COMPOSITIONS AND METHODS FOR INCREASING TEAR SECRETION

FIELD

[0001] The present disclosure relates to a composition and method for a treatment for dry eyes. More specifically, the disclosure relates to a composition and method for increasing tear production.

BACKGROUND

[0002] The terms dry eyes, dry eye syndrome, and dry eye disease are used interchangeably in the literature. There is rarely any distinction made between sore eyes resulting from intense work at a computer screen versus the more chronic dry eyes due to ongoing disease. Dry eyes is an irritating, scratchy feeling at the front of the eyes. This occurs when tear production fails to keep up with evaporation, resulting in inadequate lubrication of the eye surface. A recently published clinical consensus of ophthalmologists states that "Dry eye is a multifactorial disease characterized by a persistently unstable and/or deficient tear film (TF) causing discomfort and/or visual impairment, accompanied by variable degrees of ocular surface epitheliopathy, inflammation, and neurosensory abnormalities." (Tsubota et al. 2020). The emphasis in this citation is on "persistently unstable" tear film that is of clinical concern, versus dry eyes that are not disease conditions and the dryness of eyes that occurs for acute, non-clinical reasons such as working at a computer screen.

[0003] What is required in the field is a composition and method for increasing tear production that is simple, safe, and effective for non-clinical dry eye conditions.

SUMMARY

[0004] In the present disclosure, a composition and method for increasing tear production is provided.

[0005] Thus, by one broad aspect of the present invention, a composition is provided for topical application to increase tear production, the composition including menthol and a carrier. The menthol comprises at least 5% of the composition w/w and the carrier comprises at least one of: a triglyceride oil, a medium chain triglyceride, petroleum jelly, coconut oil, olive oil, beeswax, a wax that is semi-solid at 21 C, a vegetable wax, an animal wax, a petroleum wax, a mineral wax, a synthetic wax, vaseline, lanoline, hydrogenated rosin/glyceryl diisostearate, hydrogenated polyisobutene, polyethylene,

fatty acid cholesteryl, higher fatty acid esters, aliphatic alcohols, squalene, polyethyleneglycol, higher fatty acids, animal oil, and vegetable oil.

[0006] By a further broad aspect of the present invention, a method is provided for increasing tear production, the method including delivering a composition including menthol and a carrier to a user's eye. The menthol comprises at least 5% of the composition w/w and the carrier comprises at least one of: a triglyceride oil, a medium chain triglyceride, petroleum jelly, coconut oil, olive oil, beeswax, a wax that is semi-solid at 21 C, a vegetable wax, an animal wax, a petroleum wax, a mineral wax, a synthetic wax, vaseline, lanoline, hydrogenated rosin/glyceryl diisostearate, hydrogenated polyisobutene, polyethylene, fatty acid cholesteryl, higher fatty acid esters, aliphatic alcohols, squalene, polyethyleneglycol, higher fatty acids, animal oil, and vegetable oil.

[0007] A further understanding of the functional and advantageous aspects of the invention can be realized by reference to the following detailed description and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] Embodiments disclosed herein will be more fully understood from the following detailed description taken in connection with the accompanying drawings, which form a part of this application, and in which:

[0009] **Figure 1** is a side view of a face of a person applying a menthol composition of the present disclosure to the skin of the cheekbone below the bottom rim of a pair of glasses.

[0010] **Figure 2** is a front view of a face of a person applying the menthol composition of the present disclosure to the skin of the cheekbone below the eye, at the highest point of the cheekbone.

[0011] **Figure 3** is a side view of a person applying a menthol composition of the present disclosure to the skin of the cheekbone below the eye.

[0012] **Figure 4** is a front view of a face of a person wearing glasses to which is adhered a small tissue that holds the menthol composition applied to it.

DETAILED DESCRIPTION

[0013] The following description and drawings are illustrative of the disclosure and are not to be construed as limiting the disclosure. Numerous specific details are described to provide a thorough understanding of various embodiments of the present disclosure.

However, in certain instances, well-known or conventional details are not described in order to provide a concise discussion of embodiments of the present disclosure.

[0014] Tears are secreted by the lacrimal glands located at the upper lateral side of each eyeball. There is no storage of tears for release, but rather, tears are produced on an as-needed basis, similar to the flow of saliva. These secretions are determined by activity of the autonomic nervous system. To produce tears, local vasodilatation occurs in lacrimal glands, whose duct cells actively transport ions from circulating plasma, drawing along water, as an ultrafiltrate into the lumen, thus forming tears that flow from the gland's ducts. Tears are also stimulated on demand, as signalled by the unconsciously controlled autonomic nervous system (Tóth-Molnár and Ding 2020).

[0015] Three pathways are known to activate secretion of tears: First, tear secretion can be induced by the uniquely human behaviour of emotional tears with crying, where tear secretion is stimulated by sympathetic and parasympathetic neural pathways (Bylsma, Gračanin, and Vingerhoets 2019). Second, by pain receptors located at both the cornea and the eyeball that respond to noxious irritants, such as the *syn-Propanethial-S-oxide* released from onions, as well as by capsaicin or chemicals in bear spray or tear gas. Third, tear secretion is increased in response to cold, as happens in windy or dry conditions that cause evaporative cooling, so that tear liquid gets replaced by increased tear production (Hirata and Meng 2010; Robbins et al. 2012). People in chilly winter air experience watery eyes due to stimulation of cold receptors that are located on the cornea. Cold-receptor-induced tear production is especially obvious during winter when a person comes in from the cold. That same, non-emotional, non-painful, tear-inducing mechanism is what is mimicked by the present invention, which provides compositions and methods that alter the nature of the air around the eyes so as to evoke tear secretion.

[0016] The causes of dry eye syndrome can be broadly classified into those with deficiency of aqueous tear production, excessive tear evaporation, or a combination of both. The most common primary disease cause of chronic aqueous tear deficiency is lacrimal gland dysfunction secondary to an autoimmune disease, keratoconjunctivitis sicca. (Lam et al. 2020). Dysfunction of any component of the lacrimal gland, ocular surface, eyelids, or the nervous system can cause dry eyes. The condition becomes more common as people get older, affecting up to 30% of the general elderly population. Many factors can contribute to dry eyes, including the use of systemic and

topical (on-eye) medication, lid laxity, hormonal changes with age (low androgen or estrogen), inflammatory systemic conditions, and oxidative stress. Patients with dry eye can experience blurred vision, foreign body sensation, and pain. If left untreated, dry eye can damage the ocular surface and impair vision.

[0017] In addition to primary dry-eye disease, there are more common, non-eye-disease reasons for similar symptoms. For example, a recent review of the literature shows that depression and antidepressant use are each independently associated with dry eye disease (Rakofsky, Rakofsky, and Dunlop 2021). Antidepressants can function by different mechanisms, and those mechanisms impair tear production by attenuating the reflex-evoked signalling that is mediated by menthol-stimulated cold receptors (Dankis et al. 2021).

[0018] Most people in modern society use computers or they focus on hand-held devices that have small displays. When they are surveyed, 60-90% of computer users report being affected by dry eyes, which is also known as digital eye strain, or computer vision syndrome (CVS) (Talens-Estarelles et al. 2022; Rosenfield 2011). Many factors contribute to computer vision syndrome, not the least of which is the rate of blinking. At rest, people blink about once every 3 seconds, but when people focus on a screen, their blink rate slows to only once every 7-10 seconds; furthermore, smaller font sizes and intense focus at the task cause even lower blink rates (Rosenfield 2011; Kamøy et al. 2022). Blinking stimulates tear production, and blinking spreads the lubricant oil secreted from the meibomian glands located in the eyelids along the surface of the eye.

[0019] Pure menthol is an organic compound that is a crystalline solid that melts above a temperature of 42 degrees centigrade. It dissolves into heated fats and oils, and has the structure of a cyclic monoterpene. Menthol dissolves in lipids or organic solvents like ethanol. Menthol evaporates readily, and it is incorporated into many consumer products including toothpaste, gum, and medicines including certain proprietary eyedrops.

[0020] The mechanism by which menthol stimulates tearing is that it binds to a receptor protein known as the “transient-receptor-potential-cation-channel subfamily M member 8”, which is abbreviated as “TRPM8”. Binding to TRPM8 stimulates lacrimation by activating cold-sensitive primary afferent neurons in the cornea. A clinical trial of menthol-impregnated, heated eye pads that are placed over closed eyes, showed improvements in tear volume and tear stability (Arita et al. 2017; Arita and

Fukuoka 2020). In the year 2010, Parra et al were the first to show that the TRPM8 cold receptor causes tearing in humans and mice, and that the cold-receptor agonist, menthol, evokes tearing in mice (Parra et al. 2010). Hirata et al showed that activators of TRPM8 cause firing of corneal neurons; they also showed that dysfunction of these corneal afferents and the lacrimation reflex pathway that they activate result in some forms of dry eye disease (Hirata and Meng 2010). That is consistent with the fact that patients with dry eye exhibit less sensitivity of the cornea after mechanical, thermal, and chemical stimulation, and that the sensitivity loss appears to be related to damage to the corneal sensory innervation (Bourcier et al. 2005). Menthol was subsequently suggested as a possible treatment for dry eye (Robbins et al. 2012; Arita et al. 2017; Arita and Fukuoka 2020). If the eye becomes neurologically less sensitive to stimuli for tearing, then it makes sense to consider using approaches that increase the signal to stimulate tear production.

[0021] Some people may simply suffer from a dysfunction or hypofunction of lacrimal glands which results in insufficient water in the tear film. A reduced volume of tear fluid gives rise to aqueous-deficient dry eye, whereas impaired tear film stability underlies evaporative dry eye. Sjögren syndrome is an autoimmune syndrome that attacks lacrimal glands, causing aqueous deficiency dry eyes. Another mechanism for dry eyes involves the meibomian glands that are located in the eyelids, and that produce the meibomium that creates the surface lipid layer on the tear film. Meibomian-gland dysfunction is a chronic abnormality characterized by terminal obstruction of lipid-secreting ducts in the eyelids, resulting in more rapid evaporation of tears, known as evaporative dry eye. Meibomian gland dysfunction can cause changes to the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease (Lam et al. 2020).

[0022] Eye drops are not benign. Eye drops do not stimulate tear production, and they lessen the need to produce tears naturally. Eye drops can make dry-eye disease worse by desensitizing receptors that stimulate tear production. This decrease in afferent drive would reduce the release of natural trophic factors for tear production (Mathers 2000). Long-term use of topical drugs applied to the eyes may induce change to the ocular surface, cause ocular discomfort, tear film instability, conjunctival inflammation, subconjunctival fibrosis, epithelial apoptosis, corneal surface impairment (Baudouin et al. 2010). Most people lack the obvious technical skill to

correctly place a single drop into their own eyes (Mehuys et al. 2020). Lastly, commercial eye drops risk contamination, and have even been implicated in infection and deaths (CNN 2023). An alternative to conventional eye drops, that poses less risk of infecting the eye, and that can provide people with a different way to moisten the eyes would be very desirable.

[0023] There are many reasons why others have been directed away from considering the use menthol in the realm of eye care. In general, over-the-counter menthol-containing products emphasize that the products can cause pain to the eyes. Most menthol-containing products come with warnings to avoid eye contact, and to wash it out if contact does occur (SingleCare 2023; Poison.org 2023). The United States Food and Drug Administration (FDA) publishes warnings about severe burns associated with topical products that contain menthol alone or in combination with other active agents (Research 2019). However, those burns are attributable to menthol's pain-suppressive effect, which can mislead people to apply excessive heat to the skin in an effort to relieve joint pain. The external heat applied causes burn, but the menthol per se is not the primary cause of the burn.

[0024] Menthol has been used in pain experiments. These clinical trials involved 400 mg menthol applied in 1 mL ethanol (i.e. 40% menthol), onto a 3x3 cm (9 cm^2) area of the skin, with a covering of gauze to lessen the evaporation of ethanol during the 20 minutes of exposure. After 20 min of exposure to menthol, the gauze was removed, and the skin was used as a model for testing hyperalgessia, or enhanced intensity of pain sensation (Binder et al. 2011; Wasner et al. 2004; Mahn et al. 2014). The local application of 40% menthol "induced spontaneous pain" locally, that was measured subjectively, as sensation, averaging 8 to 20, depending on the study, on a pain scale ranging to 100. This mild sensation has been referred to as "without any relevant spontaneous pain" (Mahn et al. 2014). Those studies reporting a spontaneous pain effect due to menthol caused that pain by applying an extremely high dose, 44 mg menthol per cm^2, and then sealing it there for 20 minutes to prevent evaporation. In contrast, the present method, at its most severe, applies 40% menthol in 30 milligrams petroleum jelly vehicle (400 mg/gram=12 mg/30mg), onto a skin area of about 2 cm^2, which means that the present invention's highest dose onto skin surface equals about 5.2 mg per cm^2. Therefore, the present invention involves an amount of menthol per square centimeter, nearly an order of magnitude less than what was used for the

menthol pain model; furthermore, the present invention promotes, rather than restricts, evaporation.

[0025] Arita et al. state in the publication of their clinical trial, that using eye pads containing menthol, but without the additional pre-heating of the pads, had no effect on tear meniscus volume (Arita et al. 2017). Lam et al. have reiterated Arita's statement that in the absence of additional heat, menthol alone had no effect on tears (Lam et al. 2020).

[0026] Ahn et al. published results of rat experiments that compared commercial eye drop preparations that were with and without menthol. They claimed that there was "ocular surface damage" in the animals treated 5 times daily with the menthol product versus the non-menthol product (Ahn et al. 2018). That claim of damage was not based on any direct assessment of the cornea, nor did they offer any evidence for their interpretation that their rats' tear lactate dehydrogenase (LDH) enzyme level might reflect surface damage. Ahn falsely claimed that LDH was a marker for eye tissue injury. LDH is not a marker of eye damage because a study of intentional corneal trauma to human subjects did not alter LDH activity in their tears (Fullard and Carney 1984). In humans, levels of LDH in tears fluctuate widely over the course of every day, with the levels highest when measured during sleep or after eyes are closed (Fullard and Carney 1984).

[0027] In summary, the evidence of menthol's ineffectiveness in tear production, as cited above was probably the result of concentrations and dosages of menthol that were too low to elicit a tearing response in humans. The research reports of no efficacy, together with the thinking that improperly handled menthol preparations cause skin pain and eye pain or even eye damage, have steered interest away from menthol as a clinically useful ingredient in the context of eye care.

PRIOR RELATED ART

[0028] An oily base has been described, that is designed to be applied by rubbing it onto the surface of the skin of the eyelids themselves, to deliver an active agent by penetrating to the eye through the skin of the eyelids. In Table 1, page 17, Tojo and Kimura list a composition that includes a composition of beeswax and isopropyl mysrstate with 5% menthol by weight (Tojo and Kimura 2010). Tojo and Kimura proposed that eye medications could be applied to the skin of the eyelids, and thereby penetrate through the skin to the eye itself. The present compositions and method of

the present invention differ substantially from Tojo and Kimura: 1. the location of the application of the medication onto the cheeks, 2. the eyes need to be kept open to deliver the menthol to the eye and 3. the menthol reaches the eyes as a vapour carried by the air passing the surface of the open eye, 4. no additional ingredient like isopropyl mysrstate is needed to deliver active agent through the skin. None of these features of the present invention was described by Tojo and Kimura.

[0029] In a completed clinical trial (ORA, Inc. 2018; at www.clinicaltrials.gov) sensitivity to stimulation of cold receptors by menthol was assessed. The pre-specified list of outcome objectives for that trial did not include anything related to tear production due to the use of menthol-containing eye drops (Rohto Hydra(R), containing 0.01% menthol). Instead, the clinical trial showed that dry-eye-disease patients had greater sensitivity to cool from using the drops than did unaffected, control subjects (Corcoran et al. 2017). The Rohto Hydra(R) eye drops commercial product with menthol that was used in the clinical trial includes no health claim in the context of menthol; the menthol is listed as one of the inactive ingredients.

[0030] Commercial eye-care products such as gels or creams containing active ingredients, for example, Systane (R) Nightime, are intended for application under the eyelids prior to sleep (Systane 2023). However, the prior art does not describe the administration of menthol or any other active agent to the skin of the body at the cheekbone, where bottom rims of glasses are located, well away from the eye, and where the active agent is delivered as a vapour that moves to the eye via the air passing the cornea.

[0031] To cause the appearance of crying, actors are known to use irritants to the eyes such as vapour from onions or camphor. Kryolan's Tear Stick is a wax stick in a lipstick mechanism that comprises menthol and camphor extracts (Sempionatto et al. 2019; Kryolan 2023). These products are applied at the bottom of the eye socket, to the skin below the lower eyelashes. The menthol-containing lipstick-style product by Narrative Cosmetics, to apply at the bottom of the eye socket, is described in the promotional material as causing tearing by “irritation” (Narrative 2023). These products are for use by actors to temporarily simulate crying by irritating the eyes’ pain receptor mechanism. The user feedback at Amazon.com about the Narative Cosmetics Tear Stick is mixed, with many users reporting no effect on tearing. Similarly, Blistex(R) LipMedex, a product marketed for chapped-lips that contains 1% menthol, also elicits

modest tearing when it is applied just below the lower eyelid. However, when Blistex(R) LipMedex was applied as described by the method of the present invention, it produced no effect (Example 10). Therefore, there is no reason to anticipate that the method described in this invention, i.e. to apply menthol farther from the eye socket, at the highest, most protruding point of the cheekbone, would be useful. Tear sticks are intended to cause eye irritation, and they are not intended to help with dryness of the eyes caused by the lack of blinking due to concentrating at computer work, or due to aging, or due to a primary disease.

[0032] Prior art that is similar to the present invention is an experiment involving human subjects onto whose cheeks was applied a preparation of menthol in concentrations as high as 10 mmol/L in paraffin ointment, to release menthol vapours over the eye (Kovács et al. 2016). Those authors detected no significant changes in the tearing rate. In contrast, the present invention does show efficacy of topical menthol, when it is applied in any of various described lipid formulations in which the menthol concentrations are two orders of magnitude higher than the highest concentration used in the prior art (Kovács et al. 2016). For example the present invention's composition of 20% menthol by weight in carrier lipid equals a menthol concentration of about 1.2 mol/L. In contrast, the highest menthol concentration used by Kovacs et al was only 0.01 mol/L (Kovács et al. 2016).

[0033] Commercial over-the-counter product pads that contain menthol include products such as Salonpas(R), that contains 3% menthol and 10% methyl salicilate. Those pads come with a warning of the risk of burns to the skin, and use near the eyes is discouraged. (FDA 2022).

[0034] One commercial product tested and which increased tearing when applied using the method of application at the cheekbone, under the lower rim of a pair of glasses, is Coldrops (R) (Vieth, Temovsky, and Vieth 2018) (Example 1). This cold remedy is intended to be taken by mouth, and consists of menthol in medium chain triglyceride. One drop of this product weighs 25 milligrams, and contains 5.42 mg menthol. One drop onto a finger can be usefully divided with the finger, applying it evenly between the two cheekbones under the eyes, providing a dose of about 2.5 milligrams menthol under each eye.

[0035] As will be shown in the following experiments that involve the method for application to the cheek, an ideal carrier for menthol is a "lotion bar". Generally, lotion

bars are bar-soap-like in appearance and texture, but they are softer than soap, and not water soluble. Lotion bars are typically composed of cocoa butter or shea butter, wax, coconut oil, and optional additives. Lotion bars are used as an alternative to skin-care creams or lotions in bottles. There are many permutations to formulations suitable for making lotion bars (Rose 2021; Limmatvapirat et al. 2021). The applicant has found that the highest menthol content in a commercially available lotion-bar-type of product is stated as 5% (ForestHills 2023).

[0036] The present disclosure provides a composition and method for increasing tear secretion of the eyes. The composition and method provide a simple and safe topical treatment for a dry eye condition.

[0037] The composition includes menthol and a carrier. For the present invention, various liquid and semi-liquid (i.e., petroleum jelly, or creamy compounds, soaps, and skin lotions and creams) vehicles can be used as the vehicle to apply menthol to the cheeks. Any vegetable, triglyceride oil, whether saturated or unsaturated oil, is suitable as a preparation to provide menthol at a preferable concentration range of 3% to 40% by weight, or more preferably menthol at 6% to 33% by weight.

[0038] One preferable preparation of the invention is a composition that consists of one part menthol crystals and four parts by weight of a formulation of lipids and fats that make up a "lotion bar" (Rose 2021).

[0039] The carrier may include at least one of plastibase, carboxyvinylpolymer, polyacrylic acid, sodium polyacrylate, cellulose derivatives, polyvinylalcohol, polyvinylpyrrolidone, polyacrylamide, alginic acid, sodium alginate, gelatine, polysaccharide thickener (e.g., gum arabic, tragacanth gum, guar gum, xanthan gum), glycerol, sorbitol, ethylene glycol and propylene glycol.

[0040] In an embodiment, the composition may be a lotion bar, with one part menthol and four parts lipids and fats by weight. Alternatively, the composition may be a liquid or a semi-liquid. The liquid or semi-liquid composition can be readily applied with a roller ball. In a further embodiment, the composition may be absorbed to an adhesive tape or to a scratch and sniff sticker, or it may be contained in a lip-balm style stick.

[0041] Referring to **FIGURE 1, 2** and **3**, a method for delivering the composition to the eye is to topically apply the composition to a user's cheek **10** below the user's eye

20. For example, the composition may be applied to the cheek prominence two to three cm **30** below the user's eye **20**, or the composition may be applied to the cheek below a bottom rim **30** of a pair of glasses **40** while the user is wearing the pair of glasses and continues to wear the glasses. The glasses **40** serve to increase a concentration of menthol vapour at a cornea of the user's eye **20**, to increase the potency of the composition.

[0042] Another method for delivering the composition to the user's eye is to topically apply the composition to the palm of the user's hand, cup the hand and hold the hand over or beside the user's eye to stimulate tear secretion. Likewise, simply holding the opening of a vessel containing the composition in front of or near the user's eye causes menthol vapor from the vessel to reach the cornea of the eye and thus to stimulate tear secretion without applying the composition directly to any part of the body.

[0043] Referring to **FIGURE 4**, a further method for delivering the composition to the eye is to apply the composition to a material **50** such as a small piece of tissue that is adhered, for example with a piece of tape **60**, to the bottom rim **30** of a pair of glasses **40** worn by the user. The user keeps the eye open, blinking as desired, and after a couple of minutes, tears are secreted.

[0044] For each of the methods of delivery, the outer surface of the cornea is the target of the menthol. Menthol escapes naturally as a vapour from its carrier lipid in the composition. The lipid vehicle stays at where it is applied to the skin, or in the vessel or material, while the menthol is released as vapour that reaches the cornea where it activates the TRPM8 receptors located at the exterior surface of the cornea, and which stimulate tear secretion.

[0045] When a total of 2 to 40 milligrams of the preparation is wiped onto the skin, the method delivers between about 0.06 mg to about 10 mg of menthol, the active agent, and is applied to an area of about 2 cm x 2 cm of skin of each cheek.

[0046] Another method of applying the composition is to provide the composition as a lotion bar, for example a lotion bar with one part menthol and four parts lipids and fats w/w. The user may use a fingertip to topically apply the lotion bar composition to the user's cheek or palm of the user's hand.

[0047] The advantage of using the lotion bar formulation described here is that this vehicle has a hardness and wipe-ability that makes it easy to take up a reproducible

and appropriate amount with a rub of the finger tip, and to apply this to the cheek or palm of the hand by rubbing the finger there. The surface area of the finger tip limits the amount of menthol-lotion bar taken up. Unlike softer preparations such as creams or petroleum jelly, slightly more pressure or more rubbing of the lotion bar with the fingertip does not increase the uptake of menthol beyond that taken by gentle rubbing. Compared to menthol in a harder, wax-like vehicle, such as pure beeswax or paraffin, the lotion bar preparation makes it easier to take up the menthol from the container and to rub the menthol preparation from the finger onto the cheek or palm of the hand without leaving much of the preparation still on the finger. Rubbing a wax onto the cheek or palm of the hand is comparatively difficult to do, since waxes are sticky and not smooth, and the wax leaves a good proportion of product on the finger.

[0048] With the 20% menthol, 80% lotion bar composition, the average weight of product taken up onto the skin of the tip of a finger is 3.1 milligram (Example 9). In other words, when using the preferred composition and method described here, one rub of the finger (rub with moderate pressure of about 60 grams, three times around in a circle of about 2.5 cm diameter) takes up a menthol amount that is about 20% of 3.1 milligrams, which equals about 0.6 milligrams of menthol applied to the cheekbone under one eye. Likewise, if a 3% menthol, 97% lotion bar composition is used, then about 0.09 milligram of menthol is applied to the cheekbone under one eye.

[0049] Another method is to topically apply menthol in oil by using a roll-on applicator, rolling along about 2 cm of skin, at the prominence of the cheekbone or palm of the hand.

[0050] In still another method, the composition may be applied to an adhesive tape and the adhesive tape placed on the user's cheek. The composition may be applied to a 25 millimetre length of 24 millimetre cellophane tape, onto which a finger touch from the 20% menthol in lotion bar is wiped. Simply stated, the composition of this invention is applied to a section of cellophane tape with a menthol preparation wiped onto it. This composition is then applied like tape across each cheek bone. The advantage of this menthol-on-tape format is that there is no cooling sensation at the cheeks, and the effect is longer lasting, like a slow-release product, because there is less warming of the menthol composition by the skin, thereby slowing the release of menthol vapour.

[0051] An alternative approach to a format involving tape or a sticker is use of menthol-containing Scratch and Sniff stickers, applied at the highest point of the cheekbone under each eye. The composition may be provided on a scratch and sniff patch or sticker and the sticker is applied to the user's cheek. When the tape or sticker is applied to the skin, then menthol, the active agent, is released by scratching the patch to release the vapour.

[0052] The composition may also be applied from a lip balm-style stick.

EXAMPLES

Example 1 – Method of use to cause tear secretion

[0053] A person familiar with the concept that menthol possesses anesthetic properties attempted to lessen the pain of a severe migraine or sinus headache by spraying one spray of a commercial menthol aerosol preparation (Coldrops Mister TM; menthol in medium chain triglyceride oil. The sprayer delivered18 mg menthol per 133 microliter spray (Vieth, Temovsky, and Vieth 2018)) directly into each nostril. The spray is intended to be sprayed into the mouth for cold relief. The result of spraying up the nose was that the procedure induced an intense sinus burning sensation and an acute worsening of headache pain, consistent with what had been reported before (Eccles 1994). However, after about ten minutes, the headache pain was much reduced from the baseline as had been predicted for use of any agonist of the TRPM8 receptor (Dussor and Cao 2016). More importantly for the present invention, the intranasal spray of menthol caused intense tearing. That experience, along with the subsequent awareness of the clinical trial of Arita et al (Arita et al. 2017; Arita and Fukuoka 2020), and that innervation is shared between sinus mucosa and the eyes, stimulated further investigation by the inventor into the feasibility of using menthol for dry eyes. One single drop of a menthol solution in medium chain triglyceride (containing 5.2 mg menthol per 25-mg drop physically dispensed from a Eurodropper, or 21% menthol wt/wt) was applied to a finger and the drop was gently divided by touching the finger, evenly onto each cheekbone, thus placing about 2.5 mg menthol per side. Specifically, the menthol composition was applied onto the skin covering the convex surface of the zygomatic bone, at the bony prominence of the cheek. In other words, a person at a computer and with dry eyes, applied the composition under each eye, just under the spot where the bottom rim of reading glasses is normally located. Tear formation, or

pain or discomfort were monitored after applying the menthol-containing oil. The result was tear formation, increased blinking because of the presence of tears, and the area of topical application on the skin of the cheek felt cool, with no sense of pain. Monitoring for the next half hour detected no further sense of dry eyes.

Example 2 – Effects of application location and posture

[0054] A method of application to the skin immediately above the eyebrows was tested. The 21% menthol in 79% medium chain triglyceride wt/wt composition of Example 1 and 2 was tested for tear production, but by applying one drop each to the skin just above each eyebrow, about two centimeters above the top eyelid when open. There was no tearing produced from this procedure. The only evident sensation was that of cool skin above each eyebrow. After five minutes without tearing effect, a clean finger was rubbed over the remaining oil that had been placed above each eyebrow, and much of the composition was able to be transferred to the cheeks, two to three centimetres below each eye. This procedure of moving the menthol oil from above the eyebrows down to the cheeks then caused tearing, i.e. a drop of tear appeared below lower eyelash within one to two minutes. This experiment emphasizes that menthol is carried by convection upward, in an anti-gravity direction. There is no effect if that convectional movement of menthol is in a direction away from the cornea.

[0055] A subsequent test of a method was carried out by placing the 20% menthol, 80% medium chain triglyceride (wt/wt) composition within only one centimeter of the lower eyelid, near the bottom of the eye socket, resulted in pain at the eye. This was because once an aqueous tear connected with the menthol in oil, the menthol was able to float up the short length of tear and it reached the eye by direct contact, and that caused pain.

[0056] A further test involved application of the 20% menthol, 80% medium chain triglyceride (wt/wt) composition to skin of the palm of a hand, which was then held cupped and held beside or facing an open eye. That method elicited tear secretion, but without sensation of cold at the cheek or at the palm where the composition was applied.

[0057] The method of application, to apply 20% menthol by weight, in medium-chain triglyceride, farther from the eye, to the skin at the most protruding part of the cheekbone without wearing glasses, but while lying supine, resulted in no effect on

tearing. This finding confirms the need to consider the directional effect of air convection due to body heat to ensure that air carries the menthol vapours across the cornea.

[0058] These experimental results show that the ideal method of placing the menthol is to keep it well below and away from the eye, ideally at the location of the lower rim of glasses, or on a cupped hand over the eye. After placing the menthol, the person's face is kept vertical in still air. This method benefits from the natural convectional flow of air up the face due to the heat of the body. This method delivers menthol vapours across the cornea, while maintaining enough distance from the eye to prevent dissolved menthol oil from floating up a tear to reach the eye thereby causing pain by direct contact.

Example 3 – Effect of wearing glasses.

[0059] Menthol vapours arising from the menthol-in-oil solution above was wiped onto the skin of the cheeks at the protruding part of the cheekbone, about three centimeters below the lower eyelids stimulated tear formation, to the point that one or more tears rolled down each cheek within four minutes. A composition that was 21% menthol in medium-chain-triglyceride, was used with the method of Example 1. But this time, the method was done while the user was wearing reading glasses. The tearing response was more rapid and more intense with glasses on. Taking off the glasses, or moving around in a room, both which increase air flow around the eyes, moderated the potency of the menthol vapours at the eyes. The user's cheeks felt particularly cool as the tears washed menthol further down the cheeks, but there was no perception of pain or irritation reported. There was a natural increased rate of blinking due to the presence of tears on the eyes after the menthol was applied to the cheeks. If the user's eyes were dry and painful before applying the one drop of menthol below the eyes, then the result of exposure to the menthol vapour was reasonably described as pleasant. If the eyes were kept closed during the five minutes after the dose was applied, then there was no apparent increase in tearing.

Example 4 – Petroleum jelly as a vehicle for menthol

[0060] Petroleum Jelly containing 20% menthol wt/wt was prepared by liquifying the mixture at 60 degrees centigrade. This was mixed in a beaker by swirling

it and allowing to re-harden at room temperature. A clean finger was rubbed gently on the top of the menthol/petroleum jelly preparation (20% wt/wt) on six separate occasions, and the change in beaker weight recorded after each occasion. The average (+/- SD) weight of the preparation taken up by the finger was 19 milligrams(+/-6). That meant that after wiping the top of the menthol in petroleum jelly, there was about 4 milligrams of menthol, taken up onto the finger. The weight of menthol taken by wiping the petroleum jelly preparation was difficult to regulate, and the amount could be affected by the finger pressure applied to the surface. Wiping the preparation at the cheekbone about 3 centimeters below the lower eyelid elicited a drop of tear to drip from the eye.

Example 5 – Coconut oil as vehicle for menthol

[0061] Menthol was prepared in liquid coconut oil at 27 degrees centigrade (by weight, 20% menthol, 80% coconut oil). This was tested in its semi-solid waxy form after storage in a refrigerator (4 degrees centigrade). A single touch of the finger was made at the surface of the semisolid, and applied as just one wipe evenly shared to both cheeks. Likewise, this composition was tested as a liquid at room temperature, by gently dipping a finger at the surface of the solution and dividing the drop with gentle touches to each cheek. Both strategies caused at least one tear to flow down each cheek within four minutes of application while the subject was working at a computer. This was repeated both while wearing glasses, as well as without glasses.

[0062] The above testing processes were repeated with a lower-dose composition (10% menthol, 90% coconut oil). Whether the drop of the preparation was taken from the liquid form by a touch of the finger to the liquid or taken from the cooled semisolid form of coconut oil by finger wipe, the tearing effect was present using 10% menthol, but the effect was milder than with the 20% preparation.

Example 6 – Olive oil as vehicle for menthol

[0063] Olive oil, which is a vegetable oil comprised of long-chain triglycerides, was used at 20% menthol and 80% olive oil w/w. This composition was tested as a liquid at room temperature, by gently dipping a finger at the surface of the solution and dividing the drop with gentle touches to each cheek onto the skin under the bottom rim of reading glasses. At least one tear to flowed down each cheek within four minutes of

application while working at a computer without wearing glasses. When the method was carried out while wearing glasses the tearing effect was more rapid and more intense.

Example 7 – Beeswax as vehicle for menthol

[0064] Bees wax containing 20% menthol wt/wt was prepared by heating bees wax and menthol crystals to 70 degrees centigrade, this was mixed to homogeneity in a beaker by swirling it, and allowed to re-harden at room temperature. Accounting for the densities of menthol and beeswax, and their contributions to the total volume of the preparation, the concentration of menthol was 1.2 mol/Liter. A clean finger was rubbed on the top of the menthol in beeswax preparation on six separate occasions, and the change in beaker weight recorded after each occasion to quantify the amount taken onto the finger. The average weight taken by wiping beeswax with the finger was 2.5 milligrams, depending on the temperature of the bees wax containing 20% menthol wt/wt preparation and whether some of it was caught by a fingernail. The preparation was wiped at the most protruding point of the cheekbone, about 3 cm below the bottom eyelid. At least one tear to flowed down each cheek within four minutes of application while working at a computer without wearing glasses. The tearing effect was more rapid when the process was repeated while wearing glasses.

Example 8 – Use of tape barrier to prevent skin cooling sensation

[0065] The cooling sensation on the cheeks from the presence of menthol preparations applied directly to the skin of the cheek may be pleasant for some users, but other users may not like it. To create a barrier to minimize the cooling effect at the cheeks, a generic, perforated, Clear Plastic First-Aid Tape, 25 mm wide, was cut into lengths of about 20 mm. A finger was placed onto the surface of the 20% menthol in petroleum jelly (w/w). That finger dip lowered the weight of the 20% menthol/petroleum container by 13 milligram, indicating that there was 13 mg of the preparation on the finger. After the finger was wiped onto the tape, the weight of the tape increased by 9 milligrams, indicating that 1.8 milligram of menthol was transferred to the tape. Then the tape was placed onto the user's left cheekbone only, at its most protruding point, as described above. The user was working indoors, without glasses, at a computer. Tears fell from the eye, as expected, given the dose of menthol

applied. The cooling of the cheek was mild, or difficult to detect. After 5 minutes, the tape was pulled off and placed at the right cheek, under the other eye from which that menthol also produced a tear within 3 minutes. The same piece of tape was then placed onto the cheek of another person, who also reported increased tearing or wetness of the eye. The tearing effect due to the menthol-petroleum jelly preparation was evident for at least 20 minutes, although with steadily declining intensity.

[0066] The experiment of the preceding paragraphs was repeated, but using conventional 19 mm-wide, matte-finish cellulose tape from an office tape dispenser. A 50 mm pull of tape was taken, and it was placed onto a scale for measuring weight to the nearest milligram. The user gently dipped a finger onto the 20% menthol/petroleum jelly preparation, and wiped it onto the tape, thus increasing the weight of the tape by 10 mg, and indicating that there was 2 mg of menthol on the tape. At baseline time, zero minutes, the tape was applied onto the right cheekbone, where tears were produced as expected, but with minimally noticeable cooling effect at the cheek. After ten minutes, the tape was removed and placed on the cheek under the left eye, where it similarly induced tearing, with minimally noticeable cooling effect at the cheek. After a further ten minutes (i.e. 20 minutes after its initial application) the tape was placed under the right eye again, where it revived tearing within two minutes.

[0067] To measure the amount of tear formation, a Shirmer test strip was applied to the lower eyelid at four minutes after applying the 20% menthol/petroleum jelly preparation on tape, to assess tear production (at a total of 24 minutes after initial application). Within three minutes, the Shirmer strip was fully saturated with tears, beyond its 36 mm mark (normal readings are about 15 mm after 5 minutes). At 30 minutes after the initial application, the tape was moved back to the left cheek, at which there was no further increased tear production.

Example 9 – Lotion bar

[0068] The formulation for the lotion bar that was used for this experiment consisted of equal parts by weight beeswax, cocoa butter, and coconut oil. The ingredients, 4 parts by weight of lotion bar and one part menthol, are dissolved by combining all the ingredients in a screw-top vessel, and heating in an oven preset to 70 degrees Celsius (158 F) to melt the ingredients, which are then gently mixed to make it homogeneous. The liquid is decanted into suitably sized, screw-top containers, and

returned to room temperature to harden. The molar concentration of 20% menthol in 80% oil (by weight) is about 1.2 mol/liter, varying slightly depending on the specific gravity of the lipids used. To use this composition, the very tip of a finger was rubbed lightly across the surface of the menthol-lotion-bar preparation, taking care not to catch any preparation on a fingernail. That tip of the finger is then rubbed onto the skin over the most protruding part of the cheekbone, the bony prominence of the cheek, just below where the bottom rims of reading glasses are normally located on the face. The composition is spread to an area of about 2 cm by 2 cm, which equals about 4 square centimetres. This application was repeated for the other side.

[0069] The results of testing different menthol percentages in lotion bar was tested ranging from 3% to 32% (Table 1). Use of the 20% by weight menthol in lotion bar, together with the method described increases tear secretion within minutes, to the point of saturating a Schirmer test strip for tear production, to beyond its measurement range. A Schirmer test strip is an absorbent paper strip with millimeter markings that is inserted for 5 minutes under the lower eyelid as an index of the amount of tear production. The tearing effect can be lessened by the user simply by increasing air circulation around the face, or by wiping the composition off the cheeks.

[0070] Table 1. Dose responses of tear-producing effect.

Dose Menthol % In Lotion Bar	Tear Response With Direct Onto Skin	Tear Response If On Tape Applied to Skin
3%	Skin Cooling, no tear	nothing detectable
6.7%	Tearing	nothing detectable
20%	saturated Schirmer strip	tearing
32.4%	saturated Schirmer strip	saturated Schirmer strip

Footnote: Tip of finger wiped across surface of lotion bar (about 3 mg taken up) and wiped directly onto the skin of cheekbones, below the bottom rim of reading glasses, or onto tape that is applied at the skin located at the bottom rim of reading glasses, and with the user wearing glasses during observation. A fresh, dry Schirmer strip weighs 17 milligrams, but saturation with tears increases its weight by 33 milligrams.

Example 10 – Lotion bar onto tape

[0071] The experiment was repeated using 6.7% menthol in lotion bar, taken onto a fingertip by rubbing the lotion bar surface for about three seconds, after which the fingertip was rubbed onto a 2x2 cm piece of medical tape which was immediately applied to the cheek location under the bottom rim of a pair of reading glasses. With glasses on, the Schirmer's test result was, 14 mm. Control, normal values were 12 and 16 for the study subject. Thus, no effect on increased tear secretion if 6.7% menthol was applied onto the tape, due to diminished menthol vapour concentration released with the tape.

[0072] The same procedure, with glasses on, was repeated, but for each eye, using a rub of 20% menthol in lotion bar applied to the a medical tape. A tear fell from each eye within 5 minutes. When a tear falls from the eye, the Schirmer strip is saturated, giving a reading exceeding the end of the 35 mm range of Schirmer-strip measurement and the tear-saturated test strip weighs 52 milligrams.

Example 11 – Use of roller-ball applicator formats

[0073] A roll-on version of the applicator was evaluated. Conventional, 10-ml Glass Roller Bottles with Stainless Steel Roller Balls that are typically used for scented oils were evaluated. Two milliliters of a composition consisting of menthol, 20% by weight in medium chain triglyceride oil was placed into conventional 10-ml clear glass bottles capped with stainless steel roller balls. The roller ball is simple, it can deliver a small dose. Measurements of weight change when the roller was applied to an area about 2 centimeter by 2 centimeter along the skin under the lower rim of reading glasses indicated about 3 milligrams of the menthol in medium chain triglyceride composition was applied under each eye. Without the menthol, the subject's 5-minute Schirmer test result was 18 millimeters. With the application of 20% menthol in medium chain triglyceride oil (weight per weight) the Schirmer test strip was saturated beyond 35 millimeters by 2.5 minutes. A lesser effect was obtained with lower amounts of menthol applied. The roller-ball composition was also used whereby the method involved applying the composition to the palm of a hand, which is then held cupped and held about 2.5 cm over or beside an open eye to release vapor and to stimulate tear secretion.

Example 12 – Evaluating method using commercial menthol lip balm

[0074] A commercially available lip balm style stick, Blistex(R) MedEx, that contains 1% menthol was wiped onto the cheek at the skin under the position of the lower rim of reading glasses. Despite some local skin cooling sensation at the application site, there was no effect on tearing, as measured by Schirmer test. However, when the Blistex MedEx was applied just below the lower eyelashes, to the skin at the bottom of the eye socket, then tearing occurred along with pain.

Example 13 – Menthol-Lotion bar in lipstick format

[0075] Lotion bar compositions of Example 9 that contained 6.7% to 32.4% menthol by weight were prepared in lip-balm-style sticks that were capped until use. The product was wiped horizontally along the cheekbone according to the method at the cheek at the location under the bottom rim of a pair of reading glasses to elicit tear secretion.

Example 14 – Lotion bar in vial held near eye

[0076] Lotion bar compositions of Example 9 that contained 6.7% to 32.4% menthol by weight were prepared in vials with openings of 3 centimeter to 4.5 centimeters. The optimal vial had a 4.4 centimeter opening, a total volume capacity of 100 milliliters, and contained 20 grams of 32% menthol/lotion bar w/w, The lid was removed and the rim of the vial opening held near or touching the orbit of the eye, that is, under or in front of an open eye. Tear secretion was evident within two minutes, at which point the vial removed from the eye and recapped.

Example 15 – Menthol composition on tissue adhered to bottom of glasses.

[0077] Two drops of 20% menthol in medium-chain triglyceride (w/w) were applied to a small piece of facial tissue and adhered with a piece of tape to the bottom rim of a pair of glasses as shown in FIGURE 4. Tear secretion was evident within three minutes, and when the tissue was removed from the glasses, there was no further sense of cooling.

Example 16 – Further examples of lipids suitable for the composition

[0078] Suitable vehicles for the present invention include oily solvents that are semi-solid at room temperature, such as the fats used for lip balms. These vehicles are generally referred to as waxes. To produce a wax-based form of the present invention,

the menthol crystals and the solvent wax are heated to a temperature just above that of the highest-melting-point fat in the composition, and mixed. The solution or mixture is transferred to an appropriate small tin, or a mold to form a stick format by allowing it to return to room temperature to become a wax. The menthol in the semi-solid stick or wax formulation is applied to the cheekbone, at the area where the bottom rim of a pair of glasses is normally located. The compound is rubbed onto the front of the face, at the highest point of the cheekbone.

[0079] By way of further examples of wax-based forms that are reasonably suitable for the present invention, I include natural waxes such as vegetable waxes (e.g., carnauba wax, Japan wax, canderilla wax), animal wax (e.g., beeswax, whale wax, wool wax), petroleum wax (e.g., paraffin wax, microcrystalline wax), mineral wax (e.g., montan wax, ozokerite), synthetic wax (e.g., carbowax), and the like, vaseline, lanoline, hydrogenated rosin/glyceryl diisostearate, hydrogenated polyisobutene, polyethylene, fatty acid cholesteryl, higher fatty acid esters (e.g., isopropyl myristate, isopropyl palmitate, oleic acid propylene glycol, hexyl laureate, decyl oleate, glyceryl monostearate), aliphatic alcohols (e.g., cetyl alcohol, isostearyl alcohol, lauryl alcohol, oleyl alcohol), squalene, squalane, polyethyleneglycol, higher fatty acids (e.g., isostearic acid, lauric acid, oleic acid, linoleic acid, linolenic acid), animal oils (e.g., lard), vegetable oils (e.g., castor oil), and the like, but any of the bases that can form solid pharmaceutical preparation, as well as a combination of them, may be employed. Among these bases, a particularly preferred example is a combination of an oily solid base such as waxes, vaseline or squalane with a higher fatty acid ester such as isopropyl myristate or isopropyl palmitate. Among them, higher fatty acid esters such as isopropyl myristate and isopropyl palmitate.

[0080] Various other ingredients may be employed in the base in order to control the nature of the semi-solid preparation. Examples of such ingredients include plastibase, carboxyvinylpolymer, polyacrylic acid, sodium polyacrylate, cellulose derivatives (methylcellulose, propylcellulose, hydroxy ethylcellulose, hydroxypropylmethylcellulose and the like), polyvinylalcohol, polyvinylpyrrolidone, polyacrylamide, alginic acid, sodium alginate, gelatine, polysaccharide thickener (e.g., gum arabic, tragacanth gum, guar gum, xanthan gum), glycerol, sorbitol, ethylene glycol, propylene glycol and the like.

[0081] Although the invention has been described with a preferred embodiment, it should be noted that the inventor can make various modifications, additions and alterations to the invention without departing from the original scope as described in the present disclosure.

WHAT IS CLAIMED IS:

1. A composition for topical application to increase tear production, the composition comprising:

menthol; and

a carrier

wherein the menthol comprises at least 5% of the composition w/w; and

the carrier comprises at least one of:

a triglyceride oil;

a medium chain triglyceride;

petroleum jelly;

coconut oil;

cocoa butter;

shea butter;

olive oil;

beeswax;

a wax that is semi-solid at 21 C;

a vegetable wax;

an animal wax;

a petroleum wax;

a mineral wax;

a synthetic wax;

vaseline;

lanoline;

hydrogenated rosin/glyceryl diisostearate;

hydrogenated polyisobutene;

polyethylene;

fatty acid cholesteryl;

higher fatty acid esters;

aliphatic alcohols;

squalene;

polyethyleneglycol;

higher fatty acids;

animal oil; and

vegetable oil.

2. The composition of claim 1, wherein the menthol comprises 5% to 40% by weight, or more preferably 6% to 33% by weight of the composition.

3. The composition of claim 1, wherein the carrier further includes at least one of:

plastibase;

carboxyvinylpolymer;

polyacrylic acid;

sodium polyacrylate;

cellulose derivatives;

polyvinylalcohol;

polyvinylpyrrolidone;

polyacrylamide;

alginic acid;

sodium alginate;

gelatine;

polysaccharide thickener (e.g., gum arabic, tragacanth gum, guar gum, xanthan gum);

glycerol;

sorbitol

ethylene glycol; and

propylene glycol.

4. The composition of claim 1, wherein the composition comprises a lotion bar of 5% to 40% menthol and remaining percentage comprises lipids and fats w/w.

5. The composition of claim 1, wherein the composition comprises a liquid or a semi-liquid for application contained in a vessel capped with a roller ball applicator for delivery onto skin.

6. The composition of claim 1, wherein the composition is absorbed to a tissue or adhesive tape.

7. The composition of claim 1, wherein the composition is absorbed to a scratch and sniff sticker.

8. The composition of claim 1, wherein the composition is contained in a lip-balm-style stick.

9. A method for increasing tear production, the method comprising:

delivering a composition including menthol and a carrier to a user's eye,

wherein the menthol comprises at least 5% of the composition w/w; and

the carrier comprises at least one of:

a triglyceride oil;

a medium chain triglyceride;

petroleum jelly;

cocoa butter;

shea butter;

coconut oil;

olive oil;

beeswax;

a wax that is semi-solid at 21 C;

a vegetable wax;

an animal wax;

a petroleum wax;

a mineral wax;

a synthetic wax;

vaseline;

lanoline;

hydrogenated rosin/glyceryl diisostearate;

hydrogenated polyisobutene;

polyethylene;

fatty acid cholesteryl;

higher fatty acid esters;

aliphatic alcohols;

squalene;

polyethyleneglycol;

higher fatty acids;

animal oil; and

vegetable oil.

10. The method of claim 9, wherein delivering the composition to the user's eye comprises at least one of:

topically applying the composition to a user's cheek below the user's eye;

topically applying the composition to a user's palm of the hand, cupping the hand and holding the hand over or beside the user's eye;

holding the user's open eye within two centimeters from an opening of a vial containing the composition in a semisolid form; and

applying the composition to an absorptive material and adhering the absorptive material to a bottom of a pair of glasses worn by the user.

11. The method of claim 10, wherein applying the composition to the user's cheek comprises applying the composition to the cheek prominence two to three centimeters below the user's eye.

12. The method of claim 10, wherein applying the composition to the user's cheek comprises applying the composition to the cheek below a bottom rim of a pair of glasses while the user is wearing the pair of glasses.

13. The method of claim 12, further wherein the user continues to wear the glasses so as to increase a concentration of menthol vapour at a cornea of the user's eye to increase potency of the menthol vapour.

14. The method of claim 9, wherein the carrier further includes at least one of:

plastibase;

carboxyvinylpolymer;

polyacrylic acid;

sodium polyacrylate;

cellulose derivatives;

polyvinylalcohol;

polyvinylpyrrolidone;

polyacrylamide;

alginic acid;

sodium alginate;

gelatine;

polysaccharide thickener (e.g., gum arabic, tragacanth gum, guar gum, xanthan gum);

glycerol;

sorbitol

ethylene glycol; and

propylene glycol.

15. The method of claim 9, wherein the menthol comprises 5% to 40% by weight, or more preferably 6% to 33% by weight of the composition, and delivering the composition comprises applying 0.06 mg to 10 mg of menthol to an area of 2 cm by 2 cm of skin of each user's cheek.

16. The method of claim 10, wherein the composition comprises a lotion bar of five percent to forty percent menthol and remaining percentage parts lipids and fats w/w and topically applying the composition comprises applying the lotion bar composition with the user's fingertip.

17. The method of claim 10, wherein topically applying the composition comprises applying the composition using a roller ball.

18. The method of claim 10, wherein topically applying the composition to a user's cheek comprises applying the composition to an adhesive tape and placing the tape on the user's cheek.

19. The method of claim 10, wherein topically applying the composition to a user's cheek comprises applying the composition as a component of a scratch and sniff sticker, and further wherein the sticker is applied to the user's cheek and the menthol is released by scratching the sticker to release the menthol.

20. The method of claim 10, wherein topically applying the composition comprises applying the composition from a lip-balm-style stick.