

METHODS AND DEVICES FOR DELIVERING ATROPINE TO THE EYE AS A MICRO-DOSE STREAM OF DROPLETS

FIELD OF THE INVENTION

- 5 [0001] The present disclosure relates to droplet delivery devices, methods of administration and uses thereof, specifically for the administration of droplets to the eye.

BACKGROUND OF THE INVENTION

- 10 [0002] Atropine formulations have been used in ophthalmology for pupil dilation and for amblyopia treatment. In addition, recent studies suggest that atropine may be used for the treatment of Myopia. Recent academic studies have suggested that some side effects associated with use of the standard 1% concentration may be avoided by using lower concentrations than of the active ingredient. These studies indicate that 1% atropine drops are not as well tolerated as lower concentrations, e.g., 0.1% and 0.01%. The lower
15 concentration formulations are typically prepared by simply diluting the 1% atropine solution. However, these low volume solutions are typically unstable for long term use.

- [0003] Moreover, a typical medical droplet as dispensed by an eye dropper bottle can vary, depending on the viscosity and surface tension of the fluid. In order to control the amount of active ingredient that is administered in a single droplet, the concentration of the
20 active ingredient is adjusted by volume. Once the concentration is defined, a correct dosage may require one drop or more. However, since the human eye can typically retain only 7 μ l of fluid at a time, even a single medical droplet can result in overflow and loss of part of the medication from the eye. Multiple drop dosage often compounds the problem of medication retention in the eye. Subjects will typically administer all droplets required for a dosage in
25 one sitting, which exacerbates the problem and can result in 50 to 90% of the medication overflowing and leaking out of the eye.

- [0004] Given the above and other limitations of current ophthalmic delivery, a need exists for an efficient delivery system for solutions to the eye, including solutions containing medicaments such as atropine.

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SUMMARY OF THE INVENTION

- [0005] In certain aspects, the disclosure provides method for delivering a composition comprising atropine to an eye of a subject in need thereof as a micro-dose stream of droplets.

The method generally includes, (a) generating a micro-dose stream of droplets including the composition comprising atropine via a piezoelectric droplet delivery device, wherein the micro-dose stream of droplets has an average ejected droplet diameter greater than 15 microns; and (b) delivering the micro-dose stream of droplets to the eye of said subject. In certain embodiments, the method treats myopia, in particular progressive myopia (nearsightedness) in adults and children, in the subject in need thereof.

[0006] In certain aspects, the piezoelectric droplet delivery device comprises an ejector mechanism, the ejector mechanism comprising a generator plate and a piezoelectric actuator, wherein the generator plate includes a plurality of openings formed through its thickness; and wherein the piezoelectric actuator is operable to directly or indirectly oscillate the generator plate, at a frequency to generate a directed stream of droplets of said low dosage volume medicament composition.

[0007] In certain embodiments, the micro-dose stream of droplets delivered to the eye of the subject is less than 13 microliters, less than 10 microliters, less than 5 microliters, 3-7 microliters, etc. In other embodiments, the micro-dose stream of droplets has an average initial ejecting velocity about of at least about 3 m/s, 4 m/s to about 12 m/s, etc. In other embodiments, the micro-dose stream of droplets has an average ejected droplet diameter of at least 15 microns, 20-60 microns, etc. In yet other embodiments, the micro-dose stream of droplets is delivered to the eye of the subject in less than 80 ms.

[0008] In certain aspects, wherein the composition comprises atropine at a concentration of at least 0.5 % by weight, at least 0.8 % by weight, 1% or more by weight, 0.5 to 1.2% by weight, etc.

[0009] In yet other aspects, the piezoelectric droplet delivery device is oriented within 25° of horizontal during generation and delivery of the micro-dose stream of droplets.

[0010] These and other features will become apparent from the following description of the preferred embodiments, claims and drawings.

DETAILED DESCRIPTION

[0011] The present disclosure provides methods and devices which improve upon prior art methods and devices for delivering atropine to the eye. Specifically, the present disclosure utilize relatively high concentrations of atropine in the solution to be administered, contrary to current trends, but delivers a much smaller dose to a subject, which thereby reduces, and even prevents, excess fluid from being unabsorbed by the target tissues.

Maintaining higher concentrations of atropine in the solution to be administered may also reduce or avoid issues with the instability of lower concentration solutions.

[0012] In certain aspects, the disclosure provides method for delivering a composition comprising atropine to an eye of a subject in need thereof as a micro-dose stream of droplets.

5 The method generally includes, (a) generating a micro-dose stream of droplets including the composition comprising atropine via a piezoelectric droplet delivery device, wherein the micro-dose stream of droplets has an average ejected droplet diameter greater than 15 microns; and (b) delivering the micro-dose stream of droplets to the eye of said subject. In certain embodiments, the method treats myopia, in particular progressive myopia
10 (nearsightedness) in adults and children, in the subject in need thereof.

[0013] In certain aspects, the present methods and devices utilize relatively high concentrations of atropine to avoid the stability problems of low concentration formulations currently favored.

[0014] In certain embodiments, the disclosure provides a piezoelectric droplet
15 delivery device configured to achieve micro-dosing that is many times more precise than conventional eye droppers. In certain aspects, the micro-dosing delivers doses of 6–8 μL in a targeted manner, directly coating the corneal surface (where 80% of intraocular drug penetration occurs) rather than the conjunctiva of the eye of the subject.

[0015] Without intending to be limited by theory, it is believed that focusing a
20 significant portion (i.e., over 50%, 60%, 70%, 80%, etc.) of the active agent to be administered to the eye of the subject directly to the corneal surface rather than the conjunctiva reduces collateral tissue exposure. In this regard, it is believed that administration directly to the corneal surface will reduce greater than 75% of the active agent's potential systemic exposure, to thereby reduce toxicity and result in potentially gentler and more
25 tolerable treatments. In other aspects, the micro-therapeutic approach of the disclosure also reduces waste associated with conventional eye droppers.

[0016] In yet other aspects, advantages of the micro-dosing approach of the disclosure includes:

[0017] **Dose reduction:** micro-dosing achieves precise volumetric control at the
30 microliter level to deliver 6–8 μL , which is the physiologic capacity of the tear film, e.g., as compared to an eye dropper pipette macro-dose of 30–50 μL which results in overdosing, ocular toxicity and systemic leaching into the plasma.

[0018] **Targeted dose instillation:** the piezoelectric droplet delivery device described herein allows for targeted delivery to the ocular surface and cornea, avoiding the

conjunctival cul-de-sac. The droplet micro-jet created by the piezoelectric vibrations is columnated and focused to provide accurate delivery to the corneal surface where the majority of ocular penetration occurs. Additionally, in certain embodiments, the device may include an LED targeting mechanism to allow proper positioning and objective alignment.

- 5 **[0019] Speed of delivery:** unlike a simple aerosolized mechanism, the piezoelectric droplet delivery device provides micro-droplet ejection control that creates a fast and targeted micro-jet delivery that provides ejected droplets to the ocular surface in less than 80 milliseconds, beating the eye's 100 millisecond blink reflex.

- 10 **[0020] Smart electronics:** in certain embodiments, the piezoelectric droplet delivery device includes smart electronics and mobile e-health technology are designed to track when a patient administers treatment. This enables physicians to monitor patient compliance accurately. In certain aspects, this technology will improve compliance and chronic disease management by empowering patients and physicians with access to dynamic, real time monitoring and compliance data for a more intelligent and personalized therapeutic paradigm.

- 15 **[0021]** In other aspects, the disclosure generally relates to piezoelectric droplet delivery devices useful, *e.g.*, in the delivery of a directed stream of droplets for ophthalmic use, more particularly, for use in the delivery of ophthalmic fluid to the eye. Droplets may be formed by an ejector mechanism from fluid contained in a reservoir coupled to the ejector mechanism. Except as otherwise described herein, the ejector mechanism and reservoir may
20 be disposable or reusable, and the components may be packaged in a housing of an ejector device.

- [0022]** In certain embodiments, devices are provided and methods are described for the reproducible delivering a therapeutically effective low volume micro-dose of a composition to a desired target (*e.g.*, an eye of a subject in need thereof, as compared to
25 standard eye dropper use and dosage volume). In certain aspects, the low volume micro-dose of a composition comprises atropine at a concentration of at least 0.5% by weight, at least 0.7% by weight, at least 0.8 % by weight, 1% by weight, etc. In certain aspects, the devices and methods are for the treatment of myopia, in particular progressive myopia (nearsightedness) in adults and children. In certain aspects, the therapeutically effective low
30 volume micro-dose of a composition may be delivered to an eye at, *e.g.*, 3/4, 1/2, 1/4, 1/6, 1/8, (*e.g.*, ~0.02-0.75) etc. of the volume of a standard eye dropper volume. By way of example, in certain embodiments, from 0.5 μ l - 15 μ l, from 3 μ l - 8 μ l, from 7 μ l - 8 μ l, less than 15 μ l, less than 13 μ l, less than 10 μ l, less than 8 μ l, less than 5 μ l, etc. of a micro-dose of a composition may be delivered to the eye of a subject, as compared to approximately 25

μl to approximately 70 μl by way of a standard eye dropper, while obtaining equivalent or improved therapeutic efficacy.

[0023] Dosing strategies also may incorporate various approaches to initiating treatment, stopping treatment, switching treatment and responding to different subject states.

5 Examples of dosing modes or strategies include once-a-day dosing, twice-a-day dosing, three times-a-day dosing, continuous dosing, bolus dosing, weekly dosing, monthly dosing, taper dosing, need-based dosing, and feedback dosing by a physician, provider, subject, or family. In addition, dosing schemes may include dosing per eye, as needed. The clinical scenarios where these can be employed include chronic disease, disease exacerbation, need for
10 suppression treatment, need for recurrence treatment, or state of treatment like medicament tolerance.

[0024] One embodiment discloses a method of delivering a therapeutically effective low volume micro-dose of a composition to an eye of a subject in need thereof, e.g., for the treatment of myopia, in particular progressive myopia (nearsightedness) in adults and
15 children, as compared to dosage volume of a standard eye dropper, the method comprising: (a) generating a directed stream of droplets of the low volume micro-dose of a composition, wherein the droplets have a desired average drop size and average initial ejecting velocity; and (b) delivering a therapeutically effective amount of the droplets of the low volume micro-dose of the composition to the eye of the subject, wherein the droplets deliver a desired
20 percentage of the ejected mass of the droplets to the eye. Again, in certain aspects, the low volume micro-dose of a composition comprises atropine at a concentration of at least 0.5% by weight, at least 0.7% by weight, at least 0.8 % by weight, 1% by weight, from 0.5 to 1.2% by weight, etc.

[0025] Devices capable of providing and delivering therapeutically effective low
25 volume micro-dose of the compositions to the eye are described herein. By way of example, the droplet delivery device may include a housing that comprises a fluid reservoir in fluid communication with an ejector mechanism. The directed stream of droplets may be generated via the ejector mechanism, the ejector mechanism comprising a generator plate and a piezoelectric actuator, wherein the generator plate includes a plurality of openings formed
30 through its thickness. The piezoelectric actuator may be operable to directly or indirectly oscillate the generator plate, at a frequency to generate a directed stream of droplets of the low volume micro-dosing composition.

[0026] Without limitation, the droplet delivery device may be as described in US 8,684,980 or WO 2018/227190, which are herein incorporated by reference in their entireties.

[0027] In one embodiment, the device further includes a fluid enclosure system to facilitate ejection of the stream of droplets. In such an embodiment, the fluid to be delivered to the eye is contained in an enclosure which holds the fluid to be dispensed in a chamber defined by the enclosure. The enclosure holds the dose of fluid in proximity to the openings of the generator plate of the ejector mechanism so that the fluid may be ejected in a short amount of time and with little residual volume left.

[0028] The enclosure has a lip positioned adjacent the generator plate. The lip may be unattached to the generate plate, but still in contact with the generator plate or may be spaced apart a short distance so that surface tension holds the fluid in the chamber. The generator plate may have a relatively small maximum amplitude when vibrated which is less than an average separation distance between the lip and the generator plate or less than a minimum separation distance between the lip and the generator plate.

[0029] The enclosure may also be shaped to cooperate with the generator plate to avoid capillary feed near the openings in the generator plate. To this end, the enclosure may be spaced apart from the generator plate so that at least 75%, at least 95%, or all of the openings are spaced at least 0.014 from the nearest part of the enclosure. The enclosure may also shaped so that all of the fluid can reach the openings of the generator plate in a short period of time. The enclosure may be configured with an internal surface shape in contact with the fluid such that at least 75%, at least 95%, or even all, of the internal surface is no more than 0.060 inch, or no more than 0.040 inch, from a nearest of the plurality of openings of the generator plate. Stated another way, the enclosure has an internal surface shaped such that the chamber is formed with at least 75%, at least 95%, or all, of the internal surface having direct line of sight to at least one of the openings of the generator plate. The inner surface of the enclosure may be hydrophobic over at least 70% of the inner surface in contact with fluid.

[0030] The lip may be biased against the generator plate with a modest force to prevent the fluid from escaping while not overly dampening vibrations. The lip may exert a force of no more than 3 gram-f on the vibrating element measured in the direction of a central axis of the vibrating element. The lip may also apply a spring load to the generator plate so that minor displacements due to temperature, pressure or shock from an impact (dropped) can be accommodated. The spring load may also help to address manufacturing tolerances which affect the load applied by the lip to the generator plate. The lip may exert a spring load on the generator plate with an average spring constant of no more than 60 gram-f/mm for displacements up to 0.050 mm. The enclosure itself may be resilient with a wall of the

enclosure having a tapered portion with a relatively thin wall to provide flexibility. The tapered portion of the wall and has a ratio of radial displacement to longitudinal displacement of at least 1 to 3, at least 1 to 2 and may be at least 1 to 1. Stated another way, the tapered portion also extends radially with respect to the open end of the enclosure for at least half of
5 an effective radius of the open end of the enclosure. The lip and/or the vibrating element may have a PTFE coating adjacent to the other to reduce friction therebetween. The coating(s) may extending around at least 270 degrees when viewed along the central axis.

[0031] The enclosure may allow air into to replace ejected fluid through the openings of the generator plate and/or between the lip and the generator plate and may include no
10 dedicated vent opening. The maximum amplitude may be somewhat small which permits air to enter the chamber while still preventing fluid from escaping from the chamber. The enclosure to generator plate interface defines an enclosed border (which may be defined by either the generator plate or the enclosure) which is somewhat larger than the extent of the openings with an excess area which extends radially outwardly at least 0.3 times the effective
15 radius of the enclosed feed area.

[0032] The enclosure may include a wall opening through the wall which exposes the chamber through the wall. The wall opening. The wall opening extends through the wall to expose the chamber through the wall without permitting fluid to escape while permitting air to enter when fluid is ejected. The wall opening has a longitudinal dimension measured from
20 the lip in the direction of the central axis and a radial dimension measured in a radial direction relative to the central axis. The enclosure also has an internal wall with a side facing the openings in the generator plate. The longitudinal dimension of the wall opening is at least 80% of a separation distance between the generator plate and the side of the enclosure facing the openings. The radial dimension of the wall opening may be no more than 10%, or no
25 more than 5%, of a circumference of the lip.

[0033] The wall opening tapers as it extends proximally away from the lip. The wall opening extends from the lip proximally and a circumferential dimension of the wall opening tapers down as the wall opening extends proximally from the lip. The wall opening tapers so that a tapered shape is oriented in the direction of the fluid inlet to the enclosure when viewed
30 along the central axis. The wall opening may also extend through the frustoconical portion of the wall and may extend proximally from the lip for at least 80% of the length of the frustoconical portion.

[0034] The fluid may be delivered rapidly and at relatively high velocity and pressure to encourage all of the fluid to gather in the chamber. The total downstream volume of the

fluid path from a pump or valve which isolates the chamber may be sized somewhat larger than the volume to permit the fluid to move within the enclosure somewhat and coalesce into a single droplet due to surface tension. The volume of the fluid may be 40%-70% of the total downstream volume.

5 **[0035]** The enclosure may also split the fluid flow into at least two (and may be three, four or more) inlets to the chamber. Each of the inlets directs the fluid at a sidewall before being directed at the plurality of openings of the generator plate. The enclosure has a main inlet which directs the flow in a direction within 30 degrees of the central axis while the inlets to the chamber are oriented 60-90 degrees from the central axis and directed at the sidewall.

10 The enclosure may be an integrally formed structure which defines the chamber.

[0036] The pump may have a first part and a second part which reciprocate between a stored position, to a forward stroke position and back to the stored position in a single cycle. A cavity is formed between the two parts in which the fluid is drawn and subsequently expelled into the chamber. An air make-up chamber may also be coupled to the pump to
15 force air into a fluid reservoir during each cycle to actively vent the fluid reservoir.

[0037] It is understood that the droplet delivery device may have be separated into reusable and disposable portions in innumerable different combinations. For example, the enclosure may form part of a reusable device together with the ejector mechanism, or may be disposable with the reservoir without departing from the scope of the invention.

20 **[0038]** In certain aspects, the stream of droplets may be generated by devices described herein in a controllable distribution of sizes, each distribution having an average droplet size. In certain embodiments, the average droplet size may be in the range of at least about 15 microns, about 15 microns to about 100 microns, about 20 microns to about 100 microns, greater than 20 microns to about 100 microns, about 20 microns to about 80
25 microns, about 25 microns to about 75 microns, about 30 microns to about 60 microns, about 35 microns to about 55 microns, *etc.*

[0039] The device may also deliver the fluid at relatively high velocity which helps the fluid “stick” to the target tissue which, in this case, is corneal tissue resulting in direct corneal surface coating with the fluid. Eye droppers, on the other hand, do not have the
30 ability to target a particular area of the eye and deliver the fluid at high velocity. Eye drops are large enough to migrate and seep into undesirable areas after delivery. In this regard, the droplets may have an average initial ejecting velocity of about 0.5 m/s to about 20 m/s, *e.g.*, about 0.5 m/s to about 15 m/s, about 0.5 m/s to about 10 m/s, about 1 m/s to about 10 m/s, about 4 m/s to about 12 m/s, about 1 m/s to about 5 m/s, about 1 m/s to about 4 m/s, at least

about 2 m/s, at least about 3 m/s, at least about 4 m/s, at least about 5 m/s, *etc.* As used herein, the ejecting size and the ejecting initial velocity are the size and velocity of the droplets when the droplets leave the ejector plate. The stream of droplets directed at a target will result in deposition of a percentage of the mass of the droplets including their composition onto the desired location.

5 [0040] In certain aspects of the disclosure, the ejector devices will eject droplets without substantial evaporation, entrainment of air, or deflection off a target surface (*e.g.*, the surface of an eye), which facilitates consistent dosing. Average ejecting droplet size and average initial ejecting velocity are dependent on factors including fluid viscosity, surface tension, ejector plate properties, geometry, and dimensions, as well as operating parameters of the piezoelectric actuator including its drive frequency. In some implementations, about 10 60% to about 100%, about 65% to about 100%, about 75% to about 100%, about 80% to about 100%, about 85% to about 100%, about 90% to about 100%, about 95% to about 100%, *etc.*, of the ejected mass of droplets are deposited on the surface of the eye, such 15 deposition being repeatable independent of operating and use conditions.

[0041] The direction of flow of the stream of droplets may be horizontal, or any direction a user chooses to aim the actuation mechanism during use. In certain aspects, the device may be oriented substantially horizontal, *e.g.*, within 5° of horizontal, 10° of horizontal, 15° of horizontal, 20° of horizontal, 25° of horizontal, *etc.*, and may aid the user in aiming the device. For example, a light, mirror or other visual alignment feature may be used 20 as is known in the art. Horizontal delivery with alignment assistance may also improve ease of use and repeatability compared to an eyedropper which has no “aiming” mechanism and the drop is too large to target just corneal tissue. In this regard, it has been found that the same amount of drug with horizontal targeted corneal delivery and coating achieves higher 25 pharmacodynamic effect compared to same amount of drug given in an eyedropper.

[0042] Droplet performance is generally related to particle diameter. Without intending to be limited, ejected droplets are slowed to a stop by air drag (*i.e.*, stopping distance of the ejected droplets). Ejected droplets also fall vertically due to gravity. After a short acceleration time, the droplets reach terminal velocity where the drag force equals the 30 force of gravity. The ejected droplets may carry air along with them, which creates an entrained airstream, which aids to then carry the ejected droplets beyond the calculated stopping distance. However, increased levels of entrained air may cause the ejected droplets to flow across an impact surface (*e.g.*, an eye surface) because the entrained airflow must turn 90 degrees at such a surface. Small, ejected droplets (*e.g.*, droplets having an average

diameter less than about 17 microns, less than about 15 microns, *etc.*) are carried along the surface of the eye by the airstream and may not impact the surface. Contrasted to this, larger ejected droplets create less entrained air than an equivalent mass of smaller droplets, and have enough momentum to impact the surface. The ejected droplet stopping distance is a measure of this effect.

[0043] Many factors, including those described herein, can influence the desired dosage. Once the desired dosage is determined, and also if needed, desired frequency, such doses can be delivered. Frequency of dosing can vary by number of times, periodicity or both.

10 [0044] The term “therapeutically effective” amount refers to an amount of an active agent used to treat, ameliorate, prevent, or eliminate the identified ophthalmic condition (*e.g.*, disease or disorder), or to exhibit a detectable therapeutic or preventive effect. The effect can be detected by, for example, chemical markers, antigen levels, or time to a measurable event, such as morbidity or mortality. The precise effective amount for a subject will depend upon
15 the subject’s body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician. Any of the agents can be provided in an effective amount.

[0045] In an aspect, the concentration of an active ingredient in a medicament is
20 measured as a percentage of the active ingredient in solution. In an aspect, the concentration of active ingredient ranges from about 0.0001% to about 5%. In another aspect, the concentration of active ingredient in a medicament ranges from about 0.05% to about 1%. In other aspects, the concentration of active ingredient ranges from about about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.75%, about 1%, about 1.5%, about 2%,
25 about 2.5%, about 3%, about 4%, and about 5% measured as a weight percentage of the solution. However, given the lower dosing amounts afforded by the methods of the present disclosure, higher concentrations may be used depending on the intended use.

[0046] The present invention has been described with reference to certain embodiments, however, various modifications may be made without departing from the
30 features and aspects of the invention.