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(54) **METHOD TO PREVENT AND TREAT DIABETIC RETINOPATHY BY CALCIUM CHANNEL BLOCKERS, ANGIOTENSIN CONVERTING ENZYME INHIBITORS, AND ANGIOTENSIN RECEPTOR BLOCKERS**

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(57) **ABSTRACT**

Methods are provided to prevent and to treat diabetic retinopathy by using Calcium channel blockers, Angiotensin-Converting Enzyme (ACE) Inhibitors, or angiotensin receptor blockers (ARB), and more particularly, to a method to prevent and treat diabetic retinopathy by using calcium channel blockers, Angiotensin-Converting Enzyme Inhibitors, or angiotensin receptor blockers that may not need to be taken orally, but may also be administered by ophthalmic preparation directly onto or into the eye where diabetic retinopathy is formed, to increase the capillary network and augment the blood supply to the anatomy of the eye.

METHOD TO PREVENT AND TREAT DIABETIC RETINOPATHY BY CALCIUM CHANNEL BLOCKERS, ANGIOTENSIN CONVERTING ENZYME INHIBITORS, AND ANGIOTENSIN RECEPTOR BLOCKERS

INCORPORATION BY REFERENCE TO RELATED APPLICATION

[0001] This application is a continuation of PCT application No. PCT/US2023/036853, filed Nov. 6, 2023 and claims the benefit of U.S. Provisional Application No. 63/423,250, filed Nov. 7, 2022. The aforementioned application is incorporated by reference herein in its entirety, and each is hereby expressly made a part of this specification.

FIELD OF THE DISCLOSURE

[0002] Methods are provided to prevent, treat, ameliorate, or reduce diabetic retinopathy by using calcium channel blockers, Angiotensin-Converting Enzyme (ACE) inhibitors, or angiotensin receptor blockers (ARB), and more particularly, to a method to prevent and treat diabetic retinopathy by using calcium channel blockers, ACE inhibitors, or angiotensin receptor blockers that need not be taken orally, but may also be administered by ophthalmic preparation directly onto or into the eye where the conditions for diabetic retinopathy occur, to increase the capillary network and augment the blood supply to and within the anatomy of the eye, and the retina.

BACKGROUND OF THE DISCLOSURE

[0003] Diabetic Retinopathy, also known as diabetic eye disease, is a medical condition where ocular damage occurs, predominantly to the retina, due to diabetes mellitus. Diabetic Retinopathy is a leading cause of blindness in developed countries and is one of the largest causes of vision loss worldwide. The medical condition is not confined to one age group, such as senior patients, but is one of the largest causes of impaired vision in patients between 24 to 74 years of age.

[0004] While Diabetes Mellitus had been known for a long time, it took until the invention of the ophthalmoscope in 1851 by Herman von Holmholtz to open a new era in ophthalmology. Within a few years of the invention of the ophthalmoscope, new diseases were discovered that now affect hundreds of millions worldwide, such as macular degeneration, glaucoma, and diabetic retinopathy. In 1856 Eduardo jaeger first described yellowish macular spots in patients. Then in 1876, Wilhelm Manz detailed the non-proliferative fibrovascular degeneration of the optic disc, vitreoretinal adhesions, tractional retinal detachment, and vitreous hemorrhage. Proliferative lesions to the retina and vitreous bleeding were first described by Mackenzie in 1867. A debate began immediately after Mackenzie's first publication, about whether these symptoms were related to either diabetes or hypertension. This debate was not resolved until 1943, with the work of Arthur James Ballentyne, which finally provided evidence that diabetic retinopathy represents a unique form of vascular disease. Several multi-center trials during the last two decades enlarged our understanding of the natural history of diabetic retinopathy, and expose the importance of glycemic control in the prevention and progression of Diabetic retinopathy. Diabetic Retinopathy a Historical assessment. George kalantzis et al. Hormones (Athens) 2006 January-March

[0005] As of 2010, there were an estimated 285 million people with Diabetes Mellitus worldwide, with an estimated one-third with signs of Diabetic Retinopathy (95 million; 34.5%). The global annual incidence for the onset of Diabetic Retinopathy is 2.2% to 12.7%, with a progression rate of 3.4%-12.3%. Current Epidemiology of Diabetic retinopathy and Macular edema. Jie Ding Tuen Yin Wong. Published online May 15, 2012. Springer Science Business Media LLC 2012. The medical condition similarly impacts African American and Hispanic populations, presenting in an approximate third of the diabetic population (40 million). In the US alone there are an estimated 4.2 million adults who have Diabetic Retinopathy. Of those U.S. adults with Diabetic Retinopathy, an estimated 655,000 adults are directly at risk of losing their vision.

Pathophysiology

[0006] Both type one and type two Diabetes Mellitus are major causes of morbidity for diabetic retinopathy. Diabetic retinopathy affects up to 80 percent of those who have had both type 1 and type 2 diabetes for 20 years or more. In an estimated 90% of new cases of diabetic retinopathy, it is thought that the progression of the disease could be reduced through a combination of proper treatment and monitoring of the eyes before more aggressive forms of sight-threatening retinopathy and maculopathy develop. However, the longer a patient has diabetes, the higher his or her chances of developing diabetic retinopathy.

[0007] The causes of diabetic retinopathy are complex and may involve many interrelated factors, but are generally grouped into two overarching retinal vascular pathologies. The first pathology is hypothesized to be due to abnormal capillary permeability that leads to macular edema. The second pathology relates to ischemia and vascular occlusion that leads to retinal hypoxia and neo-vascularisation. Chronic uncontrolled hyperglycemia is thought to be a significant cause of diabetic retinopathy and is indicated in at least two studies: the Diabetes Control and Complication trial and the United Kingdom Prospective Diabetes study. These studies both found that the incidence of new cases of Diabetic retinopathy is preceded by loss of glycemic control.

[0008] Hyperglycemia has been found to alter three different components of the retina: blood flow, photosensitive cellular function, and extracellular fluid. Reduced blood flow can leave deposits of sorbitol within the retinal cells and deposit advanced glycation end products in the extracellular fluid. The advanced forms of the disease (proliferative vascular changes and neo-vascularisation) are driven by insulin's growth factor 1 and Vascular endothelial growth factor. The differences between individual patients' responses to chronic hyperglycemia are attributed to differences in the patients' genetics.

Diabetic Retinopathy Classification and Clinical Features

[0009] Classification: Diabetic Retinopathy (also referred to herein as "DR") is attributed to two types Non-proliferative Diabetic Retinopathy and Proliferative Diabetic Retinopathy. Diabetic retinopathy is a state in which the blood supply from the capillaries of the retina does not match the retina's metabolic needs. Diabetic retinopathy can be a slow and progressive process that lasts many years, and generally consists of two successive chronological phases. The initial phase is non proliferative diabetic retinopathy, which may

progress over years, and is then generally followed by proliferative diabetic retinopathy. Each stage of diabetic retinopathy represents the retina's attempts, and the resulting consequences, to correct the progressively bad capillary blood supply that is insufficient to match the retina's metabolic needs. Much of the retina's attempts to improve blood supply may be ineffective and may even be counterproductive. The after-effects of the ineffective attempts to increase blood supply may degrade (e.g. by depositing material) the blood supply from existing capillaries, and make the retina's health even worse, thereby accelerating the progression of the disease.

[0010] A. Non-proliferative Diabetic Retinopathy (also referred to herein as "NPDR") classifies cases presenting at least one or more of micro aneurism, micro hemorrhage, and cotton-wool spots. Cotton-wool spots are tiny white areas on the retina, the layer of light-sensing cells lining the back of the eye. These spots are generally thought to be caused by a lack of blood flow to the small retinal blood vessels, and in the general population, these spots would usually disappear without treatment and do not threaten vision. However, these spots can be an indication of a serious medical condition, such as Diabetic Retinopathy here.

[0011] Nonproliferative diabetic retinopathy is a more common form of early diabetic retinopathy. In this type/stage of the disease, new blood vessels are not proliferating, but the walls of the blood vessels in patients' retinas weaken and bulges may protrude from the walls of smaller blood vessels. The smaller blood vessels may leak fluid and blood into the retina, and larger retinal vessels may begin to dilate and become irregular in diameter as well. Nonproliferative diabetic retinopathy can progress from mild to severe as more blood vessels become blocked. Retinal blood vessel damage may lead to a buildup of fluid (edema) in the center portion (macula) of the retina. If macular edema decreases vision, treatment is indicated to prevent permanent vision loss.

[0012] Non-proliferative Diabetic Retinopathy ranges from mild to moderate, severe, and very severe. A mild case is characterized by the presence of a micro aneurism. A moderate case presents at least one of: a hemorrhage/microaneurism, at least one Cotton-wool spot present, One Venous bleeding present, and One Intra retinal microvascular abnormality definitively present. Severe NPDR is characterized by the presence of criteria of moderate NPDR in all quadrants of the retina. Very severe NPDR is characterized by two or more criteria for severe NPDR (e.g. two criteria of moderate NPDR in each quadrant of the retina).

[0013] B. Proliferative Diabetic Retinopathy (also referred to herein as "PDR") classifies the subset of this disease where the patient presents one or more of neovascularisation, macula detachment, and/or edema. In early Proliferative Diabetic Retinopathy, new blood vessels can be observed. High-risk factors for developing PDR are: i. neo-vascularisation of ⅓ to ½ of the optic disc area, ii. neo-vascularisation of the disc and vitreous or pre-retinal hemorrhage, and iii. Neovascularisation of >½ of the disc size and vitreous/pre-retinal hemorrhage.

[0014] The retina is one of the most metabolically active tissues of the body and is particularly sensitive to ischemia. See Franc RN diabetic retinopathy N Eng J Med 2004; 350 (1); 48 PMID 14702427. Retinal capillary loss and thickening of the retinal basement membrane are some of the early findings in Diabetes. This pathology is similar to the glomeruli, that is diabetes also can cause progressive scarring of glomeruli-glomerulosclerosis. See, Accelerated death of retinal microvascular cells in humans and experimental diabetic retinopathy Mizutani M. Kern T S Lorenzo M J Clin Invest 1996; 97 (12) 2883. For the retina, neovascularisation is often a concern for diabetic retinopathy. In neovascularisation, the increase in the initial phase of capillary death is followed by abortive attempts to re-vascularize the diseased retina, which are not fully effective because the new capillaries can become occluded frequently.

[0015] Cases of Proliferative Diabetic Retinopathy where the center of the macula is detached or the fundus is obscured by vitreous or pre-retinal hemorrhages are characterized as severe. Diabetic retinopathy can progress to this more severe type, where damaged blood vessels close off, driving the growth of new, abnormal blood vessels in the retina. These new blood vessels may be fragile and leak into the vitreous fluid of the eye. Eventually, scar tissue from the growth of new blood vessels may cause the retina to detach. Alternatively, or in addition, the new blood vessels may interfere with the normal flow of fluid out of the eye, such that pressure can build in the eyeball. This buildup can damage the optic nerve and even result in glaucoma. Severe cases of Proliferative Diabetic Retinopathy can include clinically significant Macular Edema. Macular Edema is deemed clinically significant where i. thickening of the retina is greater than 500 microns at the center of the Macula, ii. thickening of the retina is less than 500 microns at the center of the Macula but there is the presence of hard exudate and adjacent thickening of the retina, or iii. there is a zone of retinal thickening of approximately the size of the disc located less than the disc's diameter from the center of the macula. Additional characterization of the disease may be found in Aiello L M Perspective on diabetic retinopathy Am. J. Ophthalmol 2003 136:122

[0016] Clinical features: The vast majority of patients who developed Diabetic Retinopathy have no symptoms until very late stages, but if treatment is delayed until the later stages of the disease then effective treatment can be limited. However, if treated early both the symptoms and the progression of the disease may be ameliorated. The observed symptoms of diabetic retinopathy will depend on the type of eye problem caused by the disease, but can include curtain falling during a vitreous bleed, floaters during the resolution of a vitreous bleed, and a general decrease in visual acuity that cannot be corrected by refraction.

[0017] There are three major indications of diabetic retinopathy that are visible by an ophthalmoscope. A first indication is a flame shape hemorrhage that is usually proximal to the occlusion of Neo capillary. A second indication is a cotton-wool exudate that is distal to the occlusion of a capillary. The third indication is a yellow exudate, which indicates a deposit of residual lipids after a large capillary leak. This yellow exudate is also usually associated with Macular edema.

[0018] The prevalence of Diabetic Retinopathy in both type 1 and type 2 diabetes cumulatively increases with time. For type one diabetes, Diabetic Retinopathy usually begins 3 to 5 years after diagnosis. After 15 to 20 years of first diagnosis with diabetes mellitus, virtually all patients are affected. See the Wisconsin epidemiological study of diabetic retinopathy. Prevalence and risk of diabetic retinopathy when age of diagnosis is 30 or more. Klein R, Klein R N, Moss S E, Davis M D, DeMets D L Arch Ophthalmol, 1984;

102 (4) 527. For type two diabetes, approximately 50 to 80 percent of patients are affected by Diabetic Retinopathy after 15 to 20 years.

[0019] Severe retinopathy proves to be a risk marker of cardiovascular death in diabetic patients. See High cardiovascular mortality in patients with visual impairment caused by Diabetes Retinopathy. Rajala U, PanjupaaH; Koskela P, Keinanen-Kiukaaniem S Diabetic Care 2000; 23 (7) 957. Prevention and treatment of systemic conditions in patients with diabetes are essential for the prevention of vision loss. This includes glycemic control, blood pressure control, and lipids control. Multiple studies have demonstrated that Glycemic control and lowering A1C levels reduce the rate and progression of diabetic retinopathy. Even a small reduction in A1C levels reduces the rate of diabetic retinopathy diagnosis by 35% and the progression of the disease by 15-30%.

[0020] Similarly, the Diabetic Control and Complications Trial found that glycemic control is a major determinant of the rate of development and progression of Diabetic Retinopathy in type one Diabetes Mellitus. See The effect of intense treatment of Diabetes on the development of and progression of long term complications in insulin dependent diabetes Mellitus Diabetic control and complications trial group. Nathan D M, Genuth S, Lachin j, Clearly R Crofford O, Davis M, Rand L, Siebert C, N Eng J Med; 1993; 329 (14) 977. A United Kingdom study indicated that glycemic control is important for preventing retinopathy in type 2 DM as well.

[0021] Intensive blood glucose control with sulfonylurea or insulin compared with conventional treatment and risk of complications in patients with type 2 Diabetes. (UKPDS 33) UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998; 325 (9131): 837 See also, Progression of retinopathy with intense versus conventional treatment in the diabetic control and complication trial. Diabetic control and complication trial group. Ophthalmology 1995 102 (4) 647.

[0022] Good blood pressure control decreases the incidence of Diabetic Retinopathy and in some trials, good blood pressure levels was correlated with slower progression of diabetic retinopathy. Management of diabetic retinopathy a systemic review. Mohamad Q, Gills M C, Wong T Y, JAMA 2007; 298 (8); 902 See also Tight blood pressure control and risk of microvascular complication in type 2 diabetes UKPDS 38 UK prospective diabetic study group. BMJ 1998 317 (7160) 703. Regular exercise and other lifestyle modifications affect the rate of diabetic retinopathy. Praidou A, Harris M, Niakas D Labiris G. Physical activity and its correlation to diabetic retinopathy. J Diabetes Complications 2017; 31 456. Sleep apnea and hemodialysis increase the prevalence and rate of progression of diabetic retinopathy. Altaf Q A, Dodson P, Ali A et. al. Obstructive sleep Apnea and Retinopathy In Patients With Type 2 Diabetes. A Longitudinal study. Am J Respir Crit Care Med, 2017; 296:892

[0023] In contrast, the benefits of lowering lipids through therapy for the prevention of Diabetic Retinopathy has not been well established. For background, see Simvastatin Retards Progression of retinopathy in diabetic patients with hypercholesterolemia. Sen K, Misra A, Kumar A, Panday R M, Diabetes Res Clin Pract; 2002 56 (1) 1.

[0024] While treatments exist, there is still a need for a treatment that can prevent, delay or reverse diabetic retinopathy. Diabetic retinopathy creates damage that is generally progressive and permanent. Usually, pharmacological compositions and/or surgery are only employed to help stop further damage. However, due to the complex nature of the disease and the observed symptoms, there remains a need for intervention at multiple levels of the disease's pathology. For example, there is a need for treatments directed to the changes in vascular properties caused by diabetic retinopathy.

SUMMARY OF THE DISCLOSURE

[0025] For one or more of the forgoing reasons, there is a need for a new mode of treatment for diabetic retinopathy that increases the capillary network and augments capillary blood supply to the anatomy of the eye.

[0026] For one or more of the forgoing reasons, there is a need for a new mode of prevention for diabetic retinopathy that protects the anatomy of the eye from, and prevents the symptoms of, diabetic retinopathy, by increasing the capillary network and augmenting the capillary blood supply to the eye.

[0027] In particular, there is a need for a method to prevent retinal damage and the symptoms of retinal damage by increasing the blood supply and the capillary network to the anatomy of the eye where the defects to the anatomy of the eye will form. This may include a method to increase the capillary network and blood supply to the optic nerve and the retina.

[0028] For one or more of the forgoing reasons, there is a need for a method that treats the chronic damage to the eye and the symptoms of diabetic retinopathy, by increasing the capillary network and augmenting the capillary blood supply to the vulnerable eye anatomy, and to treat the damaged ocular tissue and the symptoms of the damaged ocular tissue. This damaged tissue may include the optic nerve and the retina.

[0029] In particular, a method to treat the damaged ocular tissue and the symptoms of damaged ocular tissue by increasing the capillaries network and augmenting the capillary blood supply to the optic nerve region where symptoms associated with diabetic retinopathy have occurred. This optic nerve region may include the optic nerve and the retina.

[0030] The embodiments are directed to a method for preventing diabetic retinopathy by direct administration of a pharmaceutical preparation of calcium channel blockers, ACE inhibitors, or angiotensin receptor blockers to prevent the process and symptoms of diabetic retinopathy.

[0031] By "diabetic retinopathy" used herein, it is meant any process in the eye that causes the appearance and symptoms of diabetic retinopathy.

[0032] In one method of the disclosure, calcium channel blockers, ACE inhibitors, or angiotensin receptor blockers may be administered directly to the retina or directly to the surface of the eye before symptoms form, so as to prevent diabetic retinopathy, for example, in men or women with normal eye function and retina health before the degenerative process starts.

[0033] In one method of the disclosure, calcium channel blockers, ACE inhibitors, or angiotensin receptor blockers may be administered directly to the intravitreal space before symptoms form, so as to prevent diabetic retinopathy, for example, in men or women with normal eye function before the degenerative process starts.

[0034] In another embodiment, calcium channel blockers, ACE inhibitors, or angiotensin receptor blockers may be administered directly to the retina area to treat and heal the symptoms of diabetic retinopathy.

[0035] In another embodiment, calcium channel blockers, ACE inhibitors, or angiotensin receptor blockers may be administered directly to the intravitreal space to treat and heal the symptoms of diabetic retinopathy.

[0036] Calcium channel blockers, ACE inhibitors, or angiotensin receptor blockers may be administered even after symptoms of diabetic retinopathy have dissipated.

[0037] Calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers are a class of pharmaceutical drugs that when taken orally dilate the arteriolar system.

[0038] Contact calcium channel blockers, ACE inhibitors, or angiotensin receptor blockers are a new class of pharmaceutical products. When applied directly to target tissue it increases the capillary network, augments the capillary blood supply, and enhances tissue repair in diverse body membrane tissues. Currently, there are over 20 pharmaceutical patented ACE inhibitor drugs that use this property to treat hypertension, and congestive heart failure. The clinical indication of calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers is therefore limited to the field of cardiovascular diseases. Calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers were extensively studied but their ability to prevent and treat diabetic retinopathy remained unknown.

[0039] The methods of the embodiments are directed to the use of an application of calcium channel blockers, ACE inhibitors, or angiotensin receptor blockers to the eye retina space. The direct contact of ACE inhibitors with the ocular tissue, and in particular, the intravitreal space, increases the capillary network and augments the blood supply to the ocular tissue. It also increases the capillary network and augments the blood supply to the ocular territory. The direct contact of ACE inhibitors with the ocular tissue may increase the capillary network and blood supply to the optic nerve and, alternatively or in combination, the retina.

[0040] Accordingly, in a generally applicable first aspect (i.e., independently combinable with any of the aspects or embodiments identified herein), the calcium channel blocker, ACE inhibitor, or angiotensin receptor blocker may be administered directly to the retinal area or by intravitreal injection before symptoms form to prevent diabetic retinopathy before the degenerative process begins.

[0041] In a generally applicable aspect (i.e., independently combinable with any of the aspects or embodiments identified herein), the calcium channel blocker, ACE inhibitor, or angiotensin receptor blocker may be administered directly to the intravitreal space before symptoms form to prevent diabetic retinopathy before the degenerative process begins.

[0042] In a generally applicable embodiment (i.e., independently combinable with any of the aspects or embodiments identified herein) of the first aspect, the calcium channel blocker, ACE inhibitor, or angiotensin receptor blocker may be administered directly to the retinal area of the eye or by intravitreal injection to treat and heal the symptoms of diabetic retinopathy.

[0043] In a generally applicable embodiment (i.e., independently combinable with any of the aspects or embodiments identified herein) of the first aspect, the calcium channel blocker, ACE inhibitor, or angiotensin receptor blocker may be directly to the retinal area of the eye or by intravitreal injection even after the diabetic retinopathy has dissipated and the eye has healed to prevent the recurrence.

[0044] In a generally applicable embodiment (i.e., independently combinable with any of the aspects or embodiments identified herein) of the first aspect, the calcium channel blocker, ACE inhibitor, or angiotensin receptor blocker may be administered directly to the intravitreal space to treat and heal the symptoms of diabetic retinopathy.

[0045] In a generally applicable embodiment (i.e., independently combinable with any of the aspects or embodiments identified herein) of the first aspect, the calcium channel blocker, ACE inhibitor, or angiotensin receptor blocker may be directly to intravitreal space even after the diabetic retinopathy has dissipated and the eye has healed to prevent the recurrence.

[0046] Calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers are classes of pharmaceutical drugs when taken orally they dilate the arteriolar system by blocking the activity of the calcium channel receptors, ACE receptors or angiotensin receptors.

[0047] Contact calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers are a new class of pharmaceutical products. When applied directly to target tissue they increase the capillary network, augment the capillary blood supply, and enhance tissue repair in diverse body membrane tissues. When in contact with the ocular tissue, these pharmaceutical products may increase the capillary network and blood supply to the optic nerve and, alternatively or in combination, the retina.

[0048] Currently, there are over 20 pharmaceutical patented ACE inhibitor or angiotensin receptor blocker drugs that use this property to treat hypertension, and congestive heart failure. The clinical indication of ACE inhibitors or angiotensin receptor blockers is therefore generally limited to the field of cardiovascular diseases.

[0049] Calcium channel blockers, ACE inhibitors and angiotensin receptor blockers were extensively studied but their ability to prevent and treat diabetic retinopathy remained unknown.

[0050] The use of application of calcium channel blockers, ACE inhibitors or angiotensin receptor blockers to the retina or the intravitreal space is provided. The direct contact with the tissue of the eye increases the capillary network and augments the blood supply to the retina.

[0051] Additionally, the use of application of calcium channel blockers, ACE inhibitors or angiotensin receptor blockers to the optic nerve and, alternatively or in combination, the retina is provided. The direct contact with the tissue of the eye increases the capillary network and augments the blood supply to the optic nerve and or the retina.

[0052] The new class may be used for the prevention and treatment of diabetic retinopathy or other syndromes associated with diabetic retinopathy.

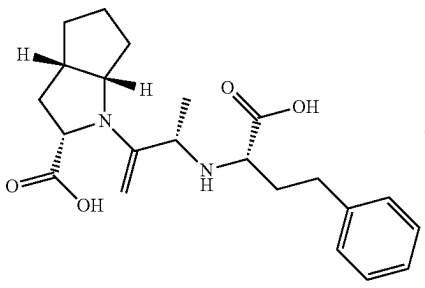
DETAILED DESCRIPTION OF THE DISCLOSURE

[0053] The following discussion addresses a number of embodiments and applications of the present disclosure. The beneficial features of the present disclosure will be evident from the described embodiments. It is to be understood that the present disclosure is not limited to such specific applications and that numerous implementations of the present disclosure may be realized. All references to patents, patent

applications, and non-patent publications mentioned in the specification are hereby incorporated by reference, in their entireties.

[0054] In some aspects, a method is provided herein to treat, prevent, reduce, ameliorate, or reduce diabetic retinopathy in a subject. In some embodiments, treating, preventing, reducing, ameliorating, or reducing diabetic retinopathy includes treating, preventing, reducing, ameliorating, or reducing one or more signs or symptoms of diabetic retinopathy. In some embodiments, a composition or a pharmaceutical composition is provided to the subject to treat, prevent, reduce, ameliorate or reduce diabetic retinopathy in the subject. In some embodiments, the composition or pharmaceutical composition includes a contact neo-vasodilator. Contact neo-vasodilators are a new class of medication. This disclosure describes the use of contact neo-vasodilators such as valsartan, a known angiotensin receptor blocker or enalapril, a known ACE inhibitor, or calcium channel blockers used in the treatment of hypertension and congestive heart failure, for the prevention and treatment of diabetic retinopathy.

[0055] In some embodiments, Ramiprilat, or other non-sulfhydryl ACE inhibitors with antihypertensive activity may have been used in treatment of high blood pressure, heart failure, or diabetic kidney disease, when applied in a pharmacological composition in an effective amount, directly into the eye, by direct administration or intravitreal injection, may be effective for treating, preventing, reducing, ameliorating, or preventing diabetic retinopathy. Without wanting to be bound by theory it is believed that an ACE inhibitor, such as ramipril or ramiprilat grows capillary networks in the eye and increases the capillary blood supply, reduces the intraocular pressure, repairs the intraocular pressure, and repairs the optic nerve in multiple form diabetic retinopathy. Ramiprilat chemical structure is shown below:



[0056] In some embodiments, ACE inhibitors, such as ramiprilat, such as enalapril, benazepril, lisinopril, ramipril, or fosinopril or angiotensin receptor blockers such as valsartan, telmisartan, olmesartan, losartan, irbesartan, candesartan and azilsartan, when administered directly to the eye, may be effective drugs for the prevention of diabetic retinopathy.

[0057] In some embodiments, Valsartan, or other angiotensin receptor blockers, or Enalapril, or other ACE inhibitors are drugs which previously may have been used in treatment of high blood pressure and or congestive heart failure, when applied in a pharmacological composition in an effective amount, directly into the eye, by direct administration or intravitreal injection, may be effective drugs for the treatment of diabetic retinopathy.

[0058] In some embodiments, angiotensin receptor blockers such as Valsartan, telmisartan, olmesartan, losartan, irbesartan, candesartan and azilsartan, when administered directly to the eye, may be effective drugs for the prevention of diabetic retinopathy. Pharmacological composition as used herein is a pharmaceutical preparation according to the disclosure, composed but not limited to ACE inhibitors, calcium channel blockers, or angiotensin receptor blockers and a suitable non-toxic pharmaceutical carrier.

[0059] Effective amount as used herein is an amount of the pharmaceutical composition of calcium channel blockers, ACE inhibitors, or angiotensin receptor blockers that is effective for treating the diabetic retinopathy. An amount of calcium channel blockers, ACE inhibitors, or angiotensin receptor blockers that is suitable for direct administration or intravitreal injection to the eye.

[0060] A method is provided of applying a pharmaceutical preparation in an effective amount of one or more vasodilators (e.g., calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, nitrates, alpha blockers, beta blockers, hydralazine, and/or angiotensin receptor-neprilysin inhibitors), directly to the tissue of the eye or into the eye via intravitreal injection to treat or prevent diabetic retinopathy.

[0061] The pharmacological preparation can comprise a calcium channel blocker. The calcium channel blocker can be in a suitable nontoxic pharmacological carrier. The pharmacological preparation can comprise an ACE inhibitor. The ACE inhibitor can be in a suitable nontoxic pharmacological carrier. The pharmacological preparation can comprise an angiotensin receptor blocker. The angiotensin receptor blocker can be in a suitable nontoxic pharmacological carrier. In some embodiments, an effective amount for treatment or prevention of diabetic retinopathy is administered. An amount of calcium channel blocker that is suitable for treatment by intravitreal injection or direct application to the tissue of the eye is administered. In some embodiments, an effective amount for treatment or prevention of diabetic retinopathy is administered. An amount of ACE inhibitor that is suitable for treatment by intravitreal injection or direct application to the tissue of the eye is administered. In some embodiments, an effective amount for treatment or prevention of diabetic retinopathy is administered. An amount of angiotensin receptor blocker that is suitable for treatment by intravitreal injection or direct application to the tissue of the eye is administered.

[0062] In some embodiments, contact vasodilators (e.g., calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, nitrates, alpha blockers, beta blockers, hydralazine, and/or angiotensin receptor-neprilysin inhibitors) are a new class of pharmaceutical medications that increase blood supply, which produces biological changes.

[0063] In the case of treatment or prevention of diabetic retinopathy, these changes can include one or more of increasing the blood supply to the vitreous tissue, the optic nerve, the choroid, the sclera, the retina, and the ocular lens. These biological changes may include a change in fluid movement in the anterior chamber and may include a change in fluid movement in the vitreous chamber.

[0064] Calcium channel blockers are a new class of pharmaceutical drugs that disrupt the entry of calcium molecules through the L type voltage operated channels to cardiac

muscle and blood vessels cells. The blockage of calcium entry causes the relief of arterial spasm. Currently there are 70 pharmaceutical patented calcium channel blocker drugs that use this property to treat hypertension, angina pectoris and cardiac arrhythmia. The clinical indication for the therapeutic use of calcium channel blockers was therefore limited, until now, to the field of cardiovascular diseases only. Calcium channel blockers were extensively studied but their ability to prevent and or to treat diabetic retinopathy remained heretofore unknown. Accordingly, new uses are provided of contact-applied calcium channel blockers for application to the tissue of the eye (e.g., vitreous tissue) or for intravitreal or intraocular injection. The new use may be used for the prevention or treatment of diabetic retinopathy. No trial of topical calcium channel blockers for the prevention or treatment of diabetic retinopathy has heretofore been published. The use is provided of contact neo-vasodilators such as nifedipine, a known calcium channel blocker used in the treatment of hypertension, for the prevention and treatment diabetic retinopathy. Nifedipine, amlodipine, felodipine, isradipine, nicardipine, nisoldipine and clevidipine are in a class of dihydropyridines calcium channel blockers. Verapamil and diltiazem are non-dihydropyridines calcium channel blockers. When applied by contact these are very effective drugs for the treatment or prevention of diabetic retinopathy.

[0065] In some embodiments, inhibitors of angiotensin converting enzyme (ACE) can be employed as vasodilators. Angiotensin II is a chemical produced by the body that primarily circulates in the blood. It causes the muscles surrounding blood vessels to contract, thereby narrowing the vessels. Angiotensin II is formed from angiotensin I in the blood by the enzyme angiotensin converting enzyme (ACE). Angiotensin I in the blood is itself formed from angiotensinogen, a protein produced by the liver and released into the blood. Angiotensin converting enzyme inhibitors (ACE inhibitors) are medications that slow (inhibit) the activity of the enzyme ACE, which decreases the production of angiotensin II. As a result, blood vessels enlarge or dilate. ACE inhibitors include, but are not limited to benazepril (Lotensin), captopril (Capoten), enalapril (Vasotec, Epaned, Lexxel), fosinopril (Monopril), lisinopril (Prinivil), moexipril (Univasc), perindopril (Aceon), quinapril (Accupril), ramipril (Altace), and trandolapril (Mavik).

[0066] In some embodiments, angiotensin II receptor blockers (ARBs) help relax the blood vessels. Angiotensin II receptor blockers block the action of angiotensin II, allowing blood vessels to dilate. Angiotensin receptor blockers include but are not limited to: azilsartan (Edarbi), candesartan (Atacand), eprosartan, irbesartan (Avapro), losartan (Cozaar), olmesartan (Benicar), telmisartan (Micardis), and valsartan (Diovan).

[0067] Other vasodilators are known in the art. These include, but are not limited to nitrates (nitroglycerin, isosorbide mononitrate and isosorbide dinitrate), Alpha blockers (doxazosin (Cardura), prazosin (Minipress), terazosin), Beta blockers (Acebutolol (Sectral), Atenolol (Tenormin), Bisoprolol fumarate (Zebeta), Carvedilol (Coreg)—Combined alpha/beta blocker, Esmilol (Brevibloc), Labetalol (Trandate, Normodyne)—Combined alpha/beta blocker, Metoprolol tartrate (Lopressor) and metoprolol succinate (Toprol-XL), Nadolol (Corgard), Nebivolol (Bystolic), Penbutolol sulfate (Levatol), Propranolol (Inderal), Sotalol (Betapace), HCTZ and bisoprolol (Ziac) is a beta blocker plus diuretic), Hydralazine, and angiotensin receptor-neprilysin inhibitors (ARNi) (Entresto, sacubitril/valsartan).

Conditions Amenable to Treatment or Prevention

[0068] Compositions and methods are provided for the prevention or treatment of diabetic retinopathy.

[0069] Application of vasodilators (e.g., calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, nitrates, alpha blockers, beta blockers, hydralazine, and/or angiotensin receptor-neprilysin inhibitors), such as Nifedipine or other calcium channel blockers, which previously may have been used in the treatment of high blood pressure, in a pharmacological composition, may be provided in an effective amount, for example in a contact form, such as, but not limited to an oil, gel, drop, and/or liquid preparation or suspension, to the tissue of the eye (vitreous tissue) or for administration by intravitreal injection, thereby treating and/or preventing the symptoms of diabetic retinopathy.

[0070] Pharmacological compositions of the embodiments include but are not limited to one or more vasodilators (e.g., calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, nitrates, alpha blockers, beta blockers, hydralazine, and/or angiotensin receptor-neprilysin inhibitors) and a suitable nontoxic pharmaceutical carrier. The pharmaceutical composition in administered in an amount effective for treating diabetic retinopathy, e.g., an amount suitable for treatment by direct application to tissue of the eye (vitreous tissue) or by intravitreal injection.

[0071] Diabetic retinopathy, associated symptoms, and treatment thereof, or use of ACE inhibitors, Angiotensin receptor blockers, or calcium channel blockers are described in the following references, each of which is incorporated by reference herein in its entirety and each of which is hereby made a part of this specification: Thylefors B, Négrel AD, Pararajasegaram R, Dadzie K Y. Global; Thylefors B. The World Health Organization's programme for the; Congdon N, O'Colmain B, Klaver C C, et al. Causes and prevalenceof visual impairment among adults in the United States. Arch; Congdon N, O'Colmain B, Klaver C C, et al. Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol 2004; 122:477;

[0072] Compositions including one or more vasodilators (e.g., calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, nitrates, alpha blockers, beta blockers, hydralazine, and/or angiotensin receptor-neprilysin inhibitors), optionally in combination with conventional therapies, and associated methods for treatment of diabetic retinopathy and related symptoms are provided.

[0073] Some embodiments relate to a pharmaceutical composition and method of treatment using the pharmaceutical composition, wherein the pharmaceutical composition comprises at least one calcium channel blocker, for example, a calcium channel blocker selected from the group consisting of amlodipine (Norvasc), diltiazem (Cardizem LA, Tiazac), felodipine (Plendil), isradipine (Dynacirc), nifedipine (Adalat, Procardia), nicardipine (Cardene), nimodipine (Nimotop), nisoldipine (Sular), verapamil (Covera-HS, Verelan PM, Calan), verapamil, diltiazem and nicardipine (Cardene IV). Some embodiments relate to a pharmaceutical composition and method of treatment using the pharmaceutical composition, wherein the pharmaceutical composition comprises at least one ACE inhibitors, for example at least one ACE inhibitor selected from the group consisting of benazepril (Lotensin), captopril (Capoten),

enalapril (Vasotec, Epaned, Lexxel), fosinopril (Monopril), lisinopril (Prinivil), moexipril (Univasc), perindopril (Aceon), quinapril (Accupril), ramipril (Altace), ramiprilat, and trandolapril (Mavik). Some embodiments relate to a pharmaceutical composition and method of treatment using the pharmaceutical composition, wherein the pharmaceutical composition comprises at least one angiotensin receptor blocker, for example at least one angiotensin receptor blocker selected from the group consisting of azilsartan (Edarbi), candesartan (Atacand), eprosartan, irbesartan (Avapro), losartan (Cozaar), olmesartan (Benicar), telmisartan (Micardis), and valsartan (Diovan). In certain embodiments, the pharmaceutical composition is in a form suitable for contact administration, e.g., to tissue of the eye (vitreous tissue) or by intravitreal administration, however other routes of administration are also considered that involve contact of the vasodilator to the tissue to be treated.

[0074] The pharmaceutical compositions for treatment of diabetic retinopathy can further comprise other pharmaceutically active ingredients. These can include drugs to control pain, for example, nonsteroidal anti-inflammatory drugs such as ibuprofen or naproxen sodium, topical anesthetics such as lidocaine, drugs to fight infections (e.g., antibiotic, antiviral, or antifungal agents). The treatment can be administered in conjunction with other therapies, e.g., the conventional therapies for diabetic retinopathy as described elsewhere herein.

[0075] The use of topical vasodilators (e.g., calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, nitrates, alpha blockers, beta blockers, hydralazine, and/or angiotensin receptor-neprilysin inhibitors) for treatment of diabetic retinopathy is a new class of drugs. The new class may be used for diabetic retinopathy, or to enhance efficacy of conventional diabetic retinopathy drugs.

[0076] In one method, the vasodilator may be applied directly to the tissue of the eye, e.g., in a form of an eyedrop. In another embodiment, the vasodilator may be injected directly into the intravitreal space to treat diabetic retinopathy. The vasodilator may be applied even after the diabetic retinopathy has been ameliorated to prevent recurrence of diabetic retinopathy.

[0077] In one method, the vasodilator may be used to treat a specific type of diabetic retinopathy or a patient population at risk of diabetic retinopathy. For example, a patient population may be selected from patients displaying type 1 diabetes, type 2 diabetes, Non-proliferative Diabetic Retinopathy, Proliferative Diabetic Retinopathy, patients with a family history of diabetic retinopathy, patients with a family history of type 1 or type 2 diabetes, patients with a genetic marker associated with either type 1 or type 2 diabetes, and patients with lifestyle risks associated with diabetic retinopathy. Within Non-proliferative Diabetic Retinopathy (NPDR), the specific type of diabetic retinopathy that is selected for treatment may be: mild NPDR, moderate NPDR, and severe NPDR.

[0078] One aspect of this disclosure is directed to treating those millions of patients that are observed for the first time with diabetic retinopathy, where, for example, mild non-proliferative diabetic retinopathy, is first detected or identified as a possibility. As current treatments of diabetic retinopathy focus on treating generally irreversible symptoms like blindness, one advantage of some methods of the disclosure may include early-stage treatment of disease. In some embodiments, vision loss may be prevented by treating the progression of the disease. In some embodiments, vision loss may be prevented by limiting the progression of the disease before the disease manifests more severe symptoms. In some embodiments, retina damage is treated or reduced by administration of a vasodilator by topical administration. In some embodiments, the topical administration is by ophthalmic drops. In some embodiments, retina damage is treated or reduced by administration of a vasodilator by intraocular administration of a vasodilator. In some embodiments, retina damage is treated or reduced by administration of a vasodilator by intravitreal administration of a vasodilator. In some embodiments, retina damage is treated or reduced by administration of a vasodilator by intrajunctival administration of a vasodilator. In some embodiments, retina damage is treated or reduced by administration of a vasodilator by subcutaneous administration of a vasodilator. In some embodiments, retina damage is treated or reduced by administration of a vasodilator by sub-Tenon administration of a vasodilator. In some embodiments, retina damage is treated or reduced by administration of a vasodilator by intracameral administration of a vasodilator. In some embodiments, retina damage is treated or reduced by administration of a vasodilator by intracameral administration of a vasodilator. In some embodiments, retina damage is treated or reduced by administration of a vasodilator by retrobulbar administration of a vasodilator.

[0079] In some embodiments, a method is provided for to treat, prevent, or reduce Non-proliferative Diabetic Retinopathy. In some embodiments, a method is provided for to treat, prevent, or reduce at least one or more of micro aneurism, micro hemorrhage, and cotton-wool spots. In some embodiments, a method is provided for to treat, prevent, or reduce one or more of mild Non-proliferative Diabetic Retinopathy, moderate Non-proliferative Diabetic Retinopathy, severe Non-proliferative Diabetic Retinopathy, and very severe Non-proliferative Diabetic Retinopathy.

[0080] In some embodiments, nonproliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by topical administration. In some embodiments, the topical administration is by ophthalmic drops. In some embodiments, nonproliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by intraocular administration of a vasodilator. In some embodiments, nonproliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by intravitreal administration of a vasodilator. In some embodiments, nonproliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by intrajunctival administration of a vasodilator. In some embodiments, nonproliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by subcutaneous administration of a vasodilator. In some embodiments, nonproliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by sub-Tenon administration of a vasodilator. In some embodiments, nonproliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by intracameral administration of a vasodilator. In some embodiments, nonproliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by intracameral administration of a vasodilator. In some embodiments, nonproliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by retrobulbar administration of a vasodilator.

[0081] In some embodiments, diabetes mellitus type 2 is treated or a condition or symptom is reduced by administration of a vasodilator by topical administration. In some embodiments, the topical administration is by ophthalmic drops. In some embodiments, diabetes mellitus type 2 is treated or reduced by administration of a vasodilator by intraocular administration of a vasodilator. In some embodiments, diabetes mellitus type 2 is treated or reduced by administration of a vasodilator by intravitreal administration of a vasodilator. In some embodiments, diabetes mellitus type 2 is treated or reduced by administration of a vasodilator by intrajunctival administration of a vasodilator. In some embodiments, diabetes mellitus type 2 is treated or reduced by administration of a vasodilator by subcutaneous administration of a vasodilator. In some embodiments, diabetes mellitus type 2 is treated or reduced by administration of a vasodilator by sub-Tenon administration of a vasodilator. In some embodiments, diabetes mellitus type 2 is treated or reduced by administration of a vasodilator by intracameral administration of a vasodilator. In some embodiments, diabetes mellitus type 2 is treated or reduced by administration of a vasodilator by intracameral administration of a vasodilator. In some embodiments, diabetes mellitus type 2 is treated or reduced by administration of a vasodilator by retrobulbar administration of a vasodilator.

[0082] In some embodiments, a method is provided for to treat, prevent, or reduce Proliferative Diabetic Retinopathy. In some embodiments, a method is provided for to treat, prevent, or reduce at least one or more of neovascularisation, macula detachment, and/or edema. In some embodiments, a method is provided for to treat, prevent, or reduce early Proliferative Diabetic Retinopathy, where, for example, new blood vessels can be observed. In some embodiments, a method is provided to treat patients with high-risk factors for developing PDR including, for example, i. neo-vascularisation of ⅓ to ½ of the optic disc area, ii. neo-vascularisation of the disc and vitreous or pre-retinal hemorrhage, and iii. Neovascularisation of >½ of the disc size and vitreous/pre-retinal hemorrhage.

[0083] In some embodiments, a method is provided for to treat, prevent, or reduce Proliferative Diabetic Retinopathy where the center of the macula is detached or the fundus is obscured by vitreous or pre-retinal hemorrhages are characterized as severe. In some embodiments, a method is provided for to treat, prevent, or reduce severe Proliferative Diabetic Retinopathy where damaged blood vessels close off, driving the growth of new, abnormal blood vessels in the retina. See Aiello LM Perspective on diabetic retinopathy Am. J. Ophthalmol 2003 136:122

[0084] In some embodiments, proliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by topical administration. In some embodiments, the topical administration is by ophthalmic drops. In some embodiments, proliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by intraocular administration of a vasodilator. In some embodiments, proliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by intravitreal administration of a vasodilator. In some embodiments, proliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by intrajunctival administration of a vasodilator. In some embodiments, proliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by subcutaneous administration of a vasodilator. In some embodiments, proliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by sub-Tenon administration of a vasodilator. In some embodiments, proliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by intracameral administration of a vasodilator. In some embodiments, proliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by intracameral administration of a vasodilator. In some embodiments, proliferative diabetic retinopathy is treated or reduced by administration of a vasodilator by retrobulbar administration of a vasodilator.

[0085] One aspect of this disclosure is directed to treating those millions of patients that are observed for the first time with retina damage, is first detected or identified as a possibility. As current treatments of diabetic retinopathy focus on treating generally irreversible symptoms like blindness, one advantage of some methods of the disclosure may include early-stage treatment of disease. In some embodiments, vision loss may be prevented by treating the progression of the disease. In some embodiments, vision loss may be prevented by limiting the progression of the disease before the disease manifests more severe symptoms. In some embodiments, retinal damage is treated or reduced by administration of a vasodilator by topical administration. In some embodiments, the topical administration is by ophthalmic drops. In some embodiments, retinal damage is treated or reduced by administration of a vasodilator by intraocular administration of a vasodilator. In some embodiments, retinal damage is treated or reduced by administration of a vasodilator by intravitreal administration of a vasodilator. In some embodiments, retinal damage is treated or reduced by administration of a vasodilator by intrajunctival administration of a vasodilator. In some embodiments, retinal damage is treated or reduced by administration of a vasodilator by subcutaneous administration of a vasodilator. In some embodiments, retinal damage is treated or reduced by administration of a vasodilator by sub-Tenon administration of a vasodilator. In some embodiments, retinal damage is treated or reduced by administration of a vasodilator by intracameral administration of a vasodilator. In some embodiments, retinal damage is treated or reduced by administration of a vasodilator by intracameral administration of a vasodilator. In some embodiments, retinal damage is treated or reduced by administration of a vasodilator by retrobulbar administration of a vasodilator.

[0086] Aspects of the disclosure relate to a method of growing a capillary network and increasing the capillary blood supply in the eye of a subject. In some embodiments, the method includes administering a pharmaceutical composition comprising ramipril or ramiprilat and a pharmaceutically acceptable excipient to the eye of the subject, thereby treating diabetic retinopathy. In some embodiments, the pharmaceutical composition comprises ramiprilat. In some embodiments, administering the pharmaceutical composition repairs the optic nerve of the subject. In some embodiments, symptom of diabetic retinopathy is spots or dark string floating in the subject's vision (e.g., floaters). In some embodiments, symptom of diabetic retinopathy blurred vision. In some embodiments, symptom of diabetic retinopathy is fluctuating vision. In some embodiments, symptom of diabetic retinopathy is dark or empty areas of the subject's vision. In some embodiments, symptom of diabetic retinopathy is vision loss.

[0087] In some embodiments, a method is provided for to treat or prevent a vitreous hemorrhage in a subject. In some embodiments, the method includes administering a pharmaceutical composition as described herein. In some embodiments, the pharmaceutical composition includes an ACE inhibitor. In some embodiments, the pharmaceutical composition includes ramipril or ramiprilat.

[0088] In some embodiments, a method is provided for to treat or prevent retinal detachment in a subject. In some embodiments, the method includes administering a pharmaceutical composition as described herein. In some embodiments, the pharmaceutical composition includes an ACE inhibitor. In some embodiments, the pharmaceutical composition includes ramipril or ramiprilat.

Definitions

[0089] The term "alcohol" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to any compound as described herein incorporating one or more hydroxy groups, or being substituted by or functionalized to include one or more hydroxy groups.

[0090] The term "derivative" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to any compound as described herein incorporating one or more derivative groups, or being substituted by or functionalized to include one or more derivative groups. Derivatives include but are not limited to esters, amides, anhydrides, acid halides, thioesters, and phosphates.

[0091] The term "hydrocarbon" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to any moiety comprising only carbon and hydrogen atoms. A functionalized or substituted hydrocarbon moiety has one or more substituents as described elsewhere herein.

[0092] The term "lipid" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to saturated and unsaturated oils and waxes, derivatives, amides, glycerides, fatty acids, fatty alcohols, sterol and sterol derivatives, tocopherols, carotenoids, among others.

[0093] The terms "pharmaceutically acceptable" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for contact with the tissues of and/or for consumption by human beings and animals without excessive toxicity, irritation, allergic response, or other problem complications commensurate with a reasonable risk/benefit ratio.

[0094] The terms "pharmaceutically acceptable salts" and "a pharmaceutically acceptable salt thereof" as used herein are broad terms, and are to be given their ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refer without limitation to salts prepared from pharmaceutically acceptable, non-toxic acids or bases. Suitable pharmaceutically acceptable salts include metallic salts, e.g., salts of aluminum, zinc, alkali metal salts such as lithium, sodium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts; organic salts, e.g., salts of lysine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), procaine, and tris; salts of free acids and bases; inorganic salts, e.g., sulfate, hydrochloride, and hydrobromide; and other salts which are currently in widespread pharmaceutical use and are listed in sources well known to those of skill in the art, such as, for example, The Merck Index. Any suitable constituent can be selected to make a salt of the therapeutic agents discussed herein, provided that it is non-toxic and does not substantially interfere with the desired activity. In addition to salts, pharmaceutically acceptable precursors and derivatives of the compounds can be employed. Pharmaceutically acceptable amides, lower alkyl derivatives, and protected derivatives can also be suitable for use in compositions and methods of preferred embodiments. While it may be possible to administer the compounds of the preferred embodiments in the form of pharmaceutically acceptable salts, it is generally preferred to administer the compounds in neutral form.

[0095] The term "pharmaceutical composition" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to a mixture of one or more pharmacologically active ingredients (e.g. vasodilators) disclosed herein with other chemical components, such as diluents or carriers. The pharmaceutical composition facilitates administration of the compound to an organism. Pharmaceutical compositions can also be obtained by reacting compounds with inorganic or organic acids or bases. Pharmaceutical compositions will generally be tailored to the specific intended route of administration.

[0096] As used herein, a "carrier" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to a compound that facilitates the incorporation of a compound into cells or tissues. For example, without limitation, dimethyl sulfoxide (DMSO) is a commonly utilized carrier that facilitates the uptake of many organic compounds into cells or tissues of a subject. Water, saline solution, ethanol, and mineral oil are also carriers employed in certain pharmaceutical compositions.

[0097] As used herein, a "diluent" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to an ingredient in a pharmaceutical composition that lacks pharmacological activity but may be pharmaceutically necessary or desirable. For example, a diluent may be used to increase the bulk of a potent drug whose mass is too small for manufacture and/or administration. It may also be a liquid for the dissolution of a drug to be administered by injection, ingestion or inhalation. A common form of diluent in the art is a buffered aqueous solution such as, without limitation, phosphate buffered saline that mimics the composition of human blood.

[0098] As used herein, an "excipient" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to a substance that is added to a pharmaceutical composition to provide, without limitation, bulk, consistency, stability, binding ability, lubrication, disintegrating ability etc., to the composition. A "diluent" is a type of excipient.

[0099] As used herein, a "subject" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to an animal that is the object of treatment, observation or experiment. "Animal" includes cold- and warm-blooded vertebrates and invertebrates such as fish, shellfish, reptiles, and, in particular, mammals. "Mammal" includes, without limitation, dolphins, mice, rats, rabbits, guinea pigs, dogs, cats, sheep, goats, cows, horses, primates, such as monkeys, chimpanzees, and apes, and, in particular, humans. In some embodiments, the subject is human.

[0100] As used herein, the terms "treating," "treatment," "therapeutic," or "therapy" are broad terms, and are to be given their ordinary and customary meaning (and are not to be limited to a special or customized meaning) and, without limitation, do not necessarily mean total cure or abolition of the disease or condition. Any alleviation of any undesired markers, signs or symptoms of a disease or condition, to any extent, can be considered treatment and/or therapy. Furthermore, treatment may include acts that may worsen the patient's overall feeling of well-being or appearance.

[0101] The terms "therapeutically effective amount" and "effective amount" as used herein are broad terms, and are to be given its ordinary and customary meaning to a person of ordinary skill in the art (and are not to be limited to a special or customized meaning), and are used without limitation to indicate an amount of an active compound, or pharmaceutical agent, that elicits the biological or medicinal response indicated. For example, a therapeutically effective amount of compound can be the amount needed to prevent, alleviate or ameliorate markers or symptoms of a condition or prolong the survival of the subject being treated. This response may occur in a tissue, system, animal or human and includes alleviation of the signs or symptoms of the disease being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art, in view of the disclosure provided herein. The therapeutically effective amount of the compounds disclosed herein required as a dose will depend on the route of administration, the type of animal, including human, being treated, and the physical characteristics of the specific animal under consideration. The dose can be tailored to achieve a desired effect, but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

[0102] The term "solvents" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and is not to be limited to a special or customized meaning), and refers without limitation to compounds with some characteristics of solvency for other compounds or means, that can be polar or nonpolar, linear or branched, cyclic or aliphatic, aromatic, naphthenic and that includes but is not limited to: alcohols, derivatives, diesters, ketones, acetates, terpenes, sulfoxides, glycols, paraffins, hydrocarbons, anhydrides, heterocyclics, among others.

[0103] The term "anatomy of the eye" refers to all the parts and subparts of and related to the eye. The anatomy of the eye may refer to, but is not limited to, each of the following individually, collectively, or in some combination of Choroid, Cornea, Fovea, Iris, Macula, Lens, Optic Nerve, Pupil, Retina, Sclera, and Vitreous Humor. As, for example, most of the optic nerve structure is outside of any specific ocular globe territory, the term "anatomy of the eye" may refer to parts and subparts of and related to the eye that are not within the eye itself.

[0104] The term "neovascularization" refers to new blood vessels forming in abnormal locations, abnormal times, and or abnormal quantities. New fibrous tissues often form afterward between the new vessels, which may decrease vision. Retinal neovascularization refers to new abnormal blood vessel growth in the retina. Neovascularization may also occur throughout the anatomy of the eye. Not all capillary formation is negative, and as described herein neovascularization may occur due to abortive attempts to form new capillaries. Accordingly, healthy and new capillary formation may reduce neovascularization.

[0105] It is to be understood that where compounds disclosed herein (e.g., calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, nitrates, alpha blockers, beta blockers, hydralazine, and/or angiotensin receptor-neprilysin inhibitors) have unfilled valencies, then the valencies are to be filled with hydrogens or isotopes thereof, e.g., hydrogen-1 (protium) and hydrogen-2 (deuterium).

[0106] It is understood that the compounds described herein (e.g., calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, nitrates, alpha blockers, beta blockers, hydralazine, and/or angiotensin receptor-neprilysin inhibitors) can be labeled isotopically. Substitution with isotopes such as deuterium may afford certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased in vivo half-life or reduced dosage requirements. Each chemical element as represented in a compound structure may include any isotope of said element. For example, in a compound structure a hydrogen atom may be explicitly disclosed or understood to be present in the compound. At any position of the compound that a hydrogen atom may be present, the hydrogen atom can be any isotope of hydrogen, including but not limited to hydrogen-1 (protium) and hydrogen-2 (deuterium). Thus, reference herein to a compound encompasses all potential isotopic forms unless the context clearly dictates otherwise.

[0107] It is understood that the methods and combinations described herein may include crystalline forms (also known as polymorphs, which include the different crystal packing arrangements of the same elemental composition of a compound), amorphous phases, salts, solvates, and hydrates, e.g., of vasodilators. In some embodiments, the compounds described herein exist in solvated forms with pharmaceutically acceptable solvents such as water, ethanol, or the like. In other embodiments, the compounds described herein exist in unsolvated form. Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and may be formed during the process of crystallization with pharmaceutically acceptable solvents such as water, ethanol, or the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. In addition, the

compounds provided herein (e.g., vasodilators) may exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

[0108] Where a range of values is provided, it is understood that the upper and lower limit, and any intervening value between the upper and lower limit of the range is included.

[0109] Any percentages, ratios or other quantities referred to herein are on a weight basis, unless otherwise indicated.

Pharmaceutical Compositions

[0110] The vasodilators (e.g., calcium channel blockers, ACE inhibitors, angiotensin receptor blockers, nitrates, alpha blockers, beta blockers, hydralazine, and/or angiotensin receptor-neprilysin inhibitors) can be prepared by any suitable method known to those in the art. For representative methods, see, for example, Francis A. Carey et al., Advanced Organic Chemistry: Part B: Reaction and Synthesis (5^{th} Ed. 2005).

[0111] Formulations including a vasodilator (e.g., a calcium channel blocker, ACE inhibitor and/or angiotensin receptor blocker) and at least one excipient are provided. It is generally preferred to administer the compounds of the embodiments in topical formulations; however, other routes of administration are also contemplated.

[0112] The pharmaceutical compositions described herein can be administered by themselves to a subject, or in compositions where they are mixed with other active agents, as in combination therapy, or with carriers, diluents, excipients or combinations thereof. Formulation is dependent upon the route of administration chosen. Techniques for formulation and administration of the compounds described herein are known to those skilled in the art (see, e.g., "Remington: The Science and Practice of Pharmacy", Lippincott Williams & Wilkins; 20th edition (Jun. 1, 2003) and "Remington's Pharmaceutical Sciences," Mack Pub. Co.; 18th and 19th editions (December 1985, and June 1990, respectively).

[0113] The pharmaceutical compositions disclosed herein may be manufactured by a process that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, tableting, or extracting processes. Many of the vasodilator (e.g., a calcium channel blocker, ACE inhibitor and/or angiotensin receptor blocker) used in the pharmaceutical combinations disclosed herein may be provided as salts with pharmaceutically acceptable counterions.

[0114] Multiple techniques of administering a compound exist in the art including, but not limited to, oral, rectal, topical, aerosol, injection and parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intravitreal, intranasal, and intraocular injections. Contemplated herein is any combination of the forgoing, or other methods as would be known to one of ordinary skill in the art (see, e.g., "Remington: The Science and Practice of Pharmacy", Lippincott Williams & Wilkins; 20th edition (Jun. 1, 2003) and "Remington's Pharmaceutical Sciences," Mack Pub. Co.; 18th and 19th editions (December 1985, and June 1990, respectively).

[0115] The compositions described herein are suitable for use in treatment or prevention of diabetic retinopathy or associated symptoms. The compositions are suitable for use in any patient where treatment or prevention of diabetic retinopathy is desirable.

[0116] The vasodilator (e.g., a calcium channel blocker, ACE inhibitor and/or angiotensin receptor blocker) can be employed in various types of formulations. Topical formulations including one or more vasodilators in combination with at least one excipient are provided. Excipients can include a nonaqueous or aqueous carrier, and one or more agents selected from moisturizing agents, pH adjusting agents, deodorants, fragrances, chelating agents, preservatives, emulsifiers, thickeners, solubilizing agents, penetration enhancers, anti-irritants, colorants, surfactants, beneficial agents, pharmaceutical agents, and other components as known in the art for use in connection with topical formulations for application to skin or ocular membranes. The formulation can be provided as an aqueous formulation, or in an anhydrous formulation which may prevent water-based irritant contact dermatitis or stinging sensation upon application. In another embodiment, the composition is formulated such that preservatives need not be employed (e.g., a preservative-free formulation) so as to avoid eye or skin irritation associated with certain preservatives.

[0117] To facilitate application, the composition may be provided as an ointment, an oil, a lotion, a paste, a powder, a gel, a solid insert, or a cream. The composition may also include additional ingredients such as a protective agent, an emollient, a humectant, an antibiotic agent, an antifungal agent, an antiviral agent, an antiprotozoal agent, an anesthetic agent, a steroidal anti-inflammatory agent, a non-steroidal anti-inflammatory agent, an antipruritic agent, an antioxidant agent, an anti-histamine agent, a vitamin or vitamin complex, a hormone, an anti-skin atrophy agent, and combinations thereof. In a further embodiment, the composition may avoid animal or cellular-based materials to avoid irritation. The composition can be applied directly to the vitreous tissue of the eye.

[0118] Methods of using vasodilator formulations are provided. The compositions may be applied topically, but may also be applied via intravitreal injection.

[0119] Some embodiments include administering vasodilator (e.g., a calcium channel blocker, ACE inhibitor and/or angiotensin receptor blocker) compositions provided herein in topical formulations; however, other routes of administration are also contemplated (e.g., intraocular or the like). Contemplated routes of administration include but are not limited to topical and intraocular. Suitable liquid forms include suspensions, emulsions, solutions, and the like. Unit dosage forms can also be provided, e.g., individual packets with a premeasured amount of the formulation, configured for administration to the tissue on a predetermined schedule (e.g., daily, weekly, etc.). Unit dosage forms configured for administration twice a day can be employed; however, in certain embodiments it can be desirable to configure the unit dosage form for administration once a day, four times a day, or more, or once every other day, every three days, weekly, or less, or on an as-needed basis.

[0120] In some embodiments, the topical and intravitreal formulations includes from about 0.001 wt. % or less to about 50 wt. % or more of active ingredient, such as the vasodilator (e.g., a calcium channel blocker, ACE inhibitor and/or angiotensin receptor blocker). In some embodiments, the topical and intravitreal formulation includes from about 0.005, 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.1,

0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, or 1 wt. % to about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, or 45 wt. %.

[0121] Compositions and formulations for topical administration to the vitreous tissue of the eye can include gels, drops, sprays, liquids, and aerosols. Conventional pharmaceutical carriers, aqueous or oily bases, thickeners and the like may be employed. Such formulations are typically provided in an eyedropper. A liquid or gel can also be placed using an applicator, e.g., a wand, a sponge, a syringe, or other suitable method.

[0122] A topical formulation can be provided in a form of a carrier containing the vasodilator, e.g., 50 ppm or less to 1000, 5000, 10000, 50000, 100000, 500000 ppm or more of the vasodilator. The topical formulation can contain from 0.01 wt. % or less (e.g., 0.001 wt. %) to 10 wt. % or more, e.g., 0.01 wt. % to 0.02 wt. %, 0.03 wt. %, 0.04 wt. %, 0.05 wt. %, 0.1 wt. %, 1 wt. % to 5 wt. % or 10 wt. % or 20 wt. % of the vasodilator. The amount of vasodilator in the base can be adjusted up or down.

[0123] Liquids and gels containing the vasodilator, optionally with other components as described herein, can be prepared using techniques as are known in the art for preparing topical formulation. See, e.g., Handbook of Cosmetic Science and Technology, Fourth Edition, edited by André O. Barel, Marc Paye, Howard I. Maibach, CRC Press, 2014, the contents of which is hereby incorporated by reference in its entirety. Various formulations are possible.

[0124] For liquid formulations (e.g., gel or lotion forms), a silicone, e.g., a cyclosiloxane or linear silicone (e.g., silicone elastomer), can be employed as a carrier. One type of suitable carrier is a dimethicone crosspolymer gel, e.g., dimethicone crosspolymer in cyclopentasiloxane. Other suitable dimethicone crosspolymers include cyclopentasiloxane, dimethicone/vinyldimethicone crosspolymer; dimethicone, dimethicone/vinyl dimethicone crosspolymer; and isodecane dimethicone/vinyl dimethicone crosspolymer.

[0125] In some embodiments, the carrier is present in an amount of from about 80 wt. % to about 95 wt. %, or 82 wt. % to 92 wt. %, e.g., in a topical formulation for application to skin.

[0126] Penetration enhancers can be employed to enhance penetration of the vasodilator into tissue. Typical amounts when employed in topical formulations are from 1% by weight to 4% by weight. Typical amounts for anti-irritation agents when employed in topical formulations are from 1% by weight to 4% by weight. Typical amounts for anti-inflammatory agents when employed in topical formulations are from 1% by weight to 4% by weight. Typical amounts for anti-inflammatory agents when employed in topical formulations are from 0.1% by weight to 2% by weight.

[0127] In some embodiments, the vasodilator can be in admixture with a suitable carrier, diluent, or excipient, and can contain auxiliary substances such as wetting or emulsifying agents, pH buffering agents, gelling or viscosity enhancing additives, preservatives, scenting agents, colors, and the like, depending upon the route of administration and the preparation desired. See, e.g., "Remington: The Science and Practice of Pharmacy", Lippincott Williams & Wilkins; 20th edition (Jun. 1, 2003) and "Remington's Pharmaceutical Sciences," Mack Pub. Co.; 18th and 19th editions (December 1985, and June 1990, respectively). Such preparations can include complexing agents, metal ions, polymeric compounds such as polyacetic acid, polyglycolic acid, hydrogels, dextran, and the like, liposomes, microemulsions, micelles, unilamellar or multilamellar vesicles, erythrocyte ghosts or spheroblasts. Suitable lipids for liposomal formulations include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. The presence of such additional components can influence the physical state, solubility, stability, rate of release, rate of clearance, and penetration of active ingredients.

[0128] The compositions for topical administration to the tissue of the eye comprise the vasodilator as described herein and a vehicle acceptable for contact with ocular tissue (e.g., vitreous tissue). The vehicle may be aqueous or nonaqueous. The vehicle used in the topical formulation may be in the form of a gel, an ointment, a liquid, a cream, or an emulsion. If the vehicle is an emulsion, the emulsion may have a continuous aqueous phase and a discontinuous nonaqueous or oil phase (oil-in-water emulsion), or a continuous nonaqueous or oil phase and a discontinuous aqueous phase (water-in-oil emulsion). When administered topically in liquid or gel form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils can be added to the active ingredient(s). Physiological saline solution, dextrose, or other saccharide solution, or glycols such as ethylene glycol, propylene glycol, or polyethylene glycol are also suitable liquid carriers. The pharmaceutical compositions can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil, such as olive or arachis oil, a mineral oil such as liquid paraffin, or a mixture thereof. Suitable emulsifying agents include naturally-occurring gums such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan mono-oleate. The emulsions can also contain coloring and scenting agents.

[0129] In certain embodiments, a silicone elastomer (e.g., dimethicone crosspolymer) is employed to increase delivery and penetration of the vasodilator into the ocular tissue (e.g., vitreous tissue).

[0130] The pharmaceutical excipients used in the topical preparations of the vasodilator compositions may be selected from the group consisting of solvents, emollients and/or emulsifiers, oil bases, preservatives, antioxidants, tonicity adjusters, penetration enhancers and solubilizers, chelating agents, buffering agents, surfactants, one or more polymers, and combinations thereof.

[0131] Suitable solvents for an aqueous or hydrophilic topical formulation include water; ethyl alcohol; isopropyl alcohol; mixtures of water and ethyl and/or isopropyl alcohols; glycerin; ethylene, propylene or butylene glycols; DMSO; and mixtures thereof. Suitable solvents for hydrophobic topical formulations include mineral oils, vegetable oils, and silicone oils. If desired, the vasodilator compositions as described herein may be dissolved or dispersed in a hydrophobic oil phase, and the oil phase may then be emulsified in an aqueous phase comprising water, alone or in combination with lower alcohols, glycerin, and/or glycols. In certain embodiments water is present, but at amounts below the threshold at which a stinging sensation when applied to damaged skin may result. Osmotic shock or osmotic stress is a sudden change in the solute concentration around a cell, causing a rapid change in the movement of

water across its cell membrane. Under conditions of high concentrations of either salts, substrates or any solute in the supernatant, water is drawn out of the cells through osmosis. This also inhibits the transport of substrates and cofactors into the cell thus "shocking" the cell. Alternatively, at low concentrations of solutes, water enters the cell in large amounts, causing it to swell and either burst or undergo apoptosis. Certain of the formulations as described herein can be advantageously employed where it is desirable to minimize osmotic shock.

[0132] Viscosity of the compositions can be maintained at the selected level using a pharmaceutically acceptable thickening agent. Suitable viscosity enhancers or thickeners which may be used to prepare a viscous gel or cream with an aqueous base include sodium polyacrylate, xanthan gum, polyvinyl pyrrolidone, acrylic acid polymer, carragenans, hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, propyl cellulose, hydroxypropyl methyl cellulose, polyethoxylated polyacrylamides, polyethoxylated acrylates, and polyethoxylated alkane thiols. Methylcellulose is preferred because it is readily and economically available and is easy to work with. Other suitable thickening agents include, for example, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, and the like. The preferred concentration of the thickener will depend upon the thickening agent selected. An amount is preferably used that will achieve the selected viscosity. Viscous compositions are normally prepared from solutions by the addition of such thickening agents, or by employing a base that has an acceptable level of viscosity.

[0133] Suitable emollients include hydrocarbon oils and waxes such as mineral oil, petrolatum, paraffin, ceresin, ozokerite, microcrystalline wax, polyethylene, squalene, perhydrosqualene, silicone oils, triglyceride esters, acetoglyceride esters, such as acetylated monoglycerides; ethoxylated glycerides, such as ethoxylated glyceryl monostearate; alkyl esters of fatty acids or dicarboxylic acids.

[0134] Suitable silicone oils for use as emollients include dimethyl polysiloxanes, methyl(phenyl) polysiloxanes, and water-soluble and alcohol-soluble silicone glycol copolymers. Suitable triglyceride esters for use as emollients include vegetable and animal fats and oils including castor oil, safflower oil, cotton seed oil, corn oil, olive oil, cod liver oil, almond oil, avocado oil, palm oil, sesame oil, and soybean oil.

[0135] Suitable esters of carboxylic acids or diacids for use as emollients include methyl, isopropyl, and butyl esters of fatty acids. Specific examples of alkyl esters including hexyl laurate, isohexyl laurate, iso-hexyl palmitate, isopropyl palmitate, decyl oleate, isodecyl oleate, hexadecyl stearate, decyl stearate, isopropyl isostearate, dilauryl lactate, myristyl lactate, and cetyl lactate; and alkenyl esters of fatty acids such as oleyl myristate, oleyl stearate, and oleyl oleate. Specific examples of alkyl esters of diacids include diisopropyl adipate, diisohexyl adipate, bis(hexyldecyl) adipate, and diisopropyl sebacate.

[0136] Other suitable classes of emollients or emulsifiers which may be used in the topical formulations include fatty acids, fatty alcohols, fatty alcohol ethers, ethoxylated fatty alcohols, fatty acid esters of ethoxylated fatty alcohols, and waxes.

[0137] Specific examples of fatty acids for use as emollients include pelargonic, lauric, myristic, palmitic, stearic, isostearic, hydroxystearic, oleic, linoleic, ricinoleic, arachidic, behenic, and erucic acids. Specific examples of fatty alcohols for use as emollients include lauryl, myristyl, cetyl, hexadecyl, stearyl, isostearyl, hydroxystearyl, oleyl, ricinoleyl, behenyl, and erucyl alcohols, as well as 2-octyl dodecanol.

[0138] Specific examples of waxes suitable for use as emollients include lanolin and derivatives thereof including lanolin oil, lanolin wax, lanolin alcohols, lanolin fatty acids, isopropyl lanolate, ethoxylated lanolin, ethoxylated lanolin alcohols, ethoxolated cholesterol, propoxylated lanolin alcohols, acetylated lanolin, acetylated lanolin alcohols, lanolin alcohols linoleate, lanolin alcohols recinoleate, acetate of lanolin alcohols recinoleate, acetate of lanolin alcohols recinoleate, acetate of ethoxylated alcohols esters, hydrogenolysates of lanolin, hydrogenated lanolin, ethoxylated hydrogenated lanolin, ethoxylated sorbitol lanolin, and liquid and semisolid lanolin. Also usable as waxes include hydrocarbon waxes, ester waxes, and amide waxes. Useful waxes include wax esters such as beeswax, spermaceti, myristyl myristate and stearyl stearate; beeswax derivatives, e.g., polyoxyethylene sorbitol beeswax; and vegetable waxes including carnauba and candelilla waxes.

[0139] Polyhydric alcohols and polyether derivatives may be used as solvents and/or surfactants in the topical formulations. Suitable polyhydric alcohols and polyethers include propylene glycol, dipropylene glycol, polypropylene glycols 2000 and 4000, poly(oxyethylene-co-oxypropylene)glycols, glycerol, sorbitol, ethoxylated sorbitol, hydroxypropylsorbitol, polyethylene glycols 200-6000, methoxy polyethylene glycols 350, 550, 750, 2000 and 5000, poly [ethylene oxide] homopolymers (100,000-5,000,000), polyalkylene glycols and derivatives, hexylene glycol, 2-methyl-2,4-pentanediol, 1,3-butylene glycol, 1,2,6-hexanetriol, 2-ethyl-1,3-hexanediol, vicinal glycols having 15 to 18 carbon atoms, and polyoxypropylene derivatives of trimethylolpropane.

[0140] Polyhydric alcohol esters may be used as emulsifiers or emollients. Suitable polyhydric alcohol esters include ethylene glycol mono- and di-fatty acid esters, diethylene glycol mono- and di-fatty acid esters, polyethylene glycol (200-6000) mono- and di-fatty acid esters, propylene glycol mono- and di-fatty esters, polypropylene glycol 2000 monooleate, polypropylene glycol 2000 monostearate, ethoxylated propylene glycol monostearate, glyceryl mono- and di-fatty acid esters, polyglycerol poly-fatty acid esters, ethoxylated glyceryl monostearate, 1,3-butylene glycol monostearate, 1,3-butylene glycol distearate, polyoxyethylene polyol fatty acid ester, sorbitan fatty acid esters, and polyoxyethylene sorbitan fatty acid esters.

[0141] Suitable emulsifiers for use in topical formulations include anionic, cationic, nonionic, and zwitterionic surfactants. Preferred ionic emulsifiers include phospholipids, such as lecithin and derivatives.

[0142] Lecithin and other phospholipids may be used to prepare liposomes containing the vasodilators as described herein. Formation of lipid vesicles occurs when phospholipids such as lecithin are placed in water and consequently form one bilayer or a series of bilayers, each separated by water molecules, once enough energy is supplied. Liposomes can be created by sonicating phospholipids in water. Low shear rates create multilamellar liposomes. Continued high-shear sonication tends to form smaller unilamellar liposomes. Hydrophobic chemicals can be dissolved into the phospholipid bilayer membrane. The lipid bilayers of the liposomes deliver the vasodilators as described herein.

[0143] The topical formulation may contain micelles, or an aggregate of surfactant molecules dispersed in an aqueous solution. Micelles may be prepared by dispersing an oil solvent in an aqueous solution comprising a surfactant, where the surfactant concentration exceeds the critical micelle concentration. The resulting formulation contains micelles, i.e., spherical oil droplets surrounded by a membrane of polar surfactant molecules, dispersed in the aqueous solvent.

[0144] Sterols including, for example, cholesterol and cholesterol fatty acid esters; amides such as fatty acid amides, ethoxylated fatty acid amides, and fatty acid alkanolamides may also be used as emollients and/or penetration enhancers.

[0145] A pharmaceutically acceptable preservative can be employed to increase the shelf life of the composition. Other suitable preservatives and/or antioxidants for use in topical formulations include benzalkonium chloride, benzyl alcohol, phenol, urea, parabens, butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), tocopherol, thimerosal, chlorobutanol, or the like, and mixtures thereof, can be employed. If a preservative, such as an antioxidant, is employed, the concentration is typically from about 0.02% to about 2% based on the total weight of the composition, although larger or smaller amounts can be desirable depending upon the agent selected. Reducing agents, as described herein, can be advantageously used to maintain good shelf life of the formulation. It is generally observed that the anhydrous formulations of the embodiments exhibit satisfactory stability, such that a preservative can be omitted from the formulation.

[0146] Suitable chelating agents for use in topical formulations include ethylene diamine tetraacetic acid, alkali metal salts thereof alkaline earth metal salts thereof, ammonium salts thereof, and tetraalkyl ammonium salts thereof.

[0147] The carrier preferably has a pH of between about 4.0 and 10.0, more preferably between about 6.8 and about 7.8. The pH may be controlled using buffer solutions or other pH modifying agents. Suitable pH modifying agents include phosphoric acid and/or phosphate salts, citric acid and/or citrate salts, hydroxide salts (i.e., calcium hydroxide, sodium hydroxide, potassium hydroxide) and amines, such as triethanolamine. Suitable buffer solutions include a buffer comprising a solution of monopotassium phosphate and dipotassium phosphate, maintaining a pH of between 5.8 and 8; and a buffer comprising a solution of monosodium phosphate and disodium phosphate, maintaining a pH of between 6 and 7.5. Other buffers include citric acid/sodium citrate, and dibasic sodium phosphate/citric acid. The vasodilator compositions of the embodiments are preferably isotonic with the blood or other body fluid of the recipient. The isotonicity of the compositions can be attained using sodium tartrate, propylene glycol or other inorganic or organic solutes. Sodium chloride is particularly preferred. Buffering agents can be employed, such as acetic acid and salts, citric acid and salts, boric acid and salts, and phosphoric acid and salts. It can be desirable to include a reducing agent in the formulation, such as vitamin C, vitamin E, or other reducing agents as are known in the pharmaceutical arts.

[0148] Surfactants can also be employed as excipients, for example, anionic detergents such as sodium lauryl sulfate, dioctyl sodium sulfosuccinate and dioctyl sodium sulfonate, cationic such as benzalkonium chloride or benzethonium chloride, or nonionic detergents such as polyoxyethylene hydrogenated castor oil, glycerol monostearate, polysorbates, sucrose fatty acid ester, methyl cellulose, or carboxymethyl cellulose.

[0149] When the vasodilator formulations of the embodiments are administered by intraocular injection, it is preferably in the form of a pyrogen-free, parenterally acceptable aqueous solution or oleaginous suspension, emulsion or solution. Suspensions can be formulated according to methods well known in the art using suitable dispersing or wetting agents and suspending agents. The preparation of acceptable aqueous or nonaqueous solutions with suitable properties, e.g., pH, isotonicity, stability, and the like, is within the skill in the art. For example, an isotonic vehicle such as 1,3-butanediol, water, isotonic sodium chloride solution, Ringer's solution, dextrose solution, dextrose and sodium chloride solution, lactated Ringer's solution, or other vehicles as are known in the art can be employed, or a fixed oil can be employed conventionally as a solvent or suspending medium, e.g., synthetic mono or diglycerides, fatty acids, or the like. The vasodilator formulations can also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

[0150] In certain embodiments, it can be advantageous to include additional agents having pharmacological activity. Anti-infective agents include, but are not limited to, anthelmintic (mebendazole), antibiotics including aminoglycosides (gentamicin, neomycin, tobramycin), antifungal antibiotics (amphotericin b, fluconazole, griseofulvin, itraconazole, ketoconazole, nystatin, micatin, tolnaftate), cephalosporins (cefaclor, cefazolin, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, cephalexin), beta-lactam antibiotics (cefotetan, meropenem), chloramphenicol, macrolides (azithromycin, clarithromycin, erythromycin), penicillins (penicillin G sodium salt, amoxicillin, ampicillin, dicloxacillin, nafcillin, piperacillin, ticarcillin), tetracyclines (doxycycline, minocycline, tetracycline), bacitracin, clindamycin, colistimethate sodium, polymyxin b sulfate, vancomycin, antivirals including acyclovir, amantadine, didanosine, efavirenz, foscarnet, ganciclovir, indinavir, lamivudine, nelfinavir, ritonavir, saquinavir, stavudine, valacyclovir, valganciclovir, zidovudine, quinolones (ciprofloxacin, levofloxacin), sulfonamides (sulfadiazine, sulfisoxazole), sulfones (dapsone), furazolidone, metronidazole, pentamidine, sulfanilamidum crystallinum, gatifloxacin, and sulfamethoxazole/trimethoprim. Anesthetics can include, but are not limited to, ethanol, bupivacaine, chloroprocaine, levobupivacaine, lidocaine, mepivacaine, procaine, ropivacaine, tetracaine, desflurane, isoflurane, ketamine, propofol, sevoflurane, codeine, fentanyl, hydromorphone, marcaine, meperidine, methadone, morphine, oxycodone, remifentanil, sufentanil, butorphanol, nalbuphine, tramadol, benzocaine, dibucaine, ethyl chloride, xylocaine, and phenazopyridine. Anti-inflammatory agents include but are not limited to, nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, celecoxib, choline magnesium trisalicylate, diclofenac potassium, diclofenac sodium, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, melenamic acid, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, rofecoxib, salsalate, sulindac, and tolmetin; and corticosteroids such as cortisone, hydrocortisone, methylprednisolone, prednisone, prednisolone, betamethesone, beclomethasone dipropionate, budesonide, dexamethasone

sodium phosphate, flunisolide, fluticasone propionate, triamcinolone acetonide, betamethasone, fluocinonide, betamethasone dipropionate, betamethasone valerate, desonide, desoximetasone, fluocinolone, triamcinolone, clobetasol propionate, and dexamethasone.

Kits for Administration of Compositions

[0151] Some embodiments of the methods and compositions provided herein include kits comprising vasodilators provided herein. In some embodiments, kits can be provided to an administering physician, other health care professional, a patient, or a caregiver. In some embodiments, a kit comprises a container which contains the vasodilator(s) in a suitable topical formulation, and instructions for administering the composition to a subject. The kit can optionally also contain one or more additional therapeutic or other agents. For example, a kit containing a vasodilator blocker in topical form can be provided along with other agents such as topical antibiotics or topical anesthetics. The kit may contain the vasodilator in bulk form, or can contain separate doses of the vasodilator for serial or sequential administration. The kit can optionally contain one or more diagnostic tools, administration tools, and/or instructions for use, e.g., syringes for intravitreal injection. The kit can contain suitable delivery devices, such as, syringes, pump dispensers, wands, single dose packets, and the like, along with instructions for administering the vasodilator compositions and any other therapeutic or beneficial agents. The kit can optionally contain instructions for storage, reconstitution (if applicable), and administration of any or all therapeutic or beneficial agents included. The kits can include a plurality of containers reflecting the number of administrations to be given to a subject, or the different products to be administered to the subject.

[0152] The topical formulation for administration to tissue of the eye, in addition to the vasodilator, can contain other ingredients.

[0153] While topical administration of the vasodilator disclosed herein can advantageously be employed, in certain embodiments other routes of administration are also contemplated, such as intravitreal or intraocular injection.

[0154] The vasodilator compositions described herein can be administered by themselves to a subject, or in compositions where they are mixed with other active agents, as in combination therapy, or with carriers, diluents, excipients or combinations thereof. Formulation is dependent upon the route of administration chosen. Techniques for formulation and administration of the compounds described herein are known to those skilled in the art (see, e.g., "Remington: The Science and Practice of Pharmacy", Lippincott Williams & Wilkins; 20th edition (Jun. 1, 2003) and "Remington's Pharmaceutical Sciences," Mack Pub. Co.; 18th and 19th editions (December 1985, and June 1990, respectively).

[0155] The vasodilator compositions disclosed herein may be manufactured into administrable forms by a process that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, tableting, or extracting processes.

[0156] Multiple techniques of administering a compound exist in the art including, but not limited to, oral, rectal, topical, aerosol, injection and parenteral delivery, including intramuscular, subcutaneous, intravenous, intramedullary injections, intrathecal, direct intraventricular, intraperitoneal, intranasal, intravitreal, and intraocular injections. Contemplated herein is any combination of the forgoing, or other methods as would be known to one of ordinary skill in the art (see, e.g., "Remington: The Science and Practice of Pharmacy", Lippincott Williams & Wilkins; 20th edition (Jun. 1, 2003) and "Remington's Pharmaceutical Sciences," Mack Pub. Co.; 18th and 19th editions (December 1985, and June 1990, respectively).

[0157] In practice, the vasodilator may be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The excipients are preferably minimized so as to ensure administration of an appropriate amount of vasodilator in a compact format. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. Thus, the vasodilator compositions provided herein can be presented as discrete units suitable for administration each containing a predetermined amount of the active ingredient. Further, the vasodilator compositions can be presented as an oil, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in-oil liquid emulsion, similar to the topical formulations described elsewhere herein, but using components suitable for human contact or consumption. In addition to the common dosage forms set out above, the vasodilator compositions provided herein can also be administered by controlled release and/or delivery devices. The vasodilator compositions can be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the vasodilator compositions are prepared by uniformly and intimately admixing the vasodilator ingredient(s) with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

[0158] A vasodilator formulation may also be administered in a local manner, for example, via injection of the vasodilator composition directly into a target area, e.g., in a depot or sustained release formulation intravitrealy or intraocularly. Furthermore, a targeted drug delivery system for the vasodilator may be used, for example, in a liposome coated with a tissue specific antibody.

[0159] The vasodilator compositions may contain the vasodilator in an amount effective for the desired therapeutic effect. In some embodiments, the vasodilator compositions are in a unit dosage form and comprise from about 0.1 mg or less to about 5000 mg or more of vasodilator per unit dosage form. In further embodiments, the vasodilator compositions comprise from about 1 to about 500 mg per unit dosage form or from about 500 to 5000 mg per unit dosage form of vasodilator. Such amounts can be selected depending upon the vasodilator employed. Such dosage forms may be solid, semisolid, liquid, an emulsion, or adapted for delivery via aerosol or the like.

[0160] The carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, lower alcohols, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

[0161] Vasodilator compositions provided herein can be prepared as solutions or suspensions of the vasodilator in

water or nonaqueous liquids. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to, for example, prevent the detrimental growth of microorganisms.

[0162] Vasodilator compositions provided herein suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the vasodilator compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. The vasodilator compositions may be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

[0163] In addition to the aforementioned carrier ingredients, the vasodilator formulations described above can include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood or other bodily fluids of the intended recipient. Vasodilator compositions can also be prepared in powder or liquid concentrate form for dilution.

[0164] Contemplated herein are vasodilator compositions including one or more vasodilators as described herein in combination with at least one additional active agent, e.g., an antibiotic. The vasodilator and the at least one additional active agent(s) may be present in a single formulation or in multiple formulations provided together, or may be unformulated. In some embodiments, the vasodilator can be administered with one or more additional agents together in a single composition. For example, the vasodilator can be administered in one composition, and at least one of the additional agents can be administered in a second composition. In a further embodiment, the vasodilator and the at least one additional active agent(s) are co-packaged in a kit. For example, a drug manufacturer, a drug reseller, a physician, a compounding shop, or a pharmacist can provide a kit comprising the vasodilator in combination with another product or component for delivery to a patient. Such additional components can include anti-infective agents, anti-inflammatory agents, anesthetics, or the like.

[0165] Some embodiments described herein relate to compositions of vasodilator, which can include a therapeutically effective amount of the vasodilator described herein and a pharmaceutically acceptable carrier, diluent, excipient or combination thereof. The vasodilator composition can include the vasodilator in an amount for example, >1%, ≥2%, ≥3%, ≥4%, ≥ 5%, ≥6%, ≥ 7%, ≥ 8%, ≥9%, ≥ 10%, ≥20%, ≥ 30%, ≥40%, ≥50%, ≥ 60%, ≥70%, ≥80%, ≥90%, ≥95%, or ≥98% of the composition.

EXAMPLES

Example 1

[0166] A patient is diagnosed with diabetic retinopathy. A composition comprising the calcium channel blocker nifedipine is directly applied to the vitreous surface of one eye while the other eye is left untreated. The treated eye is observed to have reduced symptoms of diabetic retinopathy when compared to the untreated eye.

Example 2

[0167] A patient is diagnosed with diabetic retinopathy. A composition comprising the ACE inhibitor enalapril is directly applied to the vitreous surface of one eye while the other eye is left untreated. The treated eye is observed to have reduced symptoms of diabetic retinopathy when compared to the untreated eye.

Example 3

[0168] A patient is diagnosed with diabetic retinopathy. A composition comprising the angiotensin receptor blocker losartan is directly applied to the vitreous surface of one eye while the other eye is left untreated. The treated eye is observed to have reduced symptoms of diabetic retinopathy when compared to the untreated eye.

Example 4

[0169] A patient is successfully treated for diabetic retinopathy in both eyes. A composition comprising the calcium channel blocker nifedipine is directly applied to the vitreous surface of one eye while the other eye is left untreated. The treated eye is observed to not develop diabetic retinopathy, while the untreated eye exhibits signs of recurrence of diabetic retinopathy.

Example 5

[0170] A patient is successfully treated for diabetic retinopathy in both eyes. A composition comprising the ACE inhibitor enalapril is directly applied to the vitreous surface of one eye while the other eye is left untreated. The treated eye is observed to not develop diabetic retinopathy, while the untreated eye exhibits signs of recurrence of diabetic retinopathy.

Example 6

[0171] A patient is successfully treated for diabetic retinopathy. A composition comprising the angiotensin receptor blocker losartan is directly applied to the vitreous surface of one eye while the other eye is left untreated. The treated eye is observed to not develop diabetic retinopathy, while the untreated eye exhibits signs of recurrence of diabetic retinopathy.

Example 7

[0172] A patient is diagnosed with diabetic retinopathy. A composition comprising the calcium channel blocker nifedipine is applied to the eye by intravitreal or intraocular injection while the other eye is left untreated. The treated eye is observed to have reduced symptoms of diabetic retinopathy than the untreated eye.

Example 8

[0173] A patient is diagnosed with diabetic retinopathy. A composition comprising the ACE inhibitor enalapril is applied to the eye by intravitreal or intraocular injection

while the other eye is left untreated. The treated eye is observed to have reduced symptoms of diabetic retinopathy than the untreated eye.

Example 9

[0174] A patient is diagnosed with diabetic retinopathy. A composition comprising the angiotensin receptor blocker losartan is applied to the eye by intravitreal or intraocular injection while the other eye is left untreated. The treated eye is observed to have reduced symptoms of diabetic retinopathy than the untreated eye.

Example 10

[0175] A patient is successfully treated for diabetic retinopathy in both eyes. A composition comprising the calcium channel blocker nifedipine is applied to the eye by intravitreal or intraocular injection while the other eye is left untreated. The treated eye is observed to not develop diabetic retinopathy, while the untreated eye exhibits signs of recurrence of diabetic retinopathy.

Example 11

[0176] A patient is successfully treated for diabetic retinopathy in both eyes. A composition comprising the ACE inhibitor enalapril is applied to the eye by intravitreal or intraocular injection while the other eye is left untreated. The treated eye is observed to not develop diabetic retinopathy, while the untreated eye exhibits signs of recurrence of diabetic retinopathy.

Example 12

[0177] A patient is successfully treated for diabetic retinopathy. A composition comprising the angiotensin receptor blocker losartan is applied to the eye by intravitreal or intraocular injection while the other eye is left untreated. The treated eye is observed to not develop diabetic retinopathy, while the untreated eye exhibits signs of recurrence of diabetic retinopathy.

Example 13

[0178] In this example, a patient with diabetic retinopathy is administered a topical formulation comprising ramiprilat to the eye. The administration of the topical formulation grows capillary networks and increases the capillary blood supply to the eye of the patient. As a result of the administration of the topical formulation, the patient is observed to have a reduction in intraocular pressure and repair to the optic nerve. The diabetic retinopathy is therefore treated by the topical formulation.

General Statement of Utility

[0179] Within the confines of experimental use and with patient consent, vasodilators as described in the current application have been applied to patient's eyes for the treatment, inter alia, of diabetic retinopathy. The patients were monitored during follow-up appointments and the progression of diabetic retinopathy was monitored and improvements to the patients' conditions was observed. Improvements to the patients' conditions included a reduction in symptoms of diabetic retinopathy.

Specific Statement of Utility

[0180] In particular, the group of compounds consisting of nifedipine, isradipine, felodipine, amlodipine, nicardipine, and clevidipine are of particular interest for the treatment of diabetic retinopathy. Based on prior experience and observation during the treatment of patients with these compounds, compounds of this group are effective for the treatment of diabetic retinopathy or its symptoms when applied to the eye.

[0181] Without being bound to a single theory of operation, the application of compounds described herein is believed to increase blood flow to the eye. The additional blood flow provides many benefits to the anatomy of the eye, and is expected to restore or help maintain the function of the eye. The function of the eye can be evaluated in a variety of ways. In one aspect, Diabetic retinopathy may be treated by increasing the amount of flow of vitreous fluid between the anterior and posterior chambers of the eye. In another aspect, a method of treating diabetic retinopathy may include a method to increase the capillary network and blood supply to the optic nerve and the retina. Damage to the retina may occur due to neovascularization, and a method of treating diabetic retinopathy may include a method to increase blood flow through capillaries to disrupt the negative cycle of new, but ineffective, capillary formation. A method of treating diabetic retinopathy may include a method to increase blood flow through capillaries to reduce the deposition of, inter alia, lipids or other compounds that can contribute to exudates observed within the anatomy of the eye. A method of treating diabetic retinopathy may include a method to increase blood flow through capillaries to increase the capillary network and blood supply to the retina such that symptoms of diabetic retinopathy do not progress.

[0182] Without being bound to a single theory of operation, the application of compounds described herein is believed to increase blood flow to the eye and reduce the abnormal capillary permeability that leads to macular edema. The application of compounds described herein may also increase blood flow to the eye and reduce ischemia and vascular occlusion that leads to retinal hypoxia. The application of compounds described herein may also increase blood flow to the eye and reduce neo-vascularisation. In neovascularisation, the increase in the initial phase of capillary death is followed by abortive attempts to re-vascularize the diseased retina, which are not fully effective because the new capillaries can become occluded frequently. However, this cycle is disrupted by increased blood flood that may increase one or more of oxygen, clearance of occlusions, and sustained capillary lifespan.

[0183] Without being bound to a single theory of operation, the link between poor vascular health and the pathology of diabetic retinopathy suggests that increasing blood flow and effective capillary formation will reduce the underlying genesis of diabetic retinopathy. This link may stem from the fact that the retina is one of the most metabolically active tissues of the body and is particularly sensitive to ischemia. Without being bound to a single theory of operation, the link between poor vascular health and the pathology of diabetic retinopathy suggests that increasing blood flow and effective capillary formation will reduce the symptoms of diabetic retinopathy. This link may stem from the fact that retinal capillary loss and thickening of the retinal basement membrane are some of the early findings in Diabetes.

Exemplary Pharmaceutical Compositions and Methods

[0184] Pharmaceutical Composition 1: A pharmaceutical composition for the treatment or prophylaxis of diabetic retinopathy, comprising: at least one vasodilator; and at least one pharmaceutical excipient.

[0185] Pharmaceutical Composition 2: Pharmaceutical Composition 1, for the treatment of diabetic retinopathy.

[0186] Pharmaceutical Composition 3: Pharmaceutical Composition 1, for the prophylaxis of diabetic retinopathy.

[0187] Pharmaceutical Composition 4: Any One of Pharmaceutical Compositions 1 through 3, in a form adapted for direct administration to the vitreous tissue of the eye or for intravitreal or intraocular injection to the eye.

[0188] Pharmaceutical Composition 5: Pharmaceutical Composition 4, wherein the form is selected from the group consisting of an oil, a liquid and a suspension for direct application on the vitreous surface of the eye.

[0189] Pharmaceutical Composition 6: Any One of Pharmaceutical Compositions 1 through 3, formulated as a liquid or a suspension of the at least one vasodilator, wherein the vasodilator is a contact vasodilator.

[0190] Pharmaceutical Composition 7: Any One of Pharmaceutical Compositions 1 through 6, wherein the vasodilator is a calcium channel blocker.

[0191] Pharmaceutical Composition 8: Pharmaceutical Composition 7, wherein the at least one calcium channel blocker is a dihydropyridine selected from the group consisting of nifedipine, isradipine, felodipine, amlodipine, nicardipine, and clevidipine.

[0192] Pharmaceutical Composition 9: Pharmaceutical Composition 7, wherein the at least one calcium channel blocker is a non dihydropyridine selected from the group consisting of verapamil and diltiazem.

[0193] Pharmaceutical Composition 10: Any One of Pharmaceutical Compositions 1 through 6, wherein the vasodilator is an ACE inhibitor.

[0194] Pharmaceutical Composition 11: Pharmaceutical Composition 10, wherein the ACE inhibitor is selected from the group consisting of benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril.

[0195] Pharmaceutical Composition 12: Any One of Pharmaceutical Compositions 1 through 6, wherein the vasodilator is an angiotensin receptor blocker.

[0196] Pharmaceutical Composition 13: Pharmaceutical Composition 12, wherein the angiotensin receptor blocker is selected from the group consisting of azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan.

[0197] Pharmaceutical Composition 14: Any One of Pharmaceutical Compositions 1 through 6, wherein the vasodilator is a nitrate.

[0198] Pharmaceutical Composition 15: Pharmaceutical Composition 14, wherein the nitrate is selected from the group consisting of nitroglycerin, isosorbide mononitrate and isosorbide dinitrate.

[0199] Pharmaceutical Composition 16: Any One of Pharmaceutical Compositions 1 through 6, wherein the vasodilator is an alpha blocker.

[0200] Pharmaceutical Composition 17: Pharmaceutical Composition 16, wherein the alpha blocker is selected from the group consisting of doxazosin, prazosin, and terazosin.

[0201] Pharmaceutical Composition 18: Any One of Pharmaceutical Compositions 1 through 6, wherein the vasodilator is a beta blocker.

[0202] Pharmaceutical Composition 19: Pharmaceutical Composition 18, wherein the beta blocker is selected from the group consisting of acebutolol, atenolol, bisoprolol fumarate, carvedilol, esmilol, labetalol, metoprolol tartrate, metoprolol succinate, nadolol, nebivolol, penbutolol sulfate, propranolol, sotalol, hydrochlorothiazide, and bisoprolol.

[0203] Pharmaceutical Composition 20: Any One of Pharmaceutical Compositions 1 through 6, wherein the vasodilator is hydralazine.

[0204] Pharmaceutical Composition 21: Any One of Pharmaceutical Compositions 1 through 6, wherein the vasodilator is an angiotensin receptor-neprilysin inhibitor.

[0205] Pharmaceutical Composition 22: Pharmaceutical Composition 21, wherein the angiotensin receptor-neprilysin inhibitor is sacubitril/valsartan.

[0206] Pharmaceutical Composition 23: Any One of Pharmaceutical Compositions 1 through 22, wherein the concentration of the vasodilator is about 0.0001 mg per ml to 1000 mg per ml, optionally 1 mg per ml to 10 mg per ml, optionally 1 mg per ml to 1000 mg per ml, optionally 5 mg per ml to 10 mg per ml, optionally 10 mg per ml, optionally 20 mg per ml, optionally 30 mg per ml, optionally 60 mg per ml, optionally 90 mg per ml, optionally 120 mg per ml, optionally 180 mg per ml, optionally 240 mg per ml.

[0207] Pharmaceutical Composition 24: Any One of Pharmaceutical Compositions 1 through 2, wherein the concentration of the vasodilator is from about 0.0001% by weight to about 20% by weight, optionally about 0.01% by weight, optionally about 0.1% by weight, optionally about 1% by weight, optionally about 10% by weight, optionally about 20% by weight.

[0208] Method 25: A method for the treatment or prophylaxis of diabetic retinopathy in a patient in need thereof, comprising: administering an effective amount of the pharmaceutical composition according to any one of Pharmaceutical Compositions 1 through 24 to a patient in need thereof.

[0209] Method 26: Method 25, for the treatment of diabetic retinopathy.

[0210] Method 27: Method 25, for the prophylaxis of diabetic retinopathy.

[0211] Method 28: Method 25, wherein the composition is administered once a day, optionally two or more times a day, optionally once a week, optionally two or more times a week, optionally once a month, optionally two or more times a month, optionally a plurality of times a year.

[0212] Method 29: Method 25, wherein the composition is administered to a patient without symptoms of diabetic retinopathy related to vision loss. Such a patient may present with one or more of normal intraocular pressure, or minor yet ophthalmoscopic-visible retinal damage.

[0213] Method 30: Method 25, wherein the composition is administered to a patient that is at risk of developing diabetic retinopathy. If the patient tolerates oral drug compositions well, then the patient may be proscribed a long acting formulation. Side effects of some compositions provided in this disclosure may be relatively mild, even in oral formulations that are not directly applied to the eye. For example, side effects of calcium channel blockers may include Con-

stipation, Dizziness, Fast heartbeat (palpitations), Fatigue, Flushing, Headache, Nausea, Rash, Swelling in the feet and lower legs.

[0214] Any of the features the above referenced pharmaceutical compositions, uses, and methods is applicable to any other pharmaceutical composition, use, or method identified herein. Moreover, any of the features of the above referenced pharmaceutical compositions, uses, and methods is independently combinable, partly or wholly, with other embodiments of the pharmaceutical compositions, uses, and methods described herein in any way, e.g., one, two, or three or more features may be combinable in whole or in part. Further, any of the features of the pharmaceutical compositions, uses, and methods described above may be made optional to other pharmaceutical compositions, uses, and methods described herein. Any aspect or embodiment of a method or use described herein can be performed using a composition, e.g., a pharmaceutical composition and/or a compound as described herein, and any aspect or embodiment of a composition, e.g., a pharmaceutical composition and/or a compound described herein, can be used or adapted to perform a method or use as described herein.

[0215] The above description presents the best mode contemplated for carrying out the present invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains to make and use this invention. This invention is, however, susceptible to modifications and alternate constructions from that discussed above that are fully equivalent. Consequently, this invention is not limited to the particular embodiments disclosed. On the contrary, this invention covers all modifications and alternate constructions coming within the spirit and scope of the invention as generally expressed by the following claims, which particularly point out and distinctly claim the subject matter of the invention. While the disclosure has been illustrated and described in detail in the drawings and foregoing description, such illustration and description are to be considered illustrative or exemplary and not restrictive.

[0216] All references cited herein are incorporated herein by reference in their entirety. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

[0217] Unless otherwise defined, all terms (including technical and scientific terms) are to be given their ordinary and customary meaning to a person of ordinary skill in the art, and are not to be limited to a special or customized meaning unless expressly so defined herein. It should be noted that the use of particular terminology when describing certain features or aspects of the disclosure should not be taken to imply that the terminology is being re-defined herein to be restricted to include any specific characteristics of the features or aspects of the disclosure with which that terminology is associated. Terms and phrases used in this application, and variations thereof, especially in the appended claims, unless otherwise expressly stated, should be construed as open ended as opposed to limiting. As examples of the foregoing, the term 'including' should be read to mean 'including, without limitation,' 'including but not limited to,' or the like; the term 'comprising' as used herein is synonymous with 'including,' 'containing,' or 'characterized by,' and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; the term 'having' should be interpreted as 'having at least;' the term 'includes' should be interpreted as 'includes but is not limited to;' the term 'example' is used to provide exemplary instances of the item in discussion, not an exhaustive or limiting list thereof; adjectives such as 'known', 'normal', 'standard', and terms of similar meaning should not be construed as limiting the item described to a given time period or to an item available as of a given time, but instead should be read to encompass known, normal, or standard technologies that may be available or known now or at any time in the future; and use of terms like 'preferably,' 'preferred,' 'desired,' or 'desirable,' and words of similar meaning should not be understood as implying that certain features are critical, essential, or even important to the structure or function of the invention, but instead as merely intended to highlight alternative or additional features that may or may not be utilized in a particular embodiment of the invention. Likewise, a group of items linked with the conjunction 'and' should not be read as requiring that each and every one of those items be present in the grouping, but rather should be read as 'and/or' unless expressly stated otherwise. Similarly, a group of items linked with the conjunction 'or' should not be read as requiring mutual exclusivity among that group, but rather should be read as 'and/or' unless expressly stated otherwise.

[0218] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

[0219] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article 'a' or 'an' does not exclude a plurality. A single processor or other unit may fulfill the functions of several items recited in the claims. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. Any reference signs in the claims should not be construed as limiting the scope.

[0220] It will be further understood by those within the art that if a specific number of an introduced claim recitation is intended, such an intent will be explicitly recited in the claim, and in the absence of such recitation no such intent is present. For example, as an aid to understanding, the following appended claims may contain usage of the introductory phrases 'at least one' and "one or more' to introduce claim recitations. However, the use of such phrases should not be construed to imply that the introduction of a claim recitation by the indefinite articles 'a' or 'an' limits any particular claim containing such introduced claim recitation to embodiments containing only one such recitation, even when the same claim includes the introductory phrases 'one or more' or 'at least one' and indefinite articles such as 'a' or 'an' (e.g., 'a' and/or 'an' should typically be interpreted to mean 'at least one' or 'one or more'); the same holds true for the use of definite articles used to introduce claim recitations. In addition, even if a specific number of an introduced claim recitation is explicitly recited, those skilled in the art will recognize that such recitation should typically be interpreted to mean at least the recited number (e.g., the bare

recitation of 'two recitations,' without other modifiers, typically means at least two recitations, or two or more recitations). Furthermore, in those instances where a convention analogous to 'at least one of A, B, and C, etc.' is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (e.g., 'a system having at least one of A, B, and C' would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). In those instances where a convention analogous to 'at least one of A, B, or C, etc.' is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (e.g., 'a system having at least one of A, B, or C' would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). It will be further understood by those within the art that virtually any disjunctive word and/or phrase presenting two or more alternative terms, whether in the description, claims, or drawings, should be understood to contemplate the possibilities of including one of the terms, either of the terms, or both terms. For example, the phrase 'A or B' will be understood to include the possibilities of 'A' or 'B' or 'A and B.'

[0221] All numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification are to be understood as being modified in all instances by the term 'about.' Accordingly, unless indicated to the contrary, the numerical parameters set forth herein are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of any claims in any application claiming priority to the present application, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

[0222] Furthermore, although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it is apparent to those skilled in the art that certain changes and modifications may be practiced. Therefore, the description and examples should not be construed as limiting the scope of the invention to the specific embodiments and examples described herein, but rather to also cover all modification and alternatives coming with the true scope and spirit of the invention.

What is claimed is:

1. A pharmaceutical composition for the treatment or prophylaxis of diabetic retinopathy, comprising:

at least one vasodilator; and

at least one pharmaceutical excipient.

2. The pharmaceutical composition of claim **1**, for the treatment of diabetic retinopathy.

3. The pharmaceutical composition of claim **1**, for the prophylaxis of diabetic retinopathy.

4. The pharmaceutical composition of any one of claims **1** through **3**, in a form for direct administration to the vitreous tissue of the eye or for intravitreal or intraocular injection to the eye.

5. The pharmaceutical composition of claim **4**, wherein the form is selected from the group consisting of an oil, a liquid and a suspension for direct application on the vitreous surface of the eye.

6. The pharmaceutical composition of any one of claims **1** through **3**, formulated as a liquid or a suspension of the at least one vasodilator, wherein the vasodilator is a contact vasodilator.

7. The pharmaceutical composition of any one of claims **1** through **6**, wherein the vasodilator is a calcium channel blocker.

8. The pharmaceutical composition of claim **7**, wherein the at least one calcium channel blocker is a dihydropyridine selected from the group consisting of nifedipine, isradipine, felodipine, amlodipine, nicardipine, and clevidipine.

9. The pharmaceutical composition of claim **7**, wherein the at least one calcium channel blocker is a non dihydropyridine selected from the group consisting of verapamil and diltiazem.

10. The pharmaceutical composition of any one of claims **1** through **6**, wherein the vasodilator is an ACE inhibitor.

11. The pharmaceutical composition of claim **10**, wherein the ACE inhibitor is selected from the group consisting of benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, ramiprilat, and trandolapril.

12. The pharmaceutical composition of claim **11**, wherein the ACE inhibitor is ramipril or ramiprilat.

13. The pharmaceutical composition of claim **12**, wherein the ACE inhibitor is ramiprilat.

14. The pharmaceutical composition of any one of claims **1** through **6**, wherein the vasodilator is an angiotensin receptor blocker.

15. The pharmaceutical composition of claim **14**, wherein the angiotensin receptor blocker is selected from the group consisting of azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan.

16. The pharmaceutical composition of any one of claims **1** through **6**, wherein the vasodilator is a nitrate.

17. The pharmaceutical composition of claim **16**, wherein the nitrate is selected from the group consisting of nitroglycerin, isosorbide mononitrate and isosorbide dinitrate.

18. The pharmaceutical composition of any one of claims **1** through **6**, wherein the vasodilator is an alpha blocker.

19. The pharmaceutical composition of claim **18**, wherein the alpha blocker is selected from the group consisting of doxazosin, prazosin, and terazosin.

20. The pharmaceutical composition of any one of claims **1** through **6**, wherein the vasodilator is a beta blocker.

21. The pharmaceutical composition of claim **20**, wherein the beta blocker is selected from the group consisting of acebutolol, atenolol, bisoprolol fumarate, carvedilol, esmilol, labetalol, metoprolol tartrate, metoprolol succinate, nadolol, nebivolol, penbutolol sulfate, propranolol, sotalol, hydrochlorothiazide, and bisoprolol.

22. The pharmaceutical composition of any one of claims **1** through **6**, wherein the vasodilator is hydralazine.

23. The pharmaceutical composition of any one of claims **1** through **6**, wherein the vasodilator is an angiotensin receptor-neprilysin inhibitor.

24. The pharmaceutical composition of claim **23**, wherein the angiotensin receptor-neprilysin inhibitor is sacubitril/valsartan.

25. The pharmaceutical composition of any of claims **1-24**, wherein the concentration of the vasodilator is about 0.0001 mg per ml to 1000 mg per ml, optionally 1 mg per ml to 10 mg per ml, optionally 1 mg per ml to 1000 mg per ml, optionally 5 mg per ml to 10 mg per ml, optionally 10

mg per ml, optionally 20 mg per ml, optionally 30 mg per ml, optionally 60 mg per ml, optionally 90 mg per ml, optionally 120 mg per ml, optionally 180 mg per ml, optionally 240 mg per ml.

26. The pharmaceutical composition of any of claims **1-24**, wherein the concentration of the vasodilator is from about 0.0001% by weight to about 20% by weight, optionally about 0.01% by weight, optionally about 0.1% by weight, optionally about 1% by weight, optionally about 10% by weight, optionally about 20% by weight.

27. A method for the treatment or prophylaxis of diabetic retinopathy in a patient in need thereof, comprising:

administering an effective amount of the pharmaceutical composition according to any one of claims **1** to **26** to a patient in need thereof.

28. The method of claim **27**, for the treatment of diabetic retinopathy.

29. The method of claim **27**, for the prophylaxis of diabetic retinopathy.

30. The method of any one of claims **27** to **29**, wherein the composition is administered once a day, optionally two or more times a day, optionally once a week, optionally two or more times a week, optionally once a month, optionally two or more times a month, optionally a plurality of times a year.

31. The method of any one of claims **27** to **30**, wherein composition is topically administered to the eye of the patient in need.

32. The method of any one of claims **27** to **31**, wherein topically administered is by ophthalmic drops.

33. The method of any one of claims **27** to **32**, wherein administering an effective amount of the pharmaceutical composition according to claim **1** provides capillary formation in the patient in need thereof.

34. The method of any one of claims **27** to **33**, wherein the administering an effective amount of the pharmaceutical composition according to claim **1** to a patient in need thereof, reduces the neovascularization of the eye.

35. A method for the reducing one or more symptoms of diabetic retinopathy in a patient in need thereof, comprising:

administering an effective amount of the pharmaceutical composition according to any one of claims **1** to **36** to a patient in need thereof.

36. The method of claim **35**, wherein the composition is administered once a day, optionally two or more times a day, optionally once a week, optionally two or more times a week, optionally once a month, optionally two or more times a month, optionally a plurality of times a year.

37. The method of claim **35** or **36**, wherein composition is topically administered to the eye of the patient in need.

38. The method of any one of claims **35** to **37**, wherein topically administered is by ophthalmic drops.

39. The method of any one of claims **35** to **38**, wherein administering an effective amount of the pharmaceutical composition provides capillary formation in the patient in need thereof.

40. The method of any one of claims **35** to **39**, wherein the administering an effective amount of the pharmaceutical composition to a patient in need thereof, reduces neovascularization of the eye.

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