined using the *in vitro* release method of Example 3, is less than 150% of the amount of TRPM8 antagonist released from the lens at the 1-hour time point. In other words, the amount of TRPM8 antagonist released from the lens between 1 and 2 hours is no more than 50 % of the amount that is released from the lens during the 1st hour, and preferably no more than 20% of the amount that is released from the lens during the 1st hour.

[031] In some examples the ratio of TRPM8 antagonist to TRPM8 agonist released from the lens during the first hour is at least 2 to 1, or at least 5 to 1, or at least 10 to 1 as determined by the *in vitro* release method of Example 3. In some examples the TRPM8 agonist is WS12 and the TRPM8 antagonist is M8-An and the ratio of M8-An to WS12 released from the lens during the first hour in the *in vitro* release method is at least 2 to 1, or at least 5 to 1, or at least 10 to 1. In some examples the lens releases from 0.1 µg to 0.5 µg WS12 and from 1.0 µg to 50 µg M8-An during the first hour in the *in vitro* release method.

[032] As an option, the contact lens sustains release of the TRPM8 agonist for at least 9 hours, and preferably at least 12 hours, and sustains release of the TRPM8 antagonist for no more than 3 hours, and preferably no more than 2 hours.

[033] As one example, the contact lens comprises a polymeric lens body that is the reaction product of a polymerizable composition comprising at least one siloxane monomer and at least one hydrophilic monomer and/or at least one hydrophilic polymer. Conveniently, as described in more detail below, a cured polymeric lens body for a silicone hydrogel may be extracted in an extraction solvent containing the TRPM8 agonist, such as WS12, which results in the desired amount of TRPM8 agonist (e.g., WS12) adhering to the polymeric lens body. Alternatively, or additionally, the TRPM8 agonist (e.g., WS12) may be added to the polymerizable composition. The TRPM8 agonist (e.g., WS12) may be adhered to the polymeric lens body by hydrophobic interaction, and/or may be physically entrapped by the polymer network of the polymeric lens body.

[034] The polymeric lens body may comprise any hydrogel material suitable for use as a contact lens material. A silicone hydrogel material for contact lenses is typically formed by curing a polymerizable composition (i.e., a monomer mixture) comprising at least one siloxane monomer and at least one hydrophilic monomer or at least one hydrophilic polymer, or a combination thereof. As used herein, the term “siloxane monomer” refers to any molecule that contains at least one Si-O group and at least one polymerizable functional group. Siloxane monomers used in contact lens compositions are well-known in the art (see, e.g., US Pat No. 8,658,747 and US Pat No. 6,867,245). (All patents and publications mentioned here and throughout are incorporated in their entirety by reference.) In some examples, the polymerizable composition comprises a total amount of siloxane monomer of at least 10 wt.%, 20 wt.%, or 30 wt.% up to about 40 wt.%, 50 wt.%, 60 wt.%, or 70 wt.%. Unless specified otherwise, as used herein, a given weight percentage (wt.%) of a component of the polymerizable composition is relative to the total weight of all polymerizable

ingredients and IPN polymers (as described further below) in the polymerizable composition. The weight of the polymerizable composition contributed by components, such as diluents, that do not incorporate into the final contact lens product are not included in the wt.% calculation.

[035] In a specific example, the polymerizable composition comprises a hydrophilic vinyl monomer. As used-herein, a “hydrophilic vinyl monomer” is any siloxane-free (i.e., contains no Si-O groups) hydrophilic monomer having a polymerizable carbon-carbon double bond (i.e., a vinyl group) present in its molecular structure that is not part of an acryl group, where the carbon-carbon double bond of the vinyl group is less reactive than the carbon-carbon double bond present in a polymerizable methacrylate group under free radical polymerization. As used herein, the term “acryl group” refers to the polymerizable group present in acrylate, methacrylates, acrylamides, etc. Thus, while carbon-carbon double bonds are present in acrylate and methacrylate groups, as used herein, such polymerizable groups are not considered to be vinyl groups. Further, as used herein, a monomer is “hydrophilic” if at least 50 grams of the monomer are fully soluble in 1 liter of water at 20°C (i.e., ~ 5% soluble in water) as determined visibly using a standard shake flask method. In various examples, the hydrophilic vinyl monomer is N-vinyl-N-methylacetamide (VMA), or N-vinyl pyrrolidone (NVP), or 1,4-butanediol vinyl ether (BVE), or ethylene glycol vinyl ether (EGVE), or diethylene glycol vinyl ether (DEGVE), or any combination thereof. In one example, the polymerizable composition comprises at least 10 wt.%, 15 wt.%, 20 wt.%, or 25 wt.% up to about 45 wt.%, 60 wt.%, or 75 wt.% of a hydrophilic vinyl monomer. As used herein, a given weight percentage of a particular class of component (e.g., hydrophilic vinyl monomer, siloxane monomer, or the like) in the polymerizable composition equals the sum of the wt.% of each ingredient in the composition that falls within the class. Thus, for example, a polymerizable composition that comprises 5 wt.% BVE and 25 wt.% NVP and no other hydrophilic vinyl monomer, is said to comprise 30 wt.% hydrophilic vinyl monomer. In one example, the hydrophilic vinyl monomer is a vinyl amide monomer. Exemplary hydrophilic vinyl amide

monomers are VMA and NVP. In a specific example, the polymerizable composition comprises at least 25 wt.% of a vinyl amide monomer. In a further specific example, the polymerizable composition comprises from about 25 wt.% up to about 75 wt.% of VMA or NVP, or a combination thereof. Additional hydrophilic monomers that may be included in the polymerizable composition are N,N-dimethylacrylamide (DMA), 2-hydroxyethyl methacrylate (HEMA), ethoxyethyl methacrylamide (EOEMA), ethylene glycol methyl ether methacrylate (EGMA), and combinations thereof.

[036] In addition, or as an alternative to a hydrophilic monomer, the polymerizable composition may comprise a non-polymerizable hydrophilic polymer, which results in a polymeric lens body comprising an interpenetrating polymer network (IPN) with the non-polymerizable hydrophilic polymer interpenetrating the silicone hydrogel polymer matrix. In this example, the non-polymerizable hydrophilic polymer is referred to as an IPN polymer, which acts as an internal wetting agent in the contact lens. In contrast, polymer chains within the silicone hydrogel network that form by polymerization of monomers present in the polymerizable composition are not considered to be IPN polymers. The IPN polymer may be a high molecular weight hydrophilic polymer, for example from about 50,000 to about 500,000 Daltons. In a specific example, the IPN polymer is polyvinylpyrrolidone (PVP). In other examples, the polymerizable composition is substantially free of polyvinyl pyrrolidone or other IPN polymer.

[037] As an option, one or more non-silicon containing hydrophobic monomers can be present as part of the polymerizable composition. A hydrophobic monomer can be understood to be any monomer for which 50 grams of the monomer are not visibly fully soluble in 1 liter of water at 20° C using a standard shake flask method. Examples of suitable hydrophobic monomers include methyl acrylate, or ethyl acrylate, or propyl acrylate, or isopropyl acrylate, or cyclohexyl acrylate, or 2-ethylhexyl acrylate, or methyl methacrylate (MMA), or ethyl methacrylate, or propylmethacrylate, or butyl acrylate, or 2-hydroxybutyl methacrylate, or vinyl acetate, or vinyl

propionate, or vinyl butyrate, or vinyl valerate, styrene, or chloroprene, or vinyl chloride, or vinylidene chloride, or acrylonitrile, or 1-butene, or butadiene, or methacrylonitrile, or vinyltoluene, or vinyl ethyl ether, or perfluorohexylethylthiocarbonylaminoethyl methacrylate, or isobornyl methacrylate (IBM), or trifluoroethyl methacrylate, or hexafluoroisopropyl methacrylate, or tetrafluoropropyl methacrylate, or hexafluorobutyl methacrylate, or any combinations thereof.

[038] The hydrophobic monomer, if used, can be present in the reaction product of the polymerizable composition in amounts of from 1 wt.% to about 30 wt.%, such as from 1 wt.% to 25 wt.%, from 1 wt.% to 20 wt.%, from 1 wt.% to 15 wt.%, from 2 wt.% to 20 wt.%, from 3 wt.% to 20 wt.%, from 5 wt.% to 20 wt.%, from 5 wt.% to 15 wt.%, from 1 wt.% to 10 wt.%, based on the total weight of the polymerizable composition.

[039] The polymerizable composition may additionally comprise at least one cross-linking agent. As used herein, a “cross-linking agent” is a molecule having at least two polymerizable groups. Thus, a cross-linking agent can react with functional groups on two or more polymer chains so as to bridge one polymer to another. The cross-linking agent may comprise an acryl group or a vinyl group, or both an acryl group and a vinyl group. In certain examples, the cross-linking agent is free of siloxane moieties, i.e., it is a non-siloxane cross-linking agent. A variety of cross-linking agents suitable for use in silicone hydrogel polymerizable compositions are known in the field (see, e.g., U.S. Pat. No. 8,231,218, incorporated herein by reference). Examples of suitable cross-linking agents include, without limitation, lower alkylene glycol di(meth)acrylates such as triethylene glycol dimethacrylate, diethylene glycol dimethacrylate, poly(lower alkylene) glycol di(meth)acrylates and lower alkylene di(meth)acrylates; divinyl ethers such as triethyleneglycol divinyl ether, diethyleneglycol divinyl ether, 1,4-butanediol divinyl ether and 1,4-cyclohexanedimethanol divinyl ether; divinyl sulfone; di- and trivinylbenzene; trimethylolpropane tri(meth)acrylate; pentaerythritol tetra(meth)acrylate; bisphenol A di(meth)acrylate;

methylenebis(meth)acrylamide; triallyl phthalate; 1,3-bis(3-methacryloxypropyl)tetramethyldisiloxane; diallyl phthalate; and combinations thereof.

[040] As will be appreciated by those skilled in the art, the polymerizable composition may comprise additional polymerizable or non-polymerizable ingredients conventionally used in contact lens formulations such as one or more of a polymerization initiator, a UV absorbing agent, a tinting agent, an oxygen scavenger, a chain transfer agent, or the like. In some examples, the polymerizable composition may include an organic diluent in an amount to prevent or minimize phase separation between the hydrophilic and hydrophobic components of the polymerizable composition, so that an optically clear lens is obtained. Diluents commonly used in contact lens formulations include hexanol, ethanol, and/or other primary, secondary or tertiary alcohols. In other examples, the polymerizable composition is free or substantially free (e.g., less than 500 ppm) of an organic diluent. In such examples, the use of siloxane monomers containing hydrophilic moieties such as polyethylene oxide groups, pendant hydroxyl groups, or other hydrophilic groups, may make it unnecessary to include a diluent in the polymerizable composition. Non-limiting examples of these and additional ingredients that may be included in the polymerizable composition are provided in U.S. Pat. No. 8,231,218.

[041] Non-limiting examples of silicone hydrogels that may be used include comfilcon A, fanfilcon A, stenfilcon A, senofilcon A, senofilcon C, somofilcon A, narafilecon A, delefilcon A, narafilecon A, lotrafilecon A, lotrafilecon B, balafilcon A, samfilcon A, galyfilcon A, and asmofilecon A.

[042] A specific example of a hydrogel contact lens of the present invention is one that is based on a polymerizable composition comprising from 25 wt.% to 55 wt.% of siloxane monomer(s), from 30 wt.% to 55 wt.% of a vinyl monomer selected from NVP, VMA, or combinations thereof, and optionally from about 1 wt.% to about 20 wt.% of a hydrophilic monomer selected from N,N-dimethylacrylamide (DMA), 2-hydroxyethyl methacrylate (HEMA), ethoxyethyl methacrylamide

members can be non-polar molds or polar molds. The mold assembly is disassembled (i.e., demolded) and the polymeric lens body is removed from the mold and unreacted components are extracted from the lens body using an organic solvent.

[044] Conveniently, the TRPM8 agonist, such as WS12, may be loaded into the polymeric lens during the extraction step. Generally, after curing, the polymeric lens body is swelled in an extraction solvent that contains the TRPM8 agonist (e.g., WS12). When the extracted polymeric lens body is subsequently placed in a hydration solution, such as deionized water, the extraction solvent is removed, and the TRPM8 agonist (e.g., WS12) remains adhered to the polymeric lens body.

[045] As an example, the extraction and hydration process can involve at least one extraction step in denatured ethanol (EtOH) followed by an extraction step comprising a mixture of EtOH and water, such as from about 10% to 95% EtOH in water, for example from about 30% to 80% EtOH in water, followed by at least one hydration step in deionized water, and wherein each extraction and hydration step can last from about 15 minutes to about 3 hours at a temperature of from about 20° C and to about 30°. Any extraction solvent can be used as an uploading solution for the TRPM8 agonist (e.g., WS12). In one example, the concentration of TRPM8 agonist (e.g., WS12) in the extraction solvent is from about 1.0 µg/ml to about 4.0 µg/ml (i.e., 1 ppm to about 4 ppm). In one example, the initial extraction solvent is EtOH and the second extraction solvent comprises a mixture of from 30% to 80% EtOH in water and from 1 ppm to 4 ppm TRPM8 agonist (e.g., WS12).

[046] As part of the present invention, the contact lens can be sealed in a contact lens package. The packaging solution sealed within the contact lens package may be any conventional contact-lens compatible solution. In one example, the packaging solution comprises, consists, or consists essentially, of an aqueous solution of a buffer, and/or a tonicity agent. In another example, the packaging solution contains additional agents such as one or more additional antimicrobial agents,

and/or a comfort agent, and/or a hydrophilic polymer, and/or a surfactant and/or other beneficial agent. In some examples, the packaging solution may comprise polysaccharides (e.g., hyaluronic acid, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, etc.) or other high molecular weight polymers, such as polyvinyl pyrrolidone, which are commonly used as comfort polymers or thickening agents in ophthalmic solutions and contact lens packaging solutions. In other examples, the packaging solution may comprise an ophthalmic drug. The packaging solution can have a pH in the range of about 6.8 or 7.0 up to about 7.8 or 8.0. In one example, the packaging solution comprises phosphate buffer or borate buffer. In another example, the packaging solution comprises a tonicity agent selected from sodium chloride or sorbitol in an amount to maintain osmolality in the range of about 200 to 400 mOsm/kg, and typically from about 270 mOsm/kg up to about 310 mOsm/kg.

[047] With respect to the contact lens package, this package can include or comprise a plastic base member comprising a cavity configured to retain the contact lens and packaging solution and a flange region extending outwardly around the cavity. A removable foil is attached to the flange region to provide a liquid-tight seal. The removable foil may be sealed by any conventional means such as heat sealing or gluing. Such contact lens packages, which are commonly referred to as “blister packs”, are well-known in the art (see e.g., U.S. Pat. No. 7,426,993). The sealed package may be sterilized by sterilizing amounts of radiation, including heat or steam, such as by autoclaving, or by gamma radiation, e-beam radiation, ultraviolet radiation, etc. In a specific example, the packaged contact lens is sterilized by autoclaving.

[048] The final product can be a sterile, packaged contact lens (e.g., silicone hydrogel contact lens) having ophthalmically-acceptable surface wettability.

[049] In some examples the TRPM8 agonist is loaded into the polymeric lens body, such as during an ethanol extraction step and does not substantially leach from the polymeric lens body after the lens is placed in a packaging solution. Thus, the packaging solution that the contact lens

is immersed in, before autoclaving, or immediately after autoclaving, or after 1 day thereafter, or after 30 days thereafter, or after 60 days thereafter, or after 120 days thereafter is “substantially free” of the TRPM8 agonist, meaning that any menthol compound present in the packaging solution is below the limit of detection as determined by HPLC.

[050] The following Examples illustrate certain aspects and advantages of the present invention, which should be understood not to be limited thereby.

Example 1. Preparation of WS12-Releasing Contact Lenses

[051] Silicone hydrogel contact lenses were prepared by curing the formulation for stenfilcon A in contact lens molds. The cured stenfilcon A was removed from the molds and extracted by immersing them for 215 minutes in ethanol (EtOH) containing WS12 (Tocris Bioscience) in the loading concentrations shown in Table I. The lenses were removed from the EtOH and washed in DI water for approximately 6 minutes, followed by two exchanges of DI water for approximately 30 minutes each. The lenses were transferred to 6 mL glass vials containing 3 mL phosphate buffered saline at pH 7.5 (0.78 wt.% NaCl, 0.05 wt.% sodium phosphate monobasic, and 0.36 wt.% sodium phosphate dibasic), referred to herein as PBS. The vials were sealed and autoclaved.

[052] Extraction method: Each autoclaved lens was transferred to a vial containing 3 ml EtOH and stored overnight on a 150 rpm shaker at room temperature to extract WS12 from the lens. The EtOH extracts and the PBS in which the lenses were autoclaved were submitted for analysis by HPLC (detection wavelength = 250 nm) against calibration standards to determine the average amount of WS12 loaded into each (n=5) and whether the WS12 leaches from the lens during autoclave. Results are shown in Table 1.

[053] **Table 1.**

Lens ID	WS12 loading concentration	Ave. WS12/lens	WS12 concentration in PBS packaging solution
A	5 µg/mL	0.42 µg	Not detected

B	15 µg/mL	1.28 µg	Not detected
C	50 µg/mL	4.30 µg	0.05 µg/mL

[054] Silicone hydrogel contact lenses were prepared by curing the formulation for comfilcon A in contact lens molds and subjecting the lenses to the same extraction, hydration, and autoclave procedures as described above for lenses made with stenfilcon A except that a single WS12 concentration, 15 µg/mL, was used in the ethanol extraction step. The lenses (Lens D) were submitted for HPLC analysis of WS12 content and were shown to have an average WS12 uptake of 1.04 µg/lens.

[055] Example 2. Release of WS12 from Contact Lenses During Lens Wear

[056] Lens B from Example 1 was worn by a human subject for 1, 3, and 6 hours (n=2 for each time point). At the end of each lens wear duration, the lenses were extracted in EtOH using the method described in Example 1. Extracts were submitted for HPLC analysis to determine the residual amount of WS12 remaining in the lenses and the amount of WS12 released during wear was calculated. The average amount and percent of WS12 released during lens wear is shown in Table 2.

[057] Table 2.

Time Point (hr)	Ave. amt. WS12 released per lens	Ave. percent WS12 released per lens
1	0.22 µg	17 %
3	0.51 µg	40 %
6	0.69 µg	54 %

[058] Example 3. In Vitro Release Methods

[059] In the *in vitro* release method for contact lenses containing a TRPM8 agonist, the lenses are removed from their containers and excess packaging solution is shaken off each lens. Each lens (n=3 for each time point) is transferred to a 6 mL glass vial containing 3 mL of 25 vol.%

ethanol in PBS at 35° C (EtOH release media). The vials are placed on a shaker at 125 rpm in a 35° C incubator. At the 30 minute and 1-hour sample time points 2.5 ml of the EtOH release media is removed (i.e., from 30 minute and 1-hour time point vials, respectively) and submitted for HPLC analysis. At the 1-hour time point, and subsequent time points (i.e., at 2 hr, 3 hr, 6 hr, 9 hr, 12 hr, and 16 hr), 2.5 ml of the EtOH release media is removed from each of the remaining vials and 2.5 ml fresh EtOH release media is added back to each vial. The cumulative WS12 release at each time point is calculated. For example, the 3-hour time point is the sum of the average amount of WS12 detected in the release media taken at the 1-hour, 2-hour, and 3-hour time points.

[060] The above-described *in vitro* release method results in an *in vitro* release of WS12 from contact lenses that corresponds well with the release of WS12 from contact lenses worn on eye as shown in Table 3 in comparison with Table 2.

[061] **Table 3**

Time Point (hr)	Lens B Ave. amt. WS12 released per lens	Lens B Ave. percent WS12 released per lens
0.5	0.13 µg	9 %
1	0.24 µg	17 %
3	0.44 µg	31 %
6	0.60 µg	43 %

[062] The *in vitro* release method for contact lenses containing a TRPM8 antagonist is the same as described above for the TRPM8 agonist except that the sample time points are 10 minutes, 20 minutes, 30 minutes 1 hour, 3 hours, and 5 hours.

[063] **Example 4. Dose-Escalating, One-Day Clinical Study of WS12-Releasing Contact Lenses**

[064] Two subjects were recruited into the study in which all three loading concentrations from Example 1 were evaluated. Each subject was exposed to Lens A, B and C from Example 1 for 30

minutes each in one eye, worn contralaterally. On the first study day, the subjects were exposed to contralateral wear of Lens B and Lens C, followed by contralateral wear of Lens B and Lens A on a separate day. With Lens C, one subject experienced a stinging sensation, while the other subject experienced a cooling sensation. With Lens B both subjects experienced a mild cooling/tingling sensation that lasted approximately one hour. Lens A elicited a brief cooling/wetting sensation in the subjects. Lens B was selected for further evaluation.

[065] Example 5. Thirty-Day Clinical Study of WS12-Releasing Contact Lenses

[066] Thirty-three subjects were enrolled in a 1-month, bilateral, randomized, crossover double-masked study where subjects wore both Lens B from Example 1 (test) or MyDay® brand (control) contact lenses, each for 1-month. The subjects were classified as either symptomatic (S) or asymptomatic (A) contact lens wearers using the classification system outlined in Table 4, which is adapted from the classification proposed by Young et al. (*supra*).

[067] Table 4

		Frequency of contact lens dryness / discomfort				
		Never	Rarely	Sometimes	Frequently	Constantly
Intensity of contact lens dryness discomfort	Never have it 0	A	A	A	A	A
	Not at all intense 1	A	A	A	A	A
	2	A	A	S	S	S
	3	A	A	S	S	S
	4	A	A	S	S	S
	Very intense 5	A	A	S	S	S

[068] Sixteen of the subjects were classified as symptomatic contact lens wearers, reporting a rating of 2 or more out of 5 for Intensity of contact lens dryness / discomfort and “sometimes, frequently or constantly” for Frequency of contact lens dryness/ discomfort. Seventeen of the

subjects were classified as asymptomatic contact lens wearers, reporting a rating of 0 or 1 out of 5 for Intensity of contact lens dryness / discomfort and “rarely or never” for Frequency of contact lens dryness / discomfort.

[069] After a washout period of 3-7 days during which subjects wore their habitual lenses, the second lens type from the randomization order (i.e., either the Example 1 (test) or MyDay® brand (control) contact lenses) were worn for 1-month. Ratings of comfort, dryness, cooling, pleasantness as well as CLDEQ-8 score were monitored (see Chalmers et al., *Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8) and opinion of contact lens performance*. Optom Vis Sci 2012; 89(10):1435-1442.).

[070] At the 1-week time point, the test lens was rated as significantly less pleasant at insertion than the control lens, however this difference decreased after 1 month of wear. This change may be attributed to a decrease in cooling sensation, possibly due to sensory adaptation in subjects wearing the test lens. There was no significant difference in the rating of overall comfort between test and control lenses at the 1-week or 1-month time points. Yet, twice as many subjects reported an increase in comfort with the test lens compared to the control lens after 1 month of wear. There was significantly better (i.e., lower) overall dryness ratings at both 1 week and 1 month with the test lens compared to the control lens. Tear meniscus height was measured using a Visante OCT (Carl Zeiss Meditec Inc., Dublin, Calif.) and was significantly increased after one month of wearing the test lens compared to the control lens. The CLDEQ-8 score was significantly lower after 1 month of wearing the test lens compared to the control lens. The difference was statistically significant among symptomatic subjects. After 1 month of lens wear, out of the 33 subjects, 19 (58%) preferred the test lens, 11 (33%) preferred the control lens and 3 (9%) reported no preference. Among the 16 symptomatic subjects, 11 (69%) preferred the test lens and 5 (31%) preferred the control lens. Results are depicted in Fig. 1.

[071] Example 6. M8-B Packaging Solution.

[072] Contact lenses were made with stenfilcon A as described in Example 1 above except that the ethanol in the extraction step did not contain WS12 and the PBS used for packaging the lenses contained 50 µg/ml M8-B.HCL (Cayman Chemical; CAS No. 883976-12-3). The packaged lenses were either autoclaved or left at room temperature. After autoclave, the lenses were transferred to individual vials containing 3 ml EtOH for overnight extraction as described above in Example 1. The EtOH extracts and the packaging solutions (Pkg. Soln.) from both autoclaved (With AC) and non-autoclaved lenses (No AC) were submitted for analysis by HPLC (detection wavelength = 245 nm) against calibration standards. Results are shown in Table 5.

[073] Table 5

Condition	Amt. M8-B in Packaging Solution (%)	Amt. M8-B in Lens
No AC	87.5 µg (69 %)	39.9 µg (31 %)
With AC	77.3 µg (58 %)	54.9 µg (42 %)

[074] Example 7. M8-An Release Profile

[075] Lenses were made with stenfilcon A and packaged in contact lens blister packages with 1.2 mL PBS containing 5 µg/ml, 10 µg/ml or 20 µg/ml M8-An (EMD Millipore Cat. No. 530617). The vials were autoclaved and the loading amount of M8-An contained in the autoclaved lens was determined using the ethanol extraction method of Example 1.

[076] M8-An *in vitro* release profiles were tested using the *in vitro* release method for contact lenses containing a TRPM8 antagonist described above in Example 3. The HPLC analysis detection wavelength was 275 nm. The results are shown in Table 6.

[077] Table 6.

M8-An Conc.	Ave. Amt. M8-An/lens	Cumulative release amount (% of Ave.) at each time point					
		10 min	20 min	30 min	1 hr	3 hr	5 hr
5 µg/ml	5.11 µg	1.77 µg (34.6 %)	2.99 µg (58.5 %)	3.79 µg (74.1 %)	4.75 µg (92.9 %)	5.18 µg (101.3%)	5.27 µg (103.1 %)
10µg/ml	10.12 µg	4.10 µg (40.5%)	6.46 µg (63.8%)	8.02 µg (79.2%)	9.96 µg (98.4%)	10.66 µg (105.3%)	10.79 µg (106.6%)
20 µg/ml	20.24 µg	8.51 µg (42.0 %)	13.03 µg (64.4 %)	16.15 µg (79.8 %)	19.98 µg (98.7 %)	21.25 µg (105.0 %)	21.50 µg (106.2 %)

[078] The experiment was repeated using WS12-releasing stenfilcon A lenses. The M8-An *in vitro* release profiles were substantially the same as the lenses containing no WS12. Similarly, the WS12 *in vitro* release profile from these lenses was substantially the same as that from WS12 loaded stenfilcon A lenses packaged in PBS without M8-An, indicating that the presence of both the TRPM8 agonist and the TRPM8 antagonist does not impact the release profile of either compound.

[079] The disclosure herein refers to certain illustrated examples, it is to be understood that these examples are presented by way of example and not by way of limitation. The intent of the foregoing detailed description, although discussing exemplary examples, is to be construed to cover all modifications, alternatives, and equivalents of the examples as may fall within the spirit and scope of the invention as defined by the additional disclosure.

[080] References herein to “an example” or “a specific example” or “an aspect” or “an embodiment” or similar phrase, are intended to introduce a feature or features of the WS12-releasing hydrogel contact lens or components thereof, the sealed contact lens package or components thereof, or method of manufacturing the WS12-releasing hydrogel contact lens (depending on context) that can be combined with any combination of previously-described or subsequently-described examples, aspects, embodiments (i.e. features), unless a particular combination of features is mutually exclusive, or if context indicates otherwise. Further, as used

in this specification, the singular forms “a,” “an,” and “the” include plural referents (e.g., at least one or more) unless the context clearly dictates otherwise. Thus, for example, reference to a “contact lens” includes a single lens as well as two or more of the same or different lenses.

[081] The entire contents of all cited references in this disclosure, to the extent that they are not inconsistent with the present disclosure, are incorporated herein by reference.

[082] The present invention can include any combination of the various features or embodiments described above and/or in the claims below as set forth in sentences and/or paragraphs. Any combination of disclosed features herein is considered part of the present invention and no limitation is intended with respect to combinable features.

[083] Other embodiments of the present invention will be apparent to those skilled in the art from consideration of the present specification and practice of the present invention disclosed herein. It is intended that the present specification and examples be considered as exemplary only with a true scope and spirit of the invention being indicated by the following claims and equivalents thereof.

WHAT IS CLAIMED IS:

1. A sealed contact lens package comprising: (a) a packaging solution; and (b) an unworn contact lens comprising a polymeric lens body immersed in the packaging solution, wherein an amount of a TRPM8 agonist is releasably adhered to the polymeric lens body and wherein a TRPM8 antagonist is present in the packaging solution, or releasably adhered to the polymeric lens body, or both present in the packaging solution and releasably adhered to the polymeric lens body.
2. The sealed contact lens package of claim 1, wherein the TRPM8 antagonist is M8-An.
3. The sealed contact lens package of claim 1, wherein the TRPM8 antagonist is AMTB.
4. The sealed contact lens package of any preceding claim, wherein the TRPM8 agonist is a menthol compound.
5. The sealed contact lens package of claim 4, wherein the menthol compound is WS12.
6. The sealed contact lens package of claim 5, wherein the amount of WS12 releasably adhered to the polymeric lens body is from about 0.25 µg to 10 µg.
7. The sealed contact lens package of claim 5, wherein the amount of WS12 releasably adhered to the polymeric lens body is from about 0.5 µg to 5 µg.
8. The sealed contact lens package of any preceding claim, wherein the contact lens sustains release of the TRPM8 agonist for at least 6 hours in an *in vitro* release media consisting of 25 vol.% EtOH in PBS.
9. The sealed contact lens package of any preceding claim, wherein the TRPM8 antagonist is releasably adhered to the polymeric lens body and wherein the contact lens releases at least 90

wt% of the TRPM8 antagonist from the polymeric lens body within 3 hours in an *in vitro* release media consisting of 25 vol.% EtOH in PBS.

10. The sealed contact lens package of any preceding claim, wherein the packaging solution is substantially free of the TRPM8 agonist.
11. The sealed contact lens package of any preceding claim, wherein the TRPM8 antagonist is at least partially soluble in the packaging solution and the TRPM8 agonist is insoluble in the packaging solution.
12. The sealed contact lens package of any preceding claim, wherein the polymeric lens body comprises a silicone hydrogel.
13. The sealed contact lens package of claim 12, wherein the polymeric lens body comprises a reaction product of a polymerizable composition comprising from 25 wt.% to 55 wt.% of a siloxane monomer or a combination of siloxane monomers, from 30 wt.% to 55 wt.% of a vinyl monomer selected from NVP, VMA, or combinations thereof; optionally from about 1 wt.% to about 20 wt.% of a hydrophilic monomer selected from N,N-dimethylacrylamide (DMA), 2-hydroxyethyl methacrylate (HEMA), ethoxyethyl methacrylamide (EOEMA), or ethylene glycol methyl ether methacrylate (EGMA), or any combination thereof; and/or optionally from about 1 wt.% to about 20 wt.% of a hydrophobic monomer selected from methyl methacrylate (MMA), isobornyl methacrylate (IBM), or 2-hydroxybutyl methacrylate (HOB) or any combination thereof.
14. The sealed contact lens package of any preceding claim, wherein the contact lens comprises fanfilcon A, comfilcon A, somofilcon A, riofilcon A, or stenfilcon A.

15. The sealed contact lens package of any preceding claim comprising a base member comprising a well that retains the packaging solution and contact lens and a cover that forms a liquid-tight seal with the base member.
16. A method of manufacturing the sealed contact lens package of any preceding claim, said method comprising:
 - (a) polymerizing a polymerizable composition in a contact lens mold to obtain a polymeric lens body;
 - (b) extracting, in one or more steps, the polymeric lens body in an organic solvent comprising a TRPM8 agonist;
 - (c) hydrating the polymeric lens body in a hydration liquid to obtain a silicone hydrogel contact lens;
 - (d) placing the silicone hydrogel contact lens and a packaging solution comprising a TRPM8 antagonist in a well of a contact lens packaging base member;
 - (e) sealing the packaging base member to form a sealed contact lens package; and
 - (f) autoclaving the package.
17. The method of claim 16, wherein at least some of the TRPM8 antagonist partitions into the silicone hydrogel contact lens during the autoclaving step and becomes releasably adhered to the polymeric lens body.