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(54) **Title**: COMPOSITIONS AND METHODS FOR DELIVERING A BIO-ACTIVE AGENT OR BIO-ACTIVE AGENTS

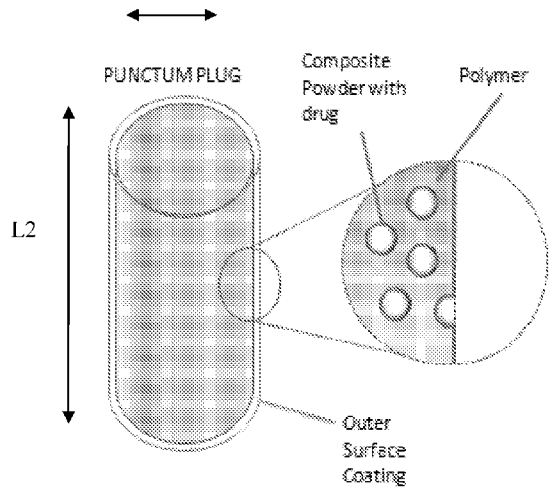


FIGURE 1A

(57) **Abstract**: In some embodiments, the present invention is a composition, including: a bulking agent, where the bulking agent is a kaolin, an absorbent material, where the absorbent material is a fumed silica, a binder, where the binder is an epoxy, and a first active agent, where the first active agent is Latanoprost.

COMPOSITIONS AND METHODS FOR DELIVERING A BIO-ACTIVE AGENT OR BIO-ACTIVE AGENTS

RELATED APPLICATIONS

[0001] This application claims the priority of U.S. provisional application U.S. Patent Appln. No. 62/084,387; filed November 25, 2014; entitled "COMPOSITIONS AND METHODS FOR DELIVERING A BIO-ACTIVE AGENT OR BIO-ACTIVE AGENTS," which is incorporated herein by reference in its entirety for all purposes.

TECHNICAL FIELD

[0002] In some embodiments, the instant invention is related to compositions and methods for delivering a bio-active agent or bio-active agents.

BACKGROUND

[0003] Glaucoma is the most frequent cause for irreversible and preventable blindness worldwide. About two percent of the population over 40 years of age suffers from glaucoma. The major risk factor and only treatable factor in glaucoma is increased intraocular pressure. While glaucoma is incurable, treatment can slow or arrest the progressive vision loss.

SUMMARY OF INVENTION

[0004] In some embodiments, the composition of the present invention is a drug-delivery device comprising: a) a composite comprising the following elements: (i) particles of inert materials, where the inert materials are adsorbed with drug on surface of particles (e.g., drug bound to particles) or inside porosity (e.g., drug housed within pores); (ii) a bulking agent; (iii) an adhesive binder; or any combination thereof, and b) an optional coating on the whole or partial outer surface of the

body/core; where the coating is complete/continuous or perforated, e.g., but not limited to, where the coating can be butvar and/or parylene.

[0005] In some embodiments, the present invention is a composition, including: a bulking agent including a kaolin and/or a pectin, an absorbent material including a fumed silica, a binder including an epoxy, and a first active agent including Latanoprost. In some embodiments, the first active agent measures between 5-50% by weight (w/w). In some embodiments, the first active agent measures between 5-45% by weight (w/w). In some embodiments, the first active agent measures between 5-40% by weight (w/w). In some embodiments, the first active agent measures between 5-35% by weight (w/w). In some embodiments, the first active agent measures between 5-30% by weight (w/w). In some embodiments, the first active agent measures between 5-25% by weight (w/w). In some embodiments, the first active agent measures between 5-20% by weight (w/w). In some embodiments, the first active agent measures between 5-15% by weight (w/w). In some embodiments, the first active agent measures between 5-10% by weight (w/w). In some embodiments, the first active agent measures between 10-50% by weight (w/w). In some embodiments, the first active agent measures between 15-50% by weight (w/w). In some embodiments, the first active agent measures between 20-50% by weight (w/w). In some embodiments, the first active agent measures between 25-50% by weight (w/w). In some embodiments, the first active agent measures between 30-50% by weight (w/w). In some embodiments, the first active agent measures between 35-50% by weight (w/w). In some embodiments, the first active agent measures between 40-50% by weight (w/w). In some embodiments, the first active agent measures between 45-50% by weight (w/w). In some embodiments, the first active agent measures between 10-45% by weight (w/w). In some embodiments, the first active agent

measures between 15-40% by weight (w/w). In some embodiments, the first active agent measures between 20-35% by weight (w/w). In some embodiments, the first active agent measures between 20-30% by weight (w/w). In some embodiments, the compound further includes a second active agent. In some embodiments, the second active agent is Timolol. In some embodiments, the second active agent measures between 5-40% by weight (w/w). In some embodiments, the second active agent measures between 5-35% by weight (w/w). In some embodiments, the second active agent measures between 5-30% by weight (w/w). In some embodiments, the second active agent measures between 5-25% by weight (w/w). In some embodiments, the second active agent measures between 5-20% by weight (w/w). In some embodiments, the second active agent measures between 5-15% by weight (w/w). In some embodiments, the second active agent measures between 5-10% by weight (w/w). In some embodiments, the second active agent measures between 10-40% by weight (w/w). In some embodiments, the second active agent measures between 15-40% by weight (w/w). In some embodiments, the second active agent measures between 20-40% by weight (w/w). In some embodiments, the second active agent measures between 25-40% by weight (w/w). In some embodiments, the second active agent measures between 30-40% by weight (w/w). In some embodiments, the second active agent measures between 35-40% by weight (w/w). In some embodiments, the second active agent measures between 10-35% by weight (w/w). In some embodiments, the second active agent measures between 15-30% by weight (w/w). In some embodiments, the second active agent measures between 20-25% by weight (w/w). In some embodiments, the composition further includes polyurethane. In some embodiments, the composition further includes a parylene coating. In some embodiments, the parylene coating measures between 2-5 micrometers (e.g., but not

limited to, 2.1 micrometers, 2.2 micrometers, etc.) in thickness. In some embodiments, the composition includes a butvar coating. In some embodiments, the butvar coating measures between 2-5 micrometers (e.g., but not limited to, 2.1 micrometers, 2.2 micrometers, etc.) in thickness. In some embodiments, the composition is in the form of a punctal plug.

[0006] In some embodiments, the present invention is a method, including: administering a composition to an eye of a mammal in need thereof, where the composition releases between 0.5-10 micrograms of a first active agent per day, and where the composition includes: a bulking agent including a kaolin, an absorbent material including a fumed silica, a binder including an epoxy, and the first active agent includes Latanoprost. In some embodiments, the first active agent measures between 5-50% by weight (w/w). In some embodiments, the first active agent measures between 5-45% by weight (w/w). In some embodiments, the first active agent measures between 5-40% by weight (w/w). In some embodiments, the first active agent measures between 5-35% by weight (w/w). In some embodiments, the first active agent measures between 5-30% by weight (w/w). In some embodiments, the first active agent measures between 5-25% by weight (w/w). In some embodiments, the first active agent measures between 5-20% by weight (w/w). In some embodiments, the first active agent measures between 5-15% by weight (w/w). In some embodiments, the first active agent measures between 5-10% by weight (w/w). In some embodiments, the first active agent measures between 10-50% by weight (w/w). In some embodiments, the first active agent measures between 15-50% by weight (w/w). In some embodiments, the first active agent measures between 20-50% by weight (w/w). In some embodiments, the first active agent measures between 25-50% by weight (w/w). In some embodiments, the first active agent measures

between 30-50% by weight (w/w). In some embodiments, the first active agent measures between 35-50% by weight (w/w). In some embodiments, the first active agent measures between 40-50% by weight (w/w). In some embodiments, the first active agent measures between 45-50% by weight (w/w). In some embodiments, the first active agent measures between 10-35% by weight (w/w). In some embodiments, the first active agent measures between 10-45% by weight (w/w). In some embodiments, the first active agent measures between 15-40% by weight (w/w). In some embodiments, the first active agent measures between 20-35% by weight (w/w). In some embodiments, the first active agent measures between 25-30% by weight (w/w). In some embodiments, the method includes a second active agent. In some embodiments, the second active agent is Timolol. In some embodiments, the second active agent includes between 5-40% by weight (w/w). In some embodiments, the second active agent measures between 5-35% by weight (w/w). In some embodiments, the second active agent measures between 5-30% by weight (w/w). In some embodiments, the second active agent measures between 5-25% by weight (w/w). In some embodiments, the second active agent measures between 5-20% by weight (w/w). In some embodiments, the second active agent measures between 5-15% by weight (w/w). In some embodiments, the second active agent measures between 5-10% by weight (w/w). In some embodiments, the second active agent measures between 10-40% by weight (w/w). In some embodiments, the second active agent measures between 15-40% by weight (w/w). In some embodiments, the second active agent measures between 20-40% by weight (w/w). In some embodiments, the second active agent measures between 25-40% by weight (w/w). In some embodiments, the second active agent measures between 30-40% by weight (w/w). In some embodiments, the second active agent measures between 35-40% by weight

(w/w). In some embodiments, the second active agent measures between 10-35% by weight (w/w). In some embodiments, the second active agent measures between 15-30% by weight (w/w). In some embodiments, the second active agent measures between 20-25% by weight (w/w). In some embodiments, the method includes a parylene coating. In some embodiments, the parylene coating measures between 2-5 micrometers (e.g., but not limited to, 2.1 micrometers, 2.2 micrometers, etc.) in thickness. In some embodiments, the composition includes a butvar coating. In some embodiments, the butvar coating measures between 2-5 micrometers (e.g., but not limited to, 2.1 micrometers, 2.2 micrometers, etc.) in thickness. In some embodiments, the composition is in the form of a punctal plug.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] The present invention will be further explained with reference to the attached drawings, wherein like structures are referred to by like numerals throughout the several views. The drawings shown are not necessarily to scale, with emphasis instead generally being placed upon illustrating the principles of the present invention. Further, some features may be exaggerated to show details of particular components.

[0008] Figures 1A-C illustrate embodiments of the composition of the present invention, showing various plugs.

[0009] Figures 2A and B illustrate embodiments of the process for generating the composition of the present invention.

[00010] Figure 3 illustrates an embodiment of the composition of the present invention, showing a release profile.

[00011] Figures 4 and 5 illustrate embodiments of placement of the compositions of the present invention. Figures 6 and 7 illustrate embodiments of applicators for placing the compositions of the present invention in an eye.

[00012] Figure 8 is a schematic depiction of liquid at the surface of a non-porous particle (left) and of liquid absorbed in the pores of fumed silica (right).

[00013] Figure 9 illustrates a calibration curve of an embodiment of the composition of the present invention.

[00014] Figure 10 illustrates a chromatogram of a standard solution.

[00015] Figure 11 illustrates a chromatogram of an embodiment of the composition of the present invention.

[00016] Figure 12 illustrates a chromatogram of an embodiment of the composition of the present invention.

[00017] Figures 13 and 14A-14B illustrate a typical chromatogram of a standard solution.

[00018] Figure 15 illustrates a signal to noise ratio of an embodiment of the composition of the present invention.

[00019] Figure 16 illustrates a signal to noise ratio of an embodiment of the composition of the present invention.

[00020] Figures 17, 18, 19A-B illustrate chromatograms of embodiments of the compositions of the present invention.

[00021] Figure 20 illustrates an embodiment of the method of the present invention.

[00022] Figures 21 and 22 illustrate graphs of release profiles of embodiments of the composition of the present invention.

[00023] Figures 23-27 illustrate graphs of release profiles of embodiments of the composition of the present invention.

[00024] Figures 28A and 28B are photographs of embodiments of the composition of the present invention.

[00025] Figure 29 is a photograph of a composite sample of an embodiment of the composition of the present invention.

[00026] Figure 30 illustrates desiccators used while generating embodiments of the compositions of the present invention.

[00027] In addition, any measurements, specifications and the like shown in the figures are intended to be illustrative, and not restrictive. Therefore, specific structural and functional details disclosed herein are not to be interpreted as limiting, but merely as a representative basis for teaching one skilled in the art to variously employ the present invention.

DESCRIPTION OF EXEMPLARY EMBODIMENTS

[00028] The figures constitute a part of this specification and include illustrative embodiments of the present invention and illustrate various objects and features thereof. Further, the figures are not necessarily to scale, some features may be exaggerated to show details of particular components. In addition, any measurements, specifications and the like shown in the figures are intended to be illustrative, and not restrictive. Therefore, specific structural and functional details disclosed herein are not to be interpreted as limiting, but merely as a representative basis for teaching one skilled in the art to variously employ the present invention.

[00029] Among those benefits and improvements that have been disclosed, other objects and advantages of this invention will become apparent from the following description taken in conjunction with the accompanying figures. Detailed embodiments of the present invention are disclosed herein; however, it is to be understood that the disclosed embodiments are merely illustrative of the invention that may be embodied in various forms. In addition, each of the examples given in connection with the various embodiments of the invention which are intended to be illustrative, and not restrictive.

[00030] Throughout the specification and claims, the following terms take the meanings explicitly associated herein, unless the context clearly dictates otherwise. The phrases "in one embodiment" and "in some embodiments" as used herein do not necessarily refer to the same embodiment(s), though it may. Furthermore, the phrases "in another embodiment" and "in some other embodiments" as used herein do not necessarily refer to a different embodiment, although it may. Thus, as described below, various embodiments of the invention may be readily combined, without departing from the scope or spirit of the invention.

[00031] In addition, as used herein, the term "or" is an inclusive "or" operator, and is equivalent to the term "and/or," unless the context clearly dictates otherwise. The term "based on" is not exclusive and allows for being based on additional factors not described, unless the context clearly dictates otherwise. In addition, throughout the specification, the meaning of "a," "an," and "the" include plural references. The meaning of "in" includes "in" and "on."

[00032] The present invention relates generally to the field of medicine combining drug in a device, for administering a bio-active agent over a prolonged period of time. More particularly, it concerns implantable ocular devices for the sustained delivery of a therapeutic compound to the eye. Figures 4-6 illustrate the lacrimal duct system of the human eye and embodiments of the compositions of the present invention placed within the lacrimal duct system of the human eye. In an embodiment, the composition of the present invention is placed in an eye by performing the following steps: (1) hold the applicator (where the ridges are on the tube); (2) insert the applicator (big tube) into the puntum; (3) push the bottom of the small tube completely up inside the big tube (this slides the plug out of the applicator and into the punctum); and (4) gently take out both applicator tubes together.

[00033] In an embodiment, Figure 7 illustrates a composition of the present invention. In an embodiment, the composition of the present invention is placed in an eye by performing the following steps: (1) hold the applicator (where the ridges are on the static tube); (2) insert the plug's inserter (metal part) into the punctum; and (3) push the moving plunger completely up with the plug (both the plug and the plunger are moving on the static metal inserter (this slides the plug out of the applicator into the punctum (the plunger remains outside the punctum); gently take out both plunger and holder together.

[00034] In some embodiments, the present invention is a composite device that configured to contain and release an amount of drug per volume. In some embodiments, the device is configured to allow multiple drug loading (e.g., but not limited to, 2 drugs, 3 drugs, 4 drugs, 5 drugs, etc.). In some embodiments, the drug molecules are physically bound to the matrix. In some embodiments, a non-metallic coating provides zero-order or near zero-order drug-release kinetics. In some embodiments, a release profile provides zero-order or near zero-order drug-release kinetics at two different rates; initially higher rate at the first several weeks, and thereafter a lower rate.

[00035] In some embodiments, the composition of the present invention is a drug-delivery device composite shaped into the desired body/shape; whereas the composite comprising of the following: (1) particles of inert materials, having a porous structure, with an increase surface area and low bulk density. Fumed silica, silica gel, activated carbon, activated alumina or zeolite products offer a porous structure with an interconnected capillary network similar to an open cell sponge. Figure 8 is a schematic depiction of liquid at the surface of a non-porous particle (left) and of liquid absorbed in the pores of fumed silica (right).

[00036] The small diameter of the pores leads to high capillary forces that draw the liquid into the particle. This physical absorption mechanism is independent of the chemical characteristics of the liquid; therefore both polar as well as non-polar liquids can be absorbed. For instance, in Fumed Silica the surface area is 10-600 m2/gr, in silica gel it is around 800 m2/gr. Hence, the finished absorbate can contain between 50–75% of the liquid actives with drug on surface of particles or inside porosity, e.g., but not limited to, fumed silica loaded (i.e., bound) with prostaglandin; (2) a bulking agent e.g., but not limited to, kaolin and/or pectin; (3) an adhesive binder, e.g., but not limited to, ceramic adhesive, e.g., but not limited to, epoxy adhesive; (4) a hydrophobic flexible polymer e.g., but not limited to, PU, or any combination thereof. In some embodiments, the physical mechanism of adsorbing liquid actives is passive.

[00037] In some embodiments, the composition of the present invention is a drug-delivery device comprising: a) a composite comprising the following elements: (i) particles of inert materials, where the inert materials are adsorbed with drug on surface of particles (e.g., drug bound to particles) or inside porosity (e.g., drug housed within pores); (ii) a bulking agent; (iii) an adhesive binder; (iv) a hydrophobic flexible polymer; or any combination thereof, and b) an optional coating on the whole or partial outer surface of the body/core; where the coating is complete/continuous or perforated, e.g., but not limited to, where the coating can be butvar and/or parylene.

[00038] In some embodiments, the composition of the present invention includes an ophthalmic drug, where the ophthalmic drug is a prostaglandin analog, beta blocker, Alpha agonist, carbonic anhydrase inhibitor, adenosine agonist, Rho Kinase inhibitor or any combination thereof. In some embodiments, the prostaglandin is cloprostenol, fluprostenol, latanoprost, travoprost, unoprostone, Latanoprostene bunod or any combination thereof. In some embodiments, more than one drug (e.g.,

2, 3, 4, 5, etc.) is loaded into the matrix to be release independently and in parallel whereas each drug is released according to (a) its natural solubility in the external medium and (b) to the barriers whether by the hydrophobic polymer, the external impermeable barrier or both. In some embodiments, the concentration of the prostaglandin in the matrix is between about 1% to about 20% by weight. In some embodiments, the concentration of the prostaglandin in the matrix is between about 10% to about 17% by weight.

[00039] In some embodiments of the composition of the present invention, the concentration of the prostaglandin in the matrix is between about 10% to about 15% by weight. In some embodiments, the concentration of the prostaglandin in the matrix is between about 10% to about 13% by weight. In some embodiments, the concentration of the prostaglandin in the matrix is between about 5% to about 20% by weight. In some embodiments, the concentration of the prostaglandin in the matrix is between about 10% to about 20% by weight. In some embodiments, the concentration of the prostaglandin in the matrix is between about 13% to about 20% by weight. In some embodiments, the concentration of the prostaglandin in the matrix is between about 15% to about 20% by weight.

[00040] In some embodiments, the composition of the present invention is a drug-delivery device comprising: a) a composite comprising the following elements: (i) particles of inert materials, where the inert materials are adsorbed with drug on surface of particles (e.g., drug bound to particles) or inside porosity (e.g., drug housed within pores); (ii) a bulking agent; (iii) an adhesive binder; and b) a optional coating on the whole or partial outer surface of the body/core; where the coating is complete/continuous or perforated, e.g., but not limited to, where the coating can be butvar and/or parylene.

[00041] In some embodiments, the composition of the present invention includes an ophthalmic drug, where the ophthalmic drug is a prostaglandin analog, beta blocker, Alpha agonist, carbonic anhydrase inhibitor, adenosine agonist, Rho Kinase inhibitor or any combination thereof. In some embodiments, the prostaglandin is cloprostenol, fluprostenol, latanoprost, travoprost, unoprostone, Latanoprostene bunod or any combination thereof. In some embodiments, more than one drug (e.g., 2, 3, 4, 5, etc.) is loaded into the matrix to be release independently and in parallel whereas each drug is released according to (a) its natural solubility in the external medium and (b) to the barriers whether by the composite, the external semi-permeable barrier or both. In some embodiments, the concentration of the prostaglandin in the matrix is between about 1% to about 50% by weight. In some embodiments, the concentration of the prostaglandin in the matrix is between about 30% to about 40% by weight.

[00042] In some embodiments of the composition of the present invention, the concentration of the prostaglandin in the matrix is between about 30% to about 40% by weight. In some embodiments, the concentration of the prostaglandin in the matrix is between about 32% to about 38% by weight. In some embodiments, the concentration of the prostaglandin in the matrix is between about 5% to about 40% by weight. In some embodiments, the concentration of the prostaglandin in the matrix is between about 10% to about 40% by weight. In some embodiments, the concentration of the prostaglandin in the matrix is between about 23% to about 40% by weight. In some embodiments, the concentration of the prostaglandin in the matrix is between about 15% to about 40% by weight.

[00043] In some embodiments of the composition of the present invention, the parylene coating is between about 0.3 μm to about 20 μm thick. In some

embodiments, the parylene coating is between about 0.3 μm to about 10 μm thick. In some embodiments, the parylene coating is between about 0.3 μm to about 5 μm thick. In some embodiments, the parylene coating is between about 0.3 μm to about 3 μm thick. In some embodiments, the parylene coating is between about 0.3μm to about 1 μm thick. In some embodiments, the parylene coating is between about 1μm to about 20 μm thick. In some embodiments, the parylene coating is between about 3μm to about 20 μm thick. In some embodiments, the parylene coating is between about 5μm to about 20 μm thick. In some embodiments, the parylene coating is between about 10μm to about 20 μm thick.

[00044] In some embodiments of the composition of the present invention, the butvar coating is between about 1 μm to about 20 μm thick. In some embodiments, the butvar coating is between about 5 μm to about 20 μm thick. In some embodiments, the butvar coating is between about 10 μm to about 20 μm thick. In some embodiments, the butvar coating is between about 15 μm to about 20 μm thick. In some embodiments, the butvar coating is between about 1 μm to about 15 μm thick. In some embodiments, the butvar coating is between about 1 μm to about 10 μm thick. In some embodiments, the butvar coating is between about 1 μm to about 5 μm thick. In some embodiments, the butvar coating is between about 5 μm to about 15 μm thick.

[00045] In some embodiments of the composition of the present invention, the core/body further comprises a canalicular extension attached to the distal tip portion of the core/body, where the canalicular extension is configured for insertion through the punctual aperture and the punctum and positioning in the lacrimal canaliculus. In some embodiments, the canalicular extension has a length L1 and the body has a length L2, wherein the ratio of the length L1 to the length L2 is between about 2:1 to

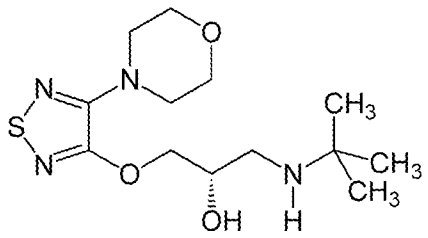
about 10:1. In some embodiments, the ratio of the length L1 to the length L2 is between about 2:1 to about 8:1. In some embodiments, the ratio of the length L1 to the length L2 is between about 2:1 to about 6:1. In some embodiments, the ratio of the length L1 to the length L2 is between about 2:1 to about 4:1. In some embodiments, the ratio of the length L1 to the length L2 is between about 4:1 to about 10:1. In some embodiments, the ratio of the length L1 to the length L2 is between about 6:1 to about 10:1. In some embodiments, the ratio of the length L1 to the length L2 is between about 8:1 to about 10:1.

[00046] In some embodiments of the composition of the present invention, the canalicular extension is configured for positioning in a lacrimal canaliculus and/or a nasolacrimal duct. In some embodiments, a core/body has an outer surface and is configured to be inserted through a punctal aperture and positioned in a punctum or lacrimal canaliculus, wherein the body is a monolithic capsule structure or cylinder shape. In some embodiments, the composition includes a parylene coating or butvar coating covering the outer surface of the body, the parylene coating or butvar coating being substantially impermeable (its surface is impermeable above thicknesses of 1.4 nanometers.) to drug (e.g., a prostaglandin); and at least one pore in the parylene coating or butvar coating pore, wherein the amount and/or size of the pore is configured to release the prostaglandin (e.g., but not limited to, Latanoprost) at a therapeutically effective dose for a period of 1 to 360 days (e.g., 1, 2, 3, 4, 5, etc. days). In some embodiments, the period measures between 1 to 180 days. In some embodiments, the period measures between 1 to 120 days. In some embodiments, the period measures between 1 to 60 days. In some embodiments, the period measures between 1 to 30 days. In some embodiments, the period measures between 30 to 180 days. In some embodiments, the period measures between 60 to 180 days. In some

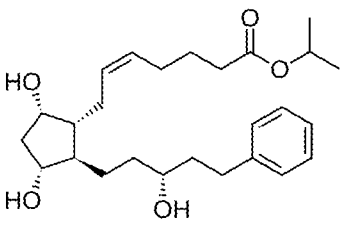
embodiments, the period measures between 90 to 180 days. In some embodiments, the period measures between 120 to 180 days. In some embodiments, the period measures between 30 to 120 days. In some embodiments, the period measures between 60 to 90 days.

[00047] In some embodiments of the composition of the present invention, the beta-adrenergic receptor antagonists can be timolol, levobunolol (Betagan), betaxolol, or any combination thereof.

[00048] In some embodiments, timolol is a non-selective beta-adrenergic receptor antagonist indicated for treating glaucoma, heart attacks, hypertension, and migraine headaches. The chemical structure for timolol is:

[00049] 

[00050] In some embodiments, latanoprost is a medication administered into the eyes of a mammal to control the progression of glaucoma or ocular hypertension by reducing intraocular pressure. It is a prostaglandin analog. The chemical structure for latanoprost is:

[00051] 

[00052] In some embodiments of the composition of the present invention, the Carbonic anhydrase inhibitors can be dorzolamide (Trusopt), ation thereofbrinzolamide (Azopt), acetazolamide (Diamox), or any combination thereof. Examples of agents used for glaucoma inclu β-blockers (e.g., timolol, betaxolol,

levobetaxolol, carteolol, levobunolol, propranolol), carbonic anhydrase inhibitors (e.g., brinzolamide and dorzolamide), α1 antagonists (e.g., nipradolol), α2 agonists (e.g. iopidine and brimonidine), miotics (e.g., pilocarpine and epinephrine), prostaglandin analogs (e.g., latanoprost, travoprost, unoprostone, and compounds set forth in U.S. Pat. Nos. 5,889,052; 5,296,504; 5,422,368; and 5,151,444), "hypotensive lipids" (e.g., bimatoprost and compounds set forth in U.S. Pat. No. 5,352,708), and neuroprotectants (e.g., compounds from U.S. Pat. No. 4,690,931, particularly eliprodil and R-eliprodil, as set forth in a pending application U.S. Ser. No. 60/203,350, and compounds from WO 94/13275, including memantine, where all patents and patent application publications are incorporated herein by reference in their entireties for all purposes. In some embodiments, the composition of the present invention can include Adenosine agonist, Rho Kinase inhibitors and molecules with combined activity such as Latanoparostene Bunod, where a "combined activity" refers to two molecules which are capable of serving two mechanisms of action for reducing intraocular pressure.

[00053] In some embodiments of the composition of the present invention, the concentration of the prostaglandin in the composite is 50% to 60% by weight, where the concentration of the prostaglandin in the final plug is between 10% to 20%.

[00054] The present invention provides a pharmaceutical composition and glaucoma treatment methods. The present invention is a composition in the form of an implant, where the implant is configured to provide for extended release times of one or more therapeutic agents. In some embodiments, the implant is in the shape of a core. In some embodiments, the implant is in the shape of a plug. In some embodiments, the therapeutic agent is a prostaglandin. In some embodiments, the prostaglandin is latanoprost.

[00055] In some embodiments of the composition of the present invention, an implant is configured to release the drug over a period of time, for example, for at least one week or for example for between about two months and about six months, after intraocular administration of a latanoprost containing implant. In some embodiments, the composition further includes timolol. In some embodiments, the period of time is between one month and one year. In some embodiments, the period of time is between one month and nine months. In some embodiments, the period of time is between one month and six months. In some embodiments, the period of time is between one month and three months. In some embodiments, the period of time is between three months and one year. In some embodiments, the period of time is between six months and one year. In some embodiments, the period of time is between nine months and one year. In some embodiments, the period of time is between three months and nine months. In some embodiments, the period of time is between three months and six months. In some embodiments, the period of time is between six months and nine months.

[00056] In an embodiment of the composition of the present invention, a composition is a pharmaceutical composition plug configured to provide an intraocular use, e.g., to treat ocular condition. In some embodiments, the pharmaceutical composition is a plug comprising a solid composite powder, where the solid composite powder is dispersed in at least one soft polymer. In some embodiments, the solid composite powder includes an organic particulate including a bio-active agent, inert carrier, binder, or any combination thereof. In some embodiments of the composition of the present invention, an organic particulate is configured to absorb a drug, i.e., is configured carry the drug (i.e., a drug carrier; e.g., but not limited to, fumed silica). The organic particulate can have a surface area

between 5 to 1000 m^2/gram (fumed silica surface area is 10-600 m2/gr; silica gel around 800 m2/gr; calcium carbonate surface area is 5-24 m2/gr).

[00057] In some embodiments of the composition of the present invention, the bio-active agent can be dissolved, dispersed, emulsified, bound, adsorbed, impregnated, mixed, or otherwise placed into a solid organic matrix. In some embodiments, the bio-active agent may be directly mixed in with the organic matrix. In some embodiments, the bio-active agent may be adsorbed to another material, e.g., a particulate and/or fibrous matter, which can be mixed with the organic matrix.

[00058] In some embodiments of the composition of the present invention, the bio-active agent is first dissolved, dispersed, or emulsified into an organic compound (or, e.g., its precursors) melt, solution, emulsion or dispersion. In some embodiments, the solid organic matrix can be comprised of polymers, oligomers, monomers, wax, oils, plasticizers, and any combinations thereof.

[00059] In some embodiments of the composition of the present invention, the organic particulate comprising the drug (e.g., a prostaglandin, e.g., latanoprost) can be mixed with at least one inert pharmaceutically acceptable excipient or carrier, such as, but not limited to, sodium citrate or dicalcium phosphate and/or (a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol and silicic acid; (b) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose and acacia; (c) humectants such as glycerol; (d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates and sodium carbonate; (e) solution retarding agents such as paraffin; (f) absorption accelerators such as quaternary ammonium compounds; (g) wetting agents such as cetyl alcohol and glycerol monostearate; (h) absorbents such as kaolin and bentonite clay and

pectin(i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or any combination thereof.

[00060] In some embodiments of the composition of the present invention, the organic particulate and the inert carrier are bound together with a binder to generate the composite matrix. In some embodiments, exemplary polymers include, but are not limited to, poly(dimethylsiloxane), polyurethanes, epoxies, methyl methacrylate polymers, acrylic copolymers, polyesters, polyamides, polyethylene, polypropylene, ethylene copolymers and terpolymers, propylene copolymers and terpolymers, fluoropolymers, vinyls, styrenics, polycarbonates, amino resins, and phenolic resins. Other exemplary polymers include crosslinked acrylic or methacrylic networks, including networks formed by ultraviolet (UV) curing. In some embodiments, the core (where the drug is absorbed or exist) comprises a thermosetting polymer. In some embodiments, exemplary waxes include, but are not limited to, paraffins, amides, esters, fatty acid derivatives, fatty alcohol derivatives, silicones, and phospholipids.

[00061] In some embodiments of the composition of the present invention, the composite matrix containing a bio-active agent (e.g., but not limited to, a prostaglandin, e.g., but not limited to, latanoprost) can be in a solid form such as powder, flakes, fibers, or any combination thereof. In some embodiments, the composite can be milled and/or micronized to the size of a fine powder <100 μm or to size <30 μm, using milling apparatus like mortar and pestle, electronic grinder, etc. In some embodiments, the fine composite powder can be dispersed and/or mixed with a flexible polymer. In some embodiments, the flexible polymer can be a medical polymer such as, e.g., including a polymer having hydrophilic and/or hydrophobic characteristics. In some embodiments, exemplary polymers include, but are not

limited to: a silicone, a polyacrylate, a polyurethane, or a combination of two or more of the polymers.

[00062] In some embodiments of the composition of the present invention, polyurethanes can be shaped as desired, or its permeability can be tailored as desired, to achieve a pre-determined release rate of the bio-active agent from the device to the patient. In some embodiments, the polymer comprises one or more polymers, made of the homopolymers or heteropolymers.

[00063] In some embodiments of the composition of the present invention, a mixture includes (1) a polymer and (2) a powder, which is formed into a solid, self-supporting shape. In some embodiments, the self-supporting shape can be the desired shape of the composition (i.e., the solid core), further processed by, e.g., trimming or cutting, into the desired shape. In some embodiments, a shape can be, but is not limited to, a cylinder, plug, coin, disk, plate, cube, sphere, fiber, box, diamond, ring, "S", "L", "T", web, net, mesh, "U", or "V".

[00064] In some embodiments of the composition of the present invention, an outer shell coating may be added to the exterior of a solid core. In some embodiments, the coating comprises a second non-biodegradable polymer that is substantially impermeable to a therapeutic compound (e.g., but not limited to, a prostaglandin, e.g., latanoprost). In some embodiments, the coating is at least less permeable (e.g., 1% less permeable, 5% less permeable, 10% less permeable, 20% less permeable, 30% less permeable, 40% less permeable, 50% less permeable, 60% less permeable, 70% less permeable, etc.) to the therapeutic compound compared with the permeability of the therapeutic compound to the first non-biodegradable polymer. In some embodiments, the outer shell coating can be butvar and/or parylene.

[00065] Figure 1A-C illustrates an embodiment of the present invention, showing a schematic drawing of the device, with composite powder dispersed in polymer.

[00066] Figure 2A and 2B illustrates an embodiment of the present invention, showing a schematic drawing of the process.

[00067] Figure 3 illustrates an embodiment of the present invention, showing a graph of *in vitro* percentage cumulative release of latanoprost from a plug sample over a test period measuring 7 days.

[00068] Figures 4-7illustrate embodiments of the placement of the composition of the present invention in a human eye.

[00069] Figure 8 is a schematic depiction of liquid at the surface of a non-porous particle (left) and of liquid absorbed in the pores of fumed silica (right).

[00070] The present invention describes a drug delivery device including: 1) particles of inert materials, absorbed with drug on surface of particles or inside porosity; 2) inert polymer matrix, where drug-inert particles are dispersed, where the polymer has no chemical interaction with drug and is providing mechanical package, and where the concentration of drug on particles, and the loading of particles in polymer matrix, is configured to control drug reservoir capacity; 3) an hydrophobic flexible polymer, which connects the polymer matrix into a shape and creates a barrier for drug release; 4) where the hydrophobic polymer is insufficient for controlling the release, a perforated outer barrier is applied to the solid core. In some embodiments, the permeability, and/or size and number of apertures in barrier are configured to control a release rate of the drug (e.g., but not limited to, a prostaglandin, but not limited to, e.g. latanoprost).

[00071] In some embodiments, the composition of the present invention includes: (i) a first pharmaceutical agent, a bulking agent, at least one inert material configured to have an increased surface area and a bulk density of between 1-3 gr/cm3 (e.g., but not limited to, 1 gr/cm3, 1.1 gr/cm3, 1.2 gr/cm3, etc.). In some embodiments, the first pharmaceutical agent is a prostaglandin or a prostaglandin analog. In some embodiments, the prostaglandin is selected from a group including: cloprostenol, fluprostenol, latanoprost, travoprost, unoprostone, and any combination thereof. In some embodiments, the composition further includes a second pharmaceutical agent, where the second pharmaceutical agent is an alpha agonist selected from the group including: iopidine and/or brimonidine. In some embodiments, the second pharmaceutical agent is a beta-blocker, where the beta-blocker is selected from the group including: timolol, betaxolol, levobetaxolol, carteolol, levobunolol, propranolol, and any combination thereof. In some embodiments, the composition further includes a third pharmaceutical agent, where the third pharmaceutical agent is an alpha agonist selected from the group including: iopidine and/or brimonidine.

[00072] In some embodiments, the composition of the present invention includes: cloprostenol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: cloprostenol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: cloprostenol, brimonidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: cloprostenol, timolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: cloprostenol, timolol, iopidine, kaolin, and fumed silica. In some

embodiments, the composition of the present invention includes: cloprostenol, timolol, brimonidine, kaolin, and fumed silica.

[00073] In some embodiments, the composition of the present invention includes: cloprostenol, betaxolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: cloprostenol, betaxolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: cloprostenol, betaxolol, brimonidine, kaolin, and fumed silica.

[00074] In some embodiments, the composition of the present invention includes: cloprostenol, levobetaxolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: cloprostenol, levobetaxolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: cloprostenol, levobetaxolol, brimonidine, kaolin, and fumed silica.

[00075] In some embodiments, the composition of the present invention includes: cloprostenol, carteolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: cloprostenol, carteolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: cloprostenol, carteolol, brimonidine, kaolin, and fumed silica.

[00076] In some embodiments, the composition of the present invention includes: cloprostenol, levobunolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: cloprostenol, levobunolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: cloprostenol, levobunolol, brimonidine, kaolin, and fumed silica.

[00077] In some embodiments, the composition of the present invention includes: cloprostenol, propranolol, kaolin, and fumed silica. In some embodiments,

the composition of the present invention includes: cloprostenol, propranolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: cloprostenol, propranolol, brimonidine, kaolin, and fumed silica.

[00078] In some embodiments, the composition of the present invention includes: fluprostenol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: fluprostenol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: fluprostenol, brimonidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: fluprostenol, timolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: fluprostenol, timolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: fluprostenol, timolol, brimonidine, kaolin, and fumed silica.

[00079] In some embodiments, the composition of the present invention includes: fluprostenol, betaxolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: fluprostenol, betaxolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: fluprostenol, betaxolol, brimonidine, kaolin, and fumed silica.

[00080] In some embodiments, the composition of the present invention includes: fluprostenol, levobetaxolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: fluprostenol, levobetaxolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: fluprostenol, levobetaxolol, brimonidine, kaolin, and fumed silica.

[00081] In some embodiments, the composition of the present invention includes: fluprostenol, carteolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: fluprostenol, carteolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: fluprostenol, carteolol, brimonidine, kaolin, and fumed silica.

[00082] In some embodiments, the composition of the present invention includes: fluprostenol, levobunolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: fluprostenol, levobunolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: fluprostenol, levobunolol, brimonidine, kaolin, and fumed silica.\

[00083] In some embodiments, the composition of the present invention includes: fluprostenol, propranolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: fluprostenol, propranolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: fluprostenol, propranolol, brimonidine, kaolin, and fumed silica.

[00084] In some embodiments, the composition of the present invention includes: latanoprost, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: latanoprost, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: latanoprost, brimonidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: latanoprost, timolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: latanoprost, timolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: latanoprost, timolol, brimonidine, kaolin, and fumed silica.

[00085] In some embodiments, the composition of the present invention includes: latanoprost, betaxolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: latanoprost, betaxolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: latanoprost, betaxolol, brimonidine, kaolin, and fumed silica.

[00086] In some embodiments, the composition of the present invention includes: latanoprost, levobetaxolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: latanoprost, levobetaxolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: latanoprost, levobetaxolol, brimonidine, kaolin, and fumed silica.

[00087] In some embodiments, the composition of the present invention includes: latanoprost, carteolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: latanoprost, carteolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: latanoprost, carteolol, brimonidine, kaolin, and fumed silica.

[00088] In some embodiments, the composition of the present invention includes: latanoprost, levobunolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: latanoprost, levobunolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: latanoprost, levobunolol, brimonidine, kaolin, and fumed silica.

[00089] In some embodiments, the composition of the present invention includes: latanoprost, propranolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: latanoprost, propranolol, iopidine,

kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: latanoprost, propranolol, brimonidine, kaolin, and fumed silica.

[00090] In some embodiments, the composition of the present invention includes: travoprost, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: travoprost, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: travoprost, brimonidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: travoprost, timolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: travoprost, timolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: travoprost, timolol, brimonidine, kaolin, and fumed silica.

[00091] In some embodiments, the composition of the present invention includes: travoprost, betaxolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: travoprost, betaxolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: travoprost, betaxolol, brimonidine, kaolin, and fumed silica.

[00092] In some embodiments, the composition of the present invention includes: travoprost, levobetaxolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: travoprost, levobetaxolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: travoprost, levobetaxolol, brimonidine, kaolin, and fumed silica.

[00093] In some embodiments, the composition of the present invention includes: travoprost, carteolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: travoprost, carteolol, iopidine, kaolin,

and fumed silica. In some embodiments, the composition of the present invention includes: travoprost, carteolol, brimonidine, kaolin, and fumed silica.

[00094] In some embodiments, the composition of the present invention includes: travoprost, levobunolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: travoprost, levobunolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: travoprost, levobunolol, brimonidine, kaolin, and fumed silica.

[00095] In some embodiments, the composition of the present invention includes: travoprost, propranolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: travoprost, propranolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: travoprost, propranolol, brimonidine, kaolin, and fumed silica.

[00096] In some embodiments, the composition of the present invention includes: unoprostone, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: unoprostone, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: unoprostone, brimonidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: unoprostone, timolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: unoprostone, timolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: unoprostone, timolol, brimonidine, kaolin, and fumed silica.

[00097] In some embodiments, the composition of the present invention includes: unoprostone, betaxolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: unoprostone, betaxolol, iopidine,

kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: unoprostone, betaxolol, brimonidine, kaolin, and fumed silica.

[00098] In some embodiments, the composition of the present invention includes: unoprostone, levobetaxolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: unoprostone, levobetaxolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: unoprostone, levobetaxolol, brimonidine, kaolin, and fumed silica.

[00099] In some embodiments, the composition of the present invention includes: unoprostone, carteolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: unoprostone, carteolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: unoprostone, carteolol, brimonidine, kaolin, and fumed silica.

[000100] In some embodiments, the composition of the present invention includes: unoprostone, levobunolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: unoprostone, levobunolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: unoprostone, levobunolol, brimonidine, kaolin, and fumed silica.

[000101] In some embodiments, the composition of the present invention includes: unoprostone, propranolol, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: unoprostone, propranolol, iopidine, kaolin, and fumed silica. In some embodiments, the composition of the present invention includes: unoprostone, propranolol, brimonidine, kaolin, and fumed silica.

[000102] In some embodiments, where the composition of the present invention includes at least one active agent (e.g., but not limited to, Latanoprost, unoprostone,

propranolol, timolol, etc.), the same amounts of bulking agents and inert materials (e.g., but not limited to, fumed silica, epoxy, and kaolin) will be used to generate the composition as shown in the examples below.

[000103] **EXAMPLE: Preparation of Plug/Solid Core**

[000104] In an example of an embodiment of the composition of the present invention, plug samples containing Latanoprost were prepared. Samples were incubated at 37 degrees Celsius for varying times to determine time effect on Latanoprost release profile from the sample into a polar solution (PBS).

[000105] Particulate preparation

[000106] Initially, a bio-active agent was adsorbed or loaded on fumed silica (FS). The bio-active agent was Latanoprost (LP). 0.16g of FS was mixed with 0.25g LP dissolved in 2g solvents 1 THF: 1 Ethanol (w/w). Additional examples of polar solvents are: Methanol, Isopropanol, Acetone, and/or Ethyl acetate. The LP/FS mixture was dried at ambient temperature for 24 hours.

[000107] Composite matrix preparation

[000108] 0.13g of kaolin powder and 0.4g of FS particulate and 0.13g medical grade epoxy (EPO-TEK 301, manufactured by Epo-Tek from USA) were mixed together. The mixture was mixed until a paste was formed, where the paste had a viscosity of about 250,000 CP. The paste was cured at ambient temperature for 24 hours. The resulting composition had the characteristics of a solid composite.

[000109] Composite Milling and Molding

[000110] The solid composite was milled using pestle and mortar. The composite fine powder was mixed with polyurethane in a ratio of 40%:60%. The mixture molded in a polyacetal (DELRIN) mold for 12 hours at ambient room temperature and removed from the mold. This formed the plug shape.

[000111] Solution Preparation – releasing medium buffer

[000112] The solution included the following: 0.01M PBS, 0.005% BAK, and 0.1% TRITON X-100.

[000113] Plug coating process

[000114] The outer layer coating of the plug can be: (1) Butvar 5% (W/V) in Tetrahydrofuran (THF) as solvent or (2) Parylene coating - Polyurethane plugs were coated with 2-5 μm of parylene using a vapor deposition process. To coat the plug, the plugs were placed in a vacuum deposition chamber (Simtal Coating Ltd.) and a vacuum was drawn in the chamber to approximately 0.1 torr. A parylene dimer (di-para-xylylene) was vaporized at approximately 150° C. Then pyrolysis of the monomer (para-xylylene) was affected at approximately 680° C. and 0.5 torr (e.g., but not limited to, the Aryl-chlorine bond in dichloro[2.2]paracyclophane breaks at 680 °C (standard pyrolysis temperature). The monomer then entered the deposition chamber at approximately room temperature (approximately 25° C.) and was adsorbed and polymerized onto the polyurethane plug.

[000115] Final plug sample properties

[000116] Composites weight 14.1 grams with 18% Latanoprost. See Table 1 for details:

[000117] Table 1:

	Plug Sample Name	Hours at 37	Composite Weight	PBS+BAK(0.005%)+TRITON(0.1%)		Accumulative
		in PBS + BAK +Triton	mg	g	PPM	PPM
1	LP18S-1014-6HR	6	14.1	0.527	63.8	63.8
2	LP18S-1014-12HR	12	14.1	0.504	51.1	114.9
3	LP18S-1014-24HR	24	14.1	0.553	26.8	141.7
4	LP18S-1014-48HR	48	14.1	0.560	41.6	183.3
5	LP18S-1014-96HR	96	14.1	0.503	42.5	225.8
6	LP18S-1014-7D	168	14.1	0.548	33.9	259.7

[000118] The shell can be parylene or butvar. The organic matrix can be kaolin and/or epoxy. The drug absorbing material is fumed silica. No encapsulation of drug.

[000119] In an embodiment, active agent is latanoprost, organic matrix is kaolin, the absorbance material is fumed silica. The solvents for the drug are ethanol and HFE. Drying is performed for 24 hours at RT. The Binder (i.e., for mixing with the drug powder) is epoxy. Molding to plug is RT molding. Additional components may include 0.1% Triton and 0.005% BAK.

[000120]

[000121] Example: method of using HPLC-UV to quantify Latanoprost API from a solution in the presence of benzalkonium chloride (BAK) and triton X-100.

[000122] 51 samples of Latanoprost in PBS buffer with BAK and Triton X-100 were analyzed according to the following conditions:

[000123] Column: Synergy, MAX-RP 250mm 4.6 mm, 4micrometer

[000124] Flow rate: 1 mL/min

[000125] Detector: UV at 210nm

[000126] Inj. Volume: 5 microliters

[000127] Sample Temperature: 10±5°C

[000128] Column Temperature: 25±5°C

[000129] Mobile phase A: 0.05M phosphate buffer pH = 3: Acetonitrile ("ACN") (40:60, v/v)

[000130] Mobile phase B: ACN

[000131] Gradient program:

Time (min)	Mobile Phase (A)	Mobile Phase (B)
0	100	0
1.0	100	0
15.0	50	50
15.1	100	0
20.0	100	0

Run Time: 20min

[000132]

[000133] Results:

Sample ID	TAR RUN # 9+9+10	Days at 37°C in PBS + BAK +Triton	Composite Weight 5 mg	PBS+BAK(0.005%)+TRITON(0.1%) 0.5 g	Amount of Latanoprost (µg/mL)	Amount Latanopr (µg)
	6-47	168	4.60	0.5020	70.7	41.9
	6-48	168	5.10	0.5040	96.6	48.8
	6-49	168	4.80	0.5160	114.3	59.0
10-1	LP14-0315-1W-CO1	1	5.71	0.5331	28.0	14.9
10-2	LP14-0315-3W-CO1	3	5.71	0.5339	52.3	27.9
10-3	LP14-0315-5W-CO1	5	5.71	0.5316	50.3	26.7
10-4	LP14-0315-7W-CO1	7	5.71	0.5336	43.9	23.4
10-5	LP14-0315-9W-CO1	9	5.71	0.5343	35.4	18.9
10-6	LP14-0315-14W-CO1	14	5.71	0.5345	46.1	24.6
10-7	LP14-0315-21W-CO1	21	5.71	0.5331	60.3	32.2
10-8	LP14-0315-28W-CO1	28	5.71	0.5315	50.2	26.7
10-12	LP14-0315-1W-CO2	1	5.81	0.5320	45.6	24.3
10-13	LP14-0315-3W-CO2	3	5.81	0.5319	47.4	25.2
10-14	LP14-0315-5W-CO2	5	5.81	0.5293	44.8	23.7
10-15	LP14-0315-7W-CO2	7	5.81	0.5187	43.0	22.3
10-16	LP14-0315-9W-CO2	9	5.81	0.5191	42.2	21.9
10-17	LP14-0315-14W-CO2	14	5.81	0.5364	51.7	27.7
10-18	LP14-0315-21W-CO2	21	5.81	0.5140	62.3	32.0
10-19	LP14-0315-28W-CO2	28	5.81	0.5099	62.7	32.0
10-23	LP14-0315-1W-P1	1	4.80	0.5080	17.9	9.1
10-24	LP14-0315-3W-P1	3	4.80	0.5158	37.5	19.4
10-25	LP14-0315-5W-P1	5	4.80	0.5136	35.7	18.4
10-26	LP14-0315-7W-P1	7	4.80	0.5132	42.9	22.0
10-27	LP14-0315-9W-P1	9	4.80	0.5146	36.9	19.0
10-28	LP14-0315-14W-P1	14	4.80	0.5007	53.7	26.9
10-29	LP14-0315-21W-P1	21	4.80	0.5093	66.8	34.2
10-30	LP14-0315-28W-P1	28	4.80	0.5122	60.3	30.9
10-34	LP14-0315-1W-P2	1	5.15	0.5282	22.7	11.9
10-35	LP14-0315-3W-P2	3	5.15	0.5211	33.1	17.2
10-36	LP14-0315-5W-P2	5	5.15	0.5195	29.9	15.5
10-37	LP14-0315-7W-P2	7	5.15	0.5281	34.4	18.1
10-38	LP14-0315-9W-P2	9	5.15	0.5206	47.6	24.4
10-39	LP14-0315-14W-P2	14	5.15	0.5151	58.6	30.2
10-40	LP14-0315-21W-P2	21	5.15	0.5264	74.5	39.8
10-41	LP14-0315-28W-P2	28	5.15	0.5192	51.4	26.7
9-1	LP14-0315-1W-PY1	1	4.46	0.5303	3.8	2.0
9-2	LP14-0315-3W-PY1	3	4.46	0.5320	6.7	3.6
9-3	LP14-0315-5W-PY1	5	4.46	0.5309	6.1	3.2
9-4	LP14-0315-7W-PY1	7	4.46	0.5306	6.2	3.3
9-5	LP14-0315-9W-PY1	9	4.46	0.5317	6.3	3.4
9-6	LP14-0315-14W-PY1	14	4.46	0.5381	12.2	6.6
9-7	LP14-0315-21W-PY1	21	4.46	0.5342	12.1	6.4
9-8	LP14-0315-28W-PY1	28	4.46	0.5365	12.2	6.5
9-12	LP14-0315-1W-PY2	1	4.23	0.5367	4.7	2.5
9-13	LP14-0315-3W-PY2	3	4.23	0.5352	8.5	4.5
9-14	LP14-0315-5W-PY2	5	4.23	0.5303	7.1	3.8
9-15	LP14-0315-7W-PY2	7	4.23	0.5320	6.6	3.5
9-16	LP14-0315-9W-PY2	9	4.23	0.5325	4.7	2.5
9-17	LP14-0315-14W-PY2	14	4.23	0.5337	7.8	4.2
9-18	LP14-0315-21W-PY2	21	4.23	0.5322	9.6	5.1
9-19	LP14-0315-28W-PY2	28	4.23	0.5305	9.5	5.0

[000134]

[000135] The composite weight was not taken into account in the above table.

[000136] Calculations: the samples were injected as is and quantified against Latanoprost RM from Neore Pharma Group Col. Ltd., using 6 points calibration curve from concentrations of 0.5-50 micrograms/mL.

[000137] Example: chromatographic method using HPLC-UV to quantify Latanoprost API from a solution in the presence of BAK and triton X-100.

[000138] Thirty two samples of Latanoprost in PBS buffer with BAK and Triton X-100 were analyzed using the following conditions:

[000139] Column: Synergy, MAX-RP 250 4.6 mm, 4 micrometer

[000140] Flow rate: 1 mL/min

[000141] Detector: uV at 210nm

[000142] Inj. Volume: 5 microliters

[000143] Sample Temperature: 10±5°C

[000144] Column Temperature: 25±5°C

[000145] Mobile phase A: 0.05M phosphate buffer pH=3 (40:60, v/v)

[000146] Mobile phase B: ACN

[000147] Gradient program:

Time (min)	Mobile Phase (A)	Mobile Phase (B)
0	100	0
1.0	100	0
15.0	50	50
15.1	100	0
20.0	100	0

[000148] Run Time: 20min

[000149] Results:

	COMPOSITE FS60 + PU NEXTAR RUN 7	Days at 37°C in PBS + BAK +Triton	Composite Weight 3 mg	PBS+BAK(0.005%)+ TRITON(0.1%) 0.5g	Amount of Latanoprost (µg/mL)
1	Conc2 (PBS + BAK+ TRITON+ LP)	28 days at 4°C	3.70	0.516	389.5
2	Conc3 (PBS + BAK+ TRITON+ LP)	28 days at 37°C	3.5	0.634	1521.0
3	LP14-1114-1D-E	1	2.0	0.548	48.6
4	LP14-1114-3D-E	3	2.0	0.566	28.8
5	LP14-1114-5D-E	5	2.0	0.583	25.5
6	LP14-1114-7D-E	7	2.0	0.571	23.7
7	LP14-1114-9D-E	9	2.0	0.553	24.5
8	LP14-1114-14D-E	14	2.0	0.546	37.2
9	LP14-1114-1D-F	1	3.6	0.526	0.57
10	LP14-1114-3D-F	3	3.6	0.542	1.02
11	LP14-1114-5D-F	5	3.6	0.599	0.81
12	LP14-1114-7D-F	7	3.6	0.549	1.31
13	LP14-1114-9D-F	9	3.6	0.494	1.41
14	LP14-1114-14D-F	14	3.6	0.507	3.36
15	LP14-1114-1D-G	1	2.8	0.544	6.0
16	LP14-1114-3D-G	3	2.8	0.515	3.7
17	LP14-1114-5D-G	5	2.8	0.575	3.7
18	LP14-1114-7D-G	7	2.8	0.523	6.2
19	LP14-1114-9D-G	9	2.8	0.618	3.7
20	LP14-1114-14D-G	14	2.8	0.584	8.0
21	LP14-1114-1D-H	1	3.3	0.587	24.0
22	LP14-1114-3D-H	3	3.3	0.611	26.4
23	LP14-1114-5D-H	5	3.3	0.546	30.8
24	LP14-1114-7D-H	7	3.3	0.531	32.7
25	LP14-1114-9D-H	9	3.3	0.504	32.9
26	LP14-1114-14D-H	14	3.3	0.536	40.6
27	LP14-1114-1D-I	1	2.6	0.510	10.6
28	LP14-1114-3D-I	3	2.6	0.580	15.7
29	LP14-1114-5D-I	5	2.6	0.541	14.7
30	LP14-1114-7D-I	7	2.6	0.553	21.0
31	LP14-1114-9D-I	9	2.6	0.539	16.1
32	LP14-1114-14D-I	14	2.6	0.549	27.3

[000150]

[000151] Calculations: the samples were injected and quantified against Latanoprost RM using 6 points weighted calibration curve from 0.5 - 50 micrograms/mL concentrations.

[000152] Example: Chromatographic method by HPLC-UV which will be suitable to quantify Latanoprost API from solution in presence of BAK and triton X-100.

[000153] Thirty four samples of latanoprost in PBS buffer with BAK and Triton X-100 were tested using the following method:

[000154] Column: Synergy, MAX-RP 250 4.6 mm, 4 micrometer

[000155] Flow rate: 1 mL/min

[000156] Detector: uV at 210nm

[000157] Inj. Volume: 100 microliters

[000158] Sample Temperature: 10±5°C

[000159] Column Temperature: 25±5°C

[000160] Mobile phase A: 0.05M phosphate buffer pH=3 (40:60, v/v)

[000161] Mobile phase B: ACN

[000162] Gradient program:

Time (min)	Mobile Phase (A)	Mobile Phase (B)
0	100	0
1.0	100	0
15.0	50	50
15.1	100	0
20.0	100	0

[000163] Run Time: 20min

[000164] Results (using 5 microliters injection volume):

Sample No.	COMPOSITE FS60 + FU (UN 6	Days at 37°C in PBS + BAK +Triton	Composite Weight (mg)	PBS+BAK(0.005%)+ TRITON(0.1%) (g)	Amount of Latanoprost (µg/mL)	Amount of Latanoprost (µg)
1	Con2 (PBS + BAK+ TRITON+ LP)	28 days at 4°C	5.60	0.5073	218	106.6
2	Con3 (PBS + BAK+ TRITON+ LP)	28 days at 37°C	4.4	0.5060	229	116.6
3	LP14-1114-3D-A	3	4.8	0.5033	31.8	16.0
4	LP14-1114-5D-A	5	4.8	0.5370	25.5	13.4
5	LP14-1114-7D-A	7	4.8	0.5188	27.1	14.1
6	LP14-1114-9D-A	9	4.8	0.5257	38.6	20.1
7	LP14-1114-14D-A	14	4.8	0.5159	54.3	28.2
8	LP14-1114-21D-A	21	4.8	0.5027	41.4	20.8
9	LP14-1114-25D-A	25	4.8	0.5076	34.0	17.3
10	LP14-1114-28D-A	28	4.8	0.5243	36	18.9
11	LP14B-1114-3D-B	3	5.1	0.5019	45.0	22.6
12	LP14B-1114-5D-B	5	5.1	0.5143	34.0	17.5
13	LP14B-1114-7D-B	7	5.1	0.5215	34.8	18.1
14	LP14B-1114-9D-B	9	5.1	0.4927	57.3	28.2
15	LP14B-1114-14D-B	14	5.1	0.4983	83.3	41.3
16	LP14B-1114-21D-B	21	5.1	0.5095	61.6	31.4
17	LP14B-1114-25D-B	25	5.1	0.5277	48.1	25.8
18	LP14B-1114-28D-B	28	5.1	0.5065	55.5	28.1
19	LP14-1114-3D-C	3	4.8	0.5128	41.0	21.0
20	LP14-1114-5D-C	5	4.8	0.5085	37.6	19.2
21	LP14-1114-7D-C	7	4.8	0.5292	42.9	22.3
22	LP14-1114-9D-C	9	4.8	0.5224	70.4	36.8
23	LP14-1114-14D-C	14	4.8	0.5036	95.4	48.0
24	LP14-1114-21D-C	21	4.8	0.5257	64.8	34.1
25	LP14-1114-25D-C	25	4.8	0.5054	63.5	32.1
26	LP14-1114-28D-C	28	4.8	0.5097	58.5	29.8
27	LP14B-1114-3D-D	3	5.0	0.5282	36.4	19.2
28	LP14B-1114-5D-D	5	5.0	0.5133	31.5	16.2
29	LP14B-1114-7D-D	7	5.0	0.5365	34.3	18.4
30	LP14B-1114-9D-D	9	5.0	0.5285	38.1	20.1
31	LP14B-1114-14D-D	14	5.0	0.5097	64.7	33.0
32	LP14B-1114-21D-D	21	5.0	0.5134	49.1	25.3
33	LP14B-1114-25D-D	25	5.0	0.5089	38.8	19.8
34	LP14B-1114-28D-D	28	5.0	0.5071	38.6	19.6
Notes:						
The composite weight does not taken into account.						

[000165]

[000166] Calculations: the samples were injected and quantified against latanoprost RM using 6 points calibration curve from 0.04-50 micrograms/mL concentrations.

[000167] Example: HPLC method for determining Timolol Maleate (TM) in solution containing latanoprost, PBS, benzalkonium chloride (BAK) and triton x-100, using a C-18 column and a UV detection at 285 nm for TM and 210 nm for Latanoprost.

[000168] Forty eight samples were analyzed using a Waters Alliance HPLC equipped with UV Detector, a micro analytical balance, Mettler Toledo, MX (QC-601), and a magnetic stirrer.

[000169] Linearity of TM was demonstrated in the range from 1-265 micrograms/mL with a square correlation coefficient of 1.0. The limit of quantitation was evaluated on standard solution at concentration of 1 microgram/mL and a signal to noise ratio of 88 was found.

[000170] Linearity of Latanoprost was demonstrated in the range from 0.48 – 240 micrograms/mL with a square correlation coefficient of 0.9999. The limit of quantitation was evaluated on standard solution at concentration of 0.48 micrograms/mL and a signal to noise ratio of 14.8 was found.

[000171] Analytical method development and conditions: HPLC method was developed for the determination and quantitation of Timolol Maleate and Latanoprost in aqueous solution containing PBS, BAK and Triton X-100. The chromatographic conditions were as follows:

Parameter	Analytical condition
HPLC Column	Synergi, 4µ, MAX-RP 80A, 250×4.6mm, 5µm Cat. No. OOG-4337-EO, Nextar No. 86A-1.
Mobile Phase	A: 0.1% TFA in water : Acetonitrile 70:30,(v/v) B: 0.1% TFA in Acetonitrile
Gradient Program	see table below
Flow Rate	1.0 mL/min
Injection Volume	20 µL
Auto sampler temperature	10°C ± 5°C
Column oven temperature	40°C ± 5°C
Detection	UV at 210 nm for Latanoprost UV at 285 nm for TM

Gradient Program:

Time (min)	Mobile Phase (A)	Mobile Phase (B)
0	100	0
3.0	100	0
16.0	0	100
16.1	100	0
22.0	100	0

[000172]

[000173] The sample diluent was 85% water and 15% methanol.

[000174] Results: the following parameters were evaluated during the method development: specificity, linearity and range, detection limit and quantitation limit.

[000175] Specificity: the sample diluent (85% water:15% methanol) was injected for the specificity test. No interference was detected at the retention time of TM and Latanoprost.

[000176] Linearity tests:

[000177] TM: The linearity of Tm was evaluated from a concentration of 0.53-265 micrograms/mL. Seven standard solutions were prepared separately in order to test the linearity of the HPLC method: 0.53 micrograms/mL, 2.65 micrograms/mL, 13.3 micrograms/mL, 26.5 micrograms/mL, 53.0 micrograms/mL, 132.6 micrograms/mL, and 265.3 micrograms/mL. The correlation between the instrument response and concentration was demonstrated with a squared correlation coefficient of 1.0. Figure 12 shows the chromatogram results of the TM standard solution at 53 micrograms/mL, where an injection volume of 20 microliters was used for a run time of 22 minutes.

[000178] Latanoprost: The linearity of Latanoprost was evaluated from a concentration of 0.48 micrograms/mL to 241 micrograms/mL. Seven standard solutions were prepared separately to test the linearity of the HPLC method: 0.48 micrograms/mL, 2.41 micrograms/mL, 12.0 micrograms/mL, 24.1 micrograms/mL, 48.1 micrograms/mL, 120.3 micrograms/mL, and 240.6 micrograms/mL. A correlation between the instrument response and concentration was demonstrated with a squared correlation coefficient (R2) of 1.0. Figures 13 and 14A-B illustrate a typical chromatogram of a standard solution at a concentration of 48 micrograms/mL and calibration curve results, respectively.

[000179] Limit of quantitation and limit of detection:

[000180] Limit of quantitation for TM: the limit of detection (LOD) and the limit of quantitation (LOQ) values were determined by testing standard solution at a concentration of 0.53 micrograms/mL. As used herein, LOD refers to the lowest amount of analyte that can be detected above baseline noise, but not necessarily quantified as an exact value. As used herein, LOQ refers to the lowest amount of analyte which can be reproducibly quantitated above the baseline noise. The signal-to-noise ratio (S/N) for LOD should be about 3 and for LOQ about 10. A signal to noise ratio of 89 was found at standard solution containing 0.53 micrograms/mL. Figure 15 shows a signal to noise ratio of 88.589 for TM at 285nm.

[000181] Limit of quantitation for Latanoprost: The LOD and the LOQ values were determined. The signal-to noise ratio (S/N) for LOD is about 3 and for LOQ is about 10. A signal to noise ratio of 14.8 was found at standard solution containing 0.48 micrograms/mL, and is shown in Figure 16.

[000182] System suitability parameters: The system suitability test is performed to demonstrate that the system is fit for the purpose of the analysis, and the following parameters were tested: percent RSD of 5 replicates of the standard solution, tailing factor (T), resolution (R), and number of theoretical plates (N). The table below shows the results of a sample:

[000183]

API Name	Tailing Factor (T)	Theoretical Plates (P)	Resolution* (R)
TM	1.3	8469	2.0
Latanoprost	1.3	112292	1.2

* Resolution of API to nearest peak

[000184] System precision: the system precision was demonstrated on control standard at a nominal concentration of 50 micrograms/mL. The percent relative standard deviation (RSD) was calculated from the beginning of the sequence log until

the end of the sequence log. RSD of less than 2% was found for both API's in all standard injections. The results are shown in the table below:

Std	TM	Latanoprost
Replicate	Peak area (AU)	Peak area (AU)
Injection 1	989723	1157736
Injection 2	984361	1152543
Injection 3	990732	1143846
Injection 4	982226	1139423
Injection 5	981758	1135124
Injection 6	975390	1129086
Injection 7	976605	1128033
Injection 8	982001	1131109
Injection 9	977782	1130783
Mean	**982286**	**1138631**
(%) RSD	**0.5**	**0.9**

[000185]

[000186] Sample preparation: the sample solutions were shaken using a vortex shaker and transferred into an HPLC vial. The sample solutions were injected into HPLC as is without further dilution. Results are shown in the table below:

Sample ID	NEXTAR RUN 12 (TIMOLOL)	Days at 37°C	Composite Weight (mg)	Sample Volume (mL)	Amount of Latanoprost (µg/mL)	Amount of Latanoprost (µg)	Amount of Timolol (µg/mL)	Amount of Timolol (µg)
12-1	LP&TML-0615-1d-CO1	1	5.91	0.524	17.2	9.0	1049.1	549.7
12-2	LP&TML-0615-3d-CO1	3	5.91	0.526	53.8	28.3	446.4	234.8
12-3	LP&TML-0615-5d-CO1	5	5.91	0.501	74.3	37.2	162.2	81.3
12-4	LP&TML-0615-7d-CO1	7	5.91	0.514	78.1	40.1	56.3	28.9
12-5	LP&TML-0615-9d-CO1	9	5.91	0.519	55.5	28.8	11.0	5.7
12-6	LP&TML-0615-14d-CO1	14	5.91	0.519	104.3	54.1	5.6	2.9
12-7	LP&TML-0615-21d-CO1	21	5.91	0.518	85.2	44.1	0.9	0.5
12-8	LP&TML-0615-28d-CO1	28	5.91	0.520	89.2	46.4	1.9	1.0
12-12	LP&TML-0615-1d-CO2	1	6.00	0.517	17.6	9.1	944.2	488.1
12-13	LP&TML-0615-3d-CO2	3	6.00	0.517	52.8	27.3	448.2	231.7
12-14	LP&TML-0615-5d-CO2	5	6.00	0.527	59.0	31.1	162.2	85.5
12-15	LP&TML-0615-7d-CO2	7	6.00	0.516	82.2	42.4	77.1	39.8
12-16	LP&TML-0615-9d-CO2	9	6.00	0.520	59.2	30.8	20.5	10.7
12-17	LP&TML-0615-14d-CO2	14	6.00	0.516	88.4	45.6	9.7	5.0
12-18	LP&TML-0615-21d-CO2	21	6.00	0.518	102.6	53.1	1.1	0.6
12-19	LP&TML-0615-28d-CO2	28	6.00	0.518	98.0	50.8	0.3	0.2
12-23	LP&TML-0615-1d-P1	1	3.90	0.525	17.6	9.2	106.7	56.0
12-24	LP&TML-0615-3d-P1	3	3.90	0.518	30.1	15.6	100.4	52.0
12-25	LP&TML-0615-5d-P1	5	3.90	0.520	32.5	16.9	64.8	33.7
12-26	LP&TML-0615-7d-P1	7	3.90	0.521	38.3	20.0	61.8	32.2
12-27	LP&TML-0615-9d-P1	9	3.90	0.517	26.2	13.5	31.6	16.3
12-28	LP&TML-0615-14d-P1	14	3.90	0.514	39.5	20.3	63.5	32.6
12-29	LP&TML-0615-21d-P1	21	3.90	0.515	51.2	26.4	40.9	21.1
12-30	LP&TML-0615-28d-P1	28	3.90	0.521	39.5	20.6	13.6	7.1
12-34	LP&TML-0615-1d-P2	1	3.50	0.524	9.1	4.8	74.4	39.0
12-35	LP&TML-0615-3d-P2	3	3.50	0.520	26.0	13.5	69.1	36.0
12-36	LP&TML-0615-5d-P2	5	3.50	0.517	28.6	14.8	48.6	25.1
12-37	LP&TML-0615-7d-P2	7	3.50	0.522	29.2	15.2	43.6	22.8
12-38	LP&TML-0615-9d-P2	9	3.50	0.518	20.6	10.7	22.6	11.7
12-39	LP&TML-0615-14d-P2	14	3.50	0.522	35.5	18.5	51.9	27.1
12-40	LP&TML-0615-21d-P2	21	3.50	0.516	31.0	16.0	35.0	18.1
12-41	LP&TML-0615-28d-P2	28	3.50	0.521	31.2	16.3	21.5	11.2
12-45	LP&TML-0615-1d-TPU	1	7.36	0.523	14.9	7.8	1079.0	564.3
12-49	LP&TML-0615-3d-TPU	3	7.36	0.523	54.9	28.7	463.8	242.6
12-50	LP&TML-0615-5d-TPU	5	7.36	0.526	64.6	34.0	140.5	73.9
12-51	LP&TML-0615-7d-TPU	7	7.36	0.512	71.8	36.8	52.0	26.6
12-52	LP&TML-0615-9d-TPU	9	7.36	0.515	68.9	35.6	10.2	5.3
12-53	LP&TML-0615-14d-TPU	14	7.36	0.530	90.3	47.9	4.4	2.3
12-54	LP&TML-0615-21d-TPU	21	7.36	0.528	88.9	47.0	0.9	0.5
12-55	LP&TML-0615-28d-TPU	28	7.36	0.530	92.5	49.0	0.2	0.1
12-60	LP&TML-0615-1d-TPUSP-4	1	7.35	0.532	7.8	4.1	902.7	480.2
12-61	LP&TML-0615-7d-TPUSP-4	7	7.35	0.511	80.1	40.9	693.6	354.4
12-62	LP&TML-0615-1d-TPUSP-4	1	5.35	0.508	21.9	11.1	834.5	423.9
12-63	LP&TML-0615-7d-TPUSP-4	7	5.35	0.507	97.0	49.2	896.4	454.5
12-64	LP&TML-0615-1d-Powder	1	4.11	0.564	68.5	34.5	7.3	3.7
12-65	LP&TML-0615-7d-Powder	7	4.11	0.530	129.7	68.7	2.2	1.2

[000187]

[000188] The composite weight was not taken into the calculations of the above table.

[000189] The squared correlation of the linear calibration curve was 1.0 for both API's. The samples were quantified against Latanoprost from Neore Pharmaceutical Group and TM from Signam-Aldrich, Cat. No. T6394.

[000190] Figures 17, 18 and 19A-B illustrate chromatograms: Figure 19A is a diluent chromatogram at 285nm for Timolol Maleate; Figure 19B is a diluent chromatogram at 210nm for Latanoprost; Figure 19C is a typical sample chromatogram at 285nm for Timolol Maleate; Figure 19D is a typical sample chromatogram at 210 for Latanoprost.

[000191] Examples of Release Profiles

[000192] Two latanoprost plugs were loaded with either 280 micrograms of latanoprost or 1000 micrograms, where the plugs had the dimensions: diameter was 0.9mm and length was 3 mm. For the plug loaded with 280 micrograms of latanoprost, about 150-200 micrograms was released within 170 days at rates from 5 micrograms/day to 0.5 micrograms/day. For the plug loaded with 1000 micrograms of latanoprost, about 300-350 micrograms of latanoprost was released within 110 days at rates from 10 micrograms/day to 2 micrograms/day. For the 1000 microgram loaded plugs, the plugs can be coated to release 70-80 micrograms within 110 days at rates of 2-0.5 micrograms/day. Figures 1B and 1C illustrate the latanoprost plug and the timolol plug, respectively. The plug can contain between 0-35% Latanoprost w/w (e.g., 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, etc.). The plug can contain between 0-35% Timolol w/w (e.g., 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, etc.).

[000193] A plug loaded with 400 micrograms Timolol and 250 micrograms Latanoprost, where the plug has dimensions of a diameter measuring 0.9mm and a length measuring 3mm, the release profile was about 300 micrograms of timolol and about 160 micrograms of Latanoprost within 30 days at rates of 50-5 micrograms/day for TM and 10 to 5 micrograms/day for latanoprost.

[000194] Example: particulate preparation

[000195] A solvent mixture was prepared, including THF:Ethanol in a 1:1 (w/w) ratio. First, Latanoprost is mixed with these solvents and then Latanoprost is added to fumed silica (Sigma Aldrich 0.2-0.3 micrometers as the average particle size, CAS 112945-52-5). For example: FS60 (60% drug, e.g., Latanoprost) : 0.3 g FS + (0.2g Latanoprost + 5 g solvent), where FS is fumed silica. The mixture is then dried at room temperature for about 2 days. The percent moisture (relative humidity, "RH") can be between 30-70%.

[000196] Example: composite matrix

[000197] To prepare an epoxy solution, 1g Part A (Bisphenol A) is added to 0.25g Part B (Reactive diluent; Epo-tek 301). Kaolin, FS60, and epoxy are mixed, and later molded into a shape (e.g., a punctual plug shape). Then, the mixture is cured at room temperature for 2 days. In an example, the composite (36% drug, e.g., Latanoprost) : 0.2g Kolin + 0.2g epoxy + 0.6g FS60 is mixed, molded into a shape, and cured.

[000198] Example: dispersed composite matrix in polyurethane

[000199] To prepare an epoxy solution, 1g Part A is added to 0.25g Part B. Kaolin (Sigma, CAS 1332-58-7), FS60, and Epoxy are mixed and this mixture is cured at room temperature for 2 days. The composite is ground and vacuum dried for 24 hours. The polyurethane solution is prepared using 4g Part A and 1 g Part B (polyurethane steralloy 2781, Hapco Inc.). The Polyurethane is mixed with composite powder, and then molded into a shape (e.g., a punctual plug). For example, a plug having 14% drug (e.g., Latanoprost) would be generated by adding a composite powder to polyurethane to yield 0.5g (composite powder) and 0.75g polyurethane.

[000200] Example: two active agents dispersed in polyurethane

[000201] Part 1: particulate preparation

[000202] The particulate was prepared by mixing solvents, e.g., tetrahydrofuran (THF) : ethanol in a 1:1 (w/w) ratio. Then, Latanoprost was mixed with the solvents and added to fumed silica. Timolol (TML) was then mixed with the solvents and added to fumed silica. For example, FS60TML (60% Timolol drug) : 0.3g FS + (0.2g TML + 5 g solvent), then FS60LTP (60% Latanoprost drug) : 0.3g FS + (0.2g Latanoprost drug + 5g solvent), and then the mixture is dried for two days at room temperature (relative humidity is between 30-70%).

[000203] Part 2: composite matrix

[000204] The epoxy solution was prepared using 1g Part A and 0.25g Part B. Kaolin, FS60LTP, FS60TML, and epoxy were mixed and then cured at room temperature for 2 days at a relative humidity of between 30-70%. The composite was then ground, creating <10 micrometer sized particles (e.g., but not limited to, between 0.001, 0.01, 0.1, 1, 2, 3 micrometers, etc.), and vacuum dried. The polyurethane solution was then prepared using 4g Part A and 1g Part B, and the polyurethane preparation was then mixed with the composite powder and subsequently molded into a shape, e.g., a punctual plug.

[000205] In another example of generating a composite matrix, the epoxy solution was prepared using 1g Part A and 0.25g Part B. Kaolin, FS60LTP, FA60TML, and epoxy were then mixed and this mixture was cured at room temperature for two days. The composite was ground into powder, creating <10 micrometer sized particles (e.g., but not limited to, between 0.001, 0.01, 0.1, 1, 2, 3 micrometers, etc.) and subsequently vacuum dried. For example, a composite matrix formulation was generated using 0.6g FS60TML, 0.4g FS60LTP, 0.33g Kaolin and 0.4g Epoxy, yielding a final dose in composition having 20% Timolol and 13.5% Latanoprost.

[000206] Part 3: dispersed composite powder in polyurethane

[000207] The polyurethane solution was prepared using 4g Part A and 1g Prt B. This preparation was then mixed with composite powder and molded. For example, the plug with 8.1% Timolol and 5.4% Latanoprost was generated using 0.35g (Timolol and Latanoprost) composite powder and polyurethane, and then molded into a shape, e.g., a punctual plug. For example, a plug having 8.1% Timolol and 5.4% Latanoprost would be generated using 0.35g (20.3% Timolol and 13.5% Latanoprost composite powder) and 0.53g polyurethane.

[000208] Example: In vitro studies

[000209] The general protocol for the analytics study design was as follows: (1) preparing the following solution: phosphate buffered saline (10X PBS) + benzalkonium chloride(BAK) (0.005%) + Triton-X (0.1%), and adding 0.5mL of this solution into 1.5mL vials. The plugs were weighed (about 5mg / plug), and then each plug was placed into vials (i.e., one plug per vial) containing solution. The vials containing the plugs were then agitated in a heater at 37°C at 30 rpm. The samples were taken according to time intervals by removing the plug sample from the vial and putting vials in a refrigerator at 4 degrees C. A figure describing these steps is shown as Figure 20. Figure 21 is a graph showing 6 months release of Latanoprost. Figure 22 is a graph showing release of Latanoprost per day.

[000210] Figure 23 illustrates the cumulative Latanoprost release of a parylene coated punctual plug (e.g., but not limited to, where the microhole is between 0.5-5.0 microns (e.g., but not limited to, 0.5 microns, 0.6 microns, 0.7 microns, etc.)), where the parylene coating measures between 0.2-5.0 microns in thickness (e.g., but not limited to, 0.2 microns, 0.3 microns, 0.4 microns, 0.5 microns, 0.6 microns, etc..)

[000211] Figure 24 illustrates a three month release profile, comparing EXP-LP02= Only composite (without polyurethane), EXP-LP01= Composite powder in polyurethane, and EXP-LP01C= Coated Composite powder in polyurethane.

[000212] Each EXP graph made of duplicate), LP-02, and LP01C experiments. Figure 25 illustrates a three month release profile, showing the amount of Latanoprost released per day.

[000213] Figure 26 illustrates the cumulative drug released, e.g., Timolol (TML) and Latanoprost (LP), from the punctual plugs.

[000214] Figure 27 illustrates the amount of LP(5%) and TML(8%) released from a 5mg punctual plug per day.

[000215] Example: comparison of Latanoprost composite, Latanoprost-polyurethane and parylene coated plugs

[000216] Three types of punctual plug were prepared for an HPLC analytics test: (1) polyurethane/fused silica with composite powder containing drug (PU:FS60) at a ratio of 60:40, with the final drug content of 14%; (2) polyurethane/fused silica (PU:FS60) with composite powder containing drug and having a parylene coating with a final drug content of 14%; and (3) Only composite (FS60+Kaolin+Epoxy) having a final drug content of 14.62%.

[000217] Reagents:

- Kaolin USP Sigma C.N k1512-500G, Lot. No
- Hexan, ANHYDROUS, 95%, Sigma C.N 296090-1L, Lot. No
- Silica, Fumed Avg. Part. Size. 0.2-0.3 Sigma C.N S5505-500G, Lot. No
- EPOXY EPO-TEK Part A Batch PB116550 date of Exp 03.2015
- EPOXY EPO-TEK Part B Batch PB116544 date of Exp 03.2015
- THF, tetrahydrofuran CAS Number 109-99-9
- Ethyl alcohol (Ethanol) 96% CAS 64-17-5
- Latanoprost CAS 1302-9-82-4 Lot PG01-20140101 Mfg date 05/01/2014 Manufacturer codes - R-0673.14 , 584-03
- Polyurethane HAPCO - Steralloy™ FDG – Elastomeric, No.2781 (4A: B)
- Triton™ X-100 , SIGMA-ALDRICH 5ml – CAS Number 9002-93-1

[000218]

[000219] Equipment:

- Kern ABJ 80-4NM Analytical balance 0,1 mg
- Freezer EL2280 Electra.
- Mini dry bath –Minilb-100,Miulab instruments, Lumitron ltd
- Mortar and pestle
- Orbital Shaker – SSM1, Stuart – England
- Desiccators (Pre-dried in oven for 2 hours, 200˚C) 334278 SIGMA-ALDRICH, Molecular sieves, 3 Å, pellets, 3.2 mm.

[000220]

[000221] Additional materials used:

- Molding block - pressing and molding the composite with PU into cylinder shape
- Aluminum foil
- Plastic cups

[000222]

[000223] Sample preparation methodology:

Only composite samples (type 3):

1. **Particulate Preparation(FS60) for only composite sample**
   - 6ml solvents mixture of THF : Ethanol 1 : 1 (w/w)
   - First Latanoprost mixing with solvents and then adding FS
   - FS60: 0.29g FS + (0.44g LP + 5 g solvent) → Drying 2 days RT

2. **Matrix Preparation (See table 4.1 below for amounts)**
   - EPOXY solution preparation→ 1g Part A and 0.25g Part B
   - Kaolin + FS60 + Epoxy → Dried at Room Temp for 2 days
   - **LP14.5% Composite** plug to 5 mg sample (cylinder shape)

Table 4.1

Matrix	FS60(gr)	KAOLIN(gr)	EPOXY(gr)	Final LP
LP14.5% Composite	**0.054**	**0.0824**	**0.0863**	**14.62%**

PU + Composite powder (type 1 and type 2)

1. **Particulate Preparation(FS60) for PU+Composite powder**
   - 10ml solvents mixture of THF : Ethanol 1 : 1 (w/w)
   - First Latanoprost mixing with solvents and then adding FS
   - FS60: 0.6648g FS + (1g LP + 10 g solvent) → Drying 2 days RT

2. **Matrix Preparation (See table 4.2 below for amounts)**
   - EPOXY solution preparation→ 1g Part A and 0.25g Part B
   - Kaolin + FS60 + Epoxy → Dried at Room Temp for 2 days

- Grinding dried **LP-FS60** using mortar.
- Drying grinded **LP-FS60** using desiccators for 3 days.

Table 4.2 Composite

Matrix	FS60(gr)	KAOLIN(gr)	EPOXY(gr)	Final LP
LP35.5%-Composite (for PU)	**1.203**	**0.421**	**0.409**	**35.53%**

3. PU Sample preparation: Polyurethane HAPCO 2781 solution preparation→

   4g Part A and 1g Part B.

[000224] Samples:

Plug Sample (PU	LP35.5%-Composite-15-03-2015 (gr)	PU (gr)	Final LP %
LP14%	**0.509**	**0.78**	**14.0%**

[000225]

[000226]

- **Solution preparation for the incubation of the plugs (PBS + BAK + Triton)**
- Weighting BAK and TRITON (see table for amounts)
- Adding PBS

TRITON %	TRITON (gr)	BAK %	BAK (gr)	PBS ml
0.1006	**0.0403**	**0.0056**	**0.0023**	**40.00**

Samples:

- Preparing controls according to the table
- Adding 0.5ml gr solution to 1.5 vials
- Putting samples into vials
- Putting vials into heater at 37 degrees C
- Putting heater onto agitator on 30 RPM
- Remove samples according to "sink condition method"

[000204] Sample

	SAMPLES	Days at 37	Composite Weight	PBS+BAK(0.005%)+TRITON(0.1%)	
	NEXTAR RUN 9	in PBS + BAK +Triton	5 mg	0.5 g	PLUG DESIGN
10-1	LP14-0315-1W-CO1	1	5.71	0.5331	ONLY COMPOSITE
10-2	LP14-0315-3W-CO1	3	5.71	0.5339	ONLY COMPOSITE
10-3	LP14-0315-5W-CO1	5	5.71	0.5318	ONLY COMPOSITE
10-4	LP14-0315-7W-CO1	7	5.71	0.5336	ONLY COMPOSITE
10-5	LP14-0315-9W-CO1	9	5.71	0.5343	ONLY COMPOSITE
10-6	LP14-0315-14W-CO1	14	5.71	0.5345	ONLY COMPOSITE
10-7	LP14-0315-21W-CO1	21	5.71	0.5331	ONLY COMPOSITE
10-8	LP14-0315-28W-CO1	28	5.71	0.5315	ONLY COMPOSITE
10-9	LP14-0315-48W-CO1	48	5.71	0.5290	ONLY COMPOSITE
10-10	LP14-0315-79W-CO1	79	5.71	0.5341	ONLY COMPOSITE
10-11	LP14-0315-109W-CO1	109	5.71	0.5300	ONLY COMPOSITE
10-12	LP14-0315-1W-CO2	1	5.81	0.5320	ONLY COMPOSITE
10-13	LP14-0315-3W-CO2	3	5.81	0.5319	ONLY COMPOSITE
10-14	LP14-0315-5W-CO2	5	5.81	0.5293	ONLY COMPOSITE
10-15	LP14-0315-7W-CO2	7	5.81	0.5187	ONLY COMPOSITE
10-16	LP14-0315-9W-CO2	9	5.81	0.5191	ONLY COMPOSITE
10-17	LP14-0315-14W-CO2	14	5.81	0.5264	ONLY COMPOSITE
10-18	LP14-0315-21W-CO2	21	5.81	0.5140	ONLY COMPOSITE
10-19	LP14-0315-28W-CO2	28	5.81	0.5099	ONLY COMPOSITE
10-20	LP14-0315-48W-CO2	48	5.81	0.5177	ONLY COMPOSITE
10-21	LP14-0315-79W-CO2	79	5.81	0.5078	ONLY COMPOSITE
10-22	LP14-0315-109W-CO2	109	5.81	0.5124	ONLY COMPOSITE
10-23	LP14-0315-1W-P1	1	4.80	0.5080	POWDER with PU
10-24	LP14-0315-3W-P1	3	4.80	0.5158	POWDER with PU
10-25	LP14-0315-5W-P1	5	4.80	0.5138	POWDER with PU
10-26	LP14-0315-7W-P1	7	4.80	0.5132	POWDER with PU
10-27	LP14-0315-9W-P1	9	4.80	0.5146	POWDER with PU
10-28	LP14-0315-14W-P1	14	4.80	0.5007	POWDER with PU
10-29	LP14-0315-21W-P1	21	4.80	0.5203	POWDER with PU
10-30	LP14-0315-28W-P1	28	4.80	0.5122	POWDER with PU
10-31	LP14-0315-48W-P1	48	4.80	0.5217	POWDER with PU
10-32	LP14-0315-79W-P1	79	4.80	0.5150	POWDER with PU
10-33	LP14-0315-109W-P1	109	4.80	0.5230	POWDER with PU
10-34	LP14-0315-1W-P2	1	5.15	0.5232	POWDER with PU
10-35	LP14-0315-3W-P2	3	5.15	0.5211	POWDER with PU
10-36	LP14-0315-5W-P2	5	5.15	0.5195	POWDER with PU
10-37	LP14-0315-7W-P2	7	5.15	0.5261	POWDER with PU
10-38	LP14-0315-9W-P2	9	5.15	0.5206	POWDER with PU
10-39	LP14-0315-14W-P2	14	5.15	0.5151	POWDER with PU
10-40	LP14-0315-21W-P2	21	5.15	0.5204	POWDER with PU
10-41	LP14-0315-28W-P2	28	5.15	0.5192	POWDER with PU
10-42	LP14-0315-48W-P2	48	5.15	0.5158	POWDER with PU
10-43	LP14-0315-79W-P2	79	5.15	0.5197	POWDER with PU
10-44	LP14-0315-109W-P2	109	5.15	0.5191	POWDER with PU
9-1	LP14-0315-1W-PY1	1	4.46	0.5303	COATED POWDER with PU
9-2	LP14-0315-3W-PY1	3	4.46	0.5320	COATED POWDER with PU
9-3	LP14-0315-5W-PY1	5	4.46	0.5309	COATED POWDER with PU
9-4	LP14-0315-7W-PY1	7	4.46	0.5306	COATED POWDER with PU
9-5	LP14-0315-9W-PY1	9	4.46	0.5317	COATED POWDER with PU
9-6	LP14-0315-14W-PY1	14	4.46	0.5381	COATED POWDER with PU
9-7	LP14-0315-21W-PY1	21	4.46	0.5342	COATED POWDER with PU
9-8	LP14-0315-28W-PY1	28	4.46	0.5366	COATED POWDER with PU
9-9	LP14-0315-48W-PY1	48	4.46	0.5357	COATED POWDER with PU
9-10	LP14-0315-79W-PY1	79	4.46	0.5366	COATED POWDER with PU
9-11	LP14-0315-109W-PY1	109	4.46	0.5316	COATED POWDER with PU
9-12	LP14-0315-1W-PY2	1	4.23	0.5267	COATED POWDER with PU
9-13	LP14-0315-3W-PY2	3	4.23	0.5152	COATED POWDER with PU
9-14	LP14-0315-5W-PY2	5	4.23	0.5303	COATED POWDER with PU
9-15	LP14-0315-7W-PY2	7	4.23	0.5220	COATED POWDER with PU
9-16	LP14-0315-9W-PY2	9	4.23	0.5329	COATED POWDER with PU
9-17	LP14-0315-14W-PY2	14	4.23	0.5137	COATED POWDER with PU
9-18	LP14-0315-21W-PY2	21	4.23	0.5222	COATED POWDER with PU
9-19	LP14-0315-28W-PY2	28	4.23	0.5305	COATED POWDER with PU
9-20	LP14-0315-48W-PY2	48	4.23	0.5297	COATED POWDER with PU
9-21	LP14-0315-79W-PY2	79	4.23	0.5339	COATED POWDER with PU
9-22	LP14-0315-109W-PY2	109	4.23	0.5286	COATED POWDER with PU

[000205] Example: sample testing of polyurethane coated plugs

[000206] Plugs tested: Polyurethane:FS60 (60% Fused Silica :40% Latanoprost); final drug content is 14.4%. Samples were incubated at 37 degrees Celsius for

varying time periods to determine the time effect of Latanoprost release profile from the sample into the PBS solution.

[000207] Reagents and Equipment:

Reagents

- Kaolin USP Sigma C.N k1512-500G,
- Hexan, ANHYDROUS, 95%, Sigma C.N 296090-1L,
- Silica, Fumed Avg. Part. Size. 0.2-0.3 Sigma C.N S5505-500G,
- EPOXY EPO-TEK Part A Batch PB046370
- EPOXY EPO-TEK Part B Batch PB046149
- Toluene Sigma CAS 108-88-3
- THF, tetrahydrofuran CAS Number 109-99-9
- Ethyl alcohol (Ethanol) 96% CAS 64-17-5
- Latanoprost CAS 1302-9-82-4 Lot PG01-20140101 Manufacturer codes - R-0673.14 , 584-03
- Triton™ X-100 , SIGMA-ALDRICH 5ml – CAS Number 9002-93-1
- Polyurethane PMC780 DRY shore80 2A:1B (not medical PU)

EQUIPMENT

- Kern ABJ 80-4NM Analytical balance 0,1 mg
- Freezer EL2280 Electra.
- Mini dry bath –Miniib-100,Miulab instruments, Lumitron ltd
- Mortar and pestle
- Orbital Shaker – SSM1, Stuart – England
- Desiccators (Pre-dried in oven for 2 hours, 200˚C) 334278 SIGMA-ALDRICH, Molecular sieves, 3 Å, pellets, 3.2 mm.

OTHER MATERIALS

- Molding block - pressing and molding the composite with PU into cylinder shape
- Aluminium foil
- Plastic cups

[000208] Sample preparation methodology:

Particulate Preparation(FS60) LP-FS60

- 6ml solvents mixture of THF : Ethanol 1 : 1 (w/w)
- First Latanoprost mixing with solvents and then adding FS
- FS60: 0.2g FS + (0.3g LP + 5 g solvent) → Drying 2 days RT
- FS with 5% TRITON (1gr FS + 0.053g TRITON + 10g Ethanol)

Matrix Preparation (See tables 4.2 for amounts)

- EPOXY solution preparation→ 1g Part A and 0.25g Part B
- Kaolin + FS60 + Epoxy → Dried at Room Temp for 2 days

- Grinding dried **LP-FS60** using mortar and pestle.
- Drying grinded **LP-FS60** using desiccators for 3 days.

Composite

Matrix	FS60(gr)	KAOLIN(gr)	EPOXY(gr)	Final LP
LP36%-Composite	0.34	0.11	0.11	36.0%

- **Sample Preparation (See table below for amounts)**
  - Polyurethane PMC780 solution preparation→ 2g Part A and 1g Part B

Samples

Sample	Company	Type	Shore	Parylene Coating	Butvar Coating	Exposure degree
E	Smooth-on	PMC 780	80	NO	NO	CONTROL
F	Smooth-on	PMC 780	80	YES	NO	Micro hole
G	Smooth-on	PMC 780	80	YES	NO	One side
H	Smooth-on	PMC 780	80	NO	YES	NO
I	Smooth-on	PMC 780	80	YES	NO	Two sides

Final Samples

Plug Sample	LP36%-Composite-09-2014 (gr)	PU (gr)	Final LP %
LP14%	0.055	0.085	14%

- **Solution Preparation**
  - 0.01M PBS + 0.005% BAK + 0.1% TRITON X-100

Table 4.5 Samples

2. SAMPLES PREPARATION: FS60 (Particulate Preparation)

- Weighing 3g HFE + 3g Ethanol = 6ml solvents mixture
- Weighing 0.3g LP
- Mixing gently LP with 2g solvents mixture using magnetic stirrer
- Weighing 0.2g FS
- Adding LP with solvents to 0.2g FS
- Mixing gently materials using spatula to avoid air
- Keeping in RT for 2 days

[000209] Figure 28A shows the sample at the beginning of a 2 day incubation at RT. Figure 28B shows the sample after 2 days at RT.

[000210] Composite preparation:

- Weighing FS60 and KAOLIN (see table for amounts)
- Mixing gently materials using spatula
- Adding EPOXY (Final solution A+B) (see table for amounts)
- Mixing materials using spatula
- Cutting 2 PE sheets
- Putting small composite granules (Cuscus shape)
- Staying in Refrigeration (4 Celsius) for two days

[000211] The composite samples are shown in Figure 29.

Final formulation

Ethanol	% (X100)	5% (X100)	FS(X100)	% drug in composite	Epoxy	Kaolin	FS concentrate
gr	Final	gr	gr		gr	gr	gr
0.300	0.120	0.001	0.015	**35.675**	0.130	0.111	0.375
Final 2.3							

Composite Milling

- Putting granules into mortar and use pestle to mill the granules to fine powder.
- Adding dried desiccators into plastic cup and adding powder to a small cup.

[000212] Figure 30 shows the dried desiccators placed in a plastic cup and adding powder to the 10 mL cup.

PU + composite:

- **Weighting 0.055 Composite**
- **Weighting part A and part B of PU**
- **Mixing for 5 minutes PU**
- **Weighting 0.085 PU**
- **Mixing PU and Composite into smooth paste (e.g., no particles were observed in this mixture)**
- **Putting the paste onto the molding block.**
- **Curing for 48hr in an ambient temperature**

Plug Sample	LP36%-Composite-09-2014 (gr)	PU (gr)	Final LP %
LP14%	0.056	0.086	14.0%

- **Solution preparation (PBS + BAK + Triton)**
- Weighting BAK and TRITON (see table for amounts)

- Adding PBS

TRITON %	TRITON (gr)	BAK %	BAK (gr)	PBS ml
0.095	0.0285	0.0060	0.0018	30.026

Samples

- Preparing controls according to the table
- Adding 0.5ml gr solution to 1.5 vials
- Weighting 5mg samples (0.005gr)
- Putting samples into vials
- Putting vials into heater at 37 degrees C
- Putting heater onto agitator on 30 RPM
- Remove samples according to "sink condition method" for example: Samples No. 3,11,19,27 Removing composites from vial after 3 days and putting vials in the refrigerator than put the composite in new vials 1,3,5,7,9, etc. (See, e.g., Figure 20)

	COMPOSITE FS60 + PU	Days at 37	Composite Weight	PBS+BAK(0.005%)+TRITON(0.1%)
	NEXTAR RUN 7	in PBS + BAK +Triton	3 mg	0.5 g
1	Con2 (PBS + BAK+ TRITON+ LP)	28 days at 4 Celcius	3.70	0.516
2	Con3 (PBS + BAK+ TRITON+ LP)	28 days at 37	3.5	0.634
3	LP14-1114-1D-E	1	2.0	0.548
4	LP14-1114-3D-E	3	2.0	0.566
5	LP14-1114-5D-E	5	2.0	0.583
6	LP14-1114-7D-E	7	2.0	0.571
7	LP14-1114-9D-E	9	2.0	0.553
8	LP14-1114-14D-E	14	2.0	0.546
9	LP14-1114-1D-F	1	3.6	0.526
10	LP14-1114-3D-F	3	3.6	0.542
11	LP14-1114-5D-F	5	3.6	0.599
12	LP14-1114-7D-F	7	3.6	0.549
13	LP14-1114-9D-F	9	3.6	0.494
14	LP14-1114-14D-F	14	3.6	0.507
15	LP14-1114-1D-G	1	2.8	0.544
16	LP14-1114-3D-G	3	2.8	0.515
17	LP14-1114-5D-G	5	2.8	0.575
18	LP14-1114-7D-G	7	2.8	0.523
19	LP14-1114-9D-G	9	2.8	0.618
20	LP14-1114-14D-G	14	2.8	0.564
21	LP14-1114-1D-H	1	3.3	0.587
22	LP14-1114-3D-H	3	3.3	0.611
23	LP14-1114-5D-H	5	3.3	0.546
24	LP14-1114-7D-H	7	3.3	0.531
25	LP14-1114-9D-H	9	3.3	0.504
26	LP14-1114-14D-H	14	3.3	0.536
27	LP14-1114-1D-I	1	2.6	0.510
28	LP14-1114-3D-I	3	2.6	0.580
29	LP14-1114-5D-I	5	2.6	0.541
30	LP14-1114-7D-I	7	2.6	0.553
31	LP14-1114-9D-I	9	2.6	0.539
32	LP14-1114-14D-I	14	2.6	0.549

[000213] Example: Timolol and Latanoprost

[000214] This example focuses on a sample containing:

[000215] PU (Hapco2781):FS60-(60% Latanoprost:40%Timolol), final Timolol content % is 8.1% and the final Latanoprost content % is 5.4%.

[000216] Reagents and equipment:

Reagents

- Kaolin USP Sigma C.N k1512-500G,
- Hexan, ANHYDROUS, 95%, Sigma C.N 296090-1L
- Silica, Fumed Avg. Part. Size. 0.2-0.3 Sigma C.N S5505-500G,
- EPOXY EPO-TEK Part A Batch PB116550
- EPOXY EPO-TEK Part B Batch PB116544
- THF, tetrahydrofuran CAS Number 109-99-9
- Ethyl alcohol (Ethanol) 96% CAS 64-17-5
- Latanoprost CAS 1302-9-82-4 Lot PG01-20140101
- Manufacturer codes - R-0673.14 , 584-03 (NEORE PHARMA)
- Timolol CAS 26921-17-5 Lot 140303 Mfg date 03/2014 (NEORE PHARMA)
- Polyurethane HAPCO - Steralloy™ FDG – Elastomeric, No.2781 (4A: B)
- Triton™ X-100 , SIGMA-ALDRICH 5ml – CAS Number 9002-93-1

EQUIPMENT

- Kern ABJ 80-4NM Analytical balance 0,1 mg
- Freezer EL2280 Electra.
- Mini dry bath –Miniib-100,Miulab instruments, Lumitron ltd
- Mortar and pestle
- Orbital Shaker – SSM1, Stuart – England
- Desiccators (Pre-dried in oven for 2 hours, 200˚C) 334278 SIGMA-ALDRICH, Molecular sieves, 3 Å, pellets, 3.2 mm.

OTHER MATERIALS

- Molding block - pressing and molding the composite with PU into cylinder shape
- Aluminum foil
- Plastic cups

[000217] Sample Preparation Methodology:

Particulate Preparation(FS60LTP) LP-FS60

- 6ml solvents mixture of THF : Ethanol 1 : 1 (w/w)
- Latanoprost mixing with solvents and then adding FS
- FS60: 0.2g FS + (0.33g LP + 5 g solvent) → Drying 2 days RT

Particulate Preparation(FS60TML) TML-FS60

- 6ml solvents mixture of THF : Ethanol 1 : 1 (w/w)
- Timolol mixing with solvents and then adding FS
- FS60: 0.2g FS + (0.33g TML + 5 g solvent) → Drying 1 day RT

Composite Matrix Preparation (See table below for amounts)

- EPOXY solution preparation→ 1g Part A and 0.25g Part B
- Kaolin + FS60 + Epoxy → Dried at Room Temp for 2 days (see table below)
- Grinding dried **FS60** (for PU) using mortar.
- Drying grinded **FS60** (for PU) using desiccators for 3 days.

Composite

% drug in composite LTP	% drug in composite TIM	Epoxy	Kaolin	FS TOTAL	FS LTP	FS TIM
		g	g		g	g
13.53834586	20.3075188	0.44	0.333333333	1	0.4	0.6
				%	%	%

Sample Preparation (See tables 4.3 for amounts)

- Polyurethane HAPCO 2781 solution preparation→ 4g Part A and 1g Part B were mixed together and 0.53 grams of the mixture was used for the formulation

Samples

Plug Sample	Composite powder (gr)	PU (gr)	Final TML %	Final LP %
LP&TML-0615	**0.35**	**0.53**	**8.1%**	**5.4%**

Solution Preparation

- **0.01M PBS + 0.005% BAK + 0.1% TRITON X-100**

Table 4.5 Samples

SAMPLES NEXTAR RUN 12	Days at 37 in PBS + BAK +Triton	Composite Weight 5 mg	PBS+BAK(0.005%)+TRITON(0.1%) 0.5 g
LP&TML-0615-1d-P1	1	3.90	0.525
LP&TML-0615-3d-P1	3	3.90	0.518
LP&TML-0615-5d-P1	5	3.90	0.520
LP&TML-0615-7d-P1	7	3.90	0.521
LP&TML-0615-9d-P1	9	3.90	0.517
LP&TML-0615-14d-P1	14	3.90	0.514
LP&TML-0615-21d-P1	21	3.90	0.516
LP&TML-0615-28d-P1	28	3.90	0.521
LP&TML-0615-48d-P1	58	3.90	0.516
LP&TML-0615-79d-P1	96	3.90	0.517
LP&TML-0615-109d-P1	126	3.90	0.565
LP&TML-0615-1d-P2	1	3.50	0.524
LP&TML-0615-3d-P2	3	3.50	0.520
LP&TML-0615-5d-P2	5	3.50	0.517
LP&TML-0615-7d-P2	7	3.50	0.522
LP&TML-0615-9d-P2	9	3.50	0.519
LP&TML-0615-14d-P2	14	3.50	0.522
LP&TML-0615-21d-P2	21	3.50	0.516
LP&TML-0615-28d-P2	28	3.50	0.521

SAMPLE PREPARATION

LP-FS60 (Particulate Preparation)

- Weighing 3g HFE + 3g Ethanol = 6ml solvents mixture
- Weighing 0.2g LP
- Mixing gently LP with 5g solvents mixture using magnetic stirrer
- Weighing 0.3g FS
- Adding LP with solvents to 0.3g FS
- Mixing gently materials using spatula to avoid air
- Keeping in RT for 1 day

TML-FS60 (Particulate Preparation)

- Weighing 3g HFE + 3g Ethanol = 6ml solvents mixture
- Weighing 0.2g TML
- Mixing gently TML with 5g solvents mixture using magnetic stirrer
- Weighing 0.3g FS
- Adding LP with solvents to 0.3g FS
- Mixing gently materials using spatula to avoid air
- Keeping in RT for 1 day

Composite

- Weighing FS60 and KAOLIN (as shown in table above)
- Mixing gently materials using spatula
- Adding EPOXY (Final solution A+B) (as shown in table above)
- Mixing materials using spatula
- Cutting 2 PE sheets
- Putting small composite granules (Cuscus shape)
- Staying in RT for two days

Composite Milling and PU

- Putting granules into mortar and use pestle to mill the granules to fine powder (e.g., but not limited to, <100 microns; e.g., but not limited to, 0.01 micron, 0.1 micron, 1 micron, etc.).
- Weighting 0.350 Composite powder
- Weighting part A and part B of PU
- Mixing for 5 minutes PU
- Weighting 0.53 PU
- Mixing PU and Composite into smooth paste
- Putting the paste onto the molding block.
- Curing for 48hr (to 30/06)

Solution preparation (PBS + BAK + Triton)

- Weighting BAK and TRITON (see table for amounts)

- Adding PBS

TRITON %	TRITON (gr)	BAK %	BAK (gr)	PBS ml
0.1116	0.0447	0.0058	0.0023	40.00

Samples

- Preparing controls
- Adding 0.5ml gr solution to 1.5 vials
- Putting samples into vials
- Putting vials into heater at 37 degrees C
- Putting heater onto agitator on 30 RPM
- Remove samples according to "sink condition method"

[000218] In some embodiments, the present invention is a composition, including: a bulking agent including a kaolin, an absorbent material including a fumed silica, a binder including an epoxy, and a first active agent including Latanoprost. In some embodiments, the first active agent measures between 5-40% by weight (w/w). In some embodiments, the first active agent measures between 5-35% by weight (w/w). In some embodiments, the first active agent measures between 5-30% by weight (w/w). In some embodiments, the first active agent measures between 5-25% by weight (w/w). In some embodiments, the first active agent measures between 5-20% by weight (w/w). In some embodiments, the first active agent measures between 5-15% by weight (w/w). In some embodiments, the first active agent measures between 5-10% by weight (w/w). In some embodiments, the first active agent measures between 10-40% by weight (w/w). In some embodiments, the first active agent measures between 15-40% by weight (w/w). In some embodiments, the first active agent measures between 20-40% by weight (w/w). In some embodiments, the first active agent measures between 25-40% by weight (w/w). In some embodiments, the first active agent measures between 30-40% by weight (w/w). In some embodiments, the first active agent measures between 35-40% by weight (w/w). In some embodiments, the first active agent measures between 10-35% by weight (w/w).

In some embodiments, the first active agent measures between 15-30% by weight (w/w). In some embodiments, the first active agent measures between 20-25% by weight (w/w). In some embodiments, the compound further includes a second active agent. In some embodiments, the second active agent is Timolol. In some embodiments, the second active agent measures between 5-40% by weight (w/w). In some embodiments, the second active agent measures between 5-35% by weight (w/w). In some embodiments, the second active agent measures between 5-30% by weight (w/w). In some embodiments, the second active agent measures between 5-25% by weight (w/w). In some embodiments, the second active agent measures between 5-20% by weight (w/w). In some embodiments, the second active agent measures between 5-15% by weight (w/w). In some embodiments, the second active agent measures between 5-10% by weight (w/w). In some embodiments, the second active agent measures between 10-40% by weight (w/w). In some embodiments, the second active agent measures between 15-40% by weight (w/w). In some embodiments, the second active agent measures between 20-40% by weight (w/w). In some embodiments, the second active agent measures between 25-40% by weight (w/w). In some embodiments, the second active agent measures between 30-40% by weight (w/w). In some embodiments, the second active agent measures between 35-40% by weight (w/w). In some embodiments, the second active agent measures between 10-35% by weight (w/w). In some embodiments, the second active agent measures between 15-30% by weight (w/w). In some embodiments, the second active agent measures between 20-25% by weight (w/w). In some embodiments, the composition further includes polyurethane. In some embodiments, the composition further includes a parylene coating. In some embodiments, the parylene coating measures between 2-5 micrometers (e.g., but not limited to, 2.1 micrometers, 2.2

micrometers, etc.) in thickness. In some embodiments, the composition includes a butvar coating. In some embodiments, the butvar coating measures between 2-5 micrometers (e.g., but not limited to, 2.1 micrometers, 2.2 micrometers, etc.) in thickness. In some embodiments, the composition is in the form of a punctal plug.

[000219] In some embodiments, the present invention is a method, including: administering a composition to an eye of a mammal in need thereof, where the composition releases between 0.5-10 micrograms of a first active agent per day, and where the composition includes: a bulking agent including a kaolin, an absorbent material including a fumed silica, a binder including an epoxy, and the first active agent includes Latanoprost. In some embodiments, the first active agent measures between 5-40% by weight (w/w). In some embodiments, the first active agent measures between 5-35% by weight (w/w). In some embodiments, the first active agent measures between 5-30% by weight (w/w). In some embodiments, the first active agent measures between 5-25% by weight (w/w). In some embodiments, the first active agent measures between 5-20% by weight (w/w). In some embodiments, the first active agent measures between 5-15% by weight (w/w). In some embodiments, the first active agent measures between 5-10% by weight (w/w). In some embodiments, the first active agent measures between 10-40% by weight (w/w). In some embodiments, the first active agent measures between 15-40% by weight (w/w). In some embodiments, the first active agent measures between 20-40% by weight (w/w). In some embodiments, the first active agent measures between 25-40% by weight (w/w). In some embodiments, the first active agent measures between 30-40% by weight (w/w). In some embodiments, the first active agent measures between 35-40% by weight (w/w). In some embodiments, the first active agent measures between 10-35% by weight (w/w). In some embodiments, the first active agent

measures between 15-30% by weight (w/w). In some embodiments, the first active agent measures between 20-25% by weight (w/w). In some embodiments, the method includes a second active agent. In some embodiments, the second active agent is Timolol. In some embodiments, the second active agent includes between 5-40% by weight (w/w). In some embodiments, the second active agent measures between 5-35% by weight (w/w). In some embodiments, the second active agent measures between 5-30% by weight (w/w). In some embodiments, the second active agent measures between 5-25% by weight (w/w). In some embodiments, the second active agent measures between 5-20% by weight (w/w). In some embodiments, the second active agent measures between 5-15% by weight (w/w). In some embodiments, the second active agent measures between 5-10% by weight (w/w). In some embodiments, the second active agent measures between 10-40% by weight (w/w). In some embodiments, the second active agent measures between 15-40% by weight (w/w). In some embodiments, the second active agent measures between 20-40% by weight (w/w). In some embodiments, the second active agent measures between 25-40% by weight (w/w). In some embodiments, the second active agent measures between 30-40% by weight (w/w). In some embodiments, the second active agent measures between 35-40% by weight (w/w). In some embodiments, the second active agent measures between 10-35% by weight (w/w). In some embodiments, the second active agent measures between 15-30% by weight (w/w). In some embodiments, the second active agent measures between 20-25% by weight (w/w). In some embodiments, the method includes a parylene coating. In some embodiments, the parylene coating measures between 2-5 micrometers (e.g., but not limited to, 2.1 micrometers, 2.2 micrometers, etc.) in thickness. In some embodiments, the composition includes a butvar coating. In some embodiments, the butvar coating

measures between 2-5 micrometers (e.g., but not limited to, 2.1 micrometers, 2.2 micrometers, etc.) in thickness. In some embodiments, the composition is in the form of a punctal plug.

[000220] In some embodiments, the composition of the present invention is a drug-delivery device comprising: a) a composite comprising the following elements: (i) particles of inert materials, where the inert materials are adsorbed with drug on surface of particles (e.g., drug bound to particles) or inside porosity (e.g., drug housed within pores); (ii) a bulking agent; (iii) an adhesive binder; or any combination thereof, and b) an optional coating on the whole or partial outer surface of the body/core; where the coating is complete/continuous or perforated, e.g., but not limited to, where the coating can be butvar and/or parylene.

[000221] In some embodiments, the present invention is a composition, including: a bulking agent including a kaolin and/or a pectin, an absorbent material including a fumed silica, a binder including an epoxy, and a first active agent including Latanoprost. In some embodiments, the first active agent measures between 5-50% by weight (w/w). In some embodiments, the first active agent measures between 5-45% by weight (w/w). In some embodiments, the first active agent measures between 5-40% by weight (w/w). In some embodiments, the first active agent measures between 5-35% by weight (w/w). In some embodiments, the first active agent measures between 5-30% by weight (w/w). In some embodiments, the first active agent measures between 5-25% by weight (w/w). In some embodiments, the first active agent measures between 5-20% by weight (w/w). In some embodiments, the first active agent measures between 5-15% by weight (w/w). In some embodiments, the first active agent measures between 5-10% by weight (w/w). In some embodiments, the first active agent measures between 10-50% by weight

(w/w). In some embodiments, the first active agent measures between 15-50% by weight (w/w). In some embodiments, the first active agent measures between 20-50% by weight (w/w). In some embodiments, the first active agent measures between 25-50% by weight (w/w). In some embodiments, the first active agent measures between 30-50% by weight (w/w). In some embodiments, the first active agent measures between 35-50% by weight (w/w). In some embodiments, the first active agent measures between 40-50% by weight (w/w). In some embodiments, the first active agent measures between 45-50% by weight (w/w). In some embodiments, the first active agent measures between 10-45% by weight (w/w). In some embodiments, the first active agent measures between 15-40% by weight (w/w). In some embodiments, the first active agent measures between 20-35% by weight (w/w). In some embodiments, the first active agent measures between 20-30% by weight (w/w). In some embodiments, the compound further includes a second active agent. In some embodiments, the second active agent is Timolol. In some embodiments, the second active agent measures between 5-40% by weight (w/w). In some embodiments, the second active agent measures between 5-35% by weight (w/w). In some embodiments, the second active agent measures between 5-30% by weight (w/w). In some embodiments, the second active agent measures between 5-25% by weight (w/w). In some embodiments, the second active agent measures between 5-20% by weight (w/w). In some embodiments, the second active agent measures between 5-15% by weight (w/w). In some embodiments, the second active agent measures between 5-10% by weight (w/w). In some embodiments, the second active agent measures between 10-40% by weight (w/w). In some embodiments, the second active agent measures between 15-40% by weight (w/w). In some embodiments, the second active agent measures between 20-40% by weight (w/w). In some embodiments, the

second active agent measures between 25-40% by weight (w/w). In some embodiments, the second active agent measures between 30-40% by weight (w/w). In some embodiments, the second active agent measures between 35-40% by weight (w/w). In some embodiments, the second active agent measures between 10-35% by weight (w/w). In some embodiments, the second active agent measures between 15-30% by weight (w/w). In some embodiments, the second active agent measures between 20-25% by weight (w/w). In some embodiments, the composition further includes polyurethane. In some embodiments, the composition further includes a parylene coating. In some embodiments, the parylene coating measures between 2-5 micrometers (e.g., but not limited to, 2.1 micrometers, 2.2 micrometers, etc.) in thickness. In some embodiments, the composition includes a butvar coating. In some embodiments, the butvar coating measures between 2-5 micrometers (e.g., but not limited to, 2.1 micrometers, 2.2 micrometers, etc.) in thickness. In some embodiments, the composition is in the form of a punctal plug.

[000222] In some embodiments, the present invention is a method, including: administering a composition to an eye of a mammal in need thereof, where the composition releases between 0.5-10 micrograms of a first active agent per day, and where the composition includes: a bulking agent including a kaolin, an absorbent material including a fumed silica, a binder including an epoxy, and the first active agent includes Latanoprost. In some embodiments, the first active agent measures between 5-50% by weight (w/w). In some embodiments, the first active agent measures between 5-45% by weight (w/w). In some embodiments, the first active agent measures between 5-40% by weight (w/w). In some embodiments, the first active agent measures between 5-35% by weight (w/w). In some embodiments, the first active agent measures between 5-30% by weight (w/w). In some embodiments,

the first active agent measures between 5-25% by weight (w/w). In some embodiments, the first active agent measures between 5-20% by weight (w/w). In some embodiments, the first active agent measures between 5-15% by weight (w/w). In some embodiments, the first active agent measures between 5-10% by weight (w/w). In some embodiments, the first active agent measures between 10-50% by weight (w/w). In some embodiments, the first active agent measures between 15-50% by weight (w/w). In some embodiments, the first active agent measures between 20-50% by weight (w/w). In some embodiments, the first active agent measures between 25-50% by weight (w/w). In some embodiments, the first active agent measures between 30-50% by weight (w/w). In some embodiments, the first active agent measures between 35-50% by weight (w/w). In some embodiments, the first active agent measures between 40-50% by weight (w/w). In some embodiments, the first active agent measures between 45-50% by weight (w/w). In some embodiments, the first active agent measures between 10-35% by weight (w/w). In some embodiments, the first active agent measures between 10-45% by weight (w/w). In some embodiments, the first active agent measures between 15-40% by weight (w/w). In some embodiments, the first active agent measures between 20-35% by weight (w/w). In some embodiments, the first active agent measures between 25-30% by weight (w/w). In some embodiments, the method includes a second active agent. In some embodiments, the second active agent is Timolol. In some embodiments, the second active agent includes between 5-40% by weight (w/w). In some embodiments, the second active agent measures between 5-35% by weight (w/w). In some embodiments, the second active agent measures between 5-30% by weight (w/w). In some embodiments, the second active agent measures between 5-25% by weight (w/w). In some embodiments, the second active agent measures between 5-20% by

weight (w/w). In some embodiments, the second active agent measures between 5-15% by weight (w/w). In some embodiments, the second active agent measures between 5-10% by weight (w/w). In some embodiments, the second active agent measures between 10-40% by weight (w/w). In some embodiments, the second active agent measures between 15-40% by weight (w/w). In some embodiments, the second active agent measures between 20-40% by weight (w/w). In some embodiments, the second active agent measures between 25-40% by weight (w/w). In some embodiments, the second active agent measures between 30-40% by weight (w/w). In some embodiments, the second active agent measures between 35-40% by weight (w/w). In some embodiments, the second active agent measures between 10-35% by weight (w/w). In some embodiments, the second active agent measures between 15-30% by weight (w/w). In some embodiments, the second active agent measures between 20-25% by weight (w/w). In some embodiments, the method includes a parylene coating. In some embodiments, the parylene coating measures between 2-5 micrometers (e.g., but not limited to, 2.1 micrometers, 2.2 micrometers, etc.) in thickness. In some embodiments, the composition includes a butvar coating. In some embodiments, the butvar coating measures between 2-5 micrometers (e.g., but not limited to, 2.1 micrometers, 2.2 micrometers, etc.) in thickness. In some embodiments, the composition is in the form of a punctal plug.

[000223] While a number of embodiments of the present invention have been described, it is understood that these embodiments are illustrative only, and not restrictive, and that many modifications may become apparent to those of ordinary skill in the art. Further still, the various steps may be carried out in any desired order (and any desired steps may be added and/or any desired steps may be eliminated).

CLAIMS:

What is claimed is:

1. A composition, comprising:

a bulking agent comprising a kaolin,

an absorbent material comprising a fumed silica,

a binder comprising an epoxy, and

a first active agent comprising Latanoprost.

2. The composition of claim 1, wherein the first active agent measures between 5-40% by weight (w/w).

3. The composition of claim 1, further comprising a second active agent, wherein the second active agent comprises between 5-40% by weight (w/w) of Timolol.

4. The composition of claim 3, wherein the second active agent measures between 5-40% by weight (w/w).

5. The composition of claim 1, further comprising polyurethane.

6. The composition of claim 1, further comprising a parylene coating.

7. The composition of claim 6, wherein the parylene coating measures between 2-5 micrometers in thickness.

8. The composition of claim 1, further comprising a butvar coating.

9. The composition of claim 8, wherein the butvar coating measures between 2-5 micrometers in thickness.

10. The composition of claim 1, wherein the composition is in the form of a punctal plug.

11. A method, comprising:

administering a composition to an eye of a mammal in need thereof, wherein the composition releases between 0.5-10 micrograms of a first active agent per day, and

wherein the composition comprises:

a bulking agent comprising a kaolin,

an absorbent material comprising a fumed silica,

a binder comprising an epoxy, and

the first active agent comprises Latanoprost.

12. The method of claim 11, wherein the first active agent measures between 5-40% by weight (w/w).

13. The method of claim 11, further comprising a second active agent.

14. The method of claim 13, wherein the second active agent is Timolol.

15. The method of claim 14, wherein the second active agent comprises between 5-40% by weight of Timolol.

16. The method of claim 11, further comprising a parylene coating.

17. The method of claim 16, wherein the parylene coating measures between 2-5 micrometers in thickness.

18. The method of claim 11, further comprising a butvar coating.

19. The method of claim 18, wherein the butvar coating measures between 2-5 micrometers in thickness.

20. The method of claim 11, wherein the composition is in the form of a punctal plug.

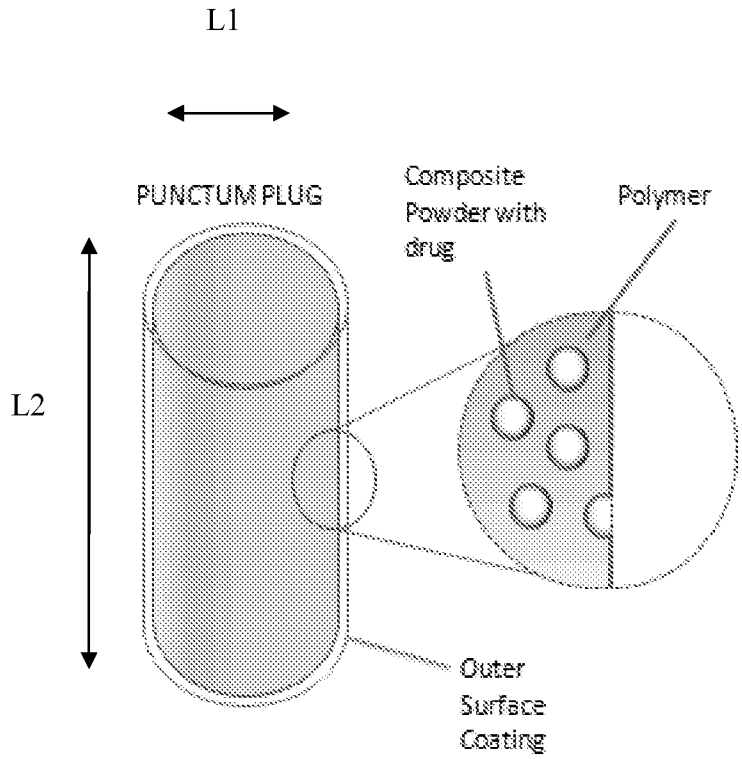


FIGURE 1A

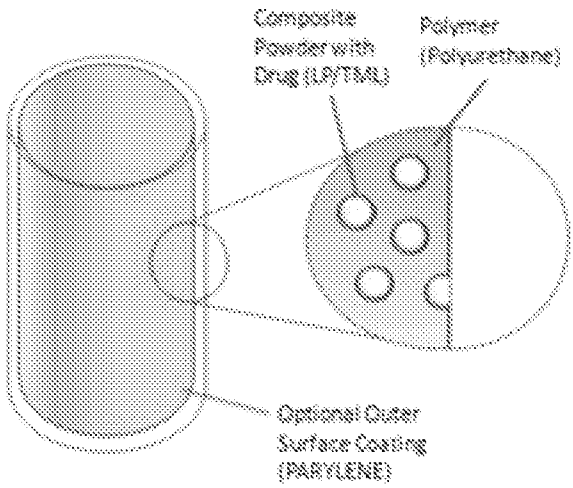


FIGURE 1B

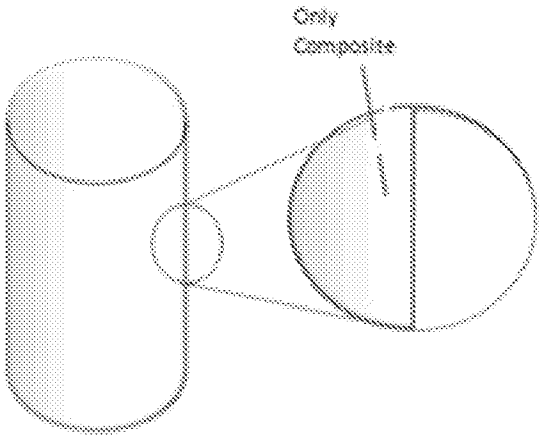


FIGURE 1C

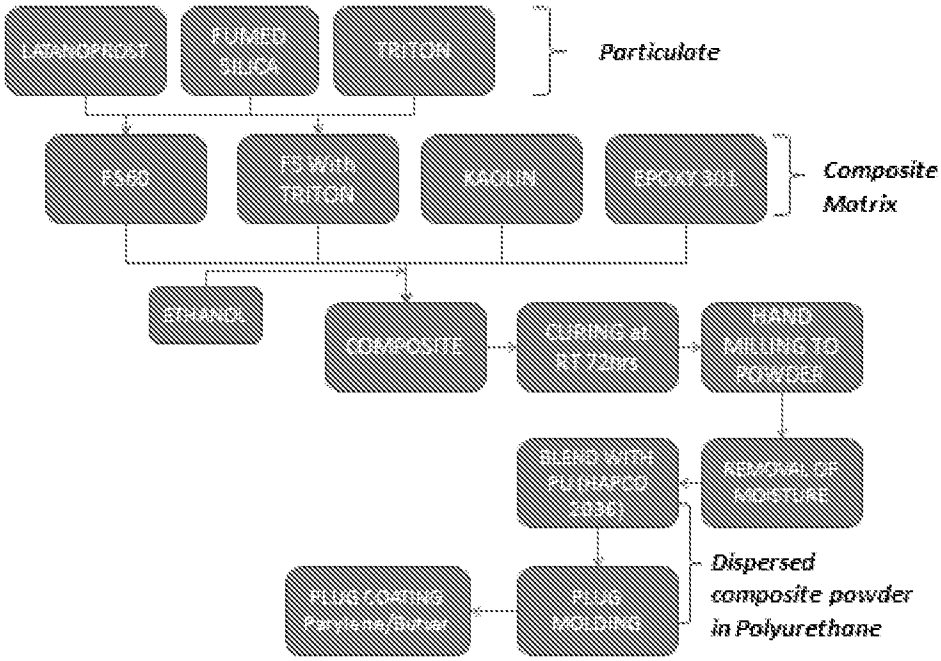


FIGURE 2A

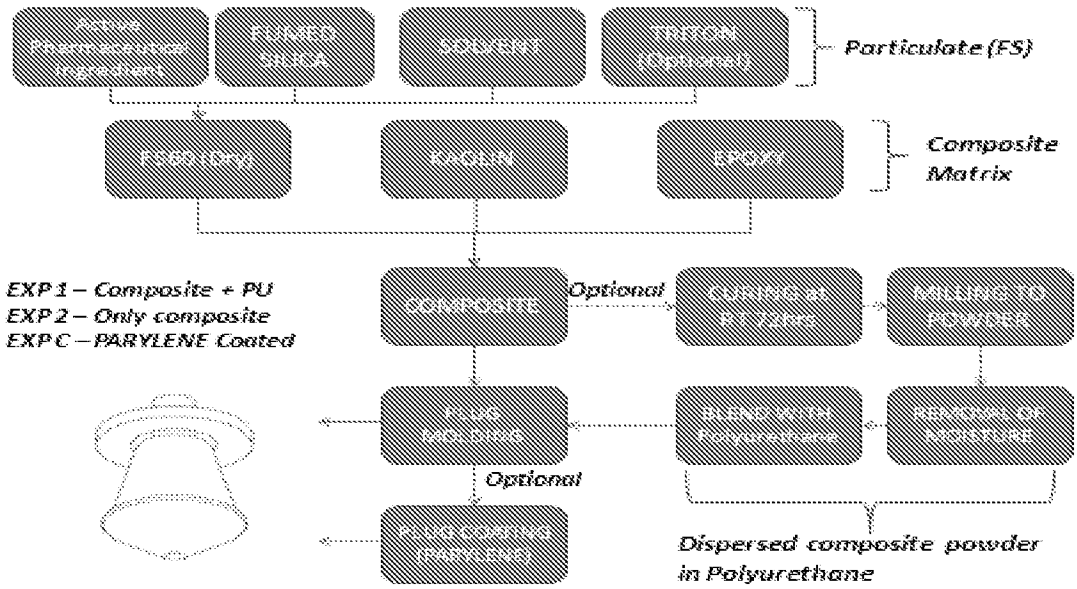


FIGURE 2B

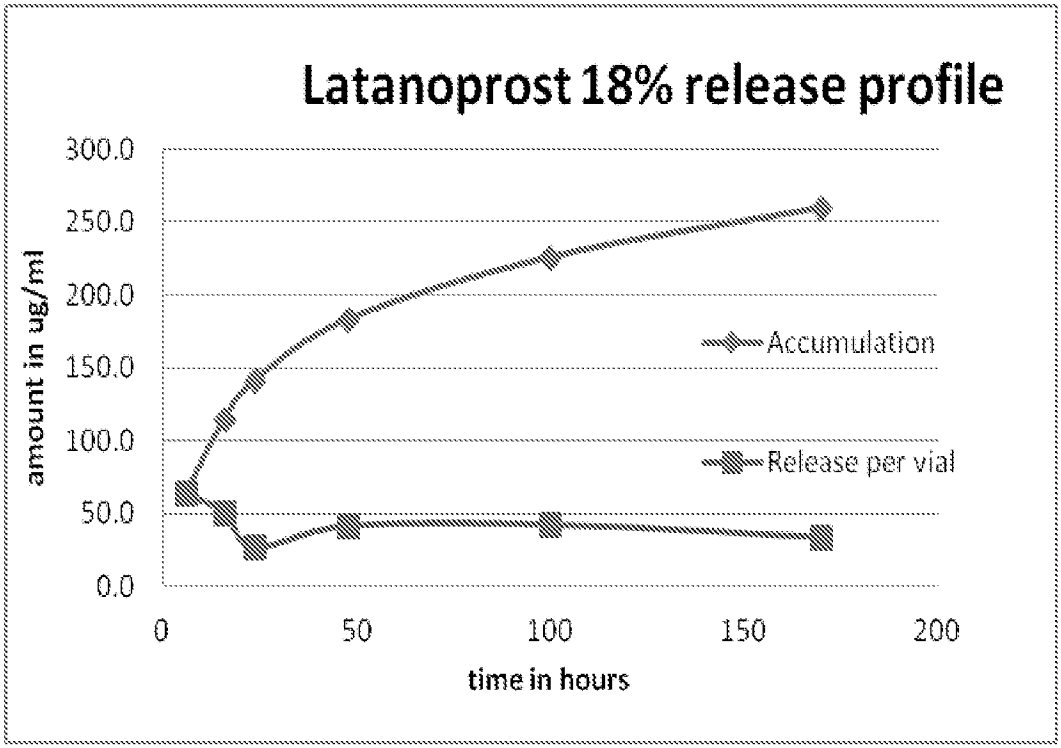

Latanoprost 18% release profile
300.0
250.0
200.0
150.0
100.0
50.0
0.0
amount in ug/ml
0
50
100
150
200
time in hours
Accumulation
Release per vial

FIGURE 3

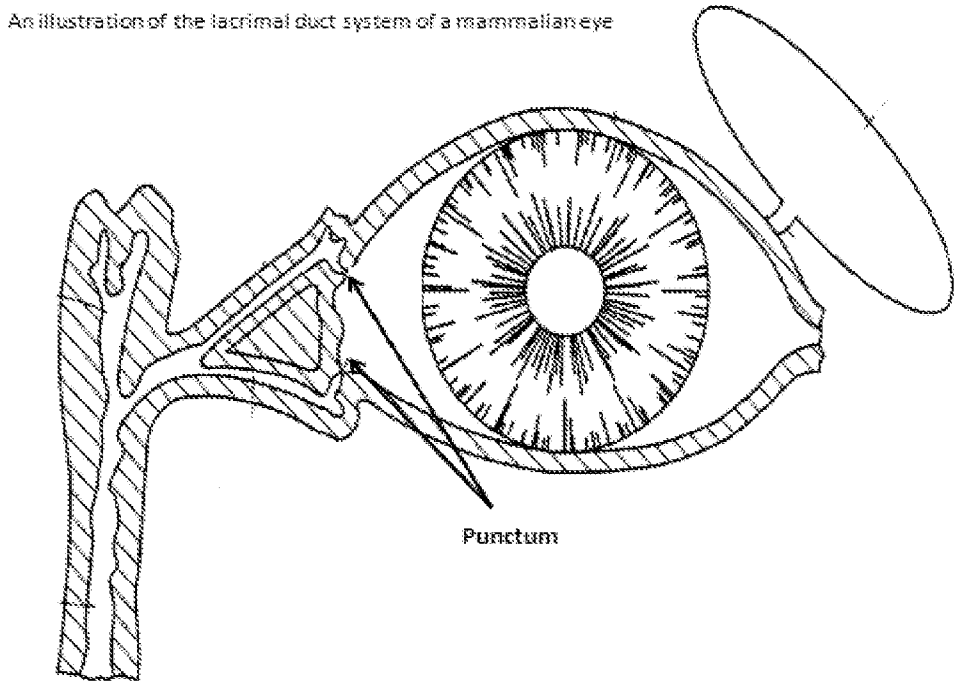


FIGURE 4

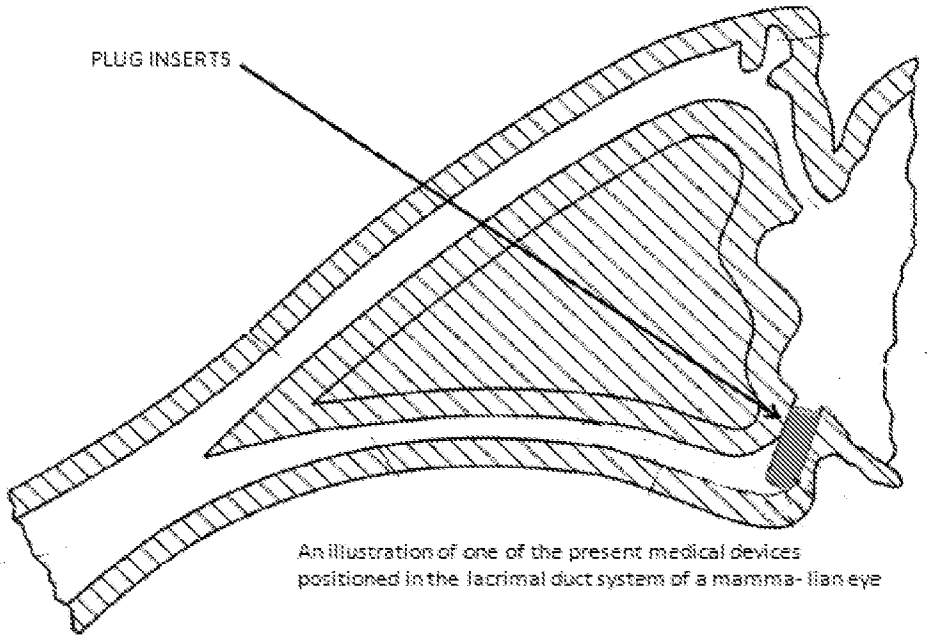


FIGURE 5

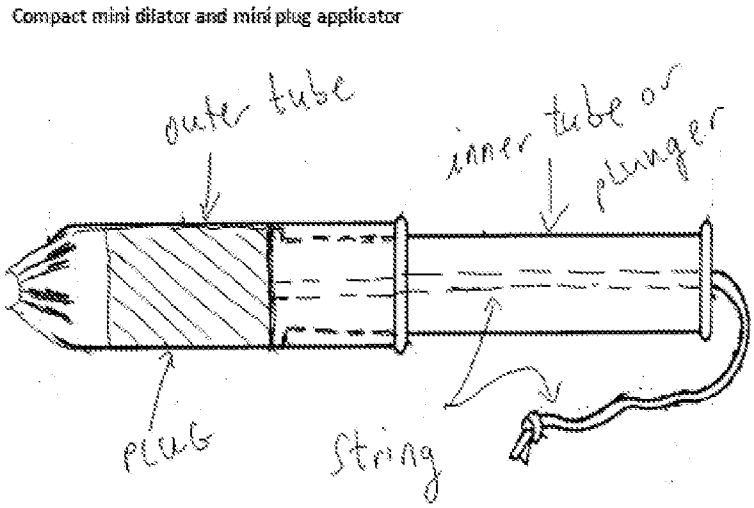


FIGURE 6

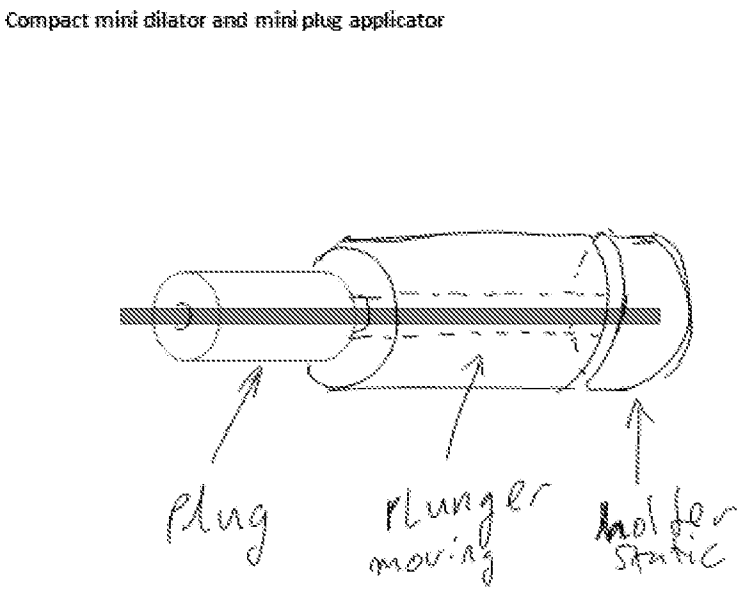


FIGURE 7

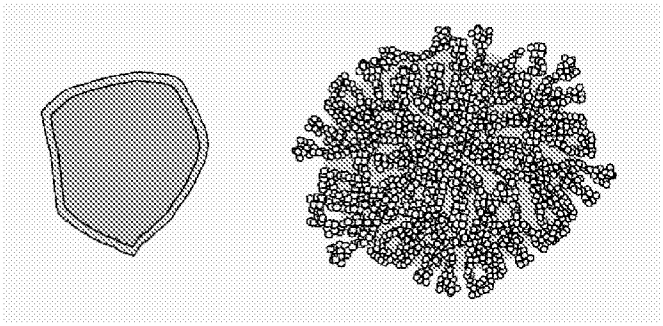


FIGURE 8

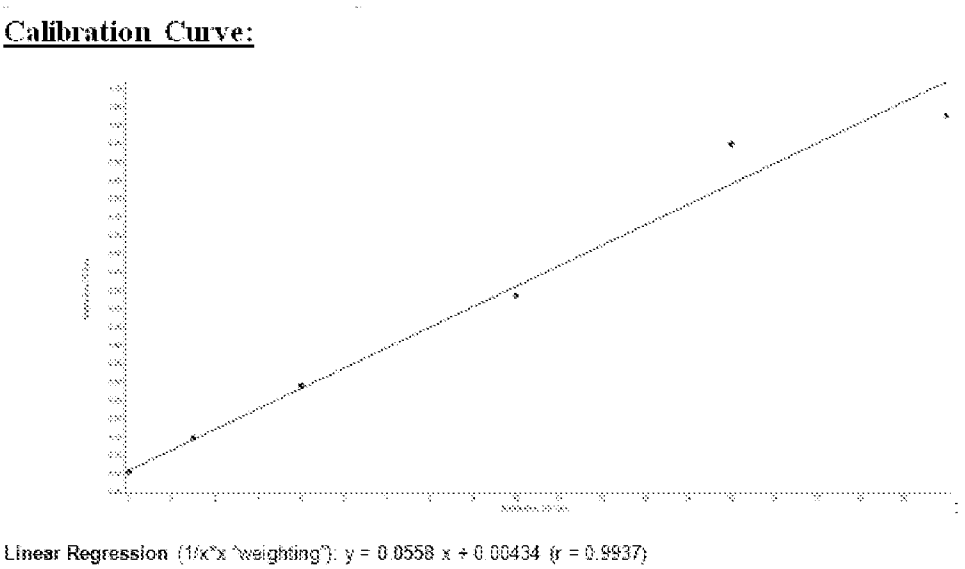
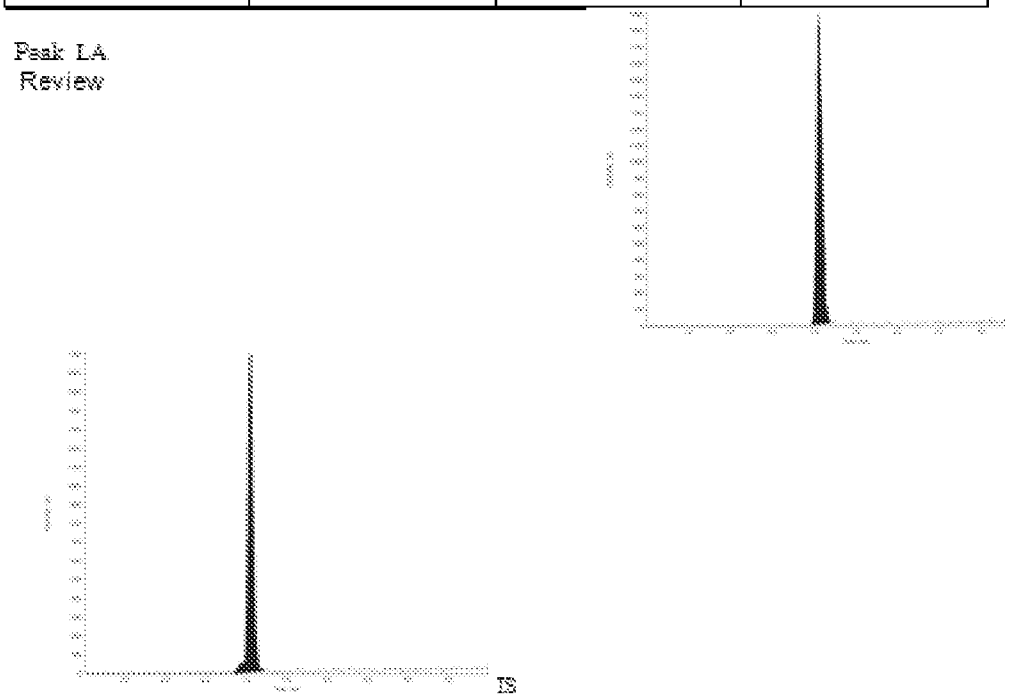


FIGURE 9

Sample Name	Lin A6	Result Table	18May15.rdb
Acquisition Date	5/17/2015 3:54:42 PM	Data File	Data17May15.wiff
Acquisition Method	Ex7.dam	Injection Vial	66
Project	Ext2015_05_04	Regression Equation	y = 0.0558 x + 0.00434 (r = 0.9937)
Instrument Name	3200 Q TRAP		



Peak Name	Sample type	Target Conc ng/mL	RT min	Analyte peak Area	IS peak Area	Peak area Ratio	Found ng/mL	% Accuracy
LA	Standard	20.00	7.10	8990	8763	1.026	18.30	91.50

FIGURE 10

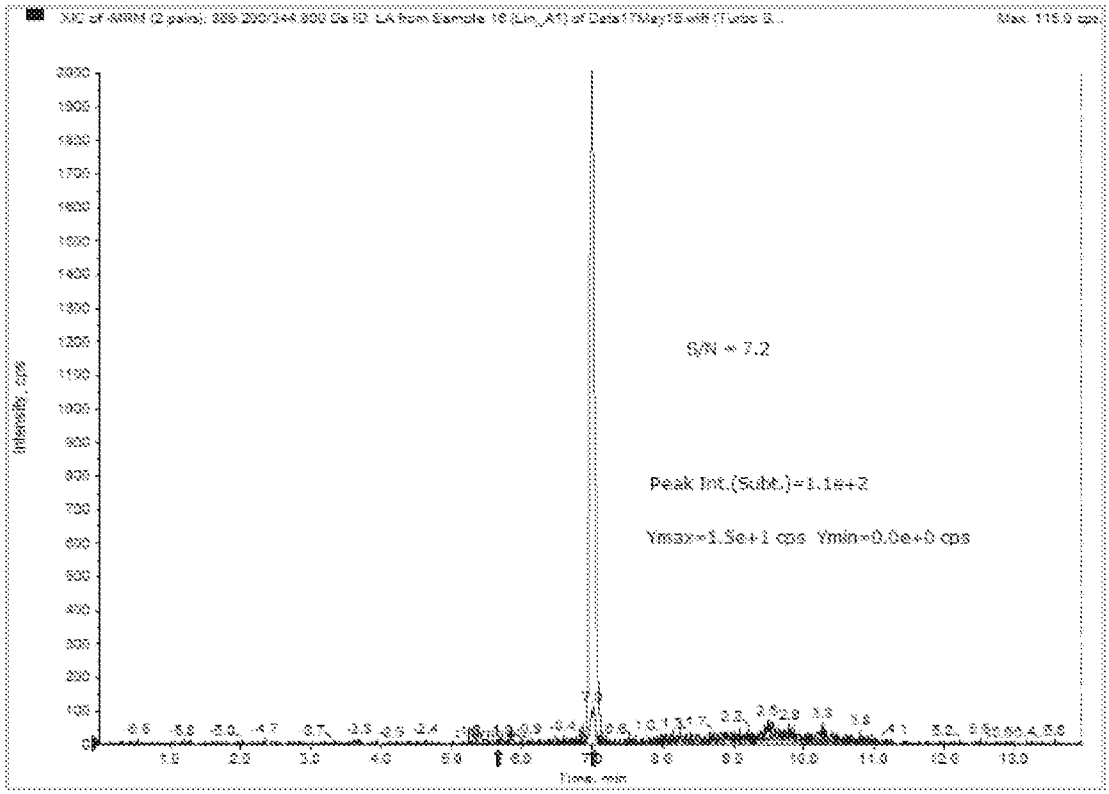


FIGURE 11

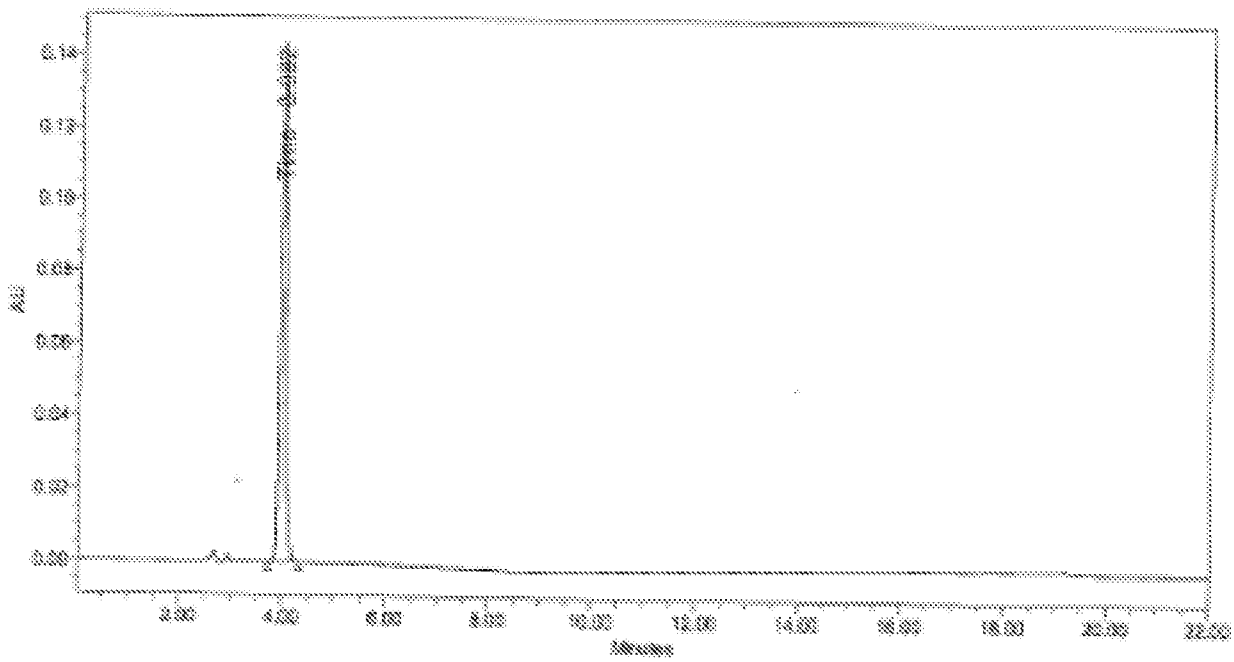


FIGURE 12

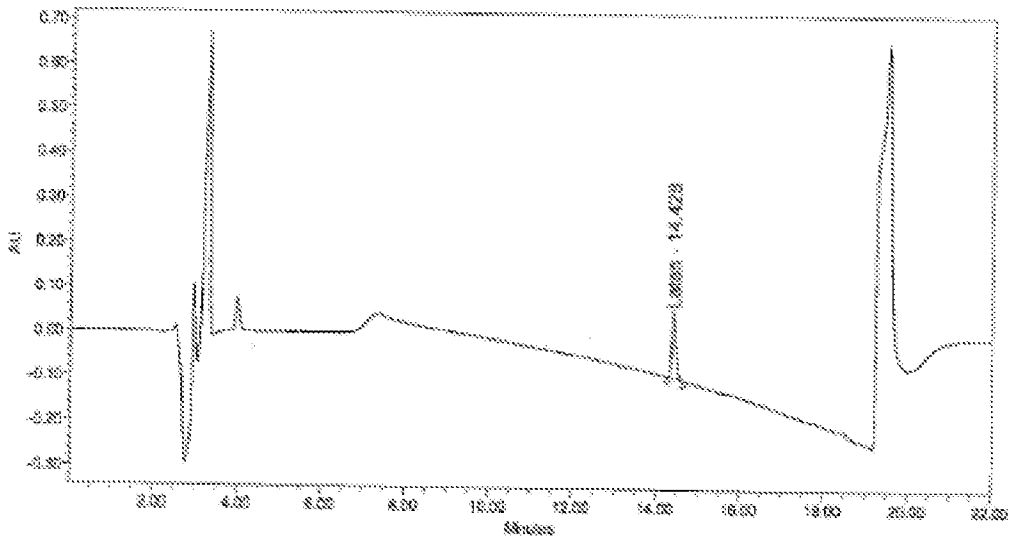


FIGURE 13

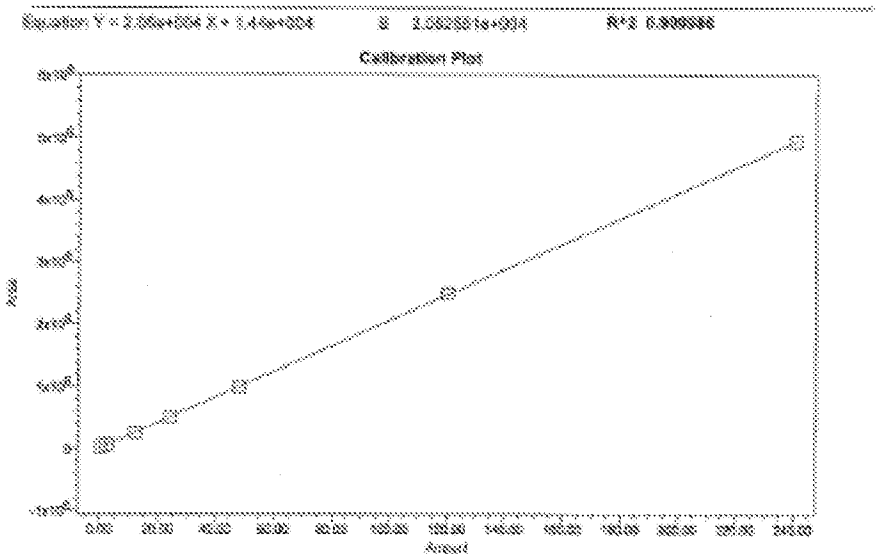


FIGURE 14A

Peak Table

	SampleName	Vial	X Value	Date Acquired	Area (µV*sec)	Manual	Ignore	Calc. Value	% Deviation
1	A1	65	0.481200	8/30/2015 3:02:53 PM	27936	No	No	0.653342	35.773
2	A2	66	2.406000	8/30/2015 3:20:01 PM	66291	No	No	2.672349	11.381
3	A3	67	12.030000	8/30/2015 3:48:09 PM	275632	No	No	11.957532	-0.652
4	A4	68	24.060000	8/30/2015 4:12:17 PM	552453	No	No	23.681128	-1.578
5	A5	69	48.120000	8/30/2015 4:36:26 PM	994841	No	No	47.767137	-0.723
6	A6	70	120.300000	8/30/2015 4:58:32 PM	2463863	No	No	120.795201	0.415
7	A7	71	240.600000	8/30/2015 5:21:41 PM	4946948	No	No	240.405302	-0.058

FIGURE 14B

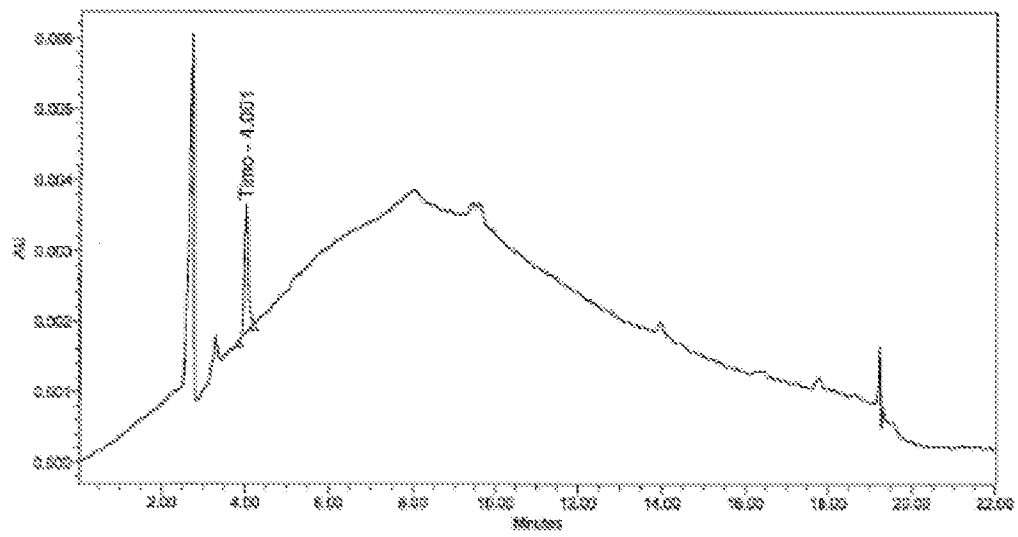


FIGURE 15

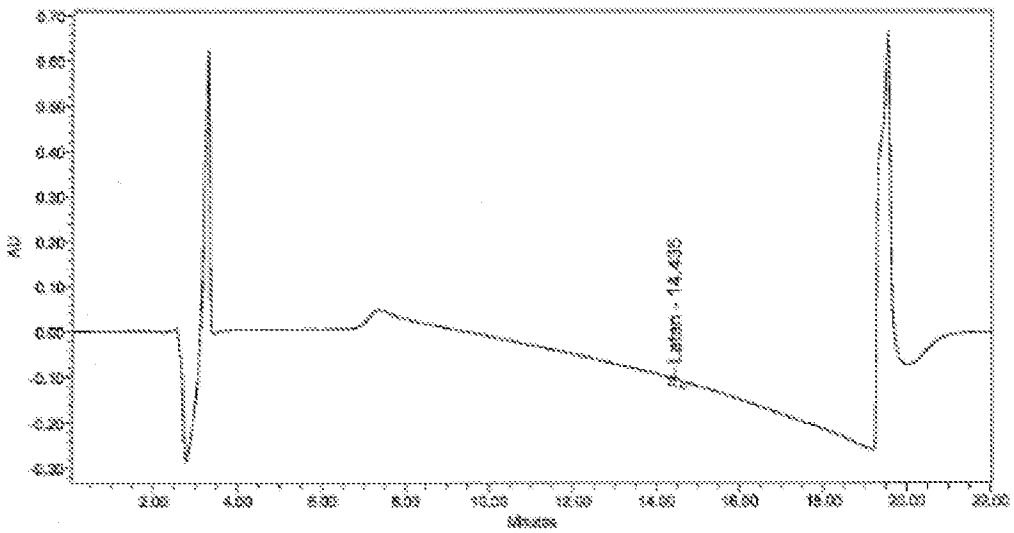


FIGURE 16

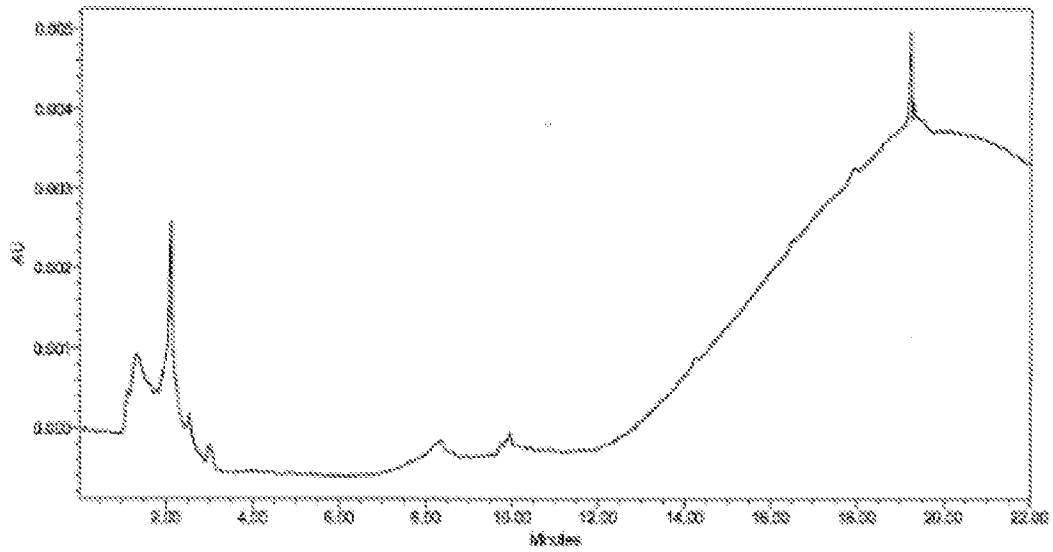


FIGURE 17

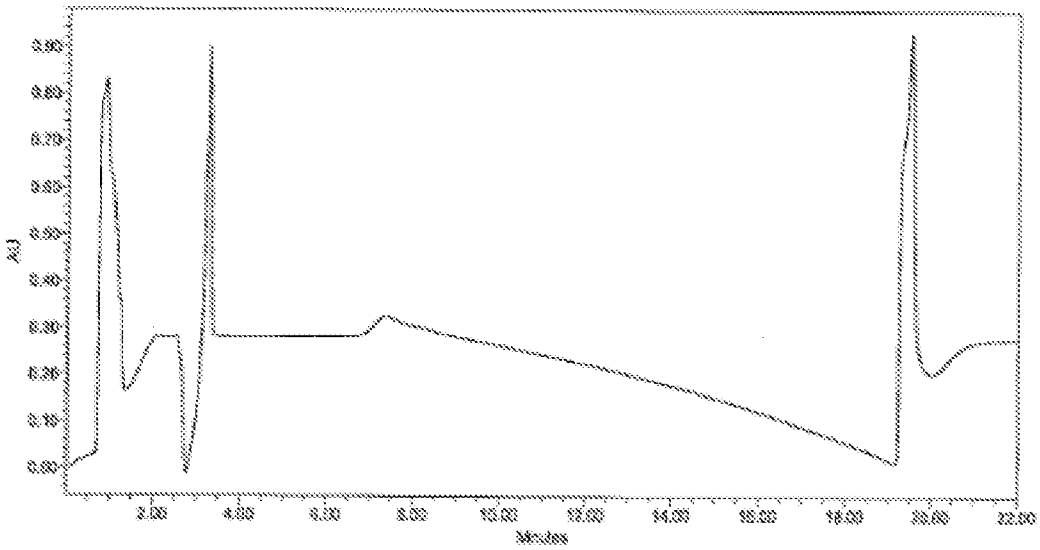


FIGURE 18

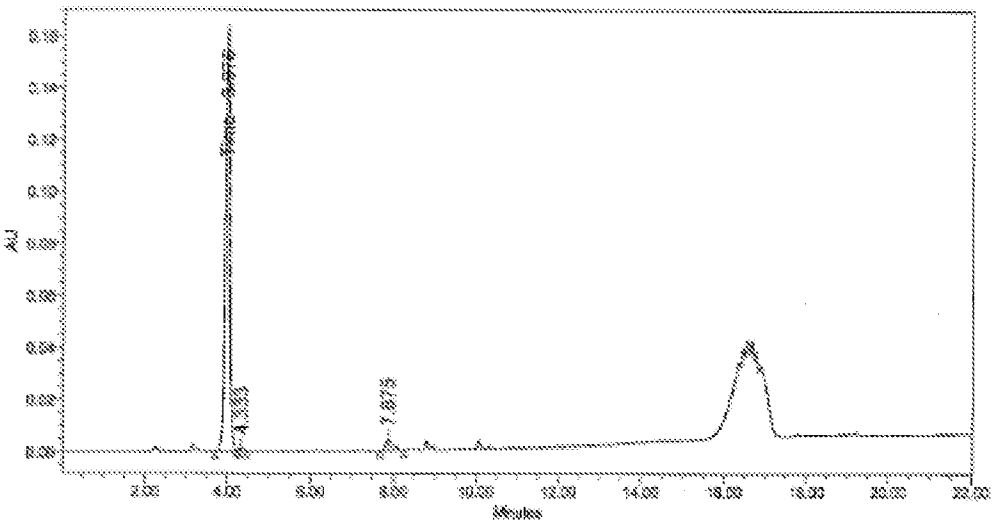


FIGURE 19A

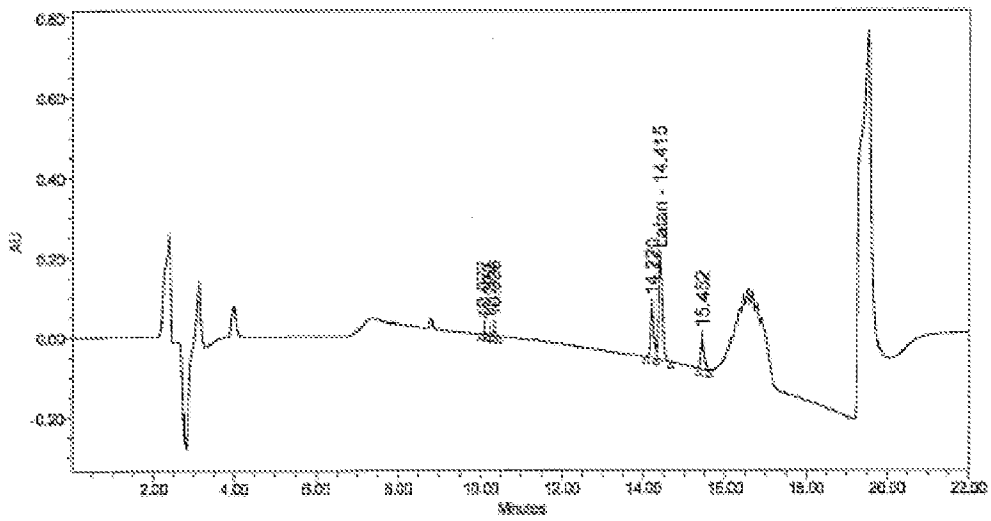


FIGURE 19B

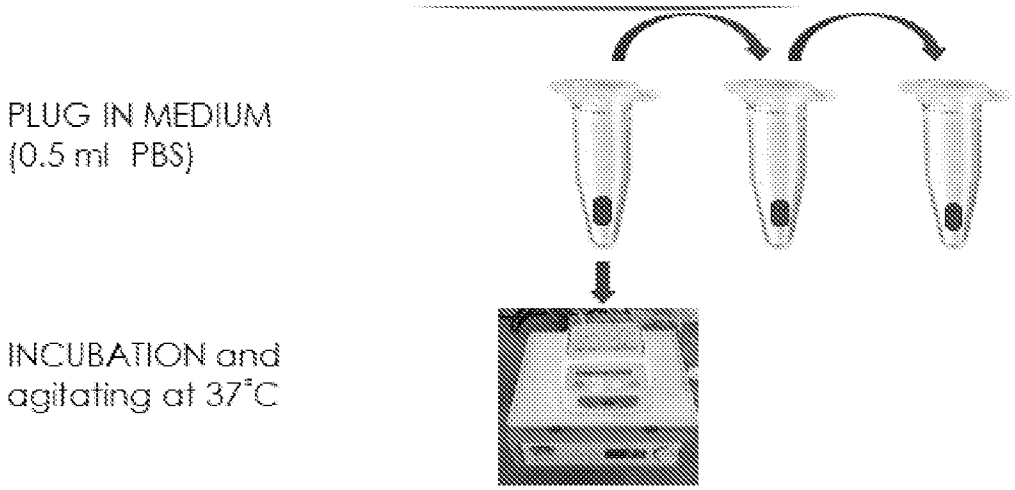


FIGURE 20

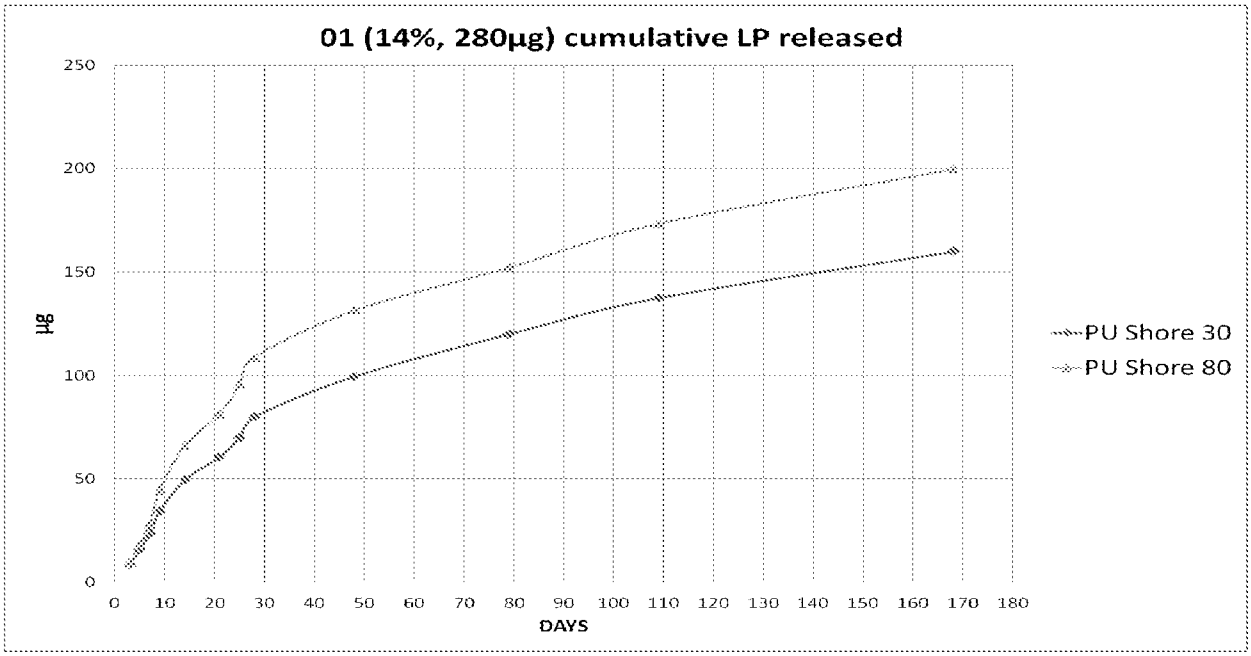


FIGURE 21

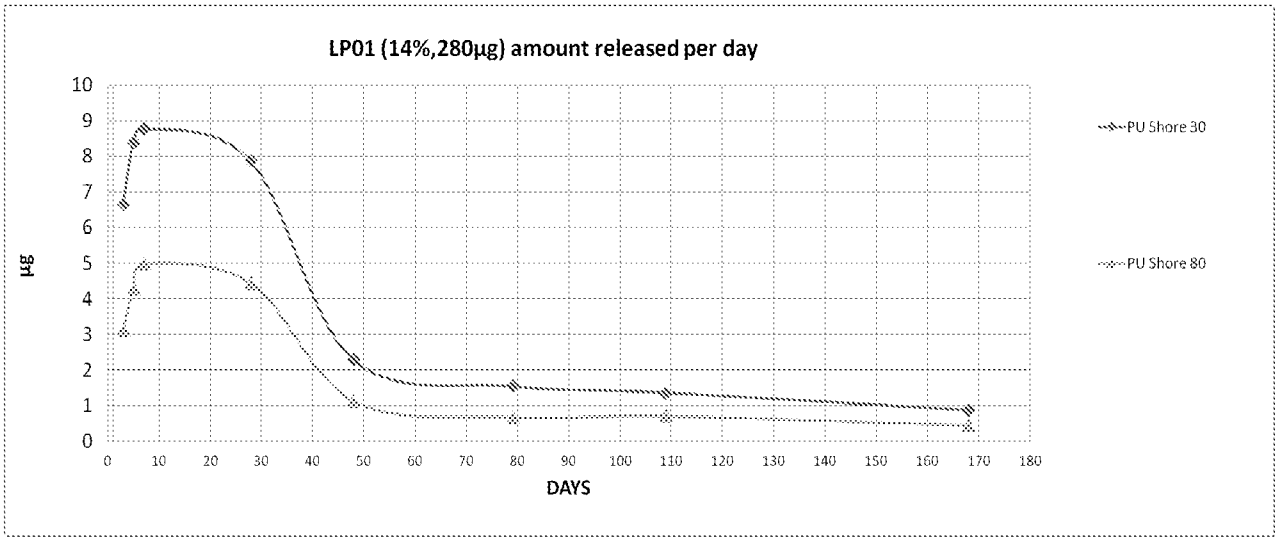


FIGURE 22

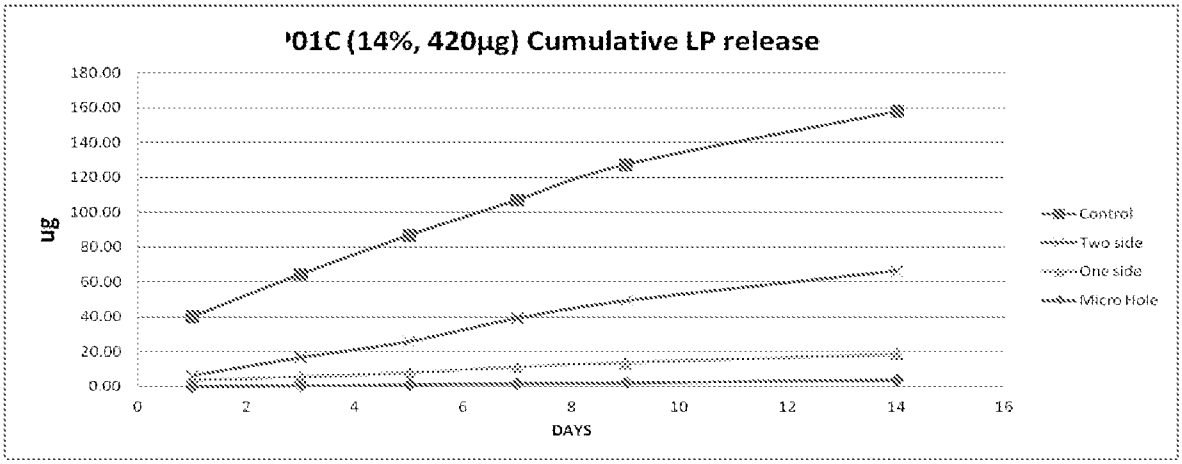


FIGURE 23

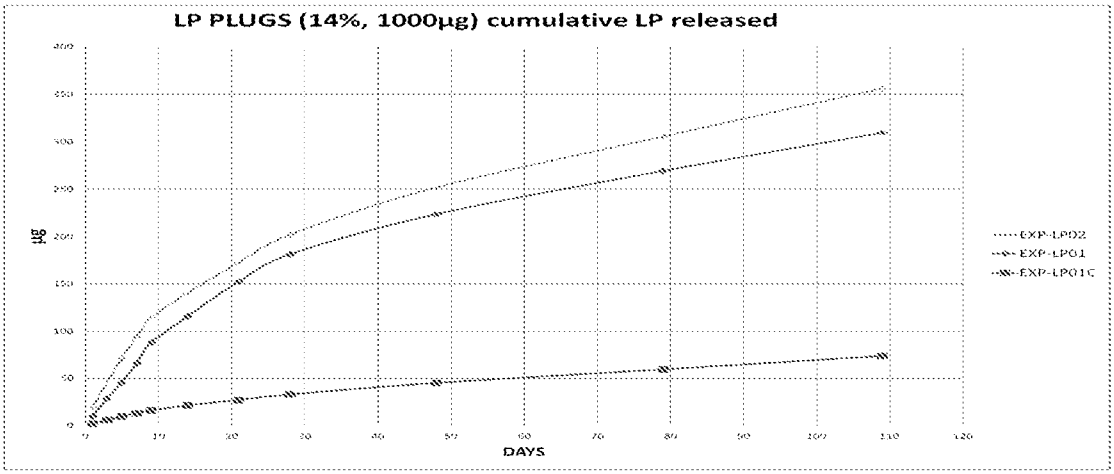


FIGURE 24

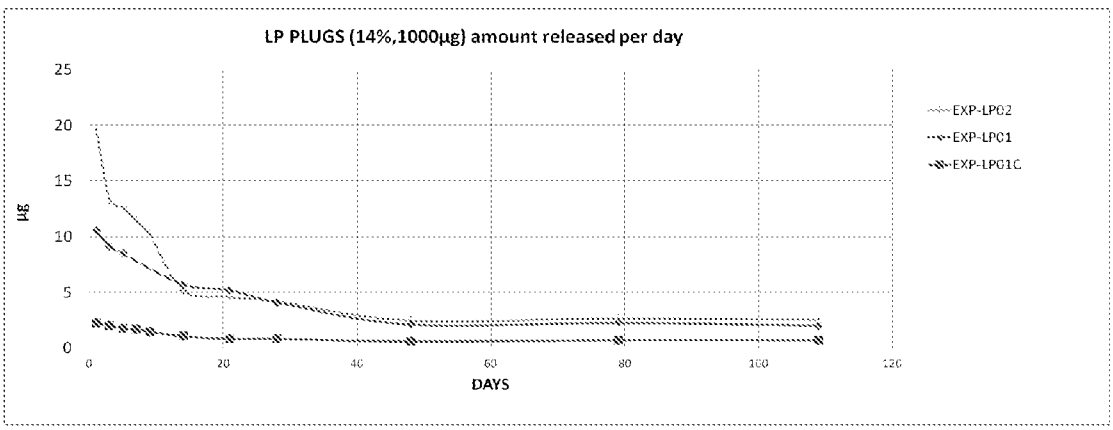


FIGURE 25

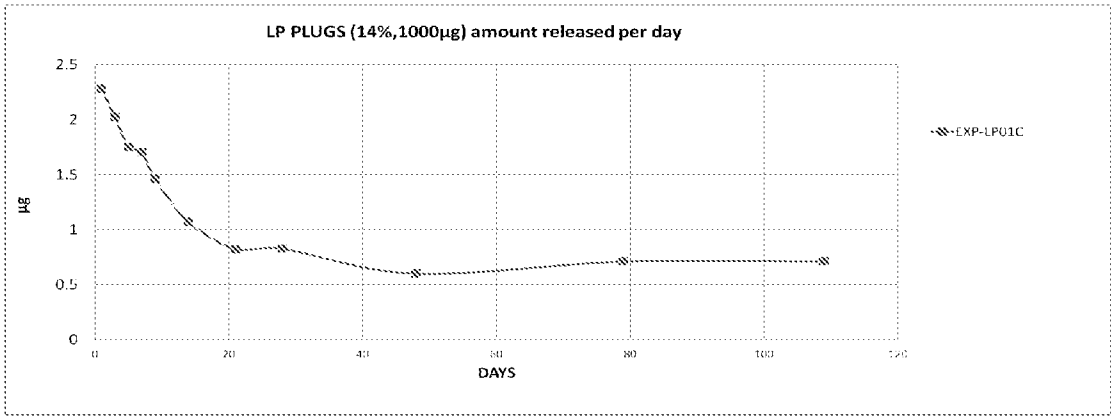


FIGURE 26

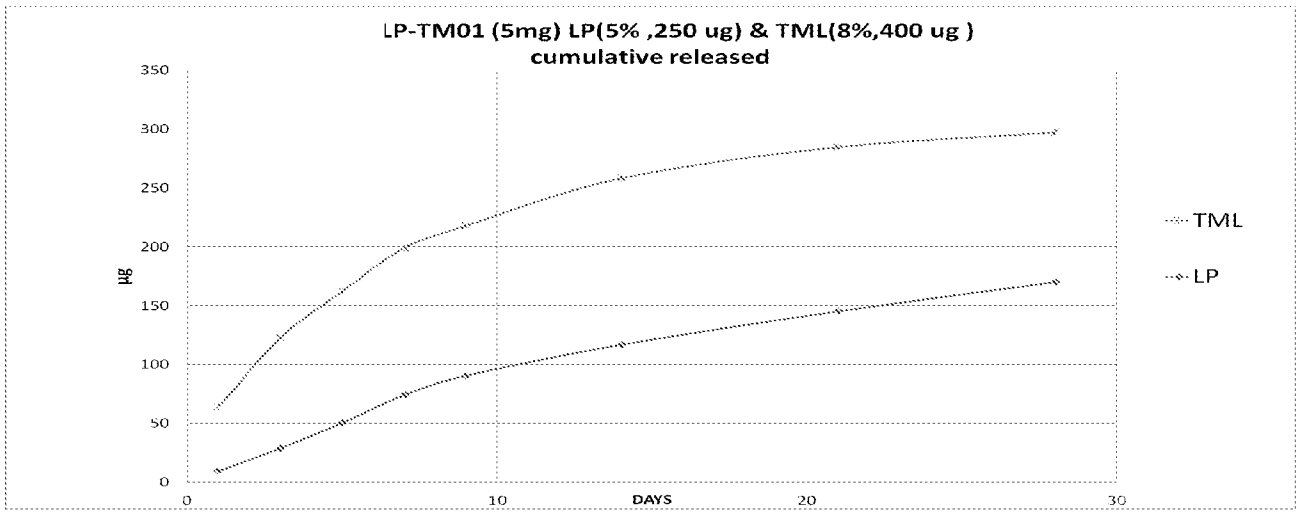


FIGURE 27

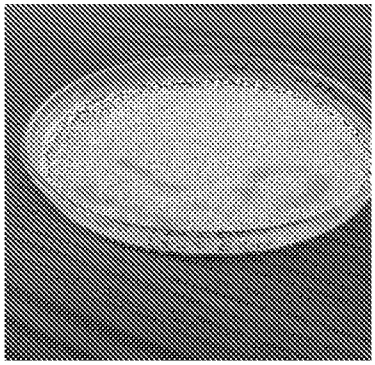


FIGURE 28A

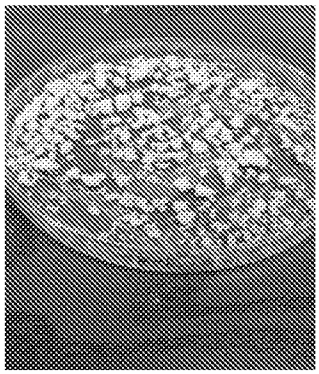


FIGURE 28B

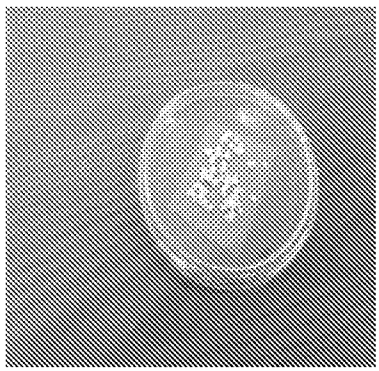


FIGURE 29

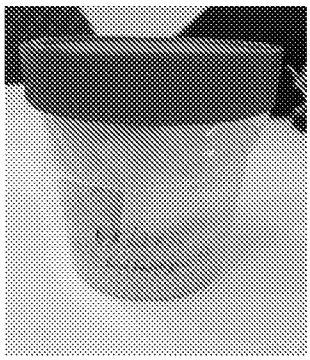


FIGURE 30

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2015/002345

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 9/02 (2016.01)
CPC - A61K 9/0024 (2016.02)
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)
IPC(8) - A61K 9/02, 9/54, 9/58 (2016.01)
CPC - A61K 9/0024, 9/0051 (2016.02)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/422, 426, 427, 428; IPC(8) - A61K 9/02, 9/54, 9/58; CPC - A61K 9/0024, 9/0051 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit, Google Scholar.
Search terms used: bulking, kaolin, clay, absorbent, fumed silica, binder, epoxy, Latanoprost, Timolol, polyurethane, parylene, butvar, punctal plug, cyc.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/0318549 A1 (BUTUNER) 24 December 2009 (24.12.2009) entire document	1-20
A	US 2009/0092654 A1 (DE JUAN JR et al) 09 April 2009 (09.04.2009) entire document	1-20
A	US 8,715,713 B2 (GHEBREMESKEL et al) 06 May 2014 (06.05.2014) entire document	1-20
A	US 2012/0187594 A1 (UTKHEDE et al) 26 July 2012 (26.07.2012) entire document	1-20
A	US 2008/0221184 A1 (YOKOYAMA) 11 September 2008 (11.09.2008) entire document	1-20

☐ 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 application or patent 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
22 March 2016	19 APR 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774