

TWO-STAGE MICROCHIP DRUG DELIVERY DEVICE AND METHODS

Cross-Reference to Related Applications

[0001] This application claims priority to U.S. Provisional Patent Application No.
5 62/929,432, filed November 1, 2019, which is incorporated herein by reference.

Field of the Disclosure

[0002] This disclosure generally relates to medical devices, including but not limited to implantable drug delivery devices for controlled release of therapeutic or prophylactic agents over extended periods.

Background

[0003] Typical drug delivery devices offer either a bolus delivery of drug or an extended release of drug. Often a bolus delivery produces an initially high plasma drug level before rapidly decreasing. In such cases, the drug concentration level may be initially higher than desired (potentially producing unwanted side effects), before passing through, and then
15 falling below, a therapeutically effective range as the drug is processed by the patient's body. Conversely, a conventional extended-release or continuous-release drug delivery device often relies on passive diffusion from and/or degradation of a matrix material to control release. With these systems, it may initially take an undesirably long time to release enough drug to reach therapeutically effective plasma drug levels, even though the drug levels may remain in
20 a therapeutically effective range for a longer period (as compared to a bolus). Thus, with both typical bolus drug delivery and extended- or continuous-release drug delivery devices, a significant period may be outside the therapeutic window for a particular drug being delivered.

[0004] Implantable devices including microchip reservoir arrays containing drug for
25 controlled release of hundreds of doses of drug over several months or years are known. Such devices are described, for example, in U.S. Patent No. 8,403,915 to Santini et al., U.S. Pat. Pub. No. 2013/0053671 to Farra, and U.S. Pat. Pub. No. 2014/0243624 to Farra. Drug release into the patient may be pulsatile. That is, each dose may be released automatically on a predetermined schedule or on demand by the patient or clinician, by diffusion out of its own
30 reservoir following opening of each reservoir.

[0005] It would be desirable to provide a drug delivery device, such as an implantable drug delivery device, that is able to keep drug plasma levels within a selected therapeutic range for

longer periods and/or to avoid or reduce undesirable lag times in reaching therapeutically effective drug levels.

Summary

[0006] Drug delivery devices, implantable drug delivery devices, and methods of drug delivery are provided.

[0007] In one aspect, a drug delivery device is provided which includes (i) a microchip element which comprises a body portion defining at least one containment reservoir therein, wherein the body portion has an exterior wall having one or more drug release apertures in fluid communication with the at least one containment reservoir, the one or more drug release apertures being closed off by one or more corresponding reservoir caps configured to be electrically activated to unclosethe one or more drug release apertures; (ii) a drug formulation, which comprise a first drug, disposed in the at least one containment reservoir; and (iii) a drug-permeable membrane secured next to the exterior wall of the body portion of the microchip element, wherein the device is configured to operate in an aqueous environment and, upon activation of the one or more reservoir caps, release the drug by diffusion through the drug-permeable membrane and into the aqueous environment. The device may further include an outer housing wall secured in a position next to, and spaced a distance from, the exterior wall of the body portion of the microchip element, the outer housing wall comprising the drug-permeable membrane, wherein a depot space is defined between the drug-permeable membrane and the exterior wall of the body portion of the microchip element.

[0008] For example, in one embodiment, an implantable drug delivery device is provided which includes a microchip element that includes a body portion defining a plurality of microreservoirs therein, wherein the body portion has an exterior wall having a plurality of drug release apertures in fluid communication with the microreservoirs, the plurality of drug release apertures being closed off by a plurality of corresponding reservoir caps configured to be ruptured by electrothermal ablation to open the drug release apertures; a drug disposed in each of the microreservoirs; a water swellable charge material disposed in each of the microreservoirs; and an outer housing wall secured in a position next to, and spaced a distance from, the exterior wall of the body portion of the microchip element, the outer housing wall including a drug-permeable membrane, wherein a depot space is defined between the drug-permeable membrane and the exterior wall of the body portion of the microchip element. In this embodiment, the device is configured to operate *in vivo* by permitting interstitial fluid, following activation of one or more of the plurality of reservoir

caps, to contact and be imbibed by the water swellable charge material disposed the microreservoirs corresponding to the activated reservoir caps, and thereby cause the charge material to swell and eject the drug out of the microreservoirs through the drug release apertures and into the depot space for subsequent diffusion through the drug-permeable membrane.

[0009] Disclosed herein is a method for controlled drug delivery to a patient. In embodiments, the method includes (i) implanting a drug delivery device into the patient, e.g., subcutaneously; (ii) activating at least one of the one or more reservoir caps to permit interstitial fluid to contact the drug in the containment reservoir corresponding to the activated reservoir cap(s); and (iii) releasing the drug from the device by diffusion of the drug through the drug-permeable membrane. For example, the contacting of the drug in the activated containment reservoir may transfer the drug into a drug depot space and therein form a drug depot, and then the drug diffuses from the device by diffusion from the drug depot through the drug-permeable membrane. The transfer of the drug from the containment reservoir to the drug depot space may comprise swelling of a water swellable charge material to eject the drug from the containment reservoir.

Brief Description of the Drawings

[0010] The detailed description is set forth with reference to the accompanying drawings. The use of the same reference numerals may indicate similar or identical items. Various embodiments may utilize elements and/or components other than those illustrated in the drawings, and some elements and/or components may not be present in various embodiments. Elements and/or components in the figures are not necessarily drawn to scale. Throughout this disclosure, depending on the context, singular and plural terminology may be used interchangeably.

[0011] **FIG. 1** is a perspective view of a drug delivery device according to one embodiment.

[0012] **FIG. 2** is a cross-sectional, perspective view of the drug delivery device of **FIG. 1**.

[0013] **FIG. 2A** is a close-up of a portion of the drug delivery device shown in **FIG. 2**.

[0014] **FIG. 3** is an exploded perspective view of the drug delivery device of **FIG. 1**.

[0015] **FIG. 4** is a perspective view of a part of the drug delivery device of **FIG. 1**.

[0016] **FIG. 5** is a cross-sectional, exploded view of a portion of the microchip element, showing two chip portions that define a single containment reservoir, according to one embodiment. The microchip element would, in preferred embodiments, include a plurality of such containment reservoirs defined in an array within the two chip portions.

- [0017] FIG. 6 is a cross-sectional view of the containment reservoir of FIG. 5, according to another embodiment. The microchip element would, in preferred embodiments, include a plurality of such containment reservoirs defined in an array within the two chip portions.
- 5 [0018] FIG. 7 is a cross-sectional, exploded view of a portion of another embodiment of a microchip element, showing two chip portions that define a plurality of containment reservoirs.
- [0019] FIG. 8 is a cross-sectional, exploded view of a portion of yet another embodiment of a microchip element, showing two chip portions that define a plurality of containment reservoirs.
- 10 [0020] FIG. 9 is a cross-sectional, exploded view of a portion of still another embodiment of a microchip element, showing two chip portions that define a single containment reservoir. The microchip element would, in preferred embodiments, include a plurality of such containment reservoirs defined in an array within the two chip portions.
- [0021] FIG. 10 is an upper perspective view of the central part of the drug delivery device of FIG. 1.
- 15 [0022] FIG. 11 is a lower perspective view of the central part of the drug delivery device of FIG. 1.
- [0023] FIG. 12 is an upper view of one embodiment of a printed circuit board in the drug delivery device of FIG. 1.
- 20 [0024] FIG. 13 is a side view of the printed circuit board of FIG. 12.
- [0025] FIG. 14 is a lower view of the printed circuit board of FIG. 12.
- [0026] FIG. 15 is a perspective view of another part of the drug delivery device of FIG. 1, showing some of the internal electronics.
- [0027] FIGS. 16A is a graph of the cumulative amount of levonorgestrel released over time from a drug delivery device according to one embodiment of the present disclosure.
- 25 [0028] FIGS. 16B is a graph of the amount of levonorgestrel released per day from a drug delivery device according to one embodiment of the present disclosure.
- [0029] FIGS. 17-19 are cross-sectional views illustrating the two-stage release of drug from a reservoir of a drug delivery device according to one embodiment of the present disclosure.
- 30 [0030] FIG. 20 is a cross-sectional view of a drug delivery device according to another embodiment of the present disclosure.

Detailed Description

[0031] Improved microchip-based drug delivery devices have been developed. In embodiments, the devices advantageously release each dose of drug in two stages. This provides improved drug-release profiles over extended periods, combining the benefits of discrete dosing and continuous dosing, which advantageously enables systemic drug concentrations to remain within a desired therapeutic window for a longer period. In some embodiments, the drug delivery devices described herein provide a nearly linear release of drug over time, e.g., where the amount of drug released from the device is the approximately the same each day during a period of several days, weeks, or longer, in which the device is in use. The device may store and release a single drug or two or more different drugs.

[0032] The term “about”, as used herein, indicates the value of a given quantity can include quantities ranging within 10% of the stated value, or optionally within 5% of the value, or in some embodiments within 1% of the value.

[0033] In embodiments, the drug delivery device includes (i) a microchip element having reservoirs containing drug for controlled release of tens or hundreds of doses of drug over several months or years; (ii) a structure defining an enclosed depot space next to the openings of the drug reservoirs; and (iii) a drug permeable membrane for controlling release of drug from the depot space. The drug permeable membrane may be part of a structure cooperating with the microchip element to define/bound the depot space. With these components, a dose of drug is released, in a first stage, from an activated reservoir and into the depot space, and then the dose of drug is released, in a second stage, from the depot space into the patient. In the first stage, drug release may be driven by diffusion and/or by swelling of an excipient material in the reservoir to displace the drug from the reservoir. In the second stage, drug release may be driven/controlled by diffusion of the drug through the drug permeable membrane. The membrane advantageously serves to slow and extend release from the bolus released into the depot space. In a preferred embodiment, a further benefit of this two stage system is that extended, controlled release does not depend of the use of bioerodible or biodegradable matrix material.

[0034] In some alternative embodiments, the drug permeable membrane is adjacent to the microchip element such that there is no gap or predefined depot space between these components. For example, the exterior wall of the microchip element may be in direct mechanical contact with the drug permeable membrane. It is still a two-stage release system, wherein, in a first stage, a drug formulation in the reservoir is permitted to imbibe water following reservoir cap activation, and then the drug, in a second stage, diffuses through the

drug permeable membrane and into the patient. The first stage optionally may include an extrusion mechanism, as described below, in which some of the wetted drug formulation (e.g., one including a water swellable material) is forced out of the reservoir and in between the outer surface of the microchip element and the drug permeable membrane, as and if
5 permitted by elastic deformation of the drug permeable membrane.

[0035] In one embodiment, the drug delivery device includes a microchip element which includes a body portion defining at least one containment reservoir therein. In a preferred embodiment, the body portion of the microchip element defines an array of discrete containment reservoirs, which may be microreservoirs. In embodiments, the body portion
10 has an exterior wall having one or more drug release apertures in fluid communication with the one or more containment reservoirs. The one or more drug release apertures initially are closed off by one or more corresponding reservoir caps, which are configured to be (electrically, chemically, or mechanically) activated to unclosethe one or more drug release apertures. In a preferred embodiment, the reservoir caps are configured to be ruptured by
15 electrothermal ablation, as known in the art. A drug formulation which comprises a drug is initially disposed in each of the one or more containment reservoirs. In this embodiment, the device further includes an outer housing wall secured in a position next to, and spaced a distance from, the exterior wall of the body portion of the microchip element, wherein the outer housing wall includes a drug-permeable membrane, and a depot space is defined
20 between the drug-permeable membrane and the exterior wall of the body portion of the microchip element.

[0036] In some embodiments, the device is configured to operate *in vivo* by permitting interstitial fluid, following activation of one or more of the plurality of reservoir caps, to contact the drug formulation in the reservoir corresponding to the activated reservoir cap(s)
25 and to facilitate transfer of the drug out of the reservoir through the drug release apertures and into the depot space for subsequent diffusion through the drug-permeable membrane. In some embodiments, the drug formulation is a solid form, e.g., as a lyophilized powder or a solid tablet, and the interstitial fluid contacts and solubilizes the drug formulation, so that the drug can diffuse out of the reservoir and into the depot space. In some embodiments, the
30 reservoir further includes a water-swellable material, which swells upon contact with the interstitial fluid, causing the drug to be extruded (pushed out) of the reservoir into the depot space. (The process is sometime referred to herein as an “extrusion mechanism”.) This may occur before and/or simultaneously with solubilization of the drug. The water-swellable

material may be provided in a form and position separate from the drug formulation, e.g., in layer adjacent to the drug formulation and distal to release aperture.

Drug, Drug Formulation, and Other Reservoir Contents

[0037] The drug delivery devices described herein can be used to delivery any suitable drug. As used herein, the term “drug” includes prophylactic or therapeutic agents, and may be used interchangeably with “active pharmaceutical ingredient” or “API” as those terms are known in the art. Non-limiting examples of drugs include hormones, anti-infectives, antineoplastics, biologicals, cardiovascular agents, central nervous system agents, immunologic agents, metabolic agents, immunomodulators, and pyschotherapeutic agents. In one embodiment, the drug is an incretin memetic, such as exenatide.

[0038] Non-limiting examples of hormones include sex hormones, contraceptives, growth hormones, growth hormone receptor blockers, 5 α -reductase inhibitors, adrenal cortical steroids, adrenal corticosteroid inhibitors, somatostatins, parathyroid hormone, and thyroid drugs, and suitable analogs thereof. The hormone may be derived from an animal or may be synthetically created. The hormone may be related to the reproductive system. For example, the drug included in the present drug delivery devices may be a contraceptive hormone. In some embodiments, the drug may include levonorgestrel, testosterone, estradiol, estrone, estriol, progesterone, or metabolites or variants thereof.

[0039] The term “drug formulation” as used herein refers to the drug form loaded into the reservoirs of the microchip element. It may consist solely of the drug, or it may further include one or more pharmaceutically acceptable excipients. In a preferred embodiment, the drug formulation is in a dry solid form. For example, the dry solid form may be a powder, granules, or tablets (e.g., microtablets). In other embodiments, the drug formulation may be in the form of a liquid, a solution, a suspension, a gel, or a paste. In one case, the drug formulation is a nanoparticle drug formulation. As used herein, a “nanoparticle drug formulation” refers to a drug formulation where the drug is provided in particles which have an average diameter of from about 1 nm to about 100 nm.

[0040] The drug particle size is important for the extrusion mechanism in which the drug is transferred from the reservoirs into the depot space. The particle size may be specific to each active pharmaceutical ingredient selected for delivery. The particles need to be smaller than the drug release aperture, or opening, from the reservoir. In some embodiments, the drug release aperture has a diameter of about 100 microns. In some embodiments with the extrusion mechanism, the drug particle size ranges from about 1 micron to about 40 microns, with a median size of about 5 to 12 microns. In some other embodiments with the extrusion

mechanism, the drug particle size is smaller than 1 micron. For example, the drug particles may be nanoparticles, e.g., having a size range from 25 nm to 950 nm, from 50 nm to 800 nm, or from 50 nm to 200 nm.

[0041] In some embodiments, the microchip element is configured to release a single drug.

5 In other embodiments, the microchip element is configured to release two or more different drugs. The release of the two or more drugs may be simultaneous, sequential, or in an overlapping combination thereof. In one case, the two or more different drugs may be combined into one drug formulation in each reservoir in an array of the reservoirs in a microchip element. In another case, one of the two or more drugs is formulated in first drug
10 formulation, which is loaded into a first subset of reservoirs in an array of device reservoirs, and a second of the two or more drugs is formulated in second drug formulation, which is loaded into a second subset of reservoirs (not overlapping with the first subset) in the array of device reservoirs.

[0042] As mentioned above, the reservoirs of the microchip element may further include a
15 water-swallowable material, which is configured to swell upon contact with a biological fluid *in vivo* (following opening of the reservoir *in vivo*) to thereby cause the drug to be displaced out of the reservoir into the depot space. In a preferred embodiment, the biological fluid is interstitial fluid. As used herein, "water swallowable material" refers to a biocompatible material which swells in water, such as hygroscopic materials, hydrogels, and superabsorbers,
20 as known in the art. Non-limiting examples of water swallowable materials include hydrophilic polymers and polymeric networks such as poly(acrylic acid), poly(acrylic acid-co-acrylamide), poly (2-hydroxyethyl methacrylate), poly(2-hydroxypropyl methacrylate), poly(isobutylene-co-maleic acid), carbopol, hydroxypropyl methylcellulose, polyethylene oxide, and hyaluronic acid.

25 **[0043]** In one embodiment, the water swallowable material is in the form of a charge layer adjacent to a layer of the drug formulation, wherein the drug formulation layer is disposed between the charge layer and the one or more drug release apertures of the reservoir in which the drug formulation layer and charge layer are disposed. In one case, the charge layer and drug formulation layer are part of the same tablet or microtablet, which formed and then
30 loaded into the reservoir of the microchip element. In another case, the charge layer and drug formulation layer are produced and/or loaded in the reservoir of the microchip element in sequential steps.

[0044] In another embodiment, the water swallowable material is combined with the drug formulation. For example, the water swallowable charge material may be dispersed with the

drug in the drug formulation, e.g., as a powder mixture or mixed with the drug in a microtablet. In another example, the water swellable material may be in the form of a coating on tablets or granules of drug.

[0045] In such embodiments, it has been found that certain parameters are particularly important to the efficient operation of the extrusion mechanism. These include (1) the density and dimensions of the microtablet, and (2) the ratio of the drug particles to the swelling agent. In a preferred embodiment, each reservoir is filled with a microtablet, which is a mixture of drug particles and swelling agent. The microtablet properties of density and height may be tuned. Ranges of these properties have been tested. In some embodiments (for example with a formulation comprising levonorgestrel and hyaluronic acid), the density of the microtablet ranges from 1 to 1.3 mg/mm³, and the height of the microtablet ranges from 0.67 mm to 0.95 mm. In some other embodiments, the density may be outside of these ranges, for example, if the particular materials of the composition have a higher or lower achievable density, and if a different height is selected for use in reservoir design having different dimensions. The ratio of the drug particles to the swelling agent is selected to provide swelling agent in an amount effective to both (i) swell the mixture to a volume that greatly exceeds the volume of the reservoir, to thereby extrude as much of the reservoir contents from the reservoir as possible, and (ii) maintain separation/dispersion of the drug particles so that they cannot agglomerate and block the apertures. Various ratios have been tested, including microtablet compositions up to 65% drug, with the balance being swelling agent or other excipients. It was found (for example with a formulation comprising levonorgestrel and hyaluronic acid) that the highest extrusion efficiency was obtained with 42% drug or less, by weight. The extrusion efficiency, however, must be balanced against the amount of drug released for therapeutic efficacy. Therefore, in some preferred embodiments, the composition of the microtablet is from about 10% to about 50% drug particles, e.g., about 20% to about 45% drug particles, about 30% to about 42%, by weight, with the balance being excipients including swelling agent. In other embodiments, for example with other formulations, the preferred amounts may be outside of these ranges.

Microchip Element Body and Reservoir Caps

[0046] The microchip element includes a body portion defining the one or more containment reservoirs. The containment reservoirs may simply be referred to herein as “reservoirs.” In some embodiments, the microchip element is one known in the art, for example, as described in U.S. Patent No. 8,403,915 to Santini et al., U.S. Pat. Pub. No. 2013/0053671 to Farra, and U.S. Pat. Pub. No. 2014/0243624 to Farra, U.S. Pat. Pub. No.

2016/0354780 to Farra, each of which is hereby incorporated by reference. In a preferred embodiment, the microchip element includes an array of discrete reservoirs and is composed of two substrate portions bonded together to hermetically seal each reservoir after the drug formulation is loaded into the reservoirs of the array. In some embodiments, the two
5 substrate portions include a sealing chip and reservoir chip. Non-limiting examples of the sealing chips and reservoir chips forming the body portion and reservoirs of the microchip element are shown in FIGS. 5, 6, 7, 8, and 9, and described below. Reservoir caps closing off the drug release apertures in an exterior wall of the microchip element are also illustrated.

[0047] In some embodiments, the drug delivery device described herein includes a single
10 microchip element. In some other embodiments, the drug delivery device described herein includes two or more microchip elements. In a preferred embodiment, the drug delivery device includes two microchip elements, wherein the exterior walls of the microchip elements are on opposite sides of the device, such that release of the drug from each microchip element is in a direction opposite from the other. In another embodiment, there are
15 two microchip elements on either side but placed in direct opposition to each other without other elements of the device (i.e. electronic components, hermetic enclosure) in between.

[0048] The reservoirs of the microchip element each include one or more drug apertures. In a preferred embodiment, these apertures are (initially) closed off by reservoir caps, which are configured to be activated to uncloze the drug release apertures. Such reservoir cap
20 activation can occur by various electrical, mechanical, and/or chemical means known in the art, for example, as described in U.S. Pat. No. 7,070,590 to Santini et al., U.S. Pat. No. 6,527,762 to Santini et al., U.S. Pat. No. 6,491,666 to Santini et al., U.S. Pat. No. 7,604,628 to Santini et al., and U.S. Pat. No. 7,455,667 to Uhland et al., which are hereby incorporated by reference herein in pertinent part. In a preferred embodiment, the reservoir caps are
25 configured to be activated by electrothermal ablation, as described in U.S. Pat. No. 7,455,667 to Uhland et al. In such a case, the reservoir caps are consist of, or include, an electrically conductive material, such as a thin metal film (e.g., gold), and the drug delivery device is configured to apply an electrical current through the reservoir cap(s) of the reservoir to be opened, through an electrical input lead and an electrical output lead, which are each
30 electrically connected to each reservoir cap, to rupture the reservoir cap.

[0049] In a preferred embodiment, the reservoirs of the microchip element are microreservoirs. As used herein, the term “microreservoir” refers to a reservoir having a volume equal to or less than 500 μL (e.g., less than 250 μL , less than 100 μL , less than 50 μL , less than 25 μL , less than 10 μL , etc.). In another embodiment, the containment reservoirs is a

“macroreservoir” which generally refers to a reservoir having a volume greater than 500 μL (e.g., greater than 600 μL , greater than 750 μL , greater than 900 μL , greater than 1 mL, etc.) and less than 5 mL (e.g., less than 4 mL, less than 3 mL, less than 2 mL, less than 1 mL, etc.). The terms “reservoir” and “containment reservoir” are intended to encompass both

5 microreservoirs and macroreservoirs unless explicitly indicated to be limited to either one or the other.

Outer Housing Wall, Drug-Permeable Membrane, and Depot Space

[0050] In embodiments, the drug delivery device includes an outer housing wall that includes one or more drug-permeable membranes. In a preferred embodiment, the outer

10 housing wall is spaced apart from the exterior wall of the body portion of the microchip element to form therebetween, a depot space. That is, the depot space is defined between the drug-permeable membrane(s) and the exterior of the microchip element that has the drug release openings/reservoir caps. In a preferred embodiment, the outer housing wall is part of a rigid shell structure that frames and/or supports the one or more drug-permeable

15 membranes. The shell structure may further include a housing ring on this sides generally perpendicular to the sides with the drug-permeable membrane. In various embodiments, the outer housing wall includes one, two, three, four, or more windows, wherein each window frames a drug-permeable membrane. If there are two or more windows, then each window may have its own drug-permeable membrane or may frame a portion of a single drug-

20 permeable membrane.

[0051] The outer wall and the shell structure are made of a biocompatible material that has suitable mechanical properties and is suitable for long term implantation in a patient. Typically, the rigid components are made of a biocompatible metal or alloy, such as a stainless steel or titanium. In some embodiments, the shell of the drug delivery device has a

25 maximum dimension in any direction from about 10 mm to about 50 mm.

[0052] The drug-permeable membrane may be any suitable biocompatible material that is able to provide the desired controlled release rate of a selected drug. The drug-permeable membrane may be a biocompatible polymeric membrane. In a preferred embodiment, the membrane is an elastomeric material, such as a silicone or polyurethane. In embodiments,

30 the drug-permeable is water-permeable, so that when the drug delivery device is in an aqueous environment, e.g., following *in vivo* implantation, water (from/or the biological fluid, e.g., interstitial fluid) may diffuse through the drug-permeable membrane and into the depot space, and then, at least in some embodiments, into the opened drug containment reservoir. In some embodiments, the drug permeable membrane may be non-porous, such

that drug release is controlled by trans-wall diffusion through the membrane. In some other embodiments the drug permeable membrane includes pores, such that drug release is controlled by diffusion through the passing pores in the membrane.

5 [0053] The rate of diffusion of drug through the drug-permeable membrane may be controlled, in part, by the thickness of the membrane, the surface area of the membrane exposed to the drug, and the distance or “gap” from the membrane to the surface of the reservoir caps. In some embodiments, the drug-permeable membrane has a thickness from about 100 μm to about 1000 μm , for example from about 200 μm to about 600 μm , or from about 250 μm to about 500 μm . In some embodiments, the drug-permeable membrane is 10 silicone and has a thickness from about 300 μm to about 500 μm , e.g., from about 350 μm to about 400 μm . Various membrane thicknesses have been tested, including those as thin as 36 microns and as thick as 650 microns. In one preferred embodiment, the membrane thickness is nominally 70 microns (measured at 72 microns).

15 [0054] The rate is also controlled in part by the total surface area of the membrane, along with the thickness and composition of the material (e.g., the particular grade of the silicone material). In one embodiment, the required drug delivery rate is achieved with a silicone membrane and device design which utilizes 200 mm^2 of surface area with 72 micron thickness. In other embodiments, one or more of the material of construction, the thickness, and the surface area may differ.

20 [0055] In an alternative embodiment, there is essentially no gap between the membrane and the reservoir caps of the microchip element. For example, the outer surface of the device, including but not limited to the reservoir cap-comprising face of the microchip elements, may be partially or fully encapsulated by the membrane.

Other Device/System Components

25 [0056] In embodiments, the drug delivery devices further include electronics for controlling and powering reservoir activation and for wireless transmission of power and/or data to/from the device. In some embodiments, the electrical component providing these functions are included in/on one or more printed circuit boards (PCBs), and/or are incorporated into one or more of the chips of the microchip element, as described in U.S. Pat. Pub. No. 2013/0053671 30 to Farra and U.S. Pat. Pub. No. 2014/0243624 to Farra, which are incorporated herein by reference. In some embodiments, the drug delivery device includes two PCBs comprising a hermetic material, such as alumina or silicon nitride in certain embodiments, which are arranged to define a hermetic enclosure containing the electronic components therebetween. As used herein, the term “hermetic” refers to preventing undesirable ingress or egress of

chemicals (e.g., water vapor, water, oxygen, etc.) over the useful life of the device. For purposes herein, a material/seal that transmits helium (He) at a rate less than 1×10^{-9} atm*cc/sec is termed hermetic. In one case, the distal sides of these PCBs (outside of the hermetic enclosure) each are connected to a microchip element of the device.

5 Methods of Using the Drug Delivery Device

[0057] The devices described herein may be used to provide controlled administration of a drug to a patient in need thereof. The term “patient” refers to a human or other mammalian subject. In various embodiments, the devices may be adapted for use in humans, whether male or female, adult or child, or for use in animals, such as for veterinary or livestock applications.

[0058] In some embodiments, the method of controlled drug delivery to a patient includes (i) implanting a drug delivery device as described herein into the patient at an implant location in the patient’s body; and then (ii) activating the one or more reservoir caps of a first selected reservoir or subset of reservoirs to open those reservoirs of the microchip element.

15 When the device is implanted at the implant location, interstitial fluid from tissue at the implant location diffuses into and fills the depot space. Once the reservoir(s) is/are opened, the interstitial fluid in the depot space enters the reservoir(s) to contact the drug formulation and the water swellable material, if any, contained therein. In turn, this causes the drug to be transferred into the drug depot space and therein form a drug depot (the first stage of drug release), which may be in the form of a mass disposed on the exterior surface of the microchip element. This transfer may be driven by diffusion, extrusion (positive displacement) caused by swelling of the water swellable material if present, or a combination thereof. In one case, the transfer of the drug from the containment reservoir to the drug depot space includes swelling of a water swellable charge material to eject the drug from the containment reservoir. Next, the drug in the drug depot diffuses through the drug-permeable membrane (the second stage of drug release), exiting the device entering and into the patient’s body, where it can diffuse into the vasculature for systemic delivery. At a later time, step (ii) is repeated, activating the one or more reservoir caps of a second selected reservoir or subset of reservoirs to open those reservoirs of the microchip element. This later time may be selected to replenish the drug in the depot space before the second stage release rate falls to sub-therapeutic levels as the depot is depleted.

[0059] In embodiments, the device is configured to release doses of drug from the reservoirs at spaced intervals over an extended period of several months or years. In some embodiments, the implanted device can be controlled wirelessly, which may include

reversibly turning the device off and on as needed, activating drug release on demand, re-programming a drug release schedule, and/or collecting data, if any, sensed/recorded by the implanted device.

5 [0060] The drug delivery devices can be used to treat or prevent a wide range of diseases or conditions, depending on the particular drug or drug combination administered using the device. Non-limiting examples include reproductive health applications, including contraception.

[0061] In one embodiment, the time period between reservoir activations is pre-determined, e.g., based on a programmed schedule. In another embodiment, the time period between
10 reservoir activations is based on a measured *in vivo* drug concentration (e.g., plasma drug level) or another sensed value or condition in the patient. In such embodiments, the sensor used to measure the drug concentration or other biometric parameter may be part of the implantable drug delivery device or it may be part of a separate device, either implanted in or external to the patient.

15 [0062] The implanting step (i) may include making a small incision in the patient's skin and inserting the drug delivery device at a suitable subcutaneous tissue site. In some minimally-invasive forms of the device, it may be inserted or injected into a tissue site in the patient using a cannula, trocar, or other minimally invasive medical instrument. In other embodiments, the implanting step may include implanting the device into another suitable
20 tissue site in the patient, such as an intraperitoneal space. Other tissue sites are envisioned, and the choice may depend, for example, on the treatment the patient needs, the drug, whether local or systemic administration of the drug is desired.

Illustrative Embodiments

[0063] One embodiment of a drug delivery device as described above is shown in **FIGS. 1**
25 and **2**. **FIG. 1** shows the exterior of the device in one perspective, and **FIG. 2** shows in a cut-away view showing the interior of the device in another perspective. The drug delivery device **101** includes a first outer housing wall **119a**, a second outer housing wall **119b**, and a housing ring **130**. The first outer housing wall **119a**, second outer housing wall **119b**, and housing ring **130** are secured together to form a device shell, with the parts having a
30 hermetical seal between them. In one embodiment, the parts of the shell are metal and fused together by a welding process, e.g., laser welding or brazing, as known in the art. As shown, the housing ring **130** includes an optional projecting edge **147** extending perpendicularly from the housing ring **130**, away from the drug delivery device **101**. The projecting edge **147** includes holes **149** suitable for use in suturing the device to nearby tissue, to secure the

device in place within an implant site in a patient. The first and second outer housing walls **119a**, **119b** each include a rigid frame **125a**, **125b**, respectively, which supports a drug-permeable membrane **103a**, **103b**, respectively. As shown in **FIG. 1**, the rigid frame **125a** defines/surrounds the periphery of four windows **127** of the drug permeable membrane **103a**.
5 As shown in **FIG. 2**, the first and second outer housing walls **119a**, **119b** and the housing ring **130** cover microchip elements **105a**, **105b**, such that the only access between the outside of the drug delivery device **101** and the microchip element is through the windows **127** of the drug permeable membranes **103a**, **103b**.

[0064] The first microchip element **105a** has a body portion **107a**, and the second
10 microchip element **105b** having a body portion **107b**. Each of the body portions **107a** and **107b** defines an array of containment reservoirs **109**. Each of the body portions **107a** and **107b** has an exterior wall **111a** and **111b**, respectively. As can be seen in **FIG. 2**, each of the first and second drug permeable membranes **103a**, **103b** is secured in a position next to, and spaced a distance from, the exterior wall **111a**, **111b**, respectively. In this arrangement, a
15 first depot space **121a** is created between the exterior wall **111a** and the microchip element **105a**, and a second depot space **121b** is created between the exterior wall **111b** and the microchip element **105b**. In this way, drug exiting reservoirs **109** of microchip element **105a** through drug release apertures **113** will enter first depot space **121a**, and drug exiting reservoirs **109** of microchip element **105b** through drug release apertures **113** will enter first
20 depot space **121b**. As shown in **FIG. 2A**, each containment reservoir **109** includes an array of drug release apertures **113**, which are closed off by a corresponding array of reservoir caps **115**.

[0065] The first and second microchip elements **105a**, **105b** are respectively fixed onto first and second printed circuit boards (PCBs) **131a**, **131b**. The first and second PCBs **131a**, **131b**
25 include substrates **133a**, **133b**, respectively. The substrates **133a**, **133b** mechanically support and electrically connect electronic components using conductive pathways, tracks, or signal traces as known in the art. The first and second PCBs **131a** and **131b** may include a biocompatible and hermetic substrate material, such as alumina or silicon nitride. The first and second PCBs **131a**, **131b** combined with the housing ring **130** form a hermetic enclosure
30 **129**.

[0066] A number of electronic components are fixed to one or both of the first and second PCBs **131a** and **131b** and located in the hermetic enclosure **129**. The components illustrated in **FIG. 3** include battery **145**, battery insulator film **167**, battery insulator foam **143**, capacitors **139**, real time clock **137**, and ASIC **141**.

[0067] As shown in **FIGS. 3** and **4**, each of first and second PCBs **131a**, **131b** include a number of leads **135** on each of the first and second substrate **133a** and **133b**, respectively. At least some of these leads connect a power source with an input lead and an output lead which are electrically connected to each reservoir cap **115**, so that each reservoir cap **115** can be activated by passing an electrical current through the reservoir cap **115**, via the input lead and output lead, so that the reservoir cap **115** ruptures (e.g., by electrothermal ablation as described above) to release or expose the contents of the containment reservoir **109**.

[0068] **FIG. 3** shows the first and second outer housing walls **119a**, **119b**, contact springs **165**, the first and second rigid frames **125a**, **125b**, the first and second drug-permeable membranes **103a**, **103b**, and the windows **127** of the drug permeable membranes **103a**, **103b**. **FIG. 3** also shows the first and second microchip elements **105a**, **105b**, separated from the substrates **133a**, **133b** of the first and second PCBs **131a**, **131b**.

[0069] **FIG. 4** shows the drug delivery device of **FIG. 1** without the first and second outer housing walls **119a**, **119b** and without the first and second drug-permeable membranes **103a**, **103b**. Accordingly, one can see the second PCB **131b** onto which microchip element **105b** is fixed, with exterior wall **111b** of microchip element **105b** facing outward.

[0070] **FIG. 5** depicts the construction of one embodiment of a microchip element, focusing on a single reservoir. Although not shown, these two structural components shown would extend laterally and repeat to define an array of reservoirs. This microchip element may be used in a drug delivery device as described herein. As shown, microchip element **505** has a body portion **507** that is formed from a sealing chip **551** joined to a reservoir chip **553**. Containment reservoir **509** is defined primarily in reservoir chip **553** and closed off by sealing chip **551** after drug formulation **517** is loaded into the reservoir **509**. Containment reservoir **509** has straight (substantially non-tapered) sidewalls. The reservoir chip **553** and sealing chip **551** are joined together with sealing structures **559**, which may consist of positive and negative mating features (e.g., grooves and ridges), which are bonded together using compression cold welding to hermetically seal the reservoir **509**. U.S. Pat. Pub. No. 2016/0354780 to Farra describes compression cold welding to seal microchip elements and is hereby incorporated by reference. The sealing chip **551** includes a plurality of reservoir caps **515** which seal drug release apertures **513**. When the reservoir caps **515** are ruptured, water can enter the reservoir **509** and contact the drug formulation **517** and solubilize the drug and permit it to diffuse out of the reservoir **509** through the drug release apertures **513**.

[0071] **FIG. 6** shows microchip element **506**, which is identical to microchip **505** shown in **FIG. 5**, except instead of drug formulation **517** filling the reservoir **509**, the reservoir **509**

contains both a drug formulation **527** and a charge layer **523** comprising a water swellable material. The drug formulation is positioned between the drug release apertures **513** and the charge layer **523**, so that when the reservoir caps **515** are ruptured, water can enter the reservoir **509** and contact the drug formulation **527** and the charge layer **523**, wherein the charge layer imbibes the water and swells to eject the drug formulation **527** out of the reservoir through the drug release apertures **513**.

[0072] **FIGS. 7-9** illustrate some other possible configurations of the microchips elements. **FIG. 7** depicts microchip element **705** which has three containment reservoirs **709** in body portion **707** which is formed from a sealing chip **751** and a reservoir chip **753**. The reservoir chip **753** and sealing chip **751** are joined together with sealing structures **759**, which may consist of positive and negative mating features (e.g., grooves and ridges), which are bonded together using compression cold welding to hermetically seal the reservoir **709**. Reservoirs **709** have straight (substantially non-tapered) sidewalls. The sealing chip **751** includes reservoir caps **715** which each seal corresponding drug release apertures **713**. Each containment reservoir **709** contains a drug formulation **717**. Although not shown, reservoirs **709** could further include a water swellable material charge layer with the drug formulation **717**.

[0073] **FIG. 8** depicts microchip element **805** which has three containment reservoirs **809** in body portion **807** which is formed from a sealing chip **851** and a reservoir chip **853**. The reservoir chip **853** and sealing chip **851** are joined together with sealing structures **859**, which may consist of positive and negative mating features (e.g., grooves and ridges), which are bonded together using compression cold welding to hermetically seal the reservoir **809**. Reservoirs **809** have tapered sidewalls. In contrast to the embodiments shown in **FIGS. 5-7**, it is the reservoir chip **853** that includes the drug release apertures **813** and reservoir caps **815**. Sealing chip **851** has no apertures or reservoir caps. Each containment reservoir **809** contains a drug formulation **817**. Although not shown, reservoirs **809** could further include a water swellable material charge layer with the drug formulation.

[0074] Like **FIG. 8**, **FIG. 9** also depicts a microchip element in which the reservoir chip includes drug release apertures and reservoir caps. It shows microchip element **905** which has a containment reservoir **909** in body portion **907** which is formed from a sealing chip **951** and a reservoir chip **953**. The reservoir chip **953** and sealing chip **951** are joined together with sealing structures **959**, which may consist of positive and negative mating features (e.g., grooves and ridges), which are bonded together using compression cold welding to hermetically seal the reservoir **909**. Reservoirs **909** have straight sidewalls. The reservoir

chip **953** includes the drug release apertures **913** and reservoir caps **915**. Sealing chip **951** has no apertures or reservoir caps. The reservoir **809** contains a drug formulation **817**. Although not shown, the reservoir **809** could further include a water swellable material charge layer with the drug formulation.

5 [0075] FIGS. **10** and **11** show the drug delivery device of FIG. **1** without the first and second outer housing walls **119a**, **119b**, without the first and second drug-permeable membranes **103a**, **103b**, and without the microchip elements **105a**, **105b**. Accordingly, in FIG. **10**, one can see the first PCB **131a** which has a substrate **133a** with a number of leads **135** disposed thereon, and in FIG. **11**, one can see the second PCB **131b** which has a
10 substrate **133b** with a number of leads **135** disposed thereon.

[0076] FIGS. **12-14** show different views of the second PCB **131b**, which includes a substrate **133b**, leads **137**, various electrical components, and vias for connecting the microchip element **105b** to electronic components inside the hermetic enclosure described above.

15 [0077] FIG. **15** shows a partial assembly of the drug delivery device **101**, depicting the housing ring **130**, the second PCB **131b**, battery **145**, and battery/spring nest **163**. Other electronic components include capacitors **139**, ASIC **141**, real time clock (RTC) **137**, crystal **161** for the RTC, inductor **155**, and various passive components **157** (resistors and capacitors).

20 [0078] FIG. **17-19** illustrate the two-stage drug release method. Microchip element **705** includes three containment reservoirs **709** located in body portion **707** which is formed of a sealing chip **751** and a reservoir chip **753** bonded together with sealing structures **759**. The sealing chip **751** includes a plurality of reservoir caps **715** which each seal corresponding drug release apertures **713**. The body portion **707** of the microchip element **705** has an
25 exterior wall **711**. A depot space **121** is defined between the exterior wall **711** and the drug-permeable membrane **103**. In FIG. **17**, each containment reservoir **709** contains a drug formulation **717**, and the reservoir caps **715** are intact.

[0079] Subsequently, the reservoir cap **715** on the left is activated and ruptured. As shown in FIG. **18**, the drug formulation **713** from the activated reservoir has been transferred (by
30 diffusion or ejection/extrusion) from the left reservoir **709**, and collects in the depot space **121**. As shown in this figure, a portion of the drug formulation **717** has begun to diffuse from the depot space **121** through the drug-permeable membrane **103**. FIG. **19** shows the same system at a later time. As can be seen from the comparison of FIGS. **18** and **19**, over time, the drug reservoir **709** is substantially emptied of the drug formulation **717**, and most of the

drug formulation **717** has diffuses from the depot space **121** through the drug permeable-membrane **103**. The drug formulation in the depot space would continue to deplete, and a second reservoir could be activated to replenish the drug formulation in the depot space. These steps would be repeated as needed to provide a therapeutically effective concentration of the drug in the patient over a desired sustained period.

[0080] As mentioned above, in some embodiments, the device includes two microchip elements on opposed sides of the device and adjacent one another without electronic components positioned between the microchip elements. One embodiment of such a device is illustrated in **FIG. 20**. Device **200** includes two microchip elements **205a**, **205b** shown on the left side of the device and the electronics are disposed in the right side of the device. The electronics may include, for example, battery **245**, capacitor **239**, ACIS **241**, microprocessor **243**, and antenna **250**. The device also includes upper/lower housing body **207** and side housing **230**. Drug permeable membranes **203a**, **203b** are positioned on opposite sides (upper/lower sides) of the device. Depot spaces **821a**, **821b** are defined between the microchip elements **205a**, **205b** and the drug permeable membranes **203a**, **203b**, respectively. This design advantageously enables a thin and narrow device, in which drug capacity can be increased by increasing the number of reservoirs in one, or more likely both microchip elements by only lengthening the microchip elements, without enlarging the width or thickness of the overall device. This is beneficial to maintaining the narrow profile of the device such that is can be suitably implanted into a patient in a minimally invasive manner, and such that it can be reasonably discreet and comfortable to the patient when the device is subcutaneously located.

[0081] In some other embodiments the device include one or more microchip elements only one side of the device, and electronic components located on an opposing side of the one or more microchip elements or located in a position laterally adjacent to the one or more microchip elements. Examples of such embodiments can be envisioned as the device **101** in **FIG. 2** without microchip element **105b** and membrane **103b**, or as the device **200** of **FIG. 20** without microchip element **205b** and membrane **203b**.

[0082] The devices and methods described herein will be further understood by reference to the following non-limiting example.

Example 1

[0083] A drug delivery device was assembled according to an embodiment of the present disclosure, wherein the drug formulation included levonorgestrel, and drug-permeable membranes were made from a semi-permeable silicone material having a nominal thickness

of 70 μm . The levonorgestrel formulation included 42% spray dried levonorgestrel with hyaluronic acid 1.8. Each of the microchip elements included 100 reservoirs, each having a capacity of 2 microliters. The drug delivery device was inserted into an aqueous environment 0.5% sodium dodecyl sulfate and 0.02% sodium azide in normal saline (0.9% sodium chloride), and 4 reservoirs were electrically activated to open using an electrothermal ablation mechanism at the beginning of the test. The levonorgestrel drug formulation was released into a depot space between each of the microchip elements and the drug-permeable membranes, and then allowed to diffuse from the drug depot spaces and into the aqueous environment through the silicone membrane.

10 **[0084]** The aqueous environment was periodically sampled to measure the amount of levonorgestrel which had been released over time. An equivalent volume, chosen to maintain sink conditions, is removed and replaced with aqueous solution for every sampling. The sample is diluted as necessary to be quantified by high performance liquid chromatography (HPLC). All values are calculated against a standard curve. **FIG. 16A** shows the cumulative

15 amount of levonorgestrel which was released from this drug delivery device and **FIG. 16B** shows the amount of levonorgestrel which was released per day, as individual measured data points on days 1, 2, 3, 4, 8, 10, 11, 14, 15, 17, 18, 21, 23, 25, 28, and 30 with a solid line **B** representing a linear regression of these data points. The dashed line **A** represents a release rate of 30 μm per day—the minimum daily dose which is required for levonorgestrel to be

20 effective as a form of contraception. As can be seen from this figure, while this experimental drug delivery device releases more than the required 30 μg of levonorgestrel per day, it advantageously provides a linear release rate, as shown by the solid line **B**. That is, the drug delivery device released about the same amount of levonorgestrel (in μg) per day over the 30-day test.

25 Exemplary Embodiments

[0085] Embodiment 1. A drug delivery device, comprising: a microchip element which comprises a body portion defining at least one containment reservoir therein, wherein the body portion has an exterior wall having one or more drug release apertures in fluid communication with the at least one containment reservoir, the one or more drug release

30 apertures being closed off by one or more corresponding reservoir caps configured to be electrically activated to unclosethe one or more drug release apertures; a drug formulation, which comprise a drug, disposed in the at least one containment reservoir; and an outer housing wall secured in a position next to, and spaced a distance from, the exterior wall of the body portion of the microchip element, the outer housing wall comprising a drug-permeable

membrane, wherein a depot space is defined between the drug-permeable membrane and the exterior wall of the body portion of the microchip element.

[0086] Embodiment 2. The drug delivery device of Embodiment 1, which is configured to operate in an aqueous environment and, upon activation of the one or more reservoir caps, release the drug into the depot space and subsequently diffuse through the drug-permeable membrane and into the aqueous environment.

[0087] Embodiment 3. The drug delivery device of Embodiment 1 or 2, wherein the drug delivery device is an implantable drug delivery device and the aqueous environment is *in vivo* in a patient.

[0088] Embodiment 4. The drug delivery device of any one of Embodiments 1 to 3, wherein reservoir caps are configured to rupture by electrothermal ablation when electrically activated.

[0089] Embodiment 5. The drug delivery device of any one of Embodiments 1 to 4, wherein the drug-permeable membrane comprises a polymeric membrane.

[0090] Embodiment 6. The drug delivery device of Embodiment 5, wherein the polymeric membrane comprises silicone, polyurethane, or a combination thereof.

[0091] Embodiment 7. The drug delivery device of any one of Embodiments 1 to 4, wherein the at least one containment reservoir further comprises a water swellable charge material.

[0092] Embodiment 8. The drug delivery device of Embodiment 7, wherein the water swellable charge material is in the form of a charge layer adjacent to a layer of the drug formulation, the drug formulation layer being disposed between the charge layer and the one or more drug release apertures.

[0093] Embodiment 9. The drug delivery device of Embodiment 7, wherein the water swellable charge material is dispersed with the drug in the drug formulation.

[0094] Embodiment 10. The drug delivery device of any one of Embodiments 7 to 9, wherein the water swellable charge material comprises hyaluronic acid.

[0095] Embodiment 11. The drug delivery device of any one of Embodiments 7 to 9, wherein the water swellable charge material comprises a hydrophilic polymer.

[0096] Embodiment 12. The drug delivery device of any one of Embodiments 1 to 11, wherein the outer housing wall further comprises a rigid frame supporting the drug-permeable membrane.

[0097] Embodiment 13. The drug delivery device of Embodiment 12, wherein the rigid frame defines two or more windows of the drug-permeable membrane.

- [0098] Embodiment 14. The drug delivery device of Embodiment 12 or 13, wherein the rigid frame is part of a shell covering at least part of the microchip element.
- [0099] Embodiment 15. The drug delivery device of any one of Embodiments 1 to 14, wherein the at least one containment reservoir is a microreservoir.
- 5 [00100] Embodiment 16. The drug delivery device of any one of Embodiments 1 to 15, wherein the drug comprises a hormone, such as a contraceptive hormone.
- [00101] Embodiment 17. The drug delivery device of Embodiment 16, wherein the hormone comprise levonorgestrel.
- [00102] Embodiment 18. The drug delivery device of any one of Embodiments 1 to 17,
10 wherein the drug formulation is in solid form, such as a tablet.
- [00103] Embodiment 19. The drug delivery device of any one of Embodiments 1 to 18, further comprising: a second microchip element which comprises a body portion defining at least one containment reservoir therein, wherein the second body portion has an exterior wall having one or more drug release apertures in fluid communication with the at least one
15 containment reservoir, the one or more drug release apertures being closed off by one or more corresponding reservoir caps configured to be electrically activated to unclosethe one or more drug release apertures; a drug formulation, which comprise a drug, disposed in the at least one containment reservoir of the second microchip element; and a second outer housing wall secured in a position next to, and spaced a distance from, the exterior wall of the body
20 portion of the second microchip element, the outer housing wall comprising a second drug-permeable membrane, wherein a second depot space is defined between the second drug-permeable membrane and the exterior wall of the body portion of the second microchip element, wherein the outer housing wall of the microchip element and the second outer housing wall of the second microchip element are on opposing sides of the drug delivery
25 device.
- [00104] Embodiment 20. The drug delivery device of Embodiment 19, further comprising a hermetic enclosure disposed between the microchip element and the second microchip element.
- [00105] Embodiment 21. The drug delivery device of Embodiment 20, wherein the
30 hermetic enclosure is defined in part by a pair of printed circuit boards, each comprising a ceramic substrate.
- [00106] Embodiment 22. The drug delivery device of Embodiment 20 or 21, wherein hermetic enclosure contains electronic components configured for electrical activation of the reservoir caps of the microchip element and the second microchip element.

[00107] Embodiment 23. An implantable drug delivery device, comprising: a microchip element which comprises a body portion defining a plurality of microreservoirs therein, wherein the body portion has an exterior wall having a plurality of drug release apertures in fluid communication with the microreservoirs, the plurality of drug release apertures being
5 closed off by a plurality of corresponding reservoir caps configured to be ruptured by electrothermal ablation to open the drug release apertures; a drug disposed in each of the microreservoirs; a water swellable charge material disposed in each of the microreservoirs; and an outer housing wall secured in a position next to, and spaced a distance from, the exterior wall of the body portion of the microchip element, the outer housing wall comprising
10 a drug-permeable membrane, wherein a depot space is defined between the drug-permeable membrane and the exterior wall of the body portion of the microchip element, wherein the device is configured to operate *in vivo* by permitting interstitial fluid, following activation of one or more of the plurality of reservoir caps, to contact and be imbibed by the water swellable charge material disposed the microreservoir(s) corresponding to the activated
15 reservoir cap(s), and thereby cause the charge material to swell and eject the drug out of the microreservoir(s) through the drug release apertures and into the depot space for subsequent diffusion through the drug-permeable membrane.

[00108] Embodiment 24. The implantable drug delivery device of Embodiment 23, wherein the drug-permeable membrane comprises a polymeric membrane.

20 [00109] Embodiment 25. The implantable drug delivery device of Embodiment 24, wherein the polymeric membrane comprises silicone, polyurethane, or a combination thereof.

[00110] Embodiment 26. The implantable drug delivery device of any one of Embodiments 23 to 25, wherein the water swellable charge material is in the form of a charge layer adjacent to a layer of the drug, the drug layer being disposed between the charge layer and the drug
25 release apertures.

[00111] Embodiment 27. The implantable drug delivery device of any one of Embodiments 23 to 26, wherein the water swellable charge material comprises hyaluronic acid.

[00112] Embodiment 28. The implantable drug delivery device of any one of Embodiments 23 to 26, wherein the water swellable charge material comprises a hydrophilic polymer.

30 [00113] Embodiment 29. The implantable drug delivery device of any one of Embodiments 23 to 28, wherein the outer housing wall further comprises a rigid frame supporting the drug-permeable membrane.

[00114] Embodiment 30. The implantable drug delivery device of Embodiment 29, wherein the rigid frame defines two or more windows of the drug-permeable membrane.

- [00115] Embodiment 31. The implantable drug delivery device of Embodiment 29 or 30, wherein the rigid frame is part of a shell covering at least part of the microchip element.
- [00116] Embodiment 32. The implantable drug delivery device of any one of Embodiments 23 to 31, wherein the drug comprises a hormone, such as a contraceptive hormone.
- 5 [00117] Embodiment 33. The implantable drug delivery device of Embodiment 32, wherein the hormone comprise levonorgestrel.
- [00118] Embodiment 34. The implantable drug delivery device of any one of Embodiments 23 to 33, wherein the drug is in solid form, such as a tablet.
- [00119] Embodiment 35. The implantable drug delivery device of any one of Embodiments 10 23 to 33, further comprising a hermetic enclosure fixed to the microchip element on a side opposed from the exterior wall and the depot space.
- [00120] Embodiment 36. The implantable drug delivery device of Embodiment 35, wherein the hermetic enclosure is defined in part by a printed circuit boards, which comprises a ceramic substrate.
- 15 [00121] Embodiment 37. The implantable drug delivery device of Embodiment 35 or 36, wherein hermetic enclosure contains electronic components configured for controlling rupture of the reservoir caps.
- [00122] Embodiment 38. The implantable drug delivery device of any one of Embodiments 23 to 37, further comprising a second microchip element and a second exterior wall which 20 comprises a second drug-permeable membrane defining a second drug depot space.
- [00123] Embodiment 39. A method of controlled drug delivery to a patient, comprising: implanting the drug delivery device of any one of Embodiments 1 to 22 in the patient; activating at least one of the one or more reservoir caps to permit interstitial fluid to contact the drug in the containment reservoir corresponding to the activated reservoir cap(s) and 25 transfer the drug into the drug depot space and therein form a drug depot; and releasing the drug from the device by diffusion of the drug from the drug depot through the drug-permeable membrane.
- [00124] Embodiment 40. The method of Embodiment 39, wherein the transfer of the drug from the containment reservoir to the drug depot space comprises swelling of a water 30 swellable charge material to eject the drug from the containment reservoir.
- [00125] Embodiment 41. A method of controlled drug delivery to a patient, comprising: implanting the implantable drug delivery device of any one of Embodiments 23 to 38 at an implantation site in the patient; rupturing at least one reservoir cap to expose the water swellable charge material in the microreservoir corresponding to the activated at least one

reservoir cap to interstitial fluid at the implantation site; imbibing water from the interstitial fluid to swell the exposed water swellable charge material and eject the drug into the drug depot space, forming a drug depot therein; and releasing the drug from the device by diffusion of the drug from the drug depot through the drug-permeable membrane.

- 5 **[00126]** Embodiment 42. A drug delivery device, comprising: a microchip element which comprises a body portion defining at least one containment reservoir therein, wherein the body portion has an exterior wall having one or more drug release apertures in fluid communication with the at least one containment reservoir, the one or more drug release apertures being closed off by one or more corresponding reservoir caps configured to be
- 10 electrically activated to unclose the one or more drug release apertures; a drug formulation, which comprise a first drug, disposed in the at least one containment reservoir; and a drug-permeable membrane secured next to the exterior wall of the body portion of the microchip element, wherein the device is configured to operate in an aqueous environment and, upon activation of the one or more reservoir caps, release the drug by diffusion through the drug-
- 15 permeable membrane and into the aqueous environment.

[00127] Embodiment 43. The drug delivery device of Embodiment 42, wherein the drug delivery device is an implantable drug delivery device and the aqueous environment is in vivo in a patient.

- [00128]** Embodiment 44. The drug delivery device of Embodiment 42 or 43, wherein
- 20 reservoir caps are configured to rupture by electrothermal ablation when electrically activated.

[00129] Embodiment 45. The drug delivery device of any one of Embodiments 42 to 44, wherein the drug-permeable membrane comprises a polymeric membrane.

- [00130]** Embodiment 46. The drug delivery device of Embodiment 45, wherein the
- 25 polymeric membrane comprises silicone, polyurethane, or a combination thereof.

[00131] Embodiment 47. The drug delivery device of any one of Embodiments 42 to 46, wherein the exterior wall is in direct mechanical contact with the drug permeable membrane.

- [00132]** Embodiment 48. The drug delivery device of any one of Embodiments 42 to 47, which is configured to release the drug from the activated at least one containment reservoir
- 30 by a process comprising swelling of the drug formulation and/or by an extrusion process.

[00133] Embodiment 49. The drug delivery device of any one of Embodiments 1 to 48, wherein the at least one containment reservoir further comprises a water swellable charge material.

- [00134] Embodiment 50. The drug delivery device of Embodiment 49, wherein the water swellable charge material and the drug formulation in the at least one containment reservoir are combined in the form of at least one tablet.
- 5 [00135] Embodiment 51. The drug delivery device of Embodiment 50, wherein the at least one tablet comprises a mixture of particles of the drug with one or more excipients comprising the water swellable charge material.
- [00136] Embodiment 52. The drug delivery device of Embodiment 51, wherein the drug particles have a median size from about 5 microns to about 12 microns.
- 10 [00137] Embodiment 53. The drug delivery device of any one of Embodiments 50 to 52, wherein the at least one tablet is from about 10% to about 50% drug particles, by weight.
- [00138] Embodiment 54. The drug delivery device of any one of Embodiments 50 to 52, wherein the at least one tablet is from about 20% to about 45% drug particles, by weight.
- [00139] Embodiment 55. The drug delivery device of any one of Embodiments 50 to 52, wherein the at least one tablet is from about 30% to about 42% drug particles, by weight.
- 15 [00140] Embodiment 56. The drug delivery device of any one of Embodiments 50 to 55, wherein the at least one tablet has a density from 1 mg/mm³ to 1.3 mg/mm³, a height from 0.67 mm to 0.95 mm, or both a density from 1 mg/mm³ to 1.3 mg/mm³ and a height from 0.67 mm to 0.95 mm.
- [00141] Embodiment 57. The drug delivery device of any one of Embodiments 1 to 56, 20 wherein the drug permeable membrane has a surface area from 100 mm² to 200 mm², a thickness of from 70 μm to 75 μm, or both a surface area from 100 mm² to 200 mm² and a thickness of from 70 μm to 75 μm.
- [00142] Embodiment 58. The drug delivery device of any one of Embodiments 1 to 57, wherein the drug permeable membrane comprises silicone, has a surface area of about 200 25 mm², and has a thickness of about 72 μm.
- [00143] Embodiment 59. The drug delivery device of any one of Embodiments 1 to 58, further comprising: a second microchip element which comprises a body portion defining at least one containment reservoir therein, wherein the second body portion has an exterior wall having one or more drug release apertures in fluid communication with the at least one 30 containment reservoir, the one or more drug release apertures being closed off by one or more corresponding reservoir caps configured to be electrically activated to unclosethe one or more drug release apertures; a drug formulation, which comprise a second drug, disposed in the at least one containment reservoir of the second microchip element; and a second drug-permeable membrane secured next to the exterior wall of the body portion of the second

microchip element, wherein the device, upon activation of the one or more reservoir caps of the second microchip element, is configured to release the second drug by diffusion through the second drug-permeable membrane and into the aqueous environment.

5 **[00144]** Embodiment 60. The drug delivery device of Embodiment 59, where the second drug is identical to the first drug.

[00145] Embodiment 61. The drug delivery device of Embodiment 59 or 60, further comprising a hermetic enclosure which contains electronic components configured for electrical activation of the one or more reservoir caps of the microchip element and the second microchip element.

10 **[00146]** Embodiment 62. The drug delivery device of Embodiment 61, wherein the hermetic enclosure is disposed between the microchip element and the second microchip element.

[00147] Embodiment 63. The drug delivery device of Embodiment 61, wherein (i) the hermetic enclosure is not disposed between the microchip element and the second microchip
15 element, and (ii) the first and second microchip elements are disposed adjacent one another with their exterior walls facing in opposite directions.

[00148] Publications cited herein and the materials for which they are cited are specifically incorporated by reference. Modifications and variations of the methods and devices described herein will be obvious to those skilled in the art from the foregoing detailed
20 description. Such modifications and variations are intended to come within the scope of the appended claims.

CLAIMS

1. A drug delivery device, comprising:
 - a microchip element which comprises a body portion defining at least one containment reservoir therein, wherein the body portion has an exterior wall having one or more drug release apertures in fluid communication with the at least one containment reservoir, the one or more drug release apertures being closed off by one or more corresponding reservoir caps configured to be electrically activated to unclosethe one or more drug release apertures;
 - a drug formulation, which comprise a first drug, disposed in the at least one containment reservoir; and
 - a drug-permeable membrane secured next to the exterior wall of the body portion of the microchip element, wherein the device is configured to operate in an aqueous environment and, upon activation of the one or more reservoir caps, release the drug by diffusion through the drug-permeable membrane and into the aqueous environment.
2. The drug delivery device of claim 1, further comprising an outer housing wall secured in a position next to, and spaced a distance from, the exterior wall of the body portion of the microchip element, the outer housing wall comprising the drug-permeable membrane, wherein a depot space is defined between the drug-permeable membrane and the exterior wall of the body portion of the microchip element.
3. The drug delivery device of claim 1, wherein the outer housing wall further comprises a rigid frame supporting the drug-permeable membrane.
4. The drug delivery device of claim 3, wherein the rigid frame defines two or more windows of the drug-permeable membrane.
5. The drug delivery device of claim 3 or 4, wherein the rigid frame is part of a shell covering at least part of the microchip element.
6. The drug delivery device of any one of claims 1 to 5, wherein the drug-permeable membrane comprises a polymeric membrane.

7. The drug delivery device of claim 5, wherein the polymeric membrane comprises silicone, polyurethane, or a combination thereof.
8. The drug delivery device of any one of claims 1 to 7, wherein the at least one containment reservoir further comprises a water swellable charge material.
9. The drug delivery device of claim 8, wherein the water swellable charge material is in the form of a charge layer adjacent to a layer of the drug formulation, the drug formulation layer being disposed between the charge layer and the one or more drug release apertures.
10. The drug delivery device of claim 8, wherein the water swellable charge material is dispersed with the drug in the drug formulation.
11. The drug delivery device of any one of claims 8 to 10, wherein the water swellable charge material comprises a hydrophilic polymer.
12. The drug delivery device of any one of claims 8 to 10, wherein the water swellable charge material comprises hyaluronic acid.
13. The drug delivery device of any one of claims 1 to 12, wherein the drug formulation is in solid form, such as a tablet.
14. The drug delivery device of any one of claims 1 to 13, wherein the drug comprises a hormone.
15. The drug delivery device of claim 14, wherein the hormone is a contraceptive hormone, such as levonorgestrel.
16. The drug delivery device of any one of claims 1 to 15, wherein the at least one containment reservoir is a microreservoir.
17. The drug delivery device of any one of claims 1 to 16, wherein reservoir caps are configured to rupture by electrothermal ablation when electrically activated.
18. The drug delivery device of claim 2, which is configured to release the drug into the depot space and subsequently diffuse through the drug-permeable membrane and into the aqueous environment.

19. The drug delivery device of any one of claims 1 to 18, wherein the drug delivery device is an implantable drug delivery device and the aqueous environment is *in vivo* in a patient.
20. The drug delivery device of any one of claims 1 to 19, further comprising:
 - a second microchip element which comprises a body portion defining at least one containment reservoir therein, wherein the second body portion has an exterior wall having one or more drug release apertures in fluid communication with the at least one containment reservoir, the one or more drug release apertures being closed off by one or more corresponding reservoir caps configured to be electrically activated to unclose the one or more drug release apertures;
 - a drug formulation, which comprise a drug, disposed in the at least one containment reservoir of the second microchip element; and
 - a second drug-permeable membrane secured next to the exterior wall of the body portion of the second microchip element, wherein the device is configured, upon activation of the one or more reservoir caps of the second microchip element, to release the drug therefrom by diffusion through the second drug-permeable membrane and into the aqueous environment,
 - wherein, optionally, a second outer housing wall, which comprises the second drug permeable membrane is secured in a position next to, and spaced a distance from, the exterior wall of the body portion of the second microchip element, to define a second depot space between the second drug-permeable membrane and the exterior wall of the body portion of the second microchip element.
21. The drug delivery device of claim 20, further comprising a hermetic enclosure disposed between the microchip element and the second microchip element.
22. The drug delivery device of claim 21, wherein the hermetic enclosure is defined in part by a pair of printed circuit boards, each comprising a ceramic substrate.
23. The drug delivery device of claim 21 or 22, wherein hermetic enclosure contains electronic components configured for electrical activation of the reservoir caps of the microchip element and the second microchip element.

24. The drug delivery device of claim 2, which is an implantable drug delivery device, wherein:
- the microchip element comprises a plurality of microreservoirs and the body portion has a plurality of drug release apertures in fluid communication with the microreservoirs, the plurality of drug release apertures being closed off by a plurality of corresponding reservoir caps configured to be ruptured by electrothermal ablation to open the drug release apertures;
 - the drug is disposed in each of the microreservoirs;
 - a water swellable charge material is disposed in each of the microreservoirs;
 - and
 - the device is configured to operate *in vivo* by permitting interstitial fluid, following activation of one or more of the plurality of reservoir caps, to contact and be imbibed by the water swellable charge material disposed the microreservoirs corresponding to the activated reservoir cap(s), and thereby cause the charge material to swell and eject the drug out of the microreservoir(s) through the drug release apertures and into the depot space for subsequent diffusion through the drug-permeable membrane.
25. The drug delivery device of claim 24, wherein the polymeric membrane comprises silicone, polyurethane, or a combination thereof.
26. The drug delivery device of claim 24 or 25, wherein the water swellable charge material is in the form of a charge layer adjacent to a layer of the drug, the drug layer being disposed between the charge layer and the drug release apertures.
27. The drug delivery device of any one of claims 24 to 26, wherein the water swellable charge material comprises a hydrophilic polymer.
28. The drug delivery device of any one of claims 24 to 26, wherein the water swellable charge material comprises hyaluronic acid.
29. The drug delivery device of any one of claims 24 to 28, wherein the outer housing wall further comprises a rigid frame supporting the drug-permeable membrane.
30. The drug delivery device of claim 29, wherein the rigid frame defines two or more windows of the drug-permeable membrane.

31. The drug delivery device of claim 29 or 30, wherein the rigid frame is part of a shell covering at least part of the microchip element.
32. The drug delivery device of any one of claims 24 to 31, wherein the drug is in a solid form, such as a tablet.
33. The drug delivery device of any one of claims 24 to 32, wherein the drug comprises a hormone.
34. The drug delivery device of claim 33, wherein the hormone comprise a contraceptive hormone, such as levonorgestrel.
35. The drug delivery device of any one of claims 24 to 34, further comprising a hermetic enclosure fixed to the microchip element on a side opposed from the exterior wall and the depot space.
36. The drug delivery device of claim 35, wherein the hermetic enclosure is defined in part by a printed circuit board, which comprises a ceramic substrate.
37. The drug delivery device of claim 35 or 36, wherein hermetic enclosure contains electronic components configured for controlling rupture of the reservoir caps.
38. The drug delivery device of any one of claims 24 to 37, further comprising a second microchip element and a second exterior wall which comprises a second drug-permeable membrane, and which optionally defines a second drug depot space.
39. The drug delivery device of claim 1, wherein the exterior wall is in direct mechanical contact with the drug permeable membrane.
40. The drug delivery device of any one of claims 1 to 39, which is configured to release the drug from the activated at least one containment reservoir by a process comprising swelling of the drug formulation and/or by an extrusion process.
41. The drug delivery device of claim 40, wherein the at least one containment reservoir further comprises a water swellable charge material.

42. The drug delivery device of claim 41, wherein the water swellable charge material and the drug formulation in the at least one containment reservoir are combined in the form of at least one tablet.
43. The drug delivery device of claim 42, wherein the at least one tablet comprises a mixture of particles of the drug with one or more excipients comprising the water swellable charge material.
44. The drug delivery device of claim 43, wherein the drug particles have a median size from about 5 microns to about 12 microns.
45. The drug delivery device of any one of claims 42 to 44, wherein the at least one tablet is from about 10% to about 50% drug particles, by weight.
46. The drug delivery device of any one of claims 42 to 44, wherein the at least one tablet is from about 20% to about 45% drug particles, by weight.
47. The drug delivery device of any one of claims 42 to 44, wherein the at least one tablet is from about 30% to about 42% drug particles, by weight.
48. The drug delivery device of any one of claims 42 to 47, wherein the at least one tablet has a density from 1 mg/mm³ to 1.3 mg/mm³, a height from 0.67 mm to 0.95 mm, or both a density from 1 mg/mm³ to 1.3 mg/mm³ and a height from 0.67 mm to 0.95 mm.
49. The drug delivery device of any one of claims 40 to 48, wherein the drug permeable membrane has a surface area from 100 mm² to 200 mm², a thickness of from 70 μm to 75 μm, or both a surface area from 100 mm² to 200 mm² and a thickness of from 70 μm to 75 μm.
50. The drug delivery device of any one of claims 40 to 49, wherein the drug permeable membrane comprises silicone, has a surface area of about 200 mm², and has a thickness of about 72 μm.
51. The drug delivery device of claim 20, further comprising a hermetic enclosure, wherein (i) the hermetic enclosure is not disposed between the microchip element and the second microchip element, and (ii) the first and second microchip elements are disposed adjacent one another with their exterior walls facing in opposite directions.