

ideal and can be washed away, for example when the patient blinks so as to provide less than ideal therapeutic benefit in at least some instance.

[0005] Implantable devices have been proposed to deliver treatment to the eye. However, in at least some instances, the therapeutic agent of the implantable device can be depleted, and the device may be removed or additional therapeutic agent placed in the device.

[0006] Prior methods and apparatus to place a therapeutic fluid in a device implanted in the eye can provide less than ideal results in at least some instances. For example, the amount of therapeutic agent placed in the device may be less than ideal in at least some instances. Further at least some of the prior methods to place of a therapeutic fluid in a device implanted in an eye may take longer than would be ideal. In at least some instances, the fluid placed initial in the device may be forced out of the therapeutic device, such that the amount of therapeutic agent placed in the treatment device can be less than ideal for sustained release of the therapeutic agent.

[0007] Work in relation to embodiment of the present invention also suggests that at least some prior injection apparatus may result in leakage during injection of the therapeutic agent. In at least some instances the injected fluid may comprise amounts of therapeutic agent that may be not be suitable for direct contact with tissue, such that leakage, or potential leakage, may limit available treatment options.

[0008] In light of the above, it would be desirable to provide improved methods and apparatus to place a therapeutic agent in a device implanted in the eye to provide improved treatments of diseases of the eye.

## SUMMARY OF THE INVENTION

[0009] ~~Embodiments~~Examples of the present ~~invention~~disclosure provide improved methods and apparatus to provide a therapeutic fluid to devices implanted in the body, for example to containers of devices implanted in the eye of a patient. The methods and apparatus may comprise an injector to increase an amount of therapeutic agent injected into the device implanted in the eye, or a structure to receive the therapeutic fluid within the device implanted in the eye, or combinations thereof. The device implanted in the eye may comprise a reservoir chamber coupled to a porous structure so as to release the therapeutic agent for an extended time.

In many ~~embodiments~~examples, the

volume of the reservoir chamber is sized to fit within the eye without substantially affecting vision. The porous structure may have a high resistance to flow, and in many embodiments/examples the therapeutic fluid injected into the device may be exchanged with a fluid of the device implanted in the eye.

**[0010]** In many embodiments/examples, the container implanted in the eye comprises a fluid having a density different than the fluid therapeutic fluid of the container implanted in the body. The therapeutic fluid may comprise a formulation of a therapeutic agent having a density greater than a fluid of the device implanted in the eye, such that the therapeutic formulation injected into the implanted chamber may separate at least partially. In many embodiments/examples, the at least partial separation of the therapeutic fluid from the fluid of the implanted device can be used to improve an efficiency of exchange of the therapeutic fluid with the fluid of the chamber, so as to increase the amount of therapeutic fluid in the chamber. While the methods and apparatus as described herein can be used with many devices to increase the amount of therapeutic fluid in the implanted device, the increased the efficiency can be especially beneficial with implanted devices having a reservoir chamber comprising a substantially constant volume. Also, with implants located at least partially in the vitreous humor of the eye, the size of the reservoir chamber can somewhat limited to provide a clear optical path for vision, and the embodiments/examples described herein can be used to increase the amount of fluid placed in the chamber so as to increase the therapeutic benefit of the implanted device and provide sustained release for an extended time.

**[0011]** In many embodiments/examples, one or more of the therapeutic device or the injector can be configured to increase the amount of therapeutic fluid placed in the device based on the at least partial separation. The injector may comprise a first channel sized to extend to a first opening at a first location of the implanted device reservoir chamber so as to pass the therapeutic fluid into the chamber, and a second channel can be sized to extend to a second opening at a second location of the implanted device chamber so receive the fluid of the implanted device, such that the efficiency of the exchange can be increased based on the at least partial separation and the separation of the first location and the second location. The first channel may comprise a first lumen of at least one needle, and the second channel can be sized and shaped in many ways and may comprise a second lumen of the at least one needle. The second opening may comprise a

vent to receive fluid from the chamber of the therapeutic device and inhibit excessive pressurization of the reservoir chamber so as to maintain substantially the integrity and function of the therapeutic device implanted in the eye.

[0012] In many ~~embodiments~~examples, the injector comprises a stop coupled to the at least one needle. The first opening can be located a first distance from the stop and the second opening can be located a second distance from the stop, such that the first opening and the second opening are placed at locations of the implanted device so as to increase the at least partial separation when the stop engages a tissue surface such as the conjunctiva. In many ~~embodiments~~examples, the therapeutic fluid can be denser than the fluid of the implanted device and, and the first opening to inject the therapeutic fluid may be located below the second opening when placed in the reservoir chamber, such that the denser therapeutic fluid can be placed in the reservoir chamber below the less dense fluid of the reservoir chamber so as to enhance the at least partial separation.

[0013] The stop may comprise a soft material, such as an elastomer. The soft material may form a seal when placed against a tissue surface such as the conjunctiva, and can maintain integrity of the conjunctival epithelium when the seal engages the conjunctiva. The sealing can decrease leakage of the therapeutic fluid, which can be helpful to increase an amount of fluid placed in the reservoir chamber of the therapeutic device. The sealing of the soft stop engaging the conjunctiva may also decrease interaction of the therapeutic fluid with the conjunctiva, which can be beneficial when the therapeutic fluid comprises a concentration or amount of therapeutic agent that may have a potentially undesirable interaction with the conjunctiva, for example with an antineoplastic therapeutic agent.

[0014] In many ~~embodiments~~examples, the injector can be configured to pass a bolus of therapeutic fluid through the porous structure of the therapeutic device. The injector may comprise a valve that closes to push therapeutic fluid through the porous structure of the implanted device. The valve may comprise one or more of a mechanism, a porous structure, or a resistance to flow to pass the therapeutic fluid through the porous structure. The mechanism may comprise one or more movable components such as a slider, a piston, a sleeve or a deflectable component. The porous structure may comprise a porous material having resistance to flow that increase substantially when the displaced fluid of the implanted device contacts the porous structure. The resistance to flow may correspond to a restriction or other structure along the outflow path of the

second channel. The resistance to flow can be sufficient so as to encourage the therapeutic fluid to pass through the therapeutic structure. The structure corresponding to the resistance to flow along the outflow path may comprise a lumen coupled to a vent placed in the therapeutic device.

[0015] In many ~~embodiments~~examples, the injector comprises a flow rate to provide the at least partial separation.

[0016] In many ~~embodiments~~examples, one or more of the therapeutic device or the injector can be configured to mix the therapeutic fluid with the implanted device fluid when the therapeutic fluid is injected so as to increase the amount of therapeutic fluid in the chamber. In many ~~embodiments~~examples, the injector is configured to inject the therapeutic fluid at a rate of no more than about 100 uL per second, for example, and one or more of the injector or the implanted comprises structures to mix the therapeutic fluid with the fluid of the implanted device at the flow rate capable of providing the at least partial separation.

[0016a] In one aspect, there is provided an apparatus for injecting a therapeutic agent into a therapeutic device to treat an eye, the therapeutic device being at least partially implanted in the eye, the apparatus comprising:

an injector comprising:

\_\_\_\_\_ an exchange needle configured to penetrate the therapeutic device implanted in the eye, the exchange needle comprising:

\_\_\_\_\_ a first lumen having a first opening out from the first lumen; and

\_\_\_\_\_ a second lumen surrounding at least a portion of the first lumen and having a second opening into the second lumen,

\_\_\_\_\_ wherein the first lumen is longer than the second lumen such that the first opening from the first lumen is located distal to the second opening into the second lumen; and

\_\_\_\_\_ a chamber configured to be in fluid communication with the second lumen;

\_\_\_\_\_ wherein injection of an amount of the therapeutic agent into the therapeutic device via the first lumen displaces an amount of pre-existing fluid from the therapeutic device into the chamber via the second lumen.

[0017] ~~Also disclosed is~~In a first aspect, embodiments of the present invention provide an apparatus to treat a patient. The apparatus comprises an injector to inject a therapeutic fluid into a chamber of a therapeutic device implantable in the patient with at least partial separation of a fluid of the implantable therapeutic device from the therapeutic fluid.

[0018] ~~Also disclosed is~~In another aspect, embodiments of the present invention provide an apparatus to treat an eye. The apparatus comprises an injector to inject a therapeutic fluid into a chamber of a therapeutic device implantable in the eye with at least partial separation of a fluid of the implantable therapeutic device from the therapeutic fluid.

[0019] In many ~~embodiments~~examples, the therapeutic fluid comprises a therapeutic fluid density different from a density of the fluid of the implantable therapeutic device so as to provide the at least partial separation.

[0020] In many ~~embodiments~~examples, the fluid of the implantable therapeutic device comprises a density different from the therapeutic fluid density. The therapeutic fluid density may differ from the density of the implantable device fluid by at least about 1% so as to provide the at least partial separation, for example by at least about 2% so as to provide the at least partial separation. The therapeutic fluid density may differ from the density of the implantable device

fluid by at least about 3% so as to provide the at least partial separation. The therapeutic fluid density may differ from the density of the implantable device fluid by no more than about 30% so as to provide the at least partial separation, for example by no more than about 20% so as to provide the at least partial separation. In many ~~embodiments~~examples, the therapeutic fluid density differs from the density of the implantable device fluid by no more than about 10% so as to provide the at least partial separation.

[0021] In many ~~embodiments~~examples, a difference of the therapeutic fluid density relative to the density of the implantable device fluid is within a range from about 1% to about 30% so as to provide the at least partial separation, for example within a range from about 2% to about 20% so as to provide the at least partial separation. The difference of the therapeutic fluid density relative to the density of the implantable device fluid can be within a range from about 3% to about 10% so as to provide the at least partial separation.

[0022] In many ~~embodiments~~examples, the injector comprises at least one needle comprising a first lumen to pass the therapeutic fluid into the therapeutic device and a second lumen to receive the therapeutic fluid from the chamber, and the injector is configured to inject the therapeutic fluid at a flow rate so as to inhibit mixing of the therapeutic fluid with the implantable device fluid such that the second lumen receives a portion of the device fluid substantially separated from the therapeutic fluid.

[0023] In many ~~embodiments~~examples, the injector is configured to inject the therapeutic agent at a flow rate so as to provide the at least partial separation. The at least partial separation can be based on a therapeutic fluid density different from a therapeutic fluid density.

[0024] In many ~~embodiments~~examples, the chamber has a substantially constant volume. The substantially constant volume can be within a range from about 1 uL to about 100 uL or more. The substantially constant volume can be within a range from a range from about 15 uL to about 75 uL, for example within a range from about 25 uL to about 75 uL.

[0025] In many ~~embodiments~~examples, the injector is configured to inject the therapeutic fluid into the chamber over a period of time. The time can be within a range from about 1 second to about 30 seconds, for example within a range from about 2 seconds to about 8 seconds.

[0026] In many ~~embodiments~~examples, the injector comprises one or more of a structure resistant to flow, a restriction, a porous structure, a sintered porous structure, or a mechanism to inject the agent at the rate sufficient to provide the at least partial separation. The mechanism comprises one or more of a spring, a gas, or a liquid to inject the liquid at the rate.

[0027] In many ~~embodiments~~examples, the implantable device comprises a porous structure to release the therapeutic agent. The porous structure has a resistance to flow, and the injector structure resistant to flow comprises a resistance to flow proportional to the resistance to flow of the porous structure, such that a portion of the therapeutic fluid passes through the porous structure.

[0028] In many ~~embodiments~~examples, the implant fluid comprises a remaining portion of a first therapeutic fluid placed in the therapeutic device for at least about one week, and the therapeutic fluid is similar to the first therapeutic fluid.

[0029] In many ~~embodiments~~examples, the fluid of the implantable device comprises a remaining portion of a first amount of first therapeutic agent of a first therapeutic fluid placed in the therapeutic device and components of the vitreous humor of the eye. The remaining portion of the first therapeutic fluid placed in the implantable device may comprise a remaining amount of the therapeutic agent. The remaining amount of the therapeutic agent corresponds to no more than about half of a first amount of the first therapeutic agent so as to provide the density difference. The remaining portion may comprise a remaining stabilizer, and an amount of the remaining stabilizer may correspond to no more than about half of a first amount of the stabilizer of the first therapeutic fluid so as to provide the density difference.

[0030] In many ~~embodiments~~examples, one or more components of the vitreous humor correspond to the density of the fluid of the implantable therapeutic device less than the therapeutic fluid therapeutic fluid density so as to provide the at least partial separation.

[0031] In many ~~embodiments~~examples, the therapeutic fluid density is within a range. The range can be from about 0.5 g/cm<sup>3</sup> to about 2 g/cm<sup>3</sup> and the implantable device density is within a range from about 0.5 to about 2 g/cm<sup>3</sup>, for example within a range from about 1.01 to about 1.5 g/cm<sup>3</sup>. The therapeutic fluid density can be within a range from about 1.03 to about 1.5 g/cm<sup>3</sup>.

[0032] In many ~~embodiments~~examples, the injector comprises at least one needle having at least one lumen to couple the chamber to a syringe comprising the therapeutic agent. The at least one lumen may comprise a first lumen to pass the therapeutic fluid into the implantable device and a second lumen to receive liquid from the implantable therapeutic device. The first lumen may extend to a first opening and the second lumen may extend to a second opening, in which the first opening is spaced apart from the second opening so as to encourage the at least partial separation. The first opening can be located distal to the second opening, such that the therapeutic fluid is passed to a distal portion of the chamber and the fluid of the implantable therapeutic device is received with the proximal portion of the chamber to encourage the at least partial separation.

[0033] In many ~~embodiments~~examples, a container receives the fluid of the therapeutic device received through the second lumen, and the container comprises a vent to pass air displaced from the container. The vent can be fluidically coupled to the second opening so as to define a flow path extending from the opening to the vent.

[0034] In many ~~embodiments~~examples, the flow path comprises a resistance to flow so as to encourage the at least partial separation. The flow path may comprises one or more structures to inhibit flow of the fluid of the therapeutic device, the one or more structures comprising one or more of a size of the second opening, a restriction along the flow path or a porous structure along the flow path.

[0035] In many ~~embodiments~~examples, the injector porous structure comprises a plurality of interconnecting channels located along the flow path on a downstream portion of the container. The injector porous structure comprises a resistance to liquid flow greater than a porous structure of the implantable device such that the therapeutic fluid is passed through the porous structure of the implantable device when the fluid of the implantable device contacts the injector porous structure located along the flow path on the downstream portion of the container.

[0036] In many ~~embodiments~~examples, the second lumen is coupled to a vent and the vent comprises a resistance to flow to pressurize the chamber and pass a portion of the therapeutic fluid through the porous structure when the fluid of the implantable device passes through the vent.

[0037] In many ~~embodiments~~examples, the injector comprises a cartridge comprising the at least one needle to couple to the syringe. The cartridge may comprise a vent having a resistance to flow sufficient to encourage the at least partial separation of the therapeutic agent fluid from the fluid of the implantable device.

[0038] In many ~~embodiments~~examples, the at least one lumen comprises a first lumen to pass the therapeutic fluid into the implantable device and a second lumen to receive liquid from the implantable therapeutic device.

[0039] In many ~~embodiments~~examples, the at least one needle comprises a first needle and a second needle.

[0040] In many ~~embodiments~~examples, the at least one needle comprises a first needle having a first lumen extending along a first axis and a second needle having a second lumen extending along a second axis, and the first axis is separated from the second axis so as to increase the at least partial separation of the therapeutic fluid from the implantable device fluid.

[0041] In many ~~embodiments~~examples, the at least one needle comprises a double lumen needle having a first needle having a first lumen extending along a first axis and a second needle having a second lumen extending along the first needle such that the second needle is substantially concentric with the first axis.

[0042] In many ~~embodiments~~examples, the at least one needle comprises an axis extending along an elongate dimension of the at least one needle and wherein the at least partial separation corresponds to an angle of the axis away from horizontal when the therapeutic formulation is injected. The at least partial separation may correspond to an increase of at least about one per cent of an amount of therapeutic fluid placed in the therapeutic device when the angle away from horizontal comprises at least about 10 degrees. The at least partial separation may correspond to an increase of at least about two per cent of an amount of therapeutic fluid placed in the therapeutic device when the angle away from horizontal comprises at least about 35 degrees.

[0043] In many ~~embodiments~~examples, the injector is configured to inject the therapeutic fluid with the at least partial separation such that a 1 percent increase in density of the therapeutic fluid relative

to the density of the chamber fluid corresponds to at least about a 1 percent increase of the amount of therapeutic fluid placed in the chamber.

[0044] In many ~~embodiments~~examples, the injector is configured to inject the therapeutic fluid with the at least partial separation such that a 1 percent increase in density of the therapeutic fluid relative to the density of the chamber fluid corresponds to at least about a 2 percent increase of the amount of therapeutic fluid placed in the chamber with an injection of the therapeutic fluid into the container.

[0045] In many ~~embodiments~~examples, the injector is configured to inject the therapeutic fluid with the at least partial separation such that a 3 percent increase in density of the therapeutic fluid relative to the density of the chamber fluid corresponds to at least about a 4 percent increase of the amount of therapeutic fluid placed in the chamber with an injection of the therapeutic fluid into the container.

[0046] In many ~~embodiments~~examples, the at least about 1 percent increase of the amount of therapeutic fluid placed in the chamber corresponds to an angle of injection away from horizontal. The angle of injection away from horizontal corresponds to at least about 10 degrees away from horizontal, and may correspond to at least about 15 degrees away from horizontal.

[0047] In many ~~embodiments~~examples, the fluid of the implantable device comprises a liquid composed of water, components of the vitreous humor of the eye, and the therapeutic agent. The fluid of the implantable device may comprise a stabilizer.

[0048] In many ~~embodiments~~examples, the therapeutic fluid comprises a liquid composed of water and the therapeutic agent. The therapeutic fluid may comprise a stabilizer.

[0049] In many ~~embodiments~~examples, the fluid of the implantable device is displaced at a rate within a range from about 1 uL per second to about 200 uL per second. The fluid of the implantable device can be displaced at a rate within a range from about 2 uL per second to about 100 uL per second, for example from about 5 uL per second to about 50 uL per second.

[0050] In many ~~embodiments~~examples, the fluid of the implantable device is displaced with an efficiency of at least about 70%. The fluid of the implantable device can be displaced with an efficiency of at least about 80%, for example at least about 90%.

[0051] In many ~~embodiments~~examples, the valve comprises one or more of a float valve coupled to an opening or a hard stop coupled to a piston.

[0052] In many ~~embodiments~~examples, the injector comprises a cartridge comprising the at least one needle to couple to the syringe.

[0053] ~~Also disclosed is an~~In another aspect, embodiments of the present invention provide apparatus to treat an eye. The apparatus comprises a cartridge to inject a therapeutic fluid into a chamber of a therapeutic device implantable in the eye with at least partial separation of a fluid of the implantable therapeutic device from the therapeutic fluid.

[0054] In many ~~embodiments~~examples, the cartridge comprises a connector to couple to a syringe, a vent and at least one needle. The at least one needle comprising a first lumen and a second lumen, the first lumen sized to extend from the connector into the chamber to pass the therapeutic fluid from the syringe, the second lumen comprising the vent and sized to place the vent in the chamber and extend to a collection container so as to receive the fluid of the implantable therapeutic device with the collection container, wherein cartridge is adapted to the density of the therapeutic fluid so as to provide a refill efficiency of the chamber of at least about 70%.

[0055] In many ~~embodiments~~examples, the vent comprises a resistance to flow corresponding to a resistance to flow of a porous structure of the implantable device to pass an amount of the therapeutic fluid through the porous structure when the therapeutic device fluid is displaced.

[0056] In many ~~embodiments~~examples, the resistance to flow of the vent structure is proportional to the resistance to flow of the porous structure so as to pass the amount of the therapeutic fluid through the porous structure.

[0057] In many ~~embodiments~~examples, the resistance to flow of the vent structure is substantially greater than to the resistance to flow of the porous structure so as to pass the amount of the therapeutic fluid through the porous structure. The vent structure may comprise a channel sized to provide a substantial portion of the resistance to flow of the vent structure. The vent structure may comprise a porous material to provide a substantial portion of the resistance to flow of the vent structure.

[0058] In many ~~embodiments~~examples, the at least one needle comprises a first needle and the second needle.

[0059] In many ~~embodiments~~examples, the at least one needle comprises a double lumen needle.

[0060] ~~Also disclosed is an~~In another aspect, embodiments provide, apparatus to treat a patient. An implantable device comprises a chamber and a penetrable barrier coupled to a porous structure. The device is capable of receiving a pressure of at least about 50 PSI to the chamber and the porous structure without rupturing.

[0061] In many ~~embodiments~~examples, the device is capable of receiving a pressure of at least about 100 PSI to the chamber, the penetrable barrier and the porous structure without rupturing.

[0062] In many ~~embodiments~~examples, the device is capable of receiving a pressure of at least about 200 PSI to the chamber, the penetrable barrier and the porous structure without rupturing.

[0063] ~~Also disclosed is~~In another aspect, embodiments provide an apparatus to treat a patient. An implantable device comprises a chamber and a penetrable barrier coupled to a porous structure. The chamber comprises a proximal end and a distal end. The porous structure is located away from the distal of the chamber in increase an amount of therapeutic fluid placed in the chamber with one or more of injection or aspiration.

[0064] ~~Also disclosed is~~In another aspect, embodiments provide an apparatus to treat a patient. The apparatus comprises a therapeutic device comprising a reservoir chamber and a fluid separator within the reservoir chamber of the device to separate a therapeutic fluid injected into the device from a fluid of the implantable device.

[0065] In many ~~embodiments~~examples, the fluid separator comprises one or more of movable fluid separator or a container within the reservoir chamber of the therapeutic device.

[0066] ~~Also disclosed is~~In another aspect, embodiments provide an apparatus. The apparatus comprises an injector configured to inject air into a chamber of a device implantable in the eye to replace a fluid of the device with a therapeutic fluid.

[0067] ~~Also disclosed is~~In another aspect, embodiments provide an apparatus to treat a patient. An injector device comprises a needle and a stop. The needle comprises a tip. An implantable device

comprises a chamber and a penetrable barrier coupled to a porous structure. A structure to divert flow of a therapeutic fluid is located within the chamber. The stop is configured to position the tip of the needle within the chamber with a gap extending between the tip and the structure when the stop contacts a conjunctiva of the eye.

[0068] ~~Also disclosed is an~~~~In another aspect, embodiments provide~~ apparatus to treat an eye. A connector to couple to a container having a therapeutic fluid comprises therapeutic agent to treat the eye. At least one needle comprises a first lumen to pass the therapeutic fluid and a second lumen to receive the fluid from the therapeutic device. The first lumen extends to a first opening, and the second lumen extends to a second opening. A container receives a fluid from a therapeutic device implantable in the eye. The second lumen is fluidically coupled to the container so as to define a flow path extending from the second opening to the container. The flow path comprises a resistance so as to at least partially separate the therapeutic fluid from the fluid of the implantable device when the therapeutic fluid displaces the fluid of the implantable device.

[0069] ~~Also disclosed is an~~~~In another aspect, embodiments provide~~ an apparatus to treat an eye with a therapeutic agent. At least one needle comprises a lumen extending to an opening to inject a therapeutic fluid comprising the therapeutic agent into a chamber of a therapeutic device implantable in the eye. A vent structure is configured to receive a fluid of the therapeutic device. The vent structure comprises a resistance to flow of the fluid of the therapeutic device.

[0070] In many ~~embodiments~~examples, the resistance to flow of the vent structure corresponds to a resistance to flow of a porous structure of the therapeutic device so as to pass an amount of the therapeutic fluid through the porous structure.

[0071] In many ~~embodiments~~examples, the amount comprises at least about 0.1 per cent of an injection amount into the therapeutic device.

[0072] In many ~~embodiments~~examples, the vent structure comprises a vent and a channel coupled to the vent so as to provide the resistance to flow of the vent structure.

[0073] In many ~~embodiments~~examples, the apparatus further comprises a stop, in which the stop comprises a lower surface to engage a conjunctiva of the eye. The at least one needle extends a distance along an axis from the lower surface to the opening, and the distance is dimensioned to

place the opening and the vent in the reservoir chamber when the lower surface engages the conjunctiva.

[0074] In many ~~embodiments~~examples, the apparatus further comprises a cartridge, and the cartridge comprises the at least one needle and the vent structure. The cartridge comprises a connector to couple to a syringe, and the at least one needle comprises a first lumen and a second lumen. The first lumen can be sized to extend from the connector into the chamber to pass the therapeutic fluid from the syringe, and the second lumen may extend to the vent and be sized so as to place the vent in the chamber and extend to a collection container so as to receive the fluid of the implantable therapeutic device with the collection container. The cartridge can be adapted to the density of the therapeutic fluid so as to provide a refill efficiency of the chamber of at least about 70%.

[0075] In many ~~embodiments~~examples, the resistance to flow of the vent structure is substantially greater than the resistance to flow of the porous structure of the implantable device so as to pass the amount of the therapeutic fluid through the porous structure.

[0076] In many ~~embodiments~~examples, the resistance to flow of the vent structure is substantially less than the resistance to flow of the porous structure of the implantable device so as to pass the amount of the therapeutic fluid through the porous structure.

[0077] In many ~~embodiments~~examples, the at least one needle comprises a first needle and the second needle.

[0078] In many ~~embodiments~~examples, the at least one needle comprises a double lumen needle.

[0079] ~~Also disclosed is a~~In another aspect, embodiments provide method of treating a patient with an implantable device. A therapeutic fluid is injected into a chamber of a therapeutic device implanted in the patient, such that the therapeutic fluid entering the chamber is at least partially separated from a fluid of the chamber.

[0080] ~~Also disclosed is a~~In another aspect, embodiments provide method of treating an eye. A therapeutic fluid is injected into a chamber of a therapeutic device implanted in the eye, such that the therapeutic fluid entering the chamber is at least partially separated from a fluid of the chamber.

[0081] In many ~~embodiments~~examples, the therapeutic fluid comprises a density and the fluid of the device comprises a density different from the density of the therapeutic fluid.

[0082] In many ~~embodiments~~examples, the therapeutic device comprises a penetrable barrier on a proximal end and a porous structure on a distal end with an axis extending between the penetrable barrier and porous structure and wherein the axis is oriented away from horizontal to provide the at least partial separation. The patient can be positioned such that the porous structure is located above the penetrable barrier.

[0083] In many ~~embodiments~~examples, the patient is reclined in a chair with a tilted head such that the porous structure is located above the penetrable barrier when the implanted device is located in the pars plana region of the eye.

[0084] In many ~~embodiments~~examples, the patient is positioned such that the porous structure is located below the penetrable barrier.

[0085] In many ~~embodiments~~examples, the therapeutic fluid is injected upward to at least partially separate the therapeutic fluid from the fluid of the implanted therapeutic device.

[0086] In many ~~embodiments~~examples, the therapeutic fluid is injected downward to at least partially separate the therapeutic fluid from the fluid of the implanted therapeutic device.

[0087] In many ~~embodiments~~examples, at least one needle is advanced through a penetrable barrier of the implanted device such that a first opening of the at least one needle is placed at a distal portion of the chamber and a second opening of the at least one needle is placed at a proximal portion of the chamber such that the first opening is located below the second opening and wherein the therapeutic fluid comprises a density greater than the implanted device fluid and is passed through the first opening below the second opening so as to at least partially separate the therapeutic fluid from the therapeutic device fluid within the chamber.

[0088] In many ~~embodiments~~examples, the therapeutic fluid is injected with the at least partial separation such that a percent change in density of the therapeutic fluid corresponds to a percent change in fill efficiency of the chamber greater than the percent change in density of the therapeutic fluid.

[0089] ~~Also disclosed is~~In another aspect, ~~embodiments provide~~ a method of treating an eye. Air is injected into a chamber of a therapeutic device implanted in the eye to at least partially replace a fluid of the implanted device with a therapeutic fluid.

[0090] ~~Also disclosed is~~In another aspect, ~~embodiments provide~~ an apparatus to inject a therapeutic agent into a patient. The apparatus comprises at least one needle capable of penetrating an external tissue of the patient and extending to a depth within the patient and one or more chambers to hold a therapeutic agent coupled to the at least one needle. A deformable indicator extends at least partially around the at least one needle to indicate needle penetration of the needle to the depth.

[0091] In many ~~embodiments~~examples, the deformable visual indicator comprises a first configuration having a first cross sectional width prior to contact with the tissue and a second configuration having a second cross sectional width, in which the second cross sectional width is greater than the first cross sectional width to indicate the needle at the depth with increased visibility of the visual indicator.

[0092] In many ~~embodiments~~examples, the at least one needle is supported with an annular support structure having a distance across and wherein the deformable visual indicator comprises an annular deformable structure extending around the at least one needle, and the first cross sectional width is less than the distance across and the second cross sectional width is greater than the distance across.

[0093] In many ~~embodiments~~examples, the deformable visual indicator comprises a modulus to resist deformation to indicate the needle inserted to the depth with a force to maintain the at least one needle at the depth.

[0094] In many ~~embodiments~~examples, the deformable visual indicator visible comprises a visible color to indicate the needle at the depth to the user.

[0095] In many ~~embodiments~~examples, the at least one needle comprises a first lumen extending from the visual indicator to a first opening located first distance from the visual indicator and a second lumen extending from the visual indicator to a second opening located a second distance from the visual indicated and wherein visual indicator indicates the first opening at a first depth and the second opening at a second depth.

[0096] In many ~~embodiments~~examples, the at least one needle comprises a silicon needle having a gauge of at least about 25.

[0097] In many ~~embodiments~~examples, the deformable visual indicator comprises a Shore A hardness within a range from about 5 to about 30 to indicate the needle inserted to the depth with a force to maintain the at least one needle at the depth.

[0098] In many ~~embodiments~~examples, the apparatus further comprises an implantable therapeutic device, the implantable therapeutic device having a reservoir chamber to hold a quantity of therapeutic agent, the reservoir chamber extending along an axis of the therapeutic device, and wherein the at least one needle has an lumen extending to opening separated from the deformable visual indicator such that the opening is located in the reservoir chamber when the visual indicator is deformed to indicate the needle positioned at the distance.

[0099] In many ~~embodiments~~examples, the implantable therapeutic device comprises a porous structure to release therapeutic amounts of the therapeutic agent for an extended time. The porous structure may comprise a release rate index of no more than about 0.5 to release the therapeutic agent for an extended time of at least about one month.

[0100] In many ~~embodiments~~examples, the opening is positioned in a proximal half of the reservoir chamber when the visual indicator is deformed.

[0101] In many ~~embodiments~~examples, the opening is positioned in a distal half of the reservoir chamber when the visual indicator is deformed.

[0102] ~~In another aspect, embodiments provide~~ Also disclosed is a method of treating a patient having a tissue. At least one needle is advanced into the tissue such that a deformable visual indicator couples to the tissue and deforms to indicate the at least one needle at a depth. A therapeutic agent is injected from one or more chambers coupled to the at least one needle such that the therapeutic agent is injected through a lumen of the at least one needle at the depth when the visual indicator is deformed.

[0103] In many ~~embodiments~~examples, the deformable visual indicator comprises a first configuration having a first cross sectional width prior to contact with the tissue and a second configuration having a second cross sectional width when the indicator is coupled to the external penetrable

tissue, in which the second cross sectional width is greater than the first cross sectional width to indicate the needle at the depth with increased visibility of the visual indicator.

[0104] In many ~~embodiments~~examples, the apparatus further comprises an implantable therapeutic device. The implantable therapeutic device has a reservoir chamber to hold a quantity of therapeutic agent. The reservoir chamber has a thickness and a width sized for placement between the conjunctiva and the sclera, and wherein the at least one needle has an lumen extending to opening separated from the deformable visual indicator such that the opening is located in the reservoir chamber when the visual indicator is deformed to indicate the needle positioned at the distance.

#### BRIEF DESCRIPTION OF THE DRAWINGS

[0105] FIG. 1 shows an eye suitable for incorporation of the therapeutic device, in accordance with embodiments of the present invention;

[0106] FIG. 1A-1 shows a therapeutic device implanted at least partially within the sclera of the eye as in FIG. 1;

[0107] FIG. 1A-1-1 and 1A-1-2 show a therapeutic device implanted under the conjunctiva and extending through the sclera to release a therapeutic agent into vitreous humor of the eye so as to treat the retina of the, in accordance with embodiments of the present invention;

[0108] FIG. 1A-2 shows structures of a therapeutic device configured for placement in an eye as in FIGS. 1A-1 and 1A-1-1, according to embodiments of the present invention;

[0109] FIG. 1A-2-1 shows a therapeutic device loaded into an insertion cannula, in which the device comprises an elongate narrow shape for insertion into the sclera, and in which the device is configured to expand to a second elongate wide shape for retention at least partially in the sclera;

[0110] FIG. 1A-2-2 shows a therapeutic device comprising a reservoir suitable for loading in a cannula;

[0111] FIG. 1B shows a therapeutic device configured for placement in an eye as in FIG. 1A-1 and 1A-1-1, in accordance with embodiments of the present invention;