Systems and methods for delivering and infusing formulations containing riboflavin or its analogues, or other ophthalmic formulations, into corneal tissue are disclosed. Systems and methods are further disclosed to cross-link the corneal tissue through exposure to UVA irradiation. The systems and methods for formulation delivery employ micro-needle array delivery devices.
METHOD AND APPARATUS FOR THE DELIVERY OF PHOTO-CHEMICAL (CROSS-LINKING) TREATMENT TO CORNEAL TISSUE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 61/443,191 filed on Feb. 15, 2011 and is incorporated by reference herein.

BACKGROUND OF THE INVENTION

[0002] This invention is directed to designs and methods for delivering and infusing dosage forms containing riboflavin or its analogues, or other ophthalmic formulations, into ocular tissue (such as the cornea) using rapid and minimally invasive methods. In general, the devices created to perform these tasks have capabilities that provide a micro-needle array drug delivery method combined with a high intensity photonic excitation of ocular tissue. As a result, such devices provide effective crosslinking of collagen ocular tissue. Additionally, the embodiments of the present invention herein described are directed at the treatment of refractive myopia and other conditions (such as presbyopia) wherein reshaping of the cornea is required to obtain normal vision. The corneal reshaping is done with a thermal subsurface continuous wave infrared laser device as described in US Patent Pub. No. 20110282333 of U.S. patent application Ser. No. 13/068,126 filed May 2, 2011, which is incorporated herein by reference. Following such reshaping, CXL is performed to provide rigidity (stabilization) and prevent regression of the reshaped corneal tissue.

[0003] Collagen cross-linking (herein CXL) in the cornea is now a widespread method used to stiffen and stabilize corneal tissue. It is approved in the European Union as a medical device application for the treatment of keratoconus, a degenerative collagenous disease. CXL has been shown to prevent the progression of keratoconus by collagen stiffening. There are other conditions and diseases of the cornea where CXL treatment has been shown to be safe and effective, for example: corneal ectasia, corneal ulceration, and bullous keratopathy.

[0004] CXL is a two-step process intended to enhance tissue rigidity and shape stability. The first step involves the application of a photo-sensitizer, such as riboflavin (Vitamin B-2—herein referred to as "R/F"), which is infused into the collagen tissue in the stroma layer of the cornea. In order to create this infusion of R/F, the current prior art technique for CXL is to place a speculum onto the patient's eye to hold open the eye lid. The physician then surgically debrides (removes) the outer layer of the cornea, which is the protective epithelial layer. This debridement permits the R/F, which is typically placed directly on the corneal tissue with an eye dropper, to soak and be absorbed into the corneal tissue. This delivery and absorption process takes approximately 30 to 45 minutes, and the R/F solution is administered manually every few minutes with the eye dropper. Step two is performed after the R/F saturates the corneal stroma. Step two involves the delivery of ultraviolet light (herein "UVA") into the riboflavin soaked corneal tissue. This UVA activation of the riboflavin results in increased biomechanical rigidity or stiffness to the treated corneal tissue. The mechanism of action for the creation of such rigidity is attributed to the generation of radical oxygen species which trigger the formation of covalent bonds between and within collagen strands as well as, it is hypothesized, bridging bonds between collagen fibrils and the local extracellular matrix (ECM).

[0005] The current prior art CXL process has several significant limitations. The two most critical are: 1) the debridement of the protective epithelium tissue; and, 2) the extended time period required for the absorption of R/F into the collagen tissue. Debridement is painful to the patient, but more importantly, over 70% of the adverse events reported from CXL can be traced to debridement. CXL takes, on average, one hour per eye, which is not considered a patient-friendly procedure, especially with a speculum remaining in the patient’s eye during the entire procedure.

[0006] As previously indicated, cross-linking of corneal tissue using prior art methods has become a standard of care in the European Union (EU), primarily for the treatment of keratoconus. CXL stabilizes and thereby prevents the progressive elongation of the corneal tissue in a keratoconic patient, which if gone unabated can lead to blindness. However, following CXL treatment by such prior art methods, the keratoconic patient continues to have an irregular myopically shaped cornea. Therefore, for the treatment of refractive myopia, as well as the treatment for keratoconus, there is a need to provide safe, rapid, and effective devices and techniques for cross-linking of corneal tissue with an outcome that affords patient comfort, stability, reliable, uniformity and corneal shape retention.

[0007] Refractive myopia (i.e. <0.5 diopters) is a major eye condition throughout the world. It has increased annually over the past 20 years and is now estimated at nearly 30% prevalence in Europe and USA, at over 40% in Japan, and over 60% in many Asian countries, such as Singapore. The etiology of nearsightedness (myopia formation) is caused by a steepening of the corneal curvature which results in light being focused to a sub-optimal location in the posterior segment of the eye, instead of directly on the optic nerve (fovea) in the back of the eye.

SUMMARY OF THE INVENTIONS

[0008] Various embodiments of the present invention include a method of treating ocular tissue comprising: providing a treatment apparatus comprising micro-needles; and delivering a drug formulation to corneal ocular tissue through penetration of micro-needles into the corneal ocular tissue, and wherein the drug formulation comprises riboflavin, wherein the delivered formulation is capable of inducing crosslinking of corneal collagen tissue upon exposure to irradiation.

[0009] Further embodiments of the present invention include a method of treating ocular tissue comprising: providing a UVA applicator; and delivering UVA irradiation from the UVA applicator to corneal ocular tissue exposed to a formulation comprising riboflavin, wherein the UVA irradiation crosslinks corneal collagen tissue exposed to the formulation.

[0010] Additional embodiments of the present invention include a device for treating ocular tissue comprising: a micro-needle array disposed on a concave disk sized to fit over a corneal surface, wherein the micro-needles are configured to deliver formulation into a cornea upon penetration of the micro-needles into the corneal surface.

[0011] Other embodiments of the present invention include a device for treating ocular tissue comprising: a contact lens assembly comprising a contact lens that conforms to a corneal
surface; a skirt around the contact lens configured to sit on a region of the sclera surrounding the cornea; and a UVA applicator associated with the contact lens assembly for providing UVA irradiation through the contact lens into the cornea.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] The inventions herein have other advantages and features which will be more readily apparent from the following detailed descriptions, when taken in conjunction with the accompanying drawings, in which:

[0013] FIG. 1 depicts an in-use corneal infuser of R/F using a hollow MNA.

[0014] FIG. 2 depicts an in-use corneal injector of R/F using a MNA which has individual R/F coated micro-needles.

[0015] FIG. 3 depicts the side view of a typical single hollow micro-needle.

[0016] FIG. 4 depicts the bottom view of a typical hollow micro-needle array.

[0017] FIG. 5 depicts the side view of a typical solid micro-needle coated with R/F.

[0018] FIG. 6 depicts the bottom view of a typical solid micro-needle array.

[0019] FIG. 7 depicts an in-use UVA delivery system for the cornea.

[0020] FIG. 8a depicts a UVA applicator assembly.

[0021] FIG. 8b depicts the two parts of the UVA applicator assembly.

DETAILED DESCRIPTIONS OF THE INVENTIONS

[0022] The present inventions generally relate to various methods and embodiments to rapidly dose ocular tissue with photo-chemical exposures. Specifically, this involves a trans-epithelial drug transfection, such as riboflavin (R/F) formulations, into the collagen tissue in the corneal mid-stroma region. Additionally, these methods and embodiments also provide for photonic (typically UVA) delivery to the cornea. The R/F so delivered to corneal collagen tissue (by micro-injection) is then rapidly activated with UVA irradiation thereby inducing cross-linking of the collagen tissue.

[0023] The embodiments providing treatment for the cornea as described herein include various applications of micro-needle array (MNA) technology to provide rapid, sub-surface delivery of R/F into the corneal ocular tissue. In such methods of treatment, the MNAs may be inserted into corneal tissue through penetration of MNA's into the cornea. A R/F formulation can be delivered into the tissue through the application of MNAs. These MNAs can be solid with R/F coatings, or hollow, or dissolvable, or even a combination of solid MNAs with dissolvable tips. The MNAs used in this invention can have a diameter ranging from 40 microns to 400 microns, and a length of 100 microns to 1200 microns. They can be made from a variety of materials, such as polymeric or sucrose compounds, plastics and metals. The MNAs are produced with a base line curvature that has the flexibility to easily conform to ocular tissue upon application on ocular tissue.

[0024] For application of the MNAs into the cornea, the invention may include an auto-injector associated with the MNAs that provides a spring driven force (similar to an insulin injector) that ensures instant penetration of the MNAs into the ocular tissue. An “auto-injector” generally refers to a medical device designed to deliver a specific or selected amount (dose) of a formulation, such as a drug. In vitro studies have shown that the use of such an auto-injector for MNAs provides a uniform delivery of R/F at a therapeutically viable dose (which is in the range of 10 μl-50 μl to deliver 0.1% or higher R/F concentration) into the targeted ocular tissue in less than 1 minute or about one minute. An integral addition to the auto-injector includes the placement of a suction ring on the corneal surface in order to center the auto-injector on the pupil and protect the limbal region. This suction ring also stretches (flattens) the corneal surface so as to facilitate the MNA penetration.

[0025] Once the R/F is delivered into the stromal region of the cornea, the R/F will then diffuse in a targeted area of the stroma in 10 to 20 minutes. Clinical studies have shown that the application of MNAs, because of their microscopic size penetration, do not damage the protective (epithelial & Bowman) layers of the cornea. The transient micro-porations in the ocular tissue, which are caused by MNA penetration, will effectively close or seal within approximately one hour following MNA removal. Importantly, the length of the MNA is designed to deliver R/F at a depth in the corneal stroma that does not impinge upon the corneal endothelium and, as a result of this design, the endothelium remains safe from cellular destruction during treatment.

[0026] Several manufacturers of MNA technology are known in the art. However, the use of MNA for riboflavin (R/F) photo-sensitizer transport for ocular cross-linking has not been reported to the inventors’ knowledge. The R/F formulation used for cross-linking with hollow micro-needles may contain R/F (concentration ranging from 0.1%-0.5%) combined with deuterated water (D2O) (up to 99.9%+ concentration). The R/F formulation used for cross-linking with R/F coated micro-needles may have a coating thickness of up to 25 μm of rapidly dissolvable R/F. Formulations as disclosed in WO 2011/019940 A3 (publication of PCT/US2010/045356 filed Aug. 12, 2010), which is incorporated herein by reference, may also be used.

[0027] Embodiments of the present invention involve the simultaneous use of two contact lenses, one on the sclera in the shape of a skirt, and the second on the cornea in an elongated configuration. The sclera contact lens provides stability for the corneal contact lens during UVA delivery. Because the sclera lens is translucent, it facilitates adequate visualization. The cornea contact lens delivers a homogeneous, high irradiance, targeted diameter UVA beam. This cornea contact lens also enables the UVA to maintain precise alignment throughout the delivery process. Both the cornea and sclera contact lenses are held in place by a head band on the patient.

[0028] UVA may be delivered into the corneal tissue through fractionation and pulsation techniques and protocols as disclosed in WO2009/073600, which is incorporated by reference herein, thereby maximizing the use of dissolved oxygen in the corneal tissue. The combination of the R/F soak methods provide the end result that the time needed to cross-link collagen fibers can be significantly shortened while at the same time the cross-link densities will be higher than prior art treatments. It should be noted that the UVA beam profile matches the profile of the (convex) cornea so that the UVA is uniform over its illumination region.

[0029] The inventions set forth herein will be better understood by reference to the following detailed descriptions in connection with the accompanying drawings. Although the detailed descriptions of the inventions herein contain many specifics, these should not be construed as limiting the scope.
of the inventions but merely as illustrating different examples and aspects of the inventions. It should be appreciated that the scope of the inventions includes other embodiments not discussed in detail below. Various other modifications, changes and variations which will be apparent to those skilled in the art may be made in the arrangement, operation and details of the method and apparatus of the present inventions disclosed herein without departing from the spirit and scope of the inventions as described herein below.

[0030] Although the detailed descriptions of the inventions herein contain many specifics, these should not be construed as limiting the scope of the inventions but merely as illustrating different examples and aspects of the inventions. It should be appreciated that the scope of the inventions includes other embodiments not discussed in detail below. Various other modifications, changes and variations which will be apparent to those skilled in the art may be made in the arrangement, operation and details of the method and apparatus of the present inventions disclosed herein without departing from the spirit and scope of the inventions as described herein below.

[0031] FIG. 1 depicts an exemplary corneal R/F hollow MNA injector which provides a mid-stromal (8) trans-epithelial (50) deposition of up to 50 µL of R/F. More specifically, the R/F is delivered at a targeted depth starting at 100 µm below the corneal surface (51) and extends to a depth of 400 µm. To position the injector accurately on the cornea, a suction ring (52) is placed around the cornea, on scleral tissue near the limbus (9). The suction ring (52) is vacuum actuated through a tube 11 with a spring loaded syringe (10), which produces a gentle vacuum (~300 mNbar-400 mNbar range), thereby affixing the suction ring (52) at the desired position on the cornea. The purpose of the suction ring (52) is also to help stretch and provide tension to the cornea. This minimal reshaping facilitates penetration of the MNA. After the MNA injector has been properly positioned, the device utilizes a spring loaded actuator (4) to automatically pierce the cornea. This actuator is triggered by a switch (1). To deliver the R/F contained in the reservoir (3), a second spring actuator (2) is triggered which forces the R/F through a tube (53) to the micro-needle array (5) for delivery to the mid-stroma. Micro-needle array (5) includes a plurality of needles (7) set in a concave disk (6). There is an interlocking mechanism (not shown) which connects the MNA injector to the suction ring, ensuring the MNA's are positioned accurately and securely throughout delivery of the R/F. The hollow MNA injector delivers an R/F dose of up to 50 µL in less than 60 seconds. After depositing this R/F dose in the cornea, there is a waiting period of approximately 5 to 20 minutes to allow for uniform corneal diffusion of the R/F.

[0032] FIG. 2 depicts an exemplary corneal R/F coated MNA injector which provides a mid stromal (18) trans-epithelial (54) deposition of up to 15 µg of R/F. More specifically, the R/F is delivered at a targeted depth starting at 100 µm below the corneal surface (55) and extends to a depth of 400 µm. R/F coated MNA (14) includes a plurality of needles (16) set in a concave disk (15). To position the injector accurately on the cornea, a suction ring (56) is placed around the cornea, on scleral tissue near the limbus (19). The suction ring (56) is vacuum actuated through a tube (20) with a spring loaded syringe (17), which produces a gentle vacuum (~300 mNbar-400 mNbar range), thereby affixing the suction ring (56) at the desired position on the cornea. The purpose of the suction ring (56) is also to help stretch and provide tension to the cornea. This transient reshaping facilitates penetration of the MNA. After the MNA injector has been properly positioned, the device utilizes a spring loaded actuator (13) to automatically pierce the cornea. This actuator is triggered by a switch (12). There is an interlocking mechanism that connects the MNA injector to the suction ring (56), ensuring the MNA's are positioned accurately and securely throughout delivery of the R/F. The coated MNA injector delivers an R/F dose of up to 15 µg in less than 60 seconds. After depositing this R/F dose in the cornea, there is a waiting period of approximately 5 to 20 minutes to allow for uniform corneal diffusion of the R/F.

[0033] FIG. 3 illustrates an exemplary single hollow micro-needle, which contains channels (23) for transporting R/F and dual exit ports (22) for depositing R/F in the stroma. In addition, the single hollow micro-needle has a sharp non-corning tip (21) for rapid and minimally destructive penetration. The single hollow micro-needle has a length in the range of 100 µm to 600 µm.

[0034] FIG. 4 depicts an exemplary hollow MNA on a concave disk (24) with a diameter of 6 mm to 9 mm. The hollow micro-needles (25, 26) on the disk are spaced at about 0.5 mm apart. The disk contains two ports (27, 28) for suction on the outer perimeter of the concave disk (24). The needles in the hollow MNA may be fabricated with polymeric materials or metals that permit sterilization and have tips (21) having requisite sharpness. The hollow MNA needle tips (21) have a ~10 um-20 um radius of curvature that enables rapid, pain free, reliable and uniform penetration into the cornea.

[0035] FIG. 5 illustrates an exemplary single R/F coated micro-needle. The coating (30) thickness may be in the range of 20 nm. The coated micro-needle has a sharp non-corning tip (29) for rapid and minimally destructive penetration, and it has a length in the range of 100 µm to 600 µm.

[0036] FIG. 6 depicts an exemplary coated MNA on a concave disk (32) with a diameter of 6 mm to 9 mm. The coated micro-needles (33, 34) on the disk are spaced at about 1 mm apart. The disk contains two ports (35, 36) for suction on the outer perimeter. The needles in the coated MNA may be fabricated with polymeric materials or metals that permit sterilization and have tips (29) having requisite sharpness. The coated MNA needle tips have a ~10 um-20 um radius of curvature that enables rapid, pain free, reliable and uniform penetration into the cornea.

[0037] FIG. 7 illustrates an in-use UVA delivery system for activating R/F in corneal tissue and thereby causing cross-linking of such collagen tissue. This system includes a UVA source box (37) coupled to a fiber (38) that has a dual contact lens assembly (41) on the distal end. This contact lens assembly rests directly on the cornea. This fiber is stabilized by a guide (39) which is connected to a head band (40) on the patient. The contact lens assembly (41) can be adjusted to achieve proper alignment on the cornea. The UVA source box can provide UVA irradiance up to 100 mw/cm², or more narrowly 15 to 75 mw/cm², 15 to 30 mw/cm², 20 to 50 mw/cm², 25 to 35 mw/cm², or about 30 mw/cm² and delivers a uniform beam with about 8 mm, or about 9 mm or 8 to 9 mm in diameter. The beam irradiance is over 80% uniform or homogeneous over the region of delivery of irradiation.

[0038] FIGS. 8a and 8b depict the contact lens assembly (41) in detail. FIG. 8a shows a scleral skirt (44) attached to a UVA applicator (43). The scleral skirt (44) surrounds the cornea and sits on the sclera near the limbus. The skirt (44) provides a stabilizing base for the UVA applicator (43) during
UVA irradiation. The skirt (44) is made from natural pellethane rubber, or an equivalent material, and is translucent. The skirt (44) is disposable.

Fig. 8b shows the two separate parts of the contact lens assembly (41), the scleral skirt (44) and the UVA applicator (43). The UVA applicator has a custom molded plastic (non-brittle) contact lens (45) made with Zeonor 1020R, or equivalent material, that provides for over 80% uniformity or homogeneity of UVA transmission over the irradiated region, and can be ETO sterilized.

What we claim:

1. A method of treating ocular tissue comprising:
   providing a treatment apparatus comprising micro-needles; and
   delivering a drug formulation to corneal ocular tissue
   through penetration of micro-needles into the corneal
   ocular tissue, and
   wherein the drug formulation comprises riboflavin,
   wherein the delivered formulation is capable of inducing
   crosslinking of corneal collagen tissue upon exposure to
   irradiation.

2. The method of claim 1, wherein the riboflavin is deliv-
   ered through the corneal ocular tissue trans-epithelial and
   beneath the Bowman's layer into the mid-stroma.

3. The method of claim 1, wherein an auto-injector asso-
   ciated with the micro-needles provides a spring actuated
   force to press the micro-needles into corneal tissue.

4. The method of claim 3, wherein a suction ring is placed
   on a surface of the cornea to center the auto-injector on a
   pupil and stretches and flattens the corneal surface to facilitate
   penetration of the micro-needles.

5. The method of claim 1, wherein the micro-needles com-
   prise solid micro-needles, hollow micro-needles, dissolvable
   micro-needles, or a combination thereof.

6. The method of claim 1, wherein the micro-needles de-
   liver at least 10 to 50 μl into the corneal ocular tissue in
   less than 60 seconds and the formulation diffuses through the
   stromal region of the cornea in 10 to 20 minutes.

7. The method of claim 1, further comprising delivery of
   UVA to the corneal ocular tissue to crosslink corneal collagen
   tissue exposed to the delivered formulation.

8. A method of treating ocular tissue comprising:
   providing a UVA applicator; and
   delivering UVA irradiation from the UVA applicator to
   corneal ocular tissue exposed to a formulation comprising
   riboflavin, wherein the UVA irradiation crosslinks
   corneal collagen tissue exposed to the formulation.

9. The method of claim 8, wherein the UVA applicator
delivers a UVA irradiance of 25 to 35 mw/cm² with a beam of
about 8 to 9 mm in diameter.

10. The method of claim 8, further comprising positioning
a contact lens assembly over a cornea comprising the UVA
applicator.

11. The method of claim 8, wherein the irradiation com-
prises a UVA beam from the UVA applicator that matches a
convex profile of the cornea so that the irradiation is over 80%
uniform over its illumination region.

12. A device for treating ocular tissue comprising:
   a micro-needle array disposed on a concave disk sized to fit
   over a corneal surface, wherein the micro-needles are
   configured to deliver formulation into a cornea upon
   penetration of the micro-needles into the corneal
   surface.

13. The device of claim 12, further comprising a reservoir
connected to the micro-needle array for providing formu-
lation to hollow micro-needles of the micro-needle array.

14. The device of claim 13, further comprising an actuator
which forces the formulation from the reservoir into the
micro-needle array for delivery into the cornea.

15. The device of claim 12, wherein the micro-needle array
comprises micro-needles coated with the formulation which
comprises riboflavin.

16. The device of claim 12, further comprising an auto-
injector associated with the micro-needles that provides a
spring actuated force to press the micro-needle array into
corneal tissue.

17. The device of claim 16, further comprising a suction
ring for centering the auto-injector on a corneal surface con-
figured to stretch the corneal surface so as to facilitate
penetration of the micro-needle array.

18. A device for treating ocular tissue comprising:
   a contact lens assembly comprising a contact lens that
   conforms to a corneal surface;
   a skirt around the contact lens configured to sit on a region
   of the sclera surrounding the cornea; and
   a UVA applicator associated with the contact lens assembly
   for providing UVA irradiation through the contact lens
   into the cornea.

19. The device of claim 18, wherein the UVA applicator is
connected to a UVA source external to the contact lens assem-
ibly.

20. The device of claim 18, wherein the skirt comprises
rubber.

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