FIGURE 1A


(84) Designated States (unless otherwise indicated, for every kind of national protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: DRUG DELIVERY TO THE ANTERIOR AND POSTERIOR SEGMENTS OF THE EYE

(57) Abstract: The present invention relates to a method and means, in particular, drug delivery agent(s), a kit and compositions, for delivery of drugs to the chorio-retina and the optic nerve head. The method comprises contacting the surface of the eye with an effective amount of drug for treatment of chorio-retina and optic nerve head and a physiologically acceptable amount of at least one drug delivery agent, for enhancing delivery of the drug to these tissues in an ophthalmologically acceptable carrier, said drug delivery agent being selected from the group consisting of cholinergic agents, derivatives thereof or mixtures thereof. The present invention also relates to such drug delivery agent(s) or to compositions comprising such drug delivery agent(s) for use for the transfer, to the posterior segment of one or both eyes(s), of at least one second drug that treats disorders and/or diseases of the eyes. The drug delivery agent(s) can be used in conjunction with at least another drug delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.
DRUG DELIVERY TO THE ANTERIOR AND POSTERIOR SEGMENTS OF THE EYE.

1. Field of the Invention

The present invention relates to a method to deliver drugs to the anterior and posterior segments of the eye and to compositions and to a kit for such a delivery.

More specifically the present invention relates to a method, to compositions and to a kit wherein at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof or mixtures thereof, and optionally, at least another drug delivery agent which is an adrenergic agent is (are) administered with an effective amount of a drug that can treat chorio-retinal and/or optic nerve head disorders.

The present invention also relates to such drug delivery agent(s) or to compositions comprising such drug delivery agent(s), for use for the transfer, to the posterior segment of one or both eye(s), of at least one second drug that treats disorders and/or diseases of the eyes.

2. Background of the Invention and Related Prior Art

With the population living longer many disorders or diseases of the eyes have been appearing and are currently being treated by ophthalmologists. Over the past several years many advances in ophthalmic therapy have arisen in response to a rising need for improvement in this area.

Many ophthalmic disorders arise in the anterior and posterior segments of the eye. The anterior segment of the eye is the front third of the eye that includes the structures in front of the vitreous humor such as the cornea, iris, ciliary body and lens. Ophthalmic disorders associated with the anterior segment of the eye include glaucoma, cataract, congenital and developmental abnormalities, inflammatory and infectious diseases, hereditary and degenerative diseases and ocular manifestations of systemic diseases, tumors, injury and trauma.

The posterior segment of the eye is the back two-thirds of the eye that includes the anterior hyaloid membrane and all of the structures behind it such as the vitreous humor, the retina, the choroid and the optic nerve. Ophthalmic disorders resulting in the posterior segment of the eye include age-related macular degeneration, diabetic retinopathy, retinal vein occlusions, retinal arterial
occlusions, macular edema, post-operative inflammation, uveitis, retinitis, proliferative vitreoretinopathy, glaucoma neuropathy, high myopia and macular degeneration.

Administering drugs for treatment of various disorders of the eye can be performed by a variety of methods known in the art such as by topical administration, administration of eye drops, intraocular injection and systemic administration.

However most of these methods have drawbacks. Eye drops and ointments that have been used for years are not always effective due to the eye's natural protective surface. Furthermore, by using this type of administration the drugs are rarely delivered to the posterior segments of the eye in proper quantities and hence cannot be used to treat various disorders and/or diseases of the chorio-retinal and/or optic nerve head disorders.

Systemic administration requires a very high dosage of drug and like topical administration very little of the administered compound enters the eye.

For treating disorders and/or diseases of the chorio-retina and/or optic nerve head the main type of administration utilized is injecting the various drugs directly into the eye, usually into the vitreous humor or subconjunctival injections. For example ranibizumab (Lucentis®) injection is known for treating wet age-related macular degeneration. Ranibizumab is a vascular endothelial growth factor (VEGF) antagonist that blocks abnormal blood vessel growth and leakage in the eye. It must be administered once a month by a physician.

Pegatanib (Macugen®) and bevacizumab (Avastin®) are other drugs for treating age-related macular degeneration. They must be delivered directly by injection through a needle into the eye, which requires medical assistance and is usually performed in a clinical setting.

In the cases of delivering the drugs by direct injection into the eye, usually only one eye is treated at a time to prevent complications and these techniques are invasive techniques that are often very discomforting to the patient. In some instances direct injection can lead to complications in the eyes that are even more serious than the disease or disorder itself.

Due to the membrane barriers of the cornea, conjunctiva and sclera and lachrymal drainage it is quite difficult to administer successfully drugs into the posterior segment of the eye other than by injection.
In general, drugs can enter the eye through three distinct routes; i.e., (1) the corneal route which is through the anterior chamber and then through the lens, the pupil or the iris; (2) the conjunctival route which either is directly across the sclera, choroid, choriocapillaries and retinal pigment epithelium to the retina or indirectly into the retrobulbar space and then the optic nerve head; and (3) from the systemic circulation after topical, parental, oral or intranasal or any other route that delivers the drug to the blood circulation.

The use of eye drops is generally a route of delivering drugs into the posterior segment of the eyes which is considered quite ineffective due to the lack of therapeutic amounts of the drugs that can be effective in this area of the eye. See, for example Myles et al Adv. Drug Del. Rev. 57(14):2063-79). Due to this ineffectiveness, several attempts have been made to overcome this problem in the art.

Thus, U.S. Patent publication No. 2007/0020336 A1 describes the use of cyclodextrin nanotechnology for delivery to the posterior segment of the eye. This ophthalmic composition contains a drug, cyclodextrin and water in which about 0.1% to 90% (w/v) of the drug is dissolved in the solution and a solid phase consisting of particles which have a size of 10 nm to 1 mm. This composition can be in the form of eye drops.

In yet another attempt to solve the problem with non-invasive posterior segment delivery of drugs U.S. publication No. 2005/0009910 A1 describes a method and composition which uses an effective concentration of an ester prodrug of the active drug. This composition is a sustained release composition in which a polymeric microparticle system enhances the release of the drug. The prodrug is administered via injection or implantation.

WO 2007/075720 A2 describes topical mecamylamine formulations for ocular administrations for the treatment of neovascularization, abnormal angiogenesis, vascular permeability or combinations thereof of posterior and/or anterior tissues and fluids of the eye.

Although the art has advanced quite rapidly in the last few years, there is still a need in this art to provide methods and compositions to deliver drugs to treat various ophthalmic disorders and/or diseases to the posterior segments of the eyes which drug is delivered through a non-invasive route.
Thus it is an object of the present invention to overcome the problems associated with drug delivery to the posterior segment of the eye known in the art.

It is another object of the present invention to provide a method for delivering drugs to treat ophthalmic disorders or diseases that uses drugs known in the art to treat these disorders and/or diseases.

Yet another object of the present invention is to provide a non-invasive treatment for delivering drugs to treat ophthalmic disorders or diseases which is simple and less expensive.

Another object of the present invention is to provide an ophthalmic composition comprising an effective amount of a drug to treat the ophthalmic disorder and/or disease and at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, and optionally, at least another drug delivery agent which is an adrenergic agent, in an effective amount such that the drug used to treat the ophthalmic disorders and/or diseases of the eye is delivered to the posterior segment of the eye. Said adrenergic agent(s) can be selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.

In yet another aspect, the present invention provides a method to deliver drugs to the chorio-retina and optic nerve head of the eye.

Drug delivery agent(s) selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, for use to deliver drugs to treat ophthalmic disorders and/or diseases are also part of the present invention.

In yet another aspect, the present invention relates to a method for treating eye disorders and/or diseases of the eye comprising: contacting the surface of the eye with an effective amount of a cholinergic agent, in particular with pilocarpine, or with a derivative thereof or mixtures thereof.

These and other objects are achieved by the present invention as evidenced by the summary of the invention, description of the preferred embodiments and the claims.

**Summary of the Invention**

Thus, the present invention relates to a method for delivering drugs to the posterior and anterior segments of the eyes comprising: contacting the surface of
the eye with an effective amount of a drug for treating eye disorders and/or diseases of the eye and a physiologically acceptable amount of at least one (i.e., one or several) drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, in an ophtalmologically acceptable carrier. Said drug delivery agent(s) can be used in conjunction with at least another delivery agent (i.e., one or several delivery agent(s)) which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.

In another embodiment, the present invention relates to a method of treating a eye disorders and/or diseases of the eye by delivering drugs to the chorio-retina and optic nerve head of an eye comprising administering to a person or an animal in need of such treatment an effective amount of a drug for treatment of the chorio-retina and optic nerve head and a physiologically acceptable amount of at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, and, optionally at least another drug delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.

In yet another embodiment, the present invention provides a composition comprising, consisting of or consisting essentially of

a) at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, and

b) a drug for treating eye disorders and/or diseases of the eye, and

c) optionally, at least another delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.

In yet another embodiment the present invention provides a method for increasing the transfer of a drug to the posterior segment of the eye, and in particular into the eye orbit, the posterior sclera and then into chorio-retina and optic nerve head to treat disorders and/or diseases of the eye comprising contacting the surface of an eye or both eye(s) with at least one drug delivery agent selected from
the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, and a second drug that treats disorders and/or diseases of the eyes. Said drug delivery agent(s) can be used in conjunction with at least another drug delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.

In a particular embodiment of the invention, physiologically acceptable amounts of drug delivery agent(s) and/or of the second drug that treats disorders and/or diseases of the eyes are used.

Drug delivery agent(s) selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, for use for treating diseases and/or disorders of the eye and in particular for use for the transfer, to the posterior segment of one or both eye(s), of a second drug that treats disorders and/or diseases of the eyes, to treat diseases and/or disorders of the eye, is another aspect of the present invention.

In yet another embodiment the present invention provides a kit comprising or consisting of:

a) drug delivery agent(s) as defined herein or a composition comprising, consisting of or consisting essentially of said drug delivery agent(s); and

b) a drug that treats disorders and/or diseases of the eyes, and,

c) optionally, at least another delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.

The present invention also provides use of

a) at least one drug delivery agent; and

b) a pharmaceutically acceptable amount of a second drug that treats disorders and/or diseases of the eyes, and,

c) optionally, at least another delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof, for the manufacture of a medicament to treat disorders and/or diseases of the eye.
Brief Description of the Drawings

Figure 1 is an optical coherence tomography scan (O.C.T.) of a patient having diabetic retinopathy (patient H.J.) prior to treatment (A), and two months after treatment (topical administration) (B) with a cholinergic agent (pilocarpine).

Figure 2 is an optical coherence tomography scan (O.C.T.) of a patient having diabetic retinopathy (patient F.K.) prior to treatment (A), and two months after treatment (topical administration) (B) with a cholinergic agent (pilocarpine).

Figure 3 is an optical coherence tomography scan (O.C.T.) of a patient having diabetic retinopathy (patient ZA.) prior to treatment (A), and six months after treatment (topical administration) (B) with a composition comprising pilocarpine (1% w/v), ramipril (2% w/v), dexamethasone (Tobradex®; 0.1% w/v) and indomethacin (Indocollyre ®; 0.1% w/v).

Figure 4 is an optical coherence tomography scan (O.C.T.) of a patient having diabetic retinopathy (patient S.H.) prior to treatment (A), and two months after treatment (topical administration) (B) with a cholinergic agent (pilocarpine), a corticosteroid (dexamethazone), a non steroidal anti-inflammatory agent (indomethacin (Indocollyre ©)), a beta-blocking agent (timolol) and an alpha adrenergic agonist agent (brimonidin).

Figure 5 is an optical coherence tomography scan (O.C.T.) of a patient with a central vein occlusion (patient A.M.) prior to treatment (A), and two months after treatment (topical administration) (B) with a cholinergic agent (pilocarpine).

Figure 6 is an optical coherence tomography scan (O.C.T.) of a patient with a central vein occlusion in the right eye (patient R.S.) prior to treatment (A), and three months after treatment (topical administration) (B) with a composition comprising pilocarpine (1% w/v), ramipril (2% w/v), dexamethasone (Tobradex®; 0.1 % w/v) and indomethacin (Indocollyre ®; 0.1% w/v).

Figure 7 is an optical coherence tomography scan (O.C.T.) of a patient with a central vein occlusion (patient B.R.N.) prior to treatment (A), and two months after treatment (topical administration) (B) with a cholinergic agent (pilocarpine 1%), a corticosteroid (dexamethazone), a non steroidal anti-inflammatory agent (indomethacin (Indocollyre ©)), a beta-blocking agent (timolol) and an alpha adrenergic agonist agent (brimonidin).

Figure 8 is a vertical scan of an optical coherence tomography scan (O.C.T.) of a patient presenting a reduction of visual acuity of the left eye due to a macular...
degeneration (patient G.N.) prior to treatment (A), and three months after treatment (topical administration) (B) with a cholinergic agent (pilocarpine).

Figure 9 is a vertical scan of an optical coherence tomography scan (O.C.T.) of a patient with a history of decreased vision in the right eye due to ARMD (patient H.M.) prior to treatment (A), and one month after treatment (topical administration) (B) with a composition comprising pilocarpine (1% w/v), ramipril (2% w/v), dexamethasone (Tobradex®; 0.1% w/v) and indomethacin (Indoclylre®; 0.1% w/v).

Figure 10 is an optical coherence tomography scan (O.C.T.) of a patient having a history of deceased vision in the left eye (patient G.N.) prior to treatment (A) and three months after treatment (topical administration) (B) with a cholinergic agent (pilocarpine), a corticosteroid (dexamethazone), a non steroidal anti-inflammatory agent (indomethacin (Indoclylre®)), timolol and brimonidin.

**Detailed Description of the Preferred Embodiments of the Present Invention**

Unless otherwise indicated, any embodiment disclosed herein can be used independently or in combination with others embodiments disclosed herein.

As used herein the terminology "anterior segment of the eye" means the front third of the eye that includes the structures in front of the vitreous humor such as the cornea, iris, ciliary body and lens.

As used herein the terminology "posterior segments of the eye" means the back two-thirds of the eye that includes the anterior hyaloid membrane and the optical structures behind it such as the vitreous humor, retina, choroid, optic nerve and optic nerve head.

The term "optic nerve head" as used herein means the circular area in the back (posterior segment) of the eye where the optic nerve connects to the retina.

As used herein the term "chorio-retina" refers to the posterior segments of the eye in which the retina contacts the choroid, which is the middle membrane of the eye.

The terms "treating" and "treatment" mean that the eye disorder and/or eye disease is improved.

The term "eye disorders" encompasses changes in vision, in the appearance of the eye or having abnormal sensations in the eye. Eye disorders include optic
nerve disorders, chorio-retinal disorders, visual degradation (of near and/or far visual acuity or of visual field), and trauma such as injuries to the eye.

As used herein, the term "eye diseases" means any disease of the eye such as of glaucomatous neuropathy, central serous chorio retinopathy (CSCR), high myopia chorioretinopathy, pigmentosa retinopathy, diabetic retinopathy, proliferative vitreoretinopathy, retinal vein occlusion, (in particular central retinal vein occlusion or branch retinal vein occlusion), retinal arterial occlusions (in particular central retinal artery occlusion), myopia (in particular high myopia), presbyopia, age related vision degradation, macular degeneration and in particular age-related macular degeneration, exsudative macular degeneration, macular edema, uveitis (in particular anterior uveitis and/or posterior uveitis), papillitis, retinitis, endophthalmitis and post-operative inflammation of the eye. This terminology also encompasses at least one of the above diseases and thus two or more diseases of the above diseases of the eye are also contemplated by this expression.

In a particular embodiment, "eye diseases" refer to diseases that affect the posterior segment of the eye, and in particular, eye diseases selected from the group consisting of macular edema, macular degeneration and in particular age-related macular degeneration, high myopia or macular degeneration, in particular age-related macular degeneration, retinal vein occlusion (in particular central retinal vein occlusion or branch retinal vein occlusion), retinal arterial occlusions, in particular central retinal artery occlusion, diabetic retinopathy, central serous chorio retinopathy, high myopia chorio-retinopathy, pigmentosa retinopathy, proliferative vitreoretinopathy, myopia (in particular high myopia), presbyopia, posterior uveitis, retinitis, papillitis, endophthalmitis, optic nerve head inflammation, choroidal new vessels (in particular those associated with high myopia or macular degeneration, in particular age-related macular degeneration), and exsudative macular degeneration (in particular the one which is associated with high myopia or macular degeneration, in particular age-related macular degeneration).

By "eye disorders and/or diseases of the eye", it is meant herein at least one eye disorder and/or disease of the eye; this term can encompass several (two, three or more than three) eye disorders and/or diseases of the eye.

The term "animal" includes mammals, in particular humans and non-human mammals. The term "mammal" encompasses any of various warm-
blooded vertebrate animals of the class Mammalia, including humans and non-human mammalians, characterized by a covering of hair on the skin and, in the female, milk-producing mammary glands for nourishing the young.

As used herein, "ophthalmologically acceptable carrier" means any carrier that has substantially no long term or permanent detrimental effect on the eye to which it is administered, in particular any carrier that can be placed in the eye and that does not cause eye irritation. Ophthalmologically acceptable carriers include water (distilled or deionized water), saline solutions, phosphate buffered saline solutions, and other aqueous media.

By "consisting essentially of", it is meant herein that minor ingredients can be added without having a major effect.

"At least one" agent as used herein means one or several agent(s), in particular one, two three, four, five, or six agents.

By "drug delivery agent", it is meant herein an agent which is able to reach the posterior segment of the eye after it is delivered to the ocular surface of a patient or an animal in need thereof. When this agent is used in conjunction with a second drug for treating the eye, it enables this second drug to reach the posterior segment of the eye or at least enhances the amount of this second drug that reaches the posterior segment of the eye (drug delivery-enhancing agent). Hence, a drug delivery agent as used herein increases delivery of a second drug for treating eye disorders and/or diseases of the eye into the ocular tissue and in particular into the posterior segment of the eye, compared to delivery of the same second drug in the absence of this drug delivery agent.

When several drug delivery agents are used in the invention, they can be used as separate compounds or be present in the same composition. In a particular embodiment, the drug delivery agents or at least some of the drug delivery agents used are present in a composition, in combination with one or several drugs for treating eye disorders and/or diseases of the eye. These compositions are appropriate for topical administration, i.e., adapted to be applied to the surface of the eye, and in particular in the form of eye drops.

By "cholinergic agent" or "cholinergic drug", it is meant herein a compound that produces the same effects as acetylcholine (the most common neurohormone of the parasympathetic nervous system, i.e., the part of the peripheral nervous system responsible for the every day work of the body (e.g., salivation, digestion, etc.).
and muscle relaxation)). Cholinergic agents as used herein can either directly mimic
the effect of acetylcholine, or block the effects of acetylcholinesterase (an enzyme
that destroys naturally occurring acetylcholine, and thus enhance the effects
mediated by acetylcholine). They include acetylcholine's precursors and cofactors,
acetylcholine receptor agonists (for example pilocarpine, muscarine, nicotine,
suxamethonium) and cholinergic enzymes (i.e., cholinesterase inhibitors such as
phystostigmine, neostigmine or mintacol).

By "cholinergic agent derivative", it is meant herein a compound obtained via
a chemical modification of a cholinergic agent as defined herein, and which retains
the ability to either mimic the effect of acetylcholine, or block the effects of
acetylcholinesterase. These properties can be shown, for example, by applying, to
one eye of a mouse, a rat or a monkey, few drops (one, two or three) of said
derivative in solution in an ophthalmologically acceptable carrier, and applying, to
the other eye of the same animal, the same volume of the ophthalmologically
acceptable carrier alone, and measuring and comparing pupil constriction (myosis)
of both eyes.

The term "adrenergic agent" as used herein encompasses an alpha
adrenergic agonist agent, a derivative of an alpha adrenergic agonist agent, a beta-
blocking agent, a derivative of a beta-blocking agents and mixtures thereof.

As used herein, an "alpha adrenergic agonist agent" is a drug which has
effects similar to, or the same as, epinephrine (adrenaline) or which is susceptible
to epinephrine, or similar substances, such as biological receptors. This term
includes alpha 1 agonists, and alpha 2 agonists. Alpha 1 agonists stimulate
phospholipase C activity in a human and an animal body, which results in
vasoconstriction and mydriasis (excessive dilation of the pupil). Alpha 2 agonists
are able to inhibit adenyl cyclase activity in a human and an animal body and are
used notably as antihypertensives, sedatives, to reduce eye's aqueous humor
secretions and to facilitate aqueous humor outflow via the uveoscleral route.
Examples of alpha 1 agonist include neosynephrine. Examples of alpha 2 agonists
include brimonidine, apraclonidine and clonidine. Others alpha adrenergic agonist
agents that can be used in the present methods and compounds of the present
invention include methoxamine, methylnorepinephrine, oxymetazoline,
phenylephrine, neosynephrine pivalat, beta-methylepinephrine, guanfacine,
guanabenz, guanoxabenz, guanethidine, tizanidine, and mixtures thereof.
By "derivative of an alpha adrenergic agonist agent", it is meant a compound obtained via a chemical modification of an alpha 1 agonist or an alpha 2 agonist, and which retains respectively the ability to stimulate phospholipase C activity or the ability to inhibit adenylyl cyclase activity in an animal model such as a mouse, a rat or a monkey. Said derivatives are preferably amine-containing compounds, which more preferably have pKa's of greater than 7, preferably about 7.5 to 9. The alpha 1 or alpha 2 activity of a derivative of an adrenergic agonist agent can be shown for example, by applying, to one eye of a mouse, a rat or a monkey, few drops (one, two or three) of said derivative in solution in an ophthalmologically acceptable carrier, and applying, to the other eye of the same animal, the same volume of the ophthalmologically acceptable carrier alone, and comparing dilation of the pupil (in the case of an alpha 1 agonist derivative) or aqueous humor secretions (in the case of an alpha 2 agonist derivative) of both eyes. "Derivatives of an alpha adrenergic agonist agent" include imidazoline derivatives such as oxymetazoline, xylometazoline, tetrahydrozoline and the like. Also those derivatives defined in U.S. Patent Nos. 7,345,077 and 7,335,803 can also be used as derivatives in the methods, compositions and kits of the present invention.

By "beta-blocking agent" (or beta-adrenergic antagonist agent) it is meant herein a drug which blocks the action of epinephrine (adrenaline) and/or norepinephrine (noradrenaline) in a human and an animal body. These compounds are used notably to lower intraocular tension and/or to reduce eye's aqueous humor secretions. This term encompasses antagonists of the beta 1, beta 2 and beta 3 adrenergic receptors. The beta-blocking agents that can be used in the methods, the compositions and the kits of the present invention include timolol, sotalol, propranolol, penbutolol, nadolol, metoprolol, labetalol, esmolol, carteolol, bisoprolol, betaxolol, atenolol, acebutolol, levobunolol, metipranolol and mixtures thereof.

By "beta-blocking agent derivative", it is meant herein a compound obtained via a chemical modification of a beta-blocking agent as defined above, and which retains the ability to lower intraocular tension and/or to reduce eye's aqueous humor secretions in an animal model such as a mouse, a rat or a monkey. These properties can be shown for example, by applying, to one eye of a mouse, a rat or a monkey, few drops (one, two or three) of said derivative in solution in an ophthalmologically acceptable carrier, and applying, to the other eye of the same animal, the same volume of the ophthalmologically acceptable carrier alone, and
measuring and comparing intraocular tension and/or aqueous humor secretions of both eyes. Beta-blocking agent derivatives include guaiacoxyl propanolamine derivatives such as those described in U.S. Patent 5,804,603.

As used herein, x "percent weight by volume" (or "% w/v") of a given drug means x percent weight by volume of the entire formulation comprising said drug.

Thus, the present invention relates to a method for delivering drugs to the posterior and anterior segments of the eyes (of one or both eye(s)) comprising contacting the surface of the eye with an effective amount of a drug for treating eye disorders and/or diseases of the eye and a physiologically acceptable amount of at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, in an ophthalmologically acceptable carrier. Said drug delivery agent(s) can be used in conjunction with at least another (i.e., one or several) drug delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.

Accordingly, the methods, compositions and kits of the present invention provide for the treatment of many eye disorders and/or diseases of the eye, including the ones mentioned above.

In a particular embodiment of the invention, the methods, compositions and kits of the invention disclosed herein can be used for the treatment of eye disorders and/or diseases of the eye that affect the posterior segment of the eye, and in particular, eye disorders and/or diseases selected from the group consisting of diabetic retinopathy, choroidal new vessels (in particular those associated with high myopia or macular degeneration, in particular age-related macular degeneration), posterior uveitis, papillitis, endophthalmitis, retinitis, optic nerve head inflammation, retinal vein occlusion (in particular central retinal vein occlusion or branch retinal vein occlusion), retinal arterial occlusion (in particular central retinal artery occlusion), central serous chorio-retinopathy (CSCR), pigmentosa retinopathy, myopia (in particular high myopia), presbyopia, macular edema, age-related macular degeneration, exsudative macular degeneration (in particular the one that is associated with high myopia or macular degeneration, in particular age-related macular degeneration), high myopia chorio-retinopathy, proliferative
vitreoretinopathy and infection or inflammation of the posterior segment of the eye (in particular of the choroid, retina, optic nerve, and/or posterior sclera).

Alternatively or additionally, the methods, compositions and kits of the invention can be used for the treatment or the prevention of visual degradation (of near and/or far visual acuity or of visual field), in particular age related visual degradation (of near and/or far visual acuity or of visual field), uveitis (in particular anterior uveitis and/or posterior uveitis), post-operative inflammation, and eye infections or inflammation.

Alternatively or additionally, the methods, compositions and kits of the present invention can also be used for the treatment of glaucoma and/or glaucomatous neuropathy.

The methods, compositions and kits of the present invention can in particular be used for improving vision of one or both eyes, and more particularly for improving distance vision and/or near vision.

In addition, the methods, compositions and kits of the invention disclosed herein can be used to perform topical anaesthesia as a prelude to surgery.

At least one eye disorder and/or disease of the eye can be treated with the methods and compositions of the present invention and more than one or several eye disorders and/or diseases can also be treated.

In the present invention, the drug to treat the disorders and/or diseases of the eyes is administered topically in the form of suspensions, gels or ointments or in the form of eye drops or solutions along with a physiologically acceptable amount of at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, and, optionally, along with at least one other drug delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.

In a particular embodiment, active compounds are administered in accordance with the present invention to the eye admixed with an ophthalmically acceptable carrier. Any suitable, e.g., conventional, ophthalmically acceptable carrier as defined herein may be employed.

It may be desirable to formulate the drug for treating eye disorders and/or diseases of the eye and the adrenergic agent that can be used in the methods, the
compositions and the kits of the present invention as topical agents to be instilled into the eye. Such formulations may contain the active ingredient in a concentration range of approximately 0.001% to 20% weight by volume (w/v), preferably from 0.01% to 10% (w/v) or 0.05% to 10% (w/v), and more preferably from 0.1 to 3% or 0.5% to 3% (w/v). The composition itself may include, in addition to the active ingredient, excipients which are per se well known in the art for preparing ophthalmic compositions, particularly ophthalmic solutions.

The ophthalmic compositions (solutions or other formulations) that contain the drug delivery agent(s) as defined herein (i.e., the cholinergic agent(s) and, optionally, the adrenergic agent(s), and/or the drug(s) for treating disorders and/or diseases of the eyes may be administered to the mammalian eye as often as necessary to obtain an improvement of the eye disorder and/or eye disease. Those skilled in the art will recognize that the frequency of administration and duration of treatment depends on the precise nature of the active ingredient(s) and its concentration in the ophthalmic formulation, and various factors such as the type and severity of the eye disorder and/or eye disease, the age and weight of the patient or animal, the patient's or animal's general physical condition and the cause of the eye disorder and/or eye disease. Within these guidelines it is contemplated that the ophthalmic formulations (preferably ophthalmic solutions) of the present invention will be administered topically to the mammalian eye approximately once, twice or three times daily. The duration of treatment administered in accordance with the present invention may range, for example, from few weeks (at least one week) to few months (at least one month), in particular from 1 week to 6 months, preferably at least 2 weeks and less than 4 months and more preferably at least 3 weeks and less than 3 months. However, a prolonged treatment may be required. In particular, the treatment may last for life, for example in case of recurrence of the eye disorder and/or eye disease.

In a particular embodiment of the invention, the physiologically acceptable amount of the drug delivery agent(s) is administered prior to administering the effective amount of the drug(s) for treating disorders and/or diseases of the eyes; hence, in this case, the drug delivery agent(s) contact(s) the eye prior to the drug(s) for treating disorders and/or diseases of the eyes.

Cholinergic agents that can be used in the methods, the compositions and the kits of the present invention can be selected from the group consisting of
pilocarpine, aceclidine, carbachol (also known as carbamylcholine), diflupyl (or diisopropyl fluorophosphate (DFP), also known as difluorophate), mintacol, phospholine or phospholine iodide (also known as echothiophate iodide) and mixtures thereof.

Alpha adrenergic agonist agents that can be used in the methods, the compositions and the kits of the present invention can be selected from the group consisting of methoxamine, methylnorepinephrine, oxymetazoline, phenylephrine, neosynephrine, in particular neosynephrine pivalat, beta-methylepinephrine, brimonidine, apraclonidine, clonidine, guanfacine, guanabenz, guanoxabenz, guanethidine, tizanidine, and mixtures thereof.

Beta-blocking agents that can be used in the methods, the compositions and the kits of the present invention can be selected from the group consisting of timolol, sotalol, propranolol, penbutolol, nadolol, metoprolol, labetalol, esmolol, carteolol, bisoprolol, betaxolol, bisoprolol, atenolol, acebutolol, levobunolol, metipranolol and mixtures thereof.

The actual amount of the drug delivery agent(s) and the drug(s) for treating eye disorders and/or diseases of the eye to be administered in any given case will be determined by a physician taking into account the relevant circumstances, such as the type and severity of the eye disorder and/or eye disease, the age and weight of the patient or animal, the patient's or animal's general physical condition and the cause of the eye disorder and/or eye disease.

By way of example, physiologically acceptable amounts of each of the drug delivery agent(s) that are generally administered to a person or an animal in need thereof are ranging from 0.01% to 20% (w/v), preferably from 0.1% to 15% (w/v) and more preferably from 0.1% to 3% (w/v), for example from 0.1% to 2% (w/v) or 0.2% to 1% (w/v) if eyedrops are used and from 0.1% to 2% (w/v) in the case of other types of topical administration.

The effective amount of a drug for treating eye disorders and/or diseases of the eye is generally administered to a person or an animal in need thereof in a concentration ranging from 0.001 to 15% (w/v), preferably from 0.05 to 10% (w/v), and more preferably from 0.1 to 3% (w/v).

The substances or drugs used for treating disorders of the eyes and/or eye diseases can be selected from the group of calcium antagonists, angiotensin converting enzyme inhibitors, nitrates or nitric oxide generators, beta adrenergic
agonists, antioxidants and radical scavengers, dopaminergic and serotoninergic agents, monoamine oxidase inhibitors, anti-inflammatory agents, growth factors, neuroprotective agents, growth factor vasoactive agents, neuropeptides, anti-inflammatory mediators, anti-infective agents, anti-ischemic association agents, non-steroidal anti-inflammatory agents, anti-growth factor agents, immunosuppressive agents, and mixtures thereof.

At least one drug or substance for treating eye disorders and/or diseases of the eye can be used in the methods, the compositions and the kits of the present invention. For example if a person or an animal has more than one eye disorder and/or eye disease, several drugs can be administered at the same time providing that these drugs do not interact with themselves to provide adverse side effects. Thus, for example, one can administer at least one anti-inflammatory and at least one angiotensin converting enzyme inhibitor.

The drugs or combinations of drugs can be administered at room temperature.

Examples of calcium antagonists that can be used in the methods, the compositions and the kits of the present invention can selected from the group comprising verapamil, nifedipine, nimadipine, diltiazem, nicardipine, felodipine, amlodipine, isradipine and mixtures thereof.

Examples of angiotensin converting enzyme inhibitors that can be used in the methods, the compositions and the kits of the present invention are selected from the group comprising captopril, enalapril, usinopril, ramipril, kinapril, benazepril, cilazapril and mixtures thereof.

Nitrates, isorbide dinitrate, isorbide mononitrate, linsidomine and mixtures thereof are examples of nitrates or nitric oxide generators that can be used in the methods, the compositions and the kits of the present invention.

Beta adrenergic agonists that can be used in the methods, the compositions and the kits of the present invention can be selected from the group comprising salbutamol, terbutalin, isoprenalin and mixtures thereof while antioxidants and radical scavengers that can be used in the present invention can be selected from the group comprising ascorbic acid, glutathione catalases and their derivatives and mixtures thereof.
Dopaminergic and serotoninergic agent that can be used in the methods, the compositions and the kits of the present invention can be selected from the group comprising: levodopa, amantadine, bromocriptine, serotonin and mixtures thereof.

Amitriptyline, nortriptyline, selegiline and mixtures thereof are monoamine oxidase inhibitors that can be used in the methods, the compositions and the kits of the present invention.

Examples of anti-inflammatory agents that can be used in the methods, the compositions and the kits of the present invention are non-steroidal anti-inflammatory agents or steroidal anti-inflammatory agents, in particular corticosteroids, or mixtures thereof.

Examples of non-steroidal anti-inflammatory drugs that can be used in the methods, the compositions and the kits of the present invention can be selected from the group consisting of aspirin, arylalkanoic acids such as bromfenac, indometacin, oxameticin, 2-arylpropionic acids such as fenbufen, piroprofen, ketoprofen, ibuprofen, oxaprozin, and ketorolac, femamic acids, pyrazolidine derivatives such as clofezonem kebuzone and phenazone, oxicams such as dromicam and meloxicam, and COX-2 inhibitors, such as celecoxib and rofecoxib.

Examples of corticosteroids that can be used in the methods, the compositions and the kits of the present invention can be selected from the group consisting of cortisone, hydrocortisone, delta-cortisone or prednisolone, prednisone, delta-hydrocortisone or prednisolone, methylprednisolone or medrocorisone, fluorohydrocortisone or fluorcortisone, fluoromethylprednisolone or dexamethazone, fluoromethyldelta-hydrocortisone or betamethazone and paramethazone.

Growth factors such as nerve growth factors (NGF), epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factor (TGF) and mixtures thereof can be used in the methods, the compositions and the kits of the present invention.

Anti-growth factor agents that can be used in the methods, the compositions and the kits of the present invention include anti-vascular endothelial growth factor (anti-VEGF) agents, anti-insulin like growth factor (anti-IGF) agents, anti-fibroblast growth factor (anti-FGF) agents, anti-platelet derived growth factor (anti-PDGF) agents, anti-placenta growth factor agents and mixtures thereof.
Anti-VEGF agents that can be used in the methods, the compositions and the kits of the present invention can be selected from the group comprising bevacizumab (Avastin®), ranibizumab (Lucentis®), pegaptanib (Macugen®), and mixtures thereof.

Anti-inflammatory mediators that can be used in the methods, the compositions and the kits of the present invention can be selected from the group comprising cytokines, bradikinine, histamine, serotonin, thrombin, ADP, acetylcholine, adrenalin and derivatives and mixtures thereof.

Anti-infective agents that can be used in the methods, the compositions and the kits of the present invention can be selected from the group comprising antibiotics, antifungal agents, antiviral agents and mixtures thereof.

Anti-ischemic association compounds selected from the group comprising angiotensin converting enzyme inhibitors, non-steroidal anti-inflammatory agents and mixtures thereof, can also be used in the methods, the compositions and the kits of the present invention.

Immunosuppressive agents that can be used in the methods, the compositions and the kits of the present invention can be selected from the group consisting of general immunosuppressive agents, specific immunosuppressive agents and mixtures thereof. General immunosuppressive agents include azathioprin, cyclophosphamide, methotrexate, cyclosporine AFK 506, rapamycin and mixtures thereof. Specific immunosuppressive agents include monoclonal antibodies directed against T-lymphocytes or cytokines.

In a particular embodiment, a combination of drugs as set forth in table 1, or a combination of drugs comprising, consisting essentially of or consisting of a combination of drugs as set forth in Table 1 is used.

In a particular embodiment, the drugs (i.e., the drug delivery agent(s) and the drug(s) to for treating disorders and/or diseases of the eyes) are delivered to the posterior segment of the eye. Said drugs can be in particular delivered to the chorio-retina and optic nerve head of the eyes.
Table 1. Examples of combinations of drugs (i.e., combinations of drug delivery agent(s) and drug(s) for treating disorders and/or diseases of the eyes) that can be used in the methods, the compositions and the kits of the present invention. These drugs can be administered as separate ophthalmic formulations or in the same ophthalmic formulation. The drugs present in these combinations are indicated by an "x".

In another aspect, the present invention relates to a method of treating eye disorders and/or diseases of the eye by delivering drugs to the chorio-retina and optic nerve head of an eye comprising administering to a person or an animal (in particular a mammal) in need of such treatment - an effective amount of a drug for treatment of the chorio-retina and/or optic nerve head and

<table>
<thead>
<tr>
<th>Type of agent</th>
<th>Name: concentration in % (w/v)</th>
<th>Combination of drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinergic</td>
<td>Pilocarpine: 0.05-3% or 0.1-2%, e.g., 0.2%, 0.5%, 1% or 2%</td>
<td>x x x x x x x x x x</td>
</tr>
<tr>
<td></td>
<td>alpha adrenergic agonist</td>
<td>Brimonidine: 0.05-1%, e.g., 0.2%; and/or Neosynephrine: 0.1-5%, e.g., 2%; and/or Apraclonidine: 0.05-2%, e.g., 0.5%</td>
</tr>
<tr>
<td></td>
<td>beta-blocking</td>
<td>Timolol: 0.05-2%, e.g., 0.5%</td>
</tr>
<tr>
<td></td>
<td>corticosteroid</td>
<td>Dexamethasone: 0.01-2% or 0.05-1%, e.g., 0.1%</td>
</tr>
<tr>
<td></td>
<td>non steroidal anti-inflammatory</td>
<td>Indomethacin: 0.01-2% or 0.05-1%, e.g., 0.1%</td>
</tr>
<tr>
<td></td>
<td>angiotensin converting enzyme inhibitor</td>
<td>Ramipril: 0.1-5%, e.g., 2%</td>
</tr>
<tr>
<td></td>
<td>Anti-VEGF</td>
<td>bevacizumab: 0.1-5%, e.g., 2%</td>
</tr>
</tbody>
</table>

Table 1. Examples of combinations of drugs (i.e., combinations of drug delivery agent(s) and drug(s) for treating disorders and/or diseases of the eyes) that can be used in the methods, the compositions and the kits of the present invention. These drugs can be administered as separate ophthalmic formulations or in the same ophthalmic formulation. The drugs present in these combinations are indicated by an "x".

In another aspect, the present invention relates to a method of treating eye disorders and/or diseases of the eye by delivering drugs to the chorio-retina and optic nerve head of an eye comprising administering to a person or an animal (in particular a mammal) in need of such treatment - an effective amount of a drug for treatment of the chorio-retina and/or optic nerve head and
- a physiologically acceptable amount of at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof.

In a particular embodiment, the above mentioned drugs are administered topically into the eye, in particular in the form of eye drops. They can be administered separately or in the same composition.

Said method can further comprise administering to the person or the animal (in particular a mammal) in need of such treatment at least another drug delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.

Cholinergic agents that can be used in the methods, the compositions and the kits of the present invention can be selected from the group consisting of pilocarpine, aceclidine, carbachol, diflupyl, mintacol, phospholine iodide and mixtures thereof.

As set forth above the effective amount of the drug for treating chorio-retina and optic nerve head can be selected from the group comprising calcium antagonists, angiotensin converting enzyme inhibitors, nitrates or nitric oxide generators, beta-adrenergic agonists, antioxidants and radical scavengers, dopaminergic and serotonergic agents, monoamine oxidase inhibitors, anti-inflammatory agents, growth factors, neuropeptides, anti-inflammatory mediators, anti-infective agents, non-steroidal anti-inflammatory agents, anti-ischemic association agents (non-steroidal anti-inflammatory agents and angiotensin converting enzyme inhibitors), neuroprotective agents, growth factor vasoactive agents, anti-growth factor agents, in particular anti-vascular endothelial growth factor (anti-VEGF) agents, anti-insulin like growth factor (anti-IGF) agents, anti-fibroblast growth factor (anti-FGF) agents, anti-platelet derived growth factor (anti-PDGF) agents, anti-placenta growth factor agents, immunosuppressive agents and mixtures thereof. The specific drugs and amounts that can also be used in this method are set forth above.

If alpha adrenergic agonist agents are used in the methods, the compositions and the kits of the present invention, they can be selected from the group consisting of methoxamine, methylnorepinephrine, oxymetazoline, phenylephrine, neosynephrine pivalat, beta-methylepinephrine, brimonidine, apraclonidine,
clonidine, guanfacine, guanabenz, guanoxabenz, guanethidine, tizanidine, and mixtures thereof.

If beta-blocking agents are used in the methods, the compositions and the kits of the present invention, they can be selected from the group consisting of timolol, sotalol, propranolol, penbutolol, nadolol, metoprolol, labetalol, esmolol, carteolol, bisoprolol, betaxolol, bisoprolol, atenolol, acebutolol, levobunolol, metipranolol and mixtures thereof.

Accordingly, the effective amount of a drug for treatment of the chorio-retina and/or optic nerve head is administered in a concentration ranging from 0.001 to 15% (w/v), preferably from 0.05 to 10% (w/v), and more preferably from 0.1 to 3% (w/v).

The physiologically acceptable amounts of cholinergic agents, alpha adrenergic agonist agent, beta-blocking agent, derivatives thereof and of mixtures thereof that are generally administered are ranging from 0.01% to 20% (w/v), preferably from 0.1% to 15% (w/v), and more preferably from 0.1% to 3% (w/v), for example from 0.1% to 2% (w/v) or 0.2% to 1% (w/v) if eyedrops are used and from 0.1% to 2% (w/v) in the case of other types of topical administration. More specifically, the physiologically acceptable amounts of cholinergic agents (or derivatives or mixtures thereof) that are generally administered vary from 0.01% to 5% (w/v), preferably from 0.1 to 2% (w/v) and more preferably from 0.1% to 1% (w/v) or 0.2% to 0.5% (w/v) (e.g. 0.2% or 0.5%), while the physiologically acceptable amounts of alpha adrenergic agonist agent(s) (or derivatives or mixtures thereof) that are generally administered vary from 0.01% to 20% (w/v), preferably from 0.1 to 3% (w/v) and the physiologically acceptable amounts of beta-blocking agent(s) (or derivatives or mixtures thereof) vary from 0.05% to 2% (w/v), preferably 0.1% to 1% (w/v), and more preferably from 0.1% to 0.5% (w/v). In the method for treating chorio-retina and optic nerve head, the drug(s) and the physiologically acceptable amounts of drug delivery agent(s) can be administered simultaneously or the drug delivery agent(s) or at least some of the delivery agents can be administered prior to the drug(s) which are used to treat the at least one eye disorder and/or eye disease.

If the drug delivery agent(s), some of the drug delivery agent(s) or the drug delivery composition is(are) administered before the drug(s), usually it (they) is (are)
administered from 1 second to 3 hours, preferably from 5 to 60 minutes, prior to the administration of the treating drug(s).

In yet another aspect, the present invention provides a composition comprising, consisting or consisting essentially of

a) at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, and

b) at least one drug that treats eye disorders and/or diseases of the eye.

In a particular embodiment, said composition further comprises at least one drug delivery agent which is an adrenergic agent chosen among alpha adrenergic agonist agents and derivatives of alpha adrenergic agonist agents, beta-blocking agents and derivatives of beta-blocking agents.

The drug(s) for treating eye disorders and/or diseases of the eye can be selected from the group comprising calcium antagonists, angiotensin converting enzyme inhibitors, nitrates or nitric oxide generators, beta-adrenergic agonists, antioxidants and radical scavengers, dopaminergic and serotonergic agents, monoamine oxidase inhibitors, anti-inflammatory agents, growth factors, neuropeptides, anti-inflammatory mediators, anti-infective agents, non-steroidal anti-inflammatory agents, anti-ischemic association agents (non-steroidal anti-inflammatory agents and angiotensin converting enzyme inhibitors), anti-growth factor agents, in particular anti-vascular endothelial growth factor (anti-VEGF) agents, anti-insulin like growth factor (anti-IGF) agents, anti-fibroblast growth factor (anti-FGF) agents, anti-platelet derived growth factor (anti-PDGF) agents, anti-placenta growth factor agents, immunosuppressive agents and mixtures thereof.

In a particular embodiment, said drug for treating eye disorders and/or diseases of the eye is selected from the group consisting of angiotensin converting enzyme inhibitors, non-steroidal anti-inflammatory agents, anti-growth factor agents, steroidal anti-inflammatory agents, in particular corticosteroids, immunosuppressive agents and mixtures thereof. Said drug(s) are as set forth above.

In another particular embodiment, said drug for treating eye disorders and/or diseases of the eye is an anti-growth factor agent as defined herein, in particular an anti-vascular endothelial growth factor agent (anti-VEGF agent), a corticosteroid as set forth above or mixtures thereof.
In another particular embodiment, said drug for treating eye disorders and/or diseases of the eye is an angiotensin converting enzyme inhibitor and/or a non-steroidal inflammatory agent (anti-ischemic complex). In this case, the adrenergic agent is generally selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents and mixtures thereof. Said drug(s) are as set forth above.

In another particular embodiment, said drug for treating disorders and/or diseases of the eyes is a corticosteroid and/or an antt-VEGF agent. Said drug(s) are as set forth above.

The compositions of the invention can be used as a medicament. In particular, said composition are suitable for the treatment of one or several disorders and/or diseases of the eye as defined herein and in particular one or several disorders and/or diseases of the eye selected from the group comprising or consisting of diabetic retinopathy, retinal vein occlusion (in particular central retinal vein occlusion or branch retinal vein occlusion), retinal arterial occlusions, (in particular central retinal artery occlusion), age related visual degradation (near and far visual acuity; visual field), visual degradation of visual acuity and visual field, myopia, presbyopia, macular oedema, central serious chorio-retinopathy, exsudative macular degeneration (age related macular degeneration, high myopia; macular degeneration) uveitis, papillitis, glaucoma neuropathy

In a particular embodiment, the compositions of the invention can be administered topically to a person or an animal in need thereof, for example, in the form of eye drops.

The compositions of the invention can be used in the methods disclosed herein, to treat the posterior segment of the eye and in particular to treat chorio-retinal and/or optic nerve head disorders in a person or an animal.

In a particular embodiment, the compositions of the invention are administered topically (for example in the form of eye drops) to a person or an animal in need thereof, for increasing the transfer (or delivery), into the posterior segment of the eye, and in particular into the eye orbit, the posterior sclera and then into chorio-retina and optic nerve head, of at least one drug to treat disorders and/or diseases of the eye.

Cholinergic agents that can be used in the methods, the compositions and the kits of the present invention can be selected from the group consisting of
pilocarpine, aceclidine, carbachol, diflupyl, mintacol, phospholine iodide and mixtures thereof.

If alpha adrenergic agonist agents are used in the methods, the compositions and the kits of the present invention, they can be selected from the group comprising or consisting of methoxamine, methylnorepinephrine, oxymetazoline, phenylephrine, neosynephrine pivalat, beta-methylnorepinephrine, brimonidine, apraclonidine, clonidine, guanfacine, guanabenz, guanoxabenz, guanethidine, tizanidine, and mixtures thereof.

If beta-blocking agents are used in the methods, the compositions and the kits of the present invention, they can be selected from the group comprising or consisting of timolol, sotalol, propranolol, penbutolol, nadolol, metoprolol, labetalol, esmolol, carteolol, bisoprolol, betaxolol, atenolol, acebutolol, levobunolol, metipranolol and mixtures thereof.

In this composition, the angiotensin converting enzyme inhibitors that can be used can be selected from the group comprising or consisting of captopril, enalapril, usinopril, ramipril, kinapril, benazepril, cilazapril and mixtures thereof.

The non-steroidal anti-inflammatory agents that can be used in the composition can be selected from the group comprising or consisting of aspirin, arylalkanoic acids such as bromfenac, indometacin, oxametacin, 2-arylpropionic acids such as fenbufen, pirprofen, ketoprofen, ibuprofen, oxaprozin, and ketorolac, femamic acids, pyrazolidine derivatives such as clofezonem kebuzone and phenazine, ocicams such as droxicam and meloxicam, and COX-2 inhibitors, such as celecoxib and rofecoxib.

In the compositions of the present invention, the drug delivery agent(s) are generally present in amounts ranging from 0.01% to 20% (w/v), preferably from 0.1% to 15% (w/v), and more preferably from 0.1% to 3% (w/v), for example from 0.1% to 3% (w/v), 0.1% to 2% (w/v) or 0.1% to 0.5% (w/v). More specifically, the amounts of cholinergic agents (or derivatives or mixtures thereof) that are generally administered vary from 0.01% to 5% (w/v), preferably from 0.1% to 2% (w/v) and more preferably from 0.1% to 1% (w/v) or 0.2% to 0.5% (w/v) (e.g., 0.2% or 0.5%), while the amounts of alpha adrenergic agonist agent(s) (or derivatives or mixtures thereof) that are present in the compositions of the invention generally vary from 0.01% to 20% (w/v), preferably from 0.1% to 3% (w/v) and the amounts of beta-blocking agent(s) (or derivatives or mixtures thereof) that are present in the
compositions of the invention generally vary from in the amounts of 0.05% to 2% (w/v), preferably 0.1% to 1% (w/v), and more preferably from 0.1% to 0.5% (w/v). The drug for treating eye disorders and/or diseases of the eye is generally present in amounts ranging from 0.001% to 15% (w/v), preferably from 0.05% to 10% (w/v), and more preferably from 0.1% to 3% (w/v).

In a particular embodiment, the compositions of the invention comprise, consist essentially of, or consist of a combination of drugs (i.e., a combination of drug delivery agent(s) and of drugs that treats eye disorders and/or diseases) as set forth in Table 1.

A composition for the treatment and in particular the topical treatment of a disorder and/or disease of the eye as defined herein, and in particular selected from the group comprising of diabetic retinopathy, retinal vein occlusion (in particular central retinal vein occlusion, branch retinal vein occlusion and retinal artery occlusion), exudative macular degeneration (age related macular degeneration; high myopia), uveitis, papillitis, and endophthalmitis comprising, consisting or consisting essentially of

a) at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, and

b) an anti-vascular endothelial growth factor (anti-VEGF), corticosteroid(s) or mixture thereof is another embodiment of the present invention.

In a particular embodiment, said composition further comprises at least one drug delivery agent which is an adrenergic agent chosen among alpha adrenergic agonist agents and derivatives of alpha adrenergic agonist agents, beta-blocking agents and derivatives of beta-blocking agents.

Cholinergic agents that can be used in the methods, the compositions and the kits of the present invention can be selected from the group consisting of pilocarpine, aceclidine, carbachol, diflupyl, mintacol, phospholine iodide and mixtures thereof.

If alpha adrenergic agonist agents are used in the methods, the compositions and the kits of the present invention, they can be selected from the group comprising or consisting of methoxamine, methylnorepinephrine, oxymetazoline, phenylephrine, neosynephrine, in particular neosynephrine pivalat, beta-methylepinephrine, brimonidine, apraclonidine, clonidine, guanfacine, guanabenz, guanoxabenz, guanethidine, tizanidine, and mixtures thereof.
If beta-blocking agents are used in the methods, the compositions and the kits of the present invention, they can be selected from the group comprising or consisting of timolol, sotalol, propranolol, penbutolol, nadolol, metoprolol, labetalol, esmolol, carteolol, bisoprolol, betaxolol, atenolol, acebutolol, levobunolol, metipranolol and mixtures thereof.

The anti-VEGF is selected from the group comprising or consisting of bevacizumab (Avastin®), ranibizumab (Lucentis®), pegaptanib (Macugen®) and mixtures thereof.

The corticosteroids can be selected from the group consisting of cortisone, hydrocortisone, deltacortisone or prednisolone, prednisone, deltalhydrocortisone or prednisolone, methylprednisolone or medro cortisone, fluoro hydrocortisone or fluorocortisone, fluoromethylprednisolone or dexamethazone, fluoromethyl deltahydrocortisone or betamethazone and paramethazone.

The amounts of cholinergic agents, alpha adrenergic agent(s), beta-blocking agent(s), derivative(s) thereof or mixtures thereof that can be used are as set forth above.

The amounts of anti-VEGF and/or corticosteroids that can be used are generally ranging from 0.001% to 15% (w/v), preferably from 0.05% to 10% (w/v), and more preferably from 0.1% to 3% (w/v).

In yet another embodiment the present invention provides a composition for the topical treatment of disorders and/or diseases of the eye as defined herein, and in particular for the topical treatment of diabetic retinopathy, macular oedema, exudative macular degeneration, retinal vein occlusion (in particular central retinal vein occlusion or branch retinal vein occlusion), uveitis, papillitis, or endophtalmitis comprising, consisting or consisting essentially of

a) at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, and

b) angiotensin converting enzyme inhibitor(s) and/or non steroidal anti-inflammatory agent(s) and/or steroidal anti-inflammatory agent(s), in particular corticosteroid(s), or mixtures thereof.

In a particular embodiment, said composition further comprises at least one drug delivery agent which is an adrenergic agent chosen among alpha adrenergic agonist agents and derivatives of alpha adrenergic agonist agents, beta-blocking agents and derivatives of beta-blocking agents.
The drug delivery agent(s), angiotensin converting enzyme inhibitor(s), non steroidal anti-inflammatory agent(s) and corticosteroid(s) used in this composition can be any drug set forth above with respect to the other methods and compositions.

The amounts of drug delivery agent(s) that can be used are as set forth above.

The amounts of angiotensin converting enzyme inhibitor(s), non steroidal anti-inflammatory agent(s) and/or corticosteroid(s) that can be used are generally ranging from 0.001 % to 15% (w/v), preferably from 0.05% to 10% (w/v), and more preferably from 0.1% to 3% (w/v).

In yet another embodiment the present invention provides a composition for the topical treatment of disorders and/or diseases of the eye as defined herein, and in particular of age related vision degradation and presbyopia comprising or consisting of:

a) at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, and

b) an angiotensin converting enzyme inhibitor and/or a non steroidal anti-inflammatory agent and/or an anti vascular endothelial growth factor agent (anti-VEGF agent) selected from the group comprising bevacizumab (Avastin®), ranibizumab (lucentis®), pegaptanib (Macugen®) and mixtures thereof.

In a particular embodiment, said composition further comprises at least one drug delivery agent which is an adrenergic agent chosen among alpha adrenergic agonist agents and derivatives of alpha adrenergic agonist agents, beta-blocking agents and derivatives of beta-blocking agents, preferably an alpha adrenergic agonist agent and/or a derivative of an alpha adrenergic agonist agent.

The drug delivery agent(s), angiotensin converting enzyme inhibitor and non steroidal anti-inflammatory agent and corticosteroid(s) used in this composition can be any drug set forth above with respect to the other methods and compositions.

The amounts of drug delivery agent(s), derivative(s) thereof or mixtures thereof that can be used are as set forth above.

The amounts of angiotensin converting enzyme inhibitor(s), non steroidal anti-inflammatory agent(s) and/or anti-VEGF agent(s) that can be used are generally ranging from 0.001 % to 15% (w/v), preferably from 0.05% to 10% (w/v), and more preferably from 0.1 % to 3% (w/v).
In yet another aspect, the present invention provides a method for increasing the transfer (or delivery), of a drug into the posterior segment of the eye and in particular into the eye orbit, the posterior sclera and then into chorio-retina and optic nerve head to treat disorders and/or diseases of the eye as defined herein, said method comprising contacting the surface of an eye or both eyes with

a) a physiologically acceptable at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof and

b) a pharmaceutically acceptable amount of a second drug that treats disorders and/or diseases of the eyes, and,

c) optionally, at least another delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.

Cholinergic agents that can be used in the methods, the compositions and the kits of the present invention can be selected from the group consisting of pilocarpine, aceclidine, carbachol, diflupyl, mintacol, phospholine iodide and mixtures thereof.

As set forth above, if alpha adrenergic agonist agents are used in the methods, the compositions and the kits of the present invention, they can be selected from the group comprising or consisting of methoxamine, methylnorepinephrine, oxymetazoline, phenylephrine, neosynephrine pivalat, beta-methylepinephrine, brimonidine, apraclonidine, clonidine, guanfacine, guanabenz, guanoxabenz, guanethidine, tizanidine, and mixtures thereof.

If beta-blocking agents are used in the methods, the compositions and the kits of the present invention, they can be selected from the group comprising or consisting of timolol, sotalol, propranolol, penbutolol, nadolol, metoprolol, labetalol, esmolol, carteolol, bisoprolol, betaxolol, atenolol, acebutolol, levobunolol, metipranolol and mixtures thereof.

The amounts of drug delivery agent(s), derivative(s) thereof or mixtures thereof that can be used are as set forth above.

The pharmaceutically acceptable amount of a second drug that treats disorders and/or diseases of the eyes that can be used is as set forth above.
In a particular embodiment, the combination of drugs contacting the surface of one or both eye(s) is a combination of drugs as set forth in table 1, or a combination of drugs comprising, consisting essentially of or consisting of the drugs of a combination as set forth in Table 1.

Another aspect of the invention relates to drug delivery agent(s) as defined herein (i.e., cholinergic agent(s) or derivative(s) thereof as defined herein, and optionally, adrenergic agent(s) or derivative(s) thereof as defined herein), or mixture thereof, or a composition comprising, consisting of or consisting essentially of said drug delivery agent(s), for use for the transfer (or delivery) to the posterior segment of the eyes, of a second drug that treats disorders and/or diseases of the eyes, for use in the treatment of diseases and/or disorders of the eye.

Cholinergic agents that can be used in the methods, the compositions and the kits of the present invention can be selected from the group consisting of pilocarpine, aceclidine, carbachol, diflupyl, mintacol, phospholine iodide and mixtures thereof.

If alpha adrenergic agonist agents are used in the methods, the compositions and the kits of the present invention, they can be selected from the group consisting of methoxamine, methylnorepinephrine, oxymetazoline, phenylephrine, neosynephrine pivalat, beta-methylepinephrine, brimonidine, apraclonidine, clonidine, guanfacine, guanabenz, guanoxabenz, guanethidine, tizanidine, and mixtures thereof.

If beta-blocking agents are used in the methods, the compositions and the kits of the present invention, they can be selected from the group consisting of timolol, sotalol, propranolol, penbutolol, nadolol, metoprolol, labetalol, esmolol, carteolol, bisoprolol, betaxolol, atenolol, acebutolol, levobunolol, metipranolol and mixtures thereof.

The nature and amounts of drug delivery agent(s), derivative(s) thereof or mixtures thereof that can be used are as set forth above.

The second drug that treats disorders and/or diseases of the eyes that can be used in the methods, the compositions and the kits of the present invention can be selected from the group consisting of a calcium antagonists, nitrates or nitric oxide generators, beta adrenergic agonists, antioxidants and radical scavengers, dopaminergic and serotonergic agents, monoamine oxidase inhibitors, anti-inflammatory agents, growth factors, neuropeptides, anti-inflammatory mediators,
anti-infective agents, anti-ischemic association agents (non-steroidal anti-inflammatory agents and angiotensin converting enzyme inhibitors), anti-growth factor agents, in particular anti-vascular endothelial growth factor (anti-VEGF) agents, anti-insulin like growth factor (anti-IGF) agents, anti-fibroblast growth factor (anti-FGF) agents, anti-platelet derived growth factor (anti-PDGF) agents, anti-placenta growth factor agents, immunosuppressive agents and mixtures thereof. The specific drugs that can also be used in this method are set forth above. The specific drugs that are used to treat eye disorders and/or diseases can be any drug set forth above with respect to the other methods.

The pharmaceutically acceptable amount of the second drug depends upon which drug is being used. Examples of pharmaceutically acceptable amounts include amounts ranging from 0.1 to 15% (w/v), preferably from 0.5 to 10%, and more preferably from 0.5 to 3% (w/v).

In a particular embodiment, a combination of drugs as set forth in table 1, or a combination of drugs comprising, consisting essentially of or consisting of the drugs of a combination as set forth in Table 1 is used.

In a further aspect, the present invention also provides use of

a) at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, in combination with

b) a pharmaceutically acceptable amount of a second drug that treats disorders and/or diseases of the eyes, and, optionally,

c) at least another drug delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof,

for use for the treatment of disorders and/or diseases of the eye or for the manufacture of a medicament to treat disorders and/or diseases of the eye.

As set forth above, cholinergic agents that can be used in the methods, the compositions and the kits of the present invention can be selected from the group consisting of pilocarpine, aceclidine, carbachol, diflupyl, mintacol, phospholine iodide and mixtures thereof.

If alpha adrenergic agonist agents are used in the methods, the compositions and the kits of the present invention, they can be selected from the group comprising or consisting of methoxamine, methylnorepinephrine, oxymetazoline,
phenylephrine, neosynephrine pivalat, beta-methylepinephrine, brimonidine, apraclonidine, clonidine, guanfacine, guanabenz, guanoxabenz, guanethidine, tizanidine, and mixtures thereof.

If beta-blocking agents are used in the methods, the compositions and the kits of the present invention, they can be selected from the group consisting or consisting of timolol, sotalol, propranolol, penbutolol, nadolol, metoprolol, labetalol, esmolol, carteolol, bisoprolol, betaxolol, atenolol, acebutolol, levobunolol, metipranolol and mixtures thereof.

The amounts of drug delivery agent(s) that are present in this medicament are as set forth above.

The pharmaceutically acceptable amount of a second drug that treats disorders and/or diseases of the eyes that can be used is as set forth above.

In a particular embodiment, a combination of drugs as set forth in table 1, or a combination of drugs comprising, consisting essentially of or consisting of a combination of drugs as set forth in Table 1 is used.

In yet another aspect, the present invention provides a kit comprising, consisting or consisting essentially of:

- (a) at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, and
- (b) a drug that treats disorders and/or diseases of the eyes, and,
- (c) optionally, at least another drug delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.

The drug delivery agent(s) and the derivatives thereof, as well as the drug for treating disorders and/or diseases of the eyes are as set forth above.

The amounts of drug delivery agent(s) and said drug for treating disorders and/or diseases of the eyes that can be used are as set forth above.

These kits can be used in the methods of the present invention, to treat chorio-retinal and/or optic nerve head disorders in a person or an animal.

In a particular embodiment, said drug for treating disorders and/or diseases of the eyes is selected from the group consisting of angiotensin converting enzyme inhibitors, non-steroidal anti-inflammatory agents, anti-growth factor agents,
steroidal anti-inflammatory agents, in particular corticosteroids, immunosuppressive agents and mixtures thereof. These drugs are as set forth above.

In a particular embodiment, said drug for treating disorders and/or diseases of the eyes is an angiotensin converting enzyme inhibitor and/or a non-steroidal anti-inflammatory agent (anti-ischemic complex). In this case, the adrenergic agent (if present) is generally selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents and mixtures thereof. Said drug(s) are as set forth above.

In another particular embodiment, drug for treating disorders and/or diseases of the eyes is a corticosteroid and/or an anti-VEGF agent. Said drug(s) are as set forth above.

In a particular embodiment, the kit of the invention comprises or consists of the drugs of a combination of drugs as set forth in Table 1.

In a particular embodiment of the different objects of the invention disclosed herein, both (i) drug delivery agent(s) selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof (for example pilocarpine) and (ii) drug delivery agent(s) selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof are used (in particular administered topically to a person or an animal in need thereof). Hence, the drug delivery agent(s) used in the methods, the compositions and the kits of the present invention can comprise, consist essentially of, or consist of:

- one or several cholinergic agents (or derivatives thereof or mixtures thereof) as disclosed herein and one or several alpha adrenergic agonist agents (or derivatives thereof or mixtures thereof) as disclosed herein; or
- one or several cholinergic agents as disclosed herein (or derivatives thereof or mixtures thereof) and one or several beta-blocking agents (or derivatives thereof or mixtures thereof) as disclosed herein; or
- one or several cholinergic agents (or derivatives thereof or mixtures thereof) as disclosed herein and both one or several alpha adrenergic agonist agents (or derivatives thereof or mixtures thereof) as disclosed herein and one or several beta-blocking agents (or derivatives thereof or mixtures thereof) as disclosed herein.
These combinations of at least two or three drug delivery agents (that can be used as separate compounds or associated in a composition) are in particular useful for use for the transfer (or delivery), to the posterior segment of one or both eye(s), of at least one second drug that treats disorders and/or diseases of the eyes as disclosed herein, and in particular at least one second drug which is selected from the group consisting of corticosteroids (for example dexamethazone), non steroidal anti-inflammatory agents (for example indomethacin (Indocollyre ®)) and angiotensin converting enzyme inhibitors.

In a particular embodiment of the different objects of the invention disclosed herein, the combination of drugs used comprises or consists of at least a cholinergic agent or a derivative thereof (for example pilocarpine), and:

- at least an alpha adrenergic agonist agent or a derivative thereof (for example neosynephrine, brimonidine, apraclonidine or mixtures thereof); and/or
- at least a beta-blocking agent, or a derivative thereof (for example timolol);

and/or

- at least an anti-VEGF agent (for example bevacizumab (Avastin®), ranibizumab (lucentis®), pegaptanib (Macugen®) or mixtures thereof); and/or
- at least a non-steroidal anti-inflammatory agent (for example Indomethacin); and/or

- at least a corticosteroid (for example Dexamethasone); and/or

- at least an immunosuppressive agent (for example azathioprin, cyclophosphamide, methotrexate, cyclosporine AFK 506, rapamycin, or mixtures thereof). These drugs can be used as separate compounds or be present in the same composition. The amounts of drug delivery agent(s) and of the other drug(s) for treating disorders and/or diseases of the eyes that can be used are as set forth herein. Examples of such combinations of drugs are shown in Table 1.

In a particular embodiment of the different objects of the invention disclosed above, the cholinergic agent(s) used (for example pilocarpine) increase(s) the effects of or even act(s) in synergy with the other drug delivery agent(s) and/or the other drug(s) for treating eye disorders and/or diseases of the eye used in the invention. Thus, the use of cholinergic agent(s) allows to achieve a stronger therapeutic effect than the one that is obtained if no cholinergic agent(s) are used. As a consequence, lower concentrations of drug(s) for treating eye disorders and/or diseases of the eye can be administered and/or the frequency of drug
administration can be decreased. Indeed, as illustrated in the example part of the application, when cholinergic agent(s) are used, administering the treatment three or four times a day is usually sufficient for treating an eye disease or disorder, whereas in case no cholinergic agent(s) are used, it is usually necessary to administer the treatment every hour during the day to a person or an animal in need thereof.

As illustrated in the example part of this application, cholinergic agents, and in particular pilocarpine, are particularly useful for treating eye disorders and/or diseases.

Thus, another aspect of the invention relates to a method for treating eye disorders and/or diseases of the eye comprising: contacting the surface of the eye with an effective amount of a cholinergic agent as defined herein, in particular with pilocarpine, or with a derivative thereof or mixtures thereof.

In a particular embodiment of the invention, the cholinergic agent(s), and in particular pilocarpine, is (are) the only drug delivery agent(s) or even the only drug to treat eye disorders and/or diseases that is used in the above-mentioned method.

The eye disorders and/or diseases that can be treated using the above-mentioned method are as disclosed herein and can be selected in particular from the group consisting of macular edema, age-related macular degeneration, choroidal new vessels (in particular those associated with high myopia or macular degeneration, in particular age-related macular degeneration), exsudative macular degeneration (in particular the one that is associated with high myopia or macular degeneration, in particular age-related macular degeneration), retinal vein occlusion, in particular central retinal vein occlusion or branch retinal vein occlusion, retinal arterial occlusions, in particular central retinal artery occlusion, central serous chorio retinopathy (CSCR), diabetic retinopathy, high myopia chorio-retinopathy, pigmentosa retinopathy, proliferative vitreoretinopathy, myopia (in particular high myopia), presbyopia, uveitis (in particular anterior uveitis or posterior uveitis), retinitis, papillitis, endophthalmitis, optic nerve head inflammation, eye infections or inflammation, visual degradation (of near and/or far visual acuity or of visual field), in particular age related visual degradation (of near and/or far visual acuity or of visual field), and post-operative inflammation.

In a particular embodiment of this method, the ophthalmic disorders and/or diseases only affect(s) the posterior segment of the eye, and are in particular,
selected from the group consisting of macular edema, age-related macular degeneration, choroidal new vessels (in particular those associated with high myopia or macular degeneration, in particular age-related macular degeneration), exudative macular degeneration (in particular the one that is associated with high myopia or macular degeneration, in particular age-related macular degeneration), retinal vein occlusion, in particular central retinal vein occlusion or branch retinal vein occlusion, retinal arterial occlusions, in particular central retinal artery occlusion, central serous chorio retinopathy (CSCR), diabetic retinopathy, high myopia chorio-retinopathy, pigmentosa retinopathy, proliferative vitreoretinopathy, myopia (in particular high myopia), presbyopia, posterior uveitis, retinitis, papillitis, endophthalmitis and optic nerve head inflammation.

In a particular embodiment of the invention, the above-mentioned method is used for treating diabetic retinopathy, retinal vein occlusion (in particular central retinal vein occlusion or branch retinal vein occlusion), or age-related macular degeneration.

The amounts of cholinergic agent that can be used in this method are as set forth above.

The invention also relates to one or several cholinergic agent(s) as defined herein, in particular to pilocarpine, or to derivative(s) thereof or mixtures thereof, or to a composition comprising, consisting essentially or consisting of this (these) drug(s), or to a kit comprising or consisting of this (these) drug(s), for use in the treatment of eye disorders and/or diseases as disclosed herein and in particular for use in the method disclosed above, or for the manufacture of a medicament to treat disorders and/or diseases of the eye as disclosed herein. The cholinergic agent(s), derivative(s) or mixtures thereof can administered topically to one or both eye of a patient or an animal in need thereof. The eye disorders and/or diseases are as disclosed herein and in particular can be selected from the groups disclosed for the above-mentioned method. The amounts of cholinergic agent that can be used are as set forth herein.

The invention will now be illustrated by the following description of clinical examples which, of course, are not limiting in nature. Further characteristics of the invention will become clear from the following clinical observations that are, of course, provided only by way of illustration and do not in any way limit the scope of the invention.
EXAMPLES

BACKGROUND AND METHODS USED

There are two general pathways whereby a drug can reach the posterior segment of the eye from an eye drop:

1. **Corneal:** into the anterior chamber, and then through the lens, the pupil or the iris.

2. **Conjunctival:** either directly across the sclera, choroid, choriocapillaris and retinal pigment epithelium to the retina, or indirectly into the retrobulbar space and then the ONH (optic nerve head).

There is evidence that mechanically blocking of the corneal surface has little effect on drug penetration into the posterior tissues, which suggests that the conjunctival route is the more important for drug delivery.

When a large drop is allowed to flood the interpalpebral space, the fluid could fall under gravity and distend the cul-de-sac. In that case, the drug would have the opportunity to penetrate into the posterior sclera and orbit. The penetration from a drop to the posterior segment is increased by using an alpha adrenergic agonist agent or a beta-blocking agent as the drug carrier.

In the examples below, the following formulations were administered topically to patients:

- pilocarpine : 1 or 2% (w/v);
- brimonidine (Alphagan®): 0.2% (w/v);
- timolol : 0.5% (w/v).
- dexamethasone (Tobradex®): 0.1 % (w/v);
- indomethacin (Indocollyre®): 0.1% (w/v);
- ramipril: 2% (w/v); and
- fluorescein: 10% (w/v).

Unless otherwise indicated, each treated eye received daily, four times per day, of one or several drops of treatment (either one drop of each drug when these drugs where administered separately, or one drop of a composition comprising a mixture of the different drugs to be administered). An OTC scan was performed before treatment and after several months of treatment (in general after one to six months of treatment).
Example 1: DIABETIC RETINOPATHY

Diabetic retinopathy is the leading cause of new blindness in individuals under 65 years of age. Diabetic retinopathy can be classified into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). The clinical features of NPDR include microaneurysms, intraretinal hemorrhages, hard exudates, nerve fiber layer infarcts or cotton wool exudates and intra retinal microvascular abnormalities (IRMA). The clinical picture of PDR includes the features from NPDR in addition to proliferating new vessels on the optic nerve head, retina or iris.

Diabetic macular oedema is a principal cause of visual loss in diabetic patients. Two examination techniques are very useful in evaluating diabetic retinopathy: fluorescein angiography and optical coherence tomography.

Fluorescein angiography is used to detect several of the retinal vascular abnormalities. The dye delineates structural vascular alterations, such as aneurysms or neovascularization, changes in blood flow such as ischemia and vascular occlusion are seen as an interruption of the normal perfusion pattern. Abnormal vascular permeability is seen as a leaking cloud of dye-stained oedema fluid increasing overtime.

Optical coherence tomography (OCT) may be more sensitive in evaluating diabetic macular oedema than slit-lamp examination. In addition, central macular thickness correlates with visual acuity even better than fluorescein leakage.

The response of macular oedema to the administration of one drug such as an anti-VEGF agent or an anti-inflammatory treatment such as topical corticosteroids, non-steroidal anti-inflammatory agents or angiotensin converting enzyme inhibitors, can be documented accurately by OCT imaging.

Diabetic patients were treated with the following drugs given topically: a corticosteroid (dexamethasone (Tobradex®)) and non steroidal anti-inflammatory agent (indomethacin (Indocollyre ©)).

These drugs were given in combination with one or several drug carriers for enhancing the delivery of the drug to the retina: either a cholinergic agent (pilocarpine), or a cholinergic agent (pilocarpine) in combination with a beta-blocking agent (timolol) and an alpha adrenergic agonist agent (brimonidin).

The following study was undertaken on four patients.
Patient H.J. presented with a diabetic retinopathy associated with a macular oedema that was reducing her vision acuity. An OCT scan was performed prior to treatment and the results are shown in Figure 1A. Three months after treatment with a cholinergic agent (pilocarpine 2%), her visual acuity improved, and a OCT scan demonstrated a decrease in macular oedema (as shown in Figure 1B).

Patient F.K. presented with a bilateral decrease of his visual acuity because of a serious macular oedema caused by a diabetic retinopathy. An OCT scan was performed prior to treatment and the results are shown in Figure 2A. Three months after treatment with a cholinergic agent (pilocarpine), both his visual acuity and the OCT scan (shown in Figure 2B) were improved.

Patient Z.A. is a diabetic patient who presented with a diabetic retinopathy. He received topically a composition comprising pilocarpine (1% w/v), ramipril (2% (w/v), dexamethasone (Tobradex®; 0.1 % w/v) and indomethacin (Indocollyre ®; 0.1 % w/v). An OCT exam (shown in Figure 3A) was performed before the patient received the treatment. After six months of treatment, a follow up OCT scan showed that the total macula volume had decreased explaining visual improvement (see Figure 3B).

Patient S.H. presented with a diabetic retinopathy. He received topically: a cholinergic agent (pilocarpine), an alpha adrenergic agonist agent (brimonidin), a beta-blocking agent (timolol), a corticosteroid (dexamethazone) and a non steroidal anti-inflammatoiy agent (indomethacin (Indocollyre ®)). An ocular fundus, a fluoro-angiography and an OCT scan were performed prior to treatment and the results are shown in Figure 4A. Two months later, the visual acuity improved. A follow up OCT (Figure 4B) demonstrated a dramatic reduction of macular oedema and foveal thickening.

Patient J.D. has diabetic retinopathy. During two months, she receives topically, every hour during the day:
- in the left eye, one drop of a composition comprising an angiotensin converting enzyme inhibitor (ramipril; 2% (w/v); a corticosteroid (dexamethazone; 0.1% w/v) and a non steroidal anti-inflammatoiy agent (indomethacin; 0.1% w/v);and
- in the right eye, one drop of a composition comprising, in addition to the drugs administered to the left eye, a cholinergic agent (pilocarpine, 1% w/v).
After two months of treatment, her visual acuity is strongly improved in both eyes.

During the next two months, she then receives topically 4 times per day, the treatment as set forth above. After two months of treatment, her visual acuity is more strongly improved in the right eye than in the left eye. This suggests that when drugs for treating the eye are used in conjunction with a cholinergic agent and in particular with pilocarpine, one can lower the frequency of drug administration.

Example 2: RETINAL VEIN OCCLUSION

Central retinal vein occlusion (CRVO) is a common retinal vascular condition usually affecting people older than 50 years. Patients typically experience visual loss and present with dilated tortuous retinal veins and scattered intra-retinal hemorrhage in all four quadrants, cotton wool spots, optic disc swelling, and macular oedema can occur. Intra veinous fluorescein angiography shows areas of blocked fluorescence from the intra-retinal blood, staining of the vessel walls, a delayed arteriovenous phase, and nonperfused areas, and perifoveal leakage.

Three patients, instead of injection, received topically a corticosteroid (dexamethasone (Tobradex®)) and a non steroidal anti-inflammatory agent (indomethacin (Indocollyre ®)), associated with one or severl delivery drug enhancers: either a cholinergic agent (pilocarpine), or a cholinergic agent (pilocarpine) in combination with a beta-blocking agent (timolol) and an alpha adrenergic agonist agent (brimonidin).

Patient A.M. presented with a retinal central vein occlusion associated with a dramatic decrease of his visual acuity. He received topically a cholinergic agent (pilocarpine). Prior to receiving the treatment, an OCT scan was taken, which is shown in Figure 5A. After three months of treatment, his visual acuity improved. In addition, an OCT scan (shown in Figure 5B) demonstrated a decrease in macular oedema.

Patient R.S. presented with a central retinal vein occlusion in the right eye. He received topically a composition comprising pilocarpine (1% w/v), ramipril (2% (w/v), dexamethasone (Tobradex®; 0.1 % w/v) and indomethacin (Indocollyre ®; 0.1% w/v). Prior to receiving the treatment, an OCT scan (shown in Figure 6A) was taken. After three months of treatment, his visual acuity increased. A follow up OCT scan (shown in Figure 6B) demonstrated reduction in foveal thickening.
Patient B.R.N. presented with a central vein occlusion. He received topically: a cholinergic agent (pilocarpine 1%), an alpha adrenergic agonist agent (brimonidin), a beta-blocking agent (timolol), a corticosteroid (dexamethasone) and a non steroidal anti-inflammatory agent (indomethacin (Indoclyre©)). Prior to receiving the treatment, an OCT scan was taken, which is shown in Figure 7A. After three months of treatment, the visual acuity improved. A follow up OCT (Figure 7B) demonstrated a reduction of macular oedema and foveal thickening.

Example 3: age-related macular degeneration (ARMD)

Age related macular degeneration (ARMD) is the leading cause of severe vision loss among the elderly. The cause of ARMD remains elusive and complex, with both environmental and genetic contributions. ARMD has two distinct forms known as "dry" or non-neovascular ARMD and "wet", or neovascular ARMD. Most the severe vision loss in ARMD is caused by neovascular ARMD.

The best proven therapies for ARMD treat the neovascular form of the disease and include photocoagulation triamcinolone intraocular injection and anti-VEGF intraocular injection (Avastin®; Lucentis®; Macugen®).

The structural information provided by OCT is becoming a valuable diagnostic adjunct to fluorescein angiography. OCT is a valuable tool for probing the effects of these treatments.

Instead of an intraocular injection of drugs, two patients received topically a corticosteroid (dexamethasone (Tobradex®)) and a non steroidal anti-inflammatory agent (indomethacin (Indoclyre®)), associated with one or several delivery drug enhancers: either a cholinergic agent (pilocarpine), or a cholinergic agent (pilocarpine) in combination with a beta-blocking agent (timolol) and an alpha adrenergic agonist agent (brimonidin).

Patient G.N presented with a reduction of visual acuity of the left eye due to a macular degeneration. Prior to receiving the treatment, an OCT scan was taken, which is shown in Figure 8A. This OCT scan revealed a macular thickening associated with this pathology. The patient was treated topically with a cholinergic agent (pilocarpine). After three months later, both his fusal acuity and the OCT scan were improved; a decrease in macular thickening can be seen on the OTC scan shown in Figure 8B).
Patient H.M. presented with a history of decreased vision in the right eye due to ARMD. This decreased vision was related to a choroid occult new vessel. An OCT exam (shown in Figure 9A) revealed a macular thickening and a pigmentary epithelium detachment. He was treated with a composition comprising pilocarpine (1% w/v), ramipril (2% w/v), dexamethasone (Tobradex®; 0.1% w/v) and indomethacin (Indocollyre®; 0.1% w/v). After one month of treatment, the patient's vision improved. A follow up OCT (shown in Figure 9B) scan demonstrated a complete regression of macular thickening and recovery of foveal contour.

Patient G.N. presented with a history of decreased vision in the left eye. As mentioned above, he had previously been treated with pilocarpine, which improved his visual acuity but after few months, his vision decreased again. A fluorangiographic image showed choroid occult new vessel (C.N.V.). Prior to receiving a new treatment, an OCT scan was taken, which is shown in Figure 10A. The patient was treated with: a cholinergic agent (pilocarpine 1%), an alpha adrenergic agonist agent (brimonidin), a beta-blocking agent (timolol), a corticosteroid (dexamethazone) and a non steroidal anti-inflammatory agent (indomethacin (Indocollyre®)). Three months later, vision improved; a follow up OCT scan (as shown in Figure 10B) demonstrated a partial regression of macular thickening and recovery of foveal contour.

**Conclusion**

Cholinergic agents and especially pilocarpine are useful as drug delivery agents. They enable delivery, to the posterior segment of the eye, of drugs for treating the eye (for example anti-inflammatory agents, corticoids, angiotensin converting enzyme inhibitors, neuroprotective agents, immunosuppressive agents) that have been administered topically in one or both eyes of a patient.

They are especially useful for the treatment of chorioretinal vascular diseases, for example diabetic retinopathy, retinal vein occlusion and exsudative macular degeneration).

Topical administration of a cholinergic agent, and in particular of pilocarpine, in conjunction with a second drug to a patient in need thereof allows to lower the concentration of the second drug which is administered and/or to lower the frequency of administration of the treatment.
In addition, cholinergic agents, especially pilocarpine, act in synergy with other drug delivery agents, for example alpha adrenergic agonist agents and/or beta-blocking agents.

While the invention has been described in terms of various preferred embodiments, the skilled artisan will appreciate that various modifications, substitutions, omissions and changes may be made without departing from the scope thereof. Accordingly, it is intended that the scope of the present invention be limited by the scope of the following claims, including equivalents thereof.
What is Claimed is:

1. A method for delivering drugs to the posterior and anterior segments of the eyes comprising: contacting the surface of the eye with an effective amount of a drug for treating eye disorders and/or diseases of the eye and a physiologically acceptable amount at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof.

2. The method according to Claim 1, wherein the surface of the eye is further contacted with a physiologically acceptable amount of at least another drug delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.

3. The method according to Claim 1 or 2, wherein the drugs are delivered to the posterior segment of the eye.

4. The method according to any of Claims 1 to 3, wherein said drug for treating eye disorders and/or diseases of the eye and the drug delivery agent(s) are delivered to the chorio-retina and optic nerve head of the eyes.

5. The method according to any one of Claims 1 to 4, wherein the drug delivery agent(s) or at least one of the drug delivery agents contact(s) the eye prior to said effective amount of said drug for treating eye disorders and/or diseases of the eye.

6. The method according to any one of Claims 1 to 5, wherein the cholinergic agent(s) are selected from the group consisting of pilocarpine, aceclidine, carbachol, diflupyl, mintacol, phospholine iodide and mixtures thereof.

7. The method according to any one of Claims 1 to 6, wherein the alpha adrenergic agonist agent(s), when present, is(are) selected from the group of
neosynephrine, beta-methylepinephrine, brimonidine, apraclonidine, clonidine, guanfacine, guanabenz, tizandine and mixtures thereof.

8. The method according to any one of Claims 1 to 7, wherein the beta-blocking agent(s), when present, is(are) selected from the group of timolol, sotalol, propanolol, nadolol, metoprolol, labetalol, esmolol, carteolol, betaxolol, bisoprolol, acebutolol, levobunolol, metipranolol and mixtures thereof.

9. The method according to any one of Claims 1 to 8, wherein the drug for treating eye disorders and/or diseases of the eye is selected from the group comprising neuroprotective agents, growth factor vasoactive agents, calcium antagonists, angiotensin converting enzyme inhibitors, nitrates or nitric oxide generators, beta adrenergic agonists, antioxidants and radical scavengers, dopaminergic and serotonergic agents, monoamine oxidase inhibitors, anti-inflammatory agents, growth factors, neuropeptides, anti-inflammatory mediators, anti-infective agents, anti-ischemic association agents, non-steroidal anti-inflammatory agents, anti-growth factor agents, immunosuppressive agents and mixtures thereof.

10. The method according to Claim 9, wherein said anti-growth factor agents are selected from the group consisting of anti-platelet derived growth factor (anti-PDGF) agents, anti-fibroblast growth factor (anti-FGF) agents, anti-placenta growth factor agents, anti-insulin like growth factor (anti-IGF) agents and anti-vascular endothelial growth factor (anti-VEGF) agents and mixtures thereof.

11. The method according to Claim 9 or 10, wherein said anti-VEGF agents are selected from the group comprising bevacizumab (Avastin®), ranibizumab (lucentis®), pegaptanib (Macugen®) and mixtures thereof.

12. The method according to any one of Claims 9 to 10, wherein said anti-inflammatory agents are selected from the group comprising non-steroidal anti-inflammatory agents, corticosteroids, and mixtures thereof.
13. The method according to any one of Claims 9 to 10, wherein said anti-infective agents are selected from the group comprising antibiotics, antifungal agents, antiviral agents and mixtures thereof.

14. The method according to any one of Claims 9 to 13, wherein the immunosuppressive agent(s) are selected from the group consisting of (i) general immunosuppressive agents, which include azathioprin, cyclophosphamide, methotrexate, cyclosporine, AFK 506, rapamycin, (ii) specific immunosuppressive agents, which include monoclonal antibodies directed against T-lymphocytes or cytokines, and (iii) mixtures thereof.

15. A method of treating a eye disorders and/or diseases of the eye by delivering drugs to the chorio-retina and optic nerve head of an eye comprising administering to a person or an animal in need of such treatment an effective amount of a drug for treatment of the chorio-retina and optic nerve head and a physiologically acceptable amount of at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof.

16. The method according to Claim 15, comprising further administering to said person or animal a physiologically acceptable amount of at least one drug delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.

17. The method according to any one of Claims 1 to 16, wherein said disease of the eye is selected from the group comprising or consisting of glaucomatous neuropathy, diabetic retinopathy, retinal vein occlusion, in particular central retinal vein occlusion or branch retinal vein occlusion, macular choroidal neovascularization, uveitis and especially anterior and/or posterior uveitis, optic nerve head inflammation, central arterial occlusion, central serous chorio retinopathy (CSCR), visual degradation (near and far visual acuity;
visual filed), presbyopia, myopia, dry and exudative macular degeneration, age related macular degeneration or high myopia macular degeneration, papillitis, endophthalmitis and pigmentosa retinopathy.

18. The method according to Claim 17, wherein said macular choroidal neovascularization is due to age related macular degeneration or high myopia.

19. The method according to any one of Claims 1 to 18, for improving vision of eyes, and in particular, for improving distance vision and/or near vision.

20. The method according to any one of Claims 1 to 19, to perform topic anaesthesia as a prelude to surgery.

21. The method according to any one of Claims 1 to 20, wherein the drug for treatment of eye disorders and/or diseases of the eye is administered topically.

22. A composition comprising, consisting essentially or consisting of:
   a) at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, in an ophthalmologically acceptable carrier, and
   b) a drug for treating eye disorders and/or diseases of the eye, and
   c) optionally, at least another drug delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.

23. The composition according to Claim 22, wherein said drug for treating eye disorders and/or diseases of the eye is selected from the group consisting of neuroprotective agents, growth factor vasoactive agents, calcium antagonists, angiotensin converting enzyme inhibitors, nitrates or nitric oxide generators, beta adrenergic agonists, antioxidants and radical scavengers,
dopaminergic and serotoninergic agents, monoamine oxidase inhibitors, anti-inflammatory agents, growth factors, neuropeptides, anti-inflammatory mediators, anti-infective agents, anti-ischemic association agents, non-steroidal anti-inflammatory agents, corticosteroids, anti-growth factor agents, immunosuppressive agents and mixtures thereof, and is preferably selected from the group consisting of angiotensin converting enzyme inhibitors, non-steroidal anti-inflammatory agents, anti-growth factor agents, corticosteroids, immunosuppressive agents and mixtures thereof.

24. The composition according to Claim 22 or 23, wherein
   a) the adrenergic agent is an alpha adrenergic agonist agent, a derivative or derivatives thereof or mixtures thereof, and
   b) the drug for treating eye disorders and/or diseases of the eye is an angiotensin converting enzyme inhibitor and/or a non-steroidal inflammatory agent (anti-ischemic complex).

25. The composition according to any one of Claims 22 to 24, for the topical treatment of eye disorders and/or diseases of the eye selected from the group of glaucomatous neuropathy, central serous chorio retinopathy, high myopia chorio-retinopathy, pigmentosa retinopathy, diabetic retinopathy, retinal vein occlusion, in particular central retinal vein occlusion or branch retinal vein occlusion, visual degradation (near and far visual acuity; visual filed), presbyopia, myopia, age related vision degradation, central retinal artery occlusion, dry and exsudative macular degeneration (age related macular degeneration, high myopia), uveitis, papillitis, endophthalmitis and macular oedema.

26. The composition according to Claim 25, wherein said dry or exsudative macular degeneration is age related macular degeneration or high myopia macular degeneration.

27. A composition for use in the topical treatment of diabetic retinopathy, macular oedema, central retinal vein occlusion, branch retinal vein occlusion, exsudative macular degeneration (age related macular degeneration, high
myopia macular degeneration), visual degradation (near and far visual acuity; visual field), presbyopia, myopia, uveitis, papillitis, and endophthalmitis comprising, consisting of or consisting essentially of

a) at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, and

b) an anti-vascular endothelial growth factor agent (anti-VEGF agents), a corticosteroid, a non steroidal anti-inflammatory agent, an angiotensin converting enzyme inhibitor, an immunosuppressive agent or mixtures thereof and

c) optionally, at least another drug delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.

28. A composition for use in the topical treatment of diabetic retinopathy macular oedema, exudative macular degeneration, central retinal vein occlusion or branch retinal vein occlusion, uveitis, papillitis, or endophtalmitis comprising, consisting or consisting essentially of

a) at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, and

b) angiotensin converting enzyme inhibitor(s) and/or non steroidal anti-inflammatory agent(s) and/or corticosteroid(s), or mixtures thereof, and

c) optionally, at least another drug delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.

29. A composition for use in the topical treatment of age related vision degradation and presbyopia comprising, consisting or consisting essentially of
a) at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, and

b) an angiotensin converting enzyme inhibitor and/or a non-steroidal anti-inflammatory agent and/or an anti vascular endothelial growth factor agent selected from the group comprising bevacizumab (Avastin®), ranibizumab (lucentis®), pegaptanib (Macugen®) and mixtures thereof and

c) optionally, at least another drug delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, and mixtures thereof.

30. The composition according to any of claims 22 to Claim 29, wherein the cholinergic agent(s) is(are) selected from the group consisting of pilocarpine, aceclidine, carbachol, diflupyl, mintacol, phospholine iodide and mixtures thereof.

31. A composition according to any one of Claims 22 to 30, wherein said agents and/or factors are delivered to the posterior segment of the eye.

32. A method for increasing the transfer of a drug into the eye orbit, the posterior sclera and then into chorio-retina and optic nerve head to treat disorders and/or diseases of the eye comprising contacting the surface of an eye or both eyes with a physiologically acceptable amount of at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof, and a pharmaceutically acceptable amount of a second drug that treats disorders and/or diseases of the eyes.

33. The method according to claim 32, which further comprises contacting the surface of an eye or both eyes with a physiologically acceptable amount of at least a drug delivery agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.
34. The method according to claim 32 or 33, wherein the cholinergic agent(s) is(are) selected from the group consisting of pilocarpine, aceclidine, carbachol, diflupyl, mintacol, phospholine iodide and mixtures thereof.

35. A drug delivery agent for use for the transfer, to the posterior segment of one or both eye(s), of at least one second drug that treats disorders and/or diseases of the eyes, to treat diseases and/or disorders of the eye, wherein said delivery agent is selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof.

36. The drug delivery agent according to Claim 35, wherein said delivery agent and said second drug are delivered to the chorio-retina and optic nerve head.

37. The drug delivery agent according to Claim 35 or 36, wherein the cholinergic agent is selected from the group consisting of consisting of pilocarpine, aceclidine, carbachol, diflupyl, mintacol, phospholine iodide and mixtures thereof.

38. The drug delivery agent according to any one of Claims 35 to 37, wherein the drug for treating eye disorders and/or diseases of the eye is selected from the group comprising neuroprotective agents, growth factor vasoactive agents, calcium antagonists, angiotensin converting enzyme inhibitors, nitric oxide generators, agents for the treatment of vascular disease, antioxidants, radical scavengers, anti-inflammatory agents, anti-infective agents, anti-growth factor agents, immunosuppressive agent and mixtures thereof.

39. The drug delivery agent according to Claim 38, wherein the anti-growth factor agents are selected from the group consisting of anti-platelet derived growth factor (anti-PDGF) agents, anti-fibroblast growth factor (anti-FGF) agents, anti-placenta growth factor agents, anti-insulin like growth factor agents and anti-vascular endothelial growth factor (anti-VEGF) agents and mixtures thereof.
40. The drug delivery agent according to Claim 38 or 39, wherein the anti-VEGF agent is selected from the group consisting of bevacizumab (Avastin®), ranibizumab (Lucentis®), pegaptanib (Macugen®) and mixtures thereof.

41. The drug delivery agent according to any one of Claims 38 to 40, wherein the anti-inflammatory agents are selected from the group comprising corticosteroids, non-steroidal inflammatory agents, and mixtures thereof.

42. The drug delivery agent according to any one of Claims 38 to 41, wherein the anti-infective agents are selected from the group comprising antibiotics, antifungal agents, antiviral agents and mixtures thereof.

43. The drug delivery agent according to any one of Claim 38 to 42, wherein the immunosuppressive agent is selected from the group consisting of (i) general immunosuppressive agents, which include azathioprin, cyclophosphamide, methotrexate, cyclosporine AFK 506, rapamycin, (ii) specific immunosuppressive agents, which include monoclonal antibodies directed against T-lymphocytes or cytokines, and (iii) mixtures thereof.

44. A kit comprising, consisting of or consisting essentially of
   a) at least one drug delivery agent selected from the group consisting of cholinergic agents, derivatives thereof and mixtures thereof; and
   b) a drug for treating eye disorders and/or diseases of the eye, and;
   c) optionally, at least another adrenergic agent which is an adrenergic agent selected from the group consisting of alpha adrenergic agonist agents, derivatives of the alpha adrenergic agonist agents, beta-blocking agents, derivatives of the beta-blocking agents and mixtures thereof.
45. The kit according to Claim 44, wherein the cholinergic agent is selected from the group consisting of pilocarpine, aceclidine, carbachol, diflupyl, mintacol, phospholine iodide and mixtures thereof.

46. The kit according to Claim 44 or 45, wherein said drug for treating eye disorders and/or diseases of the eye is selected from the group comprising neuroprotective agents, growth factor vasoactive agents, calcium antagonists, angiotensin converting enzyme inhibitors, nitrates or nitric oxide generators, beta adrenergic agonists, antioxidants and radical scavengers, dopaminergic and serotonergic agents, monoamine oxidase inhibitors, anti-inflammatory agents, growth factors, neuropeptides, anti-inflammatory mediators, anti-infective agents, anti-ischemic association agents, non-steroidal anti-inflammatory agents, anti-growth factor agents, immunosuppressive agents and mixtures thereof.

47. A kit according to any one of claims 44 to 45 for use for the transfer, to the posterior segment of one or both eye(s), of at least one second drug that treats disorders and/or diseases of the eyes, to treat disorders and/or diseases of the eye.

48. A method for treating eye disorders and/or diseases of the eye comprising: contacting the surface of the eye with an effective amount of a cholinergic agents, in particular with pilocarpine, or with a derivative thereof or mixtures thereof, wherein the eye disorders and/or diseases is(are) selected from the group consisting of macular edema, age-related macular degeneration, choroidal new vessels (in particular those associated with high myopia or macular degeneration, in particular age-related macular degeneration), exsudative macular degeneration (in particular the one that is associated with high myopia or macular degeneration, in particular age-related macular degeneration), retinal vein occlusion, in particular central retinal vein occlusion or branch retinal vein occlusion, retinal arterial occlusions, in particular central retinal artery occlusion, central serous chorio retinopathy (CSCR), diabetic retinopathy, high myopia chorio-retinopathy, pigmentosa retinopathy, proliferative vitreoretinopathy, myopia (in particular high
myopia), presbyopia, uveitis (in particular anterior uveitis or posterior uveitis), retinitis, papillitis, endophthalmitis, optic nerve head inflammation, eye infections or inflammation, visual degradation (of near and/or far visual acuity or of visual field), in particular age related visual degradation (of near and/or far visual acuity or of visual field), and post-operative inflammation.
FIGURE 1A
**FIGURE 1B**
FIGURE 2A
**FIGURE 2B**
FIGURE 3A
FIGURE 4A
FIGURE 4B
FIGURE 5A
**FIGURE 5B**

### Table: Parameters and Measurements

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- **OD**: 1, 2, 3, 4, 5, 6
- **OS**: 1, 2, 3, 4, 5, 6

![Diagram](https://example.com/diagram.png)
FIGURE 6A
FIGURE 6B
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**OS Scans used:** 1, 2, 3, 4, 5, 6

**FIGURE 7A**
FIGURE 7B
FIGURE 8A
**FIGURE 8B**

OCT Image

Fundus Image

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Thickness Chart

Microns

A-scan
FIGURE 9A
FIGURE 10A
FIGURE 10B
## A. CLASSIFICATION OF SUBJECT MATTER

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- **A** document defining the general state of the art which is not considered to be of particular relevance
- **E** earlier document but published on or after the international filing date
- **L** document which may throw doubts on priorly claimed invention(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- **O** document referring to an oral disclosure or exhibition or other means
- **P** document published prior to the international filing date but later than the priority date claimed

### Further documents are listed in the continuation of Box C

### See patent family annex

- **X** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- **Y** document of particular relevance the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- **Y** document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents such combination being obvious to a person skilled in the art
- **A** document member of the same patent family

### Date of the actual completion of the international search

29 March 2010

### Date of mailing of the international search report

08/04/2010

### Name and mailing address of the ISA

European Patent Office
P B 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040,
Fax (+31-70) 340-3016

**Loher, Floriana**
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<td>ZADOK DAVID ET AL: &quot;Combined timolol and pilocarpine vs pilocarpine alone and timolol alone in the treatment of glaucoma&quot; AMERICAN JOURNAL OF OPHTHALMOLOGY, OPHTHALMIC PUBL, CHICAGO, IL, US, vol. 117, no. 6, 1 June 1994 (1994-06-01), pages 728-731, XP009131456 ISSN: 0002-9394 page 730, right-hand column, paragraph 2; table 2</td>
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- page 1, paragraph 1
- page 9, paragraph 2
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