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[54] SEMIFLUORINATED COMPOUNDS AND THEIR COMPOSITIONS  
半氟化合物和其組合物

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### (54) SEMIFLUORINATED COMPOUNDS AND THEIR COMPOSITIONS

SEMIFLUORIERTE VERBINDUNGEN UND DEREN ZUSAMMENSETZUNGEN

COMPOSÉS SEMIFLUORÉS ET LEURS COMPOSITIONS

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**Description**

## FIELD

- 5 **[0001]** The present invention is in the field of compositions comprising semifluorinated compounds and their use in ophthalmic administration.

## BACKGROUND

- 10 **[0002]** Semifluorinated alkanes are compounds composed of at least one non-fluorinated hydrocarbon segment and at least one perfluorinated hydrocarbon segment. Linear, unbranched semifluorinated alkanes of the general formula  $\text{CF}_3(\text{CF}_2)_n(\text{CH}_2)_m\text{CH}_3$ , wherein n and m are integers denoting the number of carbon atoms of the respective segment are described for various applications, for example commercially for unfolding and reapplying a retina, for long-term tamponade as vitreous humour substitute (H. Meinert et al., European Journal of Ophthalmology, Vol. 10(3), pp. 189-197, 2000), and as wash-out solutions for residual silicon oil after vitreo-retinal surgery.
- 15 **[0003]** Semifluorinated alkanes of the formula  $\text{CF}_3(\text{CF}_2)_n(\text{CH}_2)_m\text{CH}_3$  are described in other applications.
- [0004]** WO 2011/073134 discloses solutions of ciclosporin in a semifluorinated alkanes of the formula  $\text{CF}_3(\text{CF}_2)_n(\text{CH}_2)_m\text{CH}_3$ , optionally in the presence of a co-solvent such as ethanol, wherein the semifluorinated alkane functions as a liquid drug delivery vehicle for ciclosporin for topical treatment of keratoconjunctivitis sicca.
- 20 **[0005]** WO2014/041055 describes mixtures of semifluorinated alkanes of the formula  $\text{CF}_3(\text{CF}_2)_n(\text{CH}_2)_m\text{CH}_3$  (which may be alternatively expressed as  $\text{F}(\text{CF}_2)_n(\text{CH}_2)_m\text{H}$ ). These mixtures are described to be ophthalmically applicable as tear film substitutes or for treating patients with dry eye syndrome and/or meibomian gland dysfunction. A nomenclature which is frequently used for semifluorinated compounds having linear and unbranched segments is  $\text{FnHm}$ , wherein F means a perfluorinated hydrocarbon segment, H means a non-fluorinated segment, and n and m define the number of
- 25 carbon atoms of the respective segment. For example, F3H3 is used for perfluoropropylpropane,  $\text{CF}_3(\text{CF}_2)_2(\text{CH}_2)_2\text{CH}_3$ , i.e. 1-perfluoropropylpropane. Semifluorinated alkanes of formula  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$  and compositions comprising  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$  however have not been described, in particular for ophthalmic applications. It is therefore an object of the invention to provide compositions comprising such compounds, in particular in respect of their use in compositions for use in ophthalmic applications.

## SUMMARY OF THE INVENTION

- 35 **[0006]** In a first aspect, the invention relates to a composition comprising  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ . In particular, the invention relates to such compositions, comprising at least about 80 wt% of  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$ , and in another aspect, to such compositions comprising up to about 25 wt% of  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ .
- [0007]** In another aspect, the present invention relates to compositions comprising said compounds in the form of clear, liquid solutions.
- 40 **[0008]** In still another aspect the invention provides a composition comprising  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$  for use in the treatment of dry eye disease and/or Meibomian Gland Dysfunction and any symptoms or conditions associated with these conditions.
- [0009]** In a further aspect, the present invention provides said composition for use in the treatment of dry eye disease and/or Meibomian Gland Dysfunction and any symptoms or conditions associated thereof comprising administering said composition topically to the lacrimal sac, into the lower eyelid, to an eye surface or to an ophthalmic tissue.
- 45 **[0010]** In a yet further aspect, the present invention provides a kit comprising compositions of the present invention held in a container which comprises dispensing means adapted for topical administration of the composition to the eye or ophthalmic tissue.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0011]**

Figure 1 is a graph depicting the evaporation time of compositions consisting of the compounds  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$  as a function of the percentage of the latter compound in the composition.

Figure 2 is a graph depicting the refractive index determined for compositions consisting of the compounds  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$  as a function of the percentage of the latter compound in the composition.

Figure 3 is a graph representing results obtained from an Ex vivo Eye Irritation Test (EVEIT) comparison of compositions of  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ , a hyaluronic standard reference and 0.01% BAC positive control.

## DETAILED DESCRIPTION OF THE INVENTION

**[0012]** In a first aspect, the invention relates to a composition comprising  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ .

**[0013]** The compound  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$  may also be referred to as 2-perfluorohexyloctane, based on the hydrocarbon alkane as the root. This compound features a stereocenter at the 2-alkyl position. As understood herein, the general formula encompasses both enantiomers, enriched mixtures of the two enantiomers, as well as the racemic mixture. The compound  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  may alternatively be referred to as 1-perfluorohexyloctane, or F6H8, following the nomenclature FnHm, wherein n is an integer representing the number of carbon atoms of the linear, unbranched perfluorinated segment and m is an integer representing the number of carbon atoms of the linear, unbranched hydrocarbon segment.

**[0014]** Particularly preferred compositions of the invention are those that comprise at least about 80 wt% of  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$ . In other embodiments, the compositions comprise of at least about 90 wt% or at least about 95 wt% or at least 97 wt% of  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$ . In another preferred embodiment of the invention, the compositions comprise up to about 25 wt% of  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ . In other embodiments, the compositions comprise up to about 10 wt%, or up to about 5 wt% or up to about 3 wt% of the compound  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ .

**[0015]** As used herein, the term wt % refers to the weight of a component as a percentage fraction of the weight of the composition determined as a whole. The term about preceding a parameter such as wt% includes the precise value as well as any value falling within the degree of variability usually observed in the measurement and determination of the parameter, including standard techniques and equipment known in the art and field.

**[0016]** In a further preferred embodiment, the compositions of the invention comprising of about 97 wt% of  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and up to about 3 wt% of  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ . In yet a further embodiment, the composition may comprise of about 98 wt% of  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and up to about 1 wt% of  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ .

**[0017]** The compositions comprising these semifluorinated alkanes as defined above are preferably in the liquid form, and are preferably formulated to be administered as a clear liquid solution. In this context, clear means the absence of dispersed solid or liquid particles which cause turbidity. In other words, such clear solution is a purely monophasic liquid system, except that minor and technically irrelevant amounts of particulate impurities may be present.

**[0018]** In optional embodiments, the compositions may be formulated to be administered as a gel, suspension, microemulsion, or a spray. Preferably, the compositions are provided in sterile form.

**[0019]** Moreover, the composition is preferably formulated as a liquid solution which exhibits a refractive index that is close to that of water which is 1.333 at room temperature (RT). In a particularly preferred embodiment, the refractive index of the liquid solutions is in the range of from about 1.30 to about 1.35 at 20 °C, as determined by refractometer.

**[0020]** The compositions as defined above may also comprise further excipients as required or as useful such as one or more acids, bases, electrolytes, buffers, solutes, antioxidants, stabilizers, and if required, preservatives. In one preferred embodiment, the compositions as described herein are substantially free of water and/or substantially free of a preservative, such as benzalkonium chloride.

**[0021]** In another embodiment of the present invention, the composition as described above is substantially free of the following: (a) a polymer (b) a perfluorinated compound, and/or (c) a dissolved pharmacologically active ingredient which is not a semifluorinated alkane. Such compositions are also preferably formulated as clear liquid solutions. In another embodiment, the composition as described in any of the embodiments herein may be substantially free of a pharmacologically active ingredient, in any form and which is not a semifluorinated alkane.

**[0022]** As understood herein, the term 'substantially free' in reference to a composition constituent refers to the presence of said constituent in no more than trace amounts and that if present in trace amounts the constituent provides no technical contribution to the composition.

**[0023]** Examples of polymers which are preferably absent in the compositions of the invention include silicone polymers (polymerized siloxanes), polyether polymers and fluorinated or perfluorinated derivatives thereof.

**[0024]** Examples of perfluorinated compounds, i.e. compounds in which all the hydrogen atoms are replaced with fluorine, and which are preferably absent in the compositions of the invention include perfluoroalkanes such as perfluorodecalin, as well as halogenated perfluoroalkanes such as perfluorooctylbromide.

**[0025]** The compositions of the invention are also substantially free of a dissolved pharmacological active ingredient which is not a semifluorinated alkane; as used herein, the term "pharmacological active ingredient" refers to any type of pharmaceutically active compound or drug, i.e. one that produces a pharmacological effect and that may accordingly be useful in the prevention, diagnosis, stabilization, treatment, or generally speaking, the management of a condition or

disease.

**[0026]** In a preferred embodiment, the composition according to the present invention essentially consists of  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ . Preferably the composition essentially consists of about 97 wt% of  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and up to about 3 wt% of  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ .

**[0027]** As used herein, the term "essentially consisting of" is so-called closed language, meaning that only the mentioned constituents are present. In contrast, the terms "comprise", "comprises" and "comprising" are used herein as so-called open language, meaning that further constituents may also be present.

**[0028]** The compounds of the invention as well as the compositions comprising these, even if free of other pharmacologically active ingredients, however have beneficial therapeutic effects at the site of administration.

**[0029]** The compositions as defined above are preferably formulated to have a dynamic viscosity of not more than 10 mPa·s, and preferably not more than 4 mPa·s, as determined under standard ambient temperature and pressure (25 °C, 1 atm). Preferably, the compositions have a dynamic viscosity of between 1 and 4 mPa·s. The viscosity of the compositions may be determined using any standard viscometer device known in the art, such as a glass tube or capillary viscometer.

**[0030]** The compositions as described herein may be used in medical applications, in particular for use in ophthalmology, and in particular in the topical administration to the eye, such as to the lacrimal sac, into the lower eyelid, to an eye surface or to any ophthalmic tissue or anatomy associated with the eye that may be made available for topical administration.

**[0031]** It has been found that the compositions of the invention are beneficial for use in the treatment of diseases and conditions which would benefit from stabilization of the tear film and tear film lipid layer and lubrication of the eye surface. Thus, the compositions of the present invention are especially suited in the treatment of dry eye disease (keratoconjunctivitis sicca) and/or Meibomian Gland Dysfunction (MGD) and any symptoms thereof or associated therewith.

**[0032]** Dry eye disease, also known as keratoconjunctivitis sicca, can be distinguished into two categories, namely aqueous deficient dry eye disease and evaporative dry eye disease. These conditions are not necessarily mutually exclusive. Aqueous deficient dry eye is typically observed in patients suffering from Sjögren syndrome, or those suffering from a lacrimal gland insufficiency, lacrimal duct obstruction or reflex hyposecretion. Evaporative dry eye disease on the other hand has diverse root causes and is associated with increased/abnormal evaporative loss of the tear film, for example as a result of meibomian gland disorders, eyelid aperture disorders, blinking disorders, or ocular surface disorders.

**[0033]** Symptoms of dry eye disease include dry, scratchy, gritty, sandy or foreign body sensations in the eye; pain, soreness, stinging or burning; itching, increased need for blinking, eye fatigue, photophobia, blurry vision, redness and inflammation of the eye tissue, excess mucus discharge and crusting/clotting, contact lens intolerance, and excess reflex tearing.

**[0034]** Meibomian Gland Dysfunction (MGD) refers to a condition where the meibomian glands do not secrete enough oil or when the oily secretions are of poor or abnormal quality. Often, the oil gland openings may become plugged up or obstructed so that less oil is secreted from the glands. The oil is secreted from the glands can be granular (crusty) or otherwise abnormal, and can cause irritation to the eye and eye tissues. In the early stages, patients are often asymptomatic, but if left untreated, MGD can cause or exacerbate dry eye symptoms and eyelid inflammation. The oil glands become blocked with thickened secretions. Chronically clogged glands eventually become unable to secrete oil, which may result in permanent changes in the tear film and dry eyes.

**[0035]** Symptoms of Meibomian Gland Dysfunction include dryness, burning, itching, stickiness/crustiness, watering light sensitivity, red eyes, foreign body sensation, chalazion/styes or intermittent blurry vision.

**[0036]** In a preferred embodiment, the compositions of the invention as described above are used for the topical ophthalmic treatment of evaporative dry eye disease and or Meibomian Gland Dysfunction (MGD), and for the treatment or prevention of any one of the symptoms or conditions associated thereof. In another embodiment, the compositions as described herein may be used as a lubricant of the eye surface, so as to ameliorate one or more of the symptoms associated with dry eye disease and to wet the eye surface.

**[0037]** In another preferred embodiment of the invention, the compounds and compositions thereof as described above are used for the topical ophthalmic treatment of corneal damage. Thus, said compounds and compositions are actively supporting the corneal healing process of corneal damage, such as corneal erosions.

**[0038]** In further embodiments, the treatment of the above described conditions (e.g. corneal damage) and diseases, and their associated symptoms, also as described above is preferably carried out by a method of administering to a patient in need thereof, an effective amount of a composition as described above, comprising  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ , for example wherein the composition comprises up to about 25 wt% of  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ .

**[0039]** The advantages of the compounds and compositions described above in the context of their use according to the present invention, are believed to relate to their properties which are particularly suited for ophthalmic applications. The close proximity of the refractive indices of the compounds of the invention to that of water, means that there would

be no or minimal impact of a patient's vision subsequent to administration, unlike ophthalmic compositions based on oily carriers which can confer blurry vision on administration. The generally low viscosity and low surface tension and in particular their high wetting and spreading capabilities of these compounds also ensures that they are rapidly accommodated and adapted on administration over the surface of the eye.

[0040] As will be made clearer in the examples below, it was found that the compositions of the invention are biocompatible and exhibit no apparent cytotoxic effects. Moreover, it has been established that these compositions are not only well tolerated in the eye and has no impact on visual acuity, but also provide a beneficial effect in terms of lubrication of the eye and stabilization of the tear film, in the form of relief in symptoms of patients having mild to moderate symptoms associated with dry eye disease. Patients with dry eye disease and/or dysfunctional meibomian glands often express opaque and thicker meibum which can lead to an abnormal lipid layer in the tear film. Without wishing to be bound to theory, it is believed that the physicochemical attributes of the compounds featured in the compositions of the invention may play a role in stabilizing the lipid layer of the tear film, such as by solubilization of certain lipid components or improving the fluidity of the lipid layer, as well as provide a lubricating effect on the eye

[0041] In a further aspect, the present invention provides a method for treatment of dry eye disease and any symptoms or conditions associated thereof comprising administering the compositions of the present invention topically to the lacrimal sac, into the lower eyelid, to an eye surface or to an ophthalmic tissue. Preferably, said compositions can be administered to the eye or eye tissue up to four times per day.

[0042] Furthermore, the invention provides for a kit comprising any one of the compositions as described above, and a container for holding said composition. Said container preferably comprises a dispensing means adapted for topical administration of the composition to an eye sac, lower eyelid to an eye or ophthalmic tissue, such as an eye dropper.

[0043] In a further preferred embodiment, the dispensing means comprises a dropper of dimensions such as to dispense droplets having a volume of 8 to 15  $\mu\text{L}$ , preferably of about 8-12  $\mu\text{L}$ , more preferably of about 10  $\mu\text{L}$ . With a small droplet volume, precise dosing to the eye can be achieved and an excess amount of discharge of a substantial fraction of the composition from the eye subsequent to administration can be avoided.

[0044] The compositions of the invention moreover can be administered to the eye or eye tissue up to four times per day; preferably with one drop (ca. between 8 to 15  $\mu\text{L}$  in volume) administered per eye, and per dose. Treatment may last up to at least six weeks. In one embodiment of the invention, the compositions is administered at a dose of 1 drop of about between 8 to 15  $\mu\text{L}$  volume, preferably of about 10  $\mu\text{L}$  volume to each eye three to four times per day.

## EXAMPLES

### Preparation of $\text{CF}_3\text{-(CF}_2)_5\text{-CH(CH}_3\text{)-(CH}_2)_5\text{-CH}_3$ (2-Perfluorohexyl-octane, $\text{C}_{14}\text{F}_{13}\text{H}_{17}$ )

[0045] The compound  $\text{CF}_3\text{-(CF}_2)_5\text{-CH(CH}_3\text{)-(CH}_2)_5\text{-CH}_3$  may be prepared as follows: radical addition of perfluorohexyl iodide with 1-octene in the presence of a radical initiator (herein perfluorohexyl iodide is mixed with 1-octene and a radical initiator as AIBN and the obtained solution is maintained at 80°C for 30 min and cooled down), followed by reduction of the resulting iodo adduct with hydride (i.e.  $\text{LiAlH}_4$ ) or via hydrogenation (i.e. catalytic hydrogenation in presence of a catalyst such as  $\text{Pd/C}$ ) to form 2-perfluorohexyl-octane, followed by purification by fractional distillation.  $\text{CF}_3\text{-(CF}_2)_5\text{-CH(CH}_3\text{)-(CH}_2)_5\text{-CH}_3$ :  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 400 MHz): 2.17-2.33 (m, 1H, CH), 1.67-1.77 (m, 2H,  $\text{CH}_2$ ), 1.25-1.40 (m, 8H,  $\text{CH}_2$ ), 1.15 (d, 3H,  $\text{CH}_3$ ), 0.9 (t, 3H,  $\text{CH}_3$ )

### In vitro cytotoxicity assay

[0046] The cytotoxicity of a composition comprising 1.3 wt %  $\text{CF}_3\text{-(CF}_2)_5\text{-CH(CH}_3\text{)-(CH}_2)_5\text{-CH}_3$  and 95.8 wt%  $\text{CF}_3\text{-(CF}_2)_5\text{(CH}_2)_7\text{CH}_3$  was assessed by a cell growth inhibition test which predicts cytotoxic or necrotic effects with good correlation to animal experiments and high sensitivity.

[0047] The composition was extracted by cell culture medium (DMEM supplemented with 10% FBS) under agitation for ~24 hours. The resulting extract was then incubated with mouse cell line L929 cells for 68-72 hours, before the protein content was analyzed using a BCA (bicinchoninic acid) test as a measure for cytotoxicity. No inhibition of cell growth or cell lysis was observed.

[0048] An analogous *in vitro* cytotoxicity assay is conducted for a composition comprising about 23.7 wt%  $\text{CF}_3\text{-(CF}_2)_5\text{-CH(CH}_3\text{)-(CH}_2)_5\text{-CH}_3$  and about 75.6 wt% F6H8.

### Tear Film Analysis Studies

[0049] A composition comprising 98.3 wt% of  $\text{CF}_3\text{-(CF}_2)_5\text{(CH}_2)_7\text{CH}_3$  and 1.2 wt% of  $\text{CF}_3\text{-(CF}_2)_5\text{-CH(CH}_3\text{)-(CH}_2)_5\text{-CH}_3$  was tested in an observational study in patients with mild to moderate evaporative dry eye disease. The clear colorless liquid composition was provided in a 5 ml bottle equipped with a dropper dimensioned to dispense of droplets of ~10  $\mu\text{L}$

per drop into the eye sac. Patients wearing contact lenses were excluded from the study. After informed consent had been obtained, patients were advised to apply 3-4 drops, daily in both eyes, translating to a daily dose of 30-40  $\mu$ l. Patients returned after 5 -7 weeks for follow-up. Clinical data for 29 patients were collected at baseline and at the 5 -7 week follow-up visit.

#### a) Tear Film Analysis

**[0050]** Tear film fluid and tear film stability improved over the study period, as can be seen in the increase in Schirmer I and the TFBUT. The retrospective statistical analysis is strengthening this observation, as the difference in TFBUT at baseline and follow-up is highly significant (paired two-sided t-test:  $p=0.0026$  (right eyes) and  $p=0.0006$  (left eyes)). No changes were detected in tear osmolarity.

**[0051]** The subjective dry eye questionnaire (Ocular Surface Disease Index, OSDI) revealed that patient's subjective symptom severity decreased after the use of the composition comprising 98.3 wt% of  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and 1.2 wt% of  $\text{CF}_3(\text{CF}_2)_5\text{CH}(\text{CH}_3)(\text{CH}_2)_5\text{CH}_3$  over a 5-7 week period, as can be seen in the lower scores at follow-up and the retrospective statistical analysis (paired two sided t-test:  $p<0.0001$ ).

Parameter	Baseline	Follow up
Schirmer I (mm/5min) / Right eye	$10.7 \pm 3.7$	$16.3 \pm 8.9$
TFBUT (sec)	Right eye : $5.7 \pm 2.6$ Left eye : $5.7 \pm 2.6$	Right eye : $7.9 \pm 5.1$ Left eye : $8.6 \pm 6.0$
Osmolarity	$315.7 \pm 12.8$	$311.4 \pm 14.7$
OSDI	$53.9 \pm 22.5$	$35.8 \pm 22.9$

#### b) Corneal Staining (Oxford Grading Scheme)

**[0052]** Corneal fluorescein staining is an indicator of corneal damage (loss of cell-to-cell junctions). The data indicate a reduction of corneal damage after 5 - 7 weeks of treatment, as can be seen in the shift of numbers of patients diagnosed with Grade 1 or 2 at baseline towards Grade 0 at follow-up. This difference to the initial level of damage was statistically significant, as shown by Wilcoxon signed rank test:  $p=0.0013$  (right eyes) and  $p=0.0041$  (left eyes).

	Baseline (n=29)			Follow up (n=28)		
	Grade 0	Grade 1	Grade 2	Grade 0	Grade 1	Grade 2
Right eye (n)	8 (1)	16	4	25	2	1
Left eye (n)	8 (1)	16	4	19	9	0

#### c) Symptom Assessment by Physician

**[0053]** Patients were asked by the physician whether they currently suffer from typical dry eye symptoms both at the baseline and at the follow-up visit. As can be seen in the table below, a lower number of DED-associated symptoms were reported after 5 - 7 weeks of treatment.

	Baseline	Follow up
Red eyes	25	9
Itching	21	10
Clotted eyes	9	2
Stringy mucous	4	1
Headache	2	1

## d) Meibum Secretion analysis

**[0054]** In a healthy eye, meibum is secreted from the meibomian glands as a clear liquid. More opaque and thicker meibum is an indicator of dysfunctioning meibomian glands. Patients' meibum was descriptively examined at both the baseline and the follow-up visit. According to the data obtained, meibum quality improved in a number of cases. In seven cases, the treatment induced a reduction of expressible meibum (changing from clear meibum to none).

	Baseline	Follow up
Clear	20	17
Whitish	6	3
Thick	1	0
None	2	9

## e) Safety parameters

**[0055]** No changes were seen in either visual acuity or intraocular pressure, indicating that the use of composition comprising 98.3 wt% of  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and 1.2 wt-% of  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$  over 5-7 weeks is safe and does not interfere with these ophthalmological parameters.

	Baseline	Follow up
Visual acuity	0.8 (0.7-1.0)	0.9 (0.8-1.0)
Intraocular pressure (mm HG)	$14.9 \pm 2.6$	$14.6 \pm 3.2$

## Differential Scanning Calorimetry

**[0056]** Differential Scanning Calorimetry (DSC 1, Mettler Toledo, Greifensee, Switzerland) is used to characterize structure and phase behavior of mixtures of  $\text{CF}_3(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$  and  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$ . DSC was employed to obtain data on transitions by temperature rising scans with heating rate of  $1^\circ\text{C}/\text{min}$ . Sealed standard aluminum crucibles (40  $\mu\text{l}$ , Mettler Toledo) were used.

wt% $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$	Melting transition			
	$\Delta H$ (J/g)	Onset ( $^\circ\text{C}$ )	Peak ( $^\circ\text{C}$ )	Endset ( $^\circ\text{C}$ )
0	-36.57	-6.33	-4.53	-2.14
5.91	-33.36	-10.32	-7.99	-7.24
12.03	-29.42	-13.74	-10.44	-9.58
23.74	-24.09	-21.56	-15.38	-14.17

wt% $\text{CF}_3(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$	Low temperature transition			
	$\Delta H$ (J/g)	Onset ( $^\circ\text{C}$ )	Peak ( $^\circ\text{C}$ )	Endset ( $^\circ\text{C}$ )
0	-0.69	-45.47	-40.37	-38.32
5.91	-0.56	-50.61	-45.77	-42.93
12.03	-0.44	-55.18	-48.58	-45.53
23.74	-0.19	-60.75	-54.39	-52

**[0057]** The presence of  $\text{CF}_3(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$  in a mixture of  $\text{CF}_3(\text{CF}_2)_5-(\text{CH}_2)_7-\text{CH}_3$  (F6H8) resulted in a significant reduction in the melting temperature. The melting enthalpy is also decreased, which suggests that this semi-fluorinated alkane does not crystallize. Such differences will have a beneficial effect in respect of the application of this compound to the eye as a tear film substitute or lubricant; for example, in terms of its ability to mix with, and to modulate



the tear film lipid layer. Such effects can moreover be advantageously tuned by varying the amounts of this compound in the ophthalmic compositions of the invention.

**[0058]** DSC measurements of a series of mixtures of 23.74 wt % of  $\text{CF}_3(\text{CF}_2)_5\text{-CH}(\text{CH}_3)\text{-(CH}_2)_5\text{-CH}_3$  and  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  with tetradecane (C14) was also performed. Data on transitions were obtained with temperature rising scans (heating rates 0.2, 0.5 and 1 °C/min). Extrapolation to a heating rate of 0 °C/min was used to determine endset temperatures while average from the three measurements were used to determine onset temperatures. A decrease in the melting enthalpy was observed, compared to mixtures of tetradecane with pure  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$ , suggesting that some of the tetradecane is dissolved in the liquid fraction of  $\text{CF}_3(\text{CF}_2)_5\text{-CH}(\text{CH}_3)\text{-(CH}_2)_5\text{-CH}_3$  and that this compound has a stronger solubilizing capacity compared to  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$ .

#### Refractive Index and Evaporation Time

**[0059]** The evaporation time of mixtures of the semifluorinated alkane  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and  $\text{CF}_3(\text{CF}_2)_5\text{-CH}(\text{CH}_3)\text{-(CH}_2)_5\text{-CH}_3$  was evaluated. A droplet of 10 µL volume of each mixture was placed on a glass surface at room temperature. Time until evaporation was recorded by video-monitoring.

Sample	$\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$ / %	$\text{CF}_3(\text{CF}_2)_5\text{-CH}(\text{CH}_3)\text{-(CH}_2)_5\text{-CH}_3$ / %	Evaporation time/s	Relative Evaporation Time
1	99.84	0.16	13260	1
2	96.53	3.05	12960	0.97
3	26.3	64.1	9960	0.75

**[0060]** It was observed that an increasing percentage of the semifluorinated alkane  $\text{CF}_3(\text{CF}_2)_5\text{-CH}(\text{CH}_3)\text{-(CH}_2)_5\text{-CH}_3$  decreases the evaporation time of the mixtures (Fig. 1) By varying the amount of this semifluorinated alkane in the mixture, it may be feasible to adapt and fine-tune the composition to the requirements of the intended ophthalmic use, such as in terms of prolonging or reducing the residence time of the composition on the eye surface.

**[0061]** The refractive index of the mixtures was also determined. For topically applied ophthalmic compositions, the refractive index of the composition should preferably be similar, or adapted to that of the eye and lens, for instance as close to that of physiological tear fluid as possible. If the refractive index of a composition is not similar, when applied to the surface of the eye, a patient may experience blurring or impaired vision. It is observed, that the amount of the semifluorinated alkane  $\text{CF}_3(\text{CF}_2)_5\text{-CH}(\text{CH}_3)\text{-(CH}_2)_5\text{-CH}_3$  has an effect on refractive index (see Fig. 2, which depicts an increasing refractive index value with increased content of the 2-perfluorohexyloctane). By varying the amount of this semifluorinated alkane in the mixture, it may also be feasible to adapt the composition to the requirements of the intended ophthalmic use, for instance adapting to a patient with an altered tear fluid composition and refractive index, due to an eye condition and/or age.

#### Ex vivo Eye Irritation Test (EVEIT)

**[0062]** A comparison in respect of corneal healing process was conducted for two compositions comprising  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$ , namely compositions consisting of a mixture of the semifluorinated alkane  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and  $\text{CF}_3(\text{CF}_2)_5\text{-CH}(\text{CH}_3)\text{-(CH}_2)_5\text{-CH}_3$  (Composition A with 0.17 wt% of  $\text{CF}_3(\text{CF}_2)_5\text{-CH}(\text{CH}_3)\text{-(CH}_2)_5\text{-CH}_3$  and Composition B, with 64 wt% of  $\text{CF}_3(\text{CF}_2)_5\text{-CH}(\text{CH}_3)\text{-(CH}_2)_5\text{-CH}_3$ ) with hyaluronic acid (HYLO-COMOD®) as a reference and 0.01% BAC (benzalkonium chloride) as a positive control using an Ex Vivo Eye Irritation Test (EVEIT), similar to as described in M. Frentz et al, Altern. to Lab. Anim., 2008 (36) p 25-32; and N. Schrage et al, Graefes Arch Clin Exp Ophthalmol 2012 (250), 1330-1340).

**[0063]** *Method.* Rabbit corneas were obtained and placed in an artificial anterior ocular chamber which was gently filled with serum-free minimal essential medium (Eagle's MEM) containing Earle's salts and HEPES buffer for nutrition. The medium was constantly replenished by a micropump to imitate the physiological condition of the eye. The culture chambers were held at 32 °C under normal air without supplementary CO<sub>2</sub> and > 95 % relative humidity. Five corneas per test substance (n=5) were used except for the positive control with which two corneas (n=2) were tested.

**[0064]** After 12 h of stabilization in the culture chamber, the corneas were evaluated by microscopy and corneas with intact epithelium and without opacities were selected. Four small abrasions (2.3-4.3 mm<sup>2</sup>) were applied to the surface of the selected corneas with a cornea drill. All defects were monitored by fluorescein sodium staining (0.17 % aq. solution) and microscopy.

**[0065]** The test substances were administered one hour after induction of the corneal erosion and were applied six

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times daily onto the apex of the corneas (30-50  $\mu$ L every four hours). A soft-tipped cannula, with continuous suction was placed on the lowest part of the corneoscleral region within the culturing chamber to remove any excess fluid. Experiments were terminated after 3 days of application. Biomicroscopic images of the corneas were taken daily to document the corneal healing process using a phase-contrast microscope integrated camera (KY-F1030U, JVC, (Bad Vilbel, DE) mounted on a Z16 APO Microscope (Wetzlar, DE)). All defects were monitored by fluorescein sodium stains (0.17 % aq. solution) with yellow green fluorescence indicating the areas of epithelial defects. Erosion sizes were determined using a software tool of the microscope (DISKUS). At the end of the 3 days, the experiment was terminated and all corneas were fixed in 3.7 % formaldehyde and stained with a hematoxylin-eosin dye for microscopic evaluation. To monitor the metabolic activity of the cornea, glucose and lactate concentrations were photometrically quantified in the outflow medium from the artificial anterior chambers.

**[0066]** *Results.* Both mixtures of the semifluorinated alkanes (Composition A and B as referenced above) were observed to have a similar positive effect in respect of the corneal healing process after the induction of corneal erosion as compared with the standard reference hyaluronic acid composition (HYLO-COMOD®).

*Corneal Erosion Size Measurements/Mean mm<sup>2</sup> (SD)*

Composition	Day 0	Day 1	Day 2	Day 3
A (n=5)	12.8 (0.98)	3.018 (0.89)	0 (0)	0(0)
B (n=5)	12.23 (1.46)	3.59 (0.53)	0 (0)	0(0)
HYLO COMOD®	12.13 (1.29)	3.11 (0.76)	0.01(0.02)	0(0)
0.01% BAC	11.57 (0.86)	5.91 (0.28)	8.74 (7.6)	17.46 (6.43)

*Day 3 Histological Observations*

Composition	
A (n=5)	<ul style="list-style-type: none"> <li>- Multilayered epithelium and dense stroma in all corneas.</li> <li>- Keratocytes are well formed and arranged except if lost from initial erosion area.</li> <li>- Descemet membrane appears intact, endothelial cells are present.</li> </ul>
B (n=5)	<ul style="list-style-type: none"> <li>- Healed epithelial layer with closed multilayer of epithelial cells.</li> <li>- Dense stroma and regular formed keratocytes although typically reduced in number under the initial erosion area.</li> <li>- Descemet membrane and endothelial layer present without structural defects</li> </ul>
Hylo Comod® (reference)	<ul style="list-style-type: none"> <li>- Multilayered epithelium and dense stroma with regular arranged and formed keratocytes except under the initial erosion areas where keratocytes are totally lost in the upper stroma.</li> <li>- Descemet membrane and endothelial layer are present without any defects in structure.</li> </ul>
0.01% BAC (positive control)	<ul style="list-style-type: none"> <li>- Severe alterations of the superficial cornea with disintegration of whole corneal structures; observation of distinct edema</li> <li>- Reduced staining of background substance indicating chemical alteration of collagen</li> <li>- Severe reduction in number of keratocyte cells which also appear rounded and pycnotic.</li> <li>- Descemet membrane is present with intact endothelium</li> </ul>

**[0067]** No significant differences in terms of a positive corneal healing was noted between composition B comprising 64 wt %, based on total weight of the composition of semifluorinated alkane  $\text{CF}_3(\text{CF}_2)_5\text{-CH}(\text{CH}_3)\text{-(CH}_2)_5\text{-CH}_3$  and composition A. With both compositions, as with the reference composition, the mechanically induced epithelial erosions were found to be significantly reduced and essentially absent after day 2 of treatment. Figure 3 depicts the corneal erosion size measurements of the tested compositions, reference and positive controls for days 0-3 of the EVEIT experiment.

**[0068]** As noted in the table above, microscopic histological examination of the cross-sections of the corneas after termination of the experiment on day 3 revealed no significant remaining defects or differences in the corneas treated with compositions A, B and the reference HYLO-COMOD®.

**[0069]** Furthermore, no corneal toxicity, based on the metabolic activity as indicated by the glucose/lactate measurements was observed for these compositions.

**[0070]** In significant contrast, the positive control comprising 0.01% of the preservative BAC, a progressive increase of the induced epithelial lesions was observed over the course of the three days of the experiment.

## Claims

1. A composition comprising  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ .
2. The composition according to claim 1, comprising at least about 80 wt% of  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$ .
3. The composition according to claim 1, comprising up to about 25 wt% of  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ .
4. The composition according to any preceding claim comprising about 97 wt% of  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  and up to about 3 wt% of  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ .
5. The composition according to any preceding claim, being formulated as a clear liquid solution.
6. The composition of any preceding claim, being substantially free of:
  - (a) a polymer,
  - (b) a perfluorinated compound, and/or
  - (c) a dissolved pharmacologically active ingredient.
7. The composition of any preceding claim, having a dynamic viscosity of not more than 10 mPa·s, and preferably not more than 4 mPa·s, at ambient temperature and pressure.
8. The composition according to any of the preceding claims for use as a medicine.
9. The composition for use according to claim 8, wherein the composition is topically administered to a lacrimal sac, into a lower eyelid, to an eye surface, or to an ophthalmic tissue.
10. The composition for use according to claim 9, comprising administering the composition up to four times per day.
11. The composition for use according to any one of claims 8 to 10 in the treatment of keratoconjunctivitis sicca and/or Meibomian Gland Dysfunction or a symptom or condition associated therewith.
12. The composition for use according to any one of claims 8 to 11 in the treatment of corneal damage.
13. The composition for use according to any one of claims 8 to 11 as a lubricant of the eye surface.
14. A kit comprising a composition according to any preceding claim and a container for holding the composition, wherein said container comprises a dispensing means adapted for topical administration of the composition to a lacrimal sac, into a lower eyelid, to an eye surface, or to an ophthalmic tissue.
15. The kit of claim 14, wherein the dispensing means comprises a dropper dimensions such as to dispense droplets having a volume of 8 to 15  $\mu\text{L}$ .

## Patentansprüche

1. Zusammensetzung, die  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  und  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$  umfasst.
2. Zusammensetzung gemäß Anspruch 1, die mindestens ungefähr 80 Gew.-% an  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  umfasst.
3. Zusammensetzung gemäß Anspruch 1, die bis zu ungefähr 25 Gew.-% an  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$  umfasst.

4. Zusammensetzung gemäß einem beliebigen vorhergehenden Anspruch, die ungefähr 97 Gew.-% an  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  und bis zu ungefähr 3 Gew.-% an  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$  umfasst.
5. Zusammensetzung gemäß einem beliebigen vorhergehenden Anspruch, die als klare flüssige Lösung formuliert ist.
6. Zusammensetzung gemäß einem beliebigen vorhergehenden Anspruch, die im Wesentlichen frei ist von:
  - (a) Polymeren,
  - (b) perfluorierten Verbindungen, und/oder
  - (c) gelösten pharmakologischen Wirkbestandteilen.
7. Zusammensetzung gemäß einem beliebigen vorhergehenden Anspruch, die bei Raumtemperatur und Umgebungsdruck eine dynamische Viskosität von höchstens 10 mPa·s und vorzugsweise von höchstens 4 mPa·s aufweist.
8. Zusammensetzung gemäß beliebigen der vorhergehenden Ansprüche, zur Verwendung als Medikament.
9. Zusammensetzung zur Verwendung gemäß Anspruch 8, wobei die Zusammensetzung auf topische Weise an einen Tränensack, in ein unteres Augenlid, auf eine Augenoberfläche oder an ein Augengewebe verabreicht wird.
10. Zusammensetzung zur Verwendung gemäß Anspruch 9, wobei letztere ein Verabreichen der Zusammensetzung bis zu viermal pro Tag umfasst.
11. Zusammensetzung zur Verwendung gemäß einem beliebigen der Ansprüche 8 bis 10 in der Behandlung von Keratoconjunctivitis sicca und/oder Fehlfunktionen der Meibom-Drüse oder eines Symptoms oder eines Zustands, das/der damit in Verbindung steht.
12. Zusammensetzung zur Verwendung gemäß einem beliebigen der Ansprüche 8 bis 11 in der Behandlung von Hornhautschäden.
13. Zusammensetzung zur Verwendung gemäß einem beliebigen der Ansprüche 8 bis 11 als Gleitmittel für die Augenoberfläche.
14. Kit, das eine Zusammensetzung gemäß einem beliebigen vorhergehenden Anspruch und einen Behälter zum Aufbewahren der Zusammensetzung umfasst, wobei der Behälter ein Abgabemittel umfasst, das zur topischen Verabreichung der Zusammensetzung an einen Tränensack, in ein unteres Augenlid, auf eine Augenoberfläche oder an ein Augengewebe geeignet ist.
15. Kit nach Anspruch 14, wobei das Abgabemittel eine Tropfvorrichtung mit Abmessungen umfasst, die derart sind, dass sie Tröpfchen abgibt, welche ein Volumen von 8 bis 15  $\mu\text{L}$  haben.

## Revendications

1. Composition comprenant  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  et  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ .
2. Composition selon la revendication 1, comprenant au moins environ 80 % en poids de  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$ .
3. Composition selon la revendication 1, comprenant jusqu'à environ 25 % en poids de  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ .
4. Composition selon l'une quelconque des revendications précédentes comprenant environ 97 % en poids de  $\text{CF}_3(\text{CF}_2)_5(\text{CH}_2)_7\text{CH}_3$  et jusqu'à environ 3 % en poids de  $\text{CF}_3-(\text{CF}_2)_5-\text{CH}(\text{CH}_3)-(\text{CH}_2)_5-\text{CH}_3$ .
5. Composition selon l'une quelconque des revendications précédentes, se présentant sous la forme d'une solution liquide claire.
6. Composition selon l'une quelconque des revendications précédentes, sensiblement exempte de :

- (a) un polymère,
- (b) un composé perfluoré, et/ou
- (c) un ingrédient pharmacologiquement actif dissous

- 5      **7.** Composition selon l'une quelconque des revendications précédentes, ayant une viscosité dynamique non supérieure à 10 mPa•s et de préférence non supérieur à 4 mPa•s, à la température et à la pression ambiantes.
8. Composition selon l'une quelconque des revendications précédentes, destinée à être utilisée comme médicament.
- 10     **9.** Composition destinée à être utilisée selon la revendication 8, la composition étant administrée par voie topique à un sac lacrymal, une paupière inférieure, sur une surface oculaire ou un tissu ophtalmique.
- 10.** Composition destinée à être utilisée selon la revendication 9, comprenant l'administration de la composition jusqu'à quatre fois par jour.
- 15     **11.** Composition destinée à être utilisée selon l'une quelconque des revendications 8 à 10 dans le traitement de la kérato-conjonctivite sèche et/ou du dysfonctionnement de la glande de Meibomius, ou d'un symptôme ou d'une affection associé à celui-ci.
- 20     **12.** Composition destinée à être utilisée selon l'une quelconque des revendications 8 à 11 dans le traitement des lésions de la cornée.
- 13.** Composition destinée à être utilisée selon l'une quelconque des revendications 8 à 11 comme lubrifiant de la surface des yeux.
- 25     **14.** Kit comprenant une composition selon l'une quelconque des revendications précédentes et un récipient destiné à contenir la composition, ledit récipient comprenant un moyen de délivrance adapté à l'administration topique de la composition à un sac lacrymal, une paupière inférieure, une surface oculaire, ou un tissu ophtalmique.
- 30     **15.** Kit selon la revendication 14, le moyen de délivrance comprenant un compte-gouttes dimensionné de manière à délivrer des gouttelettes ayant un volume de 8 à 15  $\mu$ l.

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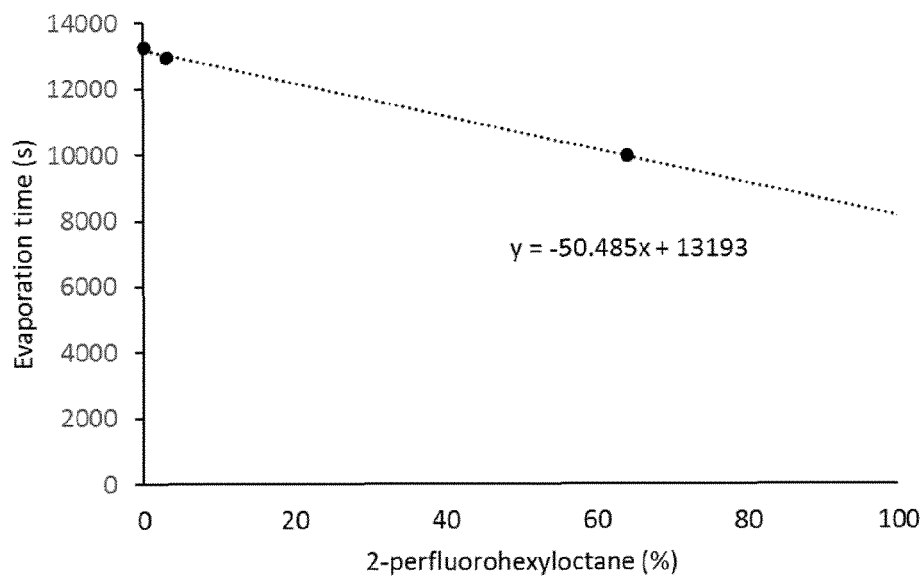


Fig. 1

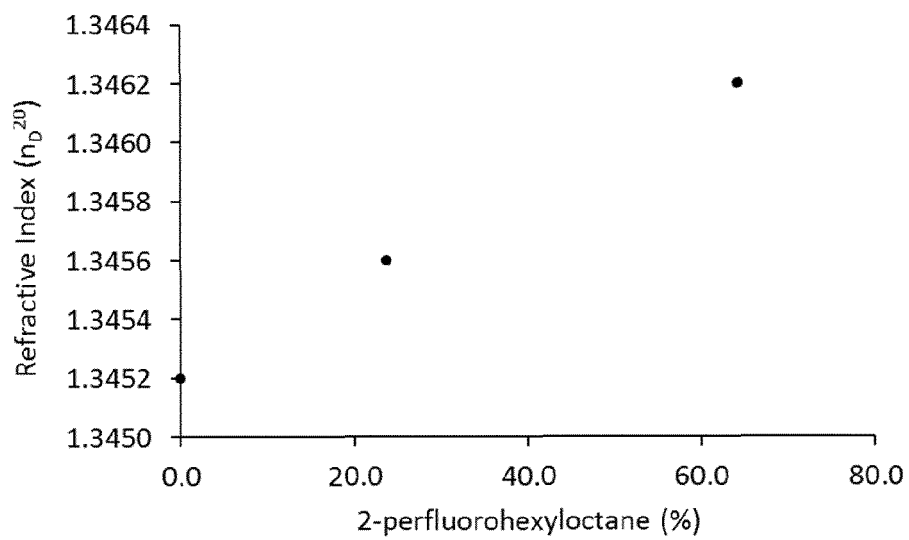


Fig. 2

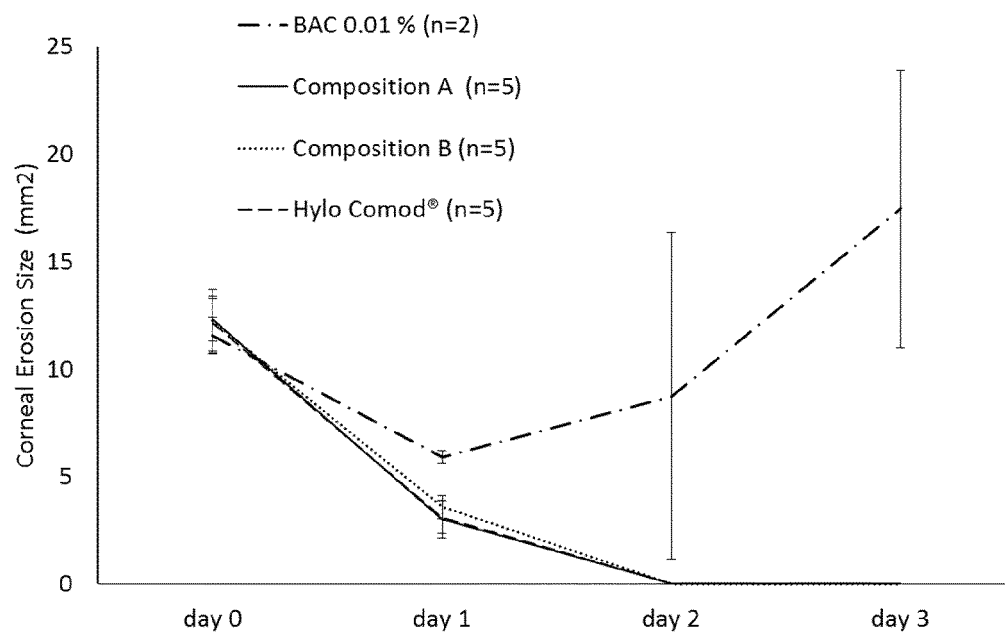


Fig. 3

**REFERENCES CITED IN THE DESCRIPTION**

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