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[Continued on next page]

(54) Title: HEAVY SILICONE OIL FOR VITREORETINAL SURGERY

(57) Abstract: The present invention concerns methods and compositions concerning a long-acting biocompatible heavier-than-water internal tamponade agent for use in vitreoretinal surgery, for example. In specific cases, the invention includes a particular silicone oil in compositions and methods encompassed herein.

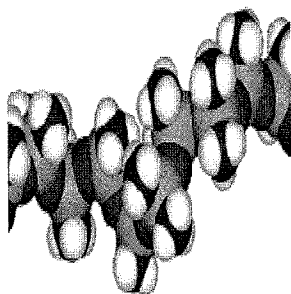
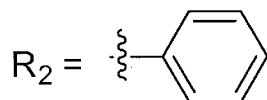
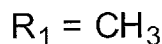
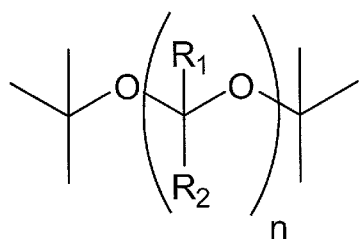


FIG. 10



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DESCRIPTION

HEAVY SILICONE OIL FOR VITREORETINAL SURGERY

This application claims priority to U.S. Provisional Patent Application Serial No. 61/330,467, filed May 3, 2010, which is incorporated by reference herein in its entirety.

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TECHNICAL FIELD

[0001] The present disclosure relates generally to vitreoretinal surgery and, in particular, biocompatible heavier-than-water internal tamponade agents that can be used in vitreoretinal surgery. In specific cases, the present disclosure concerns an internal tamponade agent comprising a biocompatible silicone oil with aromatic and alkyl side chains and having a density greater than 1.0 g/mL.

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BACKGROUND OF THE INVENTION

[0002] Retinal detachment is a disorder of the eye in which the retina is pulled away from its normal position in the back of the eye. Initial detachment may be localized, but without rapid treatment the entire retina may detach, leading to vision loss and blindness.

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[0003] The retina is a thin layer of light-sensitive tissue on the back wall of the eye. To create a focused image, the optical system of the eye focuses light on the retina much like light is focused on the film in a camera. The retina translates the focused image into neural impulses and sends them to the brain *via* the optic nerve.

[0004] The vitreous is the clear collagen gel that fills the back of the eye between the retina and the lens. The vitreous is firmly attached at the vitreous base and have points of contact throughout the retina. Typically, vitreous condensation occurs with age which contracts and may pull away from its attachment to the retina at the back of the eye as a person ages. The vitreous contraction may create a retinal break as it separates. Other diseases that result in neovascularization such as in sickle cell, radiation, diabetes, tumors, inflammatory vasculopathies, and hypertension (vascular occlusions) can similarly create fibrovascular traction on the retina resulting in retinal breaks and detachment. Prolonged retinal breaks without retinal detachment with any inflammatory initiator can also cause proliferative vitreoretinopathy that also results in membrane proliferation in the vitreous that contracts and causes retinal detachments. Injury or trauma to the eye or head can also cause a

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small tear in the retina. The resulting tear or traction on the retina allows fluid to enter under the retina and further detach or worsen a retinal detachment.

[0005] There are three types of retinal detachment: rhegmatogenous retinal detachment, exudative (serous or secondary) retinal detachment and tractional retinal detachment. A rhegmatogenous retinal detachment occurs due to a hole, tear, or break in the retina that allows fluid to pass from the vitreous space into the subretinal space between the sensory retina and the retinal pigment epithelium. An exudative retinal detachment occurs due to inflammation, injury or vascular abnormalities that results in fluid accumulating underneath the retina without the presence of a hole, tear, or break. A tractional retinal detachment occurs when fibrovascular tissue, caused by an injury, inflammation or neovascularization, pulls the sensory retina from the retinal pigment epithelium.

[0006] A substantial number of retinal detachments result from trauma, including blunt trauma to the orbit, penetrating trauma, and concussions to the head. A study of more than 500 cases of rhegmatogenous detachments found that 11% were due to trauma, and that gradual onset was the norm, with over 50% presenting more than one month after the inciting injury (Shukla *et al.*, 1986).

[0007] The risk of retinal detachment in otherwise normal eyes is around 5 in 100,000 (Ivanisevic *et al.*, 2000). Detachment is more frequent in the middle-aged or elderly population with rates of around 20 in 100,000 (Li, 2003). The lifetime risk in normal eyes is about 1 in 300. Retinal detachment is more common in those with severe myopia (above 5–6 diopters), as their eyes are longer and the retina is stretched thin. In this population, the lifetime risk increases to 1 in 20. Myopia is associated with 67% of retinal detachment cases. Patients suffering from a detachment related to myopia tend to be younger than non-myopic detachment patients.

[0008] Retinal detachment can occur more frequently after surgery for cataracts. The estimated risk of retinal detachment after cataract surgery is 5 to 16 per 1000 cataract operations. The risk may be much higher in those who are highly myopic, with a frequency of 7% reported in one study. Young age at cataract removal further increased risk in this study. Long term risk of retinal detachment after extracapsular and phacoemulsification cataract surgery at 2, 5, and 10 years was estimated in one study to be 0.36%, 0.77%, and 1.29%, respectively (Rowe *et al.*, 1999).

[0009] Tractional retinal detachments can also occur in patients with proliferative diabetic retinopathy or those with proliferative retinopathy of sickle cell disease. In proliferative retinopathy, abnormal blood vessels (neovascularization) grow within the retina and extend into the vitreous. In advanced disease, the vessels can pull the retina away from the back wall of the eye causing a traction retinal detachment.

[0010] Although retinal detachment usually occurs in one eye, there is a 15% chance of developing it in the other eye, and this risk increases in patients who have had cataracts extracted from both eyes.

[0011] A retinal detachment is commonly preceded by a posterior vitreous detachment that gives rise to these symptoms: (1) flashes of light (photopsia) that may be very brief in the extreme peripheral (outside of center) part of vision; (2) a sudden dramatic increase in the number of floaters; (3) a ring of floaters or hairs just to the temporal side of the central vision; and, (4) a slight feeling of heaviness in the eye.

[0012] Although most posterior vitreous detachments do not progress to retinal detachments, those that do produce the following symptoms: (1) a dense shadow that starts in the peripheral vision and slowly progresses towards the central vision; (2) the impression that a veil or curtain was drawn over the field of vision; (3) straight lines (scale, edge of the wall, road, *etc.*) that suddenly appear curved (positive Amsler grid test); and, (4) central visual loss.

[0013] In general, the procedure for treating the retinal tear is by finding all retinal breaks, sealing all retinal breaks and relieving the present (and future) vitreoretinal traction. There are several methods of treating a detached retina that all depend on finding and closing the breaks that have formed in the retina. These methods include cryotherapy (cryopexy), laser photocoagulation, scleral buckle surgery, pneumatic retinopexy, and vitrectomy. Cryotherapy (freezing) or laser photocoagulation are occasionally used alone to wall off a small area of retinal detachment so that the detachment does not spread.

[0014] Scleral buckle surgery is an established treatment in which the eye surgeon sews one or more silicone bands (bands, tyres) to the sclera (the white outer coat of the eyeball). The bands push the wall of the eye inward against the retinal hole, closing the break or reducing fluid flow through it and reducing the effect of vitreous traction thereby allowing the retina to re-attach. Cryotherapy (freezing) is applied around retinal breaks prior to placing the buckle. In some cases, the subretinal fluid is drained as part of the buckling

procedure. The buckle remains *in situ*. The most common side effect of a scleral operation is myopic shift. That is, the operated eye will be more short sighted after the operation.

[0015] For example, a more specific procedure for treating a retinal tear starts by first treating the retinal tear or holes with cryopexy and then attaching a small piece of silicone sponge or a firmer piece of silicone rubber to the white of the eye (sclera) over the affected area. The silicone material indents the wall of the eye, creating a buckling effect and reducing the traction of the vitreous on the retina. In the case of several tears (holes) or extensive detachment, a surgeon may create an encircling scleral buckle around the entire circumference of the eye.

[0016] The scleral buckling material is stitched to the outer surface of the sclera. Before tying the sutures that hold the buckle in place, the surgeon may make a small cut in the sclera and drain any fluid that has collected under the detached retina. The buckle usually remains in place for the lifetime of the patient. Some surgeons may choose a temporary buckle for simple retinal detachments, using a small rubber balloon that is inflated and later removed.

[0017] Another method of treating a detached retina is through pneumatic retinopexy. This operation is generally performed in the doctor's office under local anesthesia. It is another method of repairing a retinal detachment in which a gas bubble (SF_6 or C_3F_8 gas) is injected into the eye after which laser or freezing treatment is applied to the retinal hole. The patient's head is then positioned so that the bubble rests against the retinal hole. Patients may have to keep their heads tilted for several days to keep the gas bubble in contact with the retinal hole. The surface tension of the air/water interface seals the hole in the retina and allows the retinal pigment epithelium to pump the subretinal space dry and suck the retina back into place. This strict positioning requirement makes the treatment of the retinal holes and detachments that occur in the lower part of the eyeball impractical.

[0018] An additional method of treating a detached retina is through vitrectomy. Vitrectomy is an increasingly used treatment for retinal detachment. Vitrectomy involves the removal of the vitreous gel and is usually combined with filling the eye with an intraoperative tamponade agent such as a gas bubble (SF_6 or C_3F_8 gas) or silicone oil. Advantages of using gas in this operation is that there is no myopic shift after the operation and gas is absorbed within a few weeks. If silicone oil (polydimethylsiloxane -PDMS) is used to treat a detached

retina, it is necessary to remove the silicone oil after a period of 2–8 months. Silicone oil is more commonly used in cases associated with proliferative vitreo-retinopathy (PVR). A disadvantage is that a vitrectomy always leads to more rapid progression of a cataract in the operated eye.

5 [0019] Tamponade agents make contact with the retina, prevent passage of aqueous humor through a break in the retina, and displace water, because aqueous humor contains a pro-inflammatory milieu that facilitates the development of proliferative vitreoretinopathy.

 [0020] Current tamponade agents have densities less than water, making these
10 floating tamponade agents most effective for superior retinal pathologies. However, because they have poor contact with the inferior retina secondary due to gravitational and density limitations, it is less useful for closure of inferior retinal breaks and detachments, especially without post-operativeerative posturing. As a result, the inferior retina is a prime site for proliferative vitreoretinopathy secondary to the presence of growth factors in aqueous that
15 accumulated inferiorly in eyes that have been tamponaded with lighter-than-water silicone oil. In addition, current management of inferior retinal detachments require complicated patient positioning for weeks that is difficult for patient compliance to obtain successful anatomic repair of the detachment. A heavier-than-water tamponade agent would be a more effective tamponade in the management of the inferior retinal detachment or breaks by displacing
20 aqueous away and making contact at the site of pathology in the inferior retina.

 [0021] Successful tamponade agents for vitreoretinal surgery are substances that have high surface interfacial tension with water in order to prevent fluid from entering the subretinal space through the retinal tear or break. Current tamponade agents in clinical use that have high surface interfacial tension are intraocular gases (sulfur hexafluoride SF₆,
25 perfluoropropane C₃F₈) and highly purified polydimethylsiloxane silicone oil. All of these materials have densities less than 1 g/mL, making it difficult to tamponade breaks/tears or retinal pathologies located inferiorly. Furthermore, gas tamponades preclude the ability to travel by air or ascend higher altitudes due to the expanding properties of gas within the eye that can cause blindness from acute intraocular pressure rise.

30 [0022] Currently, polydimethylsiloxane silicone oil is used in the clinical setting for repairing complex retinal detachments, in particular ones that are at high risk for re-

detachment and require long-term tamponade (all intraocular gases eventually resorb). Newer heavy silicone oil substitutes have been developed with limited success: their widespread use has been restricted secondary to inflammation and subsequent development of proliferative vitreoretinopathy. They are currently being explored in clinical trials in Europe, such as fluorinated silicone oils, OxaneHD (oil-RMN3-mixture), Densiron (mixture of 30.5 vol% perfluorohexyloctane (F_6H_8) SG 1.35 g/mL with 69.5 vol% polydimethylsiloxane 5000 cS silicone oil), and heavy perfluorocarbon liquids such as perfluoro-n-octane (PFO) and perfluorodecalin. While all of these materials are denser than water and optically transparent, they have been shown to induce mild to severe intraocular inflammation leading to proliferative vitreoretinopathy. The inflammation that has been observed with these heavier-than-water agents is significantly greater than the currently clinically used lighter-than-water silicone oil. PFO causes acute retinal toxicity after several weeks, thereby limiting its use as a successful heavier than water intraocular tamponade agent.

[0023] In addition to providing a tamponade agent that prevents the level of irritation and inflammation observed with currently available tamponade agents, the present invention also allows further modification to address the problem of radical-mediated ocular damage that is associated with vitreoretinal pathologies. Free radicals are thought to be responsible for producing irreversible damage to biomolecules, such as enzyme proteins and membrane lipids, and mediate further inflammatory cascades within the eye. Ocular tissues are similarly prime targets for radiation-induced free radical damage. Higher oxygen content within the vitreous cavity after a vitrectomy has also been suggested as the mediator of free radical induced changes such as lenticular formation of a cataract after vitrectomy. Even though ocular tissues have a normal complement of protective mechanisms against free radicals, if any step in the defense system fails, the tissues within the eye are unable to cope with the continuous production of cyto-toxic species, such as free radicals.

[0024] In addition to radiation-induced free radical damage, excess nitric oxide (NO) may lead to toxic free radical formation. This toxic free radical formation produces cell death by causing DNA damage. Furthermore, damaged tissue generates larger amounts of super-oxide, thereby exacerbating excess radical formation. Nitric oxide plays a significant role in physiological and pathological processes in the retina. Also, nitric oxide is an important mediator of homeostatic processing in the eye, such as regulation of aqueous humour dynamics, retinal neurotransmission and phototransduction. High levels of nitric

oxide have been implicated in the pathogenesis of a variety of disorders, including glaucoma, proliferative diabetic retinopathy, cataract, uveitis and retinal detachment.

[0025] The antioxidative mediators in retinal pigment epithelium that protects the retina from oxidative trauma can be overwhelmed in any vitreoretinal disease. The present invention provides a category of new radical scavenger-based solutions that can protect the retina from oxidative trauma and potentially limit the inflammatory cascade within the eye. In some embodiments of the present invention, a radical scavenger is combined with the tamponade agent to provide a means for protecting the retina from oxidative trauma resulting from free radical formation.

BRIEF SUMMARY OF THE INVENTION

[0026] Heavy silicone oil substitutes have been developed with limited success; however, their widespread use has been restricted secondary to inflammation and subsequent development of proliferative vitreoretinopathy. Current heavy silicone oils are either fluorinated siloxanes, fluorohydrocarbons, or mixtures of fluorohydrocarbons and polydimethylsiloxanes (current clinically used silicone oils). Having a heavier-than-water tamponade agent available to the vitreoretinal practitioner offers added advantages in managing complex inferior retinal pathologies, for example, without difficult patient positioning or risk of post-operative overfill complications. The present invention concerns new candidate heavy silicone oil without the use of fluoride, perfluorocarbons, or olefins for use in vitreoretinal therapeutic applications by modifying side chains on existing polydimethylsiloxanes, in certain embodiments. In particular embodiments of the invention, polymers functionalized with alkyl and aromatic side chains increase the density of the polymer while preserving the overall hydrophobicity necessary to maintain a high interfacial surface tension to tamponade the retina.

[0027] Thus, the present invention is directed to compositions and methods that are useful for treating retinal defects. In particular embodiments, the present invention encompasses a long-acting biocompatible heavier-than-water internal tamponade agent that can be used in vitreoretinal surgery. In specific cases, the present invention concerns a heavier-than-water silicone oil that in certain embodiments allows the material to sink and tamponade inferior breaks and retinal detachments. This would eliminate the need for complicated prolonged patient positioning, improve compliance and possibly improve rates of

successful anatomy repair of inferior retinal detachments, thus leading to a useful tool in vitreoretinal surgery, for example. The other advantage of silicone oil is it permits immediate air travel or high altitude travel which is contraindicated with any intraocular gas and also allows the patient to still see. Intraocular gas does not allow the patient to see while the gas remains in the eye due to the high change in refractive index at gas-tissue interfaces. In certain embodiments, there is a biocompatible silicone oil that has a density greater than 1.0 with minimal inflammatory reaction for use in vitreoretinal surgery as an inferior tamponade agent. In specific cases, the silicone oil of the invention comprises a component, either or both intermolecular or intramolecular to the heavier-than-oil polymer that acts as an antioxidant.

[0028] In particular aspects of the invention, the tamponade agent alone or tamponade agent used in conjunction with the free radical scavenger provides a convenient and multifunctional solution for creating better vision in an individual in need thereof.

[0029] The foregoing has outlined rather broadly the features and technical advantages of the present invention in order that the detailed description of the invention that follows may be better understood. Additional features and advantages of the invention will be described hereinafter which form the subject of the claims of the invention. It should be appreciated by those skilled in the art that the conception and specific embodiment disclosed may be readily utilized as a basis for modifying or designing other structures for carrying out the same purposes of the present invention. It should also be realized by those skilled in the art that such equivalent constructions do not depart from the spirit and scope of the invention as set forth in the appended claims. The novel features which are believed to be characteristic of the invention, both as to its organization and method of operation, together with further objects and advantages will be better understood from the following description when considered in connection with the accompanying figures. It is to be expressly understood, however, that each of the figures is provided for the purpose of illustration and description only and is not intended as a definition of the limits of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] For a more complete understanding of the present invention, reference is now made to the following descriptions taken in conjunction with the accompanying drawing, in which:

[0031] FIG. 1A shows a particular heavy oil of the invention in Balanced Salt Solution (BSS) at room temperature, and FIG. 1B shows the same heavy oil in BSS at room temperature but five months later.

5 [0032] FIG. 2 demonstrates exemplary ERG measurements in pre-surgery New Zealand white rabbit, left eye.

[0033] FIG. 3 demonstrates ERG measurements in post-operative operation (day 6) of the left eye wherein 80/20 heavy silicone oil fill was utilized.

[0034] FIG. 4 demonstrates ERG measurements in post-operative operation (day 35) of the left eye wherein 80/20 heavy silicone oil fill was utilized.

10 [0035] FIG. 5 shows a size exclusion chromatogram (SEC) of the original polymer. Note the low molecular weight oligomers (peak 3: RT = 18.48 min, (M_w) = 421; peak 4: RT = 19.17 min, M_w = 271). The solvent was THF with a flow rate of 1 mL/min at temperature 40 °C using a standard crosslinked polystyrene-based SEC column.

15 [0036] FIG. 6 shows SEC chromatogram of the polymer after fractional precipitation. Note the less than 1000 M_w , oligomers (RT = 18.48 and 19.17 min) have decreased. Peak 1: RT = 16.93 min, M_w = 2093. The solvent was THF with a flow rate of 1 mL/min at temperature 40 °C using a standard GPC column.

20 [0037] FIG. 7 shows NMR spectrum of the purified siloxane polymer, indicating that all detectable acetone had been removed, because the acetone $-(CH_3)$ groups would appear at $\delta = 2.17$ ppm.

[0038] FIG. 8 shows NMR spectrum of an exemplary purified siloxane polymer with benzylic groups.

25 [0039] FIG. 9 shows diphenyl-1-picrylhydrazyl (DPPH) assay of radical scavenger polymers. Inset are the colors of the DPPH solution added with different scavengers after 2 hours.

[0040] FIG. 10 shows an exemplary poly-phenyl (20%):methyl (80%)-siloxane polymer compound.

[0041] FIG. 11A demonstrates rabbit eyes status post pars plana vitrectomy at day 35. FIG. 11B shows rabbit histopathology of the eyes of FIG. 11A.

[0042] FIG. 12A shows the 80%/20% ratio of methyl:phenyl side chains maintained optical clarity at Day 0 and 6 months (FIG. 12B) in BSS at room temperature. FIG. 12C demonstrates the 50/50% ratio of methyl:phenyl side chains on siloxane backbone showed signs of emulsification in BSS at week 2.

[0043] FIG. 13 shows exemplary ERG results in New Zealand White rabbit.

DETAILED DESCRIPTION OF THE INVENTION

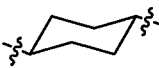
[0044] As used herein the specification, "a" or "an" may mean one or more. As used herein in the claim(s), when used in conjunction with the word "comprising", the words "a" or "an" may mean one or more than one. As used herein "another" may mean at least a second or more. In specific embodiments, aspects of the invention may "consist essentially of" one or more sequences of the invention, for example.

[0045] When used in the context of a chemical group, "hydrogen" means $-H$; "hydroxy" means $-OH$; "oxo" means $=O$; "halo" means independently $-F$, $-Cl$, $-Br$ or $-I$; "amino" means $-NH_2$ (see below for definitions of groups containing the term amino, *e.g.*, alkylamino); "hydroxyamino" means $-NHOH$; "nitro" means $-NO_2$; imino means $=NH$ (see below for definitions of groups containing the term imino, *e.g.*, alkylimino); "cyano" means $-CN$; "azido" means $-N_3$; in a monovalent context "phosphate" means $-OP(O)(OH)_2$ or a deprotonated form thereof; in a divalent context "phosphate" means $-OP(O)(OH)O-$ or a deprotonated form thereof; "mercapto" means $-SH$; "thio" means $=S$; "thioether" means $-S-$; "sulfonamido" means $-NHS(O)_2-$ (see below for definitions of groups containing the term sulfonamido, *e.g.*, alkylsulfonamido); "sulfonyl" means $-S(O)_2-$ (see below for definitions of groups containing the term sulfonyl, *e.g.*, alkylsulfonyl); "sulfinyl" means $-S(O)-$ (see below for definitions of groups containing the term sulfinyl, *e.g.*, alkylsulfinyl); and "silyl" means $-SiH_3$ (see below for definitions of group(s) containing the term silyl, *e.g.*, alkylsilyl).

[0046] For the groups below, the following parenthetical subscripts further define the groups as follows: "(Cn)" defines the exact number (n) of carbon atoms in the group. "(C $\leq$ n)" defines the maximum number (n) of carbon atoms that can be in the group, with the minimum number of carbon atoms in such at least one, but otherwise as small as

possible for the group in question, *e.g.*, it is understood that the minimum number of carbon atoms in the group “alkenyl_(C≤8)” is two. For example, “alkoxy_(C≤10)” designates those alkoxy groups having from 1 to 10 carbon atoms (*e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or any range derivable therein (*e.g.*, 3 to 10 carbon atoms). (Cn-n') defines both the minimum (n) and maximum number (n') of carbon atoms in the group. Similarly, “alkyl_(C2-10)” designates those alkyl groups having from 2 to 10 carbon atoms (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9, or 10, or any range derivable therein (*e.g.*, 3 to 10 carbon atoms)).

[0047] The term “alkyl” when used without the “substituted” modifier refers to a non-aromatic monovalent group with a saturated carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. The groups, -CH₃ (Me), -CH₂CH₃ (Et), -CH₂CH₂CH₃ (*n*-Pr), -CH(CH₃)₂ (*iso*-Pr), -CH(CH₂)₂ (cyclopropyl), -CH₂CH₂CH₂CH₃ (*n*-Bu), -CH(CH₃)CH₂CH₃ (*sec*-butyl), -CH₂CH(CH₃)₂ (*iso*-butyl), -C(CH₃)₃ (*tert*-butyl), -CH₂C(CH₃)₃ (*neo*-pentyl), cyclobutyl, cyclopentyl, cyclohexyl, and cyclohexylmethyl are non-limiting examples of alkyl groups. The term “substituted alkyl” refers to a non-aromatic monovalent group with a saturated carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The following groups are non-limiting examples of substituted alkyl groups: -CH₂OH, -CH₂Cl, -CH₂Br, -CH₂SH, -CF₃, -CH₂CN, -CH₂C(O)H, -CH₂C(O)OH, -CH₂C(O)OCH₃, -CH₂C(O)NH₂, -CH₂C(O)NHCH₃, -CH₂C(O)CH₃, -CH₂OCH₃, -CH₂OCH₂CF₃, -CH₂OC(O)CH₃, -CH₂NH₂, -CH₂NHCH₃, -CH₂N(CH₃)₂, -CH₂CH₂Cl, -CH₂CH₂OH, -CH₂CF₃, -CH₂CH₂OC(O)CH₃, -CH₂CH₂NHCO₂C(CH₃)₃, and -CH₂Si(CH₃)₃.

[0048] The term “alkanediyl” when used without the “substituted” modifier refers to a non-aromatic divalent group, wherein the alkanediyl group is attached with two σ-bonds, with one or two saturated carbon atom(s) as the point(s) of attachment, a linear or branched, cyclo, cyclic or acyclic structure, no carbon-carbon double or triple bonds, and no atoms other than carbon and hydrogen. The groups, -CH₂- (methylene), -CH₂CH₂-, -CH₂C(CH₃)₂CH₂-, -CH₂CH₂CH₂-, and , are non-limiting examples of alkanediyl groups. The term “substituted alkanediyl” refers to a non-aromatic monovalent group, wherein the alkyndiyl group is attached with two σ-bonds, with one or two saturated carbon atom(s) as the point(s) of attachment, a linear or branched, cyclo, cyclic or acyclic

structure, no carbon-carbon double or triple bonds, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The following groups are non-limiting examples of substituted alkanediyl groups: $-\text{CH}(\text{F})-$, $-\text{CF}_2-$, $-\text{CH}(\text{Cl})-$, $-\text{CH}(\text{OH})-$, $-\text{CH}(\text{OCH}_3)-$, and $-\text{CH}_2\text{CH}(\text{Cl})-$.

5 **[0049]** The term “alkenyl” when used without the “substituted” modifier refers to a monovalent group with a nonaromatic carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, and no atoms other than carbon and hydrogen. Non-limiting examples of alkenyl groups include: $-\text{CH}=\text{CH}_2$ (vinyl), $-\text{CH}=\text{CHCH}_3$,
10 $-\text{CH}=\text{CHCH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}=\text{CH}_2$ (allyl), $-\text{CH}_2\text{CH}=\text{CHCH}_3$, and $-\text{CH}=\text{CH}-\text{C}_6\text{H}_5$. The term “substituted alkenyl” refers to a monovalent group with a nonaromatic carbon atom as the point of attachment, at least one nonaromatic carbon-carbon double bond, no carbon-carbon triple bonds, a linear or branched, cyclo, cyclic or acyclic structure, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. The
15 groups, $-\text{CH}=\text{CHF}$, $-\text{CH}=\text{CHCl}$ and $-\text{CH}=\text{CHBr}$, are non-limiting examples of substituted alkenyl groups.

[0050] The term “alkynyl” when used without the “substituted” modifier refers to a monovalent group with a nonaromatic carbon atom as the point of attachment, a linear or branched, cyclo, cyclic or acyclic structure, at least one carbon-carbon triple bond, and no
20 atoms other than carbon and hydrogen. The groups, $-\text{C}\equiv\text{CH}$, $-\text{C}\equiv\text{CCH}_3$, $-\text{C}\equiv\text{CC}_6\text{H}_5$ and $-\text{CH}_2\text{C}\equiv\text{CCH}_3$, are non-limiting examples of alkynyl groups. The term “substituted alkynyl” refers to a monovalent group with a nonaromatic carbon atom as the point of attachment and at least one carbon-carbon triple bond, a linear or branched, cyclo, cyclic or acyclic structure, and at least one atom independently selected from the group consisting of N, O, F, Cl, Br, I,
25 Si, P, and S. The group, $-\text{C}\equiv\text{CSi}(\text{CH}_3)_3$, is a non-limiting example of a substituted alkynyl group.

[0051] The term “aryl” when used without the “substituted” modifier refers to a monovalent group with an aromatic carbon atom as the point of attachment, said carbon atom forming part of one or more six-membered aromatic ring structure(s) wherein the ring atoms
30 are all carbon, and wherein the monovalent group consists of no atoms other than carbon and hydrogen. Non-limiting examples of aryl groups include phenyl (Ph), methylphenyl, (dimethyl)phenyl, $-\text{C}_6\text{H}_4\text{CH}_2\text{CH}_3$ (ethylphenyl), $-\text{C}_6\text{H}_4\text{CH}_2\text{CH}_2\text{CH}_3$ (propylphenyl),

$-\text{C}_6\text{H}_4\text{CH}(\text{CH}_3)_2$, $-\text{C}_6\text{H}_4\text{CH}(\text{CH}_2)_2$, $-\text{C}_6\text{H}_3(\text{CH}_3)\text{CH}_2\text{CH}_3$ (methylethylphenyl),
 $-\text{C}_6\text{H}_4\text{CH}=\text{CH}_2$ (vinylphenyl), $-\text{C}_6\text{H}_4\text{CH}=\text{CHCH}_3$, $-\text{C}_6\text{H}_4\text{C}\equiv\text{CH}$, $-\text{C}_6\text{H}_4\text{C}\equiv\text{CCH}_3$, naphthyl,
 and the monovalent group derived from biphenyl. The term “substituted aryl” refers to a
 5 monovalent group with an aromatic carbon atom as the point of attachment, said carbon atom
 forming part of one or more six-membered aromatic ring structure(s) wherein the ring atoms
 are all carbon, and wherein the monovalent group further has at least one atom independently
 selected from the group consisting of N, O, F, Cl, Br, I, Si, P, and S. Non-limiting examples
 of substituted aryl groups include the groups: $-\text{C}_6\text{H}_4\text{F}$, $-\text{C}_6\text{H}_4\text{Cl}$, $-\text{C}_6\text{H}_4\text{Br}$, $-\text{C}_6\text{H}_4\text{I}$,
 $-\text{C}_6\text{H}_4\text{OH}$, $-\text{C}_6\text{H}_4\text{OCH}_3$, $-\text{C}_6\text{H}_4\text{OCH}_2\text{CH}_3$, $-\text{C}_6\text{H}_4\text{OC}(\text{O})\text{CH}_3$, $-\text{C}_6\text{H}_4\text{NH}_2$, $-\text{C}_6\text{H}_4\text{NHCH}_3$,
 10 $-\text{C}_6\text{H}_4\text{N}(\text{CH}_3)_2$, $-\text{C}_6\text{H}_4\text{CH}_2\text{OH}$, $-\text{C}_6\text{H}_4\text{CH}_2\text{OC}(\text{O})\text{CH}_3$, $-\text{C}_6\text{H}_4\text{CH}_2\text{NH}_2$, $-\text{C}_6\text{H}_4\text{CF}_3$, $-\text{C}_6\text{H}_4\text{CN}$,
 $-\text{C}_6\text{H}_4\text{CHO}$, $-\text{C}_6\text{H}_4\text{C}(\text{O})\text{CH}_3$, $-\text{C}_6\text{H}_4\text{C}(\text{O})\text{C}_6\text{H}_5$, $-\text{C}_6\text{H}_4\text{CO}_2\text{H}$, $-\text{C}_6\text{H}_4\text{CO}_2\text{CH}_3$,
 $-\text{C}_6\text{H}_4\text{CONH}_2$, $-\text{C}_6\text{H}_4\text{CONHCH}_3$, and $-\text{C}_6\text{H}_4\text{CON}(\text{CH}_3)_2$.

[0052] The term “aralkyl” when used without the “substituted” modifier refers
 to the monovalent group $-\text{alkanediyl-aryl}$, in which the terms alkanediyl and aryl are each
 15 used in a manner consistent with the definitions provided above. Non-limiting examples of
 aralkyls are: phenylmethyl (benzyl, Bn), 1-phenyl-ethyl, 2-phenyl-ethyl, indenyl and 2,3-
 dihydro-indenyl, provided that indenyl and 2,3-dihydro-indenyl are only examples of aralkyl
 in so far as the point of attachment in each case is one of the saturated carbon atoms. When
 the term “aralkyl” is used with the “substituted” modifier, either one or both the alkanediyl
 20 and the aryl is substituted. Non-limiting examples of substituted aralkyls are: (3-
 chlorophenyl)-methyl, 2-oxo-2-phenyl-ethyl (phenylcarbonylmethyl), 2-chloro-2-phenyl-
 ethyl, chromanyl where the point of attachment is one of the saturated carbon atoms, and
 tetrahydroquinoliny where the point of attachment is one of the saturated atoms.

[0053] The term “heteroaryl” when used without the “substituted” modifier
 25 refers to a monovalent group with an aromatic carbon atom or nitrogen atom as the point of
 attachment, said carbon atom or nitrogen atom forming part of an aromatic ring structure
 wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the
 monovalent group consists of no atoms other than carbon, hydrogen, aromatic nitrogen,
 aromatic oxygen and aromatic sulfur. Non-limiting examples of aryl groups include
 30 acridinyl, furanyl, imidazoimidazolyl, imidazopyrazolyl, imidazopyridinyl,
 imidazopyrimidinyl, indolyl, indazoliny, methylpyridyl, oxazolyl, phenylimidazolyl, pyridyl,
 pyrrolyl, pyrimidyl, pyrazinyl, quinolyl, quinazolyl, quinoxalinyl, tetrahydroquinoliny,

thienyl, triazinyl, pyrrolopyridinyl, pyrrolopyrimidinyl, pyrrolopyrazinyl, pyrrolotriazinyl, pyrroloimidazolyl, chromenyl (where the point of attachment is one of the aromatic atoms), and chromanyl (where the point of attachment is one of the aromatic atoms). The term “substituted heteroaryl” refers to a monovalent group with an aromatic carbon atom or nitrogen atom as the point of attachment, said carbon atom or nitrogen atom forming part of an aromatic ring structure wherein at least one of the ring atoms is nitrogen, oxygen or sulfur, and wherein the monovalent group further has at least one atom independently selected from the group consisting of non-aromatic nitrogen, non-aromatic oxygen, non aromatic sulfur F, Cl, Br, I, Si, and P.

[0054] The term “heteroaralkyl” when used without the “substituted” modifier refers to the monovalent group –alkanediyl–heteroaryl, in which the terms alkanediyl and heteroaryl are each used in a manner consistent with the definitions provided above. Non-limiting examples of aralkyls are: pyridylmethyl, and thienylmethyl. When the term “heteroaralkyl” is used with the “substituted” modifier, either one or both the alkanediyl and the heteroaryl is substituted.

[0055] The term “alkoxy” when used without the “substituted” modifier refers to the group –OR, in which R is an alkyl, as that term is defined above. Non-limiting examples of alkoxy groups include: –OCH₃, –OCH₂CH₃, –OCH₂CH₂CH₃, –OCH(CH₃)₂, –OCH(CH₂)₂, –O–cyclopentyl, and –O–cyclohexyl. The term “substituted alkoxy” refers to the group –OR, in which R is a substituted alkyl, as that term is defined above. For example, –OCH₂CF₃ is a substituted alkoxy group.

[0056] Similarly, the terms “alkenyloxy”, “alkynyloxy”, “aryloxy”, “aralkoxy”, “heteroaryloxy”, “heteroaralkoxy” and “acyloxy”, when used without the “substituted” modifier, refers to groups, defined as –OR, in which R is alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively, as those terms are defined above. When any of the terms alkenyloxy, alkynyloxy, aryloxy, aralkyloxy and acyloxy is modified by “substituted,” it refers to the group –OR, in which R is substituted alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl and acyl, respectively.

[0057] The term “alkylsilyl” when used without the “substituted” modifier refers to a monovalent group, defined as –SiH₂R, –SiHRR', or –SiRR'R'', in which R, R' and R'' can be the same or different alkyl groups, or any combination of two of R, R' and R'' can

be taken together to represent an alkanediyl. The groups, $-\text{SiH}_2\text{CH}_3$, $-\text{SiH}(\text{CH}_3)_2$, $-\text{Si}(\text{CH}_3)_3$ and $-\text{Si}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$, are non-limiting examples of unsubstituted alkylsilyl groups. The term “substituted alkylsilyl” refers to $-\text{SiH}_2\text{R}$, $-\text{SiHRR}'$, or $-\text{SiRR}'\text{R}''$, in which at least one of R, R' and R'' is a substituted alkyl or two of R, R' and R'' can be taken together to represent a substituted alkanediyl. When more than one of R, R' and R'' is a substituted alkyl, they can be the same or different. Any of R, R' and R'' that are not either substituted alkyl or substituted alkanediyl, can be either alkyl, either the same or different, or can be taken together to represent a alkanediyl with two or more saturated carbon atoms, at least two of which are attached to the silicon atom.

[0058] A “monomeric” is the simplest structural entity of certain materials, for example, polymers. In the case of a polymer chain, monomeric units are linked together successively along the chain, like the beads of a necklace. The skilled artisan would readily recognize that this polymer chain is often referred to as the polymer “backbone.” For example, in polyethylene, $[-\text{CH}_2\text{CH}_2-]_n$, the repeat unit is $-\text{CH}_2\text{CH}_2-$, and the polymer backbone is made of the repeating ethylene units. The subscript “n” denotes the degree of polymerization, that is, the number of repeat units linked together. When the value for “n” is left undefined, it simply designates repetition of the formula within the brackets as well as the polymeric nature of the material. Where the polymer backbone comprises two or more different monomeric units, the degree of polymerization may be denoted by one or more of the following subscripts “m, n, o, p,” The concept of a monomeric unit applies equally to where the connectivity between the monomeric units extends three dimensionally, such as in cross-linked polymers, thermosetting polymers, etc.

[0059] A “heteropolymer” or “copolymer” is a polymer derived from two (or more) monomeric units, as opposed to a homopolymer where only one monomeric unit is used. Since a copolymer consists of at least two types of monomeric units, copolymers can be classified based on how these units are arranged along the polymer backbone. These include: alternating, periodic, statistical and block copolymers. Alternating copolymers have regular alternating A and B units, where “A” denotes a monomeric unit that is chemically or structurally different from a second monomeric unit represented by “B.” Periodic copolymers have A and B units arranged in a repeating sequence (e.g. $(\text{A-B-A-B-B-A-A-A-A-B-B-B})_n$) wherein n is equal to at least 1. Statistical Copolymers are copolymers in which the sequence of monomer residues follows a statistical rule. If the probability of finding a

given type monomer residue at a particular point in the chain is equal to the mole fraction of that monomer residue in the chain, then the polymer may be referred to as a truly random copolymer or “randomer”. Block copolymers comprise two or more homopolymer subunits linked by covalent bonds (e.g. -A-A-A-A-B-B-B-B-). The union of the homopolymer subunits may require an intermediate non-repeating subunit, known as a junction block (e.g. -A-A-A-A-O-B-B-B-B-). For example, block copolymers with two or three distinct blocks are called diblock copolymers and triblock copolymers, respectively. Copolymers may also be described in terms of the existence of or arrangement of branches in the polymer structure. Linear copolymers consist of a single main polymer backbone whereas branched copolymers consist of a single main polymer backbone with one or more polymeric side backbones.

[0060] The above definitions supersede any conflicting definition in any of the reference that is incorporated by reference herein. The fact that certain terms are defined, however, should not be considered as indicative that any term that is undefined is indefinite. Rather, all terms used are believed to describe the invention in terms such that one of ordinary skill can appreciate the scope and practice the present invention.

I. Definitions

[0061] The term “antioxidant” or “radical scavenger” are used interchangeably herein and as used herein refers to a moiety that will react with a 7-electron-containing atom on a molecule to produce a more stable 7-electron-containing atom on a molecule. That more stable 7-electron species does not readily react further with 8- or 2-electron-containing atoms to generate a new 7-electron-containing atom. This more stable 7-electron species can either remain in that state or combine with another 7-electron species, thereby preventing the generation of other 7-electron-containing atoms which can lead to degradation of the material or further molecule-changing cascades.

[0062] The term “tamponade” as used herein refers to the ability to displace aqueous humor or liquified vitreous (syneretic vitreous) from a break or opening in the retina. This mechanism is mediated by a high surface interfacial tension with water. Tamponade is also used in definition as to occlude an opening.

[0063] Retinal detachments are considered a medical emergency and may result in the complete loss of vision in the eye. Retinal detachments can occur due to vitreous traction from eye diseases or trauma on the retina causing a retinal tear or break in which fluid

can then travel into the subretinal space and detach the retina. Current intraoperative tamponade agents such as gas or polydimethylsiloxane silicone oil are used to help reattach the detached retina. These tamponade agents make contact with the retina, prevent passage of aqueous through a break in the retina, and displace water since aqueous contains a pro-inflammatory milieu that facilitates the development of proliferative vitreoretinopathy. The present invention improves on these compositions by employing characteristics that avoid disadvantages of the currently used compositions.

[0064] In certain embodiments of the present invention, the silicone oils that are utilized are considered heavy, and in specific embodiments the oil is considered heavy if it has a density greater than 1.0 g/mL. Current heavy silicone oils are either fluorinated siloxanes, fluorohydrocarbons, or mixtures of fluorohydrocarbons and polydimethylsiloxane, yet the present invention lacks any silohalogen bonds, in specific embodiments. In alternate embodiments, the heavy silicone oils are free of any silohalogen bonds or lack silohalogen bonds. By using denser side chains, along with the alkyl units, the density of polysiloxane, or other silicone oils, for example can be increased from 0.972 g/mL to greater than 1.0 g/mL. In specific embodiments of the invention, fluoride, due to its high electron affinity, acts as a leaving group, thereby stimulating significant inflammation likely through fluoride anion generation by S_N2 displacement. In certain embodiments of the invention, the siloxane backbone is modified with heavier side chains, such as dichlorobenzyl or methylphenyl groups, for example. In the cases where the chloride is on the aryl unit, it is not subject to S_N2 displacement. In particular cases, utilizing denser side chains increases the overall density of the polymer while preserving the hydrophobic properties of silicone oil, which is important in creating a high interfacial surface tension to tamponade the retina. In addition, avoiding the use of fluoride ions produces a more biocompatible polymer, in particular aspects of the invention.

[0065] The present disclosure provides a silicone oil composition that can be used in vitreoretinal surgery as a tamponade agent and a method for implementing the tamponade agent during vitreoretinal application, for example.

II. General Embodiments of the Invention

[0066] The present invention concerns one or more novel biocompatible heavy silicone oil materials, methods of their use, and engineering thereof. In specific aspects, the invention includes synthesis, characterization, and purification of heavy silicone oil. In

particular aspects, a heavy silicone oil is synthesized by adding denser side chains to the backbone to increase the overall density, for example.

[0067] The basic role of any tamponade agent is to make contact with the retina and prevent passage of aqueous through the break. Another important role is to displace aqueous from the vicinity of the break, as aqueous contains a pro-inflammatory milieu that is responsible for development of proliferative vitreoretinopathy. In general embodiments of the invention, the tamponade agent is a silicone oil. In some examples, the silicone oil has a density of greater than 1. In other examples, the silicone oil has a density of less than 1. In general, the density of the silicone oil can be manipulated by incorporating alkyl_(C = 1-18), substituted alkyl_(C = 1-18), alkenyl_(C = 2-18), substituted alkenyl_(C = 2-18), alkynyl_(C = 3-18), substituted alkynyl_(C = 3-18), aryl, substituted aryl_(C = 6-18), aralkyl_(C = 6-18), substituted aralkyl_(C = 6-18), heteroaryl_(C = 1-8), substituted heteroaryl_(C = 6-18), heteroaralkyl_(C = 6-18), substituted heteroaralkyl_(C = 6-18), alkoxy_(C = 1-18), and/or substituted alkoxy_(C = 1-18) functionalities into the polymer backbone of the silicone oil. For example, the density of polydimethylsiloxane can be increased from 0.972 g/mL to greater than 1.0 g/mL by polymerizing alkyl and/or aryl functionalized monomers that incorporate alkyl and/or aryl side chains into the polymer backbone.

[0068] Utilizing denser side chains increases the overall density of the polymer while preserving the hydrophobic properties of silicone oil, which is important in creating a high interfacial surface tension to tamponade the retina.

A. General Properties of a Specific Embodiment of Heavy Silicone Oil

[0069] In certain embodiments of the invention, the silicone oil has one or more of the following characteristics:

[0070] 1) optically transparent;

[0071] 2) biologically compatible/minimal inflammation;

[0072] 3) in certain embodiments, a specific gravity of greater than 1.0072 g/mL since the density of BSS at room temperature is 1.0072 g/mL; A minimum density is greater than 1.00 g/mL, in certain embodiments. In specific cases, there is a maximum density of no greater than 3.0 g/mL or 2.0 g/mL.

[0073] 4) in certain embodiments, high interfacial surface tension with water (≥ 40 mN/m, interface tension against water of polydimethylsiloxane)

[0074] 5) in certain embodiments, there is no silohalogen bond in the composition

[0075] The skilled artisan recognizes that the density of BSS (an exemplary aqueous humor equivalent) can be calculated based on previous formulas on water density as a function of temperature and salinity (McCutcheon, S.C., Martin, J.L, Barnwell, T.O. Jr. 1993. Water Quality in Maidment, D.R. (Editor). Handbook of Hydrology, McGraw-Hill, New York, NY (p. 11.3). BSS at 25°C is 1.007227 g/mL and at 37°C is 1.003334 g/mL.

[0076] Table 1 below displays physical properties for exemplary oils used in the art. However, in certain embodiments of the present invention, the oils includes at least in part a range of the parameters below.

TABLE 1. Physical Properties of the Silicone Oils and SFAs Used

	Admixture (Weight %)	Molecular Weight (g/mol)	Specific Gravity (g/cm ³) (25°C)	Boiling Point (°C)	Refractive Index (20° C)	Surface Tension against Air (mN/m)	Interface Tension against Water (mN/m)	Viscosity (mPa) (25° C)
Silicone oil 1000	—	—	0.97	—	1.404	20.9	39.4	≈ 1000
Silicone oil 3000	50% Sil 1000	—	0.97	—	1.404	21.1	42.5	≈ 3000
	50% Sil 5000	—	—	—	—	—	—	—
Silicone oil 5000	—	—	0.97	—	1.404	20.80	43.01	≈ 5000
Densiron 68	30.5% F6H8	—	1.06	—	1.387	19.13	40.82	≈ 1500
	69.5% % Sil 5000	—	—	—	—	—	—	—
HSO 45-3000	55% F4H5	—	1.118	—	1.366	18.7	41.3	2903
	45% SIL 100,000	—	—	—	—	—	—	—
HSO 45-5000	41.5% F4H5	—	1.076	—	1.377	18.8	44.6	5120
	58.5% SIL 60,000	—	—	—	—	—	—	—
HSO 46-3000	55% F4H6	—	1.105	—	1.369	19.2	39.5	3109
	45% SIL 100,000	—	—	—	—	—	—	—
HSO 46-5000	41.5% F4H6	—	1.064	—	1.379	19.7	39.7	5245
	58.5% SIL 60,000	—	—	—	—	—	—	—
HSO 48-3000	54.5% F4H8	—	1.085	—	1.376	20.2	40.4	3477
	45.5% SIL 100,000	—	—	—	—	—	—	—
HSO 48-5000	41.5% F4H8	—	1.054	—	1.384	20.3	40.7	5784
	58.5% SIL 60,000	—	—	—	—	—	—	—
F6H8	—	432	1.33	223	1.343	19.7	45.3	3.44
F4H5	—	290.17	1.284	134	1.320	17.43	43.03	1.05
F4H6	—	304.20	1.254	163	1.334	18.74	39.87	1.28
F4H8	—	332.25	1.208	196	1.348	19.63	27.09	1.95

Extracted from “*In Vivo* Retinal Tolerance of Various Heavy Silicone Oils.” Mackiewicz et al. IOVS 48(4): 1873-1883.

[0077] The nature of an R group that is bound to the silicone backbone will affect the density of the oil. In certain embodiments of the invention, the modifiable parameters for the tamponade composition are (1) the side chains on siloxane backbone, (2) the length of the siloxane backbone, and (3) other potential variable modifications for different engineered effects.

[0078] 1) Side chains on siloxane backbone

[0079] Currently utilized silicone oil is highly purified polydimethylsiloxane of varying viscosities. In certain embodiments of the invention, the side chains of the siloxane groups are modified to have a higher percentage of aryl groups in order to increase the overall density of the polymer. In a specific embodiment, a polydimethylphenylsiloxane with varying ratios of methyl/phenyl groups is employed. In some cases, other side chains can be utilized, such as having dichlorobenzyl, benzyl, and alkyl phenyl, for example.

[0080] 2) Length of siloxane backbone

[0081] Longer length chain polymers increase the van der Waals interaction of the substance, thereby increasing the polymer's viscosity. Prior studies have shown that higher viscosity materials have lower rates of emulsification, however, this makes the oil more difficult to manipulate in surgery during injection and aspiration, necessitating high forces when working through small gauge instruments; this makes it precarious to perform when working so closely with the retina. Ideal viscosities currently used in vitreoretinal surgeries range from 100 centiStokes to 5000 centiStokes materials, and in certain examples disclosed herein the tamponade composition includes at least one silicone oil with a viscosity in this range.

[0082] 3) Potential variable modifications for different engineered effects

[0083] In specific examples, a functional group capable of being a free radical scavenger is added to at least one of the side chains of the silicone backbone, such as methylphenyls or phenols or tert-butylphenols, for example. In other cases, free radical scavengers are added exogenously to the polymer mixture, such as the butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). Often a low water solubility of the exogenous radical scavenger, as found in BHA and BHT, is preferred so as to keep them predominantly in the polymer phase rather than in the aqueous phase of the eye. Free radicals have been shown to accelerate progression of cataract formation in vitreoretinal surgery as well as shown to be upregulated in diseases such as age-related macular degeneration. By adding free radical scavenger groups that are biocompatible, in certain cases one can prevent cataract formation and/or treat vitreoretinal diseases. In particular embodiments disclosed herein, biologically active molecules are added to the side chains to facilitate drug delivery; examples include steroids such as fluocinolone and triamcinolone or VEGF-blocking peptides such as ranibuzimab or bevacizumab. Generally, conjugated biologically active molecules

will only be effective if they mediate their biological effects through surface cellular interactions unless a targeting peptide is utilized since the silicone oil monomers are less likely to be incorporated intracellularly without a targeting peptide.

[0084] The skilled artisan recognizes that adding side chains on a siloxane backbone can destabilize silicone oils when used in an ionic solution (such as all biological environments like the aqueous humor of the eye). When adding design modifications onto a siloxane backbone, the net effect must maintain a stable environment for the silicone oil not to emulsify in ionic solutions.

[0085] Also, the variability of the methyl to phenyl groups (as examples only) can be achieved in one monomeric unit instead of by multiple monomeric units, for example, and this applies to any of the silicone oils disclosed herein, including where instead of methyl and phenyl groups being utilized, other groups are employed.

B. Free Radical Scavengers

[0086] In certain embodiments disclosed herein, the composition includes a tamponade agent, and further comprises a free radical scavenger, which may also be referred to as an antioxidant (and can be a reducing agent such as a thiol, ascorbic acid or polyphenol). The antioxidant may be given to the individual during, before, and/or after the time of treatment for the eye. Although the antioxidant may be given during the time of retinal detachment treatment as part of a tamponade composition, in some embodiments the antioxidant is given outside of the composition, for example, systemically, or subcutaneously. In specific cases, the antioxidant is present on the backbone and/or R group of the tamponade agent, whereas in other embodiments the antioxidant is otherwise part of the composition.

[0087] Any biocompatible antioxidant may be included in the silicone oil, but in particular embodiments, the silicone oil includes the antioxidant includes edaravone (MCI-186) or glutathione, for example.

EXAMPLES

[0088] The following examples are included to demonstrate preferred embodiments of the invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to

constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

5

EXAMPLE 1

TOXICITY EVALUATION

[0089] In general, animal model toxicity evaluation of heavy silicone oil in rabbit eyes is performed. A pars plana vitrectomy is performed and placement of heavy silicone oil. The eyes are examined post-operatively for signs of inflammation.

10 Electrophoretography is utilized to evaluate photoreceptor response after exposure to the bioengineered material. At each time point, the rabbits are examined for any long-term biological effects exerted by exposure to the heavy silicone oil. The retina tissue from the enucleated eyes is examined histopathologically for any signs of toxicity secondary to exposure to heavy silicone oil.

15 Animal Experimentation Protocol

[0090] Safety studies are performed prior to the use of any new materials within the human eye, in general embodiments. Rabbit eyes are an established model for the human vitreous structure. The rabbit model has been a proven and traditionally employed model for such a study, because the size of the eye permits surgical manipulation and placement of
20 silicone oil to reliably assess subtle ocular changes to evaluation toxicity. The rabbit model has been used for studying the toxicity of prior retinal tamponade agents, such as the currently used silicone oil and gases (Mackiewicz *et al.*, 2007; Yang *et al.*, 2008; Singh *et al.*, 2008). It offers the advantages of most closely approximating the human eye in both form and function to undergo similar surgical procedures, pars plana vitrectomy, and appropriately evaluation of
25 biocompatibility.

[0091] Rabbits are anesthetized and undergo a pars plana vitrectomy. Pupils are dilated using Tropicamide 1% and Phenylephrine 2.5%. Proper sterile technique and draping are performed at all times for the surgical procedure. A pars plana vitrector is inserted to remove the vitreous under direct visualization using indirect ophthalmoscopy. A nonpreserved
30 lubricant ointment and contact lens is used to visualize the entire surgical procedure. The heavy silicone oil is then placed into the vitreous cavity and appropriate closure of the rabbit

eye obtained. The rabbits are evaluated under anesthesia through direct visualization of the retina and electroretinography at specified serial intervals from the time of surgical procedure to the time of sacrifice. The rabbits are evaluated with direct visualization on post-operative day #1, week #1, and monthly up to 3 months. Depending on the clinical findings at each exam, the frequency of direct visualization follow-up may be more or less frequent to ensure appropriate monitoring and care of the rabbits. Electroretinography are performed at week #1, month #1, and month #3 exams.

[0092] Electroretinography. The rabbits are allowed to dark adapt for one hour prior to testing. Under dim red light, rabbits are anesthetized and pupils dilated with topical medication.

[0093] A drop of corneal anesthetic medicine is applied topically and placed on appropriate heating pad to maintain body temperature. A small amount of coupling gel (methylcellulose gel) is applied to the eye and a platinum electrode is placed in contact with the center of the cornea. Similar platinum reference and ground electrodes are placed on the forehead and body, respectively. Signals are amplified, acquired, and analyzed with photostimulation to elicit various retinal response waveforms to evaluate retinal function.

[0094] Histopathology is performed after appropriate euthanasia with an overdose of anesthetic DEA-III (as recommended in animal care guidelines). The eyes are then enucleated and placed for fixation immediately in 10% formalin for several days. Gross examinations of the tissues were performed. Tissues are embedded in paraffin, sectioned, and stained for examination under light microscopy.

[0095] The animals are housed in the vivarium at all times when not undergoing any biotoxicity evaluation. Appropriate comfort and pain control is maintained at all times for the animals. A veterinarian is involved in ensuring appropriate animal comfort is maintained at all times if necessary. At the end of the study, the animals are sacrificed and eyes enucleated for histopathologic study and electron microscopy.

[0096] The studies are carried out in accordance with the Association for Research in Vision and Ophthalmology (ARVO) principles of animal maintenance. The total number utilized for an exemplary study is 15. One rabbit is used to perform a brief study 2 week study on the potential safety profile of each modified heavy silicone oil. Among the initial evaluations of each silicone oil, a successful candidate that yields minimal intraocular

inflammation is identified and undergoes a larger safety profile evaluation where 9 rabbits are used to evaluate that particular silicone oil. Three study groups of 3 rabbits are evaluated for biocompatibility at 1 week, 1 month, and 3 months. Each study group yields 6 data points (3 rabbits, 6 eyes) at specified time intervals prior sacrifice for fundoscopic and functional retinal analysis by ERG. The time from surgical introduction of the heavy silicone oil to sacrifice is 1 week, 1 month, and 3 months, for example.

EXAMPLE 2

SPECIFIC EXAMPLE OF HEAVY SILICONE OIL

[0097] In specific embodiments of the invention, there is a novel heavy silicone oil that has a density greater than 1.003334 g/mL, the density of balanced salt solution (BSS) at 37°C. A specific heavy silicone oil has a density of 1.104 g/mL and an interfacial surface tension average value of 68 mN/m. Clinical grade 1000 centistokes silicone oil has a surface tension average value of 46 mN/m. The solution has remained clear and transparent in BSS for at least 5 months.

[0098] One exemplary strong candidate of various methyl/phenyl formulation was the 80/20% ratio of methyl:phenyl side chains on siloxane backbone. As shown in the FIG. 1A and 1B below, no signs of emulsification occurred in BSS at least at 5 months. The 50/50% ratio of methyl:phenyl side chains on siloxane backbone showed signs of emulsification in BSS at week 2, consistent with prior reported findings of polydiphenylsiloxanes becoming emulsified in ionic solutions (Heidenkummer *et al.*, 1991).

[0099] The inventors then tested the 80/20% (methyl/phenyl) ratio heavy silicone oil formulation in rabbit eyes. The oil showed no signs of intraocular inflammation on ophthalmoscopy at post-operative day 35. No post-operative inflammatory medications were given to the rabbit which allowed the monitoring of the native response to silicone oil. Intraocular oil fill was 95% of the eye post-vitreectomy.

[0100] ERG measurements were expected to have a deviation of 10-20% from measurement to measurement due to variations in retinal function throughout the day, as well as variations in electrode coupling to the eye. Therefore, ERG wave pattern is equally as important to evaluate as the magnitude. ERG waveform remains intact with a decrease amplitude at post-operative day 6 compared to baseline, which is an expected result post-operatively. Post-operative inflammation of any vitreoretinal surgery is known

to cause an initial post-operative decrease in ERG. FIG. 4 demonstrates a return rise in ERG at post-operative day 35 with a normal waveform.

[0101] The magnitude of the ERG is within normal limits of variation compared with the baseline ERG obtained pre-operatively. Gross sectioning showed good oil fill and no signs of retinal detachment at post-operative day 35. Histological sectioning showed mild vitreous inflammation. Mild vitreous inflammation is also typically seen with clinical grade silicone oil that is currently being utilized. The 80% methyl: 20% phenyl ratio heavy oil demonstrated post-operative inflammation no greater than currently utilized lighter-than-water silicone oil. Retinal architecture was normal with no signs of retinal degradation or distortion or apoptosis. Thus, the invention encompasses a heavier-than-water vitreous tamponade agent that has beneficial heavy vitreous properties and is biologically compatible. In some cases, a large-scale rabbit eye toxicity evaluation of the heavy oil and its various modifications is performed, including employing it in vitreoretinal surgery for vitreoretinal diseases and retinal repair, for example.

EXAMPLE 3

POLYMERS PURIFICATION PROTOCOL

[0102] Polymers were purified through fractional precipitation, which was carried out by incremental addition of phosphate buffered saline (PBS) or water to the polymer acetone solutions, as an example. Although original siloxane polymers can be dissolved in other organic solvents such as THF and CHCl_3 , acetone was chosen because it is less toxic, easier to remove and less expensive. The isolated polymers were first evaporated on an aspirator rotovap at 90°C for 1.5 hours to remove the residual acetone and water. The resulting purified polymers were investigated by SEC and ^1H NMR.

[0103] SEC is used to determine the polymer's molecular weight and weight distributions. According to the SEC analysis before purification (FIG. 5), the original polymer had several components in a broad molecular weight (M_w) distribution. Small M_w , oligomers (M_w less than 1000; retention time (RT) = 18.48 and 19.1 min) may cause immediate or delayed eye irritation. After fractional precipitation, GPC shows that some of these small M_w oligomers can be partially removed (FIG. 6).

[0104] NMR is used to determine the polymer's structure (especially the methyl:phenyl ratio) or impurities. Analysis of the purified sample by NMR (FIG. 7) indicated that there was no residual acetone after rotary evaporation and the methyl:phenyl ratio is about 80/20. ¹H NMR (400MHz, CDCl₃, ppm): 7.27 (m, 5H); 1.55 (s, H₂O) 0.28 (m, 3H).

[0105] Although particular conditions are utilized in this example, in certain embodiments the fractional precipitation comprises (a) dissolving the silicone oil in solvent thereby creating a polymer solution; (b) adding increments of an aqueous solution to the polymer solution until the silicone oil precipitates and form two layers; (c) using a separation funnel to collect the layer containing the purified silicone oil; (d) transferring the purified silicone oil under conditions to remove the majority of the acetone and water (for example, transfer into a Rotovap at 40 °C for 30 min and then 90 °C for 30 min) and (e) placing the purified silicone oil under conditions to remove excess acetone and water (for example, vacuum (0.1 Torr) at 90 °C for 1.5 hours). In specific embodiments, the solvent is a polar aprotic solvent, for example acetone. In specific embodiments, the purified silicone oil is transferred into a Rotovap at 20-40 °C for 30-40 min and then 80-110 °C for 30-40 min to remove the majority of the solvent and water. In some specific cases, the silicone oil is placed under vacuum (0.1 to 0.001 Torr) at 80-110 °C for 1.5-2 hours to remove excess solvent and water.

EXAMPLE 4

RADICAL SCAVENGER SILICONE OIL

[0106] 1. Benzyl silicone oil

[0107] Heavy silicone oil with benzylic (20%) groups was also purified using the same fractional precipitation method described above. The polymer remains clear and transparency in PBS for at least 3 months. FIG. 8 shows NMR spectrum of the purified siloxane polymer with benzylic groups.

[0108] 2. Addition of free radical scavengers to the silicone oil

[0109] Butylated hydroxytoluene (BHT) is known as a food antioxidant additive, which has a good biocompatibility. 2 wt% BHT was successfully dissolved into the silicone oils by stirring at room temperature for 2 hours. Polymer radical sequestering ability

was compared tested using 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay (FIG. 9 and Cheng, et al., 2006). FIG. 9 shows the kinetic behavior of radical scavengers.

[0110] After mixing the silicone oil with BHT, these polymers show an obvious increase of the radical sequestering ability compared to normal PDMS silicone oil. For the benzyl silicone oil (APT) without any BHT, it still shows a moderate ability to scavenge free radicals. This shows that the radical scavenging moiety can be part of the polymer backbone.

EXAMPLE 5

NOVEL HEAVY SILICONE OIL FOR VITREORETINAL APPLICATION

Synthesis, Purification, and Characterization

[0111] Denser aryl side chains (phenyl), for example, were utilized on a siloxane backbone to increase the specific gravity of silicone oil greater than 1.0033 g/mL (density of BSS at 37°C). Poly(methyl:phenyl)siloxanes were investigated in this study. These polymers were purified through fractional precipitation and solvent evaporation and then heat sterilized at 170°C. The purified polymers were then evaluated by gel permeation chromatography and ¹H-NMR spectroscopy for purity. Interfacial surface tension was measured by the pendant drop method by KSV CAM 100.

In vivo Studies

[0112] Biocompatibility of the heavy silicone oil was then tested in a 5 week preliminary pilot study in a New Zealand white rabbit. A core vitrectomy and heavy silicone oil fill were performed without the use of post-operative anti-inflammatory agents. ERG measurements, ophthalmic exams, and histology were performed to evaluate biocompatibility. All animal experiments conformed to the ARVO guidelines for animal use.

[0113] The exemplary poly-phenyl (20%): methyl (80%)-siloxane polymers (FIG. 10) were purified to greater than 99% purity by ¹H-NMR spectroscopy with a density of 1.104 g/mL. Polydispersity index was 1.3. Molecular weight was 1600-2400. The silicone oil we tested are block co-polymers. Measured viscosity was less than 1000 centistokes (cS) with an average interfacial surface tension value of 68 mN/m (clinical grade 1000 cS silicone oil has a measured interfacial tension of 45 mN/m).

In Vivo Results

[0114] *In vivo* studies of the exemplary heavy silicone oil showed no signs of intraocular inflammation on ophthalmoscopy at post-operative day 35. No post-operative inflammatory medications were given to the rabbit to monitor native response to our silicone oil.

5 Rabbit Histopathology

[0115] Gross sectioning showed good oil fill and no signs of retinal detachment at post-operative day 35. Histological sectioning showed minimal vitreous inflammation. The 80% methyl: 20% phenyl ratio heavy oil demonstrated post-operative inflammation no greater than currently utilized lighter-than-water silicone oil. Retinal architecture was normal with no signs of retinal degradation or distortion or apoptosis. (FIGS. 11A-11B).

In Vitro Results

[0116] The 80%/20% ratio of methyl:phenyl side chains maintained optical clarity at Day 0 (left) (FIG. 12A) and 6 months (right) (FIG. 12B) in BSS at room temperature. The 50/50% ratio of methyl:phenyl side chains on siloxane backbone showed signs of emulsification in BSS at week 2 (FIG. 12C).

Rabbit Electrophoretography

[0117] Exemplary ERG results in New Zealand White rabbit (FIG. 13). Right eye served as control vitrectomy. Left eye had a 95% 80/20 Heavy Silicone Oil fill. ERG was performed pre-operatively and post-operatively on day 6 and day 35.

[0118] Thus, in certain embodiments of the invention, there is purification of commercial silicone oil such that the resultant product silicone oil has a particular average ratio of methyl and phenyl side groups. It is known in the art that the greater the amount of phenyl groups, for example, the higher the density of the oil. In specific embodiments, the ratio of methyl to phenyl is about 80:20. In specific embodiments, a ratio of methyl to phenyl is employed wherein the methyl ratio is higher than 50%. In specific embodiments, the ratio of methyl to phenyl is 51:49, 52:48, 53:47, 54:46, 55:45, 56:44, 57:43, 58:42, 59:41, 60:40, 61:39, 62:38, 63:37, 64:36, 65:35, 66:34, 67:33, 68:32, 69:31, 70:30, 71:29, 72:28, 73:27, 74:26, 75:25, 76:24, 77:23, 78:22, 79:21, 80:20, 81:19, 82:18, 83:17, 84:16, 85:15, 86:14, 87:13, 88:12, 89:11, 90:10, 91:9, 92:8, 93:7, 94:6, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0.

[0119] In specific embodiments, the side chains are modified to incorporate free radical scavenger molecules to evaluate their efficacy in post-vitrectomy intraocular reactive changes.

EXAMPLE 6

5 **ADDITIONAL EMBODIMENTS OF THE HEAVY SILICONE OIL FOR VITREORETINAL APPLICATION**

[0120] Although in certain aspects the heavy silicone oil has a particular methyl:phenyl ratio, in other cases the oil has other R groups having a particular ratio, such as a particular average ratio, and the skilled artisan recognizes how to modulate the R groups to
10 affect the density of the oil. Described below are certain exemplary embodiments of utilizing the silicone oil.

Lighter-than-Water Silicone Oil

[0121] In certain aspects, the density of the silicone oil is less than water, such that the oil may be employed for suitable applications, such as for repair of superior retinal
15 defects. The skilled artisan recognizes how to synthesize such an oil based on description herein and/or knowledge in the art or manipulate solvent: aqueous solutions to precipitate out such a lighter oil from commercially available silicone oils.

Silicone Oil in Composition with Radical Scavenger

[0122] In some cases, a silicone oil of the present invention is employed with a
20 radical scavenger. The radical scavenger may be part of a composition that includes a tamponade agent and, therefore, the radical scavenger may be a separate molecule from the tamponade agent. In some cases wherein the radical scavenger is a separate molecule from the tamponade agent, the silicone oil comprises a particular ratio of methyl:phenyl groups on the silicone backbone. In other cases wherein the radical scavenger is a separate molecule
25 from the tamponade agent, the silicone oil comprises a particular ratio of groups on the silicone backbone that are not methyl and/or phenyl.

[0123] In general, the radical scavenger is any chemical moiety that can be added or incorporated into the silicone oil in order to remove, inactivate or reduce the amounts of unwanted free radicals. In some examples, the radical scavenger is an antioxidant
30 where the deleterious radical is on an oxygen atom. In some examples, the radical scavenger

includes but are not limited to Vitamin C, tocopherol, naringenin, Vitamin E, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, beta-carotene, alpha-lipoic acid and acetyl-L-carnitine, selenium, glutathione, cyanidin, cyanidin glycosides, bilirubin, probucol, polyphenols, rottlerin, flavonoids, resveratrol, genistein, tempol, food preservatives, ascorbic acid (AA, E300), tocopherol E306, propyl gallate (PG, E310), tertiary butylhydroquinone (TBHQ), butylated hydroxyanisole (BHA, E320) and butylated hydroxytoluene (BHT, E321), sumatriptan succinate, lomerizine hydrochloride, edaravone, 2-mercaptoethane sulfonate, silymarin, benzotriazoles, benzophenone and synthetic derivatives thereof.

Radical Scavenger Part of Silicone Oil

[0124] In certain cases, the radical scavenger is ionically or covalently bound to the tamponade agent and therefore part of the same molecule. The scavenger may be bound to the silicone backbone or it may be bound to an R group on the silicone backbone, or both.

[0125] In some embodiments, there is a first radical scavenger that is bound to the silicone backbone or to an R group thereon, and there is a second radical scavenger in a composition that is a separate molecule from the silicone oil. The first and second radical scavenger may be the same or different.

[0126] In general, the radical scavenger is attached to the monomeric unit before polymerization through an addition reaction, elimination reaction, substitution reaction, pericyclic reaction, rearrangement reaction and/or redox reaction. After attachment of the radical scavenger, the monomeric unit(s) is polymerized to form the radical scavenger functionalized silicone oil. The radical scavenger functionalized silicone oil is then purified by fractional precipitation and characterized using standard techniques. This general reaction protocol does not exclude protection and deprotection step. The skilled artisan would readily recognize that a plurality of steps may be involved in the complete synthesis of the radical functionalized tamponade agent.

[0127] In general, the polymer backbone is functionalized with a R group independently selected from alkyl_(C = 1-18), substituted alkyl_(C = 1-18), alkenyl_(C = 2-18), substituted alkenyl_(C = 2-18), alkynyl_(C = 3-18), substituted alkynyl_(C = 3-18), aryl, substituted aryl_(C = 6-18), aralkyl_(C = 6-18), substituted aralkyl_(C = 6-18), heteroaryl_(C = 1-8), substituted heteroaryl_(C = 6-18), heteroaralkyl_(C = 6-18), substituted heteroaralkyl_(C = 6-18), alkoxy_(C = 1-18), substituted alkoxy_(C = 1-18). In some examples the polymer backbone is functionalized with a R group independently

selected from alkyl_(C = 1-40), substituted alkyl_(C = 1-40), alkenyl_(C = 2-40), substituted alkenyl_(C = 2-40), alkynyl_(C = 3-40), substituted alkynyl_(C = 3-40), aryl, substituted aryl_(C = 6-40), aralkyl_(C = 6-40), substituted aralkyl_(C = 6-40), heteroaryl_(C = 1-40), substituted heteroaryl_(C = 6-40), heteroaralkyl_(C = 6-40), substituted heteroaralkyl_(C = 6-40), alkoxy_(C = 1-40), substituted alkoxy_(C = 1-40). In specific examples, (Cn-n') ranges from 1 to 40, 2 to 40, 5 to 40, 8 to 40, 15 to 40, 20 to 40, 25 to 40, 30 to 40, 35 to 40, 1 to 20, 2 to 20, 5 to 20, 8 to 20, or 15 to 20.

[0128] In specific examples, the radical scavenger is an antioxidant. In some examples, the radical scavenger incorporated into the polymer backbone includes, but are not limited to Vitamin C, tocopherol, naringenin, Vitamin E, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, beta-carotene, alpha-lipoic acid and acetyl-L-carnitine, selenium, glutathione, cyanidin, cyanidin glycosides, bilirubin, probucol, polyphenols, rottlerin, flavonoids, resveratrol, genistein, tempol, food preservatives, ascorbic acid (AA, E300), tocopherol E306, propyl gallate (PG, E310), tertiary butylhydroquinone (TBHQ), butylated hydroxyanisole (BHA, E320) and butylated hydroxytoluene (BHT, E321), sumatriptan succinate, lomerizine hydrochloride, edaravone, 2-mercaptoethane sulfonate, silymarin, benzotriazoles, benzophenone and synthetic derivatives thereof or even as simple as benzylic hydrogen-containing side chains such as benzyl, toluyl, or phenethyl side chains, or more generally phenalkyl side chains, or phenolic-containing side chains or thiol or arulthiol or amino or arylamino side chains.

EXAMPLE 7

[0129] Experimental details and physical properties of the final products are listed in 6 different groups: PDM-1922 group (Table 2), PMM 0025 Group (Table 3), APT-133 Group (Table 4), APT-233 Group (Table 5), APT-263 Group (Table 6) and Blending Group (Table 7). The group name follows the polymer's commercial name from Gelest Inc. (Morrisville, PA). Each group contains different methods to purify this material. The first row is the sample name and the original date the experiment was performed. The ratio of the starting materials is listed in the second row. The yield indicates how much purified polymers can be collected from this experiment. The final product is put into PBS solution and stabilized for several days (the 3rd row) before the transparency and density tests. There are three grades to describe the final product's transparency: Y(highly transparent), Medium (medium transparent) and N(not transparent). For the density test, PBS solution is to mimic

the actual environment inside the eyes. If the purified polymer sinks in PBS, it is noted as “Y”, meaning heavy silicone oil. Otherwise, it is noted as “N”.

Table 2. PDM-1922 Group (Ph:Me=80:20)

Sample name Date	PDM: Acetone: Water (PBS)	Days	Yield%	Transparency	Sinks in PBS?
Jo 1-3 6/5/09	10.8 g : 40 ml : 50 ml	65	71.3%	Y	Y
Jo 1-6 6/9/09	7g : 40 ml : 50 ml	62	44.1%	Y	Y
Jo 1-15 6/22/09	30g : 120ml : 150ml	48	64.3%	Y	Y
Jo 1-18 6/24/09	28g: 160ml : 200ml	46	47.9%	Y	Y
Jo 1-21 6/29/09	21.11 g : 120 ml : 150 ml	41	37.4%	Y	Y
Jo 1-22 7/1/09	14g : 80ml : 100ml	39	23.2%	Y	Y

5

Sample name Date	PDM: Acetone: Water (PBS)	Days	Yield%	Transparency	Sinks in PBS?
Jo 2-7 7/10	28g : 160ml : 200ml	30	45.6%	Y	Y
Jo 2-9 7/21/09	5.09g : 40ml : 50ml	19	19.3%	Y	Y
Jo 3-1 8/3/09	7.55g : 120ml : 150ml	8	27.8%	Y	Y
Jo 3-2 8/4/09	28g : 160ml : 200ml	7	47.8%	Y	Y

Table 3. PMM 0025 Group (Ph:Me=50:50)

Sample name Date	PDM: Acetone: Water	Days	Yield%	Transparency	Sinks in PBS?
Jo 1-4 6/5	10.14 g : 40 ml : 50 ml	66	30.5%	Medium	Y
Jo 1-5 6/6	10.68 g : 40 ml : 3 ml	65	27.2%	Medium	Y
Jo 1-16 6/23/09	30 g : 120 ml : 150 ml			Y	Y
Jo 3-3 8/6/09	10.2 g : 80 ml : 200 ml	5	25.6%	Y	Y
Jo 3-4 8/7/09	9.99 g : 20 ml : 200 ml	4	16.3%	Medium	Y
Jo 3-5 8/7/09	10 g : 80 ml : 200 ml	4	21.5%	Y	Y
Jo 3-6 8/8/09	10.07 g : 10 ml : 300 ml	3	7.9%	Medium	Y

Table 4. APT-133 Group (Ph:Me=80:20)

Sample name Date	PDM: Acetone: Water(PBS)	Days	Yield%	Transparency	Sinks in PBS?
Jo 1-20 6/29/09	21.94g : 80ml : 100ml	43	N/A		
Jo 2-8 7/20/09	20.72g : 80ml : 100ml	22	N/A		
Jo 2-10 7/22	20.43g : 50ml : 100ml	20	16.3%	Medium	Y
Jo 2-11 7/23	20.2g : 25ml : 100ml	19	15%	Y	Y
Jo 2-12 7/27	19.96g : 15ml : 100ml	15	13.7%	Y	Y
Jo 2-13 7/28	20.59g : 50ml : 200ml	14	20.9%	Y	Y
Jo 2-14 7/30	19.95g : 80ml : 100ml	12	30.5%	Medium	Y
Jo 2-15 7/31	20.09g : 50ml : 300ml	11	20.1%	Y	Y

Table 5. APT-233 Group

5

Sample name Date	PDM: Acetone/2-butanone: Water(PBS)	Days	Yield%	Transparency	Sinks in PBS?
Jo 1-17 6/24	10.1 g : 40 ml (acetone): : 50ml	48	N/A		
Jo 1-19 6/26	10.2 g : 40 ml (acetone): : 50 ml				
Jo 2-1 7/2	9.9 g : 40 ml (2-butanone): : 50 ml	40	57.6%	N	N
Jo 2-5 7/8	10.23 g : 40 ml (2- butanone)/ 50 ml (acetone) : 19 ml	34	24.9%	N	N

Table 6. APT-263 Group

Sample name Date	PDM: 2-butanone: Acetone	Days	Yield%	Transparency	Sinks in PBS?
Jo 2-2 7/6	10.12 g : 40 ml : 50 ml				
Jo 2-3 7/6	10 g : 40 ml : 50 ml	36	45%	Y	N
Jo 2-4 7/7	20.13 g : 80 ml : 20 ml	35	N/A		
Jo 2-6 7/9	10.21 g : 50 ml : 0 ml	33	39.4%		

Table 7. Blending Group

Sample name Date	PDM: Acetone: PBS	Days	Yield%	Transparency	Sinks in PBS?
Jo 1-7 6/10	3.49 g PDM1922 3.51 g PMM0025 40 ml Acetone 40 ml PBS	61	49.7%	Y	Y
Jo 1-8 6/10	9.55 g PMM0025 1.06 g DMST41 40 ml Acetone 50 ml PBS	61	52.7%	Medium	Y
Jo 1-9 6/10	1g PMM1043 10.04 g PMM0025 40 ml Acetone 50 ml PBS	61	58.9%	Medium	Y
Jo 1-10 6/15/09	5.31 g PDM1922 40 ml Acetone 50 ml PBS	55	36.9%	Y	Y
Jo 1-11 6/15	1.43 g DMST41 9.06 g PDM1922 40 ml Acetone 50 ml PBS	55	51%	Y	Y
Jo 1-12 6/16	.66 gDMST41 10.59 gPDM1922 40 ml Acetone 50 ml PBS	54	58.3%	Y	Y
Jo 1-13 6/18	.51 g DMST41 9.97 g PMM0025 40 ml Acetone 50 ml PBS	53	66.8%	Medium	Y

REFERENCES

[0130] All patents and publications mentioned in the specification are indicative of the level of those skilled in the art to which the invention pertains. All patents and publications are herein incorporated by reference in their entirety to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

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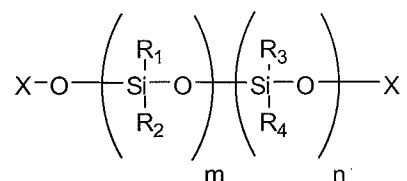
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[0139] Although the present invention and its advantages have been described in detail, it should be understood that various changes, substitutions and alterations can be made herein without departing from the spirit and scope of the invention as defined by the appended claims. Moreover, the scope of the present application is not intended to be limited to the particular embodiments of the process, machine, manufacture, composition of matter, means, methods and steps described in the specification. As one of ordinary skill in the art will readily appreciate from the disclosure of the present invention, processes, machines, manufacture, compositions of matter, means, methods, or steps, presently existing or later to be developed that perform substantially the same function or achieve substantially the same result as the corresponding embodiments described herein may be utilized according to the present invention. Accordingly, the appended claims are intended to include within their scope such processes, machines, manufacture, compositions of matter, means, methods, or steps.

CLAIMS

What is claimed is:

1. A silicone oil having the general formula:



5 wherein

R_1 is independently selected from $\text{alkyl}_{(\text{C} = 1-18)}$, substituted

$\text{alkyl}_{(\text{C} = 1-18)}$, $\text{alkenyl}_{(\text{C} = 2-18)}$, substituted $\text{alkenyl}_{(\text{C} = 2-18)}$,

$\text{alkynyl}_{(\text{C} = 3-18)}$, substituted $\text{alkynyl}_{(\text{C} = 3-18)}$, aryl, substituted

$\text{aryl}_{(\text{C} = 6-18)}$, $\text{aralkyl}_{(\text{C} = 6-18)}$, substituted $\text{aralkyl}_{(\text{C} = 6-18)}$,

10 $\text{heteroaryl}_{(\text{C} = 1-8)}$, substituted $\text{heteroaryl}_{(\text{C} = 6-18)}$, $\text{heteroaralkyl}_{(\text{C} = 6-18)}$, substituted $\text{heteroaralkyl}_{(\text{C} = 6-18)}$, $\text{alkoxy}_{(\text{C} = 1-18)}$, substituted $\text{alkoxy}_{(\text{C} = 1-18)}$;

R_2 is independently selected from $\text{alkyl}_{(\text{C} = 1-18)}$, substituted

$\text{alkyl}_{(\text{C} = 1-18)}$, $\text{alkenyl}_{(\text{C} = 2-18)}$, substituted $\text{alkenyl}_{(\text{C} = 2-18)}$,

15 $\text{alkynyl}_{(\text{C} = 3-18)}$, substituted $\text{alkynyl}_{(\text{C} = 3-18)}$, aryl, substituted

$\text{aryl}_{(\text{C} = 6-18)}$, $\text{aralkyl}_{(\text{C} = 6-18)}$, substituted $\text{aralkyl}_{(\text{C} = 6-18)}$,

$\text{heteroaryl}_{(\text{C} = 1-8)}$, substituted $\text{heteroaryl}_{(\text{C} = 6-18)}$, $\text{heteroaralkyl}_{(\text{C} = 6-18)}$, substituted $\text{heteroaralkyl}_{(\text{C} = 6-18)}$, $\text{alkoxy}_{(\text{C} = 1-18)}$, substituted

$\text{alkoxy}_{(\text{C} = 1-18)}$;

20 R_3 is independently selected from $\text{alkyl}_{(\text{C} = 1-8)}$, $\text{alkenyl}_{(\text{C} = 2-8)}$, or $\text{alkynyl}_{(\text{C} = 2-8)}$;

R₄ is independently selected from alkyl_(C = 1-8), alkenyl_(C = 2-8), or alkynyl_(C = 2-8);

X is alkylsilyl or substituted alkylsilyl; and,

wherein the ratio of m to n is between 1:100 and 100:1 and

5 the silicone oil adapted to function as a tamponade agent.

2. The silicone oil of claim 1, wherein the silicone oil is adapted to function as an tamponade agent through fractional precipitation through the following steps

(a) the silicone oil is dissolved in a non-aqueous solvent

10 thereby creating a polymer solution;

(b) increments of an aqueous solution are added to the polymer solution until purified silicone oil is precipitated;

(c) the purified silicone oil is evaporated to remove excess solvent and water.

15 3. The silicone oil of claim 2, wherein R₁ and/or R₂ is a radical scavenger.

4. The silicone oil of claim 3, wherein the ratio of m to n is 20:80.

5. The silicone oil of claim 2, wherein the silicone oil has a density greater than 1 g/mL.

6. The silicone oil of claim 5, wherein R₁ and/or R₂ is a radical scavenger.

20 7. The silicone oil of claim 5, wherein the silicone oil further comprises a radical scavenger.

8. The silicone oil of claim 2, wherein the silicone oil has a density of less than 1 g/mL.

9. The silicone oil of claim 8, wherein R₁ and/or R₂ is a radical scavenger.

10. The silicone oil of claim 8, wherein the silicone oil further comprises a radical scavenger.

11. The silicone oil of claim 1, wherein R₁ is phenyl and R₂ is phenyl.

12. The silicone oil of claim 1, wherein R₃ is methyl and R₄ is methyl.

13. The silicone oil of claim 1, wherein R₁ is phenyl, R₂ is phenyl, R₃ is methyl and R₄ is methyl.

14. The silicone oil of claim 13, wherein the ratio of m to n is about 20:80.

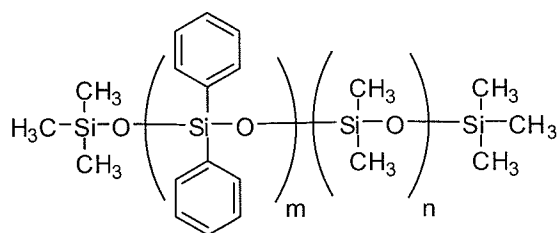
15. The silicone oil of claim 14, wherein the silicone oil has a specific gravity greater than 1 g/mL and less than 2.0 g/mL.

16. The silicone oil of claim 15, wherein the silicone oil has an interfacial surface tension with water of at least 46 mN/m.

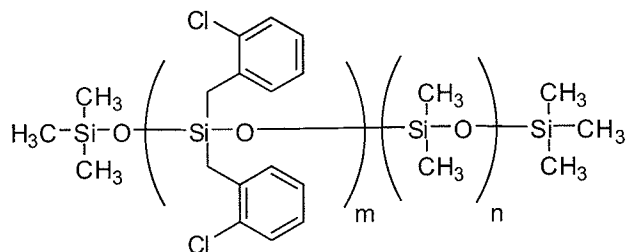
17. The silicone oil of claim 16, wherein the silicone oil is a linear polymer; and,

wherein m and n form an alternating copolymer, a periodic copolymer, a statistical copolymer or a block copolymer and the ratio of m to n is 20:80.

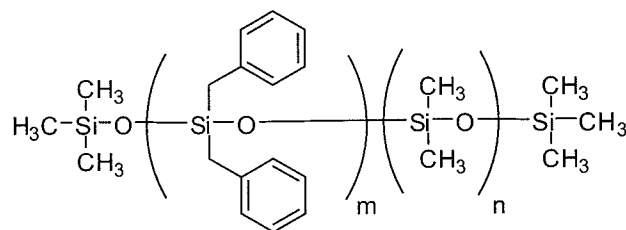
18. The silicone oil of claim 1, having the general formula:



19. The silicone oil of claim 1, having the general formula:



20. The silicone oil of claim 1, having the general formula:



21. The silicone oil of claim 1, wherein in the case where $n=0$,

5

R_1 is independently selected from $\text{alkyl}_{(C=1-18)}$, substituted $\text{alkyl}_{(C=1-18)}$, $\text{alkenyl}_{(C=2-18)}$, substituted $\text{alkenyl}_{(C=2-18)}$, $\text{alkynyl}_{(C=3-18)}$, substituted $\text{alkynyl}_{(C=3-18)}$, aryl, substituted $\text{aryl}_{(C=6-18)}$, $\text{aralkyl}_{(C=6-18)}$, substituted $\text{aralkyl}_{(C=6-18)}$, $\text{heteroaryl}_{(C=1-8)}$, substituted $\text{heteroaryl}_{(C=6-18)}$, $\text{heteroaralkyl}_{(C=6-18)}$, substituted $\text{heteroaralkyl}_{(C=6-18)}$, $\text{alkoxy}_{(C=1-18)}$, substituted $\text{alkoxy}_{(C=1-18)}$; and

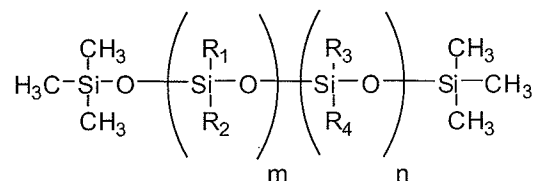
10

R_2 is independently selected from $\text{alkyl}_{(C=1-18)}$, substituted $\text{alkyl}_{(C=1-18)}$, $\text{alkenyl}_{(C=2-18)}$, substituted $\text{alkenyl}_{(C=2-18)}$, $\text{alkynyl}_{(C=3-18)}$, substituted $\text{alkynyl}_{(C=3-18)}$, aryl, substituted $\text{aryl}_{(C=6-18)}$, $\text{aralkyl}_{(C=6-18)}$, substituted $\text{aralkyl}_{(C=6-18)}$, $\text{heteroaryl}_{(C=1-8)}$, substituted $\text{heteroaryl}_{(C=6-18)}$, $\text{heteroaralkyl}_{(C=6-18)}$, substituted $\text{heteroaralkyl}_{(C=6-18)}$, $\text{alkoxy}_{(C=1-18)}$, substituted $\text{alkoxy}_{(C=1-18)}$.

15

22. A biocompatible internal tamponade agent comprising:

a silicone oil having the general formula:



wherein

5 R_1 is independently selected from $\text{alkyl}_{(\text{C} = 1-18)}$, substituted $\text{alkyl}_{(\text{C} = 1-18)}$, $\text{alkenyl}_{(\text{C} = 2-18)}$, substituted $\text{alkenyl}_{(\text{C} = 2-18)}$, $\text{alkynyl}_{(\text{C} = 3-18)}$, substituted $\text{alkynyl}_{(\text{C} = 3-18)}$, aryl, substituted aryl $_{(\text{C} = 6-18)}$, aralkyl $_{(\text{C} = 6-18)}$, substituted aralkyl $_{(\text{C} = 6-18)}$, heteroaryl $_{(\text{C} = 1-8)}$, substituted heteroaryl $_{(\text{C} = 6-18)}$, heteroaralkyl $_{(\text{C} = 6-18)}$, substituted heteroaralkyl $_{(\text{C} = 6-18)}$, alkoxy $_{(\text{C} = 1-18)}$, substituted alkoxy $_{(\text{C} = 1-18)}$;

10 R_2 is independently selected from $\text{alkyl}_{(\text{C} = 1-18)}$, substituted $\text{alkyl}_{(\text{C} = 1-18)}$, $\text{alkenyl}_{(\text{C} = 2-18)}$, substituted $\text{alkenyl}_{(\text{C} = 2-18)}$, $\text{alkynyl}_{(\text{C} = 3-18)}$, substituted $\text{alkynyl}_{(\text{C} = 3-18)}$, aryl, substituted aryl $_{(\text{C} = 6-18)}$, aralkyl $_{(\text{C} = 6-18)}$, substituted aralkyl $_{(\text{C} = 6-18)}$, heteroaryl $_{(\text{C} = 1-8)}$, substituted heteroaryl $_{(\text{C} = 6-18)}$, heteroaralkyl $_{(\text{C} = 6-18)}$, substituted heteroaralkyl $_{(\text{C} = 6-18)}$, alkoxy $_{(\text{C} = 1-18)}$, substituted alkoxy $_{(\text{C} = 1-18)}$;

15 R_3 is independently selected from $\text{alkyl}_{(\text{C} = 1-8)}$, $\text{alkenyl}_{(\text{C} = 2-8)}$, or $\text{alkynyl}_{(\text{C} = 2-8)}$;

20

R₄ is independently selected from alkyl_(C = 1-8), alkenyl_(C = 2-8), or alkynyl_(C = 2-8); and,

wherein the ratio of m to n is between 1:100 and 100:1.

23. The biocompatible internal tamponade agent of claim 22, wherein the silicone oil is purified by fractional precipitation through the following steps:

(a) the silicone oil is dissolved in non-aqueous solvent thereby creating a polymer solution;

(b) increments of an aqueous solution are added to the polymer solution until purified silicone oil is precipitated; and

(c) the purified silicone oil is evaporated to remove excess solvent and water.

24. The biocompatible internal tamponade agent of claim 23, wherein R₁ and/or R₂ is a radical scavenger.

25. The biocompatible internal tamponade agent of claim 24, wherein the ratio of m to n is 20:80.

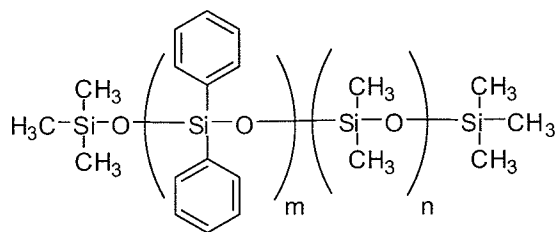
26. The biocompatible internal tamponade agent of claim 23, wherein the silicone oil has a density greater than 1 g/mL.

27. The biocompatible internal tamponade agent of claim 26, wherein R₁ and/or R₂ is a radical scavenger.

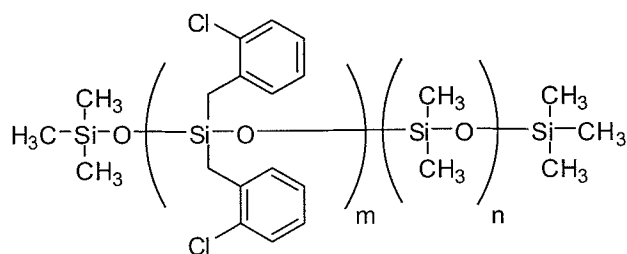
28. The biocompatible internal tamponade agent of claim 26, wherein the silicone oil further comprises a radical scavenger.

29. The biocompatible internal tamponade agent of claim 23, wherein the silicone oil has a density of less than 1 g/mL.
30. The biocompatible internal tamponade agent of claim 29, wherein R_1 and/or R_2 is a radical scavenger.
- 5 31. The biocompatible internal tamponade agent of claim 29, wherein the silicone oil further comprises a radical scavenger.
32. The biocompatible internal tamponade agent of claim 22, wherein R_1 is phenyl and R_2 is phenyl.
33. The biocompatible internal tamponade agent of claim 22, wherein R_3 is methyl and R_4 is methyl.
- 10 34. The biocompatible internal tamponade agent of claim 22, wherein R_1 is phenyl, R_2 is phenyl, R_3 is methyl and R_4 is methyl.
35. The biocompatible internal tamponade agent of claim 34, wherein the ratio of m to n is about 20:80.
- 15 36. The biocompatible internal tamponade agent of claim 35, wherein the silicone oil has a specific gravity of at least 1 g/mL and no greater than 2 g/mL.
37. The biocompatible internal tamponade agent of claim 36, wherein the silicone oil has an interfacial surface tension with water of at least 46 mN/m.
- 20 38. The biocompatible internal tamponade agent of claim 37, wherein the silicone oil is a linear polymer; and,
- wherein m and n form an alternating copolymer, a periodic copolymer, a statistical copolymer or a block copolymer and the
- 25 ratio of m to n is 20:80.

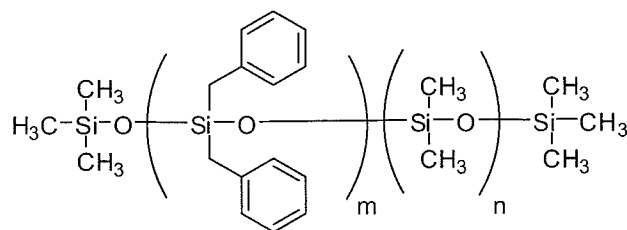
39. The biocompatible internal tamponade agent of claim 22, having the general formula:



40. The biocompatible internal tamponade agent of claim 22, having the general formula:

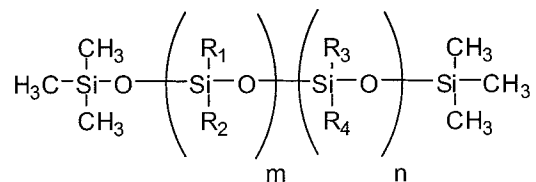


41. The biocompatible internal tamponade agent of claim 22, having the general formula:



42. A method for preparing a tamponade agent comprising the step of:
purifying a silicone oil

wherein the silicone oil has the general formula:



wherein

R_1 is independently selected from alkyl_(C = 1-18), substituted

alkyl_(C = 1-18), alkenyl_(C = 2-18), substituted alkenyl_(C = 2-18),

5 alkynyl_(C = 3-18), substituted alkynyl_(C = 3-18), aryl, substituted

aryl_(C = 6-18), aralkyl_(C = 6-18), substituted aralkyl_(C = 6-18),

heteroaryl_(C = 1-8), substituted heteroaryl_(C = 6-18), heteroaralkyl_(C = 6-18), substituted heteroaralkyl_(C = 6-18), alkoxy_(C = 1-18), substituted alkoxy_(C = 1-18);

10 R_2 is independently selected from alkyl_(C = 1-18), substituted

alkyl_(C = 1-18), alkenyl_(C = 2-18), substituted alkenyl_(C = 2-18),

alkynyl_(C = 3-18), substituted alkynyl_(C = 3-18), aryl, substituted

aryl_(C = 6-18), aralkyl_(C = 6-18), substituted aralkyl_(C = 6-18),

heteroaryl_(C = 1-8), substituted heteroaryl_(C = 6-18), heteroaralkyl_(C = 6-18), substituted heteroaralkyl_(C = 6-18), alkoxy_(C = 1-18), substituted alkoxy_(C = 1-18);

15 R_3 is independently selected from alkyl_(C = 1-8), alkenyl_(C = 2-8), or alkynyl_(C = 2-8);

R_4 is independently selected from alkyl_(C = 1-8), alkenyl_(C = 2-8), or alkynyl_(C = 2-8); and,

20 wherein the ratio of m to n is between 1:100 and 100:1.

43. The method of claim 42, wherein the step of purifying a silicone oil further comprises the step of performing a fractional precipitation.

44. The method of claim 43, wherein the step of performing a fractional precipitation further comprises the steps of:

5 (a) dissolving the silicone oil in solvent thereby creating a polymer solution;

(b) adding increments of an aqueous solution to the polymer solution until the purified silicone oil precipitates; and

10 (c) placing the purified silicone oil under conditions to remove excess solvent and water.

45. The method of claim 44, wherein the aqueous solution is a phosphate buffered saline solution or water.

46. The method of claim 42, wherein R_1 and/or R_2 is a radical scavenger.

47. The method of claim 46, wherein the ratio of m to n is 20:80.

15 48. The method of claim 42, wherein the silicone oil has a density greater than 1 g/mL.

49. The method of claim 48, wherein R_1 and/or R_2 is a radical scavenger.

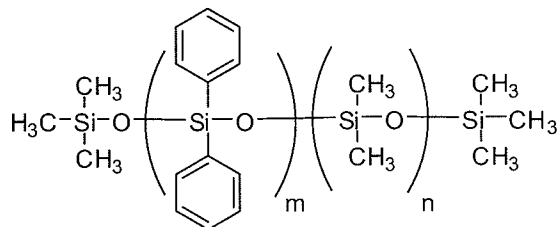
50. The method of claim 48, wherein the silicone oil further comprises a radical scavenger.

20 51. The method of claim 42, wherein the silicone oil has a density of less than 1 g/mL.

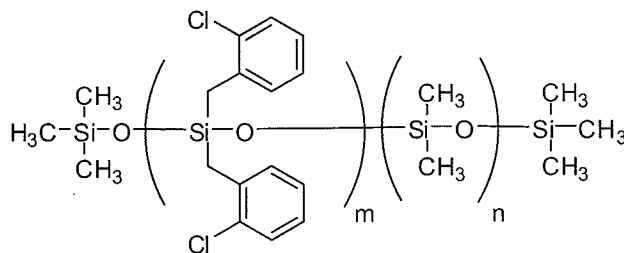
52. The method of claim 51, wherein R_1 and/or R_2 is a radical scavenger.

53. The method of claim 51, wherein the silicone oil further comprises a radical scavenger.

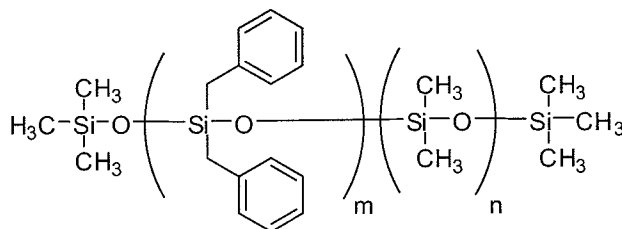
54. The method of claim 42, wherein R_1 is phenyl and R_2 is phenyl.
55. The method of claim 42, wherein R_3 is methyl and R_4 is methyl.
56. The method of claim 42, wherein R_1 is phenyl, R_2 is phenyl, R_3 is methyl and R_4 is methyl.
57. The method of claim 56, wherein the ratio of m to n is about 20:80.
58. The method of claim 57, wherein the silicone oil has a specific gravity of at least 1 g/mL and no greater than 2 g/mL.
59. The method of claim 58, wherein the silicone oil has an interfacial surface tension with water of at least 46 mN/m.
60. The method of claim 59, wherein the silicone oil is a linear polymer; and, wherein m and n form an alternating copolymer, a periodic copolymer, a statistical copolymer or a block copolymer and the ratio of m to n is 20:80.
61. The method of claim 42, wherein the silicone oil has the general formula:



62. The method of claim 42, wherein the silicone oil has the general formula:



63. The method of claim 42, wherein the silicone oil has the general formula:



64. A method of repairing a retinal defect in an eye of a subject, comprising the step of applying a composition comprising the silicone oil of claim 1 to the retinal defect.

5 65. The method of claim 64, wherein the defect is an inferior retinal defect.

66. The method of claim 64, wherein the composition is further defined as comprising a radical scavenger.

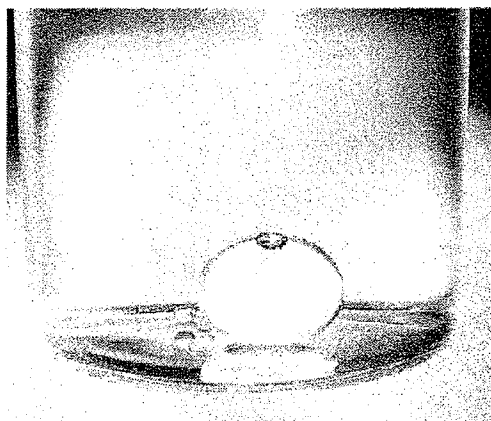
10 67. The method of claim 64, wherein the composition comprising the radical scavenger is further defined as the radical scavenger being bound to the silicone oil.

68. The method of claim 64, wherein the subject is delivered a radical scavenger.

15 69. The method of claim 68, wherein the radical scavenger is delivered to the subject systemically.

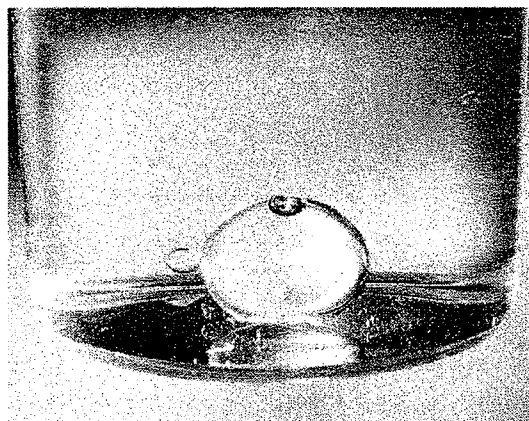
1/14

A



Day 0 – Heavy Oil in BSS at RT

B



5 months – Heavy Oil in BSS at RT

FIG. 1

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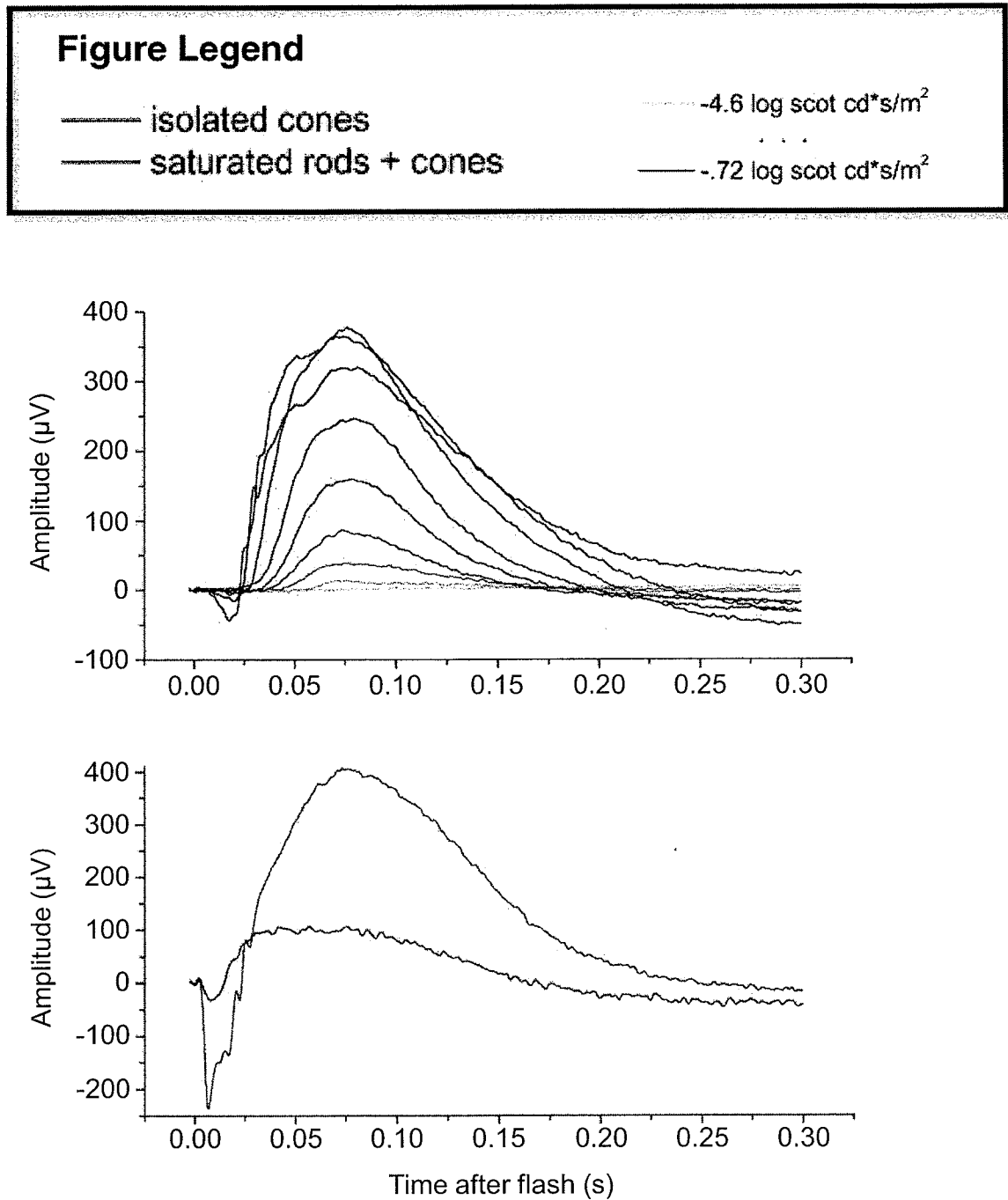


FIG. 2

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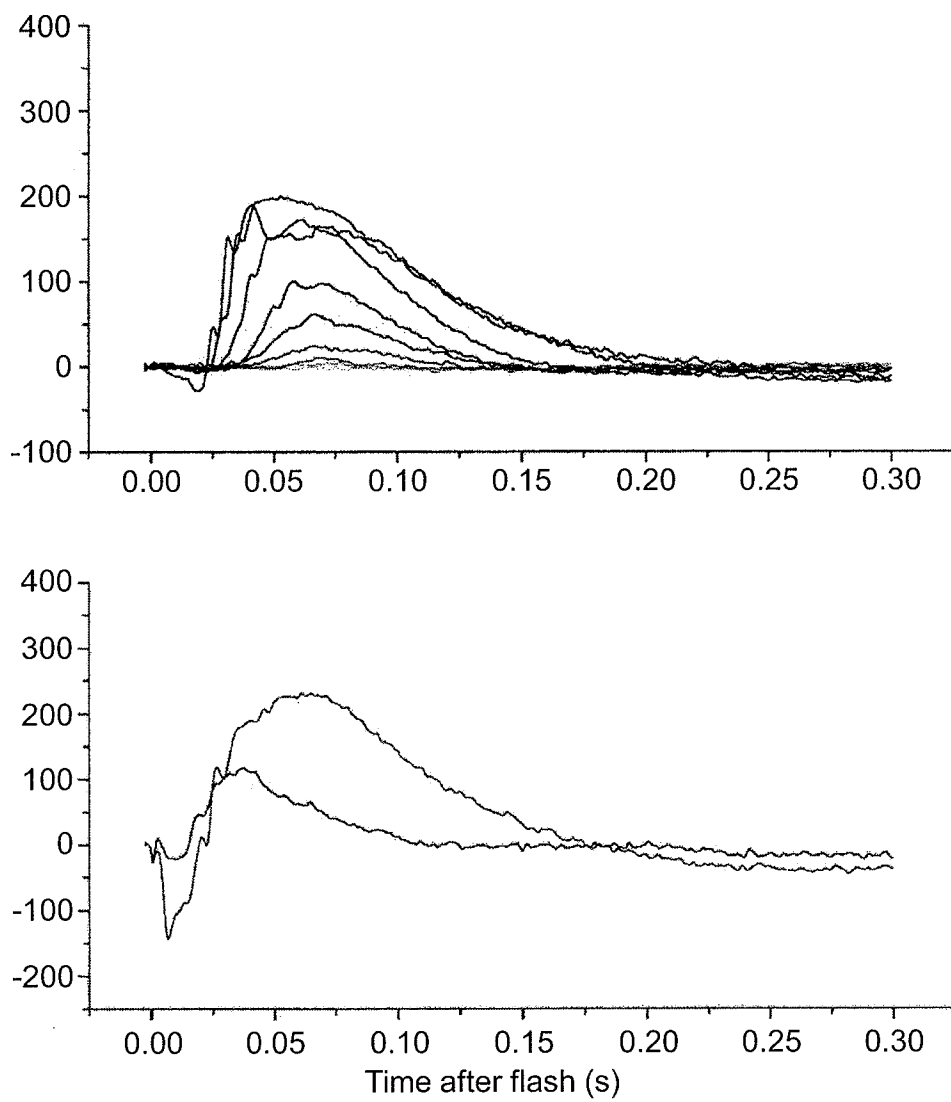


FIG. 3

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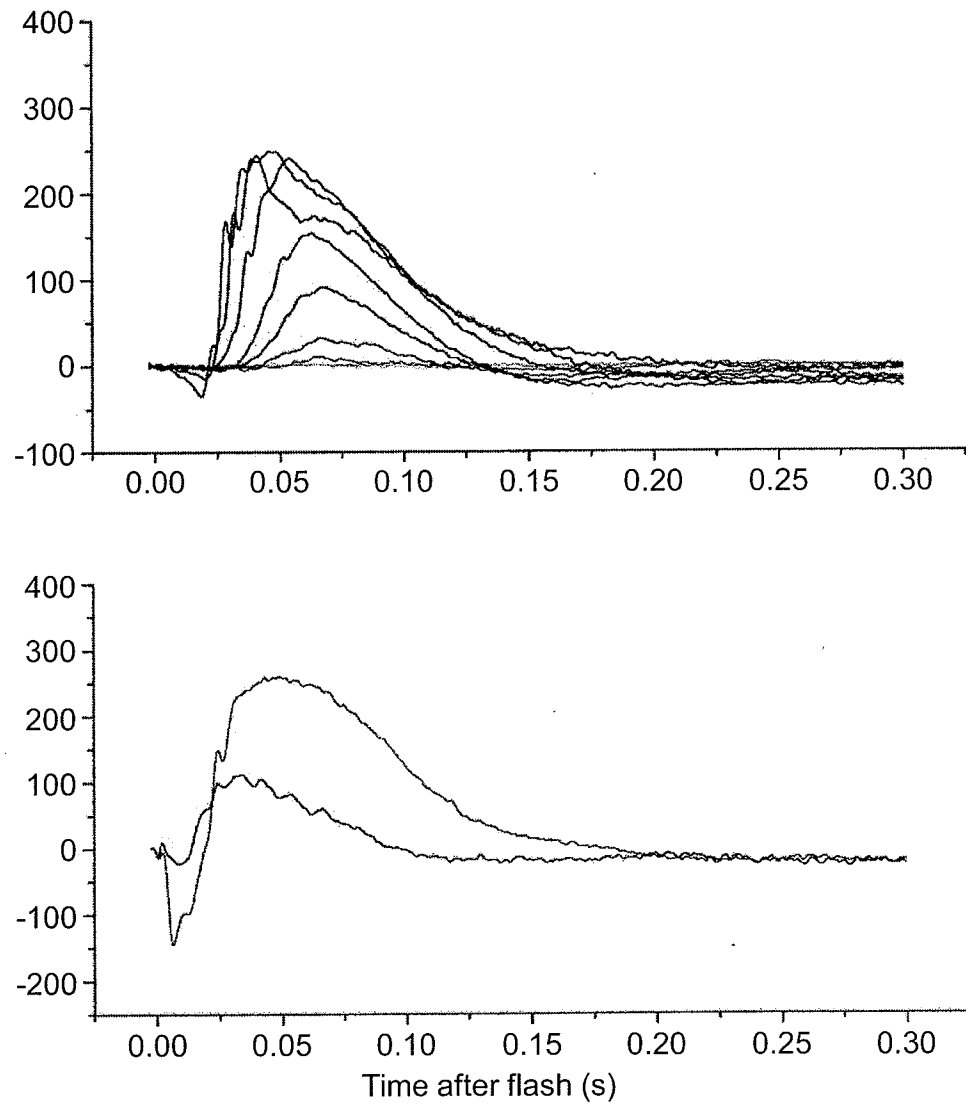


FIG. 4

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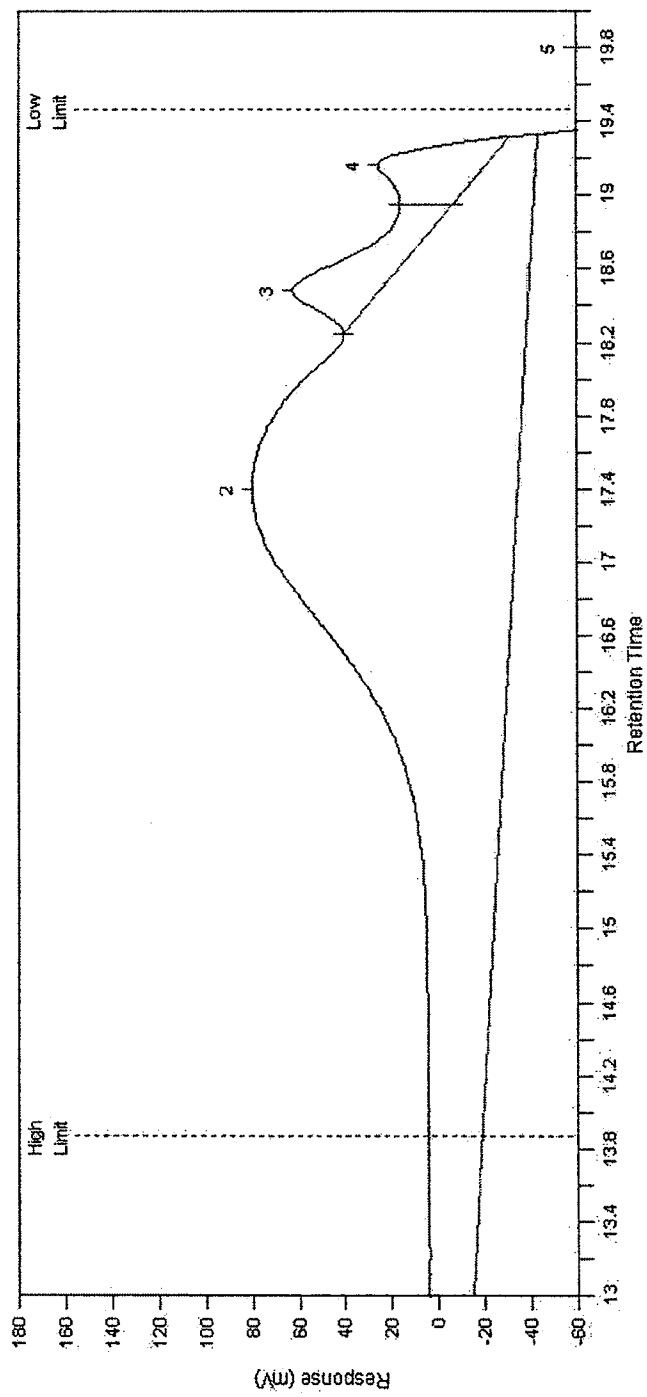


FIG. 5

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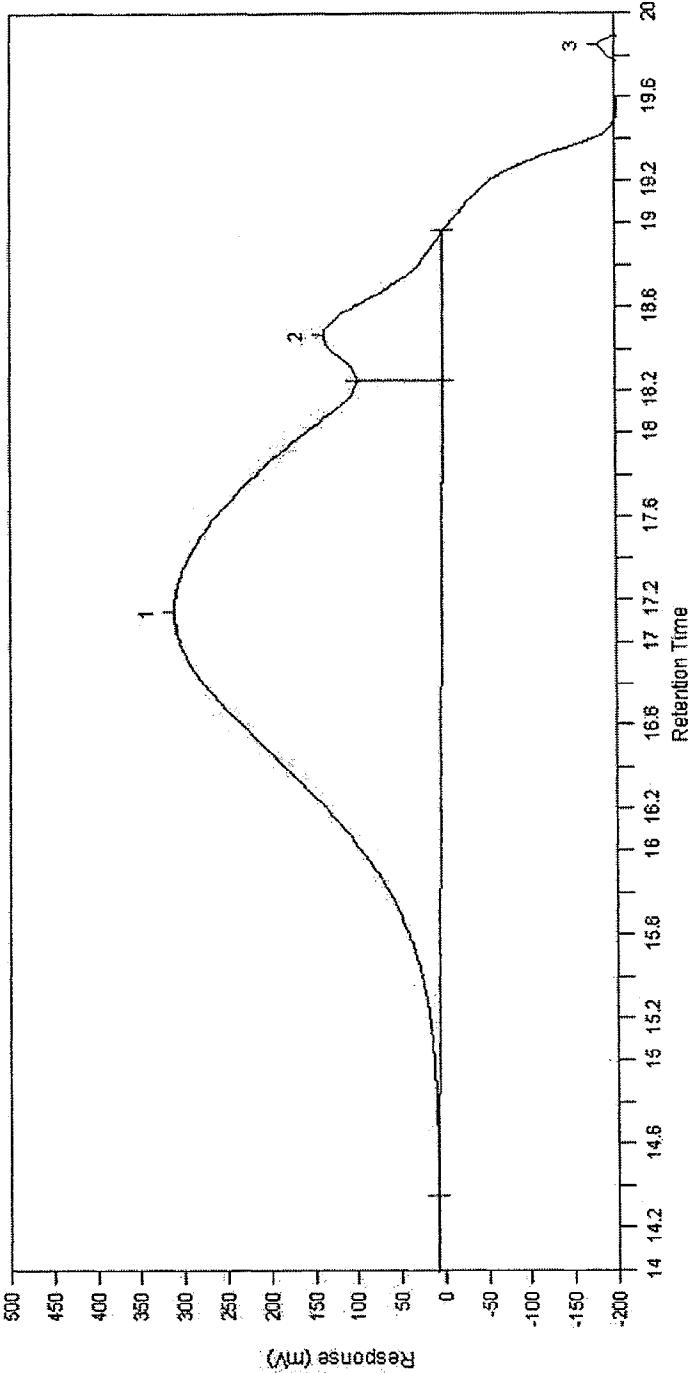


FIG. 6

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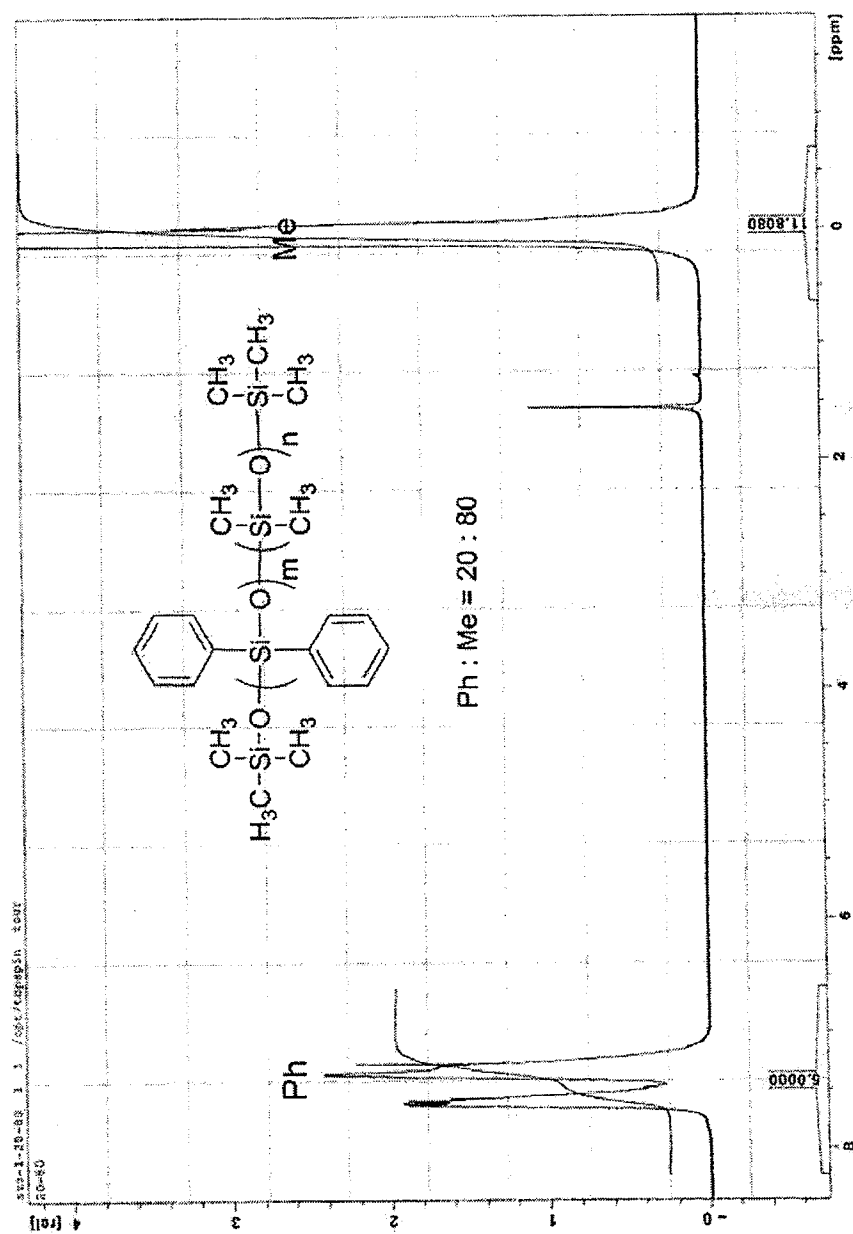


FIG. 7

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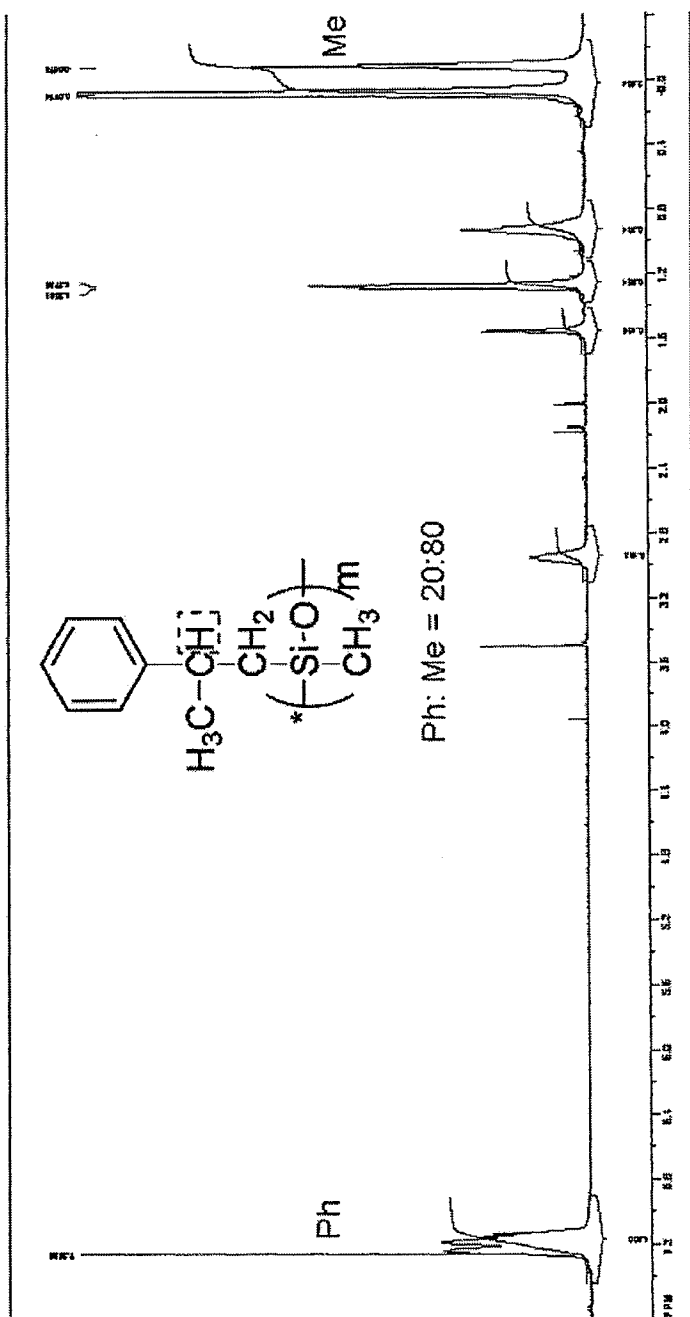


FIG. 8

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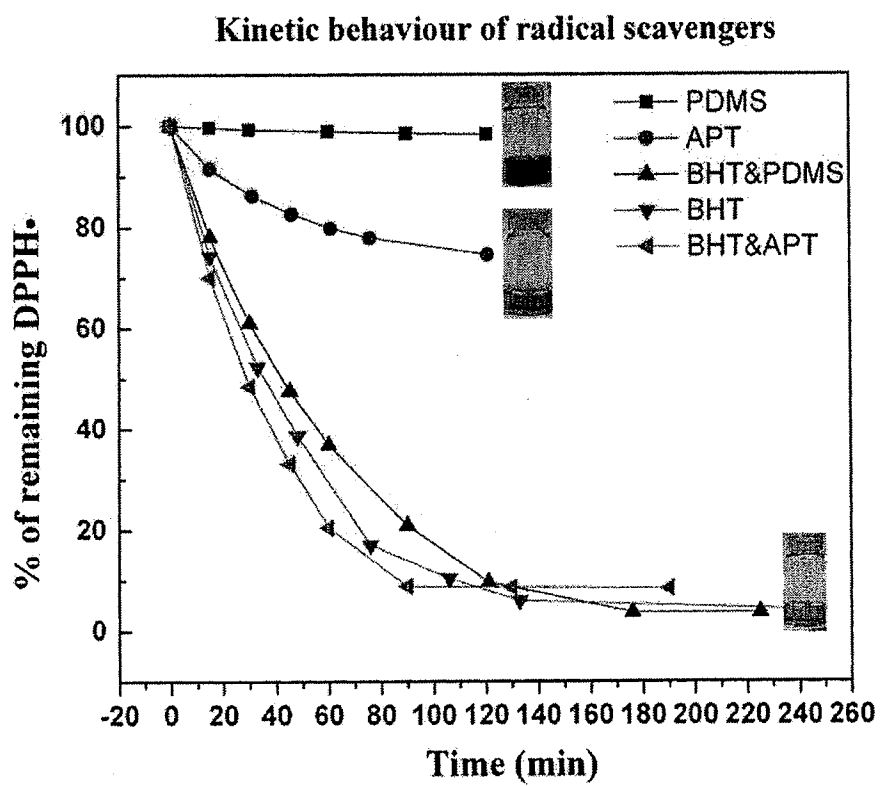


FIG. 9

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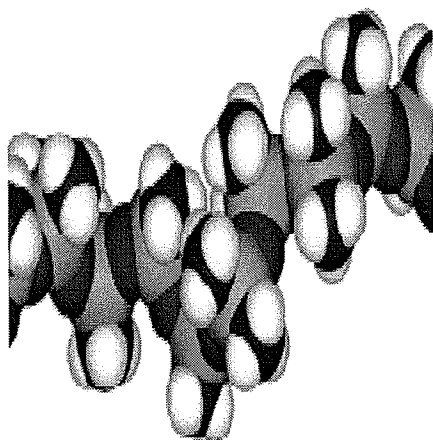
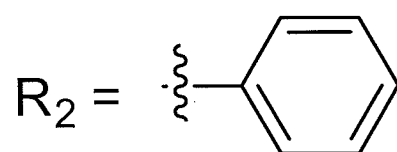
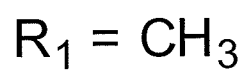
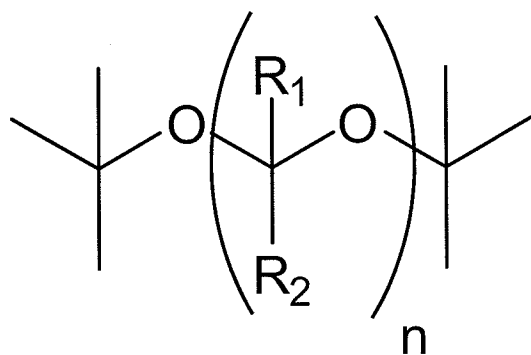


FIG. 10

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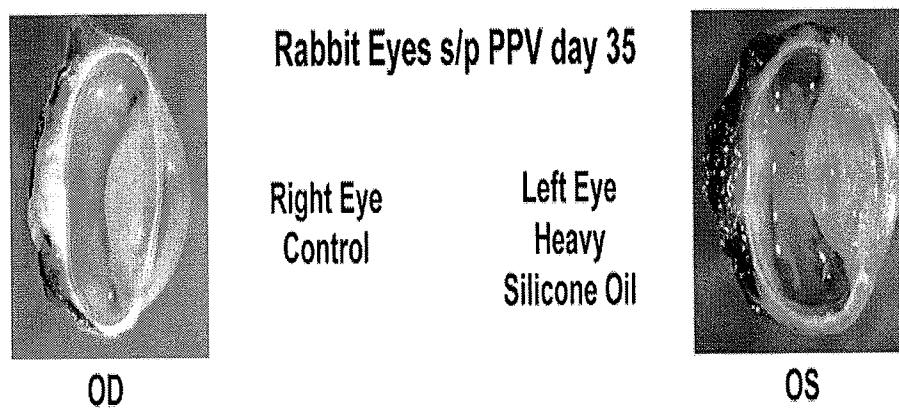


FIG. 11A

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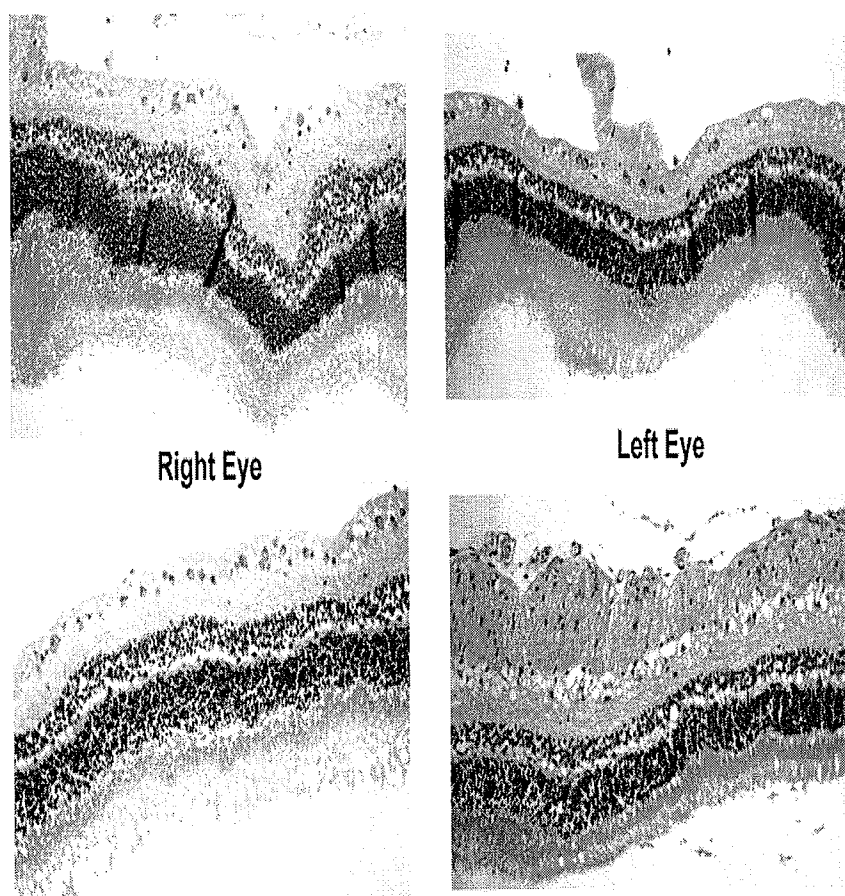
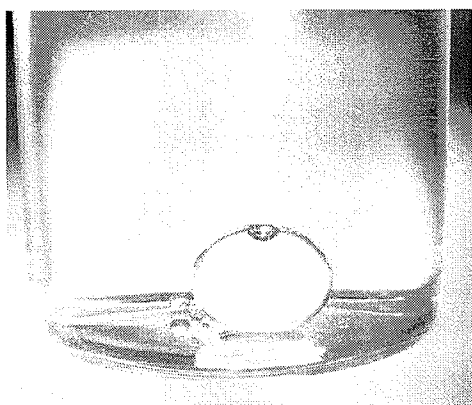


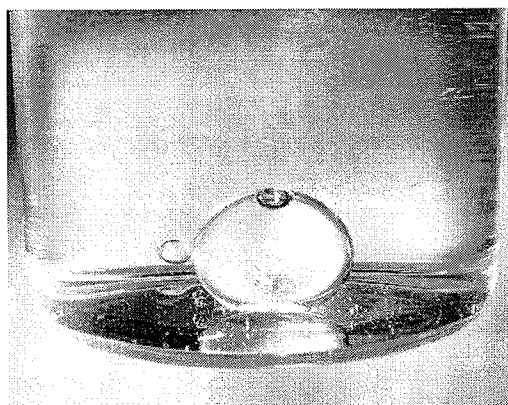
FIG. 11B

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A



B



C

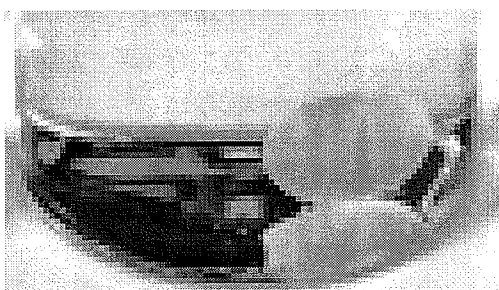


FIG. 12

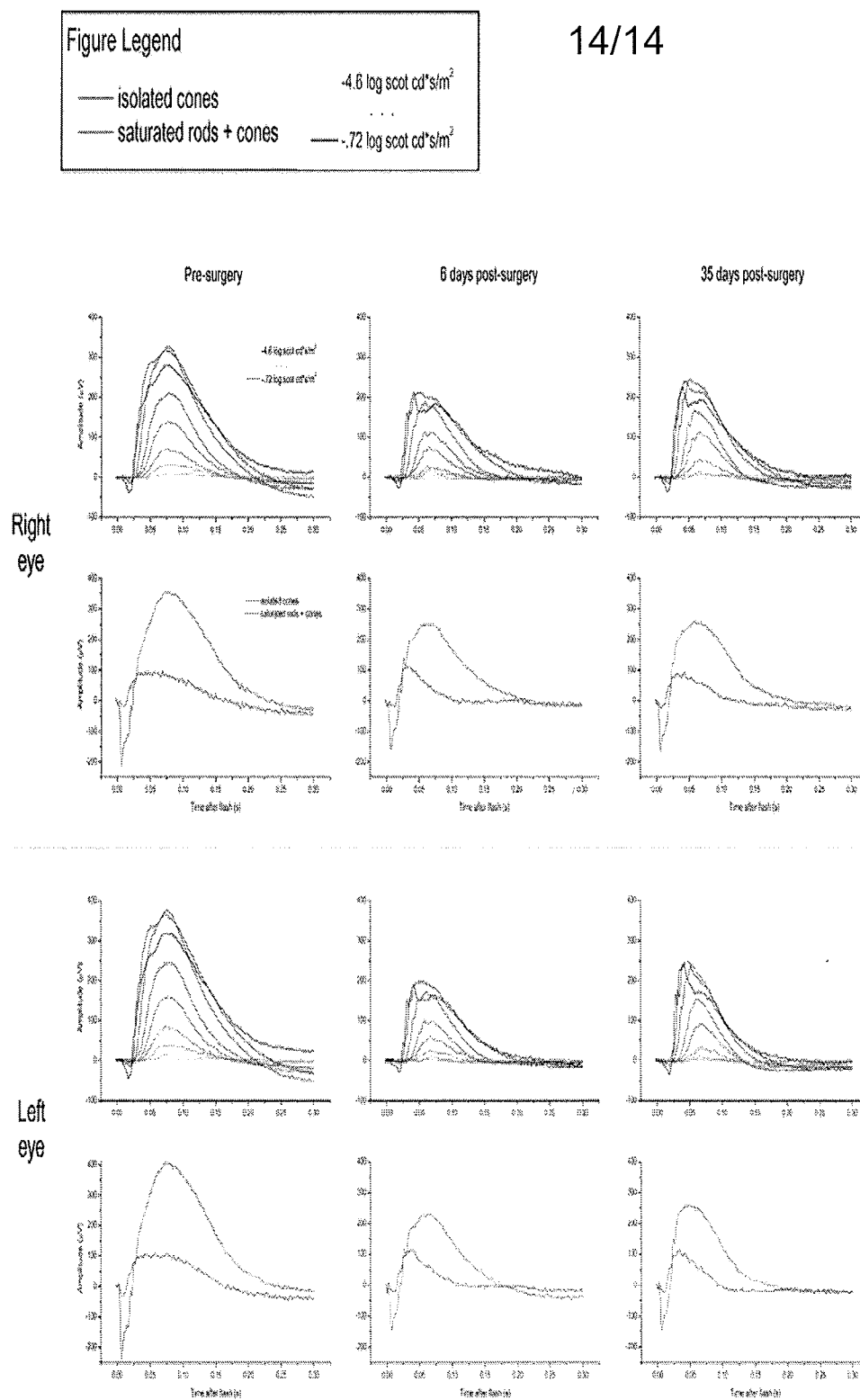


FIG. 13

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/35018

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07F 7/00, 7/04, 7/08 (2011.01)

USPC - 556/443, 465-466

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC: 556/443, 465-466

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 424/45, 47, 70.12, 401; 528/25 (see search terms below)Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Google Scholar, Google Patents, PubWEST (PGPB,USPT,EPAB,JPAB) (vitreoretinal, surgery, eye, focus, light, detach, aqueous, humor, tamponade, polydimethylsiloxane, silicone, oil, evaporate, precipitation, polymer, solvent, radical, scavenger, density, surface, tension, water, copolymer)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,480,009 A (Berger) 30 October 1984 (30.10.1984) col 2, ln 31-34; col 5, ln 2-5, ln 18-37; col 6, ln 32-33; col 33, ln 43-45; col 51, ln 37-52; col 73, ln 1-12; col 74, ln 1-12; col 79, ln 41-48; col 80, ln 41-48, ln 58-60; col 89, ln 7-10	1-69
Y	US 5,672,355 A (Refojo et al.) 30 September 1997 (30.09.1997) col 3, ln 13-20, ln 31-39; col 4, ln 50-56, ln 66-67; col 5, ln 1-4, ln 36-54; col 7, ln 38-39	1-69

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

08 Jul 2011 (08.07.2011)

Date of mailing of the international search report

18 JUL 2011

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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