

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 a second polymeric material and a porogen material;
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 the shell is a non-medicated layer.
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.
8. The implantable device of any one of claims 1-7, wherein the porogen material
comprises a bioerodible material.
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.
13. The implantable device of any one of claims 1-12, wherein the first polymeric material or the second polymeric material comprises a 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 1-12, 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).

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.

19. The implantable device of any one of claims 1-18, wherein the implantable device is rod-shaped.
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.
24. The implantable device of any one of claims 1-23, wherein the core pharmaceutical substance comprises one or more substances selected from the group consisting of L-thyroxine (T₄), L-triiodothyronine (T₃), a combination of L-thyroxine (T₄) and L-triiodothyronine (T₃), ropinirole, tenofovir, emtricitabine, a combination of tenofovir and emtricitabine, bosentan, methylphenidate, liraglutide, doxycycline, proguanil, atovaquone, a combination of proguanil and atovaquone, and nalmefene.
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.
27. The implantable device of any one of claims 3-26, wherein the shell pharmaceutical substance comprises one or more substances selected from the group consisting of L-thyroxine (T₄), L-triiodothyronine (T₃), a combination of L-thyroxine (T₄) and L-triiodothyronine (T₃), ropinirole, tenofovir, emtricitabine, a combination of tenofovir and emtricitabine, bosentan, methylphenidate, liraglutide, doxycycline, proguanil, atovaquone, a combination of proguanil and atovaquone, and nalmefene.

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.
30. The implantable device of any one of claims 3-29, further comprising a reinforcing member inside the core.
31. 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 a second polymeric material and a porogen material.
32. 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 a second polymeric material and a porogen material.
33. The method of claim 31 or claim 32, wherein the first composition is formed by combining the first polymeric material with the core pharmaceutical substance.
34. The method of any one of claims 31-33, wherein the second composition is formed by combining the second polymeric material with the porogen material.
35. The method of any one of claims 31-34, further comprising washing the implantable device.

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.
38. The method of any one of claims 31-37, wherein the second composition is a non-medicated material.
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.
44. The method of any one of claims 31-43, wherein the porogen materials comprise a bioerodible material.
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.
48. The method of any one of claims 31-47, wherein the first polymeric material or the second polymeric material comprises a bioerodible material.
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.

54. The method of any one of claims 31-53, wherein the implantable device is rod-shaped.

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.
59. The method of any one of claims 31-58, wherein the core pharmaceutical substance comprises one or more substances selected from the group consisting of L-thyroxine (T₄), L-triiodothyronine (T₃), a combination of L-thyroxine (T₄) and L-triiodothyronine (T₃), ropinirole, tenofovir, emtricitabine, a combination of tenofovir and emtricitabine, bosentan, methylphenidate, liraglutide, doxycycline, proguanil, atovaquone, a combination of proguanil and atovaquone, and nalmefene.
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.
62. The method of any one of claims 38-61, wherein the shell pharmaceutical substance comprises one or more substances selected from the group consisting of L-thyroxine (T₄), L-triiodothyronine (T₃), a combination of L-thyroxine (T₄) and L-triiodothyronine (T₃), ropinirole, tenofovir, emtricitabine, a combination of tenofovir and emtricitabine, bosentan, methylphenidate, liraglutide, doxycycline, proguanil, atovaquone, a combination of proguanil and atovaquone, and nalmefene.
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 (T₄), L-triiodothyronine (T₃), or a combination of L-thyroxine (T₄) and L-triiodothyronine (T₃).
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.