~~BRIEF~~ SUMMARY ~~OF THE INVENTION~~

[0007] The ~~invention~~disclosure provides implantable drug delivery devices comprising a core comprising a polymer (or polymer blend) and one or more drugs or pharmaceutical substances, and an outer shell comprising a polymer (or polymer blend) and one or more porogen materials. The shell can optionally additionally comprise one or more drugs or pharmaceutical substances. Surrounding the drug-containing core with a porogen-containing shell can reduce the burst release often observed with sustained release formulations. Use of a porogen material having a narrow size distribution, and the resulting narrow size distribution of the pores left in the shell after removal of the porogen, also allows better control and tuning of the release rate of the drug from the core.

[0008] In some ~~embodiment~~examples, the ~~invention~~disclosure provides an implantable device for delivery of a pharmaceutical substance comprising a core comprising a first polymeric material and a core pharmaceutical substance; and a shell comprising a second polymeric material and a porogen material. The shell can lack a pharmaceutical substance, or alternatively the shell can further comprise a pharmaceutical substance (referred to as a "shell pharmaceutical substance"). The shell can comprise about 1 wt% to about 80 wt% porogen material. In some ~~embodiment~~examples, the porogen material comprises spherical particles and at least about 90% of the spherical particles have a diameter between about 1 micrometer and about 50 micrometers. In some ~~embodiment~~examples, the porogen material comprises spherical particles with a mean diameter between about 1 micrometer and about 50 micrometers. In some ~~embodiment~~examples, the porogen material comprises spherical particles and at least about 90% of the spherical particles have a diameter that varies by 10 % or less from a mean diameter.

[0008a] In one aspect, the present disclosure refers to an implantable device for delivery of a pharmaceutical substance comprising: a core comprising a first polymeric material and a core pharmaceutical substance; and a shell comprising ethylene vinyl acetate and a porogen material, wherein the porogen material comprises particles with a mean diameter between 1 micrometer and 300 micrometers; wherein the implantable device has reduced burst release as compared to a comparison device made entirely of the first polymeric material and the core pharmaceutical substance.

[0009] The porogen material can comprise a bioerodible material. The porogen material can comprise a non-bioerodible material. The porogen material can comprise a material selected from the group consisting of an alkyl cellulose, a hydroxyalkyl cellulose, ethylcellulose, methylcellulose, hydroxymethylcellulose, a fatty acid, stearic acid, palmitic acid, myristic acid, linoleic acid, a biocompatible salt, sodium chloride, calcium chloride, and sodium phosphate; in some ~~embodiment~~examples, the porogen material comprises ethyl cellulose. In some ~~embodiment~~examples, the porogen material dissolves or dissociates from the shell upon washing the implantable device.

[0010] The first polymeric material or the second polymeric material can comprise a bioerodible material. The first polymeric material or the second polymeric material can comprise a non-bioerodible material. The first polymeric material can comprise one or more

polystyrene, polyvinyl esters, polyvinyl acetate, polyvinyl ethers, polyvinyl methyl ether, polyvinylidene halides, vinylidene fluoride based homo- or copolymer, for example, polyvinylidene fluoride (PVDF) or poly(vinylidene-co-hexafluoropropylene) (PVDF-co-HFP) and polyvinylidene chloride, rayon, rayon-triacetate, silicones, vinyl halide polymers and copolymers, polyvinyl chloride, and copolymers of these polymers with poly(ethylene glycol) (PEG).

[0012] The first polymeric material can comprise ethylene-vinyl acetate. The second polymeric material can comprise ethylene-vinyl acetate. In one ~~embodiment~~example, both the first polymeric material and the second polymeric material comprise ethylene-vinyl acetate

[0013] The implantable device can be rod-shaped. In some ~~embodiment~~examples, the implantable device has a diameter of about 1 mm to about 8 mm. In some ~~embodiment~~examples, the implantable device has a length of about 10 mm to about 80 mm. In some ~~embodiment~~examples, the implantable device is capped at one end of the implantable device. In some ~~embodiment~~examples, the implantable device is capped at both ends of the implantable device.

[0014] The core pharmaceutical substance can comprise one or more substances selected from the group consisting of L-thyroxine (T_4), L-triiodothyronine (T_3), a combination of L-thyroxine (T_4) and L-triiodothyronine (T_3), ropinirole, tenofovir, emtricitabine, a combination of tenofovir and emtricitabine, bosentan, methylphenidate, liraglutide, atovaquone, proguanil, a combination of atovaquone and proguanil, and nalmefene. In some ~~embodiment~~examples, the core pharmaceutical substance comprises triiodothyronine. In some ~~embodiment~~examples, the core pharmaceutical substance comprises ropinirole. The core pharmaceutical substance can comprise about 1 wt% to about 80 wt% of the core.

[0015] The shell pharmaceutical substance can comprise one or more substances selected from the group consisting of L-thyroxine (T_4), L-triiodothyronine (T_3), a combination of L-thyroxine (T_4) and L-triiodothyronine (T_3), ropinirole, tenofovir, emtricitabine, a combination of tenofovir and emtricitabine, bosentan, methylphenidate, liraglutide, atovaquone, proguanil, a combination of atovaquone and proguanil, and nalmefene. In some ~~embodiment~~examples, the shell pharmaceutical substance comprises triiodothyronine. In some ~~embodiment~~examples, the shell pharmaceutical substance comprises ropinirole. The shell pharmaceutical substance can comprise about 1 wt% to about 40 wt% of the shell.

[0016] The core pharmaceutical substance and the shell pharmaceutical substance (when present) can be the same pharmaceutical substance, such as triiodothyronine or ropinirole.

The core pharmaceutical substance and the shell pharmaceutical substance (when present) can be different pharmaceutical substances.

[0017] In some ~~embodiment~~examples, the implantable device further comprises a reinforcing member inside the core.

[0018] The ~~invention~~disclosure further provides methods of forming the implantable device, comprising extruding a first composition to form a core, the first composition comprising a first polymeric material and a core pharmaceutical substance; and coating the core with second composition to form a shell, the second composition comprising a second polymeric material and a porogen material. The first composition can be formed by combining the first polymeric material with the core pharmaceutical substance. The second composition can be formed by combining the second polymeric material with the porogen material.

[0018a] In one aspect, the present disclosure refers to a method of forming an implantable device comprising: extruding a first composition to form a core, the first composition comprising a first polymeric material and a core pharmaceutical substance; and coating the core with a second composition to form a shell, the second composition comprising ethylene vinyl acetate and a porogen material, wherein the porogen material comprises particles with a mean diameter between 1 micrometer and 300 micrometers.

[0019] The ~~invention~~disclosure further provides methods of forming an implantable device comprising co-extruding a first composition and a second composition, where the first composition is extruded to form a core, the first composition comprising a first polymeric material and a core pharmaceutical substance; and the co-extruded second composition forming a shell around the core, the second composition comprising a second polymeric material and a porogen material. The first composition can be formed by combining the first polymeric material with the core pharmaceutical substance. The second composition can be formed by combining the second polymeric material with the porogen material.

[0019a] In one aspect, the present disclosure refers to a method of forming an implantable device comprising: co-extruding a first composition and a second composition, where the first composition is extruded to form a core, the first composition comprising a first polymeric material and a core pharmaceutical substance; and the co-extruded second composition forming a shell around the core, the second composition comprising ethylene vinyl acetate and a porogen material, wherein the porogen material comprises particles with a mean diameter between 1 micrometer and 300 micrometers.

[0020] In some ~~embodiment~~examples of the methods, the method further comprises washing the implantable device. The implantable device can be washed with ethanol, water, or a mixture of ethanol and water. Washing the device can dissolve the porogen material, or dissociate the porogen material, from the implantable device to form a plurality of pores in the shell.

[0021] In any of the implants or methods disclosed herein, the second composition can be a non-medicated material, or the second composition can further comprise a shell pharmaceutical substance.

[0022] In any of the implants or methods disclosed herein, the second composition can comprise about 1 wt% to about 40 wt% porogen material. In some ~~embodiment~~examples, the porogen material comprises spherical particles and at least about 90% of the spherical particles have a diameter between about 1 micrometer and about 50 micrometers. In some ~~embodiment~~examples, the porogen material comprises spherical particles with a mean diameter between about 1 micrometer and about 50 micrometers. In some ~~embodiment~~examples, the porogen

material comprises spherical particles and at least about 90% of the spherical particles have a diameter that varies by 10 % or less from a mean diameter.

[0023] In any of the implants or methods disclosed herein, the porogen material comprises particles and the longest dimension of at least about 90% of the particles is between about 1 micrometer and about 50 micrometers. In some ~~embodiment~~examples, the porogen material comprises particles and the average longest dimension of the particles is between about 1 micrometer and about 50 micrometers. In some ~~embodiment~~examples, the porogen material comprises particles and the longest dimension of at least about 90% of the particles varies by 10 % or less from the average longest dimension of the particles.

[0024] In any of the implants or methods disclosed herein, the porogen material comprises particles and the mean dimension of at least about 90% of the particles is between about 1 micrometer and about 50 micrometers, where the mean dimension of the particles is the mean of the longest dimension of the particles and the shortest dimension of the particles. In some ~~embodiment~~examples, the porogen material comprises particles and the mean dimension of the particles is between about 1 micrometer and about 50 micrometers. In some ~~embodiment~~examples, the porogen material comprises particles and the mean dimension of at least about 90% of the particles varies by 10 % or less from the average of the mean dimension of the particles.

[0025] In any of the implants or methods disclosed herein, the porogen material can comprise a bioerodible material, or the porogen material can comprise a non-bioerodible material. The porogen can comprise a material selected from the group consisting of an alkyl cellulose, a hydroxyalkyl cellulose, ethylcellulose, methylcellulose, hydroxymethylcellulose, a fatty acid, stearic acid, palmitic acid, myristic acid, linoleic acid, a biocompatible salt, sodium chloride, calcium chloride, and sodium phosphate. The porogen material can comprise ethyl cellulose.

[0026] In any of the implants or methods disclosed herein, the first polymeric material or the second polymeric material can comprise a bioerodible material. In any of the implants or methods disclosed herein, the first polymeric material or the second polymeric material can comprise a non-bioerodible material.

[0027] In any of the implants or methods disclosed herein, the first polymeric material can comprise one or more materials selected from the group consisting of polybutylene terephthalate, polycarbonate, polyester, polyether ether ketone, polyethylene-co-tetrafluoroethylene, polymethylmethacrylate, polyolefin, polypropylene, polysulfones,

of atovaquone and proguanil, and nalmefene. In any of the implants or methods disclosed herein, the shell pharmaceutical substance can comprise triiodothyronine. In any of the implants or methods disclosed herein, the shell pharmaceutical substance can comprise ropinirole. The shell pharmaceutical substance can comprise about 1 wt% to about 40 wt% of the second composition.

[0034] In some ~~embodiment~~examples, the ~~invention~~disclosure provides methods of treating a disease in a subject, comprising implanting into the subject any of the implantable devices disclosed herein. The disease can be hypothyroidism, Parkinson's disease, restless leg syndrome (RLS), HIV infection, retroviral infection, pulmonary arterial hypertension, attention deficit/hyperactivity disorder, type 2 diabetes, metabolic syndrome, hyperlipidemia, obesity, malaria, alcoholism, or alcohol addiction.

[0035] In some ~~embodiment~~examples, the ~~invention~~disclosure provides any of the implantable devices disclosed herein for use in the treatment of a disease. The disease can be hypothyroidism, Parkinson's disease, restless leg syndrome (RLS), HIV infection, retroviral infection, pulmonary arterial hypertension, attention deficit/hyperactivity disorder, type 2 diabetes, metabolic syndrome, hyperlipidemia, obesity, malaria, alcoholism, or alcohol addiction.

[0036] In some ~~embodiment~~examples, the ~~invention~~disclosure provides for use of any of the implantable devices disclosed herein for treatment of a disease. The disease can be hypothyroidism, Parkinson's disease, restless leg syndrome (RLS), HIV infection, retroviral infection, pulmonary arterial hypertension, attention deficit/hyperactivity disorder, type 2 diabetes, metabolic syndrome, hyperlipidemia, obesity, malaria, alcoholism, or alcohol addiction.

[0037] In some ~~embodiment~~examples, the ~~invention~~disclosure provides for use of L-thyroxine (T_4), L-triiodothyronine (T_3), or a combination of L-thyroxine (T_4) and L-triiodothyronine (T_3) for the manufacture of any of the implantable devices described herein for the treatment of hypothyroidism, metabolic syndrome, hyperlipidemia, or obesity; use of ropinirole for the manufacture of any of the implantable devices described herein for the treatment of Parkinson's disease or restless leg syndrome; use of tenofovir, emtricitabine, or a combination of tenofovir and emtricitabine for the manufacture of any of the implantable devices described herein for the treatment of HIV infection, retroviral infection, or prophylaxis against HIV infection or retroviral infection; use of bosentan for the manufacture of any of the implantable devices described herein for the treatment of pulmonary arterial hypertension; use of methylphenidate for the manufacture of any of the implantable devices described herein for the treatment of attention deficit/hyperactivity disorder; use of liraglutide

for the manufacture of any of the implantable devices described herein for the treatment of type 2 diabetes or obesity; use of doxycycline, atovaquone, proguanil, or a combination of atovaquone and proguanil for the manufacture of any of the implantable devices described herein for the treatment of malaria, or for prophylaxis against malaria; or use of nalmefene for the manufacture of any of the implantable devices described herein for the treatment of alcoholism or alcohol addiction.

[0038] In some ~~embodiment~~examples, the ~~invention~~disclosure provides methods of providing pre-exposure prophylaxis of HIV or prophylaxis of retroviral acquisition, comprising implanting into the subject any of the implantable devices disclosed herein.

[0039] The implantable device can release an average of about 10 µg to about 150 µg of the core pharmaceutical substance per day for the first 30 days when implanted in the subject. The implantable device can release the core pharmaceutical substance when implanted in the subject with a daily variance of less than about 10 % from the daily average release for the first 30 days.

[0040] The implantable device, when implanted in a subject, can release the core pharmaceutical substance with an initial burst at least 50% lower than the initial burst from a comparison implant without the shell. The initial burst period for comparison can be the first hour after implantation, the first six hours after implantation, the first 12 hours after implantation, the first 24 hours after implantation, the first 48 hours after implantation, the first three days after implantation, the first four days after implantation, the first five days after implantation, the first six days after implantation, the first seven days after implantation, the first eight days after implantation, the first nine days after implantation, or the first ten days after implantation. In one ~~embodiment~~example, a comparison implant without the shell is an implant which has only the medicated core of the core-shell implant, and no shell. Thus, for example, in FIG. 1, a comparison implant without the shell would simply have the outer shell removed. In another ~~embodiment~~example, a comparison implant without the shell is an implant where, instead of having a core and a shell, the entire comparison implant is made of the material that forms the core with the same dimensions as the core-shell implant. Thus, for example, in FIG. 1, a comparison implant without the shell would have the outer shell replaced with additional core material containing core pharmaceutical substance, such that the comparison implant has the same dimensions as the implant of the ~~invention~~disclosure, but is uniformly made of core material, including core pharmaceutical substance.

[0041] In any of the ~~embodiment~~examples described herein, the core pharmaceutical substance can be present in the form of a salt, solvate, or hydrate of the active substance.

[0042] In another ~~aspect~~example, the implantable device provides a steady-state level, an approximately constant level, or an essentially constant level of pharmaceutical substance or drug in the blood of the patient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0043] FIG. 1 shows a drawing of one embodiment of an implant of the invention, with about 30% to about 60% porogen filler in the outer shell (the balance of the shell is made of ethylene-vinyl acetate) and about 60% T_3 in the core (the balance of the core is made of ethylene-vinyl acetate). The drawing is not to scale.

[0044] FIG. 1A shows a drawing of a cross-section **110** of an implant of the invention. The drawing is not to scale.

[0045] FIG. 2A shows T_3 plasma levels (ng/dL) in dogs with T_3 implants having 30% ethylcellulose porogen in the shell and 60% T_3 in the core.

[0046] FIG. 2B shows an expanded version of days 215 to 225 from FIG. 2A.

[0047] FIG. 3 shows T_4 plasma levels (mcg/dL) in dogs before and after removal of T_3 implants having 30% ethylcellulose porogen in the shell and 60% T_3 in the core.

[0048] FIG. 4A shows T_4 plasma levels (mcg/dL) in control dogs after removal of placebo (non-T_3 containing) implants.

[0049] FIG. 4B shows T_3 plasma levels (ng/dL) in control dogs after removal of placebo (non-T_3 containing) implants.

[0050] FIG. 4C shows TSH plasma levels in control dogs after removal of placebo (non-T_3 containing) implants.

[0051] FIG. 5 shows T_3 plasma levels (ng/dL) in dogs with a stepwise dose increase in T_3 implants having 60% ethylcellulose porogen in the shell and 60% T_3 in the core, followed by the removal of all T3 implants.

[0052] FIG. 6 shows T_4 plasma levels (mcg/dL) in dogs with a stepwise dose increase in T_3 implants having 60% ethylcellulose porogen in the shell and 60% T_3 in the core, followed by the removal of all T3 implants.

[0053] FIG. 7 shows T_3 plasma levels (ng/dL) in thyroidectomized rats versus normal rats, respectively bearing T_3 implants having 60% ethylcellulose porogen in the shell and

CLAIMS

1. An implantable device for delivery of a pharmaceutical substance comprising:

a core comprising a first polymeric material and a core pharmaceutical substance; and

a shell comprising ethylene vinyl acetate ~~a second polymeric material~~ and a porogen material,~~;~~

wherein the porogen material comprises particles with a mean diameter between 1 micrometer and 300 micrometers;

wherein the implantable device has reduced burst release as compared to a comparison device made entirely of the first polymeric material and the core pharmaceutical substance.

2. The implantable device of claim 1, wherein:

(a) (i) the shell is a non-medicated layer~~.~~; or

(ii) the shell further comprises a shell pharmaceutical substance; and/or

(b) the shell comprises about 1 wt% to about 80 wt% porogen material.

~~3. The implantable device of claim 1, wherein the shell further comprises a shell pharmaceutical substance.~~

~~4. The implantable device of any one of claims 1-3, wherein the shell comprises about 1 wt% to about 80 wt% porogen material.~~

~~5. The implantable device of any one of claims 1-4, wherein the porogen material comprises particles and at least about 90% of the particles have a longest dimension between about 1 micrometer and about 50 micrometers.~~

~~6. The implantable device of any one of claims 1-5, wherein the porogen material comprises particles with an average longest dimension between about 1 micrometer and about 50 micrometers.~~

~~7. The implantable device of any one of claims 1-6, wherein the porogen material comprises particles and at least about 90% of the particles have a mean dimension that varies by 10 % or less from the average of the mean dimension of the particles.~~

38. The implantable device of ~~any one of~~ claim~~s~~ 1 or 2~~-7~~, wherein:

(a) the porogen material comprises a bioerodible material~~.~~; or

(b) the porogen material comprises a non-bioerodible material; or

(c) the porogen material comprises a material selected from the group consisting of an alkyl cellulose, a hydroxyalkyl cellulose, ethylcellulose, methylcellulose, hydroxymethylcellulose, a fatty acid, stearic acid, palmitic acid, myristic acid, linoleic acid, a biocompatible salt, sodium chloride, calcium chloride, and sodium phosphate; or

(d) the porogen material comprises ethyl cellulose; and/or

(e) the porogen material dissolves or dissociates from the shell upon washing the implantable device.

~~9. The implantable device of any one of claims 1-7, wherein the porogen material comprises a non-bioerodible material.~~

~~10. The implantable device of any one of claims 1-7, wherein the porogen material comprises a material selected from the group consisting of an alkyl cellulose, a hydroxyalkyl cellulose, ethylcellulose, methylcellulose, hydroxymethylcellulose, a fatty acid, stearic acid, palmitic acid, myristic acid, linoleic acid, a biocompatible salt, sodium chloride, calcium chloride, and sodium phosphate.~~

~~11. The implantable device of any one of claims 1-7, wherein the porogen material comprises ethyl cellulose.~~

~~12. The implantable device of any one of claims 1-11, wherein the porogen material dissolves or dissociates from the shell upon washing the implantable device.~~

413. The implantable device of any one of claims 1-312, wherein:

(a) the first polymeric material comprises a bioerodible material; or

(b) the second first polymeric material comprises a non-bioerodible material.

14. The implantable device of any one of claims 1-12, wherein the first polymeric material or the second polymeric material comprises a non-bioerodible material.

15. The implantable device of any one of claims 1-312, wherein the first polymeric material comprises one or more materials selected from the group consisting of polybutylene terephthalate, polycarbonate, polyester, polyether ether ketone, polyethylene-co-tetrafluoroethylene, polymethylmethacrylate, polyolefin, polypropylene, polysulfones, polytetrafluoroethylene, polyurethane, polyvinylchloride, polyvinylidene fluoride, silicone, ABS resins, acrylic polymers and copolymers, acrylonitrile-styrene copolymers, alkyd resins, ethylene-vinyl acetate copolymers, copolymers of vinyl monomers with each other and olefins, ethylene-methyl methacrylate copolymers, epoxy resins, ethylene vinyl alcohol copolymer (commonly known by the generic name EVOH or by the trade name EVAL), poly(glyceryl sebacate), poly(glycolic acid-co-trimethylene carbonate), poly(hydroxybutyrate-co-valerate), poly(hydroxyvalerate), poly(lactide-co-glycolide), poly(propylene fumarate), poly(trimethylene carbonate), polyacrylonitrile, polyamides, Nylon 66, polycaprolactam, polycarbonates, polycyanoacrylates, polydioxanone, polyesters, polyethers, polyimides, polyisobutylene and ethylene-alphaolefin copolymers, polyoxymethylenes, polyphosphoester urethane, polyvinyl ketones, polyvinyl aromatics, polystyrene, polyvinyl esters, polyvinyl acetate, polyvinyl ethers, polyvinyl methyl ether, polyvinylidene halides, vinylidene fluoride based homo- or copolymer, for example, polyvinylidene fluoride (PVDF) or poly(vinylidene-co-hexafluoropropylene) (PVDF-co-HFP) and polyvinylidene chloride, rayon, rayon-triacetate, silicones, vinyl halide polymers and copolymers, polyvinyl chloride, and copolymers of these polymers with poly(ethylene glycol) (PEG); preferably wherein the first polymeric material comprises ethylene-vinyl acetate.

16. The implantable device of claim 15, wherein the first polymeric material comprises ethylene-vinyl acetate.

~~17. The implantable device of any one of claims 1-12, 15, and 16, wherein the second polymeric material comprises one or more materials selected from the group consisting of polybutylene terephthalate, polycarbonate, polyester, polyether ether ketone, polyethylene-co-tetrafluoroethylene, polymethylmethacrylate, polyolefin, polypropylene, polysulfones, polytetrafluoroethylene, polyurethane, polyvinylchloride, polyvinylidene fluoride, silicone, ABS resins, acrylic polymers and copolymers, acrylonitrile-styrene copolymers, alkyd resins, ethylene-vinyl acetate copolymers, copolymers of vinyl monomers with each other and olefins, ethylene-methyl methacrylate copolymers, epoxy resins, ethylene vinyl alcohol copolymer (commonly known by the generic name EVOH or by the trade name EVAL), poly(glyceryl sebacate), poly(glycolic acid-co-trimethylene carbonate), poly(hydroxybutyrate-co-valerate), poly(hydroxyvalerate), poly(lactide-co-glycolide), poly(propylene fumarate), poly(trimethylene carbonate), polyacrylonitrile, polyamides, Nylon 66, polycaprolactam, polycarbonates, polycyanoacrylates, polydioxanone, polyesters, polyethers, polyimides, polyisobutylene and ethylene-alphaolefin copolymers, polyoxymethylenes, polyphosphoester urethane, polyvinyl ketones, polyvinyl aromatics, polystyrene, polyvinyl esters, polyvinyl acetate, polyvinyl ethers, polyvinyl methyl ether, polyvinylidene halides, vinylidene fluoride based homo- or copolymer, for example, polyvinylidene fluoride (PVDF) or poly(vinylidene-co-hexafluoropropylene) (PVDF-co-HFP) and polyvinylidene chloride, rayon, rayon-triacetate, silicones, vinyl halide polymers and copolymers, polyvinyl chloride, and copolymers of these polymers with poly(ethylene glycol) (PEG).~~

~~18. The implantable device of claim 17, wherein the second polymeric material comprises ethylene-vinyl acetate.~~

6~~19~~. The implantable device of any one of claims 1-5~~18~~, wherein the implantable device is rod-shaped~~.~~; optionally wherein:

(a) the implantable device has a diameter of about 1 mm to about 8 mm; and/or

(b) the implantable device has a length of about 10 mm to about 80 mm; and/or

(c) the implantable device is capped at one end of the implantable device; and/or

(d) the implantable device is capped at both ends of the implantable device.

~~20. The implantable device of claim 19, wherein the implantable device has a diameter of about 1 mm to about 8 mm.~~

~~21. The implantable device of claim 19 or 20, wherein the implantable device has a length of about 10 mm to about 80 mm.~~

~~22. The implantable device of any one of claims 19-21, wherein the implantable device is capped at one end of the implantable device.~~

~~23. The implantable device of any one of claims 19-22, wherein the implantable device is capped at both ends of the implantable device.~~

7~~24~~. The implantable device of any one of claims 1-6~~23~~, wherein:

(a) the core pharmaceutical substance comprises one or more substances selected from the group consisting of L-thyroxine (T_4), L-triiodothyronine (T_3), a combination of L-thyroxine (T_4) and L-triiodothyronine (T_3), ropinirole, tenofovir, emtricitabine, a combination of tenofovir and emtricitabine, bosentan, methylphenidate, liraglutide, doxycycline, proguanil, atovaquone, a combination of proguanil and atovaquone, and nalmefene~~.~~; and/or

(b) the core pharmaceutical substance comprises ropinirole or triiodothyronine; and/or

(c) the core pharmaceutical substance comprises about 1 wt% to about 80 wt% of the core.

~~25. The implantable device of any one of claims 1-24, wherein the core pharmaceutical substance comprises ropinirole or triiodothyronine.~~

~~26. The implantable device of any one of claims 1-25, wherein the core pharmaceutical substance comprises about 1 wt% to about 80 wt% of the core.~~

8~~27~~. The implantable device of any one of claims 2(a)(ii), 2(b), or 3-7~~3-26~~, wherein:

(a) the shell pharmaceutical substance comprises one or more substances selected from the group consisting of L-thyroxine (T_4), L-triiodothyronine (T_3), a combination of L-thyroxine (T_4) and L-triiodothyronine (T_3), ropinirole, tenofovir, emtricitabine, a combination of tenofovir and emtricitabine, bosentan, methylphenidate, liraglutide, doxycycline, proguanil, atovaquone, a combination of proguanil and atovaquone, and nalmefene.; and/or

(b) the shell pharmaceutical substance comprises ropinirole or triiodothyronine; and/or

(c) the shell pharmaceutical substance comprises about 1 wt% to about 40 wt% of the outer layer.

28. The implantable device of any one of claims 3-27, wherein the shell pharmaceutical substance comprises ropinirole or triiodothyronine.

29. The implantable device of any one of claims 3-28, wherein the shell pharmaceutical substance comprises about 1 wt% to about 40 wt% of the outer layer.

930. The implantable device of any one of claims 2(a)(ii), 2(b), or 3-83-29, wherein said implantable device further comprises further comprising a reinforcing member inside the core.

1031. A method of forming an implantable device comprising:

extruding a first composition to form a core, the first composition comprising a first polymeric material and a core pharmaceutical substance; and

coating the core with a second composition to form a shell, the second composition comprising ethylene vinyl acetate a second polymeric material and a porogen material, wherein the porogen material comprises particles with a mean diameter between 1 micrometer and 300 micrometers.

1132. A method of forming an implantable device comprising:

co-extruding a first composition and a second composition, where the first composition is extruded to form a core, the first composition comprising a first polymeric

material and a core pharmaceutical substance; and the co-extruded second composition forming a shell around the core, the second composition comprising ethylene vinyl acetate ~~a second polymeric material~~ and a porogen material, wherein the porogen material comprises particles with a mean diameter between 1 micrometer and 300 micrometers.

1233. The method of claim 1031 or claim 1132, wherein the first composition is formed by combining the first polymeric material with the core pharmaceutical substance.

1334. The method of claim 10 or claim 11~~any one of claims 31-33~~, wherein the second composition is formed by combining ethylene vinyl acetate ~~the second polymeric material~~ with the porogen material.

1435. The method of any one of claims ~~31~~10-1334, further comprising washing the implantable device; optionally wherein:

(i) the implantable device is washed in ethanol, water, or a mixture of ethanol and water; and/or

(ii) washing the device dissolves the porogen material or dissociates the porogen material from the implantable device to form a plurality of pores in the shell.

~~36. The method of claim 35, wherein the implantable device is washed in ethanol, water, or a mixture of ethanol and water.~~

~~37. The method of claim 35 or claim 36, wherein washing the device dissolves the porogen material or dissociates the porogen material from the implantable device to form a plurality of pores in the shell.~~

1538. The method of any one of claims 1031-1437, wherein:

(a) the second composition is a non-medicated material~~.~~; and/or

(b) the second composition further comprises a shell pharmaceutical substance; and/or

(c) the second composition comprises about 1 wt% to about 80 wt% porogen materials.

~~39. The method of any one of claims 31-38, wherein the second composition further comprises a shell pharmaceutical substance.~~

~~40. The method of any one of claims 31-39, wherein the second composition comprises about 1 wt% to about 80 wt% porogen materials.~~

~~41. The method of any one of claims 31-40, wherein the porogen materials comprise spherical particles and at least about 90% of the spherical particles have a diameter between about 1 micrometer and about 50 micrometers.~~

~~42. The method of any one of claims 31-41, wherein the porogen materials comprise spherical particles with a mean diameter between about 1 micrometer and about 50 micrometers.~~

~~43. The method of any one of claims 31-42, wherein the porogen materials comprise spherical particles and at least about 90% of the spherical particles have a diameter that varies by 10 % or less from a mean diameter.~~

1644. The method of any one of claims 1031-1543, wherein:

(a) the porogen materials comprise a bioerodible material.; or

(b) the porogen materials comprise a non-bioerodible material; or

(c) the porogen comprises a material selected from the group consisting of an alkyl cellulose, a hydroxyalkyl cellulose, ethylcellulose, methylcellulose, hydroxymethylcellulose, a fatty acid, stearic acid, palmitic acid, myristic acid, linoleic acid, a biocompatible salt, sodium chloride, calcium chloride, and sodium phosphate; optionally wherein the porogen materials comprise ethyl cellulose.

~~45. The method of any one of claims 31-43, wherein the porogen materials comprise a non-bioerodible material.~~

~~46. The method of any one of claims 31-43, wherein the porogen comprises a material selected from the group consisting of an alkyl cellulose, a hydroxyalkyl cellulose,~~

~~ethylcellulose, methylcellulose, hydroxymethylcellulose, a fatty acid, stearic acid, palmitic acid, myristic acid, linoleic acid, a biocompatible salt, sodium chloride, calcium chloride, and sodium phosphate.~~

~~47. The method of claim 46, wherein the porogen materials comprise ethyl cellulose.~~

1748. The method of any one of claims 1031-1647, wherein:

(a) the first polymeric material ~~or the second polymeric material~~ comprises a bioerodible material.; or

(b) the first polymeric material comprises a non-bioerodible material; or

(c) the first polymeric material comprises one or more materials selected from the group consisting of polybutylene terephthalate, polycarbonate, polyester, polyether ether ketone, polyethylene-co-tetrafluoroethylene, polymethylmethacrylate, polyolefin, polypropylene, polysulfones, polytetrafluoroethylene, polyurethane, polyvinylchloride, polyvinylidene fluoride, silicone, ABS resins, acrylic polymers and copolymers, acrylonitrile-styrene copolymers, alkyd resins, ethylene-vinyl acetate copolymers, copolymers of vinyl monomers with each other and olefins, ethylene-methyl methacrylate copolymers, epoxy resins, ethylene vinyl alcohol copolymer, poly(glyceryl sebacate), poly(glycolic acid-co-trimethylene carbonate), poly(hydroxybutyrate-co-valerate), poly(hydroxyvalerate), poly(lactide-co-glycolide), poly(propylene fumarate), poly(trimethylene carbonate), polyacrylonitrile, polyamides, Nylon 66, polycaprolactam, polycarbonates, polycyanoacrylates, polydioxanone, polyesters, polyethers, polyimides, polyisobutylene and ethylene-alphaolefin copolymers, polyoxymethylenes, polyphosphoester urethane, polyvinyl ketones, polyvinyl aromatics, polystyrene, polyvinyl esters, polyvinyl acetate, polyvinyl ethers, polyvinyl methyl ether, polyvinylidene halides, vinylidene fluoride based homo- or copolymer, polyvinylidene fluoride (PVDF) or poly(vinylidene-co-hexafluoropropylene) (PVDF-co-HFP) and polyvinylidene chloride, rayon, rayon-triacetate, silicones, vinyl halide polymers and copolymers, polyvinyl chloride, and copolymers of these polymers with poly(ethylene glycol) (PEG); preferably wherein the first polymeric material comprises ethylene-vinyl acetate.

~~49. The method of any one of claims 31-47, wherein the first polymeric material or the second polymeric material comprises a non-bioerodible material.~~

~~50. The method of any one of claims 31-47, wherein the first polymeric material comprises one or more materials selected from the group consisting of polybutylene terephthalate, polycarbonate, polyester, polyether ether ketone, polyethylene-co-tetrafluoroethylene, polymethylmethacrylate, polyolefin, polypropylene, polysulfones, polytetrafluoroethylene, polyurethane, polyvinylchloride, polyvinylidene fluoride, silicone, ABS resins, acrylic polymers and copolymers, acrylonitrile-styrene copolymers, alkyd resins, ethylene-vinyl acetate copolymers, copolymers of vinyl monomers with each other and olefins, ethylene-methyl methacrylate copolymers, epoxy resins, ethylene vinyl alcohol copolymer (commonly known by the generic name EVOH or by the trade name EVAL), poly(glyceryl sebacate), poly(glycolic acid-co-trimethylene carbonate), poly(hydroxybutyrate-co-valerate), poly(hydroxyvalerate), poly(lactide-co-glycolide), poly(propylene fumarate), poly(trimethylene carbonate), polyacrylonitrile, polyamides, Nylon 66, polycaprolactam, polycarbonates, polycyanoacrylates, polydioxanone, polyesters, polyethers, polyimides, polyisobutylene and ethylene-alphaolefin copolymers, polyoxymethylenes, polyphosphoester urethane, polyvinyl ketones, polyvinyl aromatics, polystyrene, polyvinyl esters, polyvinyl acetate, polyvinyl ethers, polyvinyl methyl ether, polyvinylidene halides, vinylidene fluoride based homo- or copolymer, for example, polyvinylidene fluoride (PVDF) or poly(vinylidene-co-hexafluoropropylene) (PVDF-co-HFP) and polyvinylidene chloride, rayon, rayon triacetate, silicones, vinyl halide polymers and copolymers, polyvinyl chloride, and copolymers of these polymers with poly(ethylene glycol) (PEG).~~

~~51. The method of claim 50, wherein the first polymeric material comprises ethylene-vinyl acetate.~~

~~52. The method of any one of claims 31-47, 50, or 51, wherein the second polymeric material comprises one or more materials selected from the group consisting of polybutylene terephthalate, polycarbonate, polyester, polyether ether ketone, polyethylene-co-tetrafluoroethylene, polymethylmethacrylate, polyolefin, polypropylene, polysulfones, polytetrafluoroethylene, polyurethane, polyvinylchloride, polyvinylidene fluoride, silicone, ABS resins, acrylic polymers and copolymers, acrylonitrile-styrene copolymers, alkyd resins,~~

~~ethylene-vinyl acetate copolymers, copolymers of vinyl monomers with each other and olefins, ethylene-methyl methacrylate copolymers, epoxy resins, ethylene vinyl alcohol copolymer (commonly known by the generic name EVOH or by the trade name EVAL), poly(glyceryl sebacate), poly(glycolic acid-co-trimethylene carbonate), poly(hydroxybutyrate-co-valerate), poly(hydroxyvalerate), poly(lactide-co-glycolide), poly(propylene fumarate), poly(trimethylene carbonate), polyacrylonitrile, polyamides, Nylon 66, polycaprolactam, polycarbonates, polycyanoacrylates, polydioxanone, polyesters, polyethers, polyimides, polyisobutylene and ethylene-alphaolefin copolymers, polyoxymethylenes, polyphosphoester urethane, polyvinyl ketones, polyvinyl aromatics, polystyrene, polyvinyl esters, polyvinyl acetate, polyvinyl ethers, polyvinyl methyl ether, polyvinylidene halides, vinylidene fluoride based homo- or copolymer, for example, polyvinylidene fluoride (PVDF) or poly(vinylidene-co-hexafluoropropylene) (PVDF-co-HFP) and polyvinylidene chloride, rayon, rayon triacetate, silicones, vinyl halide polymers and copolymers, polyvinyl chloride, and copolymers of these polymers with poly(ethylene glycol) (PEG).~~

~~53. The method of claim 52, wherein the second polymeric material comprises ethylene-vinyl acetate.~~

1854. The method of any one of claims 1031-1753, wherein:

(a) the implantable device is rod-shaped.; and/or

(b) the implantable device has a diameter of about 1 mm to about 8 mm; and/or

(c) the implantable device has a length of about 10 mm to about 80 mm; and/or

(d) said method further comprises capping the implantable device at one end of the implantable device; and/or

(e) said method further comprises capping the implantable device at both ends of the implantable device.

~~55. The method of any one of claims 31-54, wherein the implantable device has a diameter of about 1 mm to about 8 mm.~~

~~56. The method of any one of claims 31-55, wherein the implantable device has a length of about 10 mm to about 80 mm.~~

~~57. The method of any one of claims 31-56, further comprising capping the implantable device at one end of the implantable device.~~

~~58. The method of any one of claims 31-57, further comprising capping the implantable device at both ends of the implantable device.~~

1959. The method of any one of claims 1131-1858, wherein:

(a) the core pharmaceutical substance comprises one or more substances selected from the group consisting of L-thyroxine (T_4), L-triiodothyronine (T_3), a combination of L-thyroxine (T_4) and L-triiodothyronine (T_3), ropinirole, tenofovir, emtricitabine, a combination of tenofovir and emtricitabine, bosentan, methylphenidate, liraglutide, doxycycline, proguanil, atovaquone, a combination of proguanil and atovaquone, and nalmefene.; and/or

(b) the core pharmaceutical substance comprises ropinirole or triiodothyronine; and/or

(c) the core pharmaceutical substance comprises about 1 wt% to about 80 wt% of the first composition.

~~60. The method of any one of claims 31-59, wherein the core pharmaceutical substance comprises ropinirole or triiodothyronine.~~

~~61. The method of any one of claims 31-60, wherein the core pharmaceutical substance comprises about 1 wt% to about 80 wt% of the first composition.~~

2062. The method of any one of claims 1538-1961, wherein:

(a) the shell pharmaceutical substance comprises one or more substances selected from the group consisting of L-thyroxine (T_4), L-triiodothyronine (T_3), a combination of L-thyroxine (T_4) and L-triiodothyronine (T_3), ropinirole, tenofovir, emtricitabine, a combination of tenofovir and emtricitabine, bosentan, methylphenidate, liraglutide, doxycycline, proguanil, atovaquone, a combination of proguanil and atovaquone, and nalmefene.; and/or

(b) the shell pharmaceutical substance comprises ropinirole or triiodothyronine; and/or

(c) the shell pharmaceutical substance comprises about 1 wt% to about 40 wt% of the second composition.

~~63. The method of any one of claims 38-62, wherein the shell pharmaceutical substance comprises ropinirole or triiodothyronine.~~

~~64. The method of any one of claims 38-63, wherein the shell pharmaceutical substance comprises about 1 wt% to about 40 wt% of the second composition.~~

~~65. A method of treating a disease in a subject comprising implanting into the subject the implantable device according to any one of claims 1-30.~~

~~66. A method of treating hypothyroidism, metabolic syndrome, hyperlipidemia, or obesity in a subject, comprising implanting into the subject the implantable device according to any one of claims 1-23, 26, 29, or 30, wherein the core pharmaceutical substance comprises L-thyroxine (T_4), L-triiodothyronine (T_3), or a combination of L-thyroxine (T_4) and L-triiodothyronine (T_3).~~

~~67. A method of providing pre-exposure prophylaxis of HIV or prophylaxis of retroviral acquisition in a subject, comprising implanting into the subject the implantable device according to any one of claims 1-23, 26, 29, or 30, wherein the core pharmaceutical substance comprises tenofovir, emtricitabine, or a combination of tenofovir and emtricitabine.~~

~~68. A method of treating HIV infection or retroviral infection in a subject, comprising implanting into the subject the implantable device according to any one of claims 1-23, 26, 29, or 30, wherein the core pharmaceutical substance comprises tenofovir, emtricitabine, or a combination of tenofovir and emtricitabine.~~

~~69. A method of providing prophylaxis against malaria in a subject, comprising implanting into the subject the implantable device according to any one of claims 1-23, 26, 29, or 30, wherein the core pharmaceutical substance comprises doxycycline, atovaquone, proguanil, or a combination of atovaquone and proguanil.~~

~~70. A method of treating Parkinson's disease in a subject, comprising implanting into the subject the implantable device according to any one of claims 1-23, 26, 29, or 30, wherein the core pharmaceutical substance comprises ropinirole.~~

~~71. A method of treating restless leg syndrome in a subject, comprising implanting into the subject the implantable device according to any one of claims 1-23, 26, 29, or 30, wherein the core pharmaceutical substance comprises ropinirole.~~

~~72. A method of treating pulmonary arterial hypertension in a subject, comprising implanting into the subject the implantable device according to any one of claims 1-23, 26, 29, or 30, wherein the core pharmaceutical substance comprises bosentan.~~

~~73. A method of treating attention deficit/hyperactivity disorder in a subject, comprising implanting into the subject the implantable device according to any one of claims 1-23, 26, 29, or 30, wherein the core pharmaceutical substance comprises methylphenidate.~~

~~74. A method of treating type 2 diabetes in a subject, comprising implanting into the subject the implantable device according to any one of claims 1-23, 26, 29, or 30, wherein the core pharmaceutical substance comprises liraglutide.~~

~~75. A method of treating obesity in a subject, comprising implanting into the subject the implantable device according to any one of claims 1-23, 26, 29, or 30, wherein the core pharmaceutical substance comprises liraglutide.~~

~~76. A method of treating alcoholism or alcohol addiction in a subject, comprising implanting into the subject the implantable device according to any one of claims 1-23, 26, 29, or 30, wherein the core pharmaceutical substance comprises nalmefene.~~

~~77. The method of any one of claims 65-76, wherein the implantable device releases an average of about 10 µg to about 150 µg of the core pharmaceutical substance per day for the first 30 days when implanted in the subject.~~

~~78. The method of any one of claims 65-77, wherein the implantable device releases the core pharmaceutical substance when implanted in the subject with a daily variance of less than about 10 % from the daily average release for the first 30 days.~~

~~79. The method of any one of claims 65-78 wherein the implantable device releases the core pharmaceutical substance when implanted in the subject with an initial burst at least 50% lower than the initial burst from a comparison implant without the shell.~~

~~80. The method of any one of claims 65-78, wherein the implantable device releases the core pharmaceutical substance when implanted in the subject with an initial burst at least 50% lower than the initial burst from a comparison implant where the shell is replaced with additional core material.~~

~~81. The method of any one of claims 65-80, wherein the implantable device is implanted subdermally in the subject.~~