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(71) Applicants: **PSIVIDA US, INC.** [US/US]; 400 Pleasant Street, Watertown, MA 02472 (US). **PSIMEDICA LIMITED** [GB/GB]; Malvern Hills Science Park, Geraldine Road, Malvern, Worcestershire WR14 3SZ (GB).

(72) Inventors: **CANHAM, Leigh, T.**; 73 Barnards Green Road, Malvern, Worcestershire WR14 3LR (GB). **GUO, Hong**; 3 Waybridge Lane, Wayland, MA 01778 (US). **NAZZARO, Martin**; 35 Mallard Road, Quincy, MA 02169 (US). **BARNETT, Christian**; 3 Lower House Farm Barns, Throckmorton, Pershore, Worcestershire WR10 2JX (GB).

(74) Agents: **HALSTEAD, David, P.** et al.; Foley Hoag LLP, Seaport West, 155 Seaport Boulevard, Boston, MA 02210-2600 (US).

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(54) **Title**: DRUG DELIVERY DEVICE COMPRISING SILICON-BASED CARRIER PARTICLES

(57) **Abstract**: This application provides a device for delivering a beneficial substance to a patient. The device comprises a shell enclosing a plurality of carrier particles. The carrier particles are porous, and a beneficial substance, such as a drug, is disposed in the pores. The drug can diffuse out of the pores, into the interior of the device, and then through at least one permeable portion of the shell. This application also provides methods of making and using these devices.

DRUG DELIVERY DEVICE COMPRISING SILICON-BASED CARRIER PARTICLES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 61/778,111 filed on March 12, 2013; the entire content of said application is incorporated herein in its entirety by this reference.

BACKGROUND

There has been considerable interest within the pharmaceutical industry in the development of dosage forms that provide controlled release of therapeutic agents over a period of time. Releasing an active substance in this way can help to improve bioavailability and ensure that appropriate concentrations of the agent are provided for a sustained period without the need for repeated dosing. In turn, this also helps to minimize the effects of patient non-compliance which is frequently an issue with other forms of administration.

With conventional dosing (tablets, injections, etc.), the concentration of drug in a given area of the body increases through an ineffective concentration and eventually reaches an effective concentration. Frequently the concentration may actually reach some toxic threshold. After a relatively short period, however, the drug concentration decreases as drug is either metabolized in the body or is eliminated. Frequently, drug levels decrease so low that therapeutic levels are no longer maintained. A second dose is then given and the cycle is repeated. The goal of a sustained release system is to maintain drug levels within the therapeutic range and ideally at a constant level.

However, many of currently available sustained release systems fall short of one or more of these goals. Certain sustained release systems lose efficacy over time due to degradation, dispersal within the body, or other unwanted biological processes. Some sustained release systems deliver the drug over too short a time scale, necessitating frequent replacement. Still other sustained release systems perform adequately for releasing one drug, but are not readily customizable to deliver a variety of different classes of therapeutics. Therefore, there is a

continuing need for the development of improved dosage forms for the controlled release of therapeutic agents.

SUMMARY

This application provides a device for delivering a beneficial substance to a patient. The device comprises a shell enclosing a plurality of carrier particles. The carrier particles are porous, and a beneficial substance, such as a drug, is disposed in the pores. The drug can diffuse out of the pores, into the interior of the device, and then through at least one permeable portion of the shell. This application also provides methods of making and using these devices.

The devices described herein have several advantageous properties. For instance, because each device is administered as a single unit, the device makes it easier for a user to administer a fixed dose. Thus, the device may reduce the chance of accidentally administering an incorrect dose and the chance of an end-user measuring a dose inaccurately. The device can also advantageously localize administration of the beneficial substance to a desired area in a patient's body, because the shell contains the particles at a desired region of the body. In addition, the device comprises a shell that advantageously protects the carrier and beneficial substance against unwanted reactions in the body. For instance, in some embodiments, the shell protects the carrier and beneficial substance against enzymatic degradation or the patient's antibodies. The shell can also protect its contents from cells that would adhere to, break down, or otherwise modify the carrier or beneficial substance. In some embodiments, the device provides improved protection to the beneficial substance during the manufacturing process. For instance, the carrier particles and/or shell can stabilize the beneficial substance during the manufacturing process, for instance during steps that involve heat. The device can also provide improved protection of the beneficial substance during storage, for instance by stabilizing the beneficial substance from interaction with air or humidity. Furthermore, the device can stabilize the beneficial substance over the course of treatment.

In certain aspects, the present disclosure provides a device comprising a shell and a plurality of particles disposed within the shell, the particles comprising a porous carrier material and a beneficial substance disposed within pores of the carrier, and the shell comprising at least one portion that is permeable to the beneficial substance.

In some aspects, the disclosure provides a method of making a device, comprising: (a) providing a tube having first and second ends; (b) inserting a plurality of particles into the tube, wherein the particles comprise porous silicon-based carrier material; (c) adding a first member to the first end of the tube; and (d) adding a second member to the second end to the tube, wherein at least one of the tube, the first member, and the second member is permeable to the beneficial substance. In some aspects, the disclosure provides a device made by this method. In some embodiments, step (b) is performed before step (c), and in some embodiments step (c) is performed before step (b).

In certain aspects, the disclosure provides a method of delivering a beneficial substance to a patient, comprising administering to a patient a device as described herein, whereby the beneficial substance is released from the device into the patient after administration.

In certain embodiments, the shell comprises a polymer. In some embodiments, the shell comprises: a tube having first and second ends; a first member positioned at the first end; and a second member positioned at the second end; wherein the particles are inside the tube and the first and second members retain the particles in the tube.

In some embodiments, the tube has a substantially cylindrical shape. In some embodiments, the tube is impermeable to the beneficial substance. For instance, in some embodiments, the tube comprises poly(lactic-co-glycolic acid) (PLGA). In some embodiments, the first member and second member are permeable to the beneficial substance. For instance, in some embodiments, the first member and second member both comprise poly(vinyl alcohol) (PVA). In some embodiments, the first member is permeable to the beneficial substance and the second member is impermeable to the beneficial substance. For instance, in some embodiments, the first member comprises poly(vinyl alcohol) (PVA). In some embodiments, the second member comprises silicone.

In certain embodiments, the tube has a length of between 1 and 4 mm. In some embodiments, the tube has a diameter of between 0.2 – 0.5 mm.

In some embodiments, the carrier material is mesoporous. In certain embodiments, the carrier material has a porosity in the range of about 30 to about 90%, for instance about 50%

to about 80% or about 70% to about 90%. In some embodiments, the carrier material is silicon-based. In some embodiments, the carrier material comprises elemental silicon. In some embodiments, the carrier material comprises silica. In some embodiments, the pores in the carrier material are substantially parallel. In some embodiments, the carrier material comprises anodized silicon. In some embodiments, the carrier material is resorbable or bio-erodible.

In certain embodiments, the particles have a largest dimension, on the average, of between about 1 micron and about 20 microns. In some embodiments, the device releases the beneficial substance at a release rate, the release rate being determined primarily by release of the beneficial substance from pores of the carrier material. In some embodiments, when the device is placed in a biological medium, the beneficial substance is released from the device according to a substantially zero-order release profile.

In some embodiments, the beneficial substance is selected from small molecules, proteins, peptides, antibodies, carbohydrates, lipids, polymers, oligonucleotides, and polynucleotides. In some embodiments, the beneficial substance is ranibizumab or bevacizumab.

In some embodiments, the device is produced using a method in which the particles comprise a beneficial substance disposed within pores of the carrier material. In certain embodiments, the method further comprises contacting the device to a beneficial substance and allowing the beneficial substance to enter pores of the carrier material. In some embodiments, adding the first member comprises contacting the first end of the tube to a polymer solution and curing the polymer solution, thereby forming a first member on the first end of the tube. In certain embodiments, adding the second member comprises contacting the second end of the tube to a polymer solution and curing the polymer solution, thereby forming a second member on the second end of the tube. In some embodiments, the first and second ends are cured simultaneously.

In some embodiments, the device releases the beneficial substance for between about one month and one year when immersed in simulated body fluid. In some embodiments, administering the device comprises injecting, implanting, or inserting the device into the patient.

The disclosure contemplates all combinations of any one or more of the foregoing aspects and/or embodiments, as well as combinations with any one or more of the embodiments set forth in the detailed description and examples.

BRIEF DESCRIPTION OF THE DRAWINGS

The devices will now be described in more detail with reference to preferred embodiments, given only by way of example, and with reference to the accompanying drawings, in which:

Figure 1 is an enlarged exploded perspective drawing of a cylindrical device for delivering a beneficial substance.

Figure 2 is an enlarged exploded perspective drawing of a device for delivering a beneficial substance, made with a tube with a square cross-section.

Figure 3 is an enlarged perspective drawing of a cylindrical device for delivering a beneficial substance.

Figure 4 is an enlarged cross-sectional view of a device for delivering a beneficial substance, in which the beneficial substance diffuses out of one end of the device.

Figure 5 is an enlarged cross-sectional view of a device for delivering a beneficial substance, in which the beneficial substance diffuses out of both ends of the device.

Figure 6 is a cumulative *in vitro* release profile of implants containing fumed silica particles loaded with latanoprost (1:1 w:w) in PBS at 37 °C over 70 days.

Figure 7 is a cumulative *in vitro* release profile of implants containing oxidized anodized silicon particles loaded with latanoprost (1:1 w:w) in PBS at 37 °C over 30 days.

DETAILED DESCRIPTION

1. Devices comprising porous carrier particles

This application provides a device for delivering a beneficial substance to a patient. The device comprises a shell enclosing a plurality of carrier particles. The carrier particles are porous, and a beneficial substance, such as a drug, is disposed in the pores. The beneficial substance can diffuse out of the pores, into the interior of the device, and then through at least one permeable portion of the shell. This application also provides methods of making and using these devices.

A. Characteristics of the shell

The shell encloses the carrier particles, keeping the carrier localized in one area of the body. At the same time, the shell allows the beneficial substance (such as a drug) to exit the shell and reach target tissues. Thus, at least a portion of the shell is permeable to the beneficial substance.

The shell can also provide structure to the device. The shell may be dimensionally stable and retain its shape in the absence of the particles. For instance, the shell may comprise a rigid tube that retains its shape even when not filled with the carrier material particles. The tube may also retain its shape in the absence of the first end and second end of the shell.

In some embodiments, the device comprises a single shell.

In certain embodiments, the shell is made from a tube with a member closing each end, so that the members hold the particles inside. A device 100 of this type is illustrated in Fig. 1, in exploded form. The tube 102 has a first end 102a and a second end 102b. A first member 104 contacts the first end 102a of the tube 102. A second member 106 contacts the second end 102b of the tube 102. The tube 102, first member 104, and second member 106 enclose a plurality of porous particles 108. The pores are suitable for receiving a beneficial substance like a drug.

While, in Figure 1, the first and second members 104 and 106 are shown having about the same thickness, they may also be given different thicknesses. In addition, in this illustration the first and second members 104 and 106 have approximately the same diameter as the tube 102. However, the members may have a slightly larger or slightly smaller diameter as long

as they are appropriately sized to retain the particles in the tube. As will be discussed in more detail in Section 2, the first and second members may be formed *in situ* at the ends of the tube, by inducing cross-linking of a polymeric layer at the ends of the tube.

Although the device of Figure 1 is substantially cylindrical, (i.e., it has a tube with a circular cross-section) other geometries are possible. The tube can have a cross-section that is a circle, an oval, a square, a rectangle, a hexagon, or any other shape that is suitable for containing particles inside. Figure 2 illustrates an exploded view of a device 200 made with a tube 202 having a square cross section. The tube 202 has a first end 202a and a second end 202b. A first member 204 contacts the first end 202a, and a second member 206 contacts the second end 202b. The tube 202, first member 204, and second member 206 enclose a plurality of porous particles 108.

Figure 3 illustrates a device 300 with the first and second members in contact with the tube. In particular, the tube 302 has a first end 302a in contact with a first member 304. The tube 302 has a second end 302b in contact with a second member 306.

In some embodiments, the length of the device (i.e., the distance between the first member and the second member) is from about 1 – 2 mm, 2 – 4 mm, 4 – 6 mm, 6 – 8 mm, 8 – 10 mm, 1 – 2 cm, 2 – 4 cm, or 4 – 10 cm. In certain embodiments, the width of the device (e.g., the diameter of the tube, or the diameter of the first and second members), is from about 0.1 – 0.2 mm, 0.2 – 0.4 mm, 0.4 – 0.6 mm, 0.6 – 0.8 mm, 0.8 – 1.0 mm, 1 – 2 mm, 2 – 4 mm, 4 – 6 mm, 6 – 8 mm, 8 – 10 mm, 1 – 2 cm, 2 – 4 cm, or 4 – 10 cm. The device may be shaped and sized for injection (e.g., less than about 4 mm long and less than about 0.5 mm in diameter, e.g., to fit through at least one of a needle having a size from about 30 gauge to about 15 gauge or a cannula having a size from about 30 gauge to about 15 gauge, preferably to fit through a less than 22-gauge cannula). When such devices are prepared for implantation within the vitreous of the eye, in some embodiments the device does not exceed about 7 mm in any direction, so that the device can be inserted through a less than 7 mm incision. Thus, in some embodiments, the devices do not exceed 7 mm in height or 3 mm in diameter.

The tube wall is preferably sufficiently thick to allow the tube to retain its shape in the absence of any other material. In some embodiments, the thickness of the tube walls ranges between about 0.01 mm and about 1.0 mm. In some embodiments, the tube wall is from

about 0.01 – 0.02 mm, 0.02 – 0.04 mm, 0.04 – 0.06 mm, 0.06 – 0.08 mm, 0.08 – 1.0 mm, 1 – 2 mm, 2 – 4 mm, or 4 – 10 mm. Exemplary diameters for the tube of the device include 0.011" +/- 0.001" for the inner diameter and 0.0145" +/- 0.001" for the outer diameter. Exemplary diameters for the tube of the device also include 0.0061 +/- 0.001" for the inner diameter and 0.0145" +/- 0.001" for the outer diameter. Exemplary diameters for the tube of the device also include 0.016" +/- 0.001" for the inner diameter and 0.018" +/- 0.001" for the outer diameter.

At least a portion of the shell is permeable to the beneficial substance. "Permeable" denotes that the shell allows an effective amount of the beneficial substance to exit the device. Certain parts of the shell may be impermeable to the beneficial substance. The term "impermeable", as used herein, means that the layer will not allow passage of the beneficial substance at a rate required to obtain the desired local or systemic physiological or pharmacological effect, during the period when the device delivers an effective amount of the beneficial substance to the patient. In some embodiments, the impermeable region has a permeability for the beneficial substance of less than 10%, 5%, 2%, 1%, 0.5%, 0.2%, 0.1%, 0.05%, 0.02%, or 0.01% of the permeability of the permeable region.

In some embodiments, the tube is permeable to the beneficial substance. In some embodiments, the first member is permeable to the beneficial substance. In some embodiments, the second member is permeable to the beneficial substance. In some embodiments, the tube is impermeable and one or both of the members are permeable. In some embodiments, to promote greater release of the beneficial substance, the tube is made of a permeable material. For instance, the tube, first member, and second member may all be permeable.

The permeability of a portion of the shell can be affected by its thickness. An impermeable member should be thick enough not to release a significant amount of beneficial substance, relative to a permeable region of the device. The thickness of an impermeable member can be, for example, between about 0.01 and about 2 mm, preferably between about 0.01 and about 0.5 mm, most preferably between about 0.01 and about 0.2 mm. A permeable member should be thick enough to contain the carrier particles in the tube, yet not so thick as to prevent release of an effective amount of the beneficial substance. The thickness of the permeable member can be, for example, between about 0.01 and about 2 mm, preferably

between about 0.01 and about 0.5 mm, most preferably between about 0.01 and about 0.2 mm.

In certain embodiments, at least a portion of the shell is porous and the beneficial substance can exit the shell through the pores. The pores should be small enough that the carrier particles do not pass through the pores in any substantial amount.

Preferably, the shell is essentially insoluble in body fluids which the material will come in contact.

In some embodiments, the shell is substantially non-biodegradable. In some embodiments, the shell does not substantially biodegrade in a biological environment prior to release of at least 90%, 95%, or 99% of the beneficial substance. In some embodiments, the shell substantially biodegrades in a biological environment after release of at least 90%, 95%, or 99% of the beneficial substance.

In some embodiments, the shell comprises a polymer. In particular, the tube, first member, and/or second member may be polymeric. Generally speaking, suitable biocompatible polymers for use in the subject devices include, but are not limited to, poly(vinyl acetate) (PVAC), poly(caprolactone) (PCL), ethylene vinyl acetate polymer (EVA), poly(ethylene glycol) (PEG), poly(vinyl alcohol) (PVA), poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), polyalkyl cyanoacrylate, polyurethane, nylons, or copolymers thereof. In polymers including lactic acid monomers, the lactic acid may be D-, L- (e.g., poly-L-lactic acid (PLLA)), or any mixture of D- and L- isomers. In some embodiments, the polymer is polyimide. In some embodiments, the polymer is PLGA that comprises lactic acid (L) and glycolic acid (G) monomers in a ratio of about 95% L and 5% G. The percentage of L may range between 80-97%. The percentage of G may range between 3-20%. In some embodiments, the polymer is heat curable, radiation curable, light (including ultraviolet) curable, evaporation curable, or curable by catalysis. In certain embodiments, the polymer is silicone, such as a silicone rubber, polydimethylsiloxane, or silicone-carbonate copolymer.

Certain polymers, like PVA, can be made more or less permeable by altering the degree of polymer cross-linking. Some polymers may be permeable or impermeable depending on the

relative characteristics of the polymer and the drug in the drug core. For instance, a given polymer may be permeable to a small molecule but impermeable to an antibody.

Exemplary polymers suitable for construction of permeable portions of the shell include PVA and PEG.

Exemplary polymers suitable for construction of impermeable portions of the shell include nylons, polyurethane, EVA, polyalkyl cyanoacrylate, poly(tetrafluoroethylene) (PTFE), polycarbonate (PC), poly(methyl methacrylate) (PMMA), high grades of ethylene vinyl acetate (EVA) (e.g., 9% vinyl, content), poly(lactic-co-glycolic acid) (PLGA), and polyvinyl alcohol (PVA), especially cross-linked PVA.

In certain embodiments, the shell comprises metal, such as gold, platinum, and (surgical) stainless steel. For instance, the tube may be made of metal. In some embodiments, the metal portion of the shell is impermeable to the beneficial substance. The metal is preferably biocompatible. In certain embodiments, the metal is biodegradable. The biocompatible and/or biodegradable metal alloy may comprise one or more of Fe (iron), Mg (magnesium), Mn (manganese), Pd (palladium), Co (cobalt), Al (aluminum), W (tungsten), B (boron), C (carbon), S (sulfur), Si (silicon), Li (lithium), Zr (zirconium), Ca (calcium), Y (yttrium), Zn (zinc). Exemplary biodegradable metals are described in H. Hermawan "Biodegradable Metals" SpringerBriefs in Materials 2012 p. 13-22 and Moravej and Martovani, "Biodegradable Metals for Cardiovascular Stent Application: Interests and New Opportunities" Int J Mol Sci. 2011; 12(7): 4250–4270.

In certain embodiments, the shell comprises silicon (for instance, elemental silicon) or silica. A silicon or silica shell may be biodegradable.

The materials for the tube, first member, and second member can be chosen to achieve the desired rate of release for the beneficial substance. For instance, a "low-flow" embodiment of the device is illustrated in cross-section in Figure 4. The device 400 comprises a tube 402 made of an impermeable material and a first member 404 made of an impermeable material. The second member 406 is made of a permeable material. The particles 408 are contained inside the device 400. The particles 408 initially release the beneficial substance 410 into the interior of the device. The beneficial substance 410 then diffuses through the permeable

second member 406 to exit the device. No substantial amount of the beneficial substance exits the device through the tube 402 or first member 404. As an example, in preferred embodiments, the tube comprises impermeable poly(dl-lactide-co-glycolide) PLGA, the first member is made of an impermeable substance such as silicone, and the second member comprises permeable poly(vinyl alcohol) (PVA).

In contrast, Figure 5 illustrates a "high-flow" embodiment of the device, in cross-section. The device 500 comprises a tube 502 made of an impermeable material. The first member 504 and second member 506 are both made of permeable material. The particles 508 are contained inside the device 500. The particles 508 initially release the beneficial substance 510 into the interior of the device. The beneficial substance 510 then diffuses through the permeable first and second members 504 and 506 to exit the device. No substantial amount of the beneficial substance exits the device through the tube 502. As an example, in preferred embodiments, the tube comprises impermeable poly(dl-lactide-co-glycolide) PLGA, and the first and second members comprise permeable poly(vinyl alcohol) (PVA).

The beneficial substance diffuses in the direction of lower chemical potential, i.e., toward the exterior surface of the device. Release of the beneficial substance from the device is controlled by several factors. It is influenced by the beneficial substance's dissolution rate, rate of release from the pores of the carrier material, and passage through the shell. The device shape, size, and materials can be chosen to achieve a desired release rate of the beneficial substance. Thus, in some embodiments, the release rate is determined primarily by dissolution of the beneficial substance. In other embodiments, the release rate is determined primarily by release of the beneficial substance from pores of the carrier material. In still other embodiments, the release rate is determined primarily by the permeability of the shell. In some embodiments, the release rate is significantly affected by any two or all three of these steps.

The rate of diffusion of the beneficial substance through the device's shell may be determined, for instance, via diffusion cell studies carried out under sink conditions. In diffusion cell studies carried out under sink conditions, the concentration of drug in the receptor compartment is essentially zero when compared to the high concentration in the donor compartment.

It will be appreciated that a material may be permeable to a drug and also substantially control the rate at which the drug diffuses or otherwise passes through the material. Consequently, a permeable portion of the shell may also be release-rate-limiting or release-rate-controlling, and the permeability of such a membrane may be one of the most significant factors controlling the release rate for a device.

In some embodiments, the device releases the beneficial substance at a rate that is essentially constant over time (i.e., zero-order kinetics). Zero-order release is desirable when the goal is to maintain a substantially constant amount of the beneficial substance to the patient over a sustained period.

B. Characteristics of the carrier material

The carrier material holds and gradually releases a beneficial substance, such as a drug. The beneficial substance resides in small pores in the carrier material. The carrier material is a plurality of particles enclosed by the device's shell. Each of the carrier particles releases beneficial substance into the interior of the device, and from there the beneficial substance then exits the shell.

In certain preferred embodiments, the particles of the device, measured at the largest diameter, have a d10 in the range 1-5 microns (meaning 10% of the particles in the device have a diameter below a number in the range of 1-5 microns), a d50 in the range 5-10 microns (meaning 50% of the particles in the device have a diameter below a number in the range of 5-10 microns), and a d90 in the range of 10-20 microns (meaning 90% of the particle in the device have a diameter below a number in the range of 10-20 microns). In some embodiments, the d10 is 1-5 microns, 1-3 microns, or 3-5 microns. In some embodiments, the d50 is 5-7 microns, 6-8 microns, 7-9 microns, or 8-10 microns. In some embodiments, the d90 is 10-15 microns or 15-20 microns. In certain embodiments, the particles of the device, measured at the largest diameter, have an average size of about 1 to about 500 microns, such as about 5 to 500 microns, about 5 to about 100 microns, or about 5 to about 20 microns. In some embodiments, greater than 60%, greater than 70%, greater than 80% or greater than 90% of the particles have a particle size of from 1-20 microns, preferably 5-15 microns, measured at the largest dimension. The particles may have an average particle size

between 1 and 20 microns such as between 5-15 microns or about 15 microns, about 16 microns, about 17 microns, about 18 microns, about 19 microns.

In some embodiments, the carrier comprises a semiconductor material such as semiconductor silicon. Examples of additional materials that may be used as porous carrier materials are germanium, ceramics, metal oxides, bone phosphate, phosphates of calcium (e.g., hydroxyapatite), other inorganic phosphates, carbon black, carbonates, sulfates, aluminates, borates, aluminosilicates, magnesium oxide, calcium oxide, iron oxides, zirconium oxides, titanium oxides, and other comparable materials.

The device may comprise a silicon-based carrier material such as elemental silicon, silicon dioxide (silica), silicon monoxide, silicates (compounds containing a silicon-bearing anion, e.g., SiF_6^{2-}, $Si_2O_7^{6-}$, or SiO_4^{4-}), or any combination of such materials. The carrier material may be, for example, semiconducting silicon, elemental silicon, polycrystalline silicon, or amorphous silicon. The silicon may be undoped, or may be doped (for example with phosphorus). The carrier material may be silicon carbide or silicon nitride. In certain preferred embodiments, the carrier material comprises a complete or partial framework of elemental silicon and that framework is substantially or fully covered by a silicon dioxide surface layer. In other preferred embodiments, the carrier material is entirely or substantially entirely silica. In certain embodiments, the silicon-based carrier material is synthetic amorphous silica. In certain embodiments, the silicon-based carrier material is fumed silica.

In certain embodiments, the carrier material comprises silica, such as greater than about 50% silica, greater than about 60 wt% silica, greater than about 70 wt% silica, greater than about 80 wt% silica, greater than about 90 wt% silica, greater than about 95 wt% silica, greater than 99 wt% silica, or even greater than 99.9 wt% silica. Porous silica may be purchased from suppliers such as Grace Davison (and sold under the trademark Davisil), Silicycle, and Macherey-Nagel.

In certain embodiments, the carrier material comprises elemental silicon, greater than 60 wt% silicon, greater than 70 wt% silicon, greater than 80 wt% silicon, greater than 90 wt% silicon, or even greater than 95 wt% silicon. Silicon may be purchased from suppliers such as Vesta Ceramics.

Purity of the silicon-based material can be quantitatively assessed using techniques such as Energy Dispersive X-ray Analysis, X-ray fluorescence, Inductively Coupled Optical Emission Spectroscopy or Glow Discharge Mass Spectroscopy.

The based carrier material may a porous, amorphous solid or a porous, crystalline solid. For example, silicon-based carrier material may comprise elemental silicon or compounds thereof, e.g., silicon dioxide or silicates, in an amorphous form. In certain embodiments, the elemental silicon or compounds thereof is present in a crystalline form. In other embodiments, the carrier material comprises amorphous silica and/or amorphous silicon. In certain embodiments, the silicon-based material is greater than about 60 wt% amorphous, greater than about 70 wt% amorphous, greater than about 80 wt% amorphous, greater than about 90 wt% amorphous, greater than about 92 wt% amorphous, greater than about 95 wt% amorphous, greater than about 99 wt% amorphous, or even greater than 99.9 wt% amorphous. In certain embodiments, the amorphous silica is fumed silica. In certain embodiments, the amorphous silica is synthetic amorphous silica.

X-ray diffraction analysis can be used to identify crystalline phases of silicon-based material. Powder diffraction can be taken, for example, on a Scintag PAD-X diffractometer, e.g., equipped with a liquid nitrogen cooled germanium solid state detector using Cu K-alpha radiation.

The carrier material may have a porosity of about 30% to about 95%, about 30% to about 90%, or about 60% to about 80%. Porosity, as used herein, is a measure of the void spaces in a material, and is a fraction of the volume of voids over the total volume of the material. In certain embodiments, the carrier material has a porosity of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or even at least about 90%. In particular embodiments, the porosity is greater than about 40%, such as greater than about 50%, greater than about 60%, or even greater than about 70%.

The carrier material of the devices may have a surface area to weight ratio selected from about 20 m^2/g to about 2000 m^2/g, such as from about 20 m^2/g to about 1000 m^2/g, or even from about 100 m^2/g to about 300 m^2/g. In certain embodiments, the surface area is greater than about 200 m^2/g, greater than about 250 m^2/g or greater than about 300 m^2/g. In certain embodiments, the surface area is about 200 m^2/g.

In certain embodiments, the beneficial substance is distributed to a pore depth from the surface of the material of at least about 10 microns, at least about 20 microns, at least about 30 microns, at least about 40 microns, at least about 50 microns, at least about 60 microns, at least about 70 microns, at least about 80 microns, at least about 90 microns, at least about 100 microns, at least about 110 microns, at least about 120 microns, at least about 130 micron, at least about 140 microns or at least about 150 microns. In certain embodiments, the beneficial substance is distributed in the pores of the carrier material substantially uniformly.

The beneficial substance may be loaded into the carrier material to a depth which is measured as a ratio of the depth to which the beneficial substance penetrates the carrier material to the total width of the carrier material. In certain embodiments, the beneficial substance is distributed to a depth of at least about 10% into the carrier material, to at least about 20% into the carrier material, at least about 30% into the carrier material, at least about 40% into the carrier material, at least about 50% into the carrier material, or at least about 60% into the carrier material.

Quantification of gross loading may be achieved by a number of analytic methods, for example, gravimetric, EDX (energy-dispersive analysis by x-rays), Fourier transform infra-red (FTIR) or Raman spectroscopy of the pharmaceutical composition or by UV spectrophotometry, titrimetric analysis, HPLC or mass spectroscopy of the eluted therapeutic agent in solution. Quantification of the uniformity of loading may be obtained by compositional techniques that are capable of spatial resolution such as cross-sectional EDX, Auger depth profiling, micro-Raman and micro-FTIR.

The carrier material preferably comprises pores that can receive a beneficial substance. Microporous carrier (pore size less than 2 nm), mesoporous carrier (pore size 2-50 nm) and macroporous carrier (pore size >50 nm) are all suitable carrier materials. In certain embodiments, the average pore size of the carrier material is selected from 2-50 nm, such as from about 5 to about 40 nm, from about 15 to about 40 nm, such as about 20 to about 30 nm. In certain embodiments, the average pore size is selected from about 2 to about 15 nm, such as about 5 to about 10 nm. In certain embodiments, the average pore size is about 30 nm. In certain embodiments, greater than 50% of the pores of the carrier material have a pore size from 2-50 nm, greater than 60% of the pores of the carrier material have a pore size from 2-

50 nm, greater than 70% of the pores of the carrier material have a pore size from 2-50 nm, greater than 80% of the pores of the carrier material have a pore size from 2-50 nm, or even greater than 90% of the pores of the carrier material have a pore size from 2-50 nm.

In certain embodiments, the carrier material comprises porous silicon dioxide, such as mesoporous silicon dioxide or amorphous silica, such as fumed silica.

In certain embodiments, the carrier material has a population of pores with a well-defined pore size, i.e., the distribution of pore sizes for the carrier material falls within a defined range. In certain embodiments, a well-defined population of pores has about 50% to about 99% of the pore sizes within about 1 nm to 15 nm of the average pore size for that population, preferably within about 10 nm, about 5 nm, or even within 3 nm or 2 nm of the average pore size for that population. In certain such embodiments, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, or even greater than about 95% of the pores of the carrier material have pore sizes within the specified range. Similarly, a population of pores with a well-defined pore size can be a population in which greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, or even greater than about 95% of the pores have pore sizes within 20%, preferably within 15%, 10%, or even 5% of the average pore size for that population.

Pore (e.g., mesopore) size distribution can be quantified using established analytical methods such as gas adsorption, high resolution scanning electron microscopy, nuclear magnetic resonance cryoporosimetry and differential scanning calorimetry.

In some embodiments, a population of pores with a well-defined pore size can be a population for which the standard deviation of the pore sizes is less than 20%, preferably less than 15%, less than 10%, or even less than 5% of the average pore size for that population.

The pore size may be preselected to the dimensional characteristics of the beneficial substance to control the release rate of the beneficial substance in a biological system. Typically, pore sizes that are too small preclude loading of the beneficial substance, while oversized pores do not interact with the beneficial substance sufficiently strongly to exert the desired control over the rate of release. For example, the average pore diameter for a carrier

material may be selected from larger pores, e.g., 15 nm to 40 nm, for high molecular weight molecules, e.g., 200,000-500,000 amu, and smaller pores, e.g., 2 nm to 10 nm, for molecules of a lower molecular weight, e.g., 10,000-50,0000 amu. For instance, average pore sizes of about 6 nm in diameter may be suitable for molecules of molecular weight around 14,000 to 15,000 amu, such as about 14,700 amu. Average pore sizes of about 10 nm in diameter may be selected for molecules of molecular weight around 45,000 to 50,000 amu, such as about 48,000 amu. Average pore sizes of about 25-30 nm in diameter may be selected for molecules of molecular weight around 150,000 amu.

The pore size may be preselected to be adapted to the molecular radius of the beneficial substance to control the release rate of the beneficial substance in a biological system. For instance, average pore sizes of about 25 nm to about 40 nm in diameter may be suitable for molecules with a largest molecular radius from about 6 nm to about 8 nm. Molecular radii may be calculated by any suitable method such as by using the physical dimensions of the molecule based on the X-ray crystallography data or using the hydrodynamic radius which represents the solution state size of the molecule. As the solution state calculation is dependant upon the nature of the solution in which the calculation is made, it may be preferable for some measurements to use the physical dimensions of the molecule based on X-ray crystallography data. As used herein, the largest molecular radius reflects half of the largest dimension of the therapeutic agent.

In certain embodiments, the average pore diameter is selected to limit the aggregation of molecules, e.g., proteins, within a pore. It would be advantageous to prevent biomolecules, such as proteins, from aggregating in a device as this is believed to impede the controlled release of molecules into a biological system. Therefore, a pore that, due to the relationship between its size and the size of a biomolecule, allows, for example, only one biomolecule to enter the pore at any one time will be preferable to a pore that allows multiple biomolecules to enter the pore together and aggregate within the pore. In certain embodiments, multiple biomolecules (e.g., proteins) may be loaded into a pore, but due to the depth of the pore, the proteins distributed throughout this depth of the pore will aggregate to a lesser extent. For instance, a pore may have a diameter slightly larger than the diameter of a protein inside the pore. In this case, the pore's narrow diameter can constrain the arrangement of proteins, decreasing aggregation.

In certain embodiments, the carrier material comprises two or more different materials with different properties (e.g., pore sizes, particle diameters, or surface characteristics), each preselected to be adapted to a different beneficial substance. For example, two different carrier materials may be admixed, one with a first population of pores whose pore size is adapted to a first beneficial substance, the other with a second population of pores whose pore size is adapted to a second beneficial substance. In some embodiments, the device comprises a first population of carrier particles having a first population of pores whose pore size is adapted to a first beneficial substance, and a second population of carrier particles having a second population of pores whose pore size is adapted to a second beneficial substance. In certain other embodiments, a particle comprises a single material that has two or more well-defined populations of pores, e.g., wherein the carrier material is made by a molecular templating technique, wherein the characteristics of the pores are preselected for two or more beneficial substances, e.g., two beneficial substances with different molecular radii. Thus, the carrier material may deliver two or more beneficial substances in the controlled manner described herein. In such embodiments, the loading of the beneficial substances is preferably ordered from largest to smallest agent, so that the largest agent selectively adsorbs into the largest pores (i.e., it does not fit into the smaller pores), so that the larger pores do not adsorb smaller agents.

In certain embodiments in which the carrier material has two or more distinct well-defined populations of pores (e.g., the distinct pore populations are substantially non-overlapping), the differences between the properties of the different populations of pores are preferably selected to limit the adsorption of each different beneficial substance to a certain population of pores. In certain embodiments, the average pore size of the two or more distinct well-defined pore populations may be selected to limit the adsorption of the larger beneficial substance into smaller pores. The average pore size differential may be defined as the difference between the average pore sizes for the different populations of pores in the carrier material. For example, an average pore size differential of at least 10 nm could indicate that the carrier material may comprise at least two populations of pores whose average pore sizes differ ("average pore size differential") by at least 10 nm., e.g., the composition may comprise two pore populations having average pore sizes of 10 nm and 20 nm, three populations of pores with average pore sizes of 10 nm, 20 nm, and 30 nm, or four populations of pores with average pore sizes of 10 nm, 20 nm, 30 nm, and 40 nm. In certain embodiments, the average pore size differential is preferably at least about 5 nm, at least

about 10 nm, at least 15 nm, at least about 20 nm, or at least about 30 nm. In certain embodiments, the two or more well-defined pore populations have distinct average pore sizes, such that the average pore sizes of any two populations differ by at least 20%, preferably at least 30%, 40%, or even 50% of the smaller average pore size.

In certain embodiments, the walls of the carrier material that separate the pores have an average width of less than 5 nm, such as about 4.8 nm, about 4.6 nm, about 4.4 nm, about 4.2 nm, about 4.0 nm, about 3.8 nm, about 3.6 nm, about 3.4 nm, about 3.2 nm, about 3.0 nm, about 2.8 nm, or even about 2.6 nm. In certain embodiments, the walls of the carrier material that separate the pores have an average width of less than about 3 nm, such as about 2.8 nm, about 2.6 nm, about 2.4 nm, about 2.2 nm, about 2.0 nm, about 1.8 nm, about 1.6 nm, about 1.4 nm, about 1.2 nm, about 1.0 nm, or even about 0.8 nm.

Dimensionality and morphology of the device can be measured, for example, by Transmission Electron Microscopy (TEM) using a 2000 JEOL electron microscope operating, for example, at 200 keV. Samples for TEM can be prepared by dispensing a large number of porous carrier materials onto a holey carbon film on a metal grid, via a dilute slurry.

In certain embodiments, the pores of the carrier material define space having a volume of about 0.1 mL/g to about 5 mL/g of the carrier material. In certain embodiments, the pore volume is about 0.2 mL/g to about 3 mL/g, such as about 0.4 mL/g to about 2.5 mL/g, such as about 1.0 mL/g to about 2.5 mL/g.

In certain embodiments, the load level of the carrier material is up to 70%, such as up to 40% by weight based on the combined weight of the carrier material and the beneficial substance. The load level is calculated by dividing the weight of the loaded beneficial substance by the combined weight of the loaded therapeutic agent and carrier material and multiplying by 100. In certain embodiments, the load level of the carrier material is greater than 10%, such as greater than 15%, greater than 20%, greater than 25%, greater than 30%, greater than 35%, greater than 40%, greater than 45% or greater than 50%. In certain embodiments, the load level of the carrier material is less than 5%. The load level may be between about 5% and about 10%. In certain embodiments, the load level of the carrier material is between about

10% and about 20%, between about 20% and about 30%, between about 30% and about 40%, between about 40% and about 50%, or between about 50% and about 60% by weight.

The load volume of the devices described herein may be evaluated in terms of the volume of the pores in the porous material being occupied by the beneficial substance. The percentage of the maximum loading capacity that is occupied by the beneficial substance (that is, the percentage of the total volume of the pores in the porous carrier material that is occupied by the beneficial substance) for carrier materials may be from about 30% to about 100%, such as from about 50% to about 90%. For any given carrier material, this value may be determined by dividing the volume of the beneficial substance taken up during loading by the void volume of the carrier material prior to loading and multiplying by one hundred.

In certain embodiments, the carrier particles, measured at the largest diameter, have an average size of about 1 to about 500 microns, such as about 5 to about 100 microns. In certain embodiments, at least 80%, 90%, 99%, or even 100% of the particles in the device, measured at the largest diameter, are about 1 to about 500 microns, such as about 5 to about 500 microns, or about 2 to about 100 microns.

In order to increase the rate of loading of the beneficial substance into the particles, it may be advantageous to use relatively small particles. As smaller particles have pores with less depth for the beneficial substance to penetrate, the amount of time needed to load the particles may be reduced. This may be particularly advantageous when the pore diameters are similar in dimensions to the molecular diameters or size of the therapeutic agents. Smaller particles may be from 1-20 microns, such as about 10-20 microns, e.g., about 15-20 microns, measured at the largest dimension.

In some aspects, greater than 60%, greater than 70%, greater than 80% or greater than 90% of the particles have a particle size of from 1-20 microns, preferably 5-15 microns, measured at the largest dimension. The particles may have an average particle size between 1 and 20 microns such as between 5-15 microns or about 15 microns, about 16 microns, about 17 microns, about 18 microns, about 19 microns.

Particle size distribution, including the mean particle diameter can be measured, for example, using a Malvern Particle Size Analyzer, Model Mastersizer, from Malvern Instruments, UK.

A helium-neon gas laser beam may be projected through an optical cell containing a suspension of the carrier material. Light rays striking the carrier material are scattered through angles which are inversely proportional to the particle size. The photodetector array measures the light intensity at several predetermined angles and electrical signals proportional to the measured light flux values are then processed by a microcomputer system against a scatter pattern predicted from the refractive indices of the sample carrier material and aqueous dispersant.

Methods of preparing suitable carrier materials, including those described above, may be found in International Application WO 2012/061377, and this document is expressly incorporated by reference in its entirety.

In certain embodiments, the device also comprises one or more pharmaceutically acceptable excipients. In some embodiments, the excipient is a filler, binder, diluent, buffering agent, moistening agent, preservative, stabilizer, flavoring agent, dye, coloring agent, disintegrating agent, or surfactant. In some embodiments, a buffering agent is used to tailor the drug release rate by creating a micro-environment pH in the device. The pH can affect the dissolution rate of the beneficial substance or the permeability of the shell for the beneficial substance, thereby affecting the overall release rate. A surfactant may be used to adjust the charge, lipophilicity or hydrophilicity of the carrier, such as to enhance wettability of poorly soluble or hydrophobic compositions. Some examples of materials which can serve as pharmaceutically acceptable excipients include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) hydrophobic materials such as cocoa butter, suppository waxes, and the like; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; and (16) other non-toxic compatible substances employed in pharmaceutical formulations. The excipient may be disposed within pores of the carrier material. In other embodiments, the excipient is outside the particles and inside the device's shell. For instance, the particles may be suspended in solution and/or form a slurry, and the excipient may be in the solution.

C. Beneficial substances deliverable by the device

The device can store and deliver a therapeutically effective amount of a beneficial substance. In preferred embodiments, the beneficial substance is a therapeutic. As used herein, the term "therapeutic" encompasses the active molecule as well as salts of the active molecule. The therapeutic may be, for example, a drug or a prodrug.

In certain embodiments, the beneficial substance is selected from any agent useful in the treatment or prevention of diseases. In certain embodiments, the beneficial substance is selected from small molecule therapeutic agents, i.e., compounds with molecular weights less than 1000 amu. In preferred embodiments, the beneficial substance is selected from large molecules with molecular weight equal to or greater than 1000 amu. In certain embodiments, the beneficial substance of the invention is a biomolecule. Biomolecules, as used herein, refer to any molecule that is produced by a living organism, including large polymeric molecules such as proteins, polysaccharides, and nucleic acids as well as small molecules such as primary metabolites, secondary metabolites, and natural products or synthetic variations thereof. In particular, proteins such as antibodies, ligands, and enzymes may be used as beneficial substances in the devices described herein. In particular embodiments, the biomolecules for use in the device have molecular weights ranging from about 10,000 amu to about 500,000 amu.

In some embodiments, the beneficial substance is a protein such as an antibody. In some embodiments, the antibody is a monoclonal antibody. The antibody may be, for instance, an antigen-binding portion of a full-length antibody, e.g., a Fab fragment or a single chain variable fragment. Particular therapeutic antibodies that may be delivered by the device include ranibizumab and bevacizumab.

Polynucleotides that may be administered using the devices herein include DNA, RNA, and analogs of DNA and RNA. For example, the polynucleotides may include 2'O-Me nucleotides or dideoxynucleotides. The polynucleotides may encode proteins for gene therapy, or may be designed to reduce expression of a target gene via an antisense pathway.

In certain embodiments, the beneficial substance has a molecular weight between 10,000 and 50,000 amu, between 50,000 and 100,000 amu or between 100,000 and 150,000 amu. In certain embodiments, the beneficial substance is a protein with a molecular weight between 5,000 amu and 200,000 amu, such as about 10,000 to about 150,000 amu.

The size of a beneficial substance may alternatively be characterized by the molecular radius, which may be determined, for example, through X-ray crystallographic analysis or by hydrodynamic radius. The beneficial substance may be a protein, e.g., with a molecular radius selected from 0.5 nm to 20 nm such as about 0.5 nm to 10 nm, even from about 1 to 8 nm.

The pore size of the carrier material can be selected based at least in part on the size of the beneficial substance. A beneficial substance with molecular radius from 1 to 2.5 nm may be advantageously used with a carrier material with a minimum pore radius of from 4.5 to 5.8 nm. A beneficial substance with a molecular radius of 7 nm may be advantageously used with a carrier material with a minimum pore radius of from 11 to 13 nm, such as about 12 nm. Additional discussion of selecting an appropriate size of pore for a given beneficial substance may be found, for example, in International Application WO 2012/061377, which is expressly incorporated by reference in its entirety.

In some embodiments, the carrier particles are loaded with a liquid drug. Advantageously, carrier particles loaded with a liquid drug can be easier to handle than the liquid drug itself. Thus, the devices herein can ease the manufacturing process for controlled release devices that deliver liquid drugs. In some embodiments, the liquid drug comprises a carboxylic acid moiety. In some embodiments, the liquid beneficial substance in the device is prostaglandin or a prostaglandin analog. For instance, the liquid drug may be the free acid form of latanoprost. As another example, the liquid drug may be a free acid form of travoprost. In some embodiments, the liquid drug is prostacyclin or a prostacyclin analog such as treprostinil, iloprost, or beraprost. In some embodiments, the liquid comprises a fat-soluble vitamin such as Vitamin E.

In certain embodiments, the beneficial substance is prone to decomposition and/or inactivation, and the carrier material reduces decomposition/inactivation of the beneficial substance. The beneficial substance can be inactivated, for example, by degradation or

unfolding/denaturation. For instance, the beneficial substance might be prone to inactivation during the process of curing the first or second member (e.g., with heat or ultraviolet light) and the carrier material reduces this inactivation. For instance, the carrier material may block the agent that inactivates the beneficial substance (e.g., by absorbing the wavelength of light used for curing). As another example, the carrier may stabilize a beneficial substance against the effects of the agent that inactivates the beneficial substance, e.g., by stabilizing the beneficial substance in an active conformation and restricting protein unfolding or degradation. In some embodiments, the beneficial substance experiences at least twice, five times, ten times, 20 times, 50, times or 100 times as much inactivation (e.g., degradation or unfolding) without the carrier material as the beneficial substance within the carrier material under the same conditions during production of the device.

In some embodiments, the beneficial substance within the carrier material has a half-life at room temperature that is at least twice, five times, ten times, 20 times, 50, times or 100 times the half-life of the beneficial substance without the carrier material under the same conditions. In some embodiments, the beneficial substance within the carrier material has a shelf-life at room temperature that is at least twice, five times, ten times, 20 times, 50, times or 100 times the shelf life of the beneficial substance without the carrier material under the same conditions. In certain embodiments, the beneficial substance within the carrier material is stable at 25 °C for at least 15 days, 1 month, 2 months, 3 months, 6 months, at least 1 year, at least 1.5 years, at least 2 years, at least 2.5 years, at least 3 years or at least 4 years. Stability may be assessed, for example, by high performance size exclusion chromatography (HPSEC) or by comparing the biological activity of the stored biomolecule-loaded devices against a sample of freshly prepared biomolecule-loaded devices or against the activity of the devices as measured prior to storage. Preferably, at the end of the storage period, the activity of the stored devices is at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, at least 99.5%, at least 99.8%, or even at least 99.9% of the activity of the corresponding freshly prepared devices. Accordingly, this disclosure contemplates methods of treatment wherein biomolecule-loaded devices are stored at 25 °C for at least 6 months, at least 1 year, at least 1.5 years, at least 2 years, at least 2.5 years, at least 3 years or at least 4 years prior to administering the devices to a patient. In some embodiments, the degradation-sensitive beneficial substance is a biomolecule, such as a protein, including an antibody.

In some embodiments, the device comprises two or more beneficial substances. For instance, the device may comprise two populations of particles, each population loaded with one beneficial substance. Alternatively, a single particle may comprise two or more beneficial substances. In some such embodiments, the single particle has a population of larger pores and a population of smaller pores, and each population of pores contains one of the beneficial substances. Carriers with two populations of pores are described above in Section B.

Many different beneficial substances may be incorporated into the devices described above (e.g., such as devices comprising a shell and porous silicon-based carrier particles). For example, suitable drugs include steroids, alpha receptor agonists, beta receptor antagonists, carbonic anhydrase inhibitors, adrenergic agents, physiologically active peptides and/or proteins, antineoplastic agents, antibiotics, analgesics, anti-inflammatory agents, muscle relaxants, anti-epileptics, anti-ulcerative agents, anti-allergic agents, cardiotonics, anti-arrhythmic agents, vasodilators, antihypertensive agents, anti-diabetic agents, anti-hyperlipidemics, anticoagulants, hemolytic agents, antituberculous agents, hormones, narcotic antagonists, osteoclastic suppressants, osteogenic promoters, angiogenesis suppressors, antibacterials, non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids or other anti-inflammatory corticosteroids, alkaloid analgesics, such as opioid analgesics, antivirals, such as nucleoside antivirals or a non-nucleoside antivirals, anti-benign prostatic hypertrophy (BPH) agents, anti-fungal compounds, antiproliferative compounds, anti-glaucoma compounds, immunomodulatory compounds, cell transport/mobility impeding agents, cytokines, pegylated agents, alpha-blockers, anti-androgens, anti-cholinergic agents, purinergic agents, dopaminergic agents, local anesthetics, vanilloids, nitrous oxide inhibitors, anti-apoptotic agents, macrophage activation inhibitors, antimetabolites, neuroprotectants, calcium channel blockers, gamma-aminobutyric acid (GABA) antagonists, alpha agonists, anti-psychotic agents, tyrosine kinase inhibitors, nucleoside compounds, and nucleotide compounds, and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Suitable NSAIDs for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include diclofenac, etoldolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indoprofen, ketoprofen, ketorolac, lornoxicam, morazone, naproxen, perisoxal, pirprofen, pranoprofen, suprofen, suxibuzone, tropesin, ximoprofen, zaltoprofen,

zileuton, and zomepirac, and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Suitable carbonic anhydrase inhibitors for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include brinzolamide, acetazolamide, methazolamide, dichlorphenamide, ethoxzolamide, and dorzolamide, and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Suitable adrenergic agents for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include brimonidine, apraclonidine, bunazosin, levobetaxolol, levobunalol, carteolol, isoprenaline, fenoterol, metipranolol, and clenbuterol, and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Suitable alpha receptor agonists for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include brimonidine and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Suitable beta receptor antagonists for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include atenolol, betaxolol, and timolol, and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Suitable antiviral agents for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include nevirapine and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Suitable alkaloid analgesics for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include desmorphine, dezocine, dihydromorphine, eptazocine, ethylmorphine, glafenine, hydromorphone, isoladol, ketobenidone, p-lactophetide, levorphanol, moptazinol, metazocin, metopon, morphine, nalbuphine, nalmefene, nalorphine, naloxone, norlevorphanol, normorphine, oxmorphone,

pentazocine, phenperidine, phenylramidol, tramadol, and viminol, and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Suitable glucocorticoids for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include 21-acetoxypregnenolone, alclometasone, algestone, anacortave acetate, amcinonide, beclomethasone, betamethasone, budesonide, chloroprednisone, clobetasol, clobetasone, clocortolone, cloprednol, corticosterone, cortisone, cortivazol, deflazacort, desonide, desoximetasone, diflorasone, diflucortolone, difuprednate, enoxolone, fluazacort, flucloronide, flumethasone, flunisolide, fluocinolone acetonide, fluocinonide, flucloronide, flumethasone, flunisolide, fluocortin butyl, fluocortolone, fluorometholone, fluperolone acetate, fluprednisolone, flurandrenolide, fluticasone propionate, hydrocortamate, hydrocortisone, meprednisone, methylprednisolone, paramethasone, prednisolone, prednisolone 21-diethylaminoacetate, fluprednidene acetate, formocortal, loteprednol etabonate, medrysone, mometasone furoate, prednicarbate, prednisolone, prednisolone 25-diethylaminoacetate, prednisolone sodium phosphate, prednisone, prednival, prednylidene, triamcinolone, triamcinolone acetonide, triamcinolone benetonide, and triamcinolone hexacetonide, and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Other suitable steroids for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include halcinonide, halbetasol propionate, halometasone, halopredone acetate, isoflupredone, loteprednol etabonate, mazipredone, rimexolone, and tixocortol, and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Suitable BPH drugs for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include finasteride and osaterone, and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Suitable antineoplastic compounds for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include adriamycin, alitretinoin (9-cis-retinoic acid); bleomycins, including bleomycin A; capecitabine (5'-deoxy-5-fluoro-cytidine); carubicin; chlorozotocin, chromomycins, including chromomycin A3, cladribine; colchicine, cytarabine; daunorubicin; demecolcine, denopterin, docetaxel, doxyifluridine,

doxorubicin; dromostanolone, edatrexate, enocitabine, epirubicin, epitiostanol, estramustine; etoposide; floxuridine, fludarabine, 5-fluorouracil, formestane, gemcitabine; irinotecan; lentinan, lonidamine, melengestrol, melphalan; menogaril, methotrexate; mitolactol; nogalamycin; nordihydroguaiaretic acid, olivomycins such as olivomycin A, paclitaxel; pentostatin; pirarubicin, plicamycin, porfiromycin, prednimustine, puromycin; ranimustine, ristocetins such as ristocetin A; temozolamide; teniposide; tomudex; topotecan; tubercidin, ubenimax, valrubicin (N-trifluoroacetyladriamycin-14-valerate), vinorelbine, vinblastine, vindesine, vinorelbine, and zorubicin and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Suitable antibacterial compounds for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include capreomycins, including capreomycin IA, capreomycin IB, capreomycin IIA and capreomycin IIB; carbomycins, including carbomycin A; carumonam; cefaclor, cefadroxil, cefamandole, cefatrizine, cefazedone, cefazolin, cefbuperazone, cefcapene pivoxil, cefclidin, cefdinir, cefditoren, cefime, ceftamet, cefmenoxime, cefmetzole, cefminox, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotetan, cefotiam, cefoxitin, cefpimizole, cefpiramide, cefpirome, cefprozil, cefroxadine, cefsulodin, ceftazidime, cefteram, ceftezole, ceftibuten, ceftiofur, ceftizoxime, ceftriaxone, cefuroxime, cefuzonam, cephalexin, cephalogycin, cephaloridine, cephalosporin C, cephalothin, cephapirin, cephamycins, such as cephamycin C, cephradine, chlortetracycline; chlarithromycin, clindamycin, clometocillin, clomocycline, cloxacillin, cyclacillin, danofloxacin, demeclocyclin, destomycin A, dicloxacillin, dirithromycin, doxycyclin, epicillin, erythromycin A, ethanbutol, fenbenicillin, flomoxef, florfenicol, floxacillin, flumequine, fortimicin A, fortimicin B, forfomycin, foraltadone, fusidic acid, gentamycin, glyconiazide, guamecycline, hetacillin, idarubicin, imipenem, isepamicin, josamycin, kanamycin, leumycins such as leumycin A1, lincomycin, lomefloxacin, loracarbef, lymecycline, meropenam, metampicillin, methacycline, methicillin, mezlocillin, micronomicin, midecamycins such as midecamycin A1, mikamycin, minocycline, mitomycins such as mitomycin C, moxalactam, mupirocin, nafcillin, netilicin, norcardians such as norcardian A, oleandomycin, oxytetracycline, panipenam, pazufloxacin, penamecillin, penicillins such as penicillin G, penicillin N and penicillin O, penillic acid, pentylpenicillin, peplomycin, phenethicillin, pipacyclin, piperacilin, pirlimycin, pivampicillin, pivcefalexin, porfiromycin, propiallin, quinacillin, ribostamycin, rifabutin, rifamide, rifampin, rifamycin SV, rifapentine, rifaximin, ritipenem, rekitamycin,

rolitetracycline, rosaramicin, roxithromycin, sancycline, sisomicin, sparfloxacin, spectinomycin, streptozocin, sulbenicillin, sultamicillin, talampicillin, teicoplanin, temocillin, tetracyclin, thostrepton, tiamulin, ticarcillin, tigemonam, tilmicosin, tobramycin, tropospectromycin, trovafloxacin, tylosin, and vancomycin, and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Suitable anti-fungal compounds for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include fluconazole and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Suitable immunological response modifiers for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include muramyl dipeptide and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Suitable peptides and proteins for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include insulin, growth hormones, insulin related growth factor, heat shock proteins, and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Suitable anesthetics and pain killing agents for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include lidocaine, benzodiazepam, and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Suitable cell transport/mobility impending agents for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include cytochalasin B and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Antiproliferative/antimitotic drugs and prodrugs suitable for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include natural products such as vinca alkaloids (e.g., vinblastine, vincristine, and vinorelbine),

paclitaxel, epidipodophyllotoxins (e.g., etoposide, teniposide), antibiotics (e.g., actinomycins, daunorubicin, doxorubicin and idarubicin), anthracyclines, mitoxantrone, bleomycins, plicamycin (mithramycin) and mitomycin, enzymes (e.g., L-asparaginase); antiplatelet prodrugs; antiproliferative/antimitotic alkylating prodrugs such as nitrogen mustards (mechlorethamine, cyclophosphamide and analogs, melphalan, chlorambucil), ethylenimines and methylmelamines (hexamethylmelamine and thiotepa), alkyl sulfonates-busulfan, nitrosoureas (carmustine (BCNU) and analogs, streptozocin), triazenes, dacarbazine (DTIC); antiproliferative/antimitotic antimetabolites such as folic acid analogs (methotrexate), pyrimidine analogs (fluorouracil, floxuridine, and cytarabine), purine analogs and related inhibitors (mercaptopurine, thioguanine, pentostatin and 2-chlorodeoxyadenosine (cladribine); platinum coordination complexes (cisplatin, carboplatin), procarbazine, hydroxyurea, mitotane, aminoglutethimide; hormones (e.g., estrogen, progestin); anticoagulants (e.g., heparin, synthetic heparin salts and other inhibitors of thrombin); fibrinolytic prodrugs such as tissue plasminogen activator, streptokinase and urokinase, aspirin, dipyridamole, ticlopidine, clopidogrel, abciximab; antimigratories; antisecretories (breveldin); anti-inflammatory agents such as corticosteroids (cortisol, cortisone, fludrocortisone, flucinolone, prednisone, prednisolone, methylprednisolone, triamcinolone, betamethasone, and dexamethasone), NSAIDS (salicylic acid and derivatives, aspirin, acetaminophen, indole and indene acetic acids (indomethacin, sulindac and etodalac), heteroaryl acetic acids (tolmetin, diclofenac, and ketorolac), arylpropionic acids (e.g., ibuprofen and derivatives), anthranilic acids (mefenamic acid, and meclofenamic acid), enolic acids (piroxicam, tenoxicam, phenylbutazone, and oxyphenthatrazone), nabumetone, gold compounds (auranofin, aurothioglucose, gold sodium thiomalate), and 6-mannose phosphate; immunosuppressives (e.g., cyclosporine, tacrolimus (FK-506), sirolimus (rapamycin), azathioprine, and mycophenolate mofetil); angiogenic agents such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF); angiotensin receptor blocker; nitric oxide donors; anti-sense oligonucleotides and combinations thereof; cell cycle inhibitors, mTOR inhibitors, growth factor signal transduction kinase inhibitors, neovascularization inhibitors, angiogenesis inhibitors, and apoptosis inhibitors, and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Suitable antiviral agents for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include acyclovir, azidouridine, anismoycin, amantadine, bromovinyldeoxusidine, chlorovinyldeoxusidine, cytarabine, delavirdine,

didanosine, deoxynojirimycin, dideoxycytidine, dideoxyinosine, dideoxynucleoside, desciclovir, deoxyacyclovir, efavirenz, enviroxime, fiacitabine, foscamet, fialuridine, fluorothymidine, floxuridine, ganciclovir, hypericin, idoxuridine, interferon, interleukin, isethionate, nevirapine, pentamidine, ribavirin, rimantadine, stavudine, sargramostin, suramin, trichosanthin, tribromothymidine, trichlorothymidine, trifluorothymidine, trisodium phosphomonoformate, vidarabine, zidoviridine, zalcitabine and 3-azido-3-deoxythymidine and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Other suitable antiviral agents for use in the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles) include 2',3'-dideoxyadenosine (ddA), 2',3'-dideoxyguanosine (ddG), 2',3'-dideoxycytidine (ddC), 2',3'-dideoxythymidine (ddT), 2'3'-dideoxy-dideoxythymidine (d4T), 2'-deoxy-3'-thia-cytosine (3TC or lamivudime), 2',3'-dideoxy-2'-fluoroadenosine, 2',3'-dideoxy-2'-fluoroinosine, 2',3'-dideoxy-2'-fluorothymidine, 2',3'-dideoxy-2'-fluorocytosine, 2'3'-dideoxy-2',3'-didehydro-2'-fluorothymidine (Fd4T), 2'3'-dideoxy-2'-beta-fluoroadenosine (F-ddA), 2'3'-dideoxy-2'-beta-fluoro-inosine (F-ddI), and 2',3'-dideoxy-2'-beta-flurocytosine (F-ddC). In some embodiments, the antiviral agent is selected from trisodium phosphomonoformate, ganciclovir, trifluorothymidine, acyclovir, 3'-azido-3'-thymidine (AZT), dideoxyinosine (ddI), and idoxuridine and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof.

Beneficial substances suitable for administration to the eye and its surrounding tissues, using the devices described herein (e.g., devices comprising a shell and porous silicon-based carrier particles), to produce a local or a systemic physiologic or pharmacologic beneficial effect include neuroprotectants such as nimodipine and related compounds; antibiotics such as tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, oxytetracycline, chloramphenicol, gentamycin, and erythromycin; antibacterials such as sulfonamides, sulfacetamide, sulfamethizole, and sulfisoxazole; antivirals, including idoxuridine; and other antibacterial agents such as nitrofurazone and sodium propionate; antiallergenics such as antazoline, methapyriline, chlorpheniramine, pyrilamine, and prophenpyridamine; anti-inflammatories such as hydrocortisone, hydrocortisone acetate, dexamethasone 21-phosphate, fluocinolone, medrysone, methylprednisolone, prednisolone 21-phosphate, prednisolone acetate, fluoromethalone, betamethasone, and triamcinolone; decongestants such as

phenylephrine, naphazoline, and tetrahydrazoline; miotics and anti-cholinesterase such as pilocarpine, eserine salicylate, carbachol, di-isopropyl fluorophosphate, phospholine iodine, and demecarium bromide; mydriatics such as atropine sulfate, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine, and hydroxyamphetamine; sympathomimetics such as epinephrine; and analogs, derivatives, pharmaceutically acceptable salts, esters, prodrugs, and protected forms thereof; and prodrugs such as those described in Design of Prodrugs, edited by Hans Bundgaard, Elsevier Scientific Publishing Co., Amsterdam, 1985. Reference may be made to any standard pharmaceutical textbook such as Remington's Pharmaceutical Sciences for the identification of other agents.

Prodrugs are generally compounds that, under physiological conditions, are converted into therapeutically active agents in a patient's body. A common method for making a prodrug is to include selected moieties, such as esters, that are hydrolyzed under physiological conditions to convert the prodrug to an active biological moiety. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal. Prodrugs are typically formed by chemical modification of a biologically active moiety. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Design of Prodrugs, ed. H. Bundgaard, Elsevier, 1985.

Any pharmaceutically acceptable form of such a compound may be employed as a beneficial substance, i.e., the free base or a pharmaceutically acceptable salt or ester thereof. Pharmaceutically acceptable salts, for instance, include sulfate, lactate, acetate, stearate, hydrochloride, tartrate, maleate, and the like.

2. Methods of preparation

The devices described herein may be made in a wide variety of ways, portions of which are described above in Section 1. In preferred aspects, the device is prepared by filling a tube with carrier particles and enclosing the ends of the tube.

Carrier particles are prepared or provided. In some embodiments, the carrier particles are made porous by introducing pores into non-porous material. This may be done, for instance, by anodizing a solid such as silicon to produce parallel pores. In some embodiments,

anodization is performed together with etching, e.g., wet etching or dry etching. Thus, in some embodiments, the pores are formed by electrochemical etching.

In some embodiments, the carrier particles are porous when they are first formed. For example, in sol-gel synthesis, a solution is induced to form a porous network or gel of polymers. Sol-gel synthesis can be used, for example, to make porous silica. Porous silica can be chemically reduced to silicon by treatment with, for instance, magnesium vapor. The magnesium vapor method and related methods for reducing silica are described in International Application WO/2012/114126.

In some embodiments, part or all of a large body of carrier material is made porous, and the porous region is then milled into small particles. In other embodiments, the particles are formed of a non-porous material, and then pores are introduced into the particles.

In forming carrier particles, a mesh may be used to select particles of the desired size.

In certain embodiments, the porous silicon-based carrier material may be prepared by flame hydrolysis of silicon tetrachloride in an oxy-hydrogen flame.

Carrier particles may be loaded with a beneficial substance before or after the particles are assembled into the device.

A tube may be produced or provided. In some embodiments, the tube is extruded, e.g., from a polymeric mass. Commercially available extruders include the Randcastle model RCP-0250 Microtruder (Randcastle Extrusion Systems, Cedar Grove, N.J.), and its associated heaters, controllers, and the like. Exemplary extruders are also disclosed, for example, in U.S. Pat. Nos. 5,569,429, 5,518,672, and 5,486,328. An extruder can include an exit port that establishes a cross-sectional shape of the extruded matter. In some embodiments, the tube is cured after extrusion. In some embodiments, the tube is co-extruded with the carrier particle composition inside the tube. In preferred embodiments, the tube is formed in the absence of carrier particles, and carrier particles are inserted into the formed tube. In some embodiments, the tube is segmented into a plurality of tubular segments. Segmentation may employ shears, slicing blades, or any other technique.

The tube is filled with carrier particles. In some embodiments, the tube is several multiples of the length of the finished device, and the tube is cut to the proper length before or after being filled with carrier particles. In some embodiments, the particles are dry when they are placed in the tube, and may have the consistency of a powder or granulate. In other embodiments, the particles are in solution when they are placed in the tube, and may have the consistency of a slurry. The slurry may be drawn into the tube with capillary action or pushed in using a syringe, for example. In preferred embodiments, the carrier particles are loaded with the beneficial substance when they are placed in the tube. However, the particles may also be loaded with drug after this step, e.g., when they are in the tube but before members are added to close the tube, or even after one or both members are added.

The first member and second member are added to the first and second ends of the tube to enclose the particles. In some embodiments, one or both of the members are formed *in situ* on the end or ends of the tube. An amount of polymer solution may be applied to the end of the tube. For instance, one end of the tube can be dipped in a polymer solution one or more times, so that a film of the polymer will form on the end of the tube. Alternatively, the polymer solution may be applied to the end of the tube by dropping, spraying, brushing or other means. Once the polymer is in contact with the tube, the polymer can be cured (hardened by cross-linking) on the end of the tube. Polymers can be cured, e.g., using heat, radiation, light (including ultraviolet light or visible light such as blue light), evaporation, and catalyzation. Curing with light in the visible or near-visible ranges (e.g., of ultraviolet or blue wavelengths) sometimes avoids inactivation of the beneficial substance that can result from harsher curing techniques. In some embodiments, curing is performed using an intense light source, such as a tuned laser or the like. Each polymer can be cured using one or more suitable curing techniques, and numerous examples are known in the art. For instance, PVA may be cured with (for instance) ultraviolet light, infrared light, and/or by heating it in an oven. In certain embodiments, the desired thickness of the first or second member may be obtained by applying more than one coat of a polymer. Each coat may be dried and/or cured prior to applying the next coat.

In certain embodiments, the device shell comprises heat-cured PVA. In particular, a heat-cured first member and/or second member may be formed by applying a PVA solution to the first end of the tube and then heating the PVA. The PVA may be heated, e.g., at a temperature in the range of 60-120°C, e.g., 80°C, for at least 2 hours, preferably at least 4

hours, e.g., 5 hours. Heating may be performed, for example, in an oven or other heating element.

In some embodiments, the device and/or the components of the device are sterilized. The heat-resistant portions of the device may be heat-sterilized, e.g., by autoclaving. Other methods of sterilizing the device or its components include sterilization with radiation, ultraviolet light, immersion in alcohol, or filtration. In some embodiments, a heat-sensitive component (such as a beneficial substance, including a biomolecule) is filter-sterilized. In certain embodiments, all heat sterilization of the device or its components takes place prior to addition of the heat-sensitive component to the device. For example, the particles and/or the shell may be heat-sterilized before the beneficial substance is added to the device.

The device may be packaged, such as by preloading a needle of appropriate gauge with the device and enclosing the assembly in a suitable package for shipment to an end user.

3. Methods of use

The present disclosure provides methods for treating a patient to obtain a desired local or systemic physiological or pharmacological effect. These methods include administering the disclosed devices to the patient and allowing the beneficial substance to pass through the device to come in direct contact with the patient. The device can be administered for a sufficient period of time and under conditions to allow treatment of the disease state of concern. In certain embodiments the patient is mammalian organism, and in preferred embodiments the patient is a human.

In certain embodiments, the device is inserted into a desired location in the patient's body. For instance, the device may be injected or surgically implanted into the patient's body. When the beneficial substance acts on the eye, the device can gradually release the beneficial substance to the eye, avoiding painful repeated administrations of a different formulation of the beneficial substance. Accordingly, the device can be surgically implanted into the eye of the patient, for example the vitreous of the eye, under the retina, and onto the sclera. The device can also be inserted into numerous other locations in the body, including administration that is subcutaneous, intramuscular, intraperitoneal, intranasal, dermal, into the brain, including intracranial and intradural, into the joints, including ankles, knees, hips,

shoulders, elbows, wrists, directly into tumors, and the like. The device can also be administered orally.

In some embodiments, the device is administered to a patient by injection. Injection may use, for example, a standard gauge hypodermic needle, such as about a 30 gauge to about a 12 gauge needle, or a needle ranging in inside diameter from about 0.0055 inches to about 0.0850 inches. An injectable device can also be administered through, for example, an arthroscope, catheter, or other medical device.

For localized drug delivery, the devices may be surgically implanted at or near the site of action. This is the case for devices as described herein, used in treating ocular conditions, primary tumors, rheumatic and arthritic conditions, and chronic pain, for instance.

For systemic relief, the devices may be implanted subcutaneously, intramuscularly, intraarterially, intrathecally, or intraperitoneally, for example. This is the case when devices are to give sustained systemic levels and avoid premature metabolism. In addition, the devices may be administered orally.

The devices described herein may be particularly suitable for treating ocular conditions such as glaucoma, proliferative vitreoretinopathy, macular edema, including diabetic macular edema, age-related macular degeneration, diabetic retinopathy, uveitis, ocular neovascularization, and ocular infection. The devices may also be particularly suitable for use as an ocular device in treating patients, both human and for veterinarian use, suffering from ocular histoplasmosis, wherein the device may be surgically implanted within the vitreous of the eye.

In certain embodiments, the device may contain one or more drugs that reduce the risk of mother to child transmission of viral infections. Examples of viral infections include HIV, Bowenoid Papulosis, Chickenpox, Childhood HIV Disease, Human Cowpox, Hepatitis C, Dengue, Enteroviral, Epidermodysplasia Verruciformis, Erythema Infectiosum (Fifth Disease), Giant Condylomata Acuminata of Buschke and Lowenstein, Hand-Foot-and-Mouth Disease, Herpes Simplex, Herpes Virus 6, Herpes Zoster, Kaposi Varicelliform Eruption, Rubeola Measles, Milker's Nodules, Molluscum Contagiosum, Monkeypox, Orf, Roseola

Infantum, Rubella, Smallpox, Viral Hemorrhagic Fevers, Genital Warts, and Nongenital Warts.

In certain embodiments, the device may contain an antiviral agent that inhibits or reduces HIV infection or susceptibility to HIV infection. The device may be used to treat mammalian organisms infected with HIV and AIDS-related opportunistic infections such as cytomegalovirus infections, toxoplasmosis, pneumocystis carinii, and mycobacterium avium intercellular.

In some embodiments, the device contains one or more drugs that treat pulmonary arterial hypertension.

In certain embodiments, the device may be used to provide a controlled and sustained release of agents effective in obtaining a desired local or systemic physiological or pharmacological effect relating at least to the following areas: treatment of cancerous primary tumors, (e.g., glioblastoma); inhibition of neovascularization, including ocular neovascularization; edema, including ocular edema; inflammation, including ocular inflammation; chronic pain; arthritis; rheumatic conditions; hormonal deficiencies such as diabetes and dwarfism; and modification of the immune response such as in the prevention of transplant rejection and in cancer therapy. A wide variety of other disease states may also be prevented or treated using the delivery devices herein. Such disease states are known by those of ordinary skill in the art. For those not skilled in the art, reference may be made to Goodman and Gilman, The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press, NY, 1990; and Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Co., Easton, Pa., 1990; both of which are incorporated by reference herein.

In some embodiments, the device (e.g., a device comprising a shell enclosing porous silicon-based carrier particles) delivers ganciclovir to the eye for the treatment of cytomegalovirus (CMV) retinitis. In certain embodiments, the device (e.g., a device comprising a shell enclosing porous silicon-based carrier particles) delivers fluocinolone acetonide to the eye for the treatment of ocular neovascularization, macular edema, wet or dry age-related macular degeneration, retinal vein occlusion, or posterior uveitis. In some embodiments, the device (e.g., a device comprising a shell enclosing porous silicon-based carrier particles) delivers bevacizumab or ranibizumab for the treatment of neovascularization, including ocular

neovascularization, for example when caused by cancer, macular degeneration (especially wet age-related macular degeneration), diabetic retinopathy, neovascular glaucoma, macular edema, or retinopathy. In some embodiments, the device (e.g., a device comprising a shell enclosing porous silicon-based carrier particles) delivers latanoprost to the eye for treatment of ocular hypertension and/or glaucoma.

The devices herein may release the beneficial substance over a sustained time period when immersed in simulated body fluid or when administered to a patient. For instance, the device may release an effective amount of the beneficial substance for between 1 week - 1 year, 2 weeks - 1 year, 1 month - 1 year, 2 months - 1 year, 3 months - 1 year, or 6 months - 1 year. In some embodiments, the device releases the effective amount of the beneficial substance for 1 month - 2 yeas, 2 months - 2 years, 3 months - 2 years, or 6 months - 2 years.

The invention now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention. For example, the particular devices, beneficial substances, and experimental designs disclosed herein represent exemplary tools and methods for validating proper function. As such, it will be readily apparent that any of the disclosed specific devices, beneficial substances, and experimental plans can be substituted within the scope of the present disclosure.

EXAMPLES

Example 1: Method of making silicon particles

Mesoporous silicon flakes of approximately 5 mm^2 were pooled from membranes fabricated by anodization of 5-20 mohm cm resistivity silicon wafers. The electrolyte composition was a fixed blend (1:1 by volume) of 40% hydrofluoric acid and methanol. Flakes were extensively washed in an ethanol-water mixture, dried, and then subjected to a sequence of rotor milling and jet milling to produce a powder of defined size distribution, prior to thermal oxidation in air at 800 °C for 3 hours. The final target size distribution (d10 in the range of 1-5 microns, d50 in the range of 5-10 microns, and d90 in the range of 10-20 micron) was then achieved by sieving at small batch size or a sedimentation technique at larger batch size.

Example 2: Release profile with fumed silica

A preformed polyimide tube was loaded with a mixture of latanoprost and fumed silica particles (Cab-O-Sil) in a 1:1 (w:w) ratio. The tube was then cut into the desired length and one end of the tube was sealed with silicone, the other with polyvinyl alcohol. The tube was immersed in PBS at 37 °C for 70 days. The PBS was replaced daily, and latanoprost release was quantitatively measured by HPLC (Figure 6).

Example 3: Release profile with anodized silicon

A preformed polyimide tube was loaded with a mixture of latanoprost and oxidized anodized silicon particles in a 1:1 (w:w) ratio. The tube was then cut into the desired length and one end of the tube was sealed with silicone, the other with polyvinyl alcohol. The tube was immersed in PBS at 37 °C for 30 days. The PBS was replaced daily, and latanoprost release was quantitatively measured by HPLC (Figure 7).

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the compounds and methods of use thereof described herein. Such equivalents are considered to be within the scope of this invention and are covered by the following claims. Those skilled in the art will also recognize that all combinations of embodiments described herein are within the scope of the invention.

While the above described embodiments are in some cases described in terms of preferred characteristics (e.g., preferred ranges of the amount of effective agent, and preferred thicknesses of the preferred layers) these preferences are by no means meant to limit the invention. As would be readily understood by one skilled in the art, the preferred characteristics depend on the method of administration, the beneficial substance used, the shell and carrier materials used, the desired release rate and the like. Likewise, actual release rates and release duration depend on a variety of factors in addition to the above, such as the disease state being treated, the age and condition of the patient, the route of administration, as well as other factors which would be readily apparent to those skilled in the art.

All of the foregoing U.S. patents and other publications are expressly incorporated by reference herein in each of their entireties.

We claim:

1. A device comprising a shell and a plurality of particles disposed within the shell, the particles comprising a porous carrier material and a beneficial substance disposed within pores of the carrier, and the shell comprising at least one portion that is permeable to the beneficial substance.

2. The device of claim 1, wherein the shell comprises a polymer.

3. The device of any of claims 1-3, wherein the shell comprises:
a tube having first and second ends;
a first member positioned at the first end; and
a second member positioned at the second end;
wherein the particles are inside the tube and the first and second members retain the particles in the tube.

4. The device of claim 3, wherein the tube has a substantially cylindrical shape.

5. The device of claim 3, wherein the tube is impermeable to the beneficial substance.

6. The device of claim 5, wherein the tube comprises poly(lactic-co-glycolic acid) (PLGA).

7. The device of any of claims 3-6, wherein the first member and second member are permeable to the beneficial substance.

8. The device of claim 7, wherein the first member and second member comprise poly(vinyl alcohol) (PVA).

9. The device of any of claims 3-6, wherein the first member is permeable to the beneficial substance and the second member is impermeable to the beneficial substance.

10. The device of claim 9, wherein the first member comprises poly(vinyl alcohol) (PVA).

11. The device of claim 9 or 10, wherein the second member comprises silicone.

12. The device of any of claims 3-11, wherein the tube has a length of between 1 and 4 mm.

13. The device of any of claim 3-11, wherein the tube has a diameter of between 0.2 – 0.5 mm.

14. The device of any of claims 1-13, wherein the carrier material is mesoporous.

15. The device of any of claims 1-14, wherein the carrier material has a porosity in the range of about 50% to about 80%.

16. The device of any of claims 1-15, wherein the carrier material is silicon-based.

17. The device of any of claims 1-16, wherein the carrier material comprises elemental silicon.

18. The device of any of claims 1-17, wherein the carrier material comprises silica.

19. The device of any of claims 1-18, wherein the pores in the carrier material are substantially parallel.

20. The device of any of claims 1-19, wherein the carrier material comprises anodized silicon.

21. The device of any of claims 1-20, wherein the carrier material is resorbable or bio-erodible.

22. The device of any of claims 1-21, wherein the particles have a d50 in the range of 5-10 microns.

23. The device of any of claims 1-22, wherein the device releases the beneficial substance at a release rate, the release rate being determined primarily by release of the beneficial substance from pores of the carrier material.

24. The device of any of claims 1-23, wherein, when the device is placed in a biological medium, the beneficial substance is released from the device according to a substantially zero-order release profile.

25. The device of any of claims 1-24, wherein the beneficial substance is selected from small molecules, proteins, peptides, antibodies, carbohydrates, lipids, polymers, oligonucleotides, and polynucleotides.

26. The device of any of claims 1-25, wherein the beneficial substance is ranibizumab or bevacizumab.

27. A method of making a device, comprising:

(a) providing a tube having first and second ends;

(b) inserting a plurality of particles into the tube, wherein the particles comprise porous silicon-based carrier material;

(c) adding a first member to the first end of the tube; and

(d) adding a second member to the second end to the tube,

wherein at least one of the tube, the first member, and the second member is permeable to the beneficial substance.

28. The method of claim 27, wherein the particles comprise a beneficial substance disposed within pores of the carrier material.

29. The method of claim 27, further comprising contacting the device to a beneficial substance and allowing the beneficial substance to enter pores of the carrier material.

30. The method of claim 27, wherein step (b) is performed before step (c).

31. The method of claim 27, wherein step (c) is performed before step (b).

32. The method of any of claims 27-31, where adding the first member comprises contacting the first end of the tube to a polymer solution and curing the polymer at the first end, thereby forming a first member on the first end of the tube.

33. The method of any of claims 27-32, where adding the second member comprises contacting the second end of the tube to a polymer solution and curing the polymer at the second end, thereby forming a second member on the second end of the tube.

34. A device manufactured by the method of any of claims 27-33.

35. A method of delivering a beneficial substance to a patient, comprising administering to a patient a device according to any of claims 1-25 or 34, whereby the beneficial substance is released from the device into the patient after administration.

36. The method of claim 35, wherein the device releases the beneficial substance for between about one month and one year when immersed in simulated body fluid.

37. The method of claim 35 or 36, wherein administering the device comprises injecting, implanting, or inserting the device into the patient.

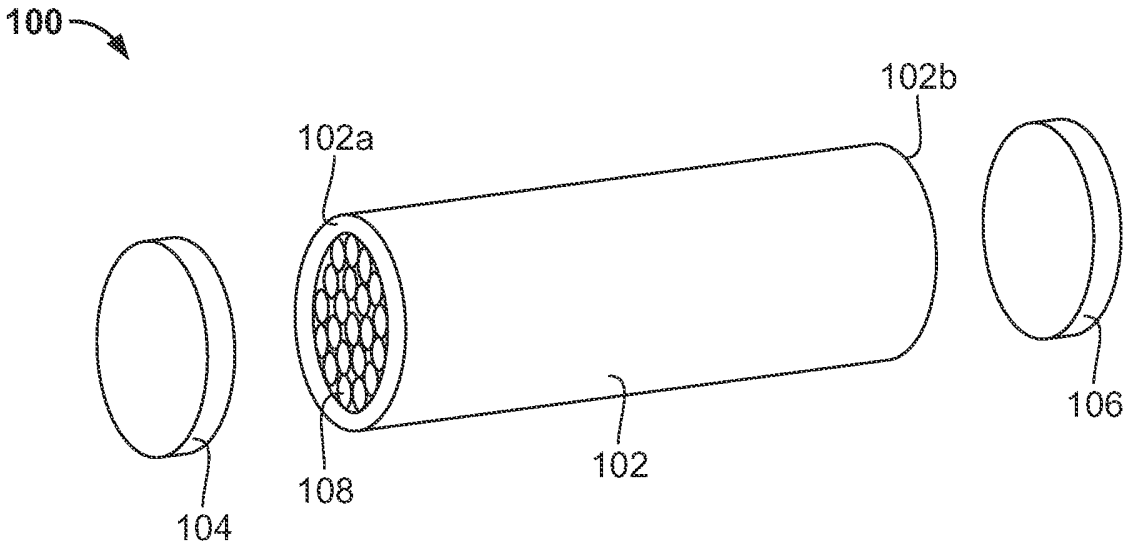


FIG. 1

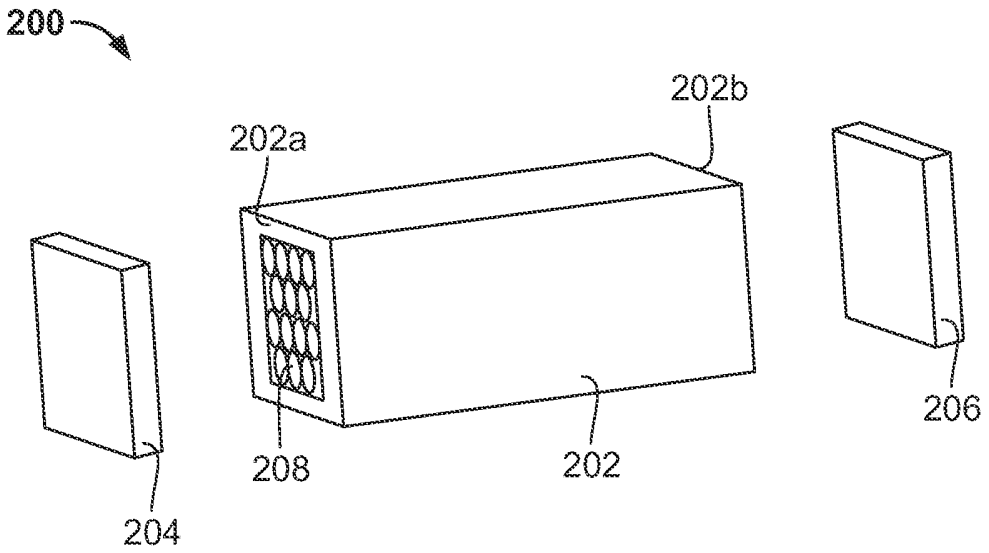


FIG. 2

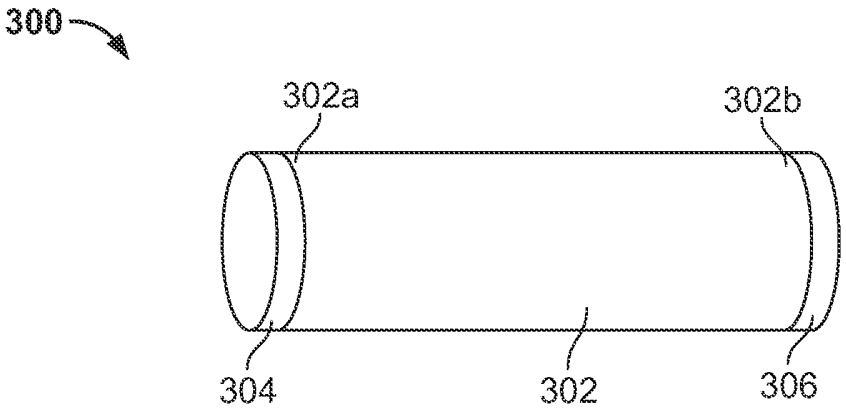


FIG. 3

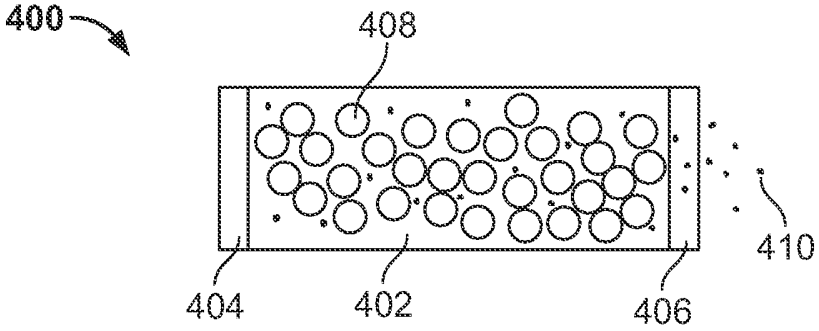


FIG. 4

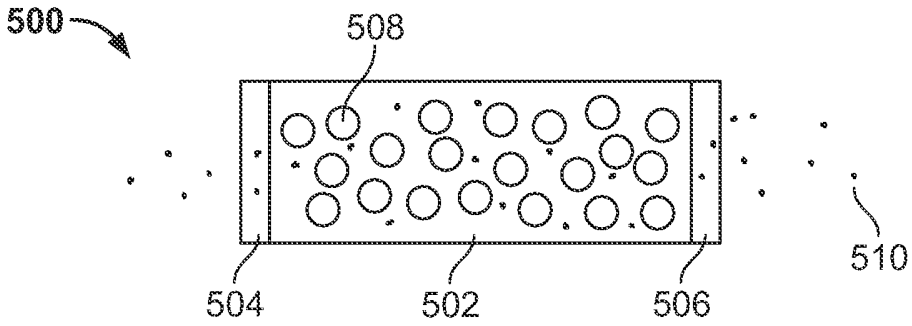


FIG. 5

Figure 6

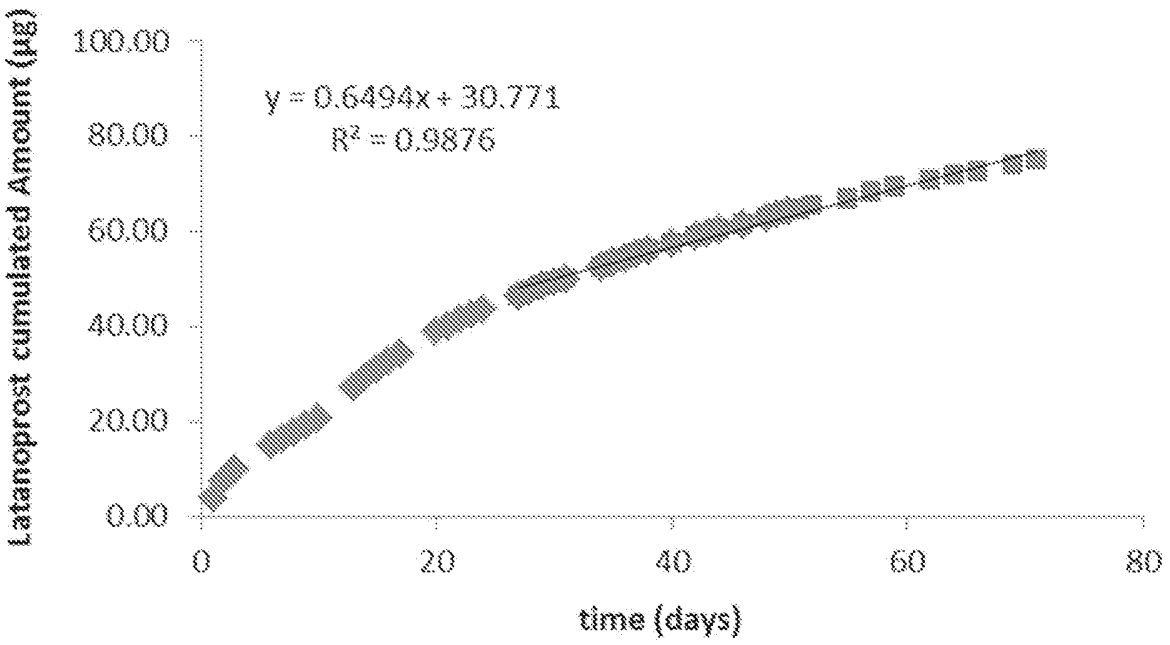
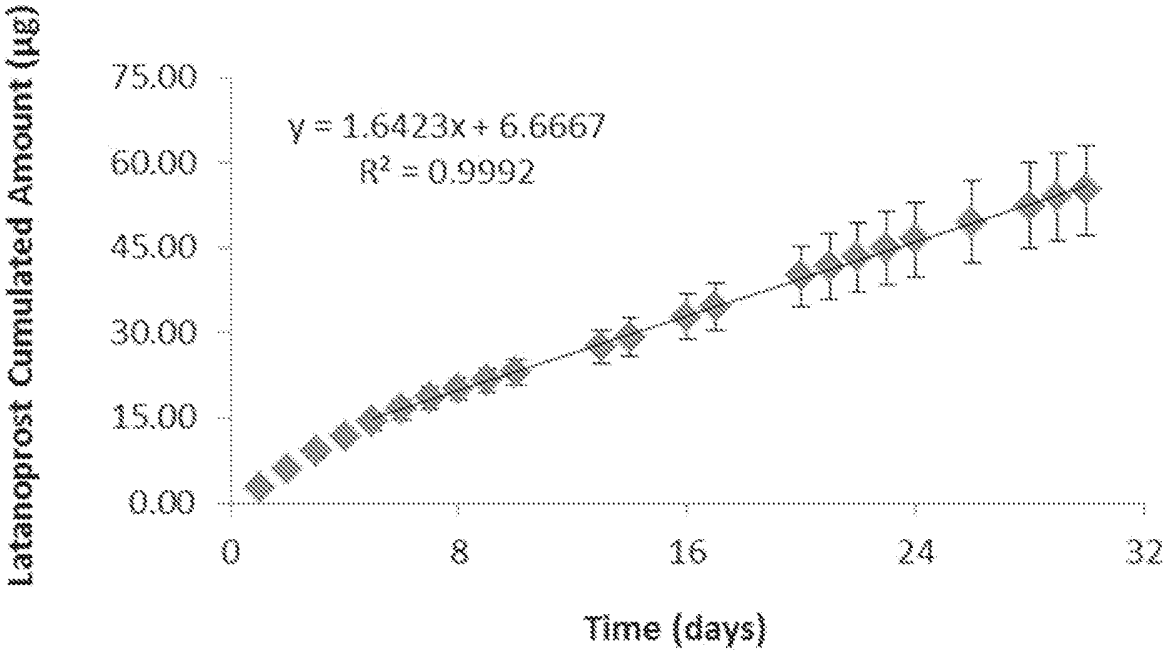


Figure 7



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 2014/024362

A. CLASSIFICATION OF SUBJECT MATTER

A61M 31/00 *(2006.01)*

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61M 31/00, 37/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatSearch (RUPTO internal), Google, FIPS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1140027 B1 (ALZA CORPORATION) 12.10.2005, fig. 6, p. 38, lines 9-15, p. 39, lines 50-56, paragraphs [0131], [0204], [0089], [0033], [0023], [0147]	1, 2, 35
Y		3-6, 27-32, 34, 36, 37
Y	WO 2012/088306 A2 (PSIVIDA US, INC.) 28.06.2012, abstract, fig. 3, 4, p. 11, line 11, p. 9, lines 3-5, p. 12, lines 20-24, p. 18, lines 18-20, p. 20, lines 10-11, p. 11, lines 10-12	3-6, 27-32, 34, 36, 37

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 May 2014 (20.05.2014)	10 July 2014 (10.07.2014)
Name and mailing address of the ISA/ FIPS Russia, 123995, Moscow, G-59, GSP-5, Berezhkovskaya nab., 30-1 Facsimile No. +7 (499) 243-33-37	Authorized officer L. Karimova Telephone No. 8(495)531-64-81

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 2014/024362

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 7-26, 33
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

(19)中华人民共和国国家知识产权局

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(71)申请人 普西维达公司
地址 美国马萨诸塞州
申请人 PSI医疗有限公司
(72)发明人 L·T·坎汉 H·郭 M·纳扎罗
C·巴奈特
(74)专利代理机构 北京市铸成律师事务所 11313
代理人 孟锐
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权利要求书2页 说明书23页 附图3页

(54)发明名称

包含硅基载体粒子的药物递送装置

(57)摘要

本申请提供一种用于向患者递送有益物质的装置。所述装置包括封围多个载体粒子的外壳。所述载体粒子是多孔的，并且诸如药物等有益物质设置于孔中。所述药物可从所述孔中扩散出来，进入所述装置内部，并且然后穿过所述外壳的至少一个可渗透部分。本申请还提供制造和使用这些装置的方法。

CN 105025974 A

1. 一种装置，其包括外壳和设置于所述外壳内的多个粒子，所述粒子包含多孔载体材料和设置于所述载体的孔内的有益物质，并且所述外壳包括对于所述有益物质可渗透的至少一个部分。

2. 如权利要求 1 所述的装置，其中所述外壳包含聚合物。

3. 如权利要求 1-3 中任一项所述的装置，其中所述外壳包括：

具有第一和第二末端的管；

安置在所述第一末端的第一构件；以及

安置在所述第二末端的第二构件；

其中所述粒子在所述管内部并且所述第一和第二构件使所述粒子保留在所述管中。

4. 如权利要求 3 所述的装置，其中所述管具有大体上圆筒形形状。

5. 如权利要求 3 所述的装置，其中所述管对于所述有益物质是不可渗透的。

6. 如权利要求 5 所述的装置，其中所述管包含乳酸 - 乙醇酸共聚物 (PLGA)。

7. 如权利要求 3-6 中任一项所述的装置，其中所述第一构件和第二构件对于所述有益物质是可渗透的。

8. 如权利要求 7 所述的装置，其中所述第一构件和第二构件包含聚（乙烯醇）(PVA)。

9. 如权利要求 3-6 中任一项所述的装置，其中所述第一构件对于所述有益物质是可渗透的，而所述第二构件对于所述有益物质是不可渗透的。

10. 如权利要求 9 所述的装置，其中所述第一构件包含聚（乙烯醇）(PVA)。

11. 如权利要求 9 或 10 所述的装置，其中所述第二构件包含硅酮。

12. 如权利要求 3-11 中任一项所述的装置，其中所述管的长度在 1 与 4mm 之间。

13. 如权利要求 3-11 中任一项所述的装置，其中所述管的直径在 0.2-0.5mm 之间。

14. 如权利要求 1-13 中任一项所述的装置，其中所述载体材料是中孔的。

15. 如权利要求 1-14 中任一项所述的装置，其中所述载体材料的孔隙率在约 50％至约 80％范围内。

16. 如权利要求 1-15 中任一项所述的装置，其中所述载体材料是硅基的。

17. 如权利要求 1-16 中任一项所述的装置，其中所述载体材料包含元素硅。

18. 如权利要求 1-17 中任一项所述的装置，其中所述载体材料包含硅石。

19. 如权利要求 1-18 中任一项所述的装置，其中所述载体材料中的所述孔是大体上平行的。

20. 如权利要求 1-19 中任一项所述的装置，其中所述载体材料包含阳极化硅。

21. 如权利要求 1-20 中任一项所述的装置，其中所述载体材料是可再吸收的或可生物蚀解的。

22. 如权利要求 1-21 中任一项所述的装置，其中所述粒子的 d50 在 5-10 微米范围内。

23. 如权利要求 1-22 中任一项所述的装置，其中所述装置以一定释放速率释放所述有益物质，所述释放速率主要由所述有益物质从所述载体材料的孔的释放情况决定。

24. 如权利要求 1-23 中任一项所述的装置，其中当所述装置放置在生物介质中时，所述有益物质根据大体上零级释放型态从所述装置释放。

25. 如权利要求 1-24 中任一项所述的装置，其中所述有益物质选自小分子、蛋白质、肽、抗体、碳水化合物、脂质、聚合物、寡核苷酸以及多核苷酸。

26. 如权利要求 1-25 中任一项所述的装置，其中所述有益物质是雷珠单抗或贝伐单抗。

27. 一种制造装置的方法，其包括：

(a) 提供具有第一和第二末端的管；

(b) 将多个粒子插入所述管，其中所述粒子包含多孔硅基载体材料；

(c) 将第一构件添加至所述管的所述第一末端；以及

(d) 将第二构件添加至所述管的所述第二末端，

其中所述管、所述第一构件以及所述第二构件中的至少一者对于所述有益物质是可渗透的。

28. 如权利要求 27 所述的方法，其中所述粒子包含设置于所述载体材料的孔内的有益物质。

29. 如权利要求 27 所述的方法，其进一步包括使所述装置接触有益物质并且使所述有益物质进入所述载体材料的孔。

30. 如权利要求 27 所述的方法，其中步骤 (b) 在步骤 (c) 之前进行。

31. 如权利要求 27 所述的方法，其中步骤 (c) 在步骤 (b) 之前进行。

32. 如权利要求 27-31 中任一项所述的方法，其中添加所述第一构件包括使所述管的所述第一末端接触聚合物溶液并且使所述聚合物在所述第一末端固化，从而在所述管的所述第一末端形成第一构件。

33. 如权利要求 27-32 中任一项所述的方法，其中添加所述第二构件包括使所述管的所述第二末端接触聚合物溶液并且使所述聚合物在所述第二末端固化，从而在所述管的所述第二末端形成第二构件。

34. 一种装置，其是通过如权利要求 27-33 中任一项所述的方法制造。

35. 一种向患者递送有益物质的方法，其包括向患者施用根据权利要求 1-25 或 34 中任一项所述的装置，藉此在施用之后使所述有益物质从所述装置释放至所述患者中。

36. 如权利要求 35 所述的方法，其中所述装置当浸没于模拟体液中时释放所述有益物质持续约一个月至一年。

37. 如权利要求 35 或 36 所述的方法，其中施用所述装置包括将所述装置注入、植入或插入所述患者中。

包含硅基载体粒子的药物递送装置

[0001] 相关申请的交叉引用

[0002] 本申请要求于2013年3月12日提交的美国临时申请号61/778,111的权益;所述申请的全部内容以全文引用的方式并入本文中。

[0003] 背景

[0004] 在制药工业内在开发在一段时间内提供治疗剂的控制释放的剂型方面一直存在相当大的关注。以此方式释放活性物质可帮助提高生物利用率并且确保适当浓度的药剂被提供持续的时间而不需要重复给药。进而,这还有助于将患者不顺从的影响缩到最低程度,在其它形式的施用情况下患者不顺从经常是一个问题。

[0005] 在常规给药(片剂、注射剂等)情况下,身体的给定区域中的药物的浓度增加至无效浓度并且最终达到有效浓度。经常地,浓度可实际上达到一定毒性阈值。然而,在相对短期之后,药物浓度降低,因为药物在体内代谢或消除。经常地,药物水平降得如此低以致不再维持治疗水平。然后给予第二剂量并且重复所述循环。持续释放系统的目标是将药物水平维持在治疗范围内并且理想地维持在恒定水平。

[0006] 然而,当前可用的持续释放系统中有许多达不到这些目标中的一个或多个。某些持续释放系统由于降解、体内分散或其它不需要的生物过程而随时间推移丧失功效。一些持续释放系统历经太短的时间尺度来递送药物,从而需要频繁更换。其它持续释放系统对于释放一种药物来说适当地运行,但不可容易地定制成递送多种不同类别的治疗剂。因此,持续需要开发用于治疗剂的控制释放的改进的剂型。

[0007] 概述

[0008] 本申请提供一种用于向患者递送有益物质的装置。装置包括封围多个载体粒子的外壳。载体粒子是多孔的,并且诸如药物等有益物质设置于孔中。药物可从孔中扩散出来,进入装置内部,并且然后穿过外壳的至少一个可渗透部分。本申请还提供制造和使用这些装置的方法。

[0009] 本文所描述的装置具有若干有利性质。举例来说,因为各装置是作为单一单元施用,所以装置使得使用者较容易施用固定剂量。因此,装置可降低意外施用不恰当剂量的可能性以及最终使用者不准确地测量剂量的可能性。装置还可以有利地使有益物质的施用定位至患者身体的所需区域,因为在身体的所需区域处外壳含有粒子。此外,装置包括有利地保护载体和有益物质免于体内的不需要的反应的外壳。举例来说,在一些实施方案中,外壳保护载体和有益物质免于酶促降解或患者的抗体。外壳还可以保护其内容物远离将粘附、分解或以其它方式改变载体或有益物质的细胞。在一些实施方案中,装置提供在制造过程期间对有益物质的改进的保护作用。举例来说,载体粒子和/或外壳可在制造过程期间,例如在涉及加热的步骤期间使有益物质稳定。装置还可以例如通过使有益物质稳定而不与空气或湿度相互作用而提供在储存期间对有益物质的改进的保护作用。此外,装置可在治疗过程内使有益物质稳定。

[0010] 在某些方面,本公开提供一种装置,其包括外壳和设置于外壳内的多个粒子,粒子包含多孔载体材料和设置于载体的孔内的有益物质,并且外壳包括对于有益物质可渗透的

至少一个部分。

[0011] 在一些方面，本公开提供一种制造装置的方法，其包括：(a) 提供具有第一和第二末端的管；(b) 将多个粒子插入管，其中粒子包含多孔硅基载体材料；(c) 将第一构件添加至管的第一末端；以及 (d) 将第二构件添加至管的第二末端，其中管、第一构件以及第二构件中的至少一者对于有益物质是可渗透的。在一些方面，本公开提供通过此方法制造的装置。在一些实施方案中，步骤 (b) 在步骤 (c) 之前进行，而在一些实施方案中步骤 (c) 在步骤 (b) 之前进行。

[0012] 在某些方面，本公开提供一种向患者递送有益物质的方法，其包括向患者施用如本文所描述的装置，藉此在施用之后使有益物质从装置释放至患者中。

[0013] 在某些实施方案中，外壳包含聚合物。在一些实施方案中，外壳包括：具有第一和第二末端的管；安置在第一末端的第一构件；以及安置在第二末端的第二构件；其中粒子在管内部并且第一和第二构件使粒子保留在管中。

[0014] 在一些实施方案中，管具有大体上圆筒形形状。在一些实施方案中，管对于有益物质是不可渗透的。举例来说，在一些实施方案中，管包含乳酸 - 乙醇酸共聚物 (PLGA)。在一些实施方案中，第一构件和第二构件对于有益物质是可渗透的。举例来说，在一些实施方案中，第一构件与第二构件均包含聚 (乙烯醇)(PVA)。在一些实施方案中，第一构件对于有益物质是可渗透的而第二构件对于有益物质是不可渗透的。举例来说，在一些实施方案中，第一构件包含聚 (乙烯醇)(PVA)。在一些实施方案中，第二构件包含硅酮。

[0015] 在某些实施方案中，管的长度在 1 与 4mm 之间。在一些实施方案中，管的直径在 0.2-0.5mm 之间。

[0016] 在一些实施方案中，载体材料是中孔的。在某些实施方案中，载体材料的孔隙率在约 30 至约 90％、例如约 50％至约 80％或约 70％至约 90％的范围内。在一些实施方案中，载体材料是硅基的。在一些实施方案中，载体材料包含元素硅。在一些实施方案中，载体材料包含硅石。在一些实施方案中，载体材料中的孔大体上平行。在一些实施方案中，载体材料包含阳极化硅。在一些实施方案中，载体材料是可再吸收的或可生物蚀解的。

[0017] 在某些实施方案中，粒子的最大尺寸平均来说在约 1 微米与约 20 微米之间。在一些实施方案中，装置以一定释放速率释放有益物质，所述释放速率主要由有益物质从载体材料的孔的释放情况决定。在一些实施方案中，当装置放置在生物介质中时，有益物质根据大体上零级释放型态从装置释放。

[0018] 在一些实施方案中，有益物质选自小分子、蛋白质、肽、抗体、碳水化合物、脂质、聚合物、寡核苷酸以及多核苷酸。在一些实施方案中，有益物质是雷珠单抗 (ranibizumab) 或贝伐单抗 (bevacizumab)。

[0019] 在一些实施方案中，装置是使用其中包含有益物质的粒子被设置于载体材料的孔内的方法来制备。在某些实施方案中，所述方法进一步包括使装置接触有益物质并且使有益物质进入载体材料的孔。在一些实施方案中，添加第一构件包括使管的第一末端接触聚合物溶液并且使聚合物溶液固化，从而在管的第一末端形成第一构件。在某些实施方案中，添加第二构件包括使管的第二末端接触聚合物溶液并且使聚合物溶液固化，从而在管的第二末端形成第二构件。在一些实施方案中，使第一和第二末端同时固化。

[0020] 在一些实施方案中，装置当浸没于模拟体液中时释放有益物质持续一个月至一

年。在一些实施方案中，施用装置包括将装置注入、植入或插入患者中。

[0021] 本公开涵盖前述方面和 / 或实施方案中的任何一个或多个的所有组合以及与详细描述和实施例中所阐述的实施方案中的任何一个或多个的组合。

[0022] 附图简述

[0023] 现将参考仅通过举例给出的优选实施方案并且参考附图更详细地描述装置，其中：

[0024] 图 1 是用于递送有益物质的圆筒形装置的放大分解透视图。

[0025] 图 2 是用具有正方形截面的管制成的用于递送有益物质的装置的放大分解透视图。

[0026] 图 3 是用于递送有益物质的圆筒形装置的放大透视图。

[0027] 图 4 是用于递送有益物质的装置的放大截面视图，其中有益物质从装置的一个末端扩散出来。

[0028] 图 5 是用于递送有益物质的装置的放大截面视图，其中有益物质从装置的两个末端扩散出来。

[0029] 图 6 是含有负载有拉坦前列素 (Latanoprost) 的气相硅石粒子 (1:1w:w) 的植入物在 PBS 中在 37℃下历时 70 天的累积体外释放曲线。

[0030] 图 7 是含有负载有拉坦前列素的氧化阳极化硅粒子 (1:1w:w) 的植入物在 PBS 中在 37℃下历时 30 天的累积体外释放曲线。

[0031] 详细说明

[0032] 1. 包含多孔载体粒子的装置

[0033] 本申请提供一种用于向患者递送有益物质的装置。装置包括封围多个载体粒子的外壳。载体粒子是多孔的，并且诸如药物等有益物质设置于孔中。有益物质可从孔中扩散出来，进入装置内部，并且然后穿过外壳的至少一个可渗透部分。本申请还提供制备和使用这些装置的方法。

[0034] A. 外壳的特征

[0035] 外壳封围载体粒子，保持载体定位于身体的一个区域中。同时，外壳允许有益物质（诸如药物）离开外壳并且到达靶组织。因此，外壳的至少一部分对于有益物质是可渗透的。

[0036] 外壳还可以为装置提供结构。外壳可在尺寸上稳定并且在不存在粒子的情况下维持其形状。举例来说，外壳可包括即使在不用载体材料粒子填充时也维持形状的硬管。管还可以在不存在外壳的第一末端和第二末端的情况下维持其形状。

[0037] 在一些实施方案中，装置包括单一外壳。

[0038] 在某些实施方案中，外壳由一个管制成，所述管具有封围各末端的构件，使得构件将粒子保持在内部。此类型的装置 100 以分解形式说明于图 1 中。管 102 具有第一末端 102a 和第二末端 102b。第一构件 104 接触管 102 的第一末端 102a。第二构件 106 接触管 102 的第二末端 102b。管 102、第一构件 104 以及第二构件 106 封围多个多孔粒子 108。孔适合用于接收像药物那样的有益物质。

[0039] 虽然在图 1 中，第一构件 104 和第二构件 106 显示具有大致相同的厚度，但是它们也可以给予不同厚度。此外，在此图解中，第一构件 104 和第二构件 106 具有与管 102 大致

相同的直径。然而，构件可具有稍微较大或稍微较小的直径，只要它们被适当调节大小以将粒子维持在管中即可。如部分 2 中将更详细讨论，第一和第二构件可通过在管末端诱发聚合层的交联而在管的末端原位形成。

[0040] 虽然图 1 的装置是大体上圆筒形的，（即，它具有带圆形截面的管），但是其它几何形状也是可能的。管可具有圆形、椭圆形、正方形、矩形、六边形或适合用于在内部容纳粒子的任何其它形状的截面。图 2 说明用具有正方形截面的管 202 制成的装置 200 的分解视图。管 202 具有第一末端 202a 和第二末端 202b。第一构件 204 接触第一末端 202a，而第二构件 206 接触第二末端 202b。管 202、第一构件 204 以及第二构件 206 封围多个多孔粒子 108。

[0041] 图 3 说明具有与管接触的第一和第二构件的装置 300。特别地，管 302 具有与第一构件 304 接触的第一末端 302a。管 302 具有与第二构件 306 接触的第二末端 302b。

[0042] 在一些实施方案中，装置的长度（即，第一构件与第二构件之间的距离）是约 1-2mm、2-4mm、4-6mm、6-8mm、8-10mm、1-2cm、2-4cm 或 4-10cm。在某些实施方案中，装置的宽度（例如，管的直径，或第一和第二构件的直径）是约 0.1-0.2mm、0.2-0.4mm、0.4-0.6mm、0.6-0.8mm、0.8-1.0mm、1-2mm、2-4mm、4-6mm、6-8mm、8-10mm、1-2cm、2-4cm 或 4-10cm。装置可被调节形状和大小用于注射（例如，小于约 4mm 长并且直径小于约 0.5mm，例如，用于适合穿过至少一个大小为约 30 号至约 15 号的针或大小为约 30 号至约 15 号的套管，优选适合穿过小于 22 号的套管）。当制备此类装置用于植入眼睛的玻璃体内时，在一些实施方案中，装置在任何方向上均不超过约 7mm，使得装置可通过小于 7mm 的切口插入。因此，在一些实施方案中，装置的高度不超过 7mm 或直径不超过 3mm。

[0043] 管壁的厚度优选足以允许管在不存在任何其它材料的情况下维持其形状。在一些实施方案中，管壁的厚度在约 0.01mm 与约 1.0mm 之间的范围内。在一些实施方案中，管壁是约 0.01-0.02mm、0.02-0.04mm、0.04-0.06mm、0.06-0.08mm、0.08-1.0mm、1-2mm、2-4mm 或 4-10mm。装置的管的示例性直径包括内径为 0.011“+/-0.001”并且外径为 0.0145“+/-0.001”。装置的管的示例性直径还包括内径为 0.0061“+/-0.001”并且外径为 0.0145“+/-0.001”。装置的管的示例性直径还包括内径为 0.016“+/-0.001”并且外径为 0.018“+/-0.001”。

[0044] 外壳的至少一部分对于有益物质是可渗透的。“可渗透”指示外壳允许有效量的有益物质离开装置。外壳的某些部分可对于有益物质是不可渗透的。如本文所用，术语“不可渗透的”意味着在装置向患者递送有效量的有益物质的期间，所述层将不允许有益物质以获得所需局部或全身性生理或药理效应所需要的速率穿过。在一些实施方案中，不可渗透的区域的有益物质渗透率小于可渗透区域的渗透率的 10%、5%、2%、1%、0.5%、0.2%、0.1%、0.05%、0.02%或 0.01%。

[0045] 在一些实施方案中，管对于有益物质是可渗透的。在一些实施方案中，第一构件对于有益物质是可渗透的。在一些实施方案中，第二构件对于有益物质是可渗透的。在一些实施方案中，管是不可渗透的而构件中的一个或两个是可渗透的。在一些实施方案中，为促进有益物质的更大程度释放，管由可渗透材料制成。举例来说，管、第一构件以及第二构件可全部是可渗透的。

[0046] 外壳的一部分的渗透率可受其厚度影响。不可渗透构件应足够厚而相对于装置的

可渗透区域不释放大量有益物质。不可渗透构件的厚度可以是例如约 0.01 与约 2mm 之间，优选约 0.01 与约 0.5mm 之间，最优选约 0.01 与约 0.2mm 之间。可渗透构件应足够厚以容纳管中的载体粒子，但又不那么厚以致阻止有效量的有益物质的释放。可渗透构件的厚度可以是例如约 0.01 与约 2mm 之间，优选约 0.01 与约 0.5mm 之间，最优选约 0.01 与约 0.2mm 之间。

[0047] 在某些实施方案中，至少外壳的一部分是多孔的并且有益物质可通过孔离开外壳。孔应足够小，使得载体粒子不以任何相当大的量穿过孔。

[0048] 优选地，外壳基本上不溶于所述材料将接触的体液。

[0049] 在一些实施方案中，外壳是大体上不可生物降解的。在一些实施方案中，在释放至少 90％、95％或 99％的有益物质之前外壳在生物环境中大体上不生物降解。在一些实施方案中，在释放至少 90％、95％或 99％的有益物质之后外壳在生物环境中大体上生物降解。

[0050] 在一些实施方案中，外壳包含聚合物。特别地，管、第一构件以及 / 或者第二构件可以是聚合的。一般说来，适合用于本发明装置的生物相容聚合物包括但不限于聚（乙酸乙烯酯）(PVAC)、聚（己内酯）(PCL)、乙烯乙酸乙烯酯聚合物 (EVA)、聚（乙二醇）(PEG)、聚（乙烯醇）(PVA)、聚（乳酸）(PLA)、聚（乙醇酸）(PGA)、乳酸 - 乙醇酸共聚物 (PLGA)、聚氰基丙烯酸烷基酯、聚氨酯、尼龙 (nylon) 或其共聚物。在包括乳酸单体的聚合物中，乳酸可以是 D- 异构体、L- 异构体（例如，聚 L- 乳酸 (PLLA)）或 D- 异构体和 L- 异构体的任何混合物。在一些实施方案中，聚合物是聚酰亚胺。在一些实施方案中，聚合物是 PLGA，其以约 95％ L 和 5％ G 的比率包含乳酸 (L) 和乙醇酸 (G) 单体。L 的百分比可在 80-97％之间的范围内。G 的百分比可在 3-20％之间的范围内。在一些实施方案中，聚合物是可加热固化、可辐射固化、可光（包括紫外线）固化、可蒸发固化或可通过催化固化的。在某些实施方案中，聚合物是硅酮，诸如硅酮橡胶、聚二甲基硅氧烷或硅酮 - 碳酸酯共聚物。

[0051] 某些聚合物 (像 PVA) 可通过改变聚合物交联的程度变得或多或少可渗透。一些聚合物可视聚合物和药物核心中的药物的相对特征而定是可渗透或不可渗透的。举例来说，给定聚合物对于小分子是可渗透的但对于抗体来说是不可参透的。

[0052] 适合用于构造外壳的可渗透部分的示例性聚合物包括 PVA 和 PEG。

[0053] 适合用于构造外壳的不可渗透部分的示例性聚合物包括尼龙、聚氨酯、EVA、聚氰基丙烯酸烷基酯、聚（四氟乙烯）(PTFE)、聚碳酸酯 (PC)、聚（甲基丙烯酸甲酯）(PMMA)、高级乙烯乙酸乙烯酯 (EVA)（例如，9％乙烯基含量）、乳酸 - 乙醇酸共聚物 (PLGA) 以及聚乙烯醇 (PVA)，尤其是交联的 PVA。

[0054] 在某些实施方案中，外壳包含金属，诸如金、铂以及（手术）不锈钢。举例来说，管可由金属制成。在一些实施方案中，外壳的金属部分对于有益物质是不可渗透的。金属优选是生物相容的。在某些实施方案中，金属是可生物降解的。生物相容和 / 或可生物降解的金属合金可包括以下的一种或多种 :Fe（铁）、Mg（镁）、Mn（锰）、Pd（钯）、Co（钴）、Al（铝）、W（钨）、B（硼）、C（碳）、S（硫）、Si（硅）、Li（锂）、Zr（锆）、Ca（钙）、Y（钇）、Zn（锌）。示例性可生物降解金属描述于 H.Hermawan“Biodegradable Metals”SpringerBriefs in Materials 2012 第 13-22 页以及 Moravej 和 Martovani,“Biodegradable Metals for Cardiovascular Stent Application:Interests and New Opportunities”Int J Mol Sci.2011 ;12(7):4250-4270 中。

[0055] 在某些实施方案中，外壳包含硅（例如，元素硅）或硅石。硅或硅石外壳可以是可生物降解的。

[0056] 可选择管、第一构件以及第二构件的材料以实现有益物质的所需释放速率。举例来说，图 4 中以截面形式说明了装置的“低流”实施方案。装置 400 包括由不可渗透材料制成的管 402 和由不可渗透材料制成的第一构件 404。第二构件 406 由可渗透材料制成。粒子 408 容纳于装置 400 内部。粒子 408 起初释放有益物质 410 至装置内部中。然后，有益物质 410 通过可渗透第二构件 406 扩散离开装置。没有大量有益物质通过管 402 或第一构件 404 离开装置。作为一个实例，在优选实施方案中，管包含不可渗透的 dl- 丙交酯 - 乙交酯共聚物 PLGA，第一构件由诸如硅酮等不可渗透物质制成，并且第二构件包含可渗透的聚（乙烯醇）(PVA)。

[0057] 相比之下，图 5 以截面形式说明了装置的“高流”实施方案。装置 500 包括由不可渗透材料制成的管 502。第一构件 504 与第二构件 506 均由可渗透材料制成。粒子 508 容纳于装置 500 内部。粒子 508 起初释放有益物质 510 至装置内部中。然后，有益物质 510 通过可渗透的第一构件 504 和第二构件 506 扩散离开装置。没有大量有益物质通过管 502 离开装置。作为一个实例，在优选实施方案中，管包含不可渗透的 dl- 丙交酯 - 乙交酯共聚物 PLGA，并且第一和第二构件包含可渗透的聚（乙烯醇）(PVA)。

[0058] 有益物质沿更低化学势方向（即朝向装置的外表面）扩散。有益物质从装置释放受若干因素控制。它受到有益物质的溶解速率、从载体材料的孔释放的速率以及外壳穿过率的影响。可选择装置形状、大小以及材料以实现有益物质的所需释放速率。因此，在一些实施方案中，释放速率主要由有益物质的溶解情况决定。在其它实施方案中，释放速率主要由有益物质从载体材料的孔的释放情况决定。在其它实施方案中，释放速率主要由外壳的渗透率决定。在一些实施方案中，释放速率显著受这些步骤中的任何两个或所有三个步骤影响。

[0059] 有益物质通过装置外壳扩散的速率可例如通过在漏槽条件下进行的扩散池研究来测定。在漏槽条件下进行的扩散池研究中，当与供体隔室中的高浓度相比时受体隔室中的药物浓度基本上是零。

[0060] 应了解，材料可对于药物是可渗透的并且同时大体上控制使药物扩散或以其它方式穿过材料的速率。因此，外壳的可渗透部分还可以是释放速率受限制或释放速率受控制的并且此类膜的渗透率可以是控制装置的释放速率的最重要因素之一。

[0061] 在一些实施方案中，装置以随时间推移基本上恒定的速率（即，零级动力学）释放有益物质。当目标是在持续时间内维持大体上恒定量的有益物质到达患者时，零级释放是所需的。

[0062] B. 载体材料的特征

[0063] 载体材料容纳并且逐渐释放有益物质，诸如药物。有益物质存在于载体材料中的小孔中。载体材料是由装置外壳封围的多个粒子。载体粒子中的每一者释放有益物质至装置内部中，并且然后有益物质从装置内部离开外壳。

[0064] 在某些优选实施方案中，装置的粒子在最大直径处测量 d10 在 1-5 微米范围内（意味着装置中的粒子中 10％的直径低于 1-5 微米范围内的数值），d50 在 5-10 微米范围内（意味着装置中的粒子中 50％的直径低于 5-10 微米范围内的数值），并且 d90 在 10-20

微米范围内（意味着装置中的粒子中90％的直径低于10-20微米范围内的数值）。在一些实施方案中，d10是1-5微米、1-3微米或3-5微米。在一些实施方案中，d50是5-7微米、6-8微米、7-9微米或8-10微米。在一些实施方案中，d90是10-15微米或15-20微米。在某些实施方案中，装置的粒子在最大直径处测量平均尺寸为约1至约500微米，诸如约5至500微米、约5至约100微米或约5至约20微米。在一些实施方案中，粒子中大于60％、大于70％、大于80％或大于90％的粒度为在最大尺寸处测量是1-20微米、优选5-15微米。粒子的平均粒径可在1与20微米之间，诸如5-15微米之间，或者是约15微米、约16微米、约17微米、约18微米、约19微米。

[0065] 在一些实施方案中，载体包含半导体材料，诸如半导体硅。可用作多孔载体材料的其它材料的实例是锗、陶瓷、金属氧化物、骨质磷酸盐、钙的磷酸盐（例如，羟磷灰石）、其它无机磷酸盐、碳黑、碳酸盐、硫酸盐、铝酸盐、硼酸盐、铝硅酸盐、氧化镁、氧化钙、铁氧化物、锆氧化物、钛氧化物以及其它类似材料。

[0066] 装置可包含硅基载体材料，诸如元素硅、二氧化硅（硅石）、一氧化硅、硅酸盐（含有带有硅的阴离子（例如SiF_6^{2-}、$Si_2O_7^{6-}$或SiO_4^{4-}）的化合物）或此类材料的任何组合。载体材料可以是例如半导体硅、元素硅、多晶硅或无定形硅。硅可以是未掺杂的，或可以是掺杂的（例如掺杂有磷）。载体材料可以是碳化硅或氮化硅。在某些优选实施方案中，载体材料包含完全的或部分的元素硅骨架，并且所述骨架大体上或完全由二氧化硅表面层覆盖。在其它优选实施方案中，载体材料完全或大体上完全是硅石。在某些实施方案中，硅基载体材料是合成的无定形硅石。在某些实施方案中，硅基载体材料是气相硅石。

[0067] 在某些实施方案中，载体材料包含硅石，诸如大于约50％硅石、大于约60wt％硅石、大于约70wt％硅石、大于约80wt％硅石、大于约90wt％硅石、大于约95wt％硅石、大于99wt％硅石或甚至大于99.9wt％硅石。多孔硅石可购自诸如以下供应商：Grace Davison（并且以商标Davisil出售）、Silicycle以及Macherey-Nagel。

[0068] 在某些实施方案中，载体材料包含元素硅、大于60wt％硅、大于70wt％硅、大于80wt％硅、大于90wt％硅或甚至大于95wt％硅。硅可购自诸如Vesta Ceramics等供应商。

[0069] 硅基材料的纯度可使用诸如以下技术来定量评估：能量分散X射线分析、X射线荧光、电感耦合发射光谱法或辉光放电质谱法。

[0070] 基于的载体材料可以是多孔无定形固体或多孔结晶固体。举例来说，硅基载体材料可包含呈无定形形式的元素硅或其化合物，例如二氧化硅或硅酸盐。在某些实施方案中，元素硅或其化合物以结晶形式存在。在其它实施方案中，载体材料包含无定形硅石和/或无定形硅。在某些实施方案中，硅基材料是大于约60wt％无定形、大于约70wt％无定形、大于约80wt％无定形、大于约90wt％无定形、大于约92wt％无定形、大于约95wt％无定形、大于约99wt％无定形或甚至大于99.9wt％无定形。在某些实施方案中，无定形硅石是气相硅石。在某些实施方案中，无定形硅石是合成的无定形硅石。

[0071] 可使用X射线衍射分析来识别硅基材料的结晶相。可例如在例如装有使用Cu K-α辐射的液氮冷却锗固态检测器的Scintag PAD-X衍射仪上进行粉末衍射。

[0072] 载体材料的孔隙率可以是约30％至约95％、30％至约90％或约60％至约80％。如本文所用，孔隙率是材料中的孔空间的度量，并且是相对于材料总体积的孔体积的分数。在某些实施方案中，载体材料的孔隙率是至少约10％、至少约20％、至少约30％、至少约

40％、至少约 50％、至少约 60％、至少约 70％、至少约 80％或甚至至少约 90％。在特定实施方案中，孔隙率大于约 40％，诸如大于约 50％、大于约 60％或甚至大于约 70％。

[0073] 装置的载体材料的表面积与重量比可选自约 20m^2/g 至约 2000m^2/g，诸如从约 20m^2/g 至约 1000m^2/g 或甚至约 100m^2/g 至约 300m^2/g。在某些实施方案中，表面积大于约 200m^2/g、大于约 250m^2/g 或大于约 300m^2/g。在某些实施方案中，表面积是约 200m^2/g。

[0074] 在某些实施方案中，有益物质被分配至距离材料表面至少约 10 微米、至少约 20 微米、至少约 30 微米、至少约 40 微米、至少约 50 微米、至少约 60 微米、至少约 70 微米、至少约 80 微米、至少约 90 微米、至少约 100 微米、至少约 110 微米、至少约 120 微米、至少约 130 微米、至少约 140 微米或至少约 150 微米的孔深度。在某些实施方案中，有益物质大体上均匀地分配于载体材料的孔中。

[0075] 有益物质可被负载至载体材料中达到一定深度，所述深度是以有益物质穿透载体材料的深度与载体材料的总宽度的比率形式度量。在某些实施方案中，有益物质被分配至进入载体材料至少约 10％至进入载体材料至少约 20％，进入载体材料至少约 30％，进入载体材料至少约 40％，进入载体材料至少约 50％或进入载体材料至少约 60％的深度。

[0076] 总负载量的定量分析可通过许多分析方法来实现，例如药物组合物的重力测量、EDX（通过 x 射线进行能量分散分析）、傅里叶变换红外光谱 (Fourier transform infra-red spectroscopy)(FTIR) 或拉曼光谱 (Raman spectroscopy) 或通过对溶液中的洗脱治疗剂的紫外分光光度分析、滴定分析、HPLC 或质谱分析。负载的均匀性的定量分析可通过能够进行空间分辨的组合技术，诸如截面 EDX、欧杰纵深分析 (Auger depth profiling)、微拉曼以及微 FTIR 来实现。

[0077] 载体材料优选包含可接收有益物质的孔。微孔载体（孔尺寸小于 2nm）、中孔载体（孔尺寸 2-50nm）以及大孔载体（孔尺寸 >50nm）全部是适合的载体材料。在某些实施方案中，载体材料的平均孔尺寸选自 2-50nm，诸如约 5 至约 40nm、约 15 至约 40nm，诸如约 20 至约 30nm。在某些实施方案中，平均孔尺寸选自约 2 至约 15nm，诸如约 5 至约 10nm。在某些实施方案中，平均孔尺寸是约 30nm。在某些实施方案中，载体材料的孔中大于 50％的孔尺寸是 2-50nm，载体材料的孔中大于 60％的孔尺寸是 2-50nm，载体材料的孔中大于 70％的孔尺寸是 2-50nm，载体材料的孔中大于 80％的孔尺寸是 2-50nm，或甚至载体材料的孔中大于 90％的孔尺寸是 2-50nm。

[0078] 在某些实施方案中，载体材料包括多孔二氧化硅，诸如中孔二氧化硅或无定形硅石，诸如气相硅石。

[0079] 在某些实施方案中，载体材料的孔群体具有明确界定的孔尺寸，即载体材料的孔尺寸分布在所界定的范围内。在某些实施方案中，明确界定的孔群体的约 50％至约 99％的孔尺寸在所述群体的平均孔尺寸约 1nm 至 15nm 内，优选在所述群体的平均孔尺寸约 10nm、约 5nm 内，或甚至在 3nm 或 2nm 内。在某些此类实施方案中，载体材料的孔中大于约 50％、大于约 60％、大于约 70％、大于约 80％、大于约 90％或甚至大于约 95％的孔尺寸在所规定的范围内。类似地，具有明确界定的孔尺寸的孔群体可以是其中大于约 50％、大于约 60％、大于约 70％、大于约 80％、大于约 90％或甚至大于约 95％的孔的孔尺寸在所述群体的平均孔尺寸的 20％以内、优选 15％、10％或甚至 5％以内的群体。

[0080] 孔（例如，中孔）径分布可使用已确立的分析方法定量，诸如气体吸附、高

分辨率扫描电子显微术、核磁共振低温孔隙率测定法(nuclear magnetic resonance cryoporosimetry)以及差示扫描量热法。

[0081] 在一些实施方案中,具有明确界定的孔尺寸的孔的群体可以是孔尺寸的标准偏差小于所述群体的平均孔尺寸的20%、优选小于15%、小于10%或甚至小于5%的群体。

[0082] 可根据有益物质的尺寸特征预先选择孔尺寸以控制生物系统中有益物质的释放速率。典型地,过小的孔尺寸阻碍有益物质的负载,而过大的孔不与有益物质足够强烈地相互作用以对释放速率施加所需控制。举例来说,载体材料的平均孔直径可选自对于高分子量分子(例如200,000-500,000amu)来说的更大孔,例如15nm至40nm;以及对于更低分子量分子(例如10,000-50,0000amu)来说的更小孔,例如2nm至10nm。举例来说,直径为约6nm的平均孔尺寸可适合用于约14,000至15,000amu(诸如约14,700amu)分子量的分子。直径为约10nm的平均孔尺寸可被选择用于约45,000至50,000amu(诸如约48,000amu)分子量的分子。直径为约25-30nm的平均孔尺寸可被选择用于约150,000amu分子量的分子。

[0083] 孔尺寸可被预先选择成适合于有益物质的分子半径,从而控制生物系统中有益物质的释放速率。举例来说,直径为约25nm至约40nm的平均孔尺寸可适合用于最大分子半径为约6nm至约8nm的分子。分子半径可通过任何适合的方法来计算,诸如通过使用基于X-射线结晶学数据的分子的外形尺寸或使用代表分子的溶液状态大小的流体动力学半径来计算。因为溶液状态计算依赖于进行计算的溶液的性质,但对于一些测量来说可能优选的是使用基于X-射线结晶学数据的分子的外形尺寸。如本文所用,最大分子半径反映治疗剂的最大尺寸的一半。

[0084] 在某些实施方案中,选择平均孔直径以限制分子(例如蛋白质)在孔内聚集。防止生物分子(诸如蛋白质)在装置中聚集将是有利的,因为这种聚集被认为阻碍分子向生物系统中的控制释放。因此,归因于孔的尺寸与生物分子的尺寸之间的关系允许例如仅一个生物分子在任一时刻进入孔的孔将优于允许多个生物分子一起进入孔并且在孔内聚集的孔。在某些实施方案中,可将多个生物分子(例如蛋白质)负载至孔中,但归因于孔的深度,在孔的整个这一深度中分配的蛋白质将在较小程度上聚集。举例来说,孔的直径可稍微大于孔内部的蛋白质的直径。在此情况下,孔的窄直径可约束蛋白质的布置,从而减少聚集。

[0085] 在某些实施方案中,载体材料包含具有不同性质(例如孔尺寸、粒径或表面特征)的两种或更多种不同材料,其各自被预先选择成适合于不同有益物质。举例来说,可混合两种不同的载体材料,一种具有孔尺寸适合于第一有益物质的第一孔群体,另一种具有孔尺寸适合于第二有益物质的第二孔群体。在一些实施方案中,装置包含第一载体粒子群体,其具有孔尺寸适合于第一有益物质的第一孔群体;以及第二载体粒子群体,其具有孔尺寸适合于第二有益物质的第二孔群体。在某些其它实施方案中,粒子包含单一材料,其具有两个或更多个明确界定的孔群体,例如其中载体材料是通过分子模板技术制备,其中孔的特征是针对两种或更多种有益物质(例如具有不同分子半径的两种有益物质)而预先选择。因此,载体材料可以本文所描述的控制方式递送两种或更多种有益物质。在此类实施方案中,有益物质的负载优选按顺序从最大试剂到最小试剂,使得最大试剂选择性吸附至最大孔中(即,它不适合进入较小孔),使得较大孔不吸附较小试剂。

[0086] 在载体材料具有两个或更多个不同的明确界定的孔群体(例如,不同的孔群体大

体上不重叠）的某些实施方案中，不同孔群体的性质之间的差异优选被选择成限制各不同有益物质吸附至某一孔群体。在某些实施方案中，两个或更多个不同的明确界定的孔群体的平均孔尺寸可被选择成限制较大有益物质吸附至较小孔中。平均孔尺寸差别可定义为载体材料中不同孔群体的平均孔尺寸之间的差异。举例来说，至少 10nm 的平均孔尺寸差别可指示载体材料可包含至少两个孔群体，其平均孔尺寸相差（“平均孔尺寸差别”）至少 10nm，例如组合物可包含平均孔尺寸为 10nm 和 20nm 的两个孔群体，平均孔尺寸为 10nm、20nm 以及 30nm 的三个孔群体，或平均孔尺寸为 10nm、20nm、30nm 以及 40nm 的四个孔群体。在某些实施方案中，平均孔尺寸差别优选是至少约 5nm、至少约 10nm、至少 15nm、至少约 20nm 或至少约 30nm。在某些实施方案中，两个或更多个明确界定的孔尺寸群体具有不同的平均孔尺寸，使得任何两个群体的平均孔尺寸相差较小平均孔尺寸的至少 20％、优选至少 30％、40％或甚至 50％。

[0087] 在某些实施方案中，分隔孔的载体材料壁的平均宽度小于 5nm，诸如是约 4.8nm、约 4.6nm、约 4.4nm、约 4.2nm、约 4.0nm、约 3.8nm、约 3.6nm、约 3.4nm、约 3.2nm、约 3.0nm、约 2.8nm 或甚至约 2.6nm。在某些实施方案中，分隔孔的载体材料壁的平均宽度小于约 3nm，诸如是约 2.8nm、约 2.6nm、约 2.4nm、约 2.2nm、约 2.0nm、约 1.8nm、约 1.6nm、约 1.4nm、约 1.2nm、约 1.0nm 或甚至约 0.8nm。

[0088] 装置的维度和形态可例如通过透射电子显微术 (TEM) 使用例如在 200keV 下操作的 2000JEOL 电子显微镜来测量。TEM 的样品可通过将大量多孔载体材料通过稀释浆液分配至金属格栅上的有孔碳膜上来制备。

[0089] 在某些实施方案中，载体材料的孔界定载体材料中体积为约 0.1mL/g 至约 5mL/g 的空间。在某些实施方案中，孔体积是约 0.2mL/g 至约 3mL/g，诸如约 0.4mL/g 至约 2.5mL/g，诸如约 1.0mL/g 至约 2.5mL/g。

[0090] 在某些实施方案中，载体材料的负载水平以载体材料和有益物质的总重量计达到 70 重量％，诸如达到 40 重量％。负载水平是通过用所负载的有益物质的重量除以所负载的治疗剂和载体材料的总重量并且乘以 100 来计算。在某些实施方案中，载体材料的负载水平大于 10％，诸如大于 15％、大于 20％、大于 25％、大于 30％、大于 35％、大于 40％、大于 45％或大于 50％。在某些实施方案中，载体材料的负载水平小于 5％。负载水平可在约 5％与约 10％之间。在某些实施方案中，载体材料的负载水平在约 10 重量％与约 20 重量％之间、约 20 重量％与约 30 重量％之间、约 30 重量％与约 40 重量％之间、约 40 重量％与约 50 重量％之间或约 50 重量％与约 60 重量％之间。

[0091] 本文所描述的装置的负载体积可用多孔材料中由有益物质占据的孔的体积来评估。载体材料中由有益物质占据的最大负载容量的百分比（即，多孔载体材料中由有益物质占据的孔的总体积的百分比）可以是约 30％至约 100％，诸如约 50％至约 90％。对于任何给定载体材料，这个值可通过负载期间所吸收的有益物质的体积除以负载之前载体材料的空隙体积并且乘以一百来确定。

[0092] 在某些实施方案中，载体粒子在最大直径处测量的平均尺寸是约 1 至约 500 微米，诸如约 5 至约 100 微米。在某些实施方案中，装置中至少 80％、90％、99％或甚至 100％的粒子在最大直径处测量是约 1 至约 500 微米，诸如约 5 至约 500 微米或约 2 至约 100 微米。

[0093] 为增加有益物质向粒子中负载的速率，可能有利的是使用相对小的粒子。因为较

小粒子的孔供有益物质穿透的深度较小，所以负载粒子所需时间的量减少。这在孔尺寸的尺寸类似于分子直径或治疗剂尺寸时可能特别有利。较小粒子在最大尺寸处测量可以是1-20 微米，诸如约 10-20 微米，例如约 15-20 微米。

[0094] 在一些方面，粒子中大于 60％、大于 70％、大于 80％或大于 90％的粒度为在最大尺寸处测量是 1-20 微米、优选 5-15 微米。粒子的平均粒径可在 1 与 20 微米之间，诸如 5-15 微米之间，或者是约 15 微米、约 16 微米、约 17 微米、约 18 微米、约 19 微米。

[0095] 粒度分布（包括平均粒径）可例如使用来自 Malvern Instruments,UK. 的 Malvern 粒度分析仪（型号 Mastersizer）来测量。氦氖气体激光束可发射穿过含有载体材料的悬浮液的光学池。撞击载体材料的光线通过与粒度成反比的角度散射。光检测器矩阵测量在若干预定角度的光强度，并且然后通过微型计算机系统针对由样品载体材料和水性分散剂的折射率预测的散射模式处理与所测量的光通量值成正比的电信号。

[0096] 制备适合的载体材料的方法（包括上文所描述的方法）可见于国际申请 WO 2012/061377 中，并且此文献明确地以全文引用的方式并入本文中。

[0097] 在某些实施方案中，装置还包括一种或多种药学上可接受的赋形剂。在一些实施方案中，赋形剂是填料、粘合剂、稀释剂、缓冲剂、湿润剂、防腐剂、稳定剂、调味剂、染料、染色剂、崩解剂或表面活性剂。在一些实施方案中，缓冲剂用于通过在装置中产生微环境 pH 值来定制药物释放速率。pH 值可影响有益物质的溶解速率或外壳对有益物质的渗透率，从而影响总体释放速率。表面活性剂可用于调节载体的电荷、亲脂性或亲水性，从而增强可溶性欠佳或疏水性组合物的可润湿性。可充当药学上可接受的赋形剂的材料的一些实例包括：(1) 糖，诸如乳糖，葡萄糖以及蔗糖；(2) 淀粉，诸如玉米淀粉和马铃薯淀粉；(3) 纤维素和其衍生物，诸如羧甲基纤维素钠、乙基纤维素以及乙酸纤维素；(4) 粉末黄蓍胶；(5) 麦芽；(6) 明胶；(7) 滑石；(8) 疏水性材料，诸如可可脂、栓剂蜡等；(9) 油，诸如花生油、棉籽油、红花油、芝麻油、橄榄油、玉米油以及大豆油；(10) 二醇，诸如丙二醇；(11) 多元醇，诸如甘油、山梨糖醇、甘露糖醇以及聚乙二醇；(12) 酯，诸如油酸乙酯和月桂酸乙酯；(13) 琼脂；(14) 缓冲剂，诸如氢氧化镁和氢氧化铝；(15) 褐藻酸；以及 (16) 用于药物制剂中的其它无毒相容物质。赋形剂可设置于载体材料的孔内。在其它实施方案中，赋形剂在粒子的外部和装置外壳的内部。举例来说，粒子可悬浮于溶液中和 / 或形成浆液，并且赋形剂可在溶液中。

[0098] C. 通过装置可递送的有益物质

[0099] 装置可储存和递送治疗有效量的有益物质。在优选实施方案中，有益物质是治疗剂。如本文所用，术语“治疗剂”涵盖活性分子以及活性分子的盐。治疗剂可以是例如药物或前药。

[0100] 在某些实施方案中，有益物质选自适合用于治疗和预防疾病的任何药剂。在某些实施方案中，有益物质选自小分子治疗剂，即分子量小于 1000amu 的化合物。在优选实施方案中，有益物质选自分子量等于或大于 1000amu 的大分子。在某些实施方案中，本发明的有益物质是生物分子。如本文所用，生物分子是指由活有机体产生的任何分子，包括大聚合分子，诸如蛋白质、多糖以及核酸，以及小分子，诸如初级代谢产物、次级代谢产物以及天然产物或其合成变化形式。特别地，诸如抗体、配体以及酶等蛋白质可用作本文所描述装置中的有益物质。在特定实施方案中，用于装置中的生物分子的分子量在约 10,000amu 至约

500,000amu 范围内。

[0101] 在一些实施方案中，有益物质是蛋白质，诸如抗体。在一些实施方案中，抗体是单克隆抗体。抗体可以是例如全长抗体的抗原结合部分，例如 Fab 片段或单一链可变片段。可通过装置递送的特定治疗剂抗体包括雷珠单抗和贝伐单抗。

[0102] 可使用本文的装置施用的多核苷酸包括 DNA、RNA 以及 DNA 和 RNA 的类似物。举例来说，多核苷酸可包括 2'O-Me 核苷酸或双脱氧核苷酸。多核苷酸可编码用于基因治疗的蛋白质，或可被设计成通过反义途径减少靶基因的表达。

[0103] 在某些实施方案中，有益物质的分子量在 10,000 与 50,000amu 之间、50,000 与 100,000amu 之间或 100,000 与 150,000amu 之间。在某些实施方案中，有益物质是分子量在 5,000amu 与 200,000amu 之间（诸如约 10,000 至约 150,000amu）的蛋白质。

[0104] 或者，有益物质的尺寸可通过分子半径来表征，所述分子半径可例如通过 X 射线结晶学分析或通过流体动力学半径来测定。有益物质可以是蛋白质，例如其中分子半径选自 0.5nm 至 20nm，诸如约 0.5nm 至 10nm，甚至约 1 至 8nm。

[0105] 载体材料的孔尺寸可至少部分地基于有益物质的尺寸来选择。分子半径为 1 至 2.5nm 的有益物质可有利地与最小孔半径为 4.5 至 5.8nm 的载体材料一起使用。分子半径为 7nm 的有益物质可有利地与最小孔半径为 11 至 13nm（诸如约 12nm）的载体材料一起使用。对选择给定有益物质的孔的适当尺寸的其它讨论可见于例如国际申请 WO 2012/061377 中，所述国际申请明确地以全文引用的方式并入本文中。

[0106] 在一些实施方案中，载体粒子负载有液体药物。有利地，负载有液体药物的载体粒子可比液体药物本身更容易处理。因此，本文的装置可使用于控制释放递送液体药物的装置的制造工艺简易。在一些实施方案中，液体药物包含羧酸部分。在一些实施方案中，装置的液体有益物质是前列腺素或前列腺素类似物。举例来说，液体药物可以是游离酸形式的拉坦前列素。作为另一个实例，液体药物可以是游离酸形式的曲伏前列素 (travoprost)。在一些实施方案中，液体药物是前列环素或前列环素类似物，诸如曲前列环素 (treprostinil)、伊洛前列素 (iloprost) 或贝前列素 (beraprost)。在一些实施方案中，液体包含脂溶性维生素，诸如维生素 E。

[0107] 在某些实施方案中，有益物质有分解和 / 或失活的倾向，并且载体材料使有益物质的分解 / 失活减轻。有益物质可例如通过降解或解折叠 / 变性来失活。举例来说，有益物质可在固化第一或第二构件（例如用热量或紫外光）的过程期间有失活的倾向，并且载体材料使这种失活减轻。举例来说，载体材料可阻断使有益物质失活（例如，通过吸收用于固化的波长的光）的试剂。作为另一个实例，载体可针对试剂使有益物质失活的作用来稳定有益物质，例如通过稳定呈活性构象的有益物质并且限制蛋白质解折叠或降解。在一些实施方案中，在装置的制备期间，有益物质在不存在载体材料情况下经历的失活（例如降解或解折叠）是在相同条件下在载体材料内的有益物质的至少两倍、五倍、十倍、20 倍、50 倍或 100 倍。

[0108] 在一些实施方案中，载体材料内的有益物质在室温下的半衰期是在相同条件下在不存在载体材料的情况下有益物质的半衰期的至少两倍、五倍、十倍、20 倍、50 倍或 100 倍。在一些实施方案中，载体材料内的有益物质在室温下的保质期是在相同条件下在不存在载体材料的情况下有益物质的保质期的至少两倍、五倍、十倍、20 倍、50 倍或 100 倍。在某些实

施方案中，载体材料内的有益物质在25℃下稳定至少15天、1个月、2个月、3个月、6个月、至少1年、至少1.5年、至少2年、至少2.5年、至少3年或至少4年。稳定性可例如通过高效尺寸排阻色谱法(HPSEC)或通过将所储存的负载生物分子的装置的生物活性相对于新制备的负载生物分子的装置的样品或相对于在储存之前所测量的装置的活性进行比较来评估。优选地，在储存期结束时，所储存装置的活性是相应新制备装置的活性的至少75%、至少80%、至少85%、至少90%、至少95%、至少98%、至少99%、至少99.5%、至少99.8%或甚至至少99.9%。因此，本公开涵盖处理方法，其中负载生物分子的装置在向患者施用装置之前被储存在25℃下至少6个月、至少1年、至少1.5年、至少2年、至少2.5年、至少3年或至少4年。在一些实施方案中，易降解的有益物质是生物分子，诸如蛋白质，包括抗体。

[0109] 在一些实施方案中，装置包含两种或更多种有益物质。举例来说，装置可包含两个粒子群体，各群体负载有一种有益物质。或者，单一粒子可包含两种或更多种有益物质。在一些此类实施方案中，单一粒子具有较大孔的群体和较小孔的群体，并且各孔群体含有有益物质中的一种。具有两个孔群体的载体描述于以上部分B中。

[0110] 许多不同有益物质可并入上文所描述的装置(例如，包括外壳和多孔硅基载体粒子的装置)。举例来说，适合的药物包括类固醇、α受体激动剂、β受体拮抗剂、碳酸酐酶抑制剂、肾上腺素能试剂、生理学活性肽和/或蛋白质、抗肿瘤剂、抗生素、止痛剂、消炎剂、肌肉松弛剂、抗癫痫剂、抗溃疡剂、抗过敏剂、强心剂、抗心律失常剂、血管扩张剂、抗高血压剂、抗糖尿病剂、抗高血脂剂、抗凝剂、溶血剂、抗结核剂、激素、麻醉药拮抗剂、破骨抑制剂、成骨促进剂、血管生成抑制剂、抗细菌剂、非类固醇消炎药(NSAID)、糖皮质激素或其它消炎性皮质类固醇、生物碱止痛剂(诸如阿片类止痛剂)、抗病毒剂(诸如核苷抗病毒剂或非核苷抗病毒剂)、抗良性前列腺肥大(BPH)剂、抗真菌化合物、抗增殖化合物、抗青光眼化合物、免疫调节化合物、细胞运输/移动阻碍剂、细胞因子、聚乙二醇化剂、α-阻断剂、抗雄激素、抗胆碱能剂、嘌呤能剂、多巴胺能剂、局部麻醉剂、辣椒素、一氧化氮抑制剂、抗凋亡剂、巨噬细胞活化抑制剂、抗代谢物、神经保护剂、钙离子通道阻断剂、γ-氨基丁酸(GABA)拮抗剂、α激动剂、抗精神病剂、酪氨酸激酶抑制剂、核苷化合物以及核苷酸化合物，以及其类似物、衍生物、药学上可接受的盐、酯、前药和受保护形式。

[0111] 适合用于本文所描述的装置(例如，包括外壳和多孔硅基载体粒子的装置)的NSAID包括双氯芬酸、依托度酸(etoldolac)、非诺洛芬(fenoprofen)、夫洛非宁(floctafenine)、氟比洛芬(flurbiprofen)、布洛芬(ibuprofen)、吲哚洛芬(indoprofen)、酮洛芬(ketoprofen)、酮咯酸(ketorolac)、氯诺昔康(lornoxicam)、吗拉宗(morazone)、萘普生(naproxen)、哌立索唑(perisoxal)、吡洛芬(pirprofen)、普拉洛芬(pranoprofen)、舒洛芬(suprofen)、琥保松(suxibuzone)、特罗佩星(tropesin)、希莫洛芬(ximoprofen)、扎托洛芬(zaltoprofen)、齐留通(zileuton)以及佐美酸(zomepirac)，以及其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0112] 适合用于本文所描述的装置(例如，包括外壳和多孔硅基载体粒子的装置)的碳酸酐酶抑制剂包括布林唑胺(brinzolamide)、乙酰唑胺、醋甲唑胺、双氯非那胺(dichlorphenamide)、依索唑胺(ethoxzolamide)以及多佐胺(dorzolamide)，以及其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0113] 适合用于本文所描述的装置(例如包括外壳和多孔硅基载体粒子的装置)

的肾上腺素能剂包括溴莫尼定(brimonidine)、阿可乐定(apraclonidine)、布那唑嗪(bunazosin)、左旋倍他洛尔(levobetaxolol)、左旋布那洛尔(levobunalol)、卡替洛尔(carteolol)、异丙肾上腺素(isoprenaline)、非诺特罗(fenoterol)、美替洛尔(metipranolol)以及克仑特罗(clenbuterol),以及其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0114] 适合用于本文所描述的装置(例如,包括外壳和多孔硅基载体粒子的装置)的α受体激动剂包括溴莫尼定和其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0115] 适合用于本文所描述的装置(例如,包括外壳和多孔硅基载体粒子的装置)的β受体拮抗剂包括阿替洛尔(atenolol)、倍他洛尔(betaxolol)以及噻吗洛尔(timolol),以及其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0116] 适合用于本文所描述的装置(例如,包括外壳和多孔硅基载体粒子的装置)的抗病毒剂包括奈韦拉平(nevirapine)和其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0117] 适合用于本文所描述的装置(例如,包括外壳和多孔硅基载体粒子的装置)的生物碱止痛剂包括地斯吗啡(desmorphine)、地佐辛(dezocine)、二氢吗啡、依他佐辛(eptazocine)、乙基吗啡、格拉非宁(glafenine)、氢吗啡酮(hydromorphone)、依索多尔(isoladol)、凯托尼酮(ketobenidone)、对乳非肽(p-lactophetide)、左啡诺(levorphanol)、莫普辛诺(moptazinol)、美他佐辛(metazocin)、美托酮(metopon)、吗啡、纳布啡(nalbuphine)、纳美芬(nalmefene)、烯丙吗啡(nalorphine)、纳洛酮(naloxone)、去甲左啡诺(norlevorphanol)、去甲吗啡(normorphine)、羟吗啡酮(oxmorphone)、喷他佐辛(pentazocine)、菲派利定(phenperidine)、苯基拉米多(phenylramidol)、曲马多(tramadol)以及维米诺(viminol),以及其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0118] 适合用于本文所描述的装置(例如,包括外壳和多孔硅基载体粒子的装置)的糖皮质激素包括21-乙酰氧基孕烯醇酮、阿氯米松(alclometasone)、阿尔孕酮(algestone)、乙酸阿奈可他(anacortave acetate)、安西奈德(amcinonide)、倍氯米松(beclomethasone)、倍他米松(betamethasone)、布地奈德(budesonide)、氯泼尼松(chloroprednisone)、氯倍他索(clobetasol)、氯倍他松(clobetasone)、氯可托龙(clocortolone)、氯泼尼醇(cloprednol)、皮质甾酮、可的松(cortisone)、可的伐唑(cortivazol)、地夫可特(deflazacort)、地奈德(desonide)、去羟米松(desoximetasone)、双氟拉松(diflorasone)、双氟可龙(diflucortolone)、二氟孕甾丁酯(difuprednate)、甘草次酸(enoxolone)、氟扎可特(fluazacort)、氟氯奈德(flucloronide)、氟米松(flumethasone)、氟尼缩松(flunisolide)、丙酮化氟新诺龙(fluocinolone acetonide)、氟辛奈德(fluocinonide)、氟氯奈德、氟米松、氟尼缩松、氟考丁酯(fluocortin butyl)、氟考龙(fluocortolone)、氟米龙(fluorometholone)、乙酸氟培龙(fluperolone acetate)、氟泼尼龙(fluprednisolone)、氟氢缩松(flurandrenolide)、丙酸氟替卡松(fluticasonepropionate)、氢可他酯(hydrocortamate)、氢化可的松(hydrocortisone)、甲泼尼松(meprednisone)、甲基泼

尼松龙(methylprednisolone)、帕拉米松(paramethasone)、泼尼松龙(prednisolone)、21-二乙基氨基乙酸泼尼松龙、乙酸氟泼尼定(fluprednidene acetate)、福莫可他(formocortal)、依碳酸氯替泼诺(loteprednol etabonate)、甲羟孕酮(medrysone)、糠酸莫米他松(mometasone furoate)、泼尼卡酯(prednicarbate)、泼尼松龙、25-二乙基氨基乙酸泼尼松龙、泼尼松龙磷酸钠、泼尼松(prednisone)、泼尼松龙戊酸酯(prednival)、泼尼立定(prednylidene)、曲安西龙(triamcinolone)、丙酮化曲安西龙(triamcinolone acetonide)、苯曲安缩松(triamcinolone benetonide)以及已曲安缩松(triamcinolonehexacetonide),以及其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0119] 其它适合用于本文所描述的装置(例如,包括外壳和多孔硅基载体粒子的装置)的类固醇包括哈西奈德(halcinonide)、丙酸哈贝他索(halbetasol propionate)、卤米松(halometasone)、乙酸卤泼尼松(halopredone acetate)、异氟泼尼松(isoflupredone)、依碳酸氯替泼诺、马泼尼酮(mazipredone)、利美索龙(rimexolone)以及替可的松(tixocortol),以及其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0120] 适合用于本文所描述的装置(例如,包括外壳和多孔硅基载体粒子的装置)的BPH药物包括非那雄胺(finasteride)和奥沙特隆(osaterone)以及其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0121] 适合用于本文所描述的装置(例如,包括外壳和多孔硅基载体粒子的装置)的抗肿瘤化合物包括阿霉素(adriamycin)、阿利维甲酸(9-顺-视黄酸);博来霉素(bleomycin),包括博来霉素A;卡培他滨(capecitabine)(5'-脱氧-5-氟-胞啶);卡柔比星(carubicin);氯脲霉素(chlorozotocin)、色霉素(包括色霉素A3)、克拉屈滨(cladribine);秋水仙碱(colchicine)、阿糖胞苷(cytarabine);柔红比星(daunorubicin);地美可辛(demecolcine)、二甲叶酸(denopterin)、多西他赛(docetaxel)、脱氧氟尿苷(doxyifluridine)、阿霉素(doxorubicin);屈他雄酮、依达曲沙(edatrexate)、依诺他滨(enocitabine)、表柔比星(epirubicin)、环硫雄醇(epitiostanol)、雌莫司汀(estramustine);依托泊苷(etoposide);氟尿苷(floxuridine)、氟达拉滨(fludarabine)、5-氟尿嘧啶(5-fluorouracil)、福美司坦(formestane)、吉西他滨(gemcitabine);伊立替康(irinotecan);香菇多糖(lentinan)、氯尼达明(lonidamine)、美仑孕酮(melengestrol)、美法仑(melphalan);美诺立尔(menogaril)、甲氨蝶呤(methotrexate);二溴卫矛醇(mitolactol);诺加霉素(nogalamycin);去甲二氢愈创木酸(nordihydroguaiaretic acid)、橄榄霉素(olivomycin)(诸如橄榄霉素A)、紫杉醇(paclitaxel);喷司他丁(pentostatin);吡柔比星(pirarubicin)、普卡霉素(plicamycin)、泊非霉素(porfiromycin)、泼尼莫司汀(prednimustine)、嘌呤霉素(puromycin);雷莫司汀(ranimustine)、瑞斯西丁(ristocetin)(诸如瑞斯西丁A);替莫唑胺(temozolamide);替尼泊苷(teniposide);托穆戴克斯(tomudex);拓扑替康(topotecan);吐伯尔西丁(tubercidin)、乌贝尼马克斯(ubenimax)、戊柔比星(N-三氟乙酰基阿霉素-14-戊酸酯)、长春瑞滨(vinorelbine)、长春花碱(vinblastine)、长春地辛(vindesine)、长春瑞滨(vinorelbine)以及佐柔比星(zorubicin),以及其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0122] 适合用于本文所描述的装置（例如，包括外壳和多孔硅基载体粒子的装置）的抗细菌化合物包括卷曲霉素 (capreomycin)，包括卷曲霉素 IA、卷曲霉素 IB、卷曲霉素 IIA 以及卷曲霉素 IIB；碳霉素 (carbomycin)，包括碳霉素 A；卡卢莫南 (carumonam)；头孢克洛 (cefaclor)、头孢羟氨苄 (cefadroxil)、头孢孟多 (cefamandole)、头孢曲嗪 (cefatrizine)、头孢西酮 (cefazedone)、头孢唑啉 (cefazolin)、头孢拉宗 (cefbuperazone)、头孢卡品匹酯 (cefcapene pivoxil)、头孢克定 (cefclidin)、头孢地尼 (cefdinir)、头孢妥仑 (cefditoren)、西菲美 (cefime)、头孢他美 (ceftamet)、头孢甲肟 (cefmenoxime)、头孢美唑 (cefmetzole)、头孢米诺 (cefminox)、头孢地嗪 (cefodizime)、头孢尼西 (cefonicid)、头孢哌酮 (cefoperazone)、头孢雷特 (ceforanide)、头孢噻肟 (cefotaxime)、头孢替坦 (cefotetan)、头孢替安 (cefotiam)、头孢西丁 (cefoxitin)、头孢咪唑 (cefpimizole)、头孢匹胺 (cefpiramide)、头孢匹罗 (cefpirome)、头孢罗齐 (cefprozil)、头孢沙定 (cefroxadine)、头孢磺啶 (cefsulodin)、头孢他啶 (ceftazidime)、头孢特仑 (cefteram)、头孢替唑 (ceftezole)、头孢布烯 (ceftibuten)、头孢噻呋 (ceftiofur)、头孢唑肟 (ceftizoxime)、头孢曲松 (ceftriaxone)、头孢呋辛 (cefuroxime)、头孢唑南 (cefuzonam)、头孢氨苄 (cephalexin)、塞发洛吉辛 (cephalogycin)、头孢利定 (cephaloridine)、头孢菌素 C(cephalosporin C)、头孢洛新 (cephalothin)、头孢匹林 (cephapirin)、头孢霉素 (cephamycin)（诸如头孢霉素 C)、头孢拉定 (cephradine)、氯四环素 (chlortetracycline)；克拉霉素 (chlarithromycin)、克林霉素 (clindamycin)、氯甲西林 (clometocillin)、氯莫环素 (clomocycline)、氯唑西林 (cloxacillin)、环己西林 (cyclacillin)、达氟沙星 (danofloxacin)、地美环素 (demeclocyclin)、越霉素 A(destomycin A)、双氯西林 (dicloxacillin)、地红霉素 (dirithromycin)、多西环素 (doxycyclin)、依匹西林 (epicillin)、红霉素 A(erythromycin A)、乙胺丁醇 (ethanbutol)、芬贝西林 (fenbenicillin)、氟氧头孢 (flomoxef)、氟苯尼考 (florfenicol)、氟氯西林 (floxacillin)、氟甲喹 (flumequine)、福提米星 A(fortimicin A)、福提米星 B、磷霉素 (forfomycin)、福拉他酮 (foraltadone)、夫西地酸、庆大霉素 (gentamycin)、葡烟腙 (glyconiazide)、胍甲环素 (guamecycline)、海他西林 (hetacillin)、伊达比星 (idarubicin)、亚胺培南 (imipenem)、异帕米星 (isepamicin)、交沙霉素 (josamycin)、卡那霉素 (kanamycin)、利优霉素 (leumycin)（诸如利优霉素 A1)、林可霉素 (lincomycin)、洛美沙星 (lomefloxacin)、氯碳头孢 (loracarbef)、赖甲四环素 (lymecycline)、美洛培南 (meropenam)、美坦西林 (metampicillin)、美他环素 (methacycline)、甲氧西林 (methicillin)、美洛西林 (mezlocillin)、小诺米星 (micronomicin)、麦地霉素 (midecamycin)（诸如麦迪霉素 A1)、米卡霉素 (mikamycin)、米诺环素 (minocycline)、丝裂霉素 (mitomycin)（诸如丝裂霉素 C)、拉氧头孢 (moxalactam)、莫匹罗星 (mupirocin)、萘夫西林 (nafcillin)、奈替米星 (netilicin)、诺卡地安 (norcardian)（诸如诺卡地安 A)、竹桃霉素 (oleandomycin)、氧四环素 (oxytetracycline)、帕尼培南 (panipenam)、帕珠沙星 (pazufloxacin)、培那西林 (penamecillin)、青霉素 (penicillin)（诸如青霉素 G、青霉素 N 以及青霉素 O)、青霉二酸 (penillic acid)、戊基青霉素、培洛霉素 (peplomycin)、非奈西林 (phenethicillin)、匹哌环素 (pipacyclin)、哌拉西林 (piperacilin)、吡利霉素 (pirlimycin)、匹伐西

林 (pivampicillin)、匹凡乐辛 (pivcefalexin)、泊非霉素、普洛阿林 (propiallin)、喹那西林 (quinacillin)、核糖霉素 (ribostamycin)、利福布汀 (rifabutin)、利福米特 (rifamide)、利福平 (rifampin)、利福霉素 SV(rifamycin SV)、利福喷汀 (rifapentine)、利福昔明 (rifaximin)、利替培南 (ritipenem)、乐他霉素 (rekitamycin)、罗利环素 (rolitetracycline)、罗沙米星 (rosaramicin)、罗红霉素 (roxithromycin)、山环素 (sancycline)、西索米星 (sisomicin)、司帕沙星 (sparfloxacin)、状观霉素 (spectinomycin)、链佐星 (streptozocin)、磺苄西林 (sulbenicillin)、舒他西林 (sultamicillin)、酞氨西林 (talampicillin)、替考拉宁 (teicoplanin)、替莫西林 (temocillin)、四环素 (tetracyclin)、索斯曲酮 (thostrepton)、泰妙菌素 (tiamulin)、替卡西林 (ticarcillin)、替吉莫南 (tigemonam)、替米考星 (tilmicosin)、妥布霉素 (tobramycin)、特罗泊霉素 (tropospectromycin)、曲氟沙星 (trovafloxacin)、泰乐菌素 (tylosin) 以及万古霉素 (vancomycin)，以及其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0123] 适合用于本文所描述的装置（例如，包括外壳和多孔硅基载体粒子的装置）的抗真菌化合物包括氟康唑 (fluconazole) 和其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0124] 适合用于本文所描述的装置（例如，包括外壳和多孔硅基载体粒子的装置）的免疫反应调节剂包括胞壁酰二肽 (muramyl dipeptide) 和其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0125] 适合用于本文所描述的装置（例如，包括外壳和多孔硅基载体粒子的装置）的肽和蛋白质包括胰岛素、生长激素、胰岛素相关生长因子、热激蛋白以及其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0126] 适合用于本文所描述的装置（例如，包括外壳和多孔硅基载体粒子的装置）的麻醉剂和镇痛剂包括利多卡因 (lidocaine)、苯并地西泮 (benzodiazepam) 以及其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0127] 适合用于本文所描述的装置（例如，包括外壳和多孔硅基载体粒子的装置）的细胞运输 / 移动阻碍剂包括细胞松弛素 B 和其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0128] 适合用于本文所描述的装置（例如，包括外壳和多孔硅基载体粒子的装置）的抗增殖 / 抗有丝分裂药物和前药包括天然产物，诸如长春花生物碱（例如，长春花碱、长春新碱 (vincristine) 以及长春瑞滨）、帕西他赛、表鬼臼毒素 (epidipodophyllotoxin)（例如，依托泊苷 (etoposide)、替尼泊苷 (teniposide)）、抗生素（例如，放线菌素 (actinomycin)、柔红比星、阿霉素以及伊达比星）、蒽环类、米托蒽醌 (mitoxantrone)、博来霉素、普卡霉素 (plicamycin)（光辉霉素 (mithramycin)）和丝裂霉素、酶（例如 L- 天冬酰胺酶）；抗血小板前药；抗增殖 / 抗有丝分裂的烷基化前药，诸如氮芥（二氯甲基二乙胺、环磷酰胺和类似物、美法仑、苯丁酸氮芥）、乙烯亚胺和甲基三聚氰胺（六甲基三聚氰胺和硫替派 (thiotepa)）、磺酸烷基酯 - 白消安 (busulfan)、亚硝基脲（卡莫司汀 (carmustine)(BCNU) 和类似物、链佐星）、三氮烯 (triazene)、达卡巴嗪 (dacarbazine)(DTIC)；抗增殖 / 抗有丝分裂的抗代谢物，诸如叶酸类似物（甲氨蝶呤）、嘧啶类似物（氟尿嘧啶、氟尿苷以及阿糖胞苷）、嘌呤

类似物以及相关抑制剂（巯基嘌呤、硫鸟嘌呤、喷司他丁以及2-氯脱氧腺苷（克拉屈滨）；铂配位络合物（顺铂(cisplatin)、卡铂(carboplatin)）、丙卡巴肼(procarbazine)、羟基脲、米托坦(mitotane)、氨鲁米特(aminoglutethimide)；激素（例如雌激素、孕酮）；抗凝剂（例如，肝素、合成肝素盐以及其它凝血酶抑制剂）；溶解纤维蛋白的前药，诸如组织纤溶酶原活化剂、链激酶和尿激酶、阿司匹林(aspirin)、双嘧达莫(dipyridamole)、噻氯匹定(ticlopidine)、氯吡格雷(clopidogrel)、阿昔单抗(abciximab)；抗迁移剂；抗分泌剂（布雷菲德菌素(breveldin)）；消炎剂，诸如皮质类固醇（考的索(cortisol)、可的松、氟氢可的松(fludrocortisone)、氟新诺龙(flucinolone)、泼尼松(prednisone)、泼尼松龙、甲基泼尼松龙、曲安西龙、倍他米松以及地塞米松(dexamethasone)）、NSAID（水杨酸和衍生物、阿司匹林、乙酰胺酚、吲哚以及茚乙酸（吲哚美辛(indomethacin)、舒林酸(sulindac)以及依托度酸(etodalac)）、杂芳基乙酸（托美汀(tolmetin)、双氯芬酸以及酮咯酸）、芳基丙酸（例如布洛芬和衍生物）、邻氨基苯甲酸（甲灭酸(mefenamic acid)和甲氯灭酸(meclofenamic acid)）、烯醇酸（吡罗昔康(piroxicam)、替诺昔康(tenoxicam)、苯基保泰松(phenylbutazone)以及羟苯噻唑酮(oxyphenthatrazone)）、萘丁美酮(nabumetone)、金化合物（金诺芬(auranofin)、金硫葡糖(aurothioglucose)、硫代苹果酸金钠）以及6-甘露糖磷酸酯；免疫抑制剂（例如环孢菌素(cyclosporine)、他克莫司(tacrolimus)(FK-506)、西罗莫司(sirolimus)（雷帕霉素(rapamycin)）、硫唑嘌呤(azathioprine)以及吗替麦考酚酸酯）；血管生成剂，诸如血管内皮细胞生长因子(VEGF)、成纤维细胞生长因子(FGF)；血管紧张素受体阻断剂；氧化氮供体；反义寡核苷酸以及其组合；细胞周期抑制剂、mTOR抑制剂、生长因子信号转导激酶抑制剂、新血管形成抑制剂、血管生成抑制剂以及凋亡抑制剂，以及其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0129] 适合用于本文所描述的装置（例如，包括外壳和多孔硅基载体粒子的装置）的抗病毒剂包括阿昔洛韦(acyclovir)、阿兹尿苷(azidouridine)、茴香霉素(anismoycin)、阿曼他汀(amantadine)、溴乙烯基脱氧尿苷(bromovinyldeoxusidine)、氯乙烯基脱氧尿苷(chlorovinyldeoxusidine)、阿糖胞苷、地拉韦定(delavirdine)、地达诺新(didanosine)、脱氧野尻霉素(deoxynojirimycin)、双脱氧胞苷、双脱氧肌苷、双脱氧核苷、地昔洛韦(desciclovir)、脱氧阿普洛韦、依法韦仑(efavirenz)、恩韦肟(enviroxime)、非西他滨(fiacitabine)、膦甲酸(foscamet)、非阿尿苷(fialuridine)、氟胸苷(fluorothymidine)、氟尿苷(floxuridine)、更昔洛韦(ganciclovir)、金丝桃素(hypericin)、碘尿苷(idoxuridine)、干扰素、白介素、羟乙基磺酸盐、奈韦拉平(nevirapine)、戊烷脒(pentamidine)、病毒唑(ribavirin)、金刚乙胺、司他夫定(stavudine)、沙格莫丁(sargramostin)、苏拉明(suramin)、栝蒌素(trichosanthin)、三溴胸苷、三氯胸苷、三氟胸苷、膦一甲酸三钠(trisodium phosphomonoformate)、阿糖腺苷(vidarabine)、齐多韦定(zidoviridine)、扎西他滨(zalcitabine)以及3-叠氮基-3-脱氧胸苷，以及其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0130] 其它适合用于本文所描述的装置（例如，包括外壳和多孔硅基载体粒子的装置）的抗病毒剂包括2',3'-双脱氧腺苷(ddA)、2',3'-双脱氧鸟苷(ddG)、2',3'-双脱氧胞苷(ddC)、2',3'-双脱氧胸苷(ddT)、2'3'-双脱氧-双脱氧胸苷(d4T)、2'-脱氧-3'-硫杂-胞

嘧啶 (3TC 或拉米夫定)、2',3'- 双脱氧 -2'- 氟腺苷、2',3'- 双脱氧 -2'- 氟肌苷、2',3'- 双脱氧 -2'- 氟胸苷、2',3'- 双脱氧 -2'- 氟胞嘧啶、2'3'- 双脱氧 -2',3'- 双脱氢 -2'- 氟胸苷 (Fd4T)、2'3'- 双脱氧 -2'- β- 氟腺苷 (F-ddA)、2'3'- 双脱氧 -2'- β- 氟 - 肌苷 (F-ddI) 以及 2',3'- 双脱氧 -2'- β- 氟胞嘧啶 (F-ddC)。在一些实施方案中,抗病毒剂选自膦一甲酸三钠、更昔洛韦、三氟胸苷、阿昔洛韦、3'- 叠氮基 -3'- 胸苷 (AZT)、双脱氧肌苷 (ddI) 以及碘尿苷,以及其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式。

[0131] 适合用于使用本文所描述的装置 (例如,包括外壳和多孔硅基载体粒子的装置) 向眼睛和其周围组织施用以产生局部或全身性生理或药理学有益作用的有益物质包括神经保护剂,诸如尼莫地平 (nimodipine) 和相关化合物 ;抗生素,诸如四环素、氯四环素、杆菌肽 (bacitracin)、新霉素 (neomycin)、多粘菌素 (polymyxin)、短杆菌肽 (gramicidin)、氧四环素、氯霉素 (chloramphenicol)、庆大霉素以及红霉素 ;抗细菌剂,诸如磺酰胺、磺乙酰胺、磺胺甲噻二唑以及磺胺异噁唑 ;抗病毒剂,包括碘尿苷 ;以及其它抗细菌剂,诸如硝基糠腙 (nitrofurazone) 和丙酸钠 ;抗过敏剂,诸如安他唑啉 (antazoline)、美他吡林 (methapyriline)、氯芬胺 (chlorpheniramine)、吡拉明 (pyrilamine) 以及苯吡胺 ;消炎剂,诸如氢化可的松、乙酸氢化可的松、21- 磷酸地塞米松、氟新诺龙 (fluocinolone)、甲羟孕酮、甲基泼尼松龙、21- 磷酸泼尼松龙、乙酸氢化泼尼松龙、氟米龙 (fluoromethalone)、倍他米松以及曲安西龙 ;减充血剂,诸如苯肾上腺素、萘唑啉以及四氢唑林 ;缩瞳剂和抗胆碱酯酶,诸如匹鲁卡品 (pilocarpine)、水杨酸毒扁豆碱 (eserine salicylate)、卡巴胆碱 (carbachol)、氟磷酸二异丙酯、碘依可酯以及地美溴铵 ;散瞳剂,诸如硫酸阿托品 (atropine sulfate)、环喷托酯 (cyclopentolate)、后马托品 (homatropine)、东莨菪碱 (scopolamine)、托吡卡胺 (tropicamide)、优卡托品 (eucatropine) 以及羟基安非他明 (hydroxyamphetamine) ;拟交感神经药,诸如肾上腺素 ;以及其类似物、衍生物、药学上可接受的盐、酯、前药以及受保护形式 ;以及前药,诸如描述于 Design of Prodrugs,Hans Bundgaard 编 ,ElsevierScientific Publishing Co.,Amsterdam,1985 中的前药。可参考任何标准药物教科书 (诸如 Remington's Pharmaceutical Sciences) 来识别其它药剂。

[0132] 前药通常是在生理条件下在患者身体中转化成治疗活性剂的化合物。一种用于制备前药的常用方法是包括选定部分 (诸如酯),其在生理条件下水解以将前药转化成活性生物部分。在其它实施方案中,前药是通过宿主动物的酶活性来转化。前药是典型地通过对生物活性部分进行化学修饰来形成。用于选择和制备适合的前药衍生物的常规程序描述在例如 Design of Prodrugs,H.Bundgaard 编 ,Elsevier,1985 中。

[0133] 此类化合物的任何药学上可接受的形式均可用作有益物质,即其游离碱或药学上可接受的盐或酯。举例来说,药学上可接受的盐包括硫酸盐、乳酸盐、乙酸盐、硬脂酸盐、盐酸盐、酒石酸盐、马来酸盐等。

[0134] 2. 制备方法

[0135] 本文所描述的装置可以多种方式制备,其部分描述于以上部分 1 中。在优选方面,装置是通过用载体粒子填充管并且封围管的末端来制备。

[0136] 制备或提供了载体粒子。在一些实施方案中,通过将孔引入非多孔材料中来将载体粒子制成多孔的。举例来说,这可通过将诸如硅等固体阳极化以产生平行孔来完成。在一些实施方案中,阳极化是与蚀刻 (例如,湿式蚀刻或干式蚀刻) 一起进行。因此,在一些

实施方案中，孔是通过电化学蚀刻形成。

[0137] 在一些实施方案中，载体粒子在最初形成时是多孔的。举例来说，在溶胶－凝胶合成中，诱导溶液形成聚合物的多孔网络或凝胶。溶胶－凝胶合成可用于例如制备多孔硅石。多孔硅石可通过用例如镁蒸气处理而化学还原为硅。用于还原硅石的镁蒸气法和相关方法描述于国际申请 WO/2012/114126 中。

[0138] 在一些实施方案中，将大量载体材料中的一部分或全部制成多孔的，并且然后将多孔区域研磨成小粒子。在其它实施方案中，粒子由非多孔材料形成，并且然后将孔引入粒子中。

[0139] 在形成载体粒子时，可使用网筛来选择所需尺寸的粒子。

[0140] 在某些实施方案中，多孔硅基载体材料可通过四氯化硅在氢氧火焰中的火焰水解反应来制备。

[0141] 载体粒子可在粒子组装至装置中之前或之后负载有益物质。

[0142] 可制备或提供一个管。在一些实施方案中，管例如由聚合团块挤出的。可商购获得的挤出机包括 Randcastle 型号 RCP-0250 Microtruder(Randcastle Extrusion Systems,Cedar Grove,N.J.)，以及其相关加热器、控制器等。示例性挤出机还公开于例如美国专利号 5,569,429、5,518,672 以及 5,486,328 中。挤出机可包括形成挤出物质的截面形状的出口孔。在一些实施方案中，在挤出之后将管固化。在一些实施方案中，管是与管内部的载体粒子组合物共挤出。在优选实施方案中，管在不存在载体粒子的情况下形成，并且将载体粒子插入所形成的管。在一些实施方案中，将管分割成多个管状段。分割可使用剪刀、切刀或任何其它技术来进行。

[0143] 将管用载体粒子填充。在一些实施方案中，管是若干多种长度的成品装置，并且管在用载体粒子填充之前或之后被切成适当的长度。在一些实施方案中，当粒子被放在管中时它们是干燥的，并且可具有粉末或颗粒稠密度。在其它实施方案中，当粒子被放在管中时是呈溶液形式，并且可具有浆液稠密度。浆液可例如以毛细管作用抽吸进入或使用注射器推入管中。在优选实施方案中，当载体粒子放在管中时将它们负载有益物质。然而，还可以在此步骤后，例如当粒子在管中但在添加构件以封闭管之前，或甚至在添加一个或两构件之后将粒子负载药物。

[0144] 将第一构件和第二构件添加至管的第一和第二末端以封围粒子。在一些实施方案中，构件中的一个或两个是在管的末端原位形成。可将一定量的聚合物溶液施加至管的末端。举例来说，可将管的一个末端浸入聚合物溶液中一次或多次，使得将在管的末端上形成聚合物膜。或者，可通过滴涂、喷涂、刷涂或其它手段将聚合物溶液施加至管的末端。一旦聚合物与管接触，聚合物即可在管的末端固化（因交联而变硬）。可例如使用热量、辐射、光（包括紫外光或可见光，诸如蓝光）、蒸发以及催化来固化聚合物。用可见或近可见区（例如紫外线或蓝光波长）的光固化有时避免了可能由恶劣固化技术引起的有益物质的失活。在一些实施方案中，固化是使用强光源（诸如调谐激光等）进行。各聚合物可使用一种或多种适合的固化技术来固化，并且许多实例是本领域中已知的。举例来说，PVA 可用（例如）紫外光、红外光和／或通过将其在烘箱中加热来固化。在某些实施方案中，通过施加多于一个聚合物涂层可获得所需厚度的第一或第二构件。各涂层可在施加下一涂层之前干燥和／或固化。

[0145] 在某些实施方案中，装置外壳包含热固化的 PVA。特别地，热固化的第一构件和 / 或第二构件可通过施加 PVA 溶液至管的第一末端并且然后加热 PVA 来形成。PVA 可例如在 60-120℃（例如 80℃）范围内的温度下加热至少 2 小时，优选至少 4 小时，例如 5 小时。加热可例如在烘箱或其它加热元件中进行。

[0146] 在一些实施方案中，对装置和 / 或装置的组件进行灭菌。装置的耐热部分可例如通过热压处理进行加热灭菌。对装置或其组件灭菌的其它方法包括用辐射、紫外光、浸入乙醇或过滤进行灭菌。在一些实施方案中，热敏组件（诸如有益物质，包括生物分子）是过滤灭菌。在某些实施方案中，装置或其组件的所有加热灭菌均在将热敏组件添加至装置中之前进行。举例来说，可将粒子和 / 或外壳在将有益物质添加至装置中之前进行加热灭菌。

[0147] 可将装置包装起来，诸如通过将适当规格的针预负载装置并且将组件封闭在适合的包装中以便运送给最终用户。

[0148] 3. 使用方法

[0149] 本公开提供用于治疗患者以获得所需局部或全身性生理或药理学作用的方法。这些方法包括向患者施用所公开的装置并且使有益物质穿过装置从而与患者直接接触。可将装置施用足够的时间并且在允许治疗相关疾病病况的条件下施用。在某些实施方案中，患者是哺乳动物有机体，并且在优选实施方案中，患者是人。

[0150] 在某些实施方案中，将装置插入患者身体中的所需位置。举例来说，可将装置注入或手术植入患者身体中。当有益物质作用于眼睛时，装置可逐渐释放有益物质至眼睛中，从而避免有益物质的不同制剂的令人痛苦的重复施用。因此，可将装置手术植入患者的眼睛，例如眼睛的玻璃体、视网膜下方以及巩膜上。还可以将装置插入体内的许多其它位置，包括皮下施用、肌肉内施用、腹膜内施用、鼻内施用、经皮肤施用、施用至脑中（包括颅内和硬膜内）、施用至关节（包括踝、膝、髋、肩、肘、腕）中、直接施用至肿瘤中等。还可以经口施用装置。

[0151] 在一些实施方案中，装置是通过注射向患者施用。注射可使用例如标准规格皮下注射针，诸如约 30 号至约 12 号针，或内径从约 0.0055 英寸变化到约 0.0850 英寸的针。可注射装置还可以通过例如关节镜、导管或其它医疗装置来施用。

[0152] 对于定位药物递送，可将装置手术植入作用位点处或其附近。如本文所描述的装置用于治疗例如眼部病状、原发性肿瘤、风湿和关节炎病状以及慢性疼痛就是这种情况。

[0153] 对于全身性缓解，可将装置例如皮下、肌肉内、动脉内、鞘内或腹膜内植入。当装置要给出持续全身性水平并且避免过早代谢时就是这种情况。此外，装置可经口施用。

[0154] 本文所描述的装置可特别适合用于治疗眼部病状，诸如青光眼、增殖性玻璃体视网膜病变、黄斑水肿（包括糖尿病性黄斑水肿）、年龄相关性黄斑变性、糖尿病性视网膜病变、葡萄膜炎、眼部新血管形成以及眼部感染。装置还可以特别适合在治疗罹患眼部组织胞浆菌病的患者（人与兽医用途）时用作眼部装置，其中装置可以是手术植入眼睛的玻璃体内。

[0155] 在某些实施方案中，装置可含有降低母亲到儿童的病毒感染传播的风险的一种或多种药物。病毒感染的实例包括 HIV、鲍温样丘疹病 (Bowenoid Papulosis)、水痘、儿童期 HIV 疾病、人牛痘、丙型肝炎、登革热 (Dengue)、肠道病毒、疣状表皮发育不良、传染性红斑（第五病 (Fifth Disease)）、布施克 - 罗文斯二氏巨大尖锐湿疣 (Giant Condylomata

Acuminata of Buschke and Lowenstein)、手足口病 (Hand-Foot-and-Mouth Disease)、单纯性疱疹、疱疹病毒 6、带状疱疹、卡波西水痘样疹 (Kaposi Varicelliform Eruption)、麻疹、挤奶者结节 (Milker's Nodules)、接触传染性软疣、猴痘、羊痘 (Orf)、婴儿玫瑰疹、风疹、天花、病毒性出血热、生殖器疣以及非生殖器疣。

[0156] 在某些实施方案中,装置可含有抑制或降低 HIV 感染或对 HIV 感染的敏感性的抗病毒剂。装置可用于治疗感染 HIV 和 AIDS 相关机会性感染 (诸如巨细胞病毒感染、弓形体病、卡氏肺孢子虫 (pneumocystis carinii) 以及胞内鸟分枝杆菌) 的哺乳动物有机体。

[0157] 在一些实施方案中,装置含有治疗肺动脉高压的一种或多种药物。

[0158] 在某些实施方案中,装置可用于提供在获得至少与以下方面相关的所需局部或全身性生理或药理学作用中有效的试剂的控制和持续释放 :治疗癌症原发性肿瘤 (例如,成胶质细胞瘤);抑制新血管形成,包括眼部新血管形成 ;水肿,包括眼水肿 ;炎症,包括眼部炎症 ;慢性疼痛 ;关节炎 ;风湿性病状 ;激素缺乏,诸如糖尿病和侏儒症 ;以及调节免疫反应,诸如在预防移植排斥中和在癌症治疗中。使用本文的递送装置还可以预防或治疗多种其它疾病病况。此类疾病病况是本领域一般技术人员已知的。不擅长本领域技术者可参考 Goodman 和 Gilman,The Pharmacological Basis of Therapeutics, 第 8 版 ,Pergamon Press,NY,1990 ;以及 Remington's Pharmaceutical Sciences, 第 18 版,Mack Publishing Co.,Easton,Pa.,1990 ;这两个参考文献均以引用的方式并入本文中。

[0159] 在一些实施方案中,装置 (例如,包括封围多孔硅基载体粒子的外壳的装置) 向眼睛中递送更昔洛韦,用于治疗巨细胞病毒性 (CMV) 视网膜炎。在某些实施方案中,装置 (例如,包括封围多孔硅基载体粒子的外壳的装置) 向眼睛中递送氟新诺龙曲安奈德,用于治疗眼部新血管形成、黄斑水肿、湿性或干性年龄相关性黄斑变性、视网膜静脉阻塞或后葡萄膜炎。在一些实施方案中,装置 (例如,包括封围多孔硅基载体粒子的外壳的装置) 递送贝伐单抗或雷珠单抗,用于治疗新血管形成,包括眼部新血管形成 (例如当由癌症引起时)、黄斑变性 (尤其是年龄相关性黄斑变性)、糖尿病性视网膜病变、新生血管性青光眼、黄斑水肿或视网膜病变。在一些实施方案中,装置 (例如,包括封围多孔硅基载体粒子的外壳的装置) 向眼睛中递送拉坦前列素,用于治疗高眼压和 / 或青光眼。

[0160] 本文的装置当浸没于模拟体液时或当向患者施用时可历经持续时间段释放有益物质。举例来说,装置可释放有效量的有益物质持续 1 周 -1 年、2 周 -1 年、1 个月 -1 年、2 个月 -1 年、3 个月 -1 年或 6 个月 -1 年。在一些实施方案中,装置释放有效量的有益物质持续 1 个月 -2 年、2 个月 -2 年、3 个月 -2 年或 6 个月 -2 年。

[0161] 现在大体上描述了本发明,参考以下实施例将更容易理解,所述实施例仅仅出于说明本发明的某些方面和实施方案的目的而被包括,而不旨在限制本发明。举例来说,本文所公开的特定装置、有益物质以及实验设计代表用于验证适当功能的示例性工具和方法。因此,将容易清楚的是所公开的具体装置、有益物质以及实验计划中的任一者均可在本公开范围内被取代。

实施例

[0162] 实施例 1 :制备硅粒子的方法

[0163] 从通过将 5-20 莫姆厘米 (mohm cm) 电阻率的硅晶片阳极化所制造的膜汇集约

5mm^{2}的中孔硅薄片。电解质组合物是40％氢氟酸与甲醇的固定掺合物（以体积计1:1)。将薄片在乙醇－水混合物中充分洗涤，干燥，并且然后进行一系列转子研磨和喷射研磨以产生具有规定尺寸分布的粉末，然后在空气中在800℃下热氧化3小时。然后，通过以小批量大小进行筛分或以更大批量大小下进行的沉降技术来实现最终目标尺寸分布（d10在1-5微米范围内，d50在5-10微米范围内，并且d90在10-20微米范围内）。

[0164] 实施例2：气相硅石情况下的释放型态

[0165] 将预成形聚酰亚胺管以1:1(w:w)比率负载拉坦前列素和气相硅石粒子(Cab-O-Sil)的混合物。将管切成期望的长度，并将管的一个末端用硅酮密封，将另一末端用聚乙烯醇密封。将管在37℃下浸没于PBS中70天。每天更换PBS，并且通过HPLC定量测量拉坦前列素释放（图6)。

[0166] 实施例3：阳极化硅情况下的释放型态

[0167] 将预成形聚酰亚胺管以1:1(w:w)比率负载拉坦前列素和氧化的阳极化硅粒子的混合物。将管切成期望的长度，并将管的一个末端用硅酮密封，将另一末端用聚乙烯醇密封。将管在37℃下浸没于PBS中30天。每天更换PBS，并且通过HPLC定量测量拉坦前列素释放（图7)。

[0168] 等效物

[0169] 本领域技术人员将认可，或仅仅使用常规实验就能够确定本文所描述的化合物和其使用方法的许多等效物。此类等效物被视为在本发明范围内并且由以下权利要求书覆盖。本领域技术人员还将认识到本文所描述的实施方案的所有组合均在本发明范围内。

[0170] 虽然上文所描述的实施方案在一些情况下是根据优选特征（例如，优选范围的有效药剂量和优选厚度的优选层）的进行描述，但这些优选项决不意在限制本发明。如本领域技术人员将容易理解，优选特征取决于施用方法、所用有益物质、所用外壳和载体材料、所需释放速率等。同样地，实际释放速率和释放持续时间取决于除以上各项以外的多种因素，诸如正在治疗的疾病病况、患者的年龄和病状、施用途径以及本领域技术人员将容易显而易知的其它因素。

[0171] 所有前述美国专利和其它公布各自明确地以全文引用的方式并入本文中。

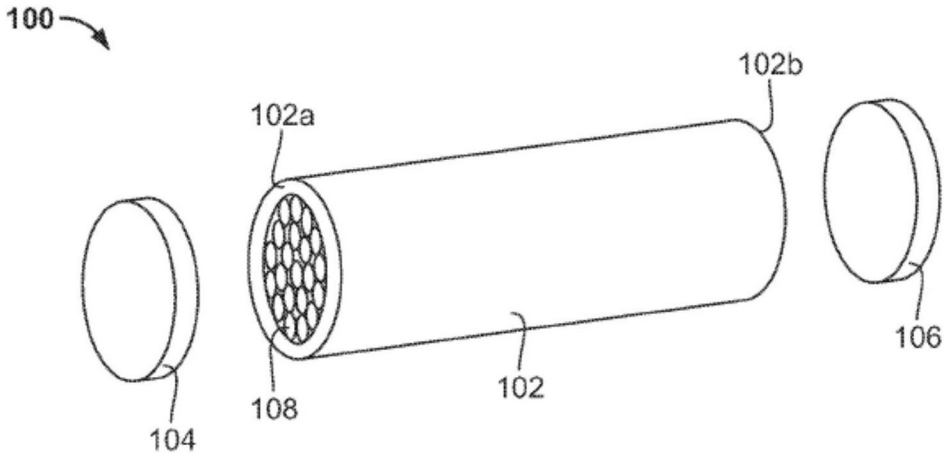
100
102b
102a
106
104
108
102

图 1

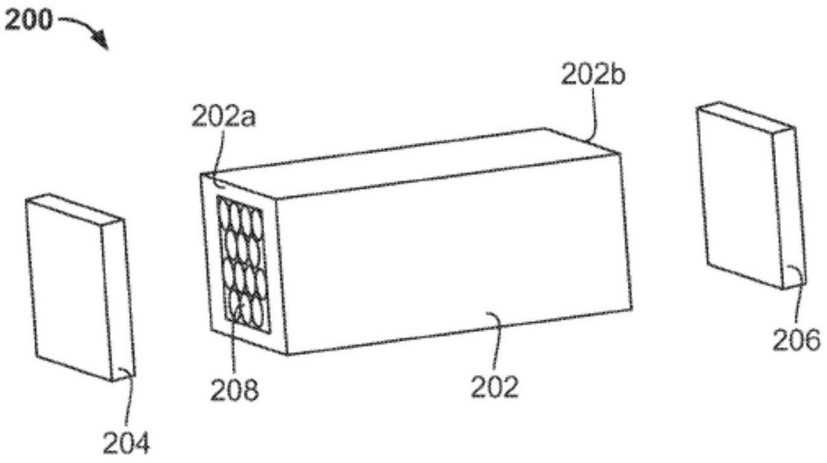
200
202b
202a
206
204
208
202

图 2

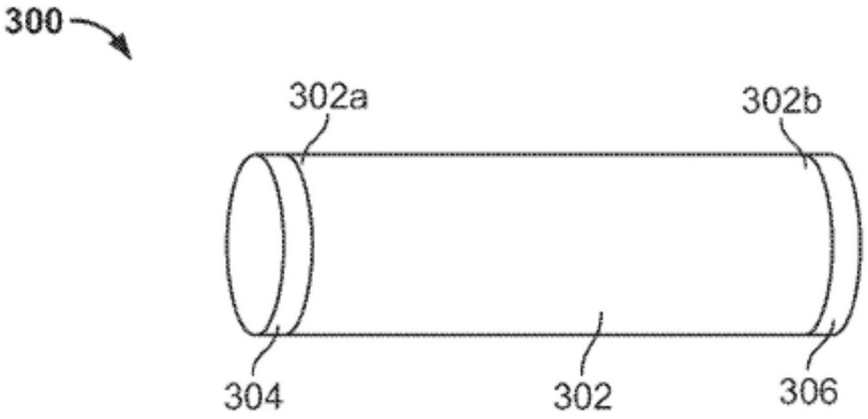
300
302a
302b
304
302
306

图 3

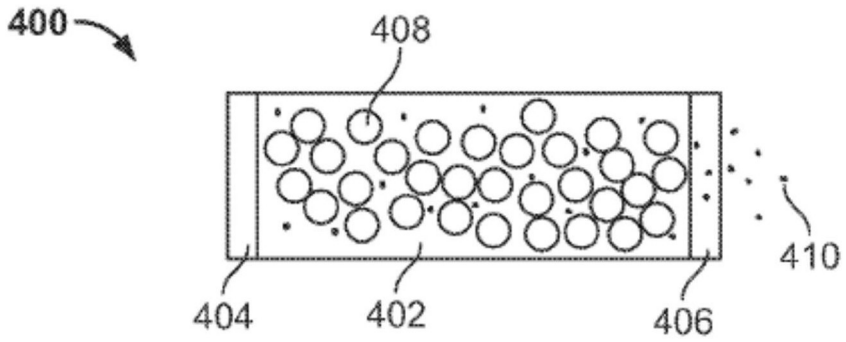
400
408
410
404
402
406

图 4

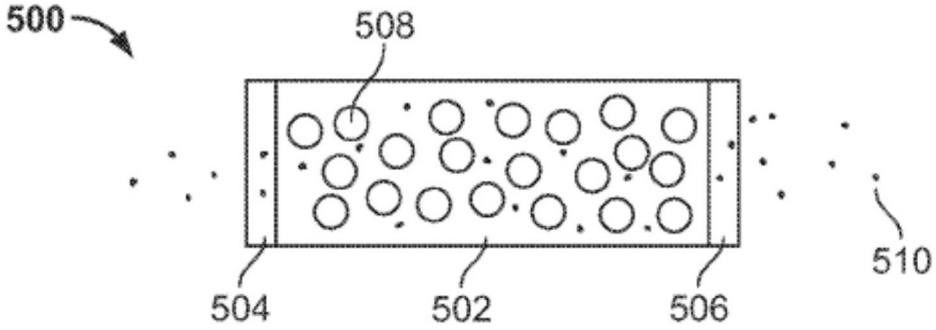
500
508
510
504
502
506

图 5

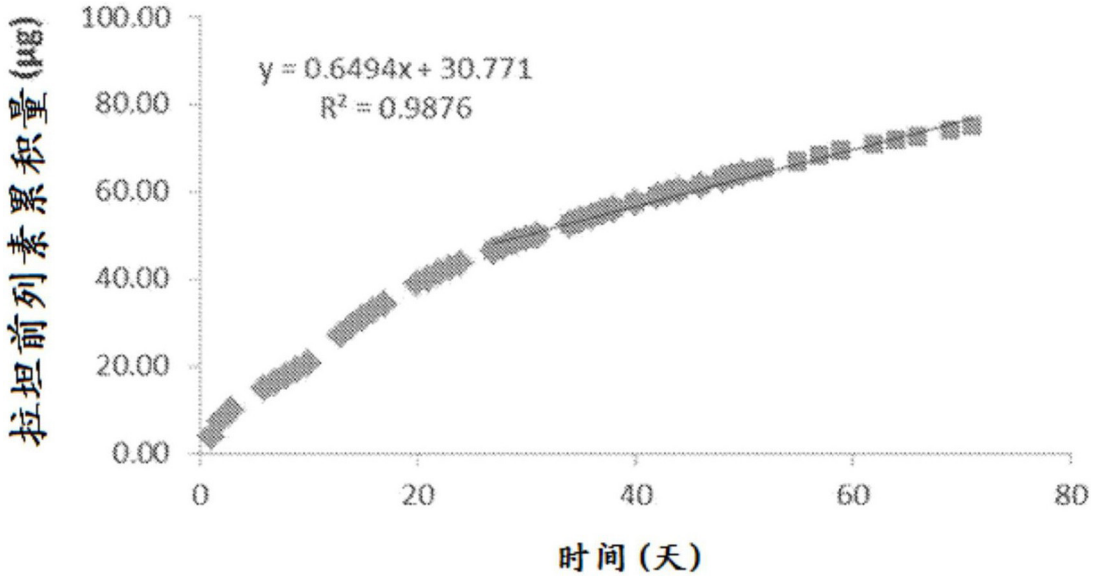
拉坦前列素累积量(μg)
100.00
80.00
60.00
40.00
20.00
0.00
y = 0.6494x + 30.771
R² = 0.9876
0
20
40
60
80
时间(天)

图 6

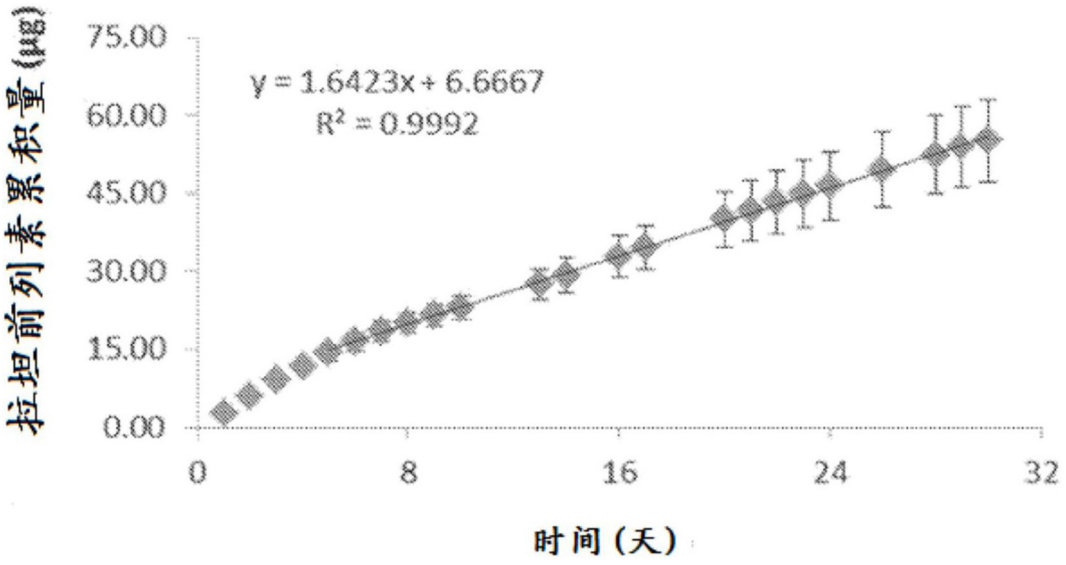
拉坦前列素累积量(μg)
75.00
60.00
45.00
30.00
15.00
0.00
y = 1.6423x + 6.6667
R² = 0.9992
0
8
16
24
32
时间(天)

图 7