# APPARATUS AND FORMULATIONS FOR SUPRACHOROIDAL DRUG DELIVERY

## Cross-Reference to Related Application

**[0001]** The priority of provisional US application Serial No. 60/776,903, filed February 22, 2006 is claimed pursuant to 35 USC 119(e). The provisional application is incorporated herein by reference in its entirety.

## Field of the Invention

**[0002]** The invention relates to the field of drug delivery into the eye.

## Background of Invention

**[0003]** The eye is a complex organ with a variety of specialized tissues that provide the optical and neurological processes for vision. Accessing the eye for medical treatment is hindered by the small size and delicate nature of the tissues. The posterior region of the eye, including the retina, macula and optic nerve, is especially difficult to access due to the recessed position of the eye within the orbital cavity. In addition, topical eye drops penetrate poorly into the posterior region, further restricting treatment options.

**[0004]** The suprachoroidal space is a potential space in the eye that is located between the choroid, which is the inner vascular tunic, and the sclera, the outer layer of the eye. The suprachoroidal space extends from the anterior portion of the eye near the ciliary body to the posterior end of the eye near the optic nerve. Normally the suprachoroidal space is not evident due to the close apposition of the choroid to the sclera from the intraocular pressure of the eye. Since there is no substantial attachment of the choroid to the sclera, the tissues separate to form the suprachoroidal space when fluid accumulation or other conditions occur. The suprachoroidal space provides a potential route of access from the anterior region of the eye to treat the posterior region.

**[0005]** The present invention is directed to drug formulations for administration to the suprachoroidal space and an apparatus to deliver drugs and other substances in minimally invasive fashion to the suprachoroidal space.

## Summary

**[0006]** Drug formulations are provided characterized by a zero shear viscosity of at least 300,000 mPas. A subclass of the drug formulations is further characterized by a viscosity of not more than about 400 mPas at 1000 $s^{-1}$ shear rate.

**[0007]** For injection into the suprachoroidal space of an eye comprising a biologically active substance and a thixotropic polymeric excipient that acts as a gel-like material to spread after injection and uniformly distribute and localize the drug in a region of the suprachoroidal space. In one embodiment, gel-like material crosslinks after injection into the suprachoroidal space. The biologically active substance may comprise microparticles or microspheres. The polymeric excipient may comprise hyaluronic acid, chondroitin sulfate, gelatin, polyhydroxyethylmethacrylate, dermatin sulfate, polyethylene oxide, polyethylene glycol, polypropylene oxide, polypropylene glycol, alginate, starch derivatives, a water soluble chitin derivative, a water soluble cellulose derivative or polyvinylpyrollidone.

**[0008]** In another embodiment, a drug formulation is provided for delivery to the suprachoroidal space of an eye comprising a biologically active substance and microspheres with an outer diameter in the range of about 1 to 33 microns. The microparticles or microspheres additionally may comprise a controlled release coating and/or a tissue affinity surface.

**[0009]** The biologically active substance preferably comprises an antibiotic, a steroid, a non-steroidal anti-inflammatory agent, a neuroprotectant, an anti-VEGF agent, or a neovascularization suppressant.

**[00010]** Devices are also provided for minimally invasive delivery of a drug formulation into the suprachoroidal space of the eye comprising a needle having a leading tip shaped to allow passage through scleral tissues without damage to the underlying choroidal tissues, and a sensor to guide placement of the tip to deliver the formulation adjacent to or within the suprachoroidal space.

**[00011]** The sensor may provide an image of the scleral tissues. The sensor preferably responds to ultrasound, light, or differential pressure.

**[00012]** In another embodiment, devices are provided for minimally invasive delivery of a drug formulation into the suprachoroidal space of the eye comprising a needle having a leading tip shaped to allow passage through scleral tissues, and an inner tip that provides an inward distending action to the choroid upon contacting the choroid to prevent trauma thereto.

**[00013]** Methods are provided for administering drugs to the eye comprising placing a formulation comprising a biologically active substance and a polymer excipient in the suprachoroidal space such that the excipient gels after delivery to localize said biologically active substance. The formulation may be placed in a

posterior or anterior region of the suprachoroidal space.

**[00014]** In another embodiment, method are provided for administering drugs to a posterior region of the eye comprising placing a formulation comprising a biologically active substance comprising microspheres or microparticles with an outer diameter in the range of about 1 to 33 microns in an anterior region of the suprachoroidal space such that the microspheres or microparticles subsequently migrate to the posterior region. The formulation preferably comprises a polymer excipient to uniformly disperse the microparticles or microspheres in the suprachoroidal space.

**[00015]** In another embodiment, a method is provided of administering drugs in the suprachoroidal space of the eye comprising the steps of placing a needle in scleral tissues toward the suprachoroidal space at a depth of at least half of the scleral thickness, and injecting a drug formulation through the needle into the sclera such that the formulation dissects the scleral tissues adjacent to the suprachoroidal space and enters the suprachoroidal space.

**[00016]** In the methods disclosed herein, the formulation preferably comprises a thixotropic polymer.

## Brief Description of the Drawings

**[00017]** Fig. 1 is an ultrasound image of a portion of the eye after injection by needle into the sclera of a hyaluronic acid surgical viscoelastic material according to Example 9.

**[00018]** Fig. 2 is an ultrasonic image of a portion of the eye during injection by needle into the sclera of a 1:1 by volume mixture of the viscoelastic material and 1% solution of polystyrene microspheres according to Example 9.

**[00019]** Figs. 3a and 3b are diagrams of an embodiment of a delivery device according to the invention having a distending and cutting or ablative tip.

**[00020]** Fig. 4 is a diagram showing the location of a delivery device according to the invention relative to the target sclera, suprachoroidal space and choroid.

**[00021]** Fig. 5 is a diagram of an embodiment of a delivery device according to the invention having a stop plate to set the depth and angle of penetration of the needle into the eye.

**[00022]** Fig. 6 is a diagram of an embodiment of a delivery device according to the invention that accommodates a microendoscope and camera to monitor the location of the cannula tip during surgery.

[00023] Fig. 7 is a diagram of an embodiment of a delivery device having a lumen for delivery of drugs through a catheter into the eye and a fiber optic line connected to an illumination source to illuminate the tip if the cannula.

[00024] Fig. 8 is a diagram of an embodiment of the use of a device according to the invention in conjunction with a high resolution imaging device to monitor the location of the tip of the cannula.

## Description of the Preferred Embodiments

[00025] The present invention comprises drug formulations, devices and related methods to access the suprachoroidal space of an eye for the purpose of delivering drugs to treat the eye. Specifically, the invention relates to drug formulations designed for suprachoroidal space administration to treat the eye, including specific regions of the eye by localization of the delivered drug. The invention also relates to the design and methods of use for a minimally invasive device to inject drug formulations and drug containing materials directly into the suprachoroidal space through a small needle.

[00026] A biologically active substance or material is a drug or other substance that affects living organisms or biological processes, including use in the diagnosis, cure, mitigation, treatment, or prevention of disease or use to affect the structure or any function of the body. A drug formulation contains a biologically active substance.

[00027] As used herein, the anterior region of the eye is that region of the eye that is generally readily accessible from the exposed front surface of the eye in its socket. The posterior region of the eye is generally the remaining region of the eye that is primarily surgically accessed through a surface of the eye that is unexposed, thus often requiring temporary retraction of the eye to gain access to that surface.

[00028] Formulations:

[00029] The drug formulations of the invention provide compatibility with the suprachoroidal space environment and may be formulated to control the distribution of the biologically active substance by migration of the formulation as well as provide for sustained release over time. The drug formulation comprises one or more biologically active substances formulated with physiologically compatible excipients that are administered, typically by injection, into the suprachoroidal space of an eye. Suitable biologically active substances include antibiotics to treat infection, steroids and non-steroidal anti-inflammatory compounds to treat inflammation and edema,

neuroprotectant agents such as calcium channel blockers to treat the optic nerve and retinal agents such as anti-VEGF compounds or neo-vascular suppressants to treat macular degeneration.

**[00030]** Formulations for localized treatment:

**[00031]** For treatment of a localized region of the eye, for example, to treat a macular lesion, the posterior retina, or the optic nerve, the drug may be prepared in a formulation to limit migration after delivery and delivered to the region of the lesion. While not intending to be bound by a particular theory, we observe that drug microparticles typically travel toward the posterior region of the suprachoroidal space under physiological conditions, presumably due to uveal-scleral fluid flow within the space. Such drug microparticles may be fabricated with sufficient size and optionally with tissue surface affinity to limit drug migration. Tissue surface affinity may be modified by the addition of polymeric or lipid surface coatings to the microparticles, or by the addition of chemical or biological moieties to the microparticle surface. Tissue affinity is thereby obtained from surface charge, hydrophobicity, or biological targeting agents such as antibodies or integrins that may be incorporated to the surface of the microparticles to provide a binding property with the tissues to limit drug migration. Alternatively or in combination, the drug may be formulated with one or more polymeric excipients to limit drug migration. A polymeric excipient may be selected and formulated to act as a viscous gel-like material *in-situ* and thereby spread into a region of the suprachoroidal space and uniformly distribute and retain the drug. The polymer excipient may be selected and formulated to provide the appropriate viscosity, flow and dissolution properties. For example, carboxymethylcellulose is a weakly thixotropic water soluble polymer that may be formulated to an appropriate viscosity at zero shear rate to form a gel-like material in the suprachoroidal space. The thixotropic effect of the polymer may be enhanced by appropriate chemical modification to the polymer to increase associative properties such as the addition of hydrophobic moieties, the selection of higher molecular weight polymer or by formulation with appropriate surfactants. Preferred is the use of highly associative polymeric excipients with strong thixotropic properties such as hyaluronic acid to maximize the localization and drug retaining properties of the drug formulation while allowing the formulation to be injected through a small gauge needle. The dissolution properties of the drug formulation may be adjusted by tailoring of the water solubility, molecular weight, and concentration of the polymeric excipient in the range of

appropriate thixotropic properties to allow both delivery through a small gauge needle and localization in the suprachoroidal space. The polymeric excipient may be formulated to increase in viscosity or to cross-link after delivery to further limit migration or dissolution of the material and incorporated drug. For example, a highly thixotropic drug formulation will have a low viscosity during injection through a small gauge needle, but dramatically increases in effective viscosity once in the suprachoroidal space at zero shear conditions. Hyaluronic acid, a strongly thixotropic natural polymer, when formulated at concentrations of 1 to 2 weight percent demonstrates a viscosity of approximately 300,000 to 7,000,000 mPas at zero shear and viscosity of 150 to 400 mPas at a shear rate of 1000 $s^{-1}$, typical of injection though a small gauge needle, with the exact viscosity depending of the molecular weight. Chemical methods to increase the molecular weight or degree of crosslinking of the polymer excipient may also be used to increase localization of the drug formulation in-situ, for example the formulation of hyaluronic acid with bisepoxide or divinylsulfone crosslinking agents. The environment in the suprachoroidal space may also be used to initiate an increase in viscosity or cross-linking of the polymer excipient, for example from the physiologic temperature, pH or ions associated with the suprachoroidal space. The gel-like material may also be formulated with surface charge, hydrophobicity or specific tissue affinity to limit migration within the suprachoroidal space.

**[00032]** Water soluble polymers that are physiologically compatible are suitable for use as polymeric excipients according to the invention include synthetic polymers such as polyvinylalcohol, polyvinylpyrollidone, polyethylene glycol, polyethylene oxide, polyhydroxyethylmethacrylate, polypropylene glycol and propylene oxide, and biological polymers such as cellulose derivatives, chitin derivatives, alginate, gelatin, starch derivatives, hyaluronic acid, chondroiten sulfate, dermatin sulfate, and other glycosoaminoglycans, and mixtures or copolymers of such polymers. The polymeric excipient is selected to allow dissolution over time, with the rate controlled by the concentration, molecular weight, water solubility, crosslinking, enzyme lability and tissue adhesive properties of the polymer. Especially advantageous are polymer excipients that confer the formulation strong thixotropic properties to enable the drug formulation to exhibit a low viscosity at high shear rates typical of delivery through a small gauge needle to facilitate administration, but exhibit a high viscosity at zero shear to localize the drug *in-situ*.

**[00033]** To treat an anterior region of the eye, a polymeric excipient to limit drug migration may be combined with a drug and injected into the desired anterior region of the suprachoroidal space.

**[00034]** One method for treating the posterior region of the eye comprises administration of a drug formulation with localizing properties directly to the posterior region of the suprachoroidal space. Drug formulations may be delivered to the posterior region of the suprachoroidal space by using a flexible microcannula placed in an anterior region of the suprachoroidal space with subsequent advancement of the distal tip to the posterior region prior to delivery of the drug and a localizing excipient. Similarly, a flexible microcannula may be advanced to the center of a desired treatment area such as a macular lesion prior to delivery of a drug formulation with properties to localize the administered drug.

**[00035]** Treatment of a localized region of the eye, especially the posterior region, is facilitated by the use of drug preparations of the present invention in combination with administration devices to deliver the preparation locally to various regions of the suprachoroidal space with a flexible device as described in US patent application 60/566,776 by the common inventors, incorporated by reference herein in its entirety.

**[00036]** Formulations for migration to a posterior region:

**[00037]** For treatment of the posterior region of the eye, for example, to treat the entire macula, choroid or the optic nerve, the drug may be prepared in a form to allow migration after delivery and delivered to an anterior region of the suprachoroidal space. The drug may be formulated in soluble form, with a rapid dissoluting polymeric excipient or as small microparticles or microspheres to allow drug migration after administration. If a polymeric excipient is used, a low viscosity, rapidly absorbed formulation may be selected to distribute the drug uniformly in the region of administration to minimize areas of overly high drug concentration, and subsequently dissolution of the excipient to allow drug migration to the posterior region of the suprachoroidal space. Of particular utility is the use of such a polymeric excipient in combination with drug microparticles or microspheres. Such use of drug migration is advantageous as the drug may be injected into an anterior region of the eye easily accessible by the physician, and used to treat a posterior region distant from the injection site such as, the posterior choroid and macula. Preferred microparticles or microspheres are those with an outer diameter in the range of about 1 to 33

microns.

**[00038]** Sustained release:

**[00039]** The use of drug microparticles, one or more polymeric excipients or a combination of both, may also be applied to confer sustained release properties to the drug formulation. The drug release rate from the microparticles may be tailored by adjusting drug solubility or application of a controlled release coating. The polymeric excipient may also provide sustained release from incorporated drugs. The polymeric excipient may, for example, be selected to limit drug diffusion or provide drug affinity to slow drug release. The dissolution rate of the polymeric excipient may also be adjusted to control the kinetics of its effect on sustained release properties.

**[00040]** Delivery devices:

**[00041]** A device for minimally invasive delivery of drugs to the suprachoroidal space may comprise a needle for injection of drugs or drug containing materials directly to the suprachoroidal space. The device may also comprise elements to advance the needle through the conjunctiva and sclera tissues to or just adjacent to the suprachoroidal space without perforation or trauma to the inner choroid layer. The position of the leading tip of the delivery device may be confirmed by non-invasive imaging such as ultrasound or optical coherence tomography, external depth markers or stops on the tissue-contacting portion of the device, depth or location sensors incorporated into the device or a combination of such sensors. For example, the delivery device may incorporate a sensor at the leading tip such as a light pipe or ultrasound sensor to determining depth and the location of the choroid or a pressure transducer to determine a change in local fluid pressure from entering the suprachoroidal space.

**[00042]** The leading tip of the delivery device is preferably shaped to facilitate penetration of the sclera, either by cutting, blunt dissection or a combination of cutting and blunt dissection. Features of the device may include energy delivery elements to aid tissue penetration such as ultrasound, high fluid pressure, or tissue ablative energy at the distal tip. The outer diameter of the tissue contacting portion of the device is preferably about the size of a 20 to 25 gauge needle (nominal 0.0358 to 0.0203 inch outer diameter) to allow minimally invasive use without requiring additional features for tissue dissection or wound closure. Suitable materials for the delivery device include high modulus materials such as metals including stainless steel, tungsten and nickel titanium alloys, and structural polymers such as nylon,

polyethylene, polypropylene, polyimide and polyetheretherketone, and ceramics. The tissue contacting portions of the device may also comprise surface treatments such as lubricious coatings to assist in tissue penetration or energy reflective or absorptive coatings to aid in location and guidance during medical imaging..

**[00043]** The needle may be mounted or slidably disposed at a shallow angle to a plate or fixation mechanism to provide for localization and control of the angle and depth of insertion. The plate, such as shown in **Fig. 4**, may contain an injection port to allow advancement of the needle through the plate that has been pre-positioned on the surface of the globe (eye surface). The plate may further comprise a vacuum assist seal 12 to provide stabilization of the plate to the target site on the ocular surface. An external vacuum source such as a syringe or vacuum pump is connected by line 13 to the plate to provide suction. The plate should preferably have a bottom side or bottom flanges which are curved suitably to curvature of the globe. The needle 11 is advanced through the sclera 1 until entering the suprachoroidal space 2 but not into choroid 3.

**[00044]** Elements to seal the needle tract during injection such as a flexible flange or vacuum seal along the tract may also be incorporated to aid delivery. Referring to **Fig. 4**, the location of the delivery device 11 is shown with respect to the target sclera 1, suprachoroidal space 2, and choroid 3 by positioning with a vacuum interfacial seal 12 attached to a suction line 13.

**[00045]** The device may also comprise elements to mechanically open the suprachoroidal space, in order to allow injection of microparticulate drugs or drug delivery implants which are larger than can be delivered with a small bore needle. In one embodiment, such a delivery device may comprise a first element provided to penetrate the scleral tissue to a specified depth, and a second element, which can advance, and atraumatically distend the choroid inwards, maintaining a pathway to the suprachoroidal space. The second element may be disposed within or placed adjacent to the first element. An embodiment of a device having such elements is shown in **Figs. 3a** and **3b**.

**[00046]** Referring to **Fig. 3a** a delivery device with a distending tip is shown. The delivery device comprises a cutting or ablative tip 4 a choroidal distention tip 8 at the distal end of the device, and an ultrasonic sensor 6 used to guide the device through the tissues. A luer connector 7 is provided at the proximal end (away from the cutting tip) of the device. The knob 5 is connected to the mechanism for

activating the distention tip 8. The device is placed facing the sclera 1 to address the suprachoroidal space 2 adjacent to the choroid 3. The device is then advanced in scleral tissues using the depth sensor for guidance. When the depth sensor indicates that the tip 4 is to or just adjacent to the suprachoroidal space 2, the distension tip 8 is activated to prevent damage to the choroid. Referring to **Fig. 3b**, the knob 5 has been activated to advance the distention tip to its activated position 9 which results in a distended choroid 10. A pathway to the suprachoroidal space 2 is thereby attained without trauma to the choroid from the ablative tip 4.

**[00047]** In another embodiment, the delivery device comprises a thin walled needle fabricated with a short, high angle bevel at the leading tip to allow the bevel to be advanced into or through scleral tissues. Maintaining the beveled section with the opening directed inward prevents the drug from being expressed away from the suprachoroidal space. Various types of access and delivery may be achieved through the precise placement of the needle tip into or through the scleral tissues. If the needle is advanced through the sclera and into the suprachoroidal space, the needle may then be used for direct injections into the space or to serve as an introducer for the placement of other devices such as a microcannula. If the needle is placed in close proximity to the inner boundary of the sclera, injection of drug formulations through the needle will allow fluid dissection or flow through any remaining interposing scleral tissue and delivery to the suprachoroidal space. An embodiment of a device useful in such manner is shown in **Fig. 8**.

**[00048]** In **Fig. 8**, a system to inject a substance into the suprachoroidal space 2 comprises an access cannula 26 and a high resolution imaging device 27. The access cannula may accommodate a hypodermic type needle (not shown) or introducer sheath with a trocar (not shown). Furthermore, the access means may comprise a plate as shown in **Fig. 4** or **Fig. 5**. The access cannula incorporates a beveled sharp distal tip suitably shaped for penetration of the tissues. The imaging device may comprise real-time modalities such as ultrasound, optical coherence tomography (OCT) or micro-computed tomography (MicroCT). The advancement of the access needle or introducer through the sclera is monitored using the imaging device. The access cannula 26 is advanced until the leading tip is in close proximity to the inner boundary of the sclera 28, at which point the injection of the drug is made. Injection of drug formulations through the needle will allow fluid dissection or flow through any remaining interposing scleral tissue and delivery to the suprachoroidal space 29.

**[00049]** In one embodiment, the delivery device may allow a specific angle of entry into the tissues in order to provide a tissue pathway that will maintain the tract within the sclera, or penetrate to the suprachoroidal space without contacting the choroid. Referring to **Fig. 5**, an embodiment of the device is shown with a luer connector 7 at the proximal end and a bevel needle tip 14 at the distal end. The needle is affixed to an angled stop plate 15 to set the depth and angle of penetration of the needle tip 14. The assembly is advanced until the stop plate encounters the surface of the globe, placing the needle tip at the target depth. The mounting plate may also contain sensors for indicating or directing the position of the needle tip.

**[00050]** In one embodiment, a system for obtaining minimally invasive access to the suprachoroidal space comprises an access cannula and an optical device used to determine the location of the access cannula distal tip in the tissue tract providing direct feedback upon entry to the suprachoroidal space. The color differential between the sclera (white) and the choroid (brown) may be used to provide location information or OCT methods may be used to determine the distance to the choroid interface from the sclera. The optical device may be incorporated within a microcannula, or may be an independent device such as a microendoscope or a fiber-optic sensor and transducer capable of detecting the tissue properties. The optical signal may be sent to a camera and monitor for direct visualization, as in the case of an endoscope, or to an optical signal processing system, which will indicate depth by signaling the change in tissue properties at the tip of the optical fiber. The access microcannula may be a needle or introducer-type device made of metal or plastic. The distal end of the access cannula is suitable to pierce ocular tissue. If independent, the optical device will be removed from the access microcannula after cannulation to allow access to the space for other devices or for an injectate to administer treatment. An embodiment of such a system is shown in **Fig. 6**. The optical device comprises a flexible microendoscope 18, coupled to a CCD camera 16 with the image viewed on a monitor 19. The endoscope is sized to fit slidably in an access cannula 17 that is preferably less than 1 mm in outer diameter. The access cannula 17 comprises a beveled sharp distal tip for tissue access. The distal tip of the endoscope is positioned at the proximal end of the cannula bevel to provide an image of the cannula tip. The cannula is advanced against the ocular surface at the region of the *pars plana* at a low angle, piercing the sclera 1, and advancing until the endoscope image shows access into the suprachoroidal space 2.

**[00051]** In another embodiment, the optical device of the system comprises a focal illumination source at the distal tip. The amount of light scatter and the intensity of the light will vary depending upon the type of tissues and depth of a small light spot traversing the tissues. The change may be seen from the surface by the observing physician or measured with a sensor. The focal spot may be incorporated as an illuminated beacon tip on a microcannula. Referring to **Fig. 7**, the access device comprises a flexible microcannula or microcatheter 20, sized suitably for atraumatic access into the suprachoroidal space 2. The microcatheter comprises a lumen 22 for the delivery of materials to the space 2 and a fiber optic 23 to provide for an illuminated distal tip. The fiber optic is connected to an illumination source 24 such as a laser diode, superbright LED, incandescent or similar source. The microcatheter is slidably disposed within the access cannula 21. As the access cannula is advanced through the tissues, the light 25 transilluminating the tissues will change. Scleral tissues scatter light from within the sclera tissues to a high degree, however once inside the suprachoroidal space, the light intensity and backscatter seen at the surface diminishes significantly, indicating that the illuminated tip has transited the sclera 1, and is now in the target location at the suprachoroidal space.

**[00052]** Of particular utility with a delivery device are drug formulations as previously described that are compatible with the delivery device. Drug in microparticulate form are preferred to be substantially smaller than the lumen diameter to prevent lumen obstruction during delivery. Microparticles of average outer dimension of approximately 10 to 20% of the device lumen at maximum are preferred. A useful formulation includes microspheres or microparticles with an outer diameter in the range of about 1 to 33 microns. Also preferred is the use of a polymeric excipient in the drug formulation to enable the formulation to be injected into the scleral tissues adjacent to the suprachoroidal space, with subsequent dissection of the tissue between the distal tip and the suprachoroidal space by the excipient containing fluid to form a flow path for the drug into the suprachoroidal space. Formulations with thixotropic properties are advantageous for passage through a small needle lumen as well as for fluid dissection of scleral tissue.

**[00053]** The following examples are provided only for illustrative purposes and are not intended to limit the invention in any way.

**[00054]** EXAMPLE 1

Fluorescent dyed polystyrene microspheres (Firefli™, Duke Scientific, Inc., Palo

Alto, CA) suspended in phosphate-buffered saline were used as model drug to evaluate the size range in which particulates will migrate in the suprachoroidal space from the anterior region to the posterior region.

An enucleated human cadaver eye was radially incised to the choroid in the pars plana region, which is in the anterior portion of the eye. Using a syringe terminated with a blunt 27 gauge needle, 0.15 mL of a 1% by volume microsphere suspension (mean diameter 6 micron) was delivered into the anterior region of the suprachoroidal space. The needle was withdrawn and the incision sealed with cyanoacrylate adhesive.

The eye was then perfused for 24 hours with phosphate buffered saline at 10 mm Hg pressure by introducing into the anterior chamber a 30 gauge needle attached to a reservoir via infusion tubing. The reservoir was placed on a lab jack and elevated to provide constant perfusion pressure. Several hours prior to examination, the eye was placed into a beaker of glycerin to clarify the scleral tissue by dehydration, allowing direct visualization of the suprachoroidal space.

The microspheres were visualized using a stereofluorescence microscope (Model MZ-16, Leica, Inc.) with fluorescence filters selected for the microsphere fluorescence. Under low magnification (7 to 35X) the microspheres could be clearly seen in a stream-like pattern running from the site of instillation back toward the optic nerve region, collecting primarily in the posterior region of the suprachoroidal space.

The experiment was repeated using microsphere suspensions of 1, 6, 10, 15, 24 and 33 micron diameter with the same resulting pattern of migration and distribution to the posterior region of the eye.

**[00055]** EXAMPLE 2

The experiment of Example 1 was repeated, except that a mixture of 6 and 33 micron diameter fluorescent microspheres as a model drug was suspended in a polymeric excipient comprising a surgical viscoelastic (Healon 5, Advanced Medical Optics, Inc.), a 2.3% concentration of sodium hyaluronic acid of 4,000,000 Daltons molecular weight, with thixotropic properties of a zero shear viscosity of 7,000,000 mPas and 400 mPas viscosity at 1000 $s^{-1}$ shear rate. The mixture was introduced into the suprachoroidal space in the manner of Example 1. After 24 hour perfusion, the microspheres resided solely in the suprachoroidal space at the anterior instillation site and did not show evidence of migration, demonstrating the localizing effect of the thixotropic polymeric excipient.

**[00056]** EXAMPLE 3

To demonstrate the effect of polymeric excipient viscosity on drug localization, the experiment of Example 1 was repeated, except that bevacizumab (AvastinTM, Genentech), an anti-VEG antibody, was adsorbed onto 5 micron diameter carboxylated fluorescent microspheres and mixed at equal volumes with one of three hyaluronic acid based surgical viscoelastics (Healon, Healon GV, Healon 5, Advanced Medical Optics, Inc.), each with a different viscosity and thixotropic properties. (Healon, 300,000 mPas viscosity at zero shear rate, 150 mPas viscosity at 1000 s-1 shear rate; Healon GV, 3,000,000 mPas viscosity at zero shear rate, 200 mPas at 1000s-1 shear rate; Healon 5, 7,000,000 mPas viscosity at zero shear rate, 400 mPas viscosity at 1000 s-1 shear rate.) Each mixture was introduced into the anterior region of the suprachoroidal space at the *pars plana* in the anterior region of the eye in the manner of Example 1. After 24 hours perfusion, the microspheres in Healon and Healon GV were found to be in process of migration to the posterior region of the suprachoroidal space with the formulation found at both the *pars plana* site of instillation and the posterior pole. The microspheres in Healon 5 remained dispersed in the viscoelastic localized at the original injection site in the *pars plana* region of the suprachoroidal space.

**[00057]** EXAMPLE 4:

The experiment of Example 1 was repeated, except that bevacizumab (AvastinTM, Genentech) was covalently crosslinked using 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide (EDAC, Sigma-Aldrich) onto 5 micron diameter carboxylated fluorescent microspheres and mixed at equal volumes with one of three surgical viscoelastics (Healon, Healon GV, Healon 5, Advanced Medical Optics, Inc.), each with a different viscosity and thixotropic properties as in Example 3. The mixture was introduced into the suprachoroidal space at the *pars plana* in the manner of Example 1. After 24 hour perfusion the microspheres remained exclusively in the *pars plana* region of the suprachoroidal space for all viscoelastic carriers.

**[00058]** EXAMPLE 5:

To demonstrate the effect of a crosslinking polymeric excipient on drug localization, the experiment of Example 1 was repeated, except that 10 micron diameter fluorescent microspheres were mixed into a 4% alginate solution and introduced into the suprachoroidal space at the pars plana region. Before sealing the incision site an equal volume of 1 M CaCl2 solution was instilled at the site of the microsphere/alginate suspension to initiate crosslinking of the alginate excipient. The

mixture was allowed to gel for 5 minutes before perfusing as in Example 1. The microspheres remained exclusively at the site of instillation, dispersed in the crosslinked polymer excipient.

**[00059]** EXAMPLE 6:

A drug containing injectate was prepared by suspending 1.5 mg of Triamcinolone acetonide in microparticulate form, in 15 microliters of Healon viscoelastic (Advanced Medical Optics, Irvine CA) with a zero shear viscosity of 300,000 mPas and a viscosity of 150 mPas at a shear rate of 1000 s-1. Forty porcine subjects were placed under anesthesia and the right eye prepared and draped in a sterile manner. A conjunctival peritomy was made near the superior limbus, exposing and providing surgical access to a region of sclera. A small radial incision was made in the sclera, exposing bare choroid. A flexible microcannula with a 360 micron diameter tip and 325 micron diameter body (iTrack microcannula, iScience Interventional Corp.) was inserted in to the scleral incision and advanced in a posterior direction to a target region behind the macula. The drug suspension was injected into the posterior region of the suprachoroidal space, and was observed to form a layer between the choroid and sclera at the target region. The microcannula was retracted and the scleral and conjunctival incisions closed with 7-0 Vicryl suture. The subjects were observed and eyes tissues recovered at 12 hours, 24 hours, 48 hours, 4 days, 7 days, 14 days, 30 days and 90 days. Angiographic, histologic, and photographic studies of the subjects demonstrated no sign of posterior segment pathology. Recovered samples of choroid demonstrated significant concentration of the drug, in the range of at least 1 mg per gram of tissue at all recovery time periods.

**[00060]** EXAMPLE 7:

A drug-containing formulation comprising 20 mL Healon 5 and 50 mL (1.5 mg) bevacizumab (AvastinTM, Genentech) was prepared. Eighteen porcine subjects were anesthetized and the right eye prepared and draped in a sterile manner. A conjunctival peritomy was made near the superior limbus, exposing and providing surgical access to a region of sclera. A small radial incision was made in the sclera, exposing bare choroid. A flexible microcannula with a 360 micron diameter tip and 325 micron diameter body (iTrack microcannula, iScience Interventional Corp.) was inserted in to the scleral incision and advanced in a posterior direction to a target region behind the macula. The drug formulation was injected into the posterior region of the suprachoroidal space, and was observed to form a layer between the choroid

and sclera at the target region. The microcannula was retracted and the scleral and conjunctival incisions closed with 7-0 Vicryl suture. Another 18 porcine subjects were anesthetized and each received a 50 mL bolus of bevacizumab via injection into the vitreous. Both groups of test subjects were evaluated and sacrificed at 0.5, 7, 30, 60, 90, and 120 days post-injection. Serum samples were taken and tested for bevacizumab using an enzyme-based immunoassay. Higher plasma levels of bevacizumab were found in the intravitreally injected subjects and for longer duration of time than the suprachoroidal delivery group. The right globes were removed and dissected in order to quanitate bevacizumab in specific tissues and regions using an enzyme-based immunoassay. The enzyme immunoassay demonstrated that bevacizumab delivered via intravitreal injection was distributed throughout eye, but when delivered suprachoroidally remained largely in the retina and choroid, with little found in the vitreous and anterior chamber.

**[00061]** EXAMPLE 8:

The experiment of Example 1 was repeated, except a drug formulation 0.2 mL of Healon 5, 0.6 mL of Avastin, and 24 mg of triamcinolone acetonide was prepared to provide a treatment with both anti-inflammatory and anti-VEGF properties. An approximately 5 mm long incision was made longitudinally in the pars plana region transecting the sclera, exposing the choroid of a cadaver globe that had been clarified by immersion in glycerol for approximately 30 minutes and perfused with saline at 12 mm Hg pressure. The flexible microcannula of Example 6 was primed with the drug formulation and the microcannula tip was inserted into the suprachoroidal space through the scleral incision. With the aid of the fiber optic beacon at the microcannula tip, the distal end of the microcannula was steered toward the posterior pole of the globe, stopping approximately 5 mm short of the optic nerve. Using a Viscoelastic Injector (iScience Interventional), 70 microliters of the drug formulation was injected into the posterior region of the suprachoroidal space. The microcannula was removed by withdrawing though the pars plana incision. The mixture was visible though the clarified sclera, and formed a deposit near the optic nerve with the mixture also following the catheter track. The incision was sealed with cyanoacrylate (Locktite 4011) and the globe perfused again with saline at 12 mm Hg for 3 hours. The sclera was re-cleared by immersion in glycerol to examine the administered drug formulation. The drug formulation was observed by microscopy to have formed a layer of dispersed drug within the polymer excipient in the posterior region of the

suprachoroidal space.

**[00062]** EXAMPLE 9

A series of experiments were performed to evaluate minimally invasive delivery of substances to the suprachoroidal space. The goal of the experiments was to use non-invasive imaging and fluid dissection as a means of delivering substances through scleral tissue and into the suprachoroidal space, without having direct penetration into the suprachoroidal space.

Human cadaver eyes were obtained from an eye bank and were prepared by inflating the eyes to approximately 20mm Hg pressure with phosphate buffered saline (PBS). A delivery needle was fabricated using stainless steel hypodermic tubing, 255 mm ID x 355mm OD. The needle distal tip was ground into a bi-faceted short bevel point, 400 um in length and at an angle of 50°. The fabricated needle was then silver-soldered into a standard 25 gauge x 1 inch hypodermic needle to complete the assembly.

The needle was gently advanced into scleral tissue at an acute angle (<10°) with respect to the surface of the eye. The needle entry was started in the pars plana region approximately 4 mm from the limbus, and the needle advanced posteriorly in scleral tissue to create a tract between 5 and 6 mm long without penetrating through the sclera into the suprachoroidal space. A high resolution ultrasound system (iUltrasound, iScience Surgical Corp.) was used to guide and verify placement of the needle tip within scleral tissues and to document the injections.

In the first set of experiments, a polymeric excipient alone comprising a hyaluronic acid surgical viscoelastic (Healon 5, Advanced Medical Optics, Inc) was injected. In a second set of experiments, the viscoelastic was mixed in a 1:1 ratio with a 1 % aqueous solution of 10 micron diameter polystyrene microspheres (Duke Scientific, Inc) to represent a model microparticulate drug. The viscoelastic and the mixture were delivered through the needle using a screw driven syringe (ViscoInjector, iScience Surgical Corp.) in order to control delivery volume and injection pressure. The injections were made with the needle bevel turned inwards towards the center of the globe. Multiple locations on three cadaver eyes were used for the experiments.

In the first experiments, the needle tract was approximately 3 to 4 mm in length and the injectate was observed to flow back out the tract. With placement of the needle tip in a longer tract, higher injection pressure was obtained and allowed the injectate to dissect through the remaining interposing layers of the sclera and deliver to the

suprachoroidal space. Through trials it was found that needle tip placement in the outer layers of the sclera (< 1/2 scleral thickness) resulted in the delivery of the viscoelastic into an intra-scleral pocket or sometimes through to the outer surface of the globe. With the needle tip approaching the basement of the sclera, the injections dissected through the remaining interposing scleral tissue, entered the suprachoroidal space and spread to fill the suprachoroidal space in the region of the injection. **Fig. 1** shows the needle tract 30 clearly visible (after removal of the needle) and a region 31 of the suprachoroidal space filled with injectate. The sclera 1 and choroid 3 are shown. **Fig. 2** shows a region 33 of the suprachoroidal space filled with the microsphere and hyaluronic acid excipient containing injectate, and the tip of the needle 4 in the sclera and needle shadow 32.

**[00063]** EXAMPLE 10:

An experiment was performed to use micro-endoscopic imaging to allow minimally invasive access to the suprachoroidal space in a human cadaver eye. A custom fabricated, flexible micro-endoscope (Endoscopy Support Services, Brewster NY) with an outer diameter of 350 microns containing an imaging bundle with 1200 pixels was mounted on a micrometer adjusted stage. The stage was mounted on a vertical stand allowing for controlled up and down travel of the endoscope. The micro-endoscope was attached to a 1/2" chip CCD camera and then to a video monitor. A 20 gauge hypodermic needle was placed over the endoscope to provide a means for piercing the tissues for access.

The camera was turned on and an external light source with a light pipe (Model MI-150, Dolan Jenner, Boxborough, MA) was used to provide transcleral imaging illumination. The needle was advanced until the distal tip was in contact with the scleral surface of a human cadaver whole globe approximately 4 mm posterior of the limbus. The micro-endoscope was then lowered until the white scleral surface could be seen through the end of the needle. The needle was then slowly advanced into the scleral tissue by slight back-and-forth rotation. As the needle was advanced in this manner, the endoscope was lowered to follow the tract created by the needle. At or within the sclera, the endoscopic image was seen as white or whitish-grey. As the needle pierced the scleral tissues, the image color changed to dark brown indicating the presence of the dark choroidal tissues, demonstrating surgical access of the suprachoroidal space.

**[00064]** EXAMPLE 11:

An experiment was performed to use fiber-optic illuminated guidance to allow minimally invasive access to the suprachoroidal space in a human cadaver eye. A flexible microcannula with an illuminated distal tip (iTrack-250A, iScience Interventional, Menlo Park, CA) was placed into a 25 gauge hypodermic needle. The microcannula comprised a plastic optical fiber that allowed for illumination of the distal tip. The microcatheter fiber connector was attached to a 635 nm (red) laser diode fiber optic illuminator (iLumin, iScience Interventional) and the illuminator turned on to provide a steady red light emanating for the microcannula tip. The microcannula was fed through the 25 gauge needle up to the distal bevel of the needle but not beyond.

The needle was slowly advanced in the pars plana region of a human cadaver whole globe until the needle tip was sufficiently embedded in the scleral tissues to allow a slight advancement of the microcannula. The illumination from the microcannula tip was seen clearly as the scleral tissues diffused the light to a significant extent. As the needle was advanced slowly, the microcannula was pushed forward at the same time. When the hypodermic needle tip pierced through sufficient scleral tissue to reach the suprachoroidal space, the red light of the microcannula tip immediately dimmed as the illuminated tip passed out of the diffusional scleral tissues and into the space beneath. The microcannula was advanced while keeping the needle stationary, thereby placing the microcannula tip into the suprachoroidal space. Further advancement of the microcannula in a posterior direction in the suprachoroidal space could be seen transclerally as a focal red spot without the broad light diffusion seen when the tip was inside the scleral tissues. Using a high frequency ultrasound system (iUltraSound, iScience Interventional), the location of the microcannula in the suprachoroidal space was confirmed.

What is claimed is:

1. A drug formulation characterized by a zero shear viscosity of at least 300,000 mPas for injection into the suprachoroidal space of an eye comprising a biologically active substance and a thixotropic polymeric excipient that acts as a gel-like material to spread after injection and uniformly distribute and localize the drug in a region of the suprachoroidal space.

2. The drug formulation according to Claim 1 further characterized by a viscosity of not more than about 400 mPas at 1000 $s^{-1}$ shear rate.

3. The drug formulation according to Claim 1 wherein said gel-like material crosslinks after injection into the suprachoroidal space.

4. The drug formulation according to Claim 1 wherein said biologically active substance comprises microparticles or microspheres.

5. The drug formulation according to any one of Claims 1 to 4 wherein said polymeric excipient comprises hyaluronic acid, chondroitin sulfate, gelatin, polyhydroxyethylmethacrylate, dermatin sulfate, polyethylene oxide, polyethylene glycol, polypropylene oxide, polypropylene glycol, alginate, starch derivatives, a water soluble chitin derivative, a water soluble cellulose derivative or polyvinylpyrollidone.

6. A drug formulation for delivery to the suprachoroidal space of an eye comprising a biologically active substance and microspheres or microparticles with an outer diameter in the range of about 1 to 33 microns.

7. The drug formulation according to Claim 6 further comprising a polymer excipient to uniformly disperse said microspheres or microparticles in the suprachoroidal space.

8. The drug formulation according Claim 4 or 6 wherein the microparticles or microspheres additionally comprise a controlled release coating.

9. The drug formulation according to Claim 4 or 6 wherein the microparticles or microspheres additionally comprise a tissue affinity surface.

10. The drug formulation according to any of Claims 1 to 4 or 6 wherein the biologically active substance comprises an antibiotic, a steroid, a non-steroidal anti-inflammatory agent, a neuroprotectant, an anti-VEGF agent, or a neovascularization suppressant.

11. The drug formulation of Claim 10 wherein the biologically active substance comprises both a steroid and an anti-VEGF agent or neovascular suppressant.

12. A device for minimally invasive delivery of a drug formulation into the suprachoroidal space of the eye comprising a needle having a leading tip shaped to allow passage through scleral tissues without damage to the underlying choroidal tissues, and a sensor to guide placement of said tip to deliver said formulation adjacent to or within the suprachoroidal space.

13. The device according to Claim 12 wherein said sensor provides an image of the scleral tissues.

14. The device of Claim 12 wherein said sensor responds to ultrasound, light, or differential pressure.

15. A device for minimally invasive delivery of a drug formulation into the suprachoroidal space of the eye comprising a needle having a leading tip shaped to allow passage through scleral tissues, and an inner tip that provides an inward distending action to the choroid upon contacting the choroid to prevent trauma thereto.

16. The device according to any one of Claims 12 to 15 further containing a drug formulation comprising a polymeric excipient and a biologically active substance.

17. The device according to any one of Claims 12 to 15 further comprising a flange to seal the interface between the needle and the interposing tissues.

18. The device according to any one of Claims 12 to 15 further comprising an angled stop plate located on said device to interface with the outer surface of the eye and set the depth and angle of penetration of said leading tip relative to the eye surface.

19. A method for administering drugs to eye comprising placing formulation comprising a biologically active substance and a polymer excipient in the suprachoroidal space such that said excipient gels after delivery to localize said biologically active substance.

20. The method according to Claim 19 wherein said formulation is placed in a posterior region of the suprachoroidal space.

21. The method according to Claim 19 wherein said formulation is placed in an anterior region of the suprachoroidal space.

22. A method for administering drugs to a posterior region of the eye comprising placing a formulation comprising a biologically active substance comprising microspheres or microparticles with an outer diameter in the range of about 1 to 33 microns in an anterior region of the suprachoroidal space such that said microspheres or microparticles subsequently migrate to said posterior region.

23. The method according to Claim 22 wherein said formulation comprises a polymer excipient to uniformly disperse the microparticles or microspheres in the suprachoroidal space.

24. A method of administering drugs in the suprachoroidal space of the eye comprising the steps of placing a needle in scleral tissues toward the suprachoroidal space at a depth of at least half of the scleral thickness, and injecting a drug formulation through said needle into the sclera such that said formulation dissects the scleral tissues adjacent to said suprachoroidal space and enters said suprachoroidal space.

25. The method according to any of Claims 19 to 24 wherein said formulation comprises a thixotropic polymer.