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(54) Title: PHARMACEUTICAL NANOPARTICLES SHOWING IMPROVED MUCOSAL TRANSPORT

(57) Abstract: Particles, compositions, and methods that aid particle transport in mucus are provided. In some embodiments, the compositions and methods may involve modifying the surface coatings of particles, such as particles of pharmaceutical agents that have a low aqueous solubility. The pharmaceutical composition including such particles is well-suited for ophthalmic applications, and may be used for delivering pharmaceutical agents to the front of the eye and/or the back of the eye.

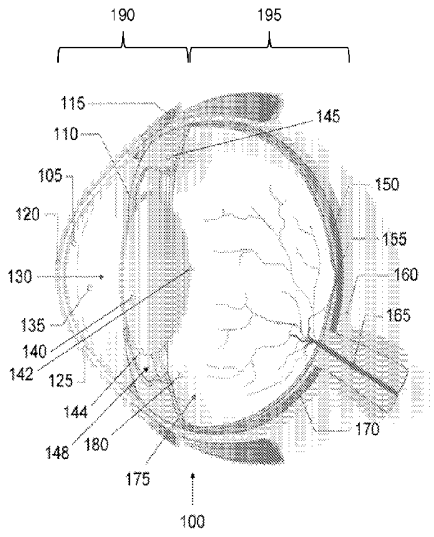


FIG. 15A

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PHARMACEUTICAL NANOPARTICLES SHOWING IMPROVED MUCOSAL TRANSPORT

Field of the Invention

[0001] The present invention generally relates to particles, compositions, and methods that aid particle transport in mucus. The particles, compositions, and methods may be used in ophthalmic and/or other applications.

Background of the Invention

[0002] A mucus layer present at various points of entry into the body, including the eyes, nose, lungs, gastrointestinal tract, and female reproductive tract, is naturally adhesive and serves to protect the body against pathogens, allergens, and debris by effectively trapping and quickly removing them via mucus turnover. For effective delivery of therapeutic, diagnostic, or imaging particles via mucus membranes, the particles must be able to readily penetrate the mucus layer to avoid mucus adhesion and rapid mucus clearance. Particles (including microparticles and nanoparticles) that incorporate pharmaceutical agents are particularly useful for ophthalmic applications. However, often it is difficult for administered particles to be delivered to an eye tissue in effective amounts due to rapid clearance and/or other reasons. Accordingly, new methods and compositions for administration (*e.g.*, topical application or direct injection) of pharmaceutical agents to the eye would be beneficial.

Summary of the Invention

[0003] The present description generally relates to particles, compositions, and methods that aid particle transport in mucus, especially particles, compositions, and methods for ophthalmic and/or other applications.

[0004] As described in more detail below, in some embodiments the compositions comprise a plurality of particles that include a corticosteroid such as loteprednol etabonate (LE) for treating an eye disease or condition. The particles include a surface-altering agent that reduces the adhesion of the particles to mucus and/or facilitates penetration of the particles through physiological mucus. Such compositions are advantageous over marketed formulations, such as Lotemax® or Alrex®, as the compositions described herein are able to more readily penetrate the mucus layer of an ocular tissue to avoid or minimize mucus

adhesion and/or rapid mucus clearance. Therefore, the compositions may be more effectively delivered to and may be retained longer in the target issue. As a result, the compositions described herein may be administered at a lower dose and/or less frequently than marketed formulations to achieve similar or superior exposure. Moreover, the relatively low and/or infrequent dosage of the compositions described herein may result in fewer or less severe side effects, a more desirable toxicity profile, and/or improved patient compliance.

[0005] In some embodiments, the compositions described herein may comprise a plurality of particles that include a receptor tyrosine kinase (RTK) inhibitor, such as sorafenib, linifanib, MGCD-265, pazopanib, cediranib, and axitinib, for treating an eye disease or condition. Compositions including such particles are also provided, including compositions that can be administered topically to the eye. For reasons described herein, such compositions may have certain advantages over conventional formulations (*e.g.*, an aqueous suspension of such pharmaceutical agents).

[0006] In certain embodiments, the compositions described herein may comprise a plurality of particles that include a non-steroidal anti-inflammatory drug (NSAID), such as a divalent or trivalent metal salt of bromfenac (*e.g.*, bromfenac calcium), diclofenac (*e.g.*, diclofenac free acid or a divalent or trivalent metal salt thereof), or ketorolac (*e.g.*, ketorolac free acid or a divalent or trivalent metal salt thereof), for treating an eye disease or condition. Compositions including such particles are also provided, including compositions that can be administered topically to the eye. For reasons described herein, such compositions may have advantages over conventional formulations (*e.g.*, an aqueous solution of the corresponding pharmaceutical agent).

[0007] In one set of embodiments, a pharmaceutical composition suitable for administration to an eye is provided. The pharmaceutical composition comprises a plurality of coated particles, comprising a core particle comprising loteprednol etabonate, wherein the loteprednol etabonate constitutes at least about 80 wt% of the core particle, and a coating comprising one or more surface-altering agents surrounding the core particle. The one or more surface-altering agents comprises at least one of: a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer, b) a synthetic polymer having

pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or c) a polysorbate. The one or more surface altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2. The one or more surface altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight. The plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron. The pharmaceutical composition also includes one or more ophthalmically acceptable carriers, additives, and/or diluents.

[0008] In another set of embodiments, a pharmaceutical composition suitable for topical administration to an eye is provided. The pharmaceutical composition comprises a plurality of coated particles, comprising a core particle comprising loteprednol etabonate, wherein the loteprednol etabonate constitutes at least about 80 wt% of the core particle, and a coating comprising one or more surface-altering agents, wherein the one or more surface-altering agents comprise at least one of a poloxamer, a poly(vinyl alcohol), or a polysorbate. The one or more surface-altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2. The one or more surface-altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight. The plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron. The pharmaceutical composition also includes one or more ophthalmically acceptable carriers, additives, and/or diluents.

[0009] In another set of embodiments, a series of methods are provided. In one embodiment, a method for treating inflammation, macular degeneration, macular edema, uveitis, dry eye, and/or other disorder in an eye of a patient is provided. The method comprises administering to an eye of the patient, a pharmaceutical composition comprising a plurality of coated particles. The pluarity of coated particles comprise a core particle comprising loteprednol etabonate, wherein the loteprednol etabonate constitutes at least about 80 wt% of the core particle, a coating comprising one or more surface-altering agents surrounding the core particle. The one or more surface-altering agents comprises at least one of: a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at

least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer, b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or c) a polysorbate. The one or more surface altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2. The one or more surface altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight. The plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron. The pharmaceutical composition also includes one or more ophthalmically acceptable carriers, additives, and/or diluents.

[00010] In another set of embodiments, a method for treating inflammation, macular degeneration, macular edema, uveitis, dry eye, and/or other disorder in an eye of a patient is provided. The method involves administering to an eye of the patient, a pharmaceutical composition comprising a plurality of coated particles, comprising a core particle comprising loteprednol etabonate, wherein the loteprednol etabonate constitutes at least about 80 wt% of the core particle, and a coating comprising one or more surface-altering agents, wherein the one or more surface-altering agents comprise at least one of a poloxamer, poly(vinyl alcohol), or a polysorbate. The one or more surface-altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2. The one or more surface-altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight. The plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron. The pharmaceutical composition also includes one or more ophthalmically acceptable carriers, additives, and/or diluents.

[00011] In another set of embodiments, a pharmaceutical composition suitable for administration to an eye is provided. The pharmaceutical composition includes a plurality of coated particles, comprising a core particle comprising a pharmaceutical agent or a salt thereof. The pharmaceutical agent or salt thereof constitutes at least about 80 wt% of the core particle, and the pharmaceutical agent or salt thereof comprises a receptor tyrosine kinase (RTK) inhibitor. The plurality of coated particles also includes a coating comprising one or more surface-altering agents surrounding the core particle, wherein the one or more surface-

altering agents comprises at least one of: a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer, b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or c) a polysorbate. The one or more surface altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2. The one or more surface altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight. The plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron. The pharmaceutical composition also includes one or more ophthalmically acceptable carriers, additives, and/or diluents.

[00012] In another set of embodiments, a method for treating macular degeneration, macular edema and/or another disorder in an eye of a patient is provided. The method involves administering to an eye of the patient, a pharmaceutical composition comprising a plurality of coated particles, comprising a core particle comprising a pharmaceutical agent or a salt thereof, wherein the pharmaceutical agent or salt thereof constitutes at least about 80 wt% of the core particle, and wherein the pharmaceutical agent or salt thereof comprises a receptor tyrosine kinase (RTK) inhibitor, and a coating comprising one or more surface-altering agents surrounding the core particle. The one or more surface-altering agents comprises at least one of:

a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer, b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or c) a polysorbate. The one or more surface altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2. The one or more surface altering agents is present in the pharmaceutical composition in an amount of between

about 0.001% to about 5% by weight. The plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron. The pharmaceutical composition also includes one or more ophthalmically acceptable carriers, additives, and/or diluents.

[00013] In another set of embodiments, a pharmaceutical composition suitable for administration to an eye is provided. The pharmaceutical composition comprises a plurality of coated particles, comprising a core particle comprising a pharmaceutical agent or a salt thereof, wherein the pharmaceutical agent or salt thereof constitutes at least about 80 wt% of the core particle, and wherein the pharmaceutical agent or salt thereof comprises bromfenac calcium, diclofenac free acid, or ketorolac free acid, and a coating comprising one or more surface-altering agents surrounding the core particle. The one or more surface-altering agents comprises at least one of: a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer, b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or c) a polysorbate. The one or more surface altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2. The one or more surface altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight. The plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron. The pharmaceutical composition also includes one or more ophthalmically acceptable carriers, additives, and/or diluents.

[00014] In another set of embodiments, a method for treating inflammation, macular degeneration, macular edema, uveitis, dry eye, glaucoma, and/or other disorder in an eye of a patient is provided. The method involves administering to an eye of the patient, a pharmaceutical composition comprising a plurality of coated particles, comprising a core particle comprising a pharmaceutical agent or a salt thereof, wherein the pharmaceutical agent or salt thereof constitutes at least about 80 wt% of the core particle, and wherein the pharmaceutical agent or salt thereof comprises bromfenac calcium, diclofenac free acid, or

ketorolac free acid. The plurality of coated particles also includes a coating comprising one or more surface-altering agents surrounding the core particle, wherein the one or more surface-altering agents comprises at least one of: a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer, b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or c) a polysorbate. The one or more surface altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2. The one or more surface altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight. The plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron. The pharmaceutical composition also includes one or more ophthalmically acceptable carriers, additives, and/or diluents.

[00015] In another set of embodiments, a pharmaceutical composition suitable for administration to an eye is provided. The pharmaceutical composition comprises a plurality of coated particles, comprising a core particle comprising a pharmaceutical agent or a salt thereof selected from the group consisting of a corticosteroid, a receptor tyrosine kinase (RTK) inhibitor, a cyclooxygenase (COX) inhibitor, an angiogenesis inhibitor, a prostaglandin analog, an NSAID, a beta blocker, and a carbonic anhydrase inhibitor. The plurality of coated particles also includes a coating comprising a surface-altering agent surrounding the core particle, wherein the one or more surface-altering agents comprises at least one of: a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer, wherein the hydrophobic block associates with the surface of the core particle, and wherein the hydrophilic block is present at the surface of the coated particle and renders the coated particle hydrophilic, b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed

and less than about 95% hydrolyzed, or c) a polysorbate. The one or more surface altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2. The one or more surface altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight. The pharmaceutical composition also includes one or more ophthalmically acceptable carriers, additives, and/or diluents.

[00016] In another set of embodiments, a method of treating, diagnosing, preventing, or managing an ocular condition in a subject is provided. The method involves administering a composition to an eye of a subject, wherein the composition comprises a plurality of coated particles, the coated particles comprising a core particle comprising a pharmaceutical agent or a salt thereof selected from the group consisting of a corticosteroid, a receptor tyrosine kinase (RTK) inhibitor, a cyclooxygenase (COX) inhibitor, an angiogenesis inhibitor, a prostaglandin analog, an NSAID, a beta blocker, and a carbonic anhydrase inhibitor, and a coating comprising one or more surface-altering agents surrounding the core particle. The one or more surface-altering agents comprises at least one of: a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer, wherein the hydrophobic block associates with the surface of the core particle, and wherein the hydrophilic block is present at the surface of the coated particle and renders the coated particle hydrophilic, or b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or c) a polysorbate. The method involves delivering the pharmaceutical agent to a tissue in the eye of the subject.

[00017] In another set of embodiments, a method of improving the ocular bioavailability of a pharmaceutical agent in a subject is provided. The method involves administering a composition to an eye of the subject, wherein the composition comprises a plurality of coated particles. The coated particles comprise a core particle comprising a pharmaceutical agent or a salt thereof selected from the group consisting of a corticosteroid, a receptor tyrosine kinase (RTK) inhibitor, a cyclooxygenase (COX) inhibitor, an angiogenesis inhibitor, a

prostaglandin analog, an NSAID, a beta blocker, and a carbonic anhydrase inhibitor, and a coating comprising a surface-altering agent surrounding the core particle. The coating on the core particle is present in a sufficient amount to improve the ocular bioavailability of the pharmaceutical agent when administered in the composition, compared to the ocular bioavailability of the pharmaceutical agent when administered as a core particle without the coating.

[00018] In another set of embodiments, a method of improving the concentration of a pharmaceutical agent in a tissue of a subject is provided. The method involves administering a composition to an eye of the subject, wherein the composition comprises a plurality of coated particles. The coated particles comprise a core particle comprising the pharmaceutical agent or a salt thereof, wherein the pharmaceutical agent is selected from the group consisting of a corticosteroid, a receptor tyrosine kinase (RTK) inhibitor, a cyclooxygenase (COX) inhibitor, an angiogenesis inhibitor, a prostaglandin analog, an NSAID, a beta blocker, and a carbonic anhydrase inhibitor, and a coating comprising a surface-altering agent surrounding the core particle. The tissue is selected from the group consisting of a retina, a macula, a sclera, or a choroid. The coating on the core particle is present in a sufficient amount to increase the concentration of the pharmaceutical agent by at least 10% in the tissue when administered in the composition, compared to the concentration of the pharmaceutical agent in the tissue when administered as a core particle without the coating.

[00019] In another set of embodiments, a method of treating an ocular condition in a subject by repeated administration of a pharmaceutical composition is provided. The method involves

administering two or more doses of a pharmaceutical composition comprising loteprednol etabonate to an eye of a subject, wherein the period between consecutive doses is at least about 4 hours, at least about 6 hours, at least about 8 hours, at least about 12 hours, at least about 36 hours, or at least about 48 hours, wherein the amount of loteprednol etabonate delivered to a tissue of an eye is effective to treat an ocular condition in the subject.

[00020] In another set of embodiments, a method of treating an ocular condition in a subject by repeated administration of a pharmaceutical composition is provided. The method involves administering two or more doses of a pharmaceutical composition comprising one or more pharmaceutical agents to an eye of a subject, wherein the period between consecutive

doses is at least about 4 hours, at least about 6 hours, at least about 8 hours, at least about 12 hours, at least about 36 hours, or at least about 48 hours. The one or more pharmaceutical agents is selected from the group consisting of loteprednol etabonate, sorafenib, linifanib, MGCD-265, pazopanib, cediranib, axitinib, bromfenac calcium, diclofenac free acid, ketorolac free acid and a combination thereof. The amount of the pharmaceutical agent delivered to a tissue of an eye is effective to treat an ocular condition in the subject.

[00021] In another set of embodiments, a pharmaceutical composition suitable for treating an anterior ocular disorder by administration to an eye is provided. The pharmaceutical composition comprises a plurality of coated particles, comprising a core particle comprising a corticosteroid, and a coating comprising one or more surface-altering agents surrounding the core particle. The one or more surface-altering agents comprises at least one of: a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer, b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, orc) a polysorbate. The plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron. The coating on the core particle is present in a sufficient amount to increase the concentration of the corticosteroid by at least 50% in an anterior component of the eye selected from the group consisting of a cornea or aqueous humor 30 minutes after administration when administered to the eye, compared to the concentration of the corticosteroid in the tissue when administered as a core particle without the coating.

[00022] In another set of embodiments, a method of treating an anterior ocular disorder by administration to an eye is provided. The method involves administering a composition to an eye of a subject, wherein the composition comprises a plurality of coated particles. The plurality of coated particles comprises a core particle comprising a corticosteroid, and a coating comprising one or more surface-altering agents surrounding the core particle. The one or more surface-altering agents comprises at least one of a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration,

wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer, b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or c) a polysorbate The method involves sustaining an ophthalmically efficacious level of the corticosteroid in an anterior ocular tissue selected from the group consisting of a palpebral conjunctiva, a bulbar conjunctiva, or a cornea for at least 12 hours after administration.

[00023] Other advantages and novel features of the present invention will become apparent from the following detailed description of various non-limiting embodiments of the invention when considered in conjunction with the accompanying figures. In cases where the present specification and a document incorporated by reference include conflicting and/or inconsistent disclosure, the present specification shall control. If two or more documents incorporated by reference include conflicting and/or inconsistent disclosure with respect to each other, then the document having the later effective date shall control.

Brief Description of the Drawings

[00024] Non-limiting embodiments of the present invention will be described by way of example with reference to the accompanying figures, which are schematic and are not intended to be drawn to scale. In the figures, each identical or nearly identical component illustrated is typically represented by a single numeral. For purposes of clarity, not every component is labeled in every figure, nor is every component of each embodiment of the invention shown where illustration is not necessary to allow those of ordinary skill in the art to understand the invention. In the figures:

[00025] FIG. 1 is a schematic drawing of a mucus-penetrating particle having a coating and a core according to one set of embodiments;

[00026] FIG. 2A is a plot showing the ensemble averaged velocity$<V_{mean}>$in human cervicovaginal mucus (CVM) for 200 nm carboxylated polystyrene particles (negative control), 200 nm PEGylated polystyrene particles (positive control), and nanocrystal particles (sample) made by milling and coated with different surface-altering agents according to one set of embodiments;

[00027] FIG. 2B is a plot showing the relative velocity $\langle V_{mean} \rangle_{rel}$ in CVM for nanocrystal particles made by milling and coated with different surface-altering agents according to one set of embodiments;

[00028] FIGs. 3A-3D are histograms showing distribution of trajectory-mean velocity V_{mean} in CVM within an ensemble of nanocrystal particles coated with different surface-altering agents according to one set of embodiments;

[00029] FIG. 4 is a plot showing $\langle V_{mean} \rangle_{rel}$ in CVM for nanocrystal particles coated with different PEO-PPO-PEO Pluronic® triblock copolymers, mapped with respect to molecular weight of the PPO block and the PEO weight content (%), according to one set of embodiments;

[00030] FIG. 5 is a plot showing the mass transport through CVM for solid particles having different core materials that are coated with either Pluronic® F127 (MPP, mucus-penetrating particles) or sodium dodecyl sulfate (CP, conventional particles, a negative control), according to one set of embodiments;

[00031] FIGs. 6A-6C show drug levels of loteprednol etabonate in the palpebral conjunctiva (FIG. 6A), bulbar conjunctiva (FIG. 6B), and cornea (FIG. 6C) of New Zealand white rabbits after administration of commercial prescription loteprednol etabonate, Lotemax®, or particles of loteprednol etabonate that were coated with Pluronic® F127, according to one set of embodiments;

[00032] FIG. 7A is a plot showing the ensemble averaged velocity $\langle V_{mean} \rangle$in human cervicovaginal mucus (CVM) for $PSCOO^-$ particles coated with various poly(vinyl alcohols) (PVAs) according to one set of embodiments;

[00033] FIG. 7B is a plot showing the relative velocity $\langle V_{mean} \rangle_{rel}$ in CVM for $PSCOO^-$ particles coated with various PVAs according to one set of embodiments;

[00034] FIG. 8 is a plot showing relative velocity $\langle V_{mean} \rangle_{rel}$ in CVM for $PSCOO^-$ particles incubated with various PVAs mapped according to the PVA's molecular weight and degree of hydrolysis, according to one set of embodiments. Each data point represents $\langle V_{mean} \rangle_{rel}$ for the particles stabilized with a specific PVA.

[00035] FIGs. 9A-9B are plots showing bulk transport in CVM *in vitro* of PSCOO nanoparticles coated with various PVAs, according to one set of embodiments. Negative controls are uncoated 200 nm PSCOO particles; Positive controls are 200 nm PSCOO

particles coated with Pluronic® F127. FIGs. 9A-9B represent data obtained with two different CVM samples;

[00036] FIGs. 10A-10B are plots showing ensemble-average velocity $<V_{mean}>$ (FIG. 10A) and relative sample velocity $<V_{mean}>_{rel}$ (FIG. 10B) for poly(lactic acid) (PLA) nanoparticles (sample) prepared by emulsification with various PVAs as measured by multiple-particle tracking in CVM, according to one set of embodiments;

[00037] FIG. 11 is a plot showing relative velocity $<V_{mean}>_{rel}$ in CVM for PLA nanoparticles prepared by emulsification with various PVA's mapped according to the PVA's molecular weight and degree of hydrolysis, according to one set of embodiments. Each data point represents $<V_{mean}>_{rel}$ of the particles stabilized with a specific PVA;

[00038] FIGs. 12A-12B are plots showing ensemble-average velocity $<V_{mean}>$ (FIG. 12A) and relative sample velocity $<V_{mean}>_{rel}$ (FIG. 12B) for pyrene nanoparticles (sample) and controls as measured by multiple-particle tracking in CVM, according to one set of embodiments;

[00039] FIGs. 13A-13F are representative CVM velocity (V_{mean}) distribution histograms for pyrene/nanocrystals obtained with various surface-altering agents (SAMPLE = Pyrene nanoparticles, POSITIVE = 200 nm PS-PEG5K, NEGATIVE = 200 nm PS-COO); according to one set of embodiments;

[00040] FIG. 14 is a plot of relative velocity $<V_{mean}>_{rel}$ for pyrene nanocrystals coated with PVA in CVM mapped according to the PVA's molecular weight and degree of hydrolysis according to one set of embodiments;

[00041] FIGs. 15A-15B are schematic drawings showing the constituent parts (FIG. 15A), including the mucus layers (FIG. 15B), of an eye, according to one set of embodiments;

[00042] FIG. 15C is a schematic drawing showing MPP and CP in the ocular mucus layer after topical instillation, according to one set of embodiments. The MPP may readily penetrate the outer mucus layer toward the glycocalyx while CP may be immobilized in the outer layer of mucus. The clearance of the outer layer by the body's natural clearance mechanisms may be accompanied by CP removal whereas MPP are retained in the less rapidly cleared glycocalyx, leading to prolonged residence at the ocular surface.

[00043] FIG. 16 is a schematic drawing illustrating three main pathways through which a topically applied drug may be transported to the back of the eye, according to one set of embodiments.

[00044] FIGs. 17A-17B are plots showing that the levels of loteprednol etabonate (LE)in the cornea after an administration of LE MPP formulations are higher than the levels of LE after an administration of a commercial formulation in an ocular PK study, according to one set of embodiments. Equivalent drug doses were topically administered to the eyes of NZW rabbit at t = 0;

[00045] FIG. 18 is a plot showing distribution of MPP (loteprednol etabonate nanocrystals coated with Pluronic® F127) in ocular tissues *in vivo* 30 minutes after eye drop instillation, according to one set of embodiments. Rabbits were given one 50 μL dose of 0.5% loteprednol etabonate MPP formulation or a commercial drop, Lotemax®, in each eye. Retina, choroid, and sclera are sampled where the human macula would be located. Error bars show standard errors of the mean (SEM, n = 6);

[00046] FIG. 19 is a bar graph showing the density of Pluronic® F127 on the surface of fluticasone propionate and loteprednol etabonate nanocrystals, according to one set of embodiments;

[00047] FIG. 20 is a plot showing CVM mobility scores for loteprednol etabonate nanoparticles obtained by milling in the presence of different PEO-PPO-PEO Pluronic® triblock copolymers, mapped with respect to molecular weight of the PPO block and the PEO weight content (%), according to one set of embodiments. The scoring criterion is as follows: 0-0.5 immobile; 0.51-1.5 slightly mobile; 1.51-2.5 moderately mobile; and 2.51-3.0 very mobile. Samples that failed to produce stable nanosuspensions are demarked with * and considered immobile (mobility score <0.5);

[00048] FIG. 21 is a plot showing the mass-transport-into-mucus data of the following formulations: mucus penetrating particles comprising loteprednol etabonate and Pluronic® F127 (LE F127), particles comprising Loteprednol Etabonate and sodium dodecyl sulfate (LE SDS), and marketed formulation Lotemax®. The ratio of loteprednol etabonate to Pluronic® F127 1:1 wt% while the ratio of loteprednol etabonate to SDS is 50:1 wt%. Untreated 200 nm carboxylated polystyrene spheres and200 nm carboxylated polystyrene spheres treated with Pluronic® F127were employed as the negative and positive control, respectively;

[00049] FIG. 22 shows the chemical structures of certain degradants of loteprednol etabonate;

[00050] FIGs. 23A-23B are plots showing the pharmacokinetics (PK) of LE in ocular tissues *in vivo*. Error bars show standard errors of the mean (n = 6). FIG. 23A: Rabbits were given one 50 µL dose of 0.5% LE MPP or LE SDS in each eye. FIG. 23B: Rabbits were given one 50 µL dose of 0.5% Lotemax® or LE SDS in each eye. Data for Lotemax® were obtained from a previous experiment performed using the same techniques at the same facility;

[00051] FIG. 24 is a plot showing the pharmacokinetics of LE in ocular tissues *in vivo*. Rabbits were given one 50 µL dose of 0.5% Lotemax®, Lotemax® + F127, or LE MPPs in each eye. Error bars show standard errors of the mean (n = 6). Data for Lotemax® were obtained from a previous experiment performed using the same techniques at the same facility;

[00052] FIG. 25 is a plot showing the pharmacokinetics of LE in ocular tissues *in vivo*. Rabbits were given one 50 µL dose of 0.5% Lotemax® or 0.4% LE MPPs in each eye. Error bars show standard errors of the mean (n = 6).

[00053] FIGs. 26A-26R are plots showing pharmacokinetics of LE and its two main metabolites, PJ-91 and PJ-90, in ocular tissues (*e.g.*, conjunctiva, cornea, aqueous humor, iris and ciliary body (ICB), and central retina) and plasma *in vivo*. Rabbits were given one 50 µL dose of 0.5% Lotemax® or 0.4% LE MPP in each eye. Error bars show standard errors of the mean (n = 6).

[00054] FIG. 27 is a plot showing *in vitro* release profiles for various PEGylated MPPs loaded with fluticasone. Release conditions: 37°C, PBS with 0.5% Tween80.

[00055] FIGs. 28A-28B show representative 15-second trajectories of conventional nanoparticles (FIG. 28A) and MPPs described herein (FIG. 28B) in human cervicovaginal mucus. The MPPs avoided entrapment and were able to diffuse through mucus.

[00056] FIGs. 29A-29B are plots showing sorafenib levels in cornea (FIG. 29A) and retina (FIG. 29B) of New Zealand white rabbits following a single topical instillation of MPPs of sorafenib (*e.g.*, MPP1 and MPP2) and a non-MPP comparator (*e.g.*, an aqueous suspension of sorafenib). Error bars show standard errors of the mean (n = 6).

[00057] FIG. 30 is a plot showing the pharmacokinetics (PK) of LE in aqueous humor *in vivo*. The rabbits were given one 35 μL dose of 0.5% Lotemax® gel or 0.4% LE MPPs in each eye. Error bars show standard errors of the mean (n = 6).

[00058] FIG. 31A is a plot showing the pharmacokinetics of LE in the aqueous humor of New Zealand white rabbits *in vivo*. The rabbits were given one 50 μL dose of different percentages of LE MPPs in each eye. Error bars show standard errors of the mean (n=6).

[00059] FIG. 31B is a plot showing the AUC_{0-6} of LE in the aqueous humor of the NZW rabbits *in vivo*. The rabbits were given one 50 μL dose of different percentages of LE MPPs in each eye.

[00060] FIG. 32 is a plot showing the stability of LE MPPs in the presence of ionic components, such as sodium chloride. Triangles: 0.45% sodium chloride. Squares: 0.9% sodium chloride. LE MPPs were monitored by dynamic light scattering (DLS). Sizes at Week -1 represent particle sizes of the LE MPPs immediately after milling and before the LE MPPs were diluted to the final concentration on Week 0. FIG. 32 indicates that LE MPPs in the presence of sodium chloride were stable.

[00061] FIG. 33A is a plot showing the particle stability of LE MPPs. Two samples of LE MPPs were monitored by dynamic light scattering (DLS). One sample had been exposed to 25 kGy of gamma irradiation, and the other sample had not been exposed to gamma irradiation.

[00062] FIG. 33B is a plot showing the pharmacokinetics of LE in the cornea of New Zealand white rabbits *in vivo*. The rabbits were given one 50 μL dose of LE MPPs including 0.4% LE in each eye of the rabbit. Error bars show standard errors of the mean (n=6).

[00063] FIG. 34 is a plot showing an exemplary particle size distribution of bromfenac calcium MPPs in formulations containing the MPPs. Bromfenac calcium was milled in water, 125 mM of $CaCl_2$, or 50 mM of Tris buffer. The particle sizes were measured by dynamic light scattering. All three formulations had a Z-average diameter of about 200 nm and a polydispersity index < 0.2.

[00064] FIGs. 35A-35D are plots showing that MPPs including bromfenac calcium are stable over extended period of time when stored at room temperature. FIG. 35A: particle Z-average size of bromfenac calcium (bromfenac-Ca) MPPs diluted to a concentration of 0.09% w/v bromfenac-Ca and 0.09% w/v Pluronic®F127 (F127) and stored at room temperature for

23 days. FIG. 35B: polydispersity index of bromfenac-Ca MPPs diluted to a concentration of 0.09% w/v bromfenac-Ca and 0.09% w/v F127 and stored at room temperature for 23 days. FIG. 35C: particle Z-average size of bromfenac-Ca MPPs diluted to a concentration of 0.09% w/v bromfenac-Ca and 0.5% w/v F127 and stored at room temperature for 7 or 12 days. FIG. 35D: polydispersity index of bromfenac-Ca MPPs diluted to a concentration of 0.09% w/v bromfenac-Ca and 0.5% w/v F127 and stored at room temperature for 7 or 12 days.

[00065] FIGs. 36A-36B are plots showing the pharmacokinetics of sorafenib and linifanib in center-punch retina of New Zealand white rabbits *in vivo*. FIG. 36A: the rabbits were given one 50 μL dose of 0.5% sorafenib-MPP or 0.5% sorafenib non-MPP control in each eye. Error bars show standard errors of the mean (n=6). FIG. 36B: the rabbits were given one 50 μL dose of 2% linifanib-MPP or 2% linifanib non-MPP control in each eye. Error bars show standard errors of the mean (n = 6).

[00066] FIGs. 37A-37B are plots showing the pharmacokinetics of pazopanib and MGCD-265 in center-punch retina of New Zealand white rabbits *in vivo*. FIG. 37A: the rabbits were given one 50 μL dose of 0.5% pazopanib-MPP in each eye. Error bars show standard errors of the mean (n=6). Cellular IC_{50} is also shown for reference. FIG. 37B: the rabbits were given one 50 μL dose of 2% MGCD-265-MPP in each eye. Error bars show standard errors of the mean(n=6). Cellular IC_{50} is also shown for reference.

[00067] FIGs. 38A-38B are plots showing the pharmacokinetics of cediranib in ocular tissues of HY79b pigmented rabbits *in vivo*. FIG. 38A: the rabbits were given one 50 μL dose of 2% cediranib-MPP in the choroid. Error bars show standard errors of the mean(n=6). Cellular IC_{50} is also shown for reference. FIG. 38B: the rabbits were given one 50 μL dose of 2% cediranib-MPP in the retina. Error bars show standard errors of the mean(n=6). Cellular IC_{50} is also shown for reference.

[00068] FIGs. 39A-39B are plots showing the pharmacokinetics of axitinib in ocular tissues of Dutch belted rabbits *in vivo*. FIG. 39A: the rabbits were given one 50 μL dose of 2% axitinib-MPP in the choroid. Error bars show standard errors of the mean(n=6). Cellular IC_{50} is also shown for reference. FIG. 39B: the rabbits were given one 50 μL dose of 2% axitinib-MPP in the retina. Error bars show standard errors of the mean(n=6). Cellular IC_{50} is also shown for reference.

[00069] FIGs. 40A-40C are images showing the efficacy of axitinib-MPP in a rabbit VEGF (vascular endothelial growth factor receptor)-challenge model. Dutch belted rabbits were dosed with 50 μL of 5% axitinib-MPP every 4 hours on days 1-6. On day 3, the rabbits received an intravitreal injection of VEGF. On day 6, the rabbits were accessed for leakage via fluorescein angiography. Rabbits in the vehicle (negative control) group received vehicle every 4 hours on days 1-6. Rabbits in the Avastin® (positive control) group received one intravitreal injection of Avastin® on day 1.

[00070] FIG. 41 is a bar graph showing the bulk transport of particles containing diclofenac into human cervicovaginal mucus. Polystyrene particles containing no surface-altering agents (PS) were used as a negative, non-MPP control. Particles containing polystyrene in the core and Pluronic® F127 as the surface-altering agents(PS F127) were used as a positive, MPP control. Diclofenac F127 stands for particles containing diclofenac in the core and Pluronic® F127 as the surface-altering agents. Diclofenac SDS stands for particles containing diclofenac in the core and sodium dodecyl sulfate (SDS) as the surface-altering agents.

[00071] FIG. 42 is a plot showing the pharmacokinetics of Loteprednol Etabonate (LE) in the cornea of New Zealand white rabbits *in vivo*. Rabbits were given one 50 μL dose of each one of the three LE-MPPs (*i.e.*, LE-F127, LE-Tween80, and LE-PVA) or Lotemax® in each eye. The PVA had a molecular weight of about 2 kDa and was about 75% hydrolyzed. The dose of LE was 0.5% in all instances. Error bars show standard errors of the mean (n = 6).

[00072] FIG. 43 is a plot showing the mucus mobility of loteprednol etabonate (LE) particles including certain surface-altering agent coatings as a function of the molecular weight (MW (Da)) and hydrophobic-hydrophilic balance (HLB) value. Samples that do not form particles within the target range are indicated as "Does not formulate."

[00073] FIG. 44 is a plot showing the mucus mobility of loteprednol etabonate (LE) particles coated with various PVAs as a function of the molecular weight (MW (kDa)) and hydrolysis degree (% hydrolysis) of the PVA. Samples that do not form particles within the target range are indicated as "Does not formulate."

[00074] FIG. 45 is a plot showing PK of Axitinib in retina *in vivo*. Rabbits were given one 50 μL dose of 0.5% Axitinib-MPP or 0.5% Axitinib non-MPP control in each eye. Error bars are SEM (n=6).

[00075] FIG. 46 is a set of images showing the differences in the ocular residence time of conventional particles (CPs) and mucus-penetrating particles (MPPs) following a single topical dose of the particles to Long Evans pigmented rats.

[00076] FIG. 47 is a bar graph showing the relationship between the relative velocity of polystyrene particles coated with Pluronic® F127 in mucus and the density of the Pluronic® F127 molecules on the particle surface.

Detailed Description

[00077] Particles, compositions, and methods that aid particle transport in mucus are provided. The particles, compositions, and methods may be used, in some instances, for ophthalmic and/or other applications. In some embodiments, the compositions and methods may involve modifying the surface coatings of particles, such as particles of pharmaceutical agents that have a low aqueous solubility. Such compositions and methods can be used to achieve efficient transport of particles of pharmaceutical agents though mucus barriers in the body for a wide spectrum of applications, including drug delivery, imaging, and diagnostic applications. In certain embodiments, a pharmaceutical composition including such particles is well-suited for ophthalmic applications, and may be used for delivering pharmaceutical agents to the front of the eye, middle of the eye, and/or the back of the eye.

[00078] Particles having efficient transport through mucus barriers may be referred to herein as mucus-penetrating particles (MPPs). Such particles may include surfaces that are modified with one or more surface-altering agents that reduce the adhesion of the particles to mucus, or otherwise increase the transport of the particles through mucus barriers compared to conventional particles or non-MPPs, *i.e.*, particles that do not include such surface-altering agent(s).

[00079] In some embodiments, the particles comprise a corticosteroid such as loteprednol etabonate for treating an eye disease or condition. The corticosteroid may be present, for example, in the core of the particle. The particles include a surface-altering agent that modifies the surface of the particles to reduce the adhesion of the particles to mucus and/or to facilitate penetration of the particles through physiological mucus. Compositions including such particles are also provided, including compositions that can be administered topically to the eye. Such compositions are advantageous over marketed formulations, such as Lotemax®

or Alrex®, as the compositions described herein are able to more readily penetrate the mucus layer of an ocular tissue to avoid or minimize mucus adhesion and/or rapid mucus clearance. Therefore, the compositions may be more effectively delivered to and may be retained longer in the target issue. As a result, the compositions described herein may be administered at a lower dose and/or less frequently than marketed formulations to achieve similar or superior exposure. Moreover, the relatively low and/or infrequent dosage of the compositions may result in fewer or less severe side effects, a more desirable toxicity profile, and/or improved patient compliance. Other advantages are provided below.

[00080] In some embodiments, the particles comprise one or more receptor tyrosine kinase inhibitors (RTKi), such as sorafenib, linifanib, MGCD-265, pazopanib, cediranib, axitinib, or a combination thereof, for treating an eye disease or condition. The one or more RTKi may be present, for example, in the core of the particle. Compositions including such particles are also provided, including compositions that can be administered topically to the eye. For reasons described herein, such compositions may have advantages over certain conventional formulations (*e.g.*, an aqueous suspension of the respective RTKi).

[00081] In some embodiments, the particles comprise a non-steroidal anti-inflammatory drug (NSAID), such as a divalent metal salt of bromfenac (*e.g.*, a divalent metal salt of bromfenac, such as bromfenac calcium)), diclofenac (*e.g.*, diclofenac free acid or a divalent or trivalent metal salt thereof, such as an alkaline earth metal salt of diclofenac), or ketorolac (*e.g.*, ketorolac free acid or a divalent or trivalent metal salt thereof, such as an alkaline earth metal salt of ketorolac), for treating an eye disease or condition. The NSAID may be present, for example, in the core of the particle. Compositions including such particles are also provided, including compositions that can be administered topically to the eye. For reasons described herein, such compositions may have advantages over certain conventional formulations (*e.g.*, an aqueous solution of bromfenac sodium).

[00082] As described in more detail below, in some embodiments, the particles, compositions and/or formulations described herein may be used to diagnose, prevent, treat or manage diseases or conditions at the back of the eye, such as at the retina, macula, choroid, sclera and/or uvea, and/or diseases and conditions at the front and/or middle of the eye, such as at the cornea, conjunctiva (including palpebral and bulbar), iris and ciliary body. In some embodiments, the particles, compositions and/or formulations are designed to be

administered topically to the eye. In other embodiments, the particles, compositions and/or formulations are designed to be administered by direct injection into the eye.

[00083] Delivering drugs to the eye topically is challenging due to the limited permeability of the cornea and sclera (the tissues exposed to an instillation) and the eye's natural clearance mechanisms: drug solutions, such as in conventional ophthalmic solutions, are typically washed away from the surface of the eye very rapidly by drainage and lachrymation; and drug particles, such as in conventional ophthalmic suspensions, are typically trapped by the rapidly cleared mucus layer of the eye, and hence, are also rapidly cleared. Therefore, conventional ophthalmic solutions and suspensions currently used to treat conditions at the front of the eye are typically administered at high doses and high frequency in order to achieve and sustain efficacy. Such frequent high dosing greatly reduces patient compliance and increases the risk of local adverse effects. Topically delivering drugs to the back of the eye is even more challenging due to the lack of direct exposure to a topical instillation and because of the anatomical and physiological barriers associated with this part of the eye. Consequently, little (if any) drug reaches the back of the eye when administered as conventional topical ophthalmic solutions or suspensions.Therefore, invasive delivery techniques, such as intravitreal or perocular injections, are currently used for conditions at the back of the eye.

[00084] In some instances, the particles, compositions and/or formulations described herein that are mucus-penetrating can address these issues associated with delivery to the front of the eye (*e.g.*, dosage frequency) and the back of the eye (*e.g.*, sufficient delivery) since the particles may avoid adhesion to the mucus layer and/or may be more evenly spread across the surface of the eye, thereby avoiding the eye's natural clearance mechanisms and prolonging their residence at the ocular surface. In some embodiments, the particles may effectively penetrate through physiological mucus to facilitate sustained drug release directly to the underlying tissues, as described in more detail below.

[00085] In some embodiments, the particles described herein have a core-shell type arrangement. The core may comprise any suitable material such as a solid pharmaceutical agent or a salt thereof having a relatively low aqueous solubility, a polymeric carrier, a lipid, and/or a protein. The core may also comprise a gel or a liquid in some embodiments. The core may be coated with a coating or shell comprising a surface-altering agent that facilitates

mobility of the particle in mucus. As described in more detail below, in some embodiments the surface-altering agent may comprise a polymer (*e.g.*, a synthetic or a natural polymer) having pendant hydroxyl groups on the backbone of the polymer. The molecular weight and/or degree of hydrolysis of the polymer may be chosen to impart certain transport characteristics to the particles, such as increased transport through mucus. In certain embodiments, the surface-altering agent may comprise a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration. The molecular weights of each of the blocks may be chosen to impart certain transport characteristics to the particles, such as increased transport through mucus.

[00086] Non-limiting examples of particles are now provided. As shown in the illustrative embodiment of FIG.1, a particle 10 includes a core 16 (which may be in the form of a particle, referred to herein as a core particle) and a coating 20 surrounding the core. In one set of embodiments, a substantial portion of the core is formed of one or more solid pharmaceutical agents (*e.g.*, a drug, therapeutic agent, diagnostic agent, imaging agent) that can lead to certain beneficial and/or therapeutic effects. The core may be, for example, a nanocrystal (*i.e.*, a nanocrystal particle) of a pharmaceutical agent. In other embodiments, the core may include a polymeric carrier, optionally with one or more pharmaceutical agents encapsulated or otherwise associated with the core. In yet other cases, the core may include a lipid, a protein, a gel, a liquid, and/or another suitable material to be delivered to a subject. The core includes a surface 24 to which one or more surface-altering agents can be attached. For instance, in some cases, core 16 is surrounded by coating 20, which includes an inner surface 28 and an outer surface 32. The coating may be formed, at least in part, of one or more surface-altering agents 34, such as a polymer (*e.g.*, a block copolymer and/or a polymer having pendant hydroxyl groups), which may associate with surface 24 of the core. Surface-altering agent 34 may be associated with the core particle by, for example, being covalently attached to the core particle, non-covalently attached to the core particle, adsorbed to the core, or attached to the core through ionic interactions, hydrophobic and/or hydrophilic interactions, electrostatic interactions, van der Waals interactions, or combinations thereof. In one set of embodiments, the surface-altering agents, or portions thereof, are chosen to facilitate transport of the particle through a mucosal barrier (*e.g.*, mucus or a mucosal membrane).In certain embodiments described herein, one or more surface-altering agents 34

are oriented in a particular configuration in the coating of the particle. For example, in some embodiments in which a surface-altering agent is a triblock copolymer, such as a triblock copolymer having a hydrophilic block – hydrophobic block – hydrophilic block configuration, a hydrophobic block may be oriented towards the surface of the core, and hydrophilic blocks may be oriented away from the core surface (*e.g.*, towards the exterior of the particle). The hydrophilic blocks may have characteristics that facilitate transport of the particle through a mucosal barrier, as described in more detail below.

[00087] Particle 10 may optionally include one or more components 40 such as targeting moieties, proteins, nucleic acids, and bioactive agents which may optionally impart specificity to the particle. For example, a targeting agent or molecule (*e.g.*, a protein, nucleic acid, nucleic acid analog, carbohydrate, or small molecule), if present, may aid in directing the particle to a specific location in the subject's body. The location may be, for example, a tissue, a particular cell type, or a subcellular compartment. One or more components 40, if present, may be associated with the core, the coating, or both; *e.g.*, they may be associated with surface 24 of the core, inner surface 28 of the coating, outer surface 32 of the coating, and/or embedded in the coating. The one or more components 40 may be associated through covalent bonds, absorption, or attached through ionic interactions, hydrophobic and/or hydrophilic interactions, electrostatic interactions, van der Waals interactions, or combinations thereof. In some embodiments, a component may be attached (*e.g.*, covalently) to one or more of the surface-altering agents of the coated particle using methods known to those of ordinary skill in the art.

[00088] It should be understood that components and configurations other than those shown in FIG. 1 or described herein may be suitable for certain particles and compositions, and that not all of the components shown in FIG. 1 are necessarily present in some embodiments.

[00089] In one set of embodiments, particle 10, when introduced into a subject, may interact with one or more components in the subject such as mucus, cells, tissues, organs, particles, fluids (*e.g.*, blood), portions thereof, and combinations thereof. In some such embodiments, the coating of particle 10 can be designed to include surface-altering agents or other components with properties that allow favorable interactions (*e.g.*, transport, binding, adsorption) with one or more materials from the subject. For example, the coating may

include surface-altering agents or other components having a certain hydrophilicity, hydrophobicity, surface charge, functional group, specificity for binding, and/or density to facilitate or reduce particular interactions in the subject. One specific example includes choosing a certain hydrophilicity, hydrophobicity, surface charge, functional group, specificity for binding, and/or density of one or more surface-altering agents to reduce the physical and/or chemical interactions between the particle and mucus of the subject, so as to enhance the mobility of the particle through mucus. Other examples are described in more detail below.

[00090] In some embodiments, once a particle is successfully transported across a mucosal barrier (*e.g.*, mucus or a mucosal membrane) in a subject, further interactions between the particle in the subject may take place. Interactions may take place, in some instances, through the coating and/or the core, and may involve, for example, the exchange of materials (*e.g.*, pharmaceutical agents, therapeutic agents, proteins, peptides, polypeptides, nucleic acids, nutrients, *e.g.*) from the one or more components of the subject to particle 10, and/or from particle 10 to the one or more components of the subject. For example, in some embodiments in which the core is formed of or comprises a pharmaceutical agent, the breakdown, release and/or transport of the pharmaceutical agent from the particle can lead to certain beneficial and/or therapeutic effects in the subject. As such, the particles described herein can be used for the diagnosis, prevention, treatment or management of certain diseases or bodily conditions.

[00091] Specific examples for the use of the particles described herein are provided below in the context of being suitable for administration to a mucosal barrier (*e.g.*, mucus or a mucosal membrane) in a subject. It should be appreciated that while many of the embodiments herein are described in this context, and in the context of providing a benefit for diseases and conditions that involve transport of materials across a mucosal barrier, the invention is not limited as such and the particles, compositions, kits, and methods described herein may be used to prevent, treat, or manage other diseases or bodily conditions.

[00092] Mucus is a sticky viscoelastic gel that protects against pathogens, toxins, and debris at various points of entry into the body, including the eyes, nose, lungs, gastrointestinal tract, and female reproductive tract. Many synthetic nanoparticles are strongly mucoadhesive and become effectively trapped in the rapidly-cleared peripheral mucus layer, vastly limiting

their distribution throughout the mucosal membrane as well as penetration toward the underlying tissue. The residence time of these trapped particles is limited by the turnover rate of the peripheral mucus layer, which, depending on the organ, ranges from seconds to several hours. To ensure effective delivery of particles including pharmaceutical agents (*e.g.*, therapeutic, diagnostic, and/or imaging agents) via mucus membranes, such particles must be able to readily diffuse through the mucus barrier, avoiding mucus adhesion. As described in more detail below, delivery of particles in mucus of the eye has particular challenges.

[00093] It has been recently demonstrated that modifying surfaces of polymeric nanoparticles with a mucus-penetrating coating can minimize adhesion to mucus and thus allow rapid particle penetration across mucus barriers. Despite these improvements, only a handful of surface coatings have been shown to facilitate mucus penetration of particles. Accordingly, improvements in compositions and methods involving mucus-penetrating particles for delivery of pharmaceutical agents would be beneficial.

[00094] In some embodiments, the compositions and methods described herein involve mucus-penetrating particles without any polymeric carriers, or with minimal use of polymeric carriers. Polymer-based mucus-penetrating particles may have one or more inherent limitations in some embodiments. In particular, in light of drug delivery applications, these limitations may include one or more of the following: A) Low drug encapsulation efficiency and low drug loading: Encapsulation of drugs into polymeric particles is often inefficient, as generally less than 10% of the total amount of drug used gets encapsulated into particles during manufacturing. Additionally, drug loadings above 50% are rarely achieved. B) Convenience of usage: Formulations based on drug-loaded polymeric particles, in general, typically need to be stored as dry powder to avoid premature drug release and, thus, require either point-of-use re-constitution or a sophisticated dosing device. C) Biocompatibility: Accumulation of slowly degrading polymer carriers following repeated dosing and their toxicity over the long term present a major concern for polymeric drug carriers. D) Chemical and physical stability: Polymer degradation may compromise stability of encapsulated drugs. In many encapsulation processes, the drug undergoes a transition from a solution phase to a solid phase, which is not well-controlled in terms of physical form of the emerging solid phase (*i.e.*, amorphous vs. crystalline vs. crystalline polymorphs). This is a concern for multiple aspects of formulation performance, including physical and chemical stability and

release kinetics. E) Manufacturing complexity: Manufacturing, especially scalability, of drug-loaded polymeric MPPs is a fairly complex process that may involve multiple steps and a considerable amount of toxic organic solvents.

[00095] In some embodiments described herein, the compositions and methods of making particles, including certain compositions and methods for making particles that have increased transport through mucosal barriers, address one or more, or all, of the concerns described above. Specifically, in some embodiments, the compositions and methods do not involve encapsulation into polymeric carriers or involve minimal use of polymeric carriers. Advantageously, by avoiding or minimizing the need to encapsulate pharmaceutical agents (*e.g.*, drugs, imaging or diagnostic agents) into polymeric carriers, certain limitations of polymeric MPPs with respect to drug loading, convenience of usage, biocompatibility, stability, and/or complexity of manufacturing, may be addressed. The methods and compositions described herein may facilitate clinical development of the mucus-penetrating particle technology.

[00096] It should be appreciated, however, that in other embodiments, pharmaceutical agents may be associated with polymer carriers via encapsulation or other processes. Thus, the description provided herein is not limited in this respect. For instance, despite the above-mentioned drawbacks of certain mucus-penetrating particles including a polymeric carrier, in certain embodiments such particles may be preferred. For example, it may be preferable to use polymer carriers for controlled release purposes and/or for encapsulating certain pharmaceutical agents that are difficult to formulate into particles. As such, in some embodiments described herein, particles that include a polymer carrier are described.

[00097] As described in more detail below, in some embodiments, the compositions and methods involve the use of PVAs that aids particle transport in mucus. The compositions and methods may involve making mucus-penetrating particles (MPPs) by, for example, an emulsification process in the presence of specific PVAs. In certain embodiments, the compositions and methods involve making MPPs from pre-fabricated particles by non-covalent coating with specific PVAs. In other embodiments, the compositions and methods involve making MPPs in the presence of specific PVAs without any polymeric carriers, or with minimal use of polymeric carriers. It should be appreciated, however, that in other embodiments, polymeric carriers can be used.

[00098] PVA is a water-soluble non-ionic synthetic polymer. Due to its surface active properties, PVA is widely used in the food and drug industries as a stabilizing agent for emulsions and, in particular, to enable encapsulation of a wide variety of compounds by emulsification techniques. PVA has the "generally recognized as safe" or "GRAS" status with the Food and Drug Administration (FDA), and has been used in auricular, intramuscular, intraocular, intravitreal, iontophoretic, ophthalmic, oral, topical, and transdermal drug products and/or drug delivery systems.

[00099] In certain previous studies, many have described PVA as a mucoadhesive polymer, suggesting or reporting that incorporating PVA in the particle formulation process leads to particles that are strongly mucoadhesive. Surprisingly, and contrary to the established opinion that PVA is a mucoadhesive polymer, the inventors have discovered within the context of the invention that compositions and methods utilizing specific PVA grades aid particle transport in mucus and are not mucoadhesive in certain applications described herein. Specifically, mucus-penetrating particles can be prepared by tailoring the degree of hydrolysis and/or molecular weight of the PVA, which was previously unknown. This discovery significantly broadens the arsenal of techniques and ingredients applicable for manufacturing MPPs.

[000100] In some embodiments described herein, the compositions and methods of making particles, including certain compositions and methods for making particles that have increased transport through mucosal barriers, address one or more, or all, of the concerns described above.

[000101] It should be appreciated that while some of the description herein may relate to the use of PVAs in coatings, in other embodiments, PVAs are not used or are used in conjunction with other polymers. For example, in some embodiments, PEG, Pluronics®, and/or other surfactants (*e.g.*, a polysorbate (*e.g.*, Tween 80®)) may be included in the compositions and methods described herein (in replace of or in addition to PVAs). In other embodiments, other polymers, such as those described in more detail herein, may be used in coatings described herein.

[000102] As described in more detail below, in some embodiments, the compositions and methods involve the use of poloxamers that aid particle transport in mucus. Poloxamers are typically nonionic triblock copolymers comprising a central hydrophobic block (*e.g.*, a

poly(propylene oxide) block) flanked by two hydrophilic blocks (*e.g.*, poly(ethylene oxide) blocks). Poloxamers have the trade name Pluronic®, examples of which are provided below

[000103] As described in more detail below, in certain embodiments, the compositions and methods involve the use of polysorbates that aid particle transport in mucus. Polysorbates are typically derived from PEGylated sorbitan (a derivative of sorbitol) esterified with fatty acids. Common brand names for polysorbates include Tween®, Alkest®, Canarcel®. Examples of polysorbates include polyoxyethylene sorbitan monooleate (*e.g.*, Tween 80®), polyoxyethylene sorbitan monostearate (*e.g.*, Tween 60®), polyoxyethylene sorbitan monopalmitate (*e.g.*, Tween 40®), and polyoxyethylene sorbitan monolaurate (*e.g.*, Tween 20®).

Core Particles

[000104] As described above in reference to FIG. 1, particle 10 may include a core 16. The core may be formed of any suitable material, such as an organic material, an inorganic material, a polymer, a lipid, a protein or combinations thereof. In one set of embodiments, the core comprises a solid. The solid may be, for example, a crystalline or an amorphous solid, such as a crystalline or amorphous solid pharmaceutical agent (*e.g.*, a therapeutic agent, diagnostic agent, and/or imaging agent), or a salt thereof. In other embodiments, the core may comprise a gel or a liquid (*e.g.,* an oil-in-water or water-in-oil emulsion). In some embodiments, more than one pharmaceutical agents may be present in the core. Specific examples of pharmaceutical agents are provided in more detail below.

[000105] The pharmaceutical agent may be present in the core in any suitable amount, *e.g.*, at least about 0.01 wt%, at least about 0.1 wt%, at least about 1 wt%, at least about 5 wt%, at least about 10 wt%, at least about 20 wt%, at least about 30 wt%, at least about 40 wt%, at least about 50 wt%, at least about 60 wt%, at least about 70 wt%, at least about 80 wt%, at least about 85 wt%, at least about 90 wt%, at least about 95 wt%, or at least about 99 wt% of the core. In one embodiment, the core is formed of 100 wt% of the pharmaceutical agent. In some cases, the pharmaceutical agent may be present in the core at less than or equal to about100 wt%, less than or equal to about 90 wt%, less than or equal to about 80 wt%, less than or equal to about 70 wt%, less than or equal to about 60 wt%, less than or equal to about 50 wt%, less than or equal to about 40 wt%, less than or equal to about 30 wt%, less than or

equal to about 20 wt%, less than or equal to about 10 wt%, less than or equal to about 5 wt%, less than or equal to about 2 wt%, or less than or equal to about 1 wt%. Combinations of the above-referenced ranges are also possible (*e.g.*, present in an amount of at least about 80 wt% and less than or equal to about100 wt%). Other ranges are also possible.

[000106] In embodiments in which the core particles comprise relatively high amounts of a pharmaceutical agent (*e.g.*, at least about 50 wt% of the core particle), the core particles generally have an increased loading of the pharmaceutical agent compared to particles that are formed by encapsulating agents into polymeric carriers. This is an advantage for drug delivery applications, since higher drug loadings mean that fewer numbers of particles may be needed to achieve a desired effect compared to the use of particles containing polymeric carriers.

[000107] As described herein, in other embodiments in which a relatively high amounts of a polymer or other material forms the core, less amounts of pharmaceutical agent may be present in the core.

[000108] The core may be formed of solid materials having various aqueous solubilities (*i.e.*, a solubility in water, optionally with one or more buffers), and/or various solubilities in the solution in which the solid material is being coated with a surface-altering agent. For example, the solid material may have an aqueous solubility (or a solubility in a coating solution) of less than or equal to about or equal to about 5 mg/mL, less than or equal to about 2 mg/mL, less than or equal to about 1 mg/mL, less than or equal to about 0.5 mg/mL, less than or equal to about 0.1 mg/mL, less than or equal to about 0.05 mg/mL, less than or equal to about 0.01 mg/mL, less than or equal to about 1 μg /mL, less than or equal to about 0.1 μg /mL, less than or equal to about 0.01 μg /mL, less than or equal to about 1 ng /mL, less than or equal to about 0.1 ng /mL, or less than or equal to about 0.01 ng /mL at 25 ºC. In some embodiments, the solid material may have an aqueous solubility (or a solubility in a coating solution) of at least about 1 pg/mL, at least about 10 pg/mL, at least about 0.1 ng/mL, at least about 1 ng/mL, at least about 10 ng/mL, at least about 0.1 μg/mL, at least about 1 μg/mL, at least about 5 μg/mL, at least about 0.01 mg/mL, at least about 0.05 mg/mL, at least about 0.1 mg/mL, at least about 0.5 mg/mL, at least about 1.0 mg/mL, at least about 2 mg/mL. Combinations of the above-noted ranges are possible (*e.g.*, an aqueous solubility or a solubility in a coating solution of at least about 10 pg/mL and less than or equal to about or

equal to about 1 mg/mL). Other ranges are also possible. The solid material may have these or other ranges of aqueous solubilities at any point throughout the pH range (*e.g.*, from pH 1 to pH 14).

[000109] In some embodiments, the core may be formed of a material within one of the ranges of solubilities classified by the U.S. Pharmacopeia Convention: *e.g.,* very soluble: >1,000 mg/mL; freely soluble: 100-1,000 mg/mL; soluble: 33-100 mg/mL; sparingly soluble: 10-33 mg/mL; slightly soluble: 1-10 mg/mL; very slightly soluble: 0.1-1 mg/mL; and practically insoluble: <0.1 mg/mL.

[000110] Although a core may be hydrophobic or hydrophilic, in many embodiments described herein, the core is substantially hydrophobic. "Hydrophobic" and "hydrophilic" are given their ordinary meaning in the art and, as will be understood by those skilled in the art, in many instances herein, are relative terms. Relative hydrophobicities and hydrophilicities of materials can be determined by measuring the contact angle of a water droplet on a planar surface of the substance to be measured, *e.g.,* using an instrument such as a contact angle goniometer and a packed powder of the core material.

[000111] In some embodiments, a material (*e.g.*, a material forming a particle core) has a contact angle of at least about 20 degrees, at least about 30 degrees, at least about 40 degrees, at least about 50 degrees, at least about 60 degrees, at least about 70 degrees, at least about 80 degrees, at least about 90 degrees, at least about 100 degrees, at least about 110 degrees, at least about 120 degrees, or at least about 130 degrees. In some embodiments, a material has a contact angle of less than or equal to about 160 degrees, less than or equal to about 150 degrees, less than or equal to about 140 degrees, less than or equal to about 130 degrees, less than or equal to about 120 degrees, less than or equal to about 110 degrees, less than or equal to about 100 degrees, less than or equal to about 90 degrees, less than or equal to about 80 degrees, or less than or equal to about 70 degrees. Combinations of the above-referenced ranges are also possible (*e.g.*, a contact angle of at least about 30 degrees and less than or equal to about 120 degrees). Other ranges are also possible.

[000112] Contact angle measurements can be made using a variety of techniques; here a static contact angle measurement between a pellet of the starting material which will be used to form the core and a bead of water is referenced. The material used to form the core was received as a fine powder or otherwise was ground into a fine powder using a mortar and

pestle. In order to form a surface on which to make measurements, the powder was packed using a 7 mm pellet die set from International Crystal Labs. The material was added to the die and pressure was applied by hand to pack the powder into a pellet, no pellet press or high pressure was used. The pellet was then suspended for testing so that the top and bottom of the pellet (defined as the surface water is added to and the opposite parallel surface respectively) were not in contact with any surface. This was done by not fully removing the pellet from the collar of the die set. The pellet therefore touches the collar on the sides and makes no contact on the top or bottom. For contact angle measurements, water was added to the surface of the pellet until a bead of water with a steady contact angle over 30 seconds was obtained. The water was added into the bead of water by submerging or contacting the tip of the pipette or syringe used for addition to the bead of water. Once a stable bead of water was obtained, an image was taken and the contact angle was measured using standard practices.

[000113] In embodiments in which the core comprises an inorganic material (*e.g.*, for use as imaging agents), the inorganic material may include, for example, a metal (*e.g.*, Ag, Au, Pt, Fe, Cr, Co, Ni, Cu, Zn, and other transition metals), a semiconductor (*e.g.*, silicon, silicon compounds and alloys, cadmium selenide, cadmium sulfide, indium arsenide, and indium phosphide), or an insulator (*e.g.*, ceramics such as silicon oxide). The inorganic material may be present in the core in any suitable amount, *e.g.*, at least about 1 wt%, at least about 5 wt%, at least about 10 wt%, at least about 20 wt%, at least about 30 wt%, at least about 40 wt%, at least about 50 wt%, at least about 75 wt%, at least about 90 wt%, or at least about 99 wt%. In one embodiment, the core is formed of 100 wt% inorganic material. In some cases, the inorganic material may be present in the core at less than or equal to about100 wt%, less than or equal to about 90 wt%, less than or equal to about 80 wt%, less than or equal to about 70 wt%, less than or equal to about 60 wt%, less than or equal to about 50 wt%, less than or equal to about 40 wt%, less than or equal to about 30 wt%, less than or equal to about 20 wt%, less than or equal to about 10 wt%, less than or equal to about 5 wt%, less than or equal to about 2 wt%, or less than or equal to about 1 wt%. Combinations of the above-referenced ranges are also possible (*e.g.*, present in an amount of at least about 1 wt% and less than or equal to about 20wt%). Other ranges are also possible.

[000114] The core may, in some cases, be in the form of a quantum dot, a carbon nanotube, a carbon nanowire, or a carbon nanorod. In some cases, the core comprises, or is formed of, a material that is not of biological origin.

[000115] In some embodiments, the core includes one or more organic materials such as a synthetic polymer and/or a natural polymer. Examples of synthetic polymers include non-degradable polymers such as polymethacrylate and degradable polymers such as polylactic acid, polyglycolic acid and copolymers thereof. Examples of natural polymers include hyaluronic acid, chitosan, and collagen. Other examples of polymers that may be suitable for portions of the core include those herein suitable for forming coatings on particles, as described below. In some cases, the one or more polymers present in the core may be used to encapsulate or adsorb one or more pharmaceutical agents.

[000116] In certain embodiments, a core may include a pharmaceutical agent comprising a lipid and/or a protein. Other materials are also possible.

[000117] If a polymer is present in the core, the polymer may be present in the core in any suitable amount, *e.g.*, less than or equal to about 100 wt%, less than or equal to about 90 wt%, less than or equal to about 80 wt%, less than or equal to about 70 wt%, less than or equal to about 60 wt%, less than or equal to about 50 wt%, less than or equal to about 40 wt%, less than or equal to about 30 wt%, less than or equal to about 20 wt%, less than or equal to about 10 wt%, less than or equal to about 5 wt%, less than or equal to about 2 wt%, or less than or equal to about 1 wt%. In some cases, the polymer may be present in an amount of at least about 1 wt%, at least about 5 wt%, at least about 10 wt%, at least about 20 wt%, at least about 30 wt%, at least about 40 wt%, at least about 50 wt%, at least about 75 wt%, at least about 90 wt%, or at least about 99 wt% in the core. Combinations of the above-referenced ranges are also possible (*e.g.*, present in an amount of at least about 1 wt% and less than or equal to about 20wt%). Other ranges are also possible. In one set of embodiments, the core is formed is substantially free of a polymeric component.

[000118] The core of a particle described herein may include a mixture of more than one polymer. In some embodiments, the core, or at least a portion of the core, includes a mixture of a first polymer and a second polymer. In certain embodiments, the first polymer is a polymer described herein. In certain embodiments, the first polymer is a relatively hydrophobic polymer (*e.g.*, a polymer having a higher hydrophobicity than the second

polymer). In certain embodiments, the first polymer is not a polyalkyl ether. In certain embodiments, the first polymer is polylactide (PLA), *e.g.*, 100DL7A MW108K. In certain embodiments, the first polymer is polylactide-co-glycolide (PLGA), *e.g.*, PLGA1A MW4K. In other embodiments, however, the first polymer may be a relatively hydrophilic polymer (*e.g.*, a polymer having a higher hydrophilicity than the second polymer).

[000119] In certain embodiments, the second polymer is a block copolymer described herein (*e.g.*, a diblock copolymer or a triblock copolymer). In certain embodiments, the second polymer is a diblock copolymer including a relatively hydrophilic block (*e.g.*, a polyalkyl ether block) and a relatively hydrophobic block (*e.g.*, a non-(polyalkyl ether) block). In certain embodiments, the polyalkyl ether block of the second polymer is PEG (*e.g.*, PEG2K or PEG5K). In certain embodiments, the non-(polyalkyl ether) block of the second polymer is PLA (*e.g.*, 100DL9K, 100DL30, or 100DL95). In certain embodiments, the non-(polyalkyl ether) block of the second polymer is PLGA (*e.g.*, 8515PLGA54K, 7525PLGA15K, or 5050PLGA18K).In certain embodiments, the second polymer is 100DL9K-co-PEG2K. In certain embodiments, the second polymer is 8515PLGA54K-co-PEG2K.

[000120] It should be appreciated that while "first" and "second" polymers are described, in some embodiments, a particle or core described herein may include only one such polymer. Additionally, while specific examples of first and second polymers are provided, it should be appreciated that other polymers, such as the polymers listed herein, can be used as first or second polymers.

[000121] The first polymer and the relatively hydrophobic block of the second polymer may be the same or different polymer. In some cases, the relatively hydrophilic block of the second polymer is present primarily at or on the surface of the core that includes the first and second polymers. For instance, the relatively hydrophilic block of the second polymer may act as a surface-altering agent as described herein. In some cases, the relatively hydrophobic block of the second polymer and the first polymer are present primarily inside the surface of the core that includes the first and second polymers. Additional details are provided in Example 19.

[000122] The relatively hydrophilic block (*e.g.*, a polyalkyl ether block, such as PEG block) of the second polymer may have any suitable molecular weight. In certain embodiments, the

molecular weight of the relatively hydrophilic block of the second polymer is at least about 0.1 kDa, at least about 0.2 kDa, at least about 0.5 kDa, at least about 1 kDa, at least about 1.5 kDa, at least about 2 kDa, at least about 2.5 kDa, at least about 3 kDa, at least about 4 kDa, at least about 5 kDa, at least about 6 kDa, at least about 8 kDa, at least about 10 kDa, at least about 20 kDa, at least about 50 kDa, at least about 100 kDa, or at least about 300 kDa. In certain embodiments, the molecular weight of the relatively hydrophilic block of the second polymer is less than or equal to about 300 kDa, less than or equal to about 100 kDa, less than or equal to about 50 kDa, less than or equal to about 20 kDa, less than or equal to about 10 kDa, less than or equal to about 8 kDa, less than or equal to about 6 kDa, at least about 5 kDa, less than or equal to about 4 kDa, less than or equal to about 3 kDa, less than or equal to about 2.5 kDa, less than or equal to about 2 kDa, less than or equal to about 1.5 kDa, less than or equal to about 1 kDa, less than or equal to about 0.5 kDa, less than or equal to about 0.2 kDa, or less than or equal to about 0.1 kDa. Combinations of the above-mentioned ranges are also possible (*e.g.*, at least about 0.5 kDa and less than or equal to about 10 kDa). Other ranges are also possible. In certain embodiments, the molecular weight of the relatively hydrophilic block of the second polymer is about 2 kDa. In certain embodiments, the molecular weight of the relatively hydrophilic block of the second polymer is about 5 kDa.

[000123] The relatively hydrophobic block (*e.g.*, a non-(polyalkyl ether) block, such as PLGA or PLA block) of the second polymer may have any suitable molecular weight. In certain embodiments, the relatively hydrophobic block of the second polymer is relatively short in length and/or low in molecular weight. In certain embodiments, the molecular weight of the relatively hydrophobic block of the second polymer is less than or equal to about 300 kDa, less than or equal to about 100 kDa, less than or equal to about 80 kDa, less than or equal to about 60 kDa, less than or equal to about 54 kDa, less than or equal to about 50 kDa, less than or equal to about 40 kDa, less than or equal to about 30 kDa, less than or equal to about 20 kDa, less than or equal to about 15 kDa less than or equal to about 10 kDa, less than or equal to about 5 kDa, less than or equal to about 2 kDa, or less than or equal to about 1 kDa. In certain embodiments, the molecular weight of the PLGA or PLA block of the second polymer is at least about 0.1 kDa, at least about 0.3 kDa, at least about 1 kDa, at least about 2 kDa, at least about 4 kDa, at least about 6 kDa, at least about 7 kDa, at least about 8 kDa, at least about 9 kDa, at least about 10 kDa, at least about 12 kDa, at least about 15 kDa, at least

about 20 kDa, at least about 30 kDa, at least about 50 kDa, or at least about 100 kDa. Combinations of the above-mentioned ranges are also possible (*e.g.*, less than or equal to about 20 kDa and at least about 1 kDa). Other ranges are also possible. In certain embodiments, the molecular weight of the relatively hydrophobic block of the second polymer is about 9 kDa.

[000124] The relatively hydrophilic block (*e.g.*, a polyalkyl ether block, such as PEG block) of the second polymer may be present in any suitable amount or density at or on the surface of a core described herein. In certain embodiments, the PEG block of the second polymer is present at or on the surface of the core at at least about 0.001, at least about 0.003, at least about 0.03, at least about 0.1 at least about 0.15, at least about 0.18, at least about 0.2, at least about 0.3, at least about 0.5, at least about 1, at least about 3, at least about 30, or at least about 100 PEG chains per nm^2 of the surface area of the core. In certain embodiments, the PEG block of the second polymer is present at or on the surface of the core at less than or equal to about 100, less than or equal to about 30, less than or equal to about 10, less than or equal to about 3, less than or equal to about 1, less than or equal to about 0.5, less than or equal to about 0.3, less than or equal to about 0.2, less than or equal to about 0.18, less than or equal to about 0.15, less than or equal to about 0.1, less than or equal to about 0.03, less than or equal to about 0.01, less than or equal to about 0.003, or less than or equal to about 0.001 PEG chains per nm^2 of the surface area of the core. Combinations of the above-mentioned ranges are also possible (*e.g.*, at least about 0.03 and less than or equal to about 1 PEG chains per nm^2 of the surface area of the core). Other ranges are also possible. In certain embodiments, the PEG block of the second polymer is present at or on the surface of the core at at least about 0.18 PEG chains per nm^2 of the surface area of the core.

[000125] The relatively hydrophilic block (*e.g.*, a polyalkyl ether block, such as PEG block) of the second polymer may be present in any suitable amount in a particle or core described herein. In certain embodiments, the relatively hydrophilic block of the second polymer is present in the core at less than or equal to about less than or equal to about 90 wt%, less than or equal to about 80 wt%, less than or equal to about 70 wt%, less than or equal to about 60 wt%, less than or equal to about 50 wt%, less than or equal to about 40 wt%, less than or equal to about 30 wt%, less than or equal to about 20 wt%, less than or equal to about 10 wt%, less than or equal to about 5 wt%, less than or equal to about 4 wt%, less than or equal

to about 3 wt%, less than or equal to about 2 wt%, less than or equal to about 1 wt%, less than or equal to about 0.5 wt%, less than or equal to about 0.2 wt%, less than or equal to about 0.1 wt%, less than or equal to about 0.05 wt%, less than or equal to about 0.02 wt%, or less than or equal to about 0.01 wt% of the particle or core. In certain embodiments, the relatively hydrophilic block of the second polymer is present in the core at at least about 0.01 wt%, at least about 0.02 wt%, at least about 0.05 wt%, at least about 0.1 wt%, at least about 0.2 wt%, at least about 0.5 wt%, at least about 1 wt%, at least about 2 wt%, at least about 3 wt%, at least about 4 wt%, at least about 5 wt%, at least about 10 wt%, at least about 20 wt%, at least about 30 wt%, at least about 40 wt%, at least about 50 wt%, at least about 60 wt%, at least about 70 wt%, at least about 80 wt%, or at least about 90 wt% of the particle or core. Combinations of the above-mentioned ranges are also possible (*e.g.*, less than or equal to about 10 wt% and at least about 0.5 wt% of the particle or core). Other ranges are also possible. In certain embodiments, the relatively hydrophilic block of the second polymer is present at less than or equal to about 3 wt% of the particle or core.

[000126] The relatively hydrophilic block (*e.g.*, a polyalkyl ether block, such as PEG block) and the relatively hydrophobic block (*e.g.*, a non-(polyalkyl ether) block, such as PLGA or PLA block) of the second polymer may be present in the core in any suitable ratio. In certain embodiments, the ratio of the relatively hydrophilic block to relatively hydrophobic block of the second polymers is at least about 1:99, at least about 10:90, at least about 20:80, at least about 30:70, at least about 40:60, at least about 50:50, at least about 60:40, at least about 70:30, at least about 80:20, at least about 90:10, or at least about 99:1 w/w. In certain embodiments, the ratio of the relatively hydrophilic block to relatively hydrophobic block is less than or equal to about 99:1, less than or equal to about 90:10, less than or equal to about 80:20, less than or equal to about 70:30, less than or equal to about 60:40, less than or equal to about 50:50, less than or equal to about 40:60, less than or equal to about 30:70, less than or equal to about 20:80, less than or equal to about 10:90, or less than or equal to about 1:99 w/w. Combinations of the above-mentioned ranges are also possible (*e.g.*, greater than about 70:30 and less than or equal to about 90:10 w/w). Other ranges are also possible. In certain embodiments, the ratio of the relatively hydrophilic block to relatively hydrophobic block is about 20:80 w/w.

[000127] The first polymer (*e.g.*, PLA or PLGA) and the second polymer (*e.g.*, PLA-co-PEG or PLGA-co-PEG) may be present in the particle or core in any suitable ratio. In certain embodiments, the ratio of the first polymer to second polymer in the particle or core is at least about 1:99, at least about 10:90, at least about 20:80, at least about 30:70, at least about 40:60, at least about 50:50, at least about 60:40, at least about 65:35, at least about 70:30, at least about 75:25, at least about 80:20, at least about 85:15, at least about 90:10, at least about 95:5, or at least about 99:1 w/w. In certain embodiments, the ratio of the first polymer to second polymer in the particle or core is less than or equal to about 99:1, less than or equal to about 95:5, less than or equal to about 90:10, less than or equal to about 85:15, less than or equal to about 80:20, less than or equal to about 75:25, less than or equal to about 70:30, less than or equal to about 65:35, less than or equal to about 60:40, less than or equal to about 50:50, less than or equal to about 40:60, less than or equal to about 30:70, less than or equal to about 20:80, less than or equal to about 10:90, or less than or equal to about 1:99 w/w. Combinations of the above-mentioned ranges are also possible (*e.g.*, greater than about 70:30 and less than or equal to about 90:10 w/w). Other ranges are also possible. In certain embodiments, the ratio of the first polymer to second polymer in the particle or core is about 70:30 w/w. In certain embodiments, the ratio of the first polymer to second polymer in the particle or core is about 80:20 w/w.

[000128] The particle or core comprising a mixture of the first polymer and the second polymer described herein may further include a coating described herein. The coating may be at or on the surface of the particle (*e.g.*, the surface of the first polymer and/or the second polymer). In some embodiments, the coating includes a hydrophilic material. The coating may include one or more surface-altering agents described herein, such as a polymer, a stabilizer, and/or a surfactant (*e.g.*, a PVA, a poloxamer, a polysorbate (*e.g.*, Tween 80®)).

[000129] The core may have any suitable shape and/or size. For instance, the core may be substantially spherical, non-spherical, oval, rod-shaped, pyramidal, cube-like, disk-shaped, wire-like, or irregularly shaped. The core may have a largest or smallest cross-sectional dimension of, for example, less than or equal to about 10 μm, less than or equal to about 5 μm, less than or equal to about 1 μm, less than or equal to about 800 nm, less than or equal to about 700 nm, less than or equal to about 500 nm, less than or equal to 400 nm, less than or equal to 300 nm, less than or equal to about 200 nm, less than or equal to about 100 nm, less

than or equal to about 75 nm, less than or equal to about 50 nm, less than or equal to about 40 nm, less than or equal to about 35 nm, less than or equal to about 30 nm, less than or equal to about 25 nm, less than or equal to about 20 nm, less than or equal to about 15 nm, or less than or equal to about 5 nm. In some cases, the core may have a largest or smallest cross-sectional dimension of, for example, at least about 5 nm, at least about 20 nm, at least about 50 nm, at least about 100 nm, at least about 200 nm, at least about 300 nm, at least about 400 nm, at least about 500 nm, at least about 1 μm, or at least about 5 μm. Combinations of the above-referenced ranges are also possible (*e.g.*, a largest or smallest cross-sectional dimension of at least about 50 nm and less than or equal to about 500 nm). Other ranges are also possible. In some embodiments, the sizes of the cores formed by a process described herein have a Gaussian-type distribution. Unless indicated otherwise, the measurements of particle/core sizes herein refer to the smallest cross-sectional dimension.

[000130] Those of ordinary skill in the art are familiar with techniques to determine sizes (*e.g.*, smallest or largest cross-sectional dimensions) of particles. Examples of suitable techniques include (DLS), transmission electron microscopy, scanning electron microscopy, electroresistance counting and laser diffraction. Other suitable techniques are known to those or ordinary skill in the art. Although many methods for determining sizes of particles are known, the sizes described herein (*e.g.*, average particle sizes, thicknesses) refer to ones measured by dynamic light scattering.

Methods of Forming Core Particles and Coated Particles

[000131] The core particles described herein may be formed by any suitable method. Suitable methods may include, for example, so called top-down techniques, *i.e.* techniques based on size reduction of relatively large particles into smaller particles (*e.g.,* milling or homogenization) or so called bottom-up techniques, *i.e.* techniques based on the growth of particles from smaller particles or individual molecules (*e.g.,* precipitation or spray-freezing into liquid).

[000132] In some embodiments, core particles may be coated with a coating. For example, core particles may be provided or formed in a first step, and then the particles may be coated in a second step to form coated particles. In other embodiments, core particles may be formed

and coated substantially simultaneously (*e.g.*, in a single step). Examples of these and other methods are provided below.

[000133] In some embodiments, the coated particles described herein are formed by a method that involves using a formulation process, a milling process, and/or a dilution process. In certain embodiments, a method of forming the particles includes a milling process, optionally with a formulation process and/or a dilution process. A formulation process may be used to form a suspension or solution comprising a core material, one or more surface-altering agents, and other components, such as solvents, tonicity agents, chelating agents, salts, anti-microbial agents and/or buffers (*e.g.*, a sodium citrate and citric acid buffer), each of which is as described herein. The formulation process may be performed using a formulation vessel. The core material and other components may be added into the formulation vessel at the same time or different times. A mixture of the core material and/or one or more other components may be stirred and/or shaken, or otherwise agitated in the vessel to facilitate suspending and/or dissolving the components. The temperature and/or pressure of the fluids containing the core material, the other components, and/or the mixture may also be individually increased or decreased to facilitate the suspending and/or dissolving processes. In some embodiments, the core material and other components are processed as described herein in the formulation vessel under an inert atmosphere (*e.g.*, nitrogen or argon) and/or protected from light. The suspension or solution obtained from the formulation vessel may be subsequently subject to a milling process which may be followed by a dilution process.

[000134] In some embodiments involving a core comprising a solid material, a milling process may be used to reduce the size of the solid material to form particles in the micrometer to nanometer size range. The milling process may be performed using a mill or other suitable apparatus. Dry and wet milling processes such as jet milling, cryo-milling, ball milling, media milling, sonication, and homogenization are known and can be used in methods described herein. Generally, in a wet milling process, a suspension of the material to be used as the core is agitated with or without excipients to reduce particle size. Dry milling is a process wherein the material to be used as the core is mixed with milling media with or without excipients to reduce particle size. In a cyro-milling process, a suspension of the

material to be used as the core is mixed with milling media with or without excipients under cooled temperatures.

[000135] After milling or other suitable process for reducing the size of a core material, a dilution process may be used to form and/or modify coated particles from a suspension. The coated particles may comprise a core material, one or more surface-altering agents, and other components, such as solvents, tonicity agents, chelating agents, salts anti-microbial agents, and buffers (*e.g.*, a sodium citrate and citric acid buffer). A dilution process may be used to achieve a target dosing concentration by diluting a solution or suspension of particles that were coated during a milling step, with or without the additional of surface-altering agents and/or other components. In certain embodiments, a dilution process may be used to exchange a first surface-altering agent with a second surface-altering agent from a surface of a particle as described herein.

[000136] The dilution process may be performed using a product vessel or any other suitable apparatus. In certain embodiments, the suspension is diluted, *i.e.*, mixed or otherwise processed with a diluent, in the product vessel. The diluent may contain solvents, surface-altering agents, tonicity agents, chelating agents, salts, or anti-microbial agents, or a combination thereof, as described herein. The suspension and the diluent may be added into the product vessel at the same time or different times. In certain embodiments when the suspension is obtained from a milling process involving milling media, the milling media may be separated from the suspension before the suspension is added into the product vessel. The suspension, the diluent, or the mixture of the suspension and the diluent may be stirred and/or shaken, or otherwise agitated, to form the coated particles described herein. The temperature and/or pressure of the suspension, the diluent, or the mixture may also be individually increased or decreased to form the coated particles. In some embodiments, the suspension and the diluent are processed in the product vessel under an inert atmosphere (*e.g.*, nitrogen or argon) and/or protected from light.

[000137] In some embodiments, the core particles described herein may be produced by milling of a solid material (*e.g.*, a pharmaceutical agent) in the presence of one or more surface-altering agents. Small particles of a solid material may require the presence of one or more surface-altering agents, which may function as a stabilizer in some embodiments, in order to stabilize a suspension of particles without agglomeration or aggregation in a liquid

solution. In some such embodiments, the stabilizer may act as a surface-altering agent, forming a coating on the particle.

[000138] As described herein, in some embodiments, a method of forming a core particle involves choosing a surface-altering agent that is suitable for both milling and for forming a coating on the particle and rendering the particle mucus penetrating. For example, as described in more detail below, it has been demonstrated that 200-500 nm nanoparticles of a model compound pyrene produced by milling of pyrene in the presence of certain Pluronics® polymers resulted in particles that can penetrate physiological mucus samples at the same rate as well-established PEGylated polymeric MPPs. Interestingly, it was observed that only a subset of Pluronics® polymers tested fit the criteria of being suitable for both milling and for forming a coating on the particle that renders the particle mucus penetrating, as described in more detail below.

[000139] In a wet milling process, milling can be performed in a dispersion (*e.g.*, an aqueous dispersion) containing one or more surface-altering agents, a grinding medium, a solid to be milled (*e.g.*, a solid pharmaceutical agent), and a solvent. Any suitable amount of a surface-altering agent can be included in the solvent. In some embodiments, a surface-altering agent may be present in the solvent in an amount of at least about 0.001 % (wt% or % weight to volume (w:v)), at least about 0.01 %, at least about 0.1 %, at least about 0.5 %, at least about 1 %, at least about 2 %, at least about 3 %, at least about 4 %, at least about 5 %, at least about 6 %, at least about 7 %, at least about 8 %, at least about 10 %, at least about 12 %, at least about 15 %, at least about 20 %, at least about 40 %, at least about 60 %, or at least about 80 % of the solvent. In some cases, the surface-altering agent may be present in the solvent in an amount of about 100 % (*e.g.*, in an instance where the surface-altering agent is the solvent). In other embodiments, the surface-altering agent may be present in the solvent in an amount of less than or equal to about 100 %, less than or equal to about 80 %, less than or equal to about 60 %, less than or equal to about 40 %, less than or equal to about 20 %, less than or equal to about 15 %, less than or equal to about 12 %, less than or equal to about 10 %, less than or equal to about 8 %, less than or equal to about 7 %, less than or equal to about 6 %, less than or equal to about 5 %, less than or equal to about 4 %, less than or equal to about 3 %, less than or equal to about 2 %, or less than or equal to about 1 % of the solvent. Combinations of the above-referenced ranges are also possible (*e.g.*, an amount of

less than or equal to about 5 % and at least about 1 % of the solvent). Other ranges are also possible. In certain embodiments, the surface-altering agent is present in the solvent in an amount of about 0.01-2% of the solvent. In certain embodiments, the surface-altering agent is present in the solvent in an amount of about 0.2-20% of the solvent. In certain embodiments, the surface-altering agent is present in the solvent in an amount of about 0.1% of the solvent. In certain embodiments, the surface-altering agent is present in the solvent in an amount of about 0.4% of the solvent. In certain embodiments, the surface-altering agent is present in the solvent in an amount of about 1% of the solvent. In certain embodiments, the surface-altering agent is present in the solvent in an amount of about 2% of the solvent. In certain embodiments, the surface-altering agent is present in the solvent in an amount of about 5% of the solvent. In certain embodiments, the surface-altering agent is present in the solvent in an amount of about 10% of the solvent.

[000140] The particular range chosen may influence factors that may affect the ability of the particles to penetrate mucus such as the stability of the coating of the surface-altering agent on the particle surface, the average thickness of the coating of the surface-altering agent on the particles, the orientation of the surface-altering agent on the particles, the density of the surface altering agent on the particles, surface-altering agent:drug ratio, drug concentration, the size, dispersibility, and polydispersity of the particles formed, and the morphology of the particles formed.

[000141] The pharmaceutical agent (or salt thereof) may be present in the solvent in any suitable amount. In some embodiments, the pharmaceutical agent (or salt thereof) is present in an amount of at least about 0.001 % (wt% or % weight to volume (w:v)), at least about 0.01 %, at least about 0.1 %, at least about 0.5 %, at least about 1 %, at least about 2 %, at least about 3 %, at least about 4 %, at least about 5 %, at least about 6 %, at least about 7 %, at least about 8 %, at least about 10 %, at least about 12 %, at least about 15 %, at least about 20 %, at least about 40 %, at least about 60 %, or at least about 80 % of the solvent. In some cases, the pharmaceutical agent (or salt thereof) may be present in the solvent in an amount of less than or equal to about 100%, less than or equal to about 90%, less than or equal to about 80 %, less than or equal to about 60 %, less than or equal to about 40 %, less than or equal to about 20 %, less than or equal to about 15 %, less than or equal to about 12 %, less than or equal to about 10 %, less than or equal to about 8 %, less than or equal to about 7 %, less than

or equal to about 6 %, less than or equal to about 5 %, less than or equal to about 4 %, less than or equal to about 3 %, less than or equal to about 2 %, or less than or equal to about 1 % of the solvent. Combinations of the above-referenced ranges are also possible (*e.g.*, an amount of less than or equal to about 20 % and at least about 1 % of the solvent). In some embodiments, the pharmaceutical agent is present in the above ranges but in w:v

[000142] The ratio of surface-altering agent to pharmaceutical agent (or salt thereof) in a solvent may also vary. In some embodiments, the ratio of surface-altering agent to pharmaceutical agent (or salt thereof) may be at least 0.001:1 (weight ratio, molar ratio, or w:v ratio), at least 0.01:1, at least 0.01:1, at least 1:1, at least 2:1, at least 3:1, at least 5:1, at least 10:1, at least 25:1, at least 50:1, at least 100:1, or at least 500:1. In some cases, the ratio of surface-altering agent to pharmaceutical agent (or salt thereof) may be less than or equal to 1000:1 (weight ratio or molar ratio), less than or equal to 500:1, less than or equal to 100:1, less than or equal to 75:1, less than or equal to 50:1, less than or equal to 25:1, less than or equal to 10:1, less than or equal to 5:1, less than or equal to 3:1, less than or equal to 2:1, less than or equal to 1:1, or less than or equal to 0.1:1. Combinations of the above-referenced ranges are possible (*e.g.*, a ratio of at least 5:1 and less than or equal to 50:1). Other ranges are also possible.

[000143] Examples of surface-altering agents are provided below, and may include, for example, polymers, stabilizers, and surfactants. As described herein, in some embodiments a surface-altering agent may act as a stabilizer, a surfactant, and/or an emulsifier, e.g., during a formation of particles. In some embodiments, the surface altering agent may aid particle transport in mucus.

[000144] It should be appreciated that while in some embodiments the stabilizer used for milling forms a coating on a particle surface, which coating renders particle mucus penetrating, in other embodiments, the stabilizer may be exchanged with one or more other surface-altering agents after the particle has been formed. For example, in one set of methods, a first stabilizer/surface-altering agent may be used during a milling process and may coat a surface of a core particle, and then all or portions of the first stabilizer/surface-altering agent may be exchanged with a second stabilizer/surface-altering agent to coat all or portions of the core particle surface. In some cases, the second stabilizer/surface-altering agent may render the particle mucus penetrating more than the first stabilizer/surface-altering agent. In some

embodiments, a core particle having a coating including multiple surface-altering agents may be formed.

[000145] Any suitable grinding medium can be used for milling. In some embodiments, a ceramic and/or polymeric material and/or a metal can be used. Examples of suitable materials may include zirconium oxide, silicon carbide, silicon oxide, silicon nitride, zirconium silicate, yttrium oxide, glass, alumina, alpha-alumina, aluminum oxide, polystyrene, poly(methyl methacrylate), titanium, steel. A grinding medium may have any suitable size. For example, the grinding medium may have an average diameter of at least about 0.1 mm, at least about 0.2 mm, at least about 0.5 mm, at least about 0.8 mm, at least about 1 mm, at least about 2 mm, or at least about 5 mm. In some cases, the grinding medium may have an average diameter of less than or equal to about 5 mm, less than or equal to about 2 mm, less than or equal to about 1 mm, less than or equal to about 0.8, less than or equal to about 0.5 mm, or less than or equal to about 0.2 mm. Combinations of the above-referenced ranges are also possible (*e.g.*, an average diameter of at least about 0.5 millimeters and less than or equal to about 1 mm). Other ranges are also possible.

[000146] Any suitable solvent may be used for milling. The choice of solvent may depend on factors such as the solid material (*e.g.*, pharmaceutical agent) being milled, the particular type of stabilizer/surface-altering agent being used (*e.g.*, one that may render the particle mucus penetrating), the grinding material be used, among other factors. Suitable solvents may be ones that do not substantially dissolve the solid material or the grinding material, but dissolve the stabilizer/surface-altering agent to a suitable degree. Non-limiting examples of solvents may include water, buffered solutions, other aqueous solutions, alcohols (*e.g.*, ethanol, methanol, butanol), and mixtures thereof that may optionally include other components such as pharmaceutical excipients, polymers, pharmaceutical agents, salts, preservative agents, viscosity modifiers, tonicity modifier, taste masking agents, antioxidants, pH modifier, and other pharmaceutical excipients. In other embodiments, an organic solvent can be used. A pharmaceutical agent may have any suitable solubility in these or other solvents, such as a solubility in one or more of the ranges described above for aqueous solubility or for solubility in a coating solution.

[000147] In the presence of surface-altering agents, milling of a solid material (*e.g.*, a drug) that is relatively insoluble in water may be used to produce particles (*e.g.*, nanoparticles).

Certain surface-altering agents may, in addition to aiding particle size reduction during milling, alter the surface of the resulting particles in a way that minimizes particle interactions with mucus constituents and prevents and/or reduces mucus adhesion, thus rendering the particles mucus-penetrating, as described in more detail herein.

[000148] In other embodiments, core particles may be formed by an emulsification technique (emulsification). Generally, emulsification techniques may involve dissolving or dispersing a material to be used as the core in a solvent; this solution or dispersion is then emulsified in a second immiscible solvent, thereby forming a plurality of particles comprising the material. Suitable emulsification techniques may include formation of oil-in-water emulsions, water-in-oil emulsions, water-oil-water emulsions, oil-water-oil emulsions, solid-in-oil-in-water emulsions, and solid-in-water-in-oil emulsions, *etc.*, with or without subsequent solvent removal, for example, by evaporation or extraction. Emulsification techniques are versatile and may be useful for preparing core particles comprising pharmaceutical agents having a relatively low aqueous solubility as well as pharmaceutical agents having a relatively high aqueous solubility.

[000149] In some embodiments, the core particles described herein may be produced by emulsification in the presence of one or more surface-altering agents. In some such embodiments, the stabilizer may act as a surface-altering agent, forming a coating on the particle (*i.e.,* the emulsification and coating steps may be performed substantially simultaneously).

[000150] In some embodiments, a method of forming a core particle by emulsification involves choosing a stabilizer that is suitable for both emulsification and for forming a coating on the particle and rendering the particle mucus penetrating. For example, as described in more detail below, it has been demonstrated that 200-500 nm nanoparticles of a model polymer PLA produced by emulsification in the presence of certain PVA polymers resulted in particles that can penetrate physiological mucus samples at the same rate as well-established PEGylated polymeric MPP. Interestingly, it was observed that only a subset of PVA polymers tested fit the criteria of being suitable for both emulsification and for forming a coating on the particle that renders the particle mucus penetrating, as described in more detail below.

[000151] In other embodiments, the particles are first formed using an emulsification technique, following by coating of the particles with a surface-altering agent.

[000152] Any suitable solvent and solvent combinations can be used for emulsification. Some examples of solvents which can serve as oil phase are organic solvents such chloroform, dichloromethane, ethyl acetate, ethyl ether, petroleum ether (hexane, heptane), and oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil soybean oil, and silicone oil. Some examples of solvents which can serve as water phase are water and aqueous buffers. Other solvents are also possible.

[000153] In other embodiments, core particles may be formed by a precipitation technique. Precipitation techniques (*e.g.*, microprecipitation techniques, nanoprecipitation techniques, crystallization techniques, controlled crystallization techniques) may involve forming a first solution comprising the material to be used as the core (*e.g.*, a pharmaceutical agent) and a solvent, wherein the material is substantially soluble in the solvent. The solution may be added to a second solution comprising another solvent in which the material is substantially insoluble (*i.e.,* an anti-solvent), thereby forming a plurality of particles comprising the material. In some cases, one or more surface-altering agents, surfactants, materials, and/or bioactive agents may be present in the first and/or second solutions. A coating may be formed during the process of precipitating the core (*e.g.*, the precipitating and coating steps may be performed substantially simultaneously). In other embodiments, the particles are first formed using a precipitation technique, following by coating of the particles with a surface-altering agent.

[000154] In some embodiments, a precipitation technique may be used to form polymeric core particles with or without a pharmaceutical agent. Generally, a precipitation technique involves dissolving the polymer to be used as the core in a solvent (with or without a pharmaceutical agent present), and the solution is then added to a miscible anti-solvent (with or without excipients present) to form the core particle. In some embodiments, this technique may be useful for preparing, for example, polymeric core particles comprising pharmaceutical agents that are slightly soluble (1-10mg/L), very slightly soluble (0.1-1 mg/mL) or practically insoluble (<0.1 mg/mL) in aqueous solutions (*e.g.*, agents having a relatively low aqueous solubility).

[000155] Any suitable solvent can be used for precipitation. In some embodiments, a suitable solvent for precipitation may include, for example, acetone, acetonitrile, dimethylformamide, dimethysulfoxide, N-methyl-2-pyrrolidone, 2-pyrrolidone, tetrahydrofuran. Other organic solvents and non-organic solvents can also be used.

[000156] Any suitable anti-solvent can be used for precipitation, including the solvents described herein that may be used for milling. In one set of embodiments, an aqueous solution is used (*e.g.*, water, buffered solutions, other aqueous solutions, and alcohols such as ethanol, methanol, butanol), and mixtures thereof that may optionally include other components such as pharmaceutical excipients, polymers, and pharmaceutical agents.

[000157] Surface-altering agents for emulsification and precipitation may be polymers, stabilizers, or surfactants, including the surface-altering agents described herein that may be used for milling.

[000158] Non-limiting examples of suitable polymers suitable for forming all or portions of a core by emulsification or precipitation may include polyamines, polyethers, polyamides, polyesters, polycarbamates, polyureas, polycarbonates, polystyrenes, polyimides, polysulfones, polyurethanes, polyacetylenes, polyethylenes, polyethyeneimines, polyisocyanates, polyacrylates, polymethacrylates, polyacrylonitriles, polyarylates, polypeptides, polynucleotides, and polysaccharides. Non-limiting examples of specific polymers include poly(caprolactone) (PCL), ethylene vinyl acetate polymer (EVA), poly(lactic acid) (PLA), poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly(lactic acid-co-glycolic acid) (PLGA), poly(L-lactic acid-co-glycolic acid) (PLLGA), poly(D,L-lactide) (PDLA), poly(L- lactide) (PLLA), poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone-co-glycolide), poly(D,L-lactide-co-PEO-co-D,L-lactide), poly(D,L-lactide-co-PPO-co-D,L-lactide), polyalkyl cyanoacrylate, polyurethane, poly-L-lysine (PLL), hydroxypropyl methacrylate (HPMA), poly(ethylene glycol), poly-L-glutamic acid, poly(hydroxy acids), polyanhydrides, polyorthoesters, poly(ester amides), polyamides, poly(ester ethers), polycarbonates, polyalkylenes such as polyethylene and polypropylene, polyalkylene glycols such as poly(ethylene glycol) (PEG), polyalkylene oxides (PEO), polyalkylene terephthalates such as poly(ethylene terephthalate), polyvinyl alcohols (PVA), polyvinyl ethers, polyvinyl esters such as poly(vinyl acetate), polyvinyl halides such as poly(vinyl chloride) (PVC), polyvinylpyrrolidone, polysiloxanes, polystyrene (PS),

polyurethanes, derivatized celluloses such as alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, hydroxypropylcellulose, carboxymethylcellulose, polymers of acrylic acids, such as poly(methyl(meth)acrylate) (PMMA), poly(ethyl(meth)acrylate), poly(butyl(meth)acrylate), poly(isobutyl(meth)acrylate), poly(hexyl(meth)acrylate), poly(isodecyl(meth)acrylate), poly(lauryl(meth)acrylate), poly(phenyl(meth)acrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) (jointly referred to herein as "polyacrylic acids"), and copolymers and mixtures thereof, polydioxanone and its copolymers, polyhydroxyalkanoates, polypropylene fumarate), polyoxymethylene, poloxamers, poly(ortho)esters, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), and trimethylene carbonate, polyvinylpyrrolidone, bovine serum albumin, human serum albumin, collagen, DNA, RNA, carboxymethyl cellulose, chitosan, dextran.

[000159] Polymers suitable for forming all or portions of a core and/or surface-altering agent may also include a poly(ethylene glycol)-vitamin E conjugate (hereinafter, "PEG-VitE conjugate"). The particles, compositions, and/or formulations including a PEG-VitE conjugate, and methods of making and using the particles, compositions, and/or formulations, are provided in more detail in international PCT application publication WO2012/061703, which is incorporated herein by reference in its entirety for all purposes. In some cases, the molecular weight of the PEG portion of the PEG-VitE conjugate is greater than about 2 kDa. The molecular weight of the PEG portion of the PEG-VitE conjugate may be selected so as to aid in the formation and/or transport of the particle across a mucosal barrier as described herein. In some embodiments, use of a PEG-VitE conjugate with a PEG portion having a molecular weight greater than about 2 kDa may allow for greater penetration of the particles through a mucosal barrier as compared to use of a PEG-VitE conjugate with a PEG portion having a molecular weight less than about 2 kDa. Additionally, in certain embodiments a higher molecular weight PEG portion may facilitate drug encapsulation. The combined ability to act as a surfactant and to reduce mucoadhesion provides important benefits as compared to other commonly used surfactants for drug encapsulation. In some cases, the molecular weight of the PEG portion of the PEG-VitE conjugate is between about 2 kDa and about 8 kDa, or between about 3 kDa and about 7 kDa, or between about 4 kDa and about 6 kDa, or between about 4.5 kDa and about 6.5 kDa, or about 5 kDa.

[000160] In some embodiments, a precipitation technique may be used to form particles comprised predominantly of a pharmaceutical agent (*e.g.*, nanocrystals). Generally, such a precipitation technique involves dissolving the pharmaceutical agent to be used as the core in a solvent, which is then added to a miscible anti-solvent with or without excipients to form the core particle. In some embodiments, this technique may be useful for preparing, for example, particles of pharmaceutical agents that are slightly soluble (1-10mg/L), very slightly soluble (0.1-1 mg/mL) or practically insoluble (<0.1 mg/mL) in aqueous solutions (*e.g.*, agents having a relatively low aqueous solubility).

[000161] In some embodiments, precipitation by salt (or complex) formation may be used to form particles (*e.g.*, nanocrystals) of a salt of a pharmaceutical agent. Generally, precipitation by salt formation involves dissolving the material to be used as the core in a solvent with or without excipients followed by addition of a counter-ion or a complexing agent, which forms an insoluble salt or a complex with the pharmaceutical agent to form the core particle. This technique may be useful for preparing particles of pharmaceutical agents that are soluble in aqueous solutions (*e.g.*, agents having a relatively high aqueous solubility). In some embodiments, pharmaceutical agents having one or more charged or ionizable groups can interact with a counter-ion (*e.g.*, a cation or an anion) to form a salt complex.

[000162] A variety of counter-ions can be used to form salt complexes, including metals (*e.g.*, alkali metals, alkali earth metals and transition metals). Non-limiting examples of cationic counter-ions include zinc, calcium, aluminum, zinc, barium, and magnesium. Non-limiting examples of anionic counter-ions include phosphate, carbonate, and fatty acids. Counter-ions may be, for example, monovalent, divalent, or trivalent. Other counter-ions are known in the art and can be used in the embodiments described herein. Other ionic and non-ionic complexing agents are also possible.

[000163] A variety of different acids may be used in a precipitation process. In some embodiments, a suitable acid may include deconoic acid, hexanoic acid, mucic acid, octanoic acid. In other embodiments, a suitable acid may include acetic acid, adipic acid, L-ascorbic acid, L-aspartic acid, capric acid (decanoic acid), carbonic acid, citric acid, fumaric acid, galactaric acid, D-glucoheptonic acid, D-gluconic acid, D-glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrochloric acid, DL-lactic acid, lauric acid, maleic acid, (-)-L-malic acid, palmitic acid, phosphoric acid, sebacic

acid, stearic acid, succinic acid, sulfuric acid, (+)-L-tartaric acid, or thiocyanic acid. In other embodiments, a suitable acid may include alginic acid, benzenesulfonic acid, benzoic acid, (+)-camphoric acid, caprylic acid (octanoic acid), cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, ethanesulfonic acid, 2-hydroxy-, gentisic acid, glutaric acid, 2-oxo-, isobutyric acid, lactobionic acid, malonic acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 2-naphthoic acid, 1-hydroxy-, nicotinic acid, oleic acid, orotic acid, oxalic acid, pamoic acid, (embonic acid), propionic acid, (-)-L-pyroglutamic acid, or *p*-toluenesulfonic acid. In yet other embodiments, a suitable acid may include acetic acid, 2,2-dichloro-, benzoic acid, 4-acetamido-, (+)-camphor-10-sulfonic acid, caproic acid (hexanoic acid), cinnamic acid, formic acid, hydrobromic acid, DL-mandelic acid, nitric acid, salicylic acid, salicylic acid, 4-amino-, or undecylenic acid (undec-10-enoic acid). Mixtures of one or more such acids can also be used.

[000164] A variety of different bases may be used in a precipitation process. In some embodiments, a suitable base includes ammonia, L-arginine, calcium hydroxide, choline, glucamine, *N*-methyl-, lysine, magnesium hydroxide, potassium hydroxide, or sodium hydroxide. In other embodiments, a suitable base may include benethamine, benzathine, betaine, deanol, diethylamine, ethanol, 2-(diethylamino)-, hydrabamine, morpholine, 4-(2-hydroxyethyl)-morpholine, pyrrolidine, 1-(2-hyroxyethyl)-, or tromethamine. In other embodiments, a suitable base may include diethanolamine (2,2'-iminobis(ethanol)), ethanolamine (2-aminoethanol), ethylenediamine, 1*H*-imidazole, piperazine, triethanolamine (2,2',2''-nitrilotris(ethanol)), or zinc hydroxide. Mixtures of one or more such bases can also be used.

[000165] Any suitable solvent can be used for precipitation by salt formation, including the solvents described herein that may be used for milling. In one set of embodiments, an aqueous solution is used (*e.g.*, water, buffered solutions, other aqueous solutions, alcohols (*e.g.*, ethanol, methanol, butanol), and mixtures thereof that may optionally include other components such as pharmaceutical excipients, polymers, and pharmaceutical agents.

[000166] In the precipitation process, the salt may have a lower aqueous solubility (or solubility in the solvent containing the salt) than the pharmaceutical agent in the non-salt form. The aqueous solubility (or solubility in the solvent) of the salt may be, for example, less than or equal to about or equal to about 5 mg/mL, less than or equal to about 2 mg/mL,

less than or equal to about 1 mg/mL, less than or equal to about 0.5 mg/mL, less than or equal to about 0.1 mg/mL, less than or equal to about 0.05 mg/mL, or less than or equal to about 0.01 mg/mL, less than or equal to about 1 μg /mL, less than or equal to about 0.1 μg /mL, less than or equal to about 0.01 μg /mL, less than or equal to about 1 ng /mL, less than or equal to about 0.1 ng /mL, or less than or equal to about 0.01 ng /mL at 25 °C. In some embodiments, the salt may have an aqueous solubility (or solubility in the solvent) of at least about 1 pg/mL, at least about 10 pg/mL, at least about 0.1 ng/mL, at least about 1 ng/mL, at least about 10 ng/mL, at least about 0.1 μg/mL, at least about 1 μg/mL, at least about 5 μg/mL,, at least about 0.01 mg/mL, at least about 0.05 mg/mL, at least about 0.1 mg/mL, at least about 0.5 mg/mL, at least about 1.0 mg/mL, at least about 2 mg/mL. Combinations of the above-noted ranges are possible (*e.g.*, an aqueous solubility (or solubility in the solvent) of at least about 0.001 mg/mL and less than or equal to about or equal to about 1 mg/mL). Other ranges are also possible. The salt may have these or other ranges of aqueous solubilities at any point throughout the pH range (*e.g.*, from pH 1 to pH 14).

[000167] In some embodiments, the solvent used for precipitation includes one or more surface-altering agents as described herein, and a coating of the one or more surface-altering agents may be formed around the particle as it precipitates out of solution. The surface-altering agent may be present in the solvent at any suitable concentration, such as a concentration of at least about 0.001% (w/v), at least about 0.005% (w/v), at least about 0.01% (w/v), at least about 0.05% (w/v), at least about 0.1% (w/v), at least about 0.5% (w/v), at least about 1% (w/v), or at least about 5% (w/v) in the aqueous solution. In some instances, the surface-altering agent is present in the solvent at a concentration of less than or equal to about 5% (w/v), less than or equal to about 1% (w/v), less than or equal to about 0.5% (w/v), less than or equal to about 0.1% (w/v), less than or equal to about 0.05% (w/v), less than or equal to about 0.01% (w/v), or less than or equal to about 0.005% (w/v). Combinations of the above-referenced ranges are also possible (*e.g.*, a concentration of at least about 0.01 (w/v) and less than or equal to about 1% (w/v). Other ranges are also possible.

[000168] Another exemplary method of forming a core particle includes a freeze-drying technique. In this technique, a pharmaceutical agent or salt thereof may be dissolved in an aqueous solution, optionally containing a surface-altering agent. A counter-ion may be added to the solution, and the solution may be immediately flash frozen and freeze dried. Dry

powder can be reconstituted in a suitable solvent (*e.g.*, an aqueous solution such as water) at a desired concentration.

[000169] A counter-ion may be added to a solvent for freeze-drying in any suitable range. In some cases, the ratio of counter-ion to pharmaceutical agent (*e.g.*, salt) may be at least 0.1:1 (weight ratio or molar ratio), at least 1:1, at least 2:1, at least 3:1, at least 5:1, at least 10:1, at least 25:1, at least 50:1, or at least 100:1. In some cases, the ratio of counter-ion to pharmaceutical agent (*e.g.*, salt) may be less than or equal to 100:1 (weight ratio or molar ratio), less than or equal to 75:1, less than or equal to 50:1, less than or equal to 25:1, less than or equal to 10:1, less than or equal to 5:1, less than or equal to 3:1, less than or equal to 2:1, less than or equal to 1:1, or less than or equal to 0.1:1. Combinations of the above-referenced ranges are possible (*e.g.*, a ratio of at least 5:1 and less than or equal to 50:1). Other ranges are also possible.

[000170] If the surface-altering agent is present in the solvent prior to freeze drying, it may be present at any suitable concentration, such as a concentration of at least about 0.001% (w/v), at least about 0.005% (w/v), at least about 0.01% (w/v), at least about 0.05% (w/v), at least about 0.1% (w/v), at least about 0.5% (w/v), at least about 1% (w/v), or at least about 5% (w/v) in the aqueous solution. In some instances, the surface-altering agent is present in the solvent at a concentration of less than or equal to about 5% (w/v), less than or equal to about 1% (w/v), less than or equal to about 0.5% (w/v), less than or equal to about 0.1% (w/v), less than or equal to about 0.05% (w/v), less than or equal to about 0.01% (w/v), or less than or equal to about 0.005% (w/v). Combinations of the above-referenced ranges are also possible (*e.g.*, a concentration of at least about 0.01% (w/v) and less than or equal to about 1% (w/v). Other ranges are also possible.

[000171] The concentration of surface-altering agent present in the solvent may be above or below the critical micelle concentration (CMC) of the surface-altering agent, depending on the particular surface-altering agent used. In other embodiments, stable particles can be formed by adding excess counter-ion to a solution containing a pharmaceutical agent. The precipitate can then be washed by various methods such as centrifugation. The resultant slurry may be sonicated. One or more surface-altering agents may be added to stabilize the resultant particles.

[000172] Other methods of forming core particles are also possible. Techniques for forming core particles may include, for example, coacervation-phase separation; melt dispersion; interfacial deposition; in situ polymerization; self-assembly of macromolecules (*e.g.*, formation of polyelectrolyte complexes or polyelectrolyte-surfactant complexes); spray-drying and spray-congealing; electro-spray; air suspension coating; pan and spray coating; freeze-drying, air drying, vacuum drying, fluidized-bed drying; precipitation (*e.g.*, nanoprecipitation, microprecipitation); critical fluid extraction; and lithographic approaches (*e.g.*, soft lithography, step and flash imprint lithography, interference lithography, photolithography).

[000173] Combinations of the methods described herein and other methods are also possible. For example, in some embodiments, a core of a pharmaceutical agent is first formed by precipitation, and then the size of the core is further reduced by a milling process.

[000174] Following formation of particles of a pharmaceutical agent, the particles may be optionally exposed to a solution comprising a (second) surface-altering agent that may associate with and/or coat the particles. In embodiments in which the pharmaceutical agent already includes a coating of a first surface-altering agent, all or portions of a second surface-altering agent may be exchanged with a second stabilizer/surface-altering agent to coat all or portions of the particle surface. In some cases, the second surface-altering agent may render the particle mucus penetrating more than the first surface-altering agent. In other embodiments, a particle having a coating including multiple surface-altering agents may be formed (*e.g.*, in a single layer or in multiple layers). In other embodiments, a particle having multiple coatings (*e.g.*, each coating optionally comprising different surface-altering agents) may be formed. In some cases, the coating is in the form of a monolayer of a surface-altering agent. Other configurations are also possible.

[000175] In any of the methods described herein, a particle may be coated with a surface-altering agent by incubating the particle in a solution with the surface-altering agent for a period of at least about 1 minutes, at least about 2 minutes, at least about 5 min., at least about 10 min., at least about 15 min., at least about 20 min., at least about 30 min., at least about 60 min., or more. In some cases, incubation may take place for a period of less than or equal to about 10 hours, less than or equal to about 5 hours, or less than or equal to about 60

min. Combinations of the above referenced ranges are also possible (*e.g.*, an incubation period of less than or equal to 60 min. and at least about 2 min.).

Particle Coatings

[000176] As shown in the embodiment illustrated in FIG. 1, core 16 may be surrounded by coating 20 comprising one or more surface-altering agents. In some embodiments, the coating is formed of one or more surface-altering agents or other molecules disposed on the surface of the core. The particular chemical makeup and/or components of the coating and surface-altering agent(s) can be chosen so as to impart certain functionality to the particles, such as enhanced transport through mucosal barriers.

[000177] It should be understood that a coating which surrounds a core need not completely surround the core, although such embodiments may be possible. For example, the coating may surround at least about 10%, at least about 30%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, or at least about 99% of the surface area of a core. In some cases, the coating substantially surrounds a core. In other cases, the coating completely surrounds a core. In other embodiments, a coating surrounds less than or equal to about 100%, less than or equal to about 90%, less than or equal to about 80%, less than or equal to about 70%, less than or equal to about 60%, or less than or equal to about 50% of the surface area of a core. Combinations of the above-referenced ranges are also possible (*e.g.*, surrounding greater than 80% and less than 100% of the surface area of a core).

[000178] The components of the coating may be distributed evenly across a surface of the core in some cases, and unevenly in other cases. For example, the coating may include portions (*e.g.*, holes) that do not include any material in some cases. If desired, the coating may be designed to allow penetration and/or transport of certain molecules and components into or out of the coating, but may prevent penetration and/or transport of other molecules and components into or out of the coating. The ability of certain molecules to penetrate and/or be transported into and/or across a coating may depend on, for example, the packing density of the surface-altering agents forming the coating and the chemical and physical properties of the components forming the coating. As described herein, the coating may include one layer of material (*e.g.*, a monolayer), or multilayers of materials in some

embodiments. A single type of surface-altering agent may be present, or multiple types of surface-altering agent.

[000179] A coating of a particle can have any suitable thickness. For example, a coating may have an average thickness of at least about 1 nm, at least about 5 nm, at least about 10 nm, at least about 30 nm, at least about 50 nm, at least about 100 nm, at least about 200 nm, at least about 500 nm, at least about 1 μm, or at least about 5 μm. In some cases, the average thickness of a coating is less than or equal to about 5 μm, less than or equal to about 1 μm, less than or equal to about 500 nm, less than or equal to about 200 nm, less than or equal to about 100 nm, less than a to about 50 nm, less than or equal to about 30 nm, less than or equal to about 10 nm, or less than or equal to about 5 nm. Combinations of the above-referenced ranges are also possible (*e.g.*, an average thickness of at least about 1 nm and less than or equal to about 100 nm). Other ranges are also possible. For particles having multiple coatings, each coating layer may have one of the thicknesses described above.

[000180] In some embodiments, the compositions and methods described herein may allow for the coating of a core particle with hydrophilic surface-altering moieties without requiring covalent linking of the surface-altering moieties to the core surface. In some such embodiments, a core having a hydrophobic surface may be coated with a polymer described herein, thereby causing a plurality of surface-altering moieties to be on the core surface without substantially altering the characteristics of the core itself. For example, the surface altering agent may be adsorbed to the outer surface of the core particle. In other embodiments, however, a surface-altering agent is covalently linked to a core particle.

[000181] In certain embodiments in which the surface-altering agent is adsorbed onto a surface of a core, the surface-altering agent may be in equilibrium with other molecules of the surface-altering agent in solution, optionally with other components (*e.g.*, in a composition/formulation). In some cases, the adsorbed surface-altering agent may be present on the surface of the core at a density described herein. The density may be an average density as the surface altering agent is in equilibrium with other components in solution.

[000182] Surface-altering agents that may be suitable for use in coatings include, for example, polymers, stabilizers, and surfactants. In certain embodiments, the surface-altering agents described herein are polymers. Non-limiting examples of polymers that are suitable for use in coatings as surface-altering agents, as described in more detail below, include

poly(vinyl alcohols) (PVAs, *e.g.*, PVA 2K75, PVA 13K87, PVA 31K87, PVA 31K98, PVA 85K87, PVA 85K99, PVA 95K95, and PVA 130K87), where the numbers before and after "K" indicate PVA's molecular weight in kDa and hydrolysis degree in %, respectively, polyvinylpyrrolidones (Povidones, *e.g.*, Kollidon® 17PF, Kollidon® 30, and Kollidon® 12PF), alkyl aryl polyether alcohols (*e.g.*, Tyloxapol), polyoxyethylene alkyl ethers (*e.g.*, Brij® 35, Brij® 98, and Brij® S100), polysorbates (e.g., Tween 20 and Tween 80), and poloxamers (such as Pluronics® (*e.g.*, Pluronic® L31, Pluronic® L35, Pluronic® L44, Pluronic® L81, Pluronic® L101, Pluronic® L121, Pluronic® P65, Pluronic® P103, Pluronic® P105, Pluronic® P123, Pluronic® F38, Pluronic® F68, Pluronic® F87, Pluronic® F108, Pluronic® F127)). Derivatives of the above-noted polymers are also possible. Combinations of the above-noted polymers and others described herein may also be used as surface-altering agents in the inventive particles.

[000183] The coating and/or surface-altering agent of a particle described herein may comprise or be formed of, for example, a hydrophobic material, a hydrophilic material, and/or an amphiphilic material. In some embodiments, the coating includes a polymer, such as a synthetic polymer (*i.e.*, a polymer not produced in nature). In other embodiments, the polymer is a natural polymer (*e.g.*, a protein, polysaccharide, rubber). In certain embodiments, the polymer is a surface active polymer. In certain embodiments, the polymer is a non-ionic polymer. In certain embodiments, the polymer is a linear, synthetic non-ionic polymer. In certain embodiments, the polymer is a non-ionic block copolymer. In some embodiments, the polymer may be a copolymer, *e.g.*, where one repeat unit is relatively hydrophobic and another repeat unit is relatively hydrophilic. The copolymer may be, for example, a diblock, triblock, alternating, or random copolymer. The polymer may be charged or uncharged.

[000184] In some embodiments, a coating comprises a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer. For example, in certain embodiments, the polymer may include poly(vinyl alcohol), a partially hydrolyzed poly(vinyl acetate) or a copolymer of vinyl alcohol and vinyl acetate. In certain embodiments, a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer may include poly(ethylene glycol)-poly(vinyl acetate)-poly(vinyl alcohol) copolymers, poly(ethylene glycol)-poly(vinyl alcohol) copolymers, poly(propylene oxide)-poly(vinyl alcohol) copolymers, and poly(vinyl

alcohol)-poly(acryl amide) copolymers. Without wishing to be bound by theory, a particle including a coating comprising a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer may have reduced mucoadhesion as compared to a control particle due to, at least in part, the display of a plurality of hydroxyl groups on the particle surface. One possible mechanism for the reduced mucoadhesion is that the hydroxyl groups alter the microenvironment of the particle, for example, by ordering water and other molecules in the particle/mucus environment. An additional or alternative possible mechanism is that the hydroxyl groups shield the adhesive domains of the mucin fibers, thereby reducing particle adhesion and speeding up particle transport.

[000185] Moreover, the ability of a particle coated with a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer to be mucus penetrating may also depend, at least in part, on the degree of hydrolysis of the polymer. In some embodiments, the hydrophobic portions of the polymer (*e.g.,* portions of the polymer that are not hydrolyzed) may allow the polymer to be adhered to the core surface (*e.g.*, in the case of the core surface being hydrophobic), thus allowing for a strong association between the core and the polymer. Surprisingly, it has been found that in some embodiments involving the surface-altering agent PVA, too high of a degree of hydrolysis does not allow for sufficient adhesion between the PVA and the core (*e.g.,* in the case of the core being hydrophobic), and thus, the particles coated with such a polymer generally do not exhibit sufficient reduced mucoadhesion. In some embodiments, too low of a degree of hydrolysis does not enhance particle transport in mucus, perhaps due to the lower amounts of hydroxyl groups available for altering the microenvironment of the particle and/or shielding the adhesive domains of the mucin fibers.

[000186] A synthetic polymer having pendant hydroxyl groups on the backbone of the polymer may have any suitable degree of hydrolysis (and, therefore, varying amounts of hydroxyl groups). The appropriate level of hydrolysis may depend on additional factors such as the molecular weight of the polymer, the composition of the core, the hydrophobicity of the core, *etc.* In some embodiments, a synthetic polymer (*e.g.,* PVA or partially hydrolyzed poly(vinyl acetate) or a copolymer of vinyl alcohol and vinyl acetate) may be at least about 30% hydrolyzed, at least about 35% hydrolyzed, at least about 40% hydrolyzed, at least about 45% hydrolyzed, at least about 50% hydrolyzed, at least about 55% hydrolyzed, at least about 60% hydrolyzed, at least about 65% hydrolyzed, at least about 70% hydrolyzed, at least about

75% hydrolyzed, at least about 80% hydrolyzed, at least about 85% hydrolyzed, at least about 87% hydrolyzed, at least about 90% hydrolyzed, at least about 95% hydrolyzed, or at least about 98% hydrolyzed. In some embodiments, the synthetic polymer may be less than or equal to about 100% hydrolyzed, less than or equal to about 99% hydrolyzed, less than or equal to about 98% hydrolyzed, less than or equal to about 97% hydrolyzed, less than or equal to about 96% hydrolyzed, less than or equal to about 95% hydrolyzed, less than or equal to about 94% hydrolyzed, less than or equal to about 93% hydrolyzed, less than or equal to about 92% hydrolyzed, less than or equal to about 91% hydrolyzed, less than or equal to about 90% hydrolyzed, less than or equal to about 87% hydrolyzed, less than or equal to about 85% hydrolyzed, less than or equal to about 80% hydrolyzed, less than or equal to about 75% hydrolyzed, less than or equal to about 70% hydrolyzed, or less than or equal to about 60% hydrolyzed. Combinations of the above-mentioned ranges are also possible (*e.g.*, a polymer that is at least about 80% hydrolyzed and less than or equal to about 95% hydrolyzed). Other ranges are also possible.

[000187] The molecular weight of a synthetic polymer described herein (*e.g.,* one having pendant hydroxyl groups on the backbone of the polymer) may be selected so as to reduce the mucoadhesion of a core and to ensure sufficient association of the polymer with the core. In certain embodiments, the molecular weight of the synthetic polymer is at least about 1 kDa, at least about 2 kDa, at least about 5 kDa, at least about 8 kDa, at least about 9 kDa, at least about 10 kDa, at least about 12 kDa, at least about 15 kDa at least about 20 kDa, at least about 25 kDa, at least about 30 kDa, at least about 40 kDa, at least about 50 kDa, at least about 60 kDa, at least about 70 kDa, at least about 80 kDa, at least about 90 kDa, at least about 100 kDa at least about 110 kDa, at least about 120 kDa, at least about 130 kDa, at least about 140 kDa, at least about 150 kDa, at least about 200 kDa, at least about 500 kDa, or at least about 1000 kDa. In some embodiments, the molecular weight of the synthetic polymer is less than or equal to about 1000 kDa, less than or equal to about 500 kDa, less than or equal to about 200 kDa, less than or equal to about 180 kDa, less than or equal to about 150 kDa, less than or equal to about 130 kDa, less than or equal to about 120 kDa, less than or equal to about 100 kDa, less than or equal to about 85 kDa, less than or equal to about 70 kDa, less than or equal to about 65 kDa, less than or equal to about 60 kDa, less than or equal to about 50 kDa, or less than or equal to about 40 kDa, less than or equal to about 30 kDa,

less than or equal to about 20 kDa, less than or equal to about 15 kDa, or less than or equal to about 10 kDa. Combinations of the above-mentioned ranges are also possible (*e.g.*, a molecular weight of at least about 10 kDa and less than or equal to about 30 kDa). The above-mentioned molecular weight ranges can also be combined with the above-mentioned hydrolysis ranges to form suitable polymers.

[000188] In some embodiments, a synthetic polymer described herein is or comprises PVA. PVA is a non-ionic polymer with surface active properties. It is a synthetic polymer typically produced through hydrolysis of poly(vinyl acetate). Partially hydrolyzed PVA is comprised of two types of repeating units: vinyl alcohol units and residual vinyl acetate units. The vinyl alcohol units are relatively hydrophilic; the vinyl acetate units are relatively hydrophobic. In some instances, the sequence distribution of vinyl alcohol units and vinyl acetate units is blocky. For example, a series of vinyl alcohol units may be followed by a series of vinyl acetate units, and followed by more vinyl alcohol units to form a polymer having a mixed block-copolymer type arrangement, with units distributed in a blocky manner. In certain embodiments, the repeat units form a copolymer, *e.g.,* a diblock, triblock, alternating, or random copolymer. Polymers other than PVA may also have these configurations of hydrophilic units and hydrophobic units.

[000189] In certain embodiments, the surface-altering agent is a PVA that is less than or equal to about 98% hydrolyzed and has a molecular weight of less than or equal to about 75 kDa, or a PVA that is less than about 95% hydrolyzed. In some embodiments, the surface-altering agent is a PVA that does not have both properties of a hydrolysis degree of greater than 95% and a molecular weight of greater than 31 kDa. In certain embodiments, such surface-altering agents may be used to coat certain pharmaceutical agents such as corticosteroids (e.g., LE) and/or other compounds described herein.

[000190] In some embodiments, the hydrophilic units of a synthetic polymer described herein may be substantially present at the outer surface of the particle. For example, the hydrophilic units may form a majority of the outer surface of the coating and may help stabilize the particle in an aqueous solution containing the particle. The hydrophobic units may be substantially present in the interior of the coating and/or at the surface of the core particle, *e.g.,* to facilitate attachment of the coating to the core.

[000191] The molar fraction of the relatively hydrophilic units and the relatively hydrophobic units of a synthetic polymer may be selected so as to reduce the mucoadhesion of a core and to ensure sufficient association of the polymer with the core, respectively. As described herein, the molar fraction of the hydrophobic units of the polymer may be chosen such that adequate association of the polymer with the core occurs, thereby increasing the likelihood that the polymer remains adhered to the core. The molar fraction of the relatively hydrophilic units to the relatively hydrophobic units of a synthetic polymer may be, for example, at least 0.5:1, at least 1:1, at least 2:1, at least 3:1, at least 5:1, at least 7:1, at least 10:1, at least 15:1, at least 20:1, at least 25:1, at least 30:1, at least 40:1, at least 50:1, at least 75:1, or at least 100:1. In some embodiments, the molar fraction of the relatively hydrophilic units to the relatively hydrophobic units of a synthetic polymer may be, for example, less than or equal to 100:1, less than or equal to 75:1, less than or equal to 50:1, less than or equal to 40:1, less than or equal to 30:1, less than or equal to 25:1, less than or equal to 20:1, less than or equal to 15:1, less than or equal to 10:1, less than or equal to 7:1, less than or equal to 5:1, less than or equal to 3:1, less than or equal to 2:1, or less than or equal to 1:1. Combinations of the above-referenced ranges are also possible (*e.g.,* a ratio of at least 1:1 and less than or equal to 50:1). Other ranges are also possible.

[000192] The molecular weight of the PVA polymer may also be tailored to increase the effectiveness of the polymer to render particles mucus penetrating. Examples of PVA polymers having various molecular weights and degree of hydrolysis are shown in Table 1.

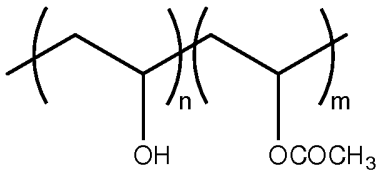
[000193] **Table 1.** Grades of PVA. The molecular weight (MW) and hydrolysis degree values were provided by the manufacturers.

PVA acronym*	MW, kDa	Hydrolysis degree, %
2K75	2	75 – 79
9K80	9 - 10	80
13K87	13 - 23	87 – 89
13K98	13 - 23	98
31K87	31 - 50	87 – 89
31K98	31 - 50	98 – 99
57K86	57 - 60	86 – 89
85K87	85 - 124	87 – 89
85K99	85 - 124	99+
95K95	95	95
105K80	104	80

130K87	130	87 – 89

*PVA acronym explanation: XXKYY, where XX stands for the PVA's lower-end molecular weight in kDa and YY stands for the PVA's lower-end hydrolysis in %.

[000194] In certain embodiments, the synthetic polymer is represented by the formula:



wherein n is an integer between 0 and 22730, inclusive; and m is an integer between 0 and 11630, inclusive. In certain embodiments, n is an integer between 25 and 20600, inclusive. In some embodiments, m is an integer between 5 and 1100, inclusive. In certain embodiments, m is an integer between 0 and 400 inclusive or between 1 and 400 inclusive. It is noted that n and m represent the total content of the vinyl alcohol and vinyl acetate repeat units in the polymer, respectively, rather than the block lengths.

[000195] The value of n may vary. In certain embodiments, n is at least 5, at least 10, at least 20, at least 30, at least 50, at least 100, at least 200, at least 300, at least 500, at least 800, at least 1000, at least 1200, at least 1500, at least 1800, at least 2000, at least 2200, at least 2400, at least 2600, at least 3000, at least 5000, at least 10000, at least 15000, at least 20000, or at least 25000. In some cases, n is less than or equal to 30000, less than or equal to 25000, less than or equal to 20000, less than or equal to 25000, less than or equal to 20000, less than or equal to 15000, less than or equal to 10000, less than or equal to 5000, less than or equal to 3000, less than or equal to 2800, less than or equal to 2400, less than or equal to 2000, less than or equal to 1800, less than or equal to 1500, less than or equal to 1200, less than or equal to 1000, less than or equal to 800, less than or equal to 500, less than or equal to 300, less than or equal to 200, less than or equal to 100, or less than or equal to 50. Combinations of the above-referenced ranges are also possible (*e.g.*, n being at least 50 and less than or equal to 2000). Other ranges are also possible.

[000196] Similarly, the value of m may vary. For instance, in certain embodiments, m is at least 5, at least 10, at least 20, at least 30, at least 50, at least 70, at least 100, at least 150, at least 200, at least 250, at least 300, at least 350, at least 400, at least 500, at least 800, at least 1000, at least 1200, at least 1500, at least 1800, at least 2000, at least 2200, at least 2400, at least 2600, at least 3000, at least 5000, at least 10000, or at least 15000. In some cases, m is

less than or equal to 15000, less than or equal to 10000, less than or equal to 5000, less than or equal to 3000, less than or equal to 2800, less than or equal to 2400, less than or equal to 2000, less than or equal to 1800, less than or equal to 1500, less than or equal to 1200, less than or equal to 1000, less than or equal to 800, less than or equal to 500, less than or equal to 400, less than or equal to 350, less than or equal to 300, less than or equal to 250, less than or equal to 200, less than or equal to 150, less than or equal to 100, less than or equal to 70, less than or equal to 50, less than or equal to 30, less than or equal to 20, or less than or equal to 10. Combinations of the above-referenced ranges are also possible (*e.g.*, m being at least 5 and less than or equal to 200). Other ranges are also possible.

[000197] In some embodiments, the particles described herein include a coating comprising a block copolymer having a relatively hydrophilic block and a relatively hydrophobic block. In some cases, the hydrophilic blocks may be substantially present at the outer surface of the particle. For example, the hydrophilic blocks may form a majority of the outer surface of the coating and may help stabilize the particle in an aqueous solution containing the particle. The hydrophobic block may be substantially present in the interior of the coating and/or at the surface of the core particle, *e.g.,* to facilitate attachment of the coating to the core. In some instances, the coating comprises a surface-altering agent including a triblock copolymer, wherein the triblock copolymer comprises a hydrophilic block – hydrophobic block – hydrophilic block configuration. Diblock copolymers having a hydrophilic block – hydrophobic block configuration are also possible. Combinations of block copolymers with other polymers suitable for use as coatings are also possible. Non-linear block configurations are also possible such as in comb, brush, or star copolymers. In some embodiments, the relatively hydrophilic block includes a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer (*e.g.,* PVA).

[000198] The molecular weight of the hydrophilic blocks and the hydrophobic blocks of the block copolymers may be selected so as to reduce the mucoadhesion of a core and to ensure sufficient association of the block copolymer with the core, respectively. The molecular weight of the hydrophobic block of the block copolymer may be chosen such that adequate association of the block copolymer with the core occurs, thereby increasing the likelihood that the block copolymer remains adhered to the core.

[000199] In certain embodiments, the combined molecular weight of the (one or more) relatively hydrophobic blocks or repeat units of a block copolymer is at least about 0.5 kDa, at least about 1 kDa, at least about 2 kDa, at least about 3 kDa, at least about 4 kDa, at least about 5 kDa, at least about 6 kDa, at least about 10 kDa, at least about 12 kDa, at least about 15 kDa, at least about 20 kDa, or at least about 50 kDa, at least about 60 kDa, at least about 70 kDa, at least about 80 kDa, at least about 90 kDa, at least about 100 kDa at least about 110 kDa, at least about 120 kDa, at least about 130 kDa, at least about 140 kDa, at least about 150 kDa, at least about 200 kDa, at least about 500 kDa, or at least about 1000 kDa. In some embodiments, the combined molecular weight of the (one or more) relatively hydrophobic blocks or repeat units is less than or equal to about 1000 kDa, less than or equal to about 500 kDa, less than or equal to about 200 kDa, less than or equal to about 150 kDa, less than or equal to about 140 kDa, less than or equal to about 130 kDa, less than or equal to about 120 kDa, less than or equal to about 110 kDa, less than or equal to about 100 kDa, less than or equal to about 90 kDa, less than or equal to about 80 kDa, less than or equal to about 50 kDa, less than or equal to about 20 kDa, less than or equal to about 15 kDa, less than or equal to about 13 kDa, less than or equal to about 12 kDa, less than or equal to about 10 kDa, less than or equal to about 8 kDa, or less than or equal to about 6 kDa. Combinations of the above-mentioned ranges are also possible (*e.g.*, at least about 3 kDa and less than or equal to about 15 kDa). Other ranges are also possible.

[000200] In some embodiments, the combined (one or more) relatively hydrophilic blocks or repeat units of a block copolymer constitute at least about 15 wt%, at least about 20 wt%, at least about 25 wt%, at least about 30 wt%, at least about 35 wt%, at least about 40 wt%, at least about 45 wt%, at least about 50 wt%, at least about 55 wt%, at least about 60 wt%, at least about 65 wt%, or at least about 70 wt% of the block copolymer. In some embodiments, the combined (one or more) relatively hydrophilic blocks or repeat units of a block copolymer constitute less than or equal to about 90 wt%, less than or equal to about 80 wt%, less than or equal to about 60 wt%, less than or equal to about 50 wt%, or less than or equal to about 40 wt% of the block copolymer. Combinations of the above-referenced ranges are also possible (*e.g.*, at least about 30 wt% and less than or equal to about 80 wt%). Other ranges are also possible.

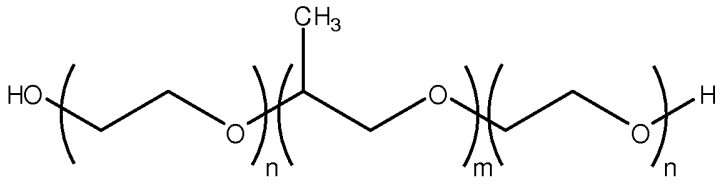
[000201] In some embodiments, the combined molecular weight of the (one or more) relatively hydrophilic blocks or repeat units of the block copolymer may be at least about 0.5 kDa, at least about 1 kDa, at least about 2 kDa, at least about 3 kDa, at least about 4 kDa, at least about 5 kDa, at least about 6 kDa, at least about 10 kDa, at least about 12 kDa, at least about 15 kDa, at least about 20 kDa, or at least about 50 kDa, at least about 60 kDa, at least about 70 kDa, at least about 80 kDa, at least about 90 kDa, at least about 100 kDa at least about 110 kDa, at least about 120 kDa, at least about 130 kDa, at least about 140 kDa, at least about 150 kDa, at least about 200 kDa, at least about 500 kDa, or at least about 1000 kDa. In certain embodiments, the combined molecular weight of the (one or more) relatively hydrophilic blocks or repeat units is less than or equal to about 1000 kDa, less than or equal to about 500 kDa, less than or equal to about 200 kDa, less than or equal to about 150 kDa, less than or equal to about 140 kDa, less than or equal to about 130 kDa, less than or equal to about 120 kDa, less than or equal to about 110 kDa, less than or equal to about 100 kDa, less than or equal to about 90 kDa, less than or equal to about 80 kDa, less than or equal to about 50 kDa, less than or equal to about 20 kDa, less than or equal to about 15 kDa, less than or equal to about 13 kDa, less than or equal to about 12 kDa, less than or equal to about 10 kDa, less than or equal to about 8 kDa, less than or equal to about 6 kDa, less than or equal to about 5 kDa, less than or equal to about 3 kDa, less than or equal to about 2 kDa, or less than or equal to about 1 kDa. Combinations of the above-mentioned ranges are also possible (*e.g.*, at least about 0.5 kDa and less than or equal to about 3 kDa). Other ranges are also possible. In embodiments in which two hydrophilic blocks flank a hydrophobic block, the molecular weights of the two hydrophilic blocks may be substantially the same or different.

[000202] In certain embodiments, the polymer of a surface-altering agent includes a polyether portion. In certain embodiments, the polymer includes a polyalkylether portion. In certain embodiments, the polymer includes polyethylene glycol tails. In certain embodiments, the polymer includes a polypropylene glycol central portion. In certain embodiments, the polymer includes polybutylene glycol as the central portion. In certain embodiments, the polymer includes polypentylene glycol as the central portion. In certain embodiments, the polymer includes polyhexylene glycol as the central portion. In certain embodiments, the polymer is a diblock copolymer of one of the polymers described herein. In certain embodiments, the polymer is a triblock copolymer of one of the polymers described herein.

As disclosed herein, any recitation of PEG may be replaced with polyethylene oxide (PEO), and any recitation of PEO may be replaced with PEG. In some embodiments, a diblock or triblock copolymer comprises a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer (*e.g.*, PVA) as one or more of the blocks (with varying degrees of hydrolysis and varying molecular weights as described herein). The synthetic polymer blocks may form the central portion or the end portions of the block copolymer.

[000203] In certain embodiments, the polymer is a triblock copolymer of a polyalkyl ether (*e.g.*, polyethylene glycol, polypropylene glycol) and another polymer (*e.g.*, a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer (*e.g.*, PVA). In certain embodiments, the polymer is a triblock copolymer of a polyalkyl ether and another polyalkyl ether. In certain embodiments, the polymer is a triblock copolymer of polyethylene glycol and another polyalkyl ether. In certain embodiments, the polymer is a triblock copolymer of polypropylene glycol and another polyalkyl ether. In certain embodiments, the polymer is a triblock copolymer with at least one unit of polyalkyl ether. In certain embodiments, the polymer is a triblock copolymer of two different polyalkyl ethers. In certain embodiments, the polymer is a triblock copolymer including a polyethylene glycol unit. In certain embodiments, the polymer is a triblock copolymer including a polypropylene glycol unit. In certain embodiments, the polymer is a triblock copolymer of a more hydrophobic unit flanked by two more hydrophilic units. In certain embodiments, the hydrophilic units are the same type of polymer. In some embodiments, the hydrophilic units include a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer (*e.g.*, PVA). In certain embodiments, the polymer includes a polypropylene glycol unit flanked by two more hydrophilic units. In certain embodiments, the polymer includes two polyethylene glycol units flanking a more hydrophobic unit. In certain embodiments, the polymer is a triblock copolymer with a polypropylene glycol unit flanked by two polyethylene glycol units. The molecular weights of the two blocks flanking the central block may be substantially the same or different.

[000204] In certain embodiments, the polymer is of the formula:



wherein n is an integer between 2 and 1140, inclusive; and m is an integer between 2 and 1730, inclusive. In certain embodiments, n is an integer between 10 and 170, inclusive. In certain embodiments, m is an integer between 5 and 70 inclusive. In certain embodiments, n is at least 2 times m, 3 times m, or 4 times m.

[000205] In certain embodiments, the coating includes a surface-altering agent comprising a (poly(ethylene glycol))-(poly(propylene oxide))-(poly(ethylene glycol)) triblock copolymer (hereinafter "PEG-PPO-PEG triblock copolymer"), present in the coating alone or in combination with another polymer such as a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer (*e.g.,* PVA). As described herein, the PEG blocks may be interchanged with PEO blocks in some embodiments. The molecular weights of the PEG (or PEO) and PPO segments of the PEG-PPO-PEG triblock copolymer may be selected so as to reduce the mucoadhesion of the particle, as described herein. Without wishing to be bound by theory, a particle having a coating comprising a PEG-PPO-PEG triblock copolymer may have reduced mucoadhesion as compared to a control particle due to, at least in part, the display of a plurality of PEG (or PEO) segments on the particle surface. The PPO segment may be adhered to the core surface (*e.g.*, in the case of the core surface being hydrophobic), thus allowing for a strong association between the core and the triblock copolymer. In some cases, the PEG-PPO-PEG triblock copolymer is associated with the core through non-covalent interactions. For purposes of comparison, the control particle may be, for example, a carboxylate-modified polystyrene particle of similar size as the coated particle in question.

[000206] In certain embodiments, a surface-altering agent includes a polymer comprising a poloxamer, having the trade name Pluronic®. Pluronic® polymers that may be useful in the embodiments described herein include, but are not limited to, F127, F38, F108, F68, F77, F87, F88, F98, L101, L121, L31, L35, L43, L44, L61, L62, L64, L81, L92, N3, P103, P104, P105, P123, P65, P84, and P85.

[000207] Examples of molecular weights of certain Pluronic® molecules are shown in Table 2.

[000208] **Table 2:** Molecular Weights of Pluronic® molecules

Pluronic®	Average MW	MW PPO	PEO wt %	MW PEO
L31	1000	900	10	100
L44	2000	1200	40	800
L81	2667	2400	10	267
L101	3333	3000	10	333
P65	3600	1800	50	1800
L121	4000	3600	10	400
P103	4286	3000	30	1286
F38	4500	900	80	3600
P123	5143	3600	30	1543
P105	6000	3000	50	3000
F87	8000	2400	70	5600
F68	9000	1800	80	7200
F127	12000	3600	70	8400
P123	5750	4030	30	1730

[000209] Although other ranges may be possible and useful in certain embodiments described herein, in some embodiments, the hydrophobic block of the PEG-PPO-PEG triblock copolymer has one of the molecular weights described above (*e.g.*, at least about 3 kDa and less than or equal to about 15 kDa), and the combined hydrophilic blocks have a weight percentage with respect to the polymer in one of the ranges described above (*e.g.*, at least about 15 wt%, at least about 20 wt%, at least about 25 wt%, or at least about 30 wt%, and less than or equal to about 80 wt%). Certain Pluronic® polymers that fall within these criteria include, for example, F127, F108, P105 and P103. Surprisingly, and as described in more detail in the Examples, it was found that these particular Pluronic® polymers rendered certain particles mucus penetrating more than other Pluronic® polymers tested that did not fall within this criteria. Additionally, other agents that did not render particles mucus penetrating (for some certain particle cores) included certain polymers such as polyvinylpyrrolidones (PVP / Kollidon), polyvinyl alcohol-polyethylene glycol graft-copolymer (Kollicoat IR), hydroxypropyl methylcellulose (Methocel); solutol HS 15, Triton X100, tyloxapol, cremophor RH 40; small molecules such as Span 20, Span 80, octyl glucoside, cetytrimethylammonium bromide (CTAB), sodium dodecyl sulfate (SDS).

[000210] It should be appreciated that the ability of a surface-altering agent to render a particle or core mucus penetrating may depend at least in part on the particular core/surface-altering agent combination, including the ability of the surface-altering agent to attach to the core and/or the density of the surface-altering agent on the core/particle surface. As such, in some embodiments a particular surface-altering agent may enhance the mobility of one type of particle or core but may not enhance the mobility of particle or core of another type.

[000211] Although much of the description herein may involve coatings comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration (*e.g.*, a PEG-PPO-PEG triblock copolymer) or coatings comprising a synthetic polymer having pendant hydroxyl groups, it should be appreciated that the coatings are not limited to these configurations and materials and that other configurations and materials are possible.

[000212] Furthermore, although many of the embodiments described herein involve a single coating, in other embodiments, a particle may include more than one coating (*e.g.*, at least two, three, four, five, or more coatings), and each coating need not be formed of or comprise a mucus penetrating material. In some cases, an intermediate coating (*i.e.*, a coating between the core surface and an outer coating) may include a polymer that facilitates attachment of an outer coating to the core surface. In many embodiments, an outer coating of a particle includes a polymer comprising a material that facilitates the transport of the particle through mucus.

[000213] As such, a coating (*e.g.*, an inner coating, an intermediate coating, and/or an outer coating) may include any suitable polymer. In some cases, the polymer may be biocompatible and/or biodegradable. In some cases, the polymeric material may comprise more than one type of polymer (*e.g.*, at least two, three, four, five, or more, polymers). In some cases, a polymer may be a random copolymer or a block copolymer (*e.g.*, a diblock copolymer, a triblock copolymer) as described herein.

[000214] Non-limiting examples of suitable polymers may include polyamines, polyethers, polyamides, polyesters, polycarbamates, polyureas, polycarbonates, polystyrenes, polyimides, polysulfones, polyurethanes, polyacetylenes, polyethylenes, polyethyeneimines, polyisocyanates, polyacrylates, polymethacrylates, polyacrylonitriles, and polyarylates. Non-limiting examples of specific polymers include poly(caprolactone) (PCL), ethylene vinyl acetate polymer (EVA), poly(lactic acid) (PLA), poly(L-lactic acid) (PLLA), poly(glycolic

acid) (PGA), poly(lactic acid-co-glycolic acid) (PLGA), poly(L-lactic acid-co-glycolic acid) (PLLGA), poly(D,L-lactide) (PDLA), poly(L- lactide) (PLLA), poly(D,L-lactide-co-caprolactone), poly(D,L-lactide-co-caprolactone-co-glycolide), poly(D,L-lactide-co-PEO-co-D,L-lactide), poly(D,L-lactide-co-PPO-co-D,L-lactide), polyalkyl cyanoacrylate, polyurethane, poly-L-lysine (PLL), hydroxypropyl methacrylate (HPMA), poly(ethylene glycol), poly-L-glutamic acid, poly(hydroxy acids), polyanhydrides, polyorthoesters, poly(ester amides), polyamides, poly(ester ethers), polycarbonates, polyalkylenes such as polyethylene and polypropylene, polyalkylene glycols such as poly(ethylene glycol) (PEG), polyalkylene oxides (PEO), polyalkylene terephthalates such as poly(ethylene terephthalate), polyvinyl alcohols (PVA), polyvinyl ethers, polyvinyl esters such as poly(vinyl acetate), polyvinyl halides such as poly(vinyl chloride) (PVC), polyvinylpyrrolidone, polysiloxanes, polystyrene (PS), polyurethanes, derivatized celluloses such as alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, hydroxypropylcellulose, carboxymethylcellulose, polymers of acrylic acids, such as poly(methyl(meth)acrylate) (PMMA), poly(ethyl(meth)acrylate), poly(butyl(meth)acrylate), poly(isobutyl(meth)acrylate), poly(hexyl(meth)acrylate), poly(isodecyl(meth)acrylate), poly(lauryl(meth)acrylate), poly(phenyl(meth)acrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate) (jointly referred to herein as "polyacrylic acids"), and copolymers and mixtures thereof, polydioxanone and its copolymers, polyhydroxyalkanoates, polypropylene fumarate), polyoxymethylene, poloxamers, poly(ortho)esters, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), and trimethylene carbonate, polyvinylpyrrolidone.

[000215] The molecular weight of a polymer may vary. In some embodiments, the molecular weight may be at least about 0.5 kDa, at least about 1 kDa, at least about 2 kDa, at least about 3 kDa, at least about 4 kDa, at least about 5 kDa, at least about 6 kDa, at least about 8 kDa, at least about 10 kDa, at least about 12 kDa, at least about 15 kDa, at least about 20 kDa, at least about 30 kDa, at least about 40 kDa, or at least about 50 kDa. In some embodiments, the molecular weight may be less than or equal to about 50 kDa, less than or equal to about 40 kDa, less than or equal to about 30 kDa, less than or equal to about 20 kDa, less than or equal to about 12 kDa, less than or equal to about 10 kDa, less than or equal to about 8 kDa, less than or equal to about 6 kDa, less than or equal to about 5 kDa, or less than

or equal to about 4 kDa. Combinations of the above-referenced ranges are possible (*e.g.*, a molecular weight of at least about 2 kDa and less than or equal to about 15 kDa). Other ranges are also possible. The molecular weight may be determined using any known technique such as light-scattering and gel permeation chromatography. Other methods are known in the art.

[000216] In certain embodiments, the polymer is biocompatible, *i.e.*, the polymer does not typically induce an adverse response when inserted or injected into a living subject; for example, it does not include significant inflammation and/or acute rejection of the polymer by the immune system, for instance, via a T-cell-mediated response. It will be recognized, of course, that "biocompatibility" is a relative term, and some degree of immune response is to be expected even for polymers that are highly compatible with living tissue. However, as used herein, "biocompatibility" refers to the acute rejection of material by at least a portion of the immune system, *i.e.*, a non-biocompatible material implanted into a subject provokes an immune response in the subject that is severe enough such that the rejection of the material by the immune system cannot be adequately controlled, and often is of a degree such that the material must be removed from the subject. One simple test to determine biocompatibility is to expose a polymer to cells *in vitro*; biocompatible polymers are polymers that typically does not result in significant cell death at moderate concentrations, *e.g.*, at concentrations of about 50 micrograms/10^6 cells. For instance, a biocompatible polymer may cause less than about 20% cell death when exposed to cells such as fibroblasts or epithelial cells, even if phagocytosed or otherwise uptaken by such cells. In some embodiments, a substance is "biocompatible" if its addition to cells *in vitro* results in less than or equal to 20% cell death, and their administration *in vivo* does not induce unwanted inflammation or other such adverse effects.

[000217] In certain embodiments, a biocompatible polymer may be biodegradable, *i.e.*, the polymer is able to degrade, chemically and/or biologically (*e.g.*, by the cellular machinery or by hydrolysis), within a physiological environment, such as within the body or when introduced to cells. For instance, the polymer may be one that hydrolyzes spontaneously upon exposure to water (*e.g.*, within a subject), and/or the polymer may degrade upon exposure to heat (*e.g.*, at temperatures of about 37 ^{o}C). Degradation of a polymer may occur at varying rates, depending on the polymer or copolymer used. For example, the half-life of the polymer

(the time at which 50% of the polymer is degraded into monomers and/or other nonpolymeric moieties) may be on the order of days, weeks, months, or years, depending on the polymer. The polymer may be biologically degraded, *e.g.*, by enzymatic activity or cellular machinery, in some cases, for example, through exposure to a lysozyme (*e.g.*, having relatively low pH). In some cases, the polymer may be broken down into monomers and/or other nonpolymeric moieties that cells can either reuse or dispose of without significant toxic effect on the cells (*i.e.*, fewer than about 20 % of the cells are killed when the components are added to cells *in vitro*). For example, polylactide may be hydrolyzed to form lactic acid, polyglycolide may be hydrolyzed to form glycolic acid, *etc.*).

[000218] Examples of biodegradable polymers include, but are not limited to, poly(ethylene glycol)-poly(propylene oxide)-poly(ethylene glycol) triblock copolymers, poly(lactide) (or poly(lactic acid)), poly(glycolide) (or poly(glycolic acid)), poly(orthoesters), poly(caprolactones), polylysine, poly(ethylene imine), poly(acrylic acid), poly(urethanes), poly(anhydrides), poly(esters), poly(trimethylene carbonate), poly(ethyleneimine), poly(acrylic acid), poly(urethane), poly(beta amino esters) or the like, and copolymers or derivatives of these and/or other polymers, for example, poly(lactide-co-glycolide) (PLGA).

[000219] In certain embodiments, a polymer may biodegrade within a period that is acceptable in the desired application. In certain embodiments, such as *in vivo* therapy, such degradation occurs in a period usually less than about five years, one year, six months, three months, one month, fifteen days, five days, three days, or even one day or less (*e.g.*, 1-4 hours, 4-8 hours, 4-24 hours, 1-24 hours) on exposure to a physiological solution with a pH between 6 and 8 having a temperature of between 25 and 37 ^{o}C. In other embodiments, the polymer degrades in a period of between about one hour and several weeks, depending on the desired application.

[000220] Although coatings and particles described herein may include polymers, in some embodiments, the particles described herein comprise a hydrophobic material that is not a polymer (*e.g.*, a non-polymer) and is not a pharmaceutical agent. For example, all or portions of a particle may be coated with a passivating layer in some embodiments. Non-limiting examples of non-polymeric materials may include certain metals, waxes, and organic materials (*e.g.*, organic silanes, perfluorinated or fluorinated organic materials).

[000221] In certain embodiments, the surface-altering agents described herein are surfactants. Surfactants may adsorb at interfaces between a relatively hydrophobic phase and a relatively hydrophilic phase and may form micelles. Non-limiting examples of surfactants that are suitable for use in coatings as surface-altering agents include phospholipids (*e.g.*, L-α-phosphatidylcholine (PC), 1,2-dipalmitoylphosphatidycholine (DPPC)), DSPC, DMPC, PEGylated phospholipids (*e.g.*, DSPE-PEG(2000) Amine) having various molecular weights of PEG, such as molecular weights described herein, oleic acid, sorbitan trioleate, sorbitan mono-oleate, sorbitan monolaurate, polyoxylene sorbitan fatty acid esters (Tweens®)/ polysorbates such as polyoxyethylene sorbitan monooleates (*e.g.*, Tween 80®), polyoxyethylene sorbitan monostearate (*e.g.*, Tween 60®), polyoxyethylene sorbitan monopalmitate (*e.g.*, Tween 40®), polyoxyethylene sorbitan monolaurate (*e.g.*, Tween 20®), sorbitan fatty acid esters (*e.g.*, Spans® (*e.g.*, Span® 20 and Span® 85), octylphenol ethoxylate surfactants (*e.g.*, Triton® X-100), ionic surfactants (*e.g.*, SDS), polyoxyethylene 15 hydroxystearates (*e.g.*, Solutol® HS 15), polyethylene glycol succinates (*e.g.*, tocopheryl polyethylene glycol succinates (TPGSs, *e.g.*, Vitamin E TPGS)), natural lecithin, oleyl polyoxyethylene ether, stearyl polyoxyethylene ether, lauryl polyoxyethylene ether, polyoxylene alkyl ethers, block copolymers of oxyethylene and oxypropylene, polyoxyethylene sterates, polyoxyethylene castor oil and their derivatives (*e.g.*, Cremophor® EL and Cremophor® RH 40), Vitamin-PEG and their derivatives, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl monooleate, glyceryl monostearate, glyceryl monoricinoleate, cetyl alcohol, stearyl alcohol, polyethylene glycol, cetyl pyridinium chloride, benzalkonium chloride, olive oil, glyceryl monolaurate, corn oil, cotton seed oil, and sunflower seed oil. Derivatives of the above-noted compounds are also possible. Combinations of the above-noted compounds and others described herein may also be used as surface-altering agents in the inventive particles.

[000222] Surface-altering agents such as surfactants may be characterized by the hydrophile-lipophile balance index (HLB). HLB values may be calculated using the Griffin approach (Griffin WC: "Classification of Surface-Active Agents by 'HLB,'" *Journal of the Society of Cosmetic Chemists* 1 (1949): 311; Griffin WC: "Calculation of HLB Values of Non-Ionic Surfactants," *Journal of the Society of Cosmetic Chemists* 5 (1954): 249), as shown in Equation 2:

$$HLB = \frac{\%\ hydrophile\ by\ weight\ of\ molecule}{5} \qquad \text{(Equation 2)}$$

[000223] In certain embodiments, the HLB value of a surfactant described herein is at least about 1, at least about 2, at least about 3, at least about 5, less than or equal to about 7, at least about 8, at least about 9, at least about 10, at least about 11, at least about 12, at least about 13, at least about 14, at least about 15, at least about 16, at least about 17, at least about 18, at least about 19, or at least about 20. In certain embodiments, the HLB value of a surfactant described herein is less than or equal to about 20, less than or equal to about 19, less than or equal to about 18, less than or equal to about 17, less than or equal to about 16, less than or equal to about 15, less than or equal to about 14, less than or equal to about 13, less than or equal to about 12, less than or equal to about 11, less than or equal to about 10, less than or equal to about 9, less than or equal to about 8, less than or equal to about 7, less than or equal to about 5, less than or equal to about 3, less than or equal to about 2, or less than or equal to about 1. Combinations of the above-referenced ranges are also possible (*e.g.*, an HLB value of at least about 8 and less than or equal to about 19). Other ranges are also possible.

[000224] In certain embodiments, the surface-altering agents described herein are stabilizers (*i.e.*, stabilizing agents). Stabilizers are typically polymers and may have no distinct hydrophobic-hydrophilic domains. Stabilizers may adsorb onto surfaces and interfaces non-covalently. For example, PVA, a water-soluble non-ionic synthetic polymer, is widely used in the food and drug industries as a stabilizer. The degree of hydrophilicity of a PVA can be altered by varying its degree of hydrolysis, owing to the chemical structure and route of synthesis of the PVA. Other non-limiting examples of stabilizers that are suitable for use in coatings as surface-altering agents include polyvinylpyrrolidones (such as ones described herein). Derivatives of the above-noted stabilizers are also possible. Combinations of the above-noted stabilizers and others described herein may be used as surface-altering agents in the inventive particles. Combinations of the above-noted polymers, surfactants, and stabilizers described herein may also be used as surface-altering agents.

Particles with reduced mucoadhesion

[000225] As described herein, in some embodiments, a method involves identifying a material such as a particle to which it is desired that its mucoadhesiveness be reduced. Materials in need of increased diffusivity through mucus may be, for example, hydrophobic,

have many hydrogen bond donors or acceptors, and/or may be highly charged. In some cases, the material may include a crystalline or amorphous solid material. The material, which may serve as a core, may be coated with a suitable polymer described herein, thereby forming a particle with a plurality of surface-altering moieties on the surface, resulting in reduced mucoadhesion. Particles herein described as having reduced mucoadhesion may alternatively be characterized as having increased transport through mucus, being mobile in mucus, or mucus-penetrating (*i.e.*, mucus-penetrating particles), meaning that the particles are transported through mucus faster than a (negative) control particle. The (negative) control particle may be a particle that is known to be mucoadhesive, *e.g.*, an unmodified particle or core that is not coated with a coating described herein, such as a 200 nm carboxylated polystyrene particle.

[000226] In certain embodiments, methods herein include preparing a pharmaceutical composition or formulation of the modified substance, *e.g.*, in a formulation adapted for delivery (*e.g.*, topical delivery) to mucus or a mucosal surface of a subject. The pharmaceutical composition with surface-altering moieties may be delivered to the mucosal surface of a subject, may pass through the mucosal barrier in the subject, and/or prolonged retention and/or increased uniform distribution of the particles at mucosal surfaces, *e.g.*, due to reduced mucoadhesion. As will be known by those of ordinary skill in the art, mucus is a viscoelastic and adhesive substance that traps most foreign particles. Trapped particles are not able to reach the underlying epithelium and/or are quickly eliminated by mucus clearance mechanisms. For a particle to reach the underlying epithelium and/or for a particle to have prolonged retention in the mucosal tissue, the particle must quickly penetrate mucus secretions and/or avoid the mucus clearance mechanisms. If a particle does not adhere substantially to the mucus, the particle may be able to diffuse in the interstitial fluids between mucin fibers and reach the underlying epithelium and/or not be eliminated by the mucus clearance mechanisms. Accordingly, modifying mucoadhesive materials, (*e.g.*, pharmaceutical agents that are hydrophobic) with a material to reduce the mucoadhesion of the particle may allow for efficient delivery of the particles to the underlying epithelium and/or prolonged retention at mucosal surfaces.

[000227] Furthermore, in some embodiments, the particles described herein having reduced mucoadhesion facilitate better distribution of the particles at a tissue surface, and/or have a

prolonged presence at the tissue surface, compared to particles that are more mucoadhesive. For example, in some cases a luminal space such as the gastrointestinal tract is surrounded by a mucus-coated surface. Mucoadhesive particles delivered to such a space are typically removed from the luminal space and from the mucus-coated surface by the body's natural clearance mechanisms. The particles described herein with reduced mucoadhesion may remain in the luminal space for relatively longer periods compared to the mucoadhesive particles. This prolonged presence may prevent or reduce clearance of the particles, and/or may allow for better distribution of the particles on the tissue surface. The prolonged presence may also affect the particle transport through the luminal space, *e.g.,* the particles may distribute into the mucus layer and may reach the underlying epithelium.

[000228] In certain embodiments, a material (*e.g.*, a core) coated with a polymer described herein may pass through mucus or a mucosal barrier in a subject, and/or exhibit prolonged retention and/or increase uniform distribution of the particles at mucosal surfaces, *e.g.*, such substances are cleared more slowly (*e.g.*, at least 2 times, 5 times, 10 times, or even at least 20 times more slowly) from a subject's body as compared to a (negative) control particle. The (negative) control particle may be a particle that is known to be mucoadhesive, *e.g.*, an unmodified particle or core that is not coated with a coating described herein, such as a 200 nm carboxylated polystyrene particle.

[000229] In certain embodiments, a particle described herein has certain a relative velocity, $\langle V_{mean} \rangle_{rel}$, which is defined as follows:

$$\langle V_{mean} \rangle_{rel} = \frac{\langle V_{mean} \rangle_{Sample} - \langle V_{mean} \rangle_{Negative\ control}}{\langle V_{mean} \rangle_{Positive\ control} - \langle V_{mean} \rangle_{Negative\ control}} \qquad \text{(Equation 1)}$$

[000230] where $\langle V_{mean} \rangle$ is the ensemble average trajectory-mean velocity, V_{mean} is the velocity of an individual particle averaged over its trajectory, the sample is the particle of interest, the negative control is a 200 nm carboxylated polystyrene particle, and the positive control is a 200 nm polystyrene particle densely PEGylated with 2 kDa - 5 kDa PEG.

[000231] Relative velocity may be used to compare velocity of a test sample to that of both a positive control and a negative control. It therefore normalizes velocity data with respect to natural variabilities in mucus samples from different donors and is believed to be a rigorous way to define the mobility of particles in mucus. The relative velocity can be measured by a multiple particle tracking technique. For instance, a fluorescent microscope equipped with a

CCD camera can be used to capture 15 s movies at a temporal resolution of 66.7 ms (15 frames/s) under 100x magnification from several areas within each sample for each type of particles: sample, negative control, and positive control. The sample, negative and positive controls may be fluorescent particles to observe tracking. Alternatively non-fluorescent particles may be coated with a fluorescent molecule, a fluorescently tagged surface agent or a fluorescently tagged polymer. An advanced image processing software (*e.g.*, Image Pro or MetaMorph) can be used to measure individual trajectories of multiple particles over a time-scale of at least 3.335 s (50 frames).

[000232] In some embodiments, a particle described herein has a relative velocity of greater than or equal to about 0.3, greater than or equal to about 0.4, greater than or equal to about 0.5, greater than or equal to about 0.6, greater than or equal to about 0.7, greater than or equal to about 0.8, greater than or equal to about 0.9, greater than or equal to about 1.0, greater than or equal to about 1.1, greater than or equal to about 1.2, greater than or equal to about 1.3, greater than or equal to about 1.4, greater than or equal to about 1.5, greater than or equal to about 1.6, greater than or equal to about 1.7, greater than or equal to about 1.8, greater than or equal to about 1.9 or greater than or equal to about 2.0 in mucus. In some embodiments, a particle described herein has a relative velocity of less than or equal to about 10.0, less than or equal to about 8.0, less than or equal to about 6.0, less than or equal to about 4.0, less than or equal to about 3.0, less than or equal to about 2.0, less than or equal to about 1.9, less than or equal to about 1.8, less than or equal to about 1.7, less than or equal to about 1.6, less than or equal to about 1.5, less than or equal to about 1.4, less than or equal to about 1.3, less than or equal to about 1.2, less than or equal to about 1.1, less than or equal to about 1.0, less than or equal to about 0.9, less than or equal to about 0.8, or less than or equal to about 1.7 in mucus. Combinations of the above-noted ranges are possible (*e.g.*, a relative velocity of greater than or equal to about 0.5 and less than or equal to about 6.0). Other ranges are also possible. The mucus may be, for example, human cervicovaginal mucus.

[000233] In certain embodiments, a particle described herein can diffuse through mucus or a mucosal barrier at a greater rate or diffusivity than a control particle or a corresponding particle (*e.g.*, a corresponding particle that is unmodified and/or is not coated with a coating described herein). In some cases, a particle described herein may pass through mucus or a mucosal barrier at a rate of diffusivity that is at least about 10 times, 20 times, 30 times, 50

times, 100 times, 200 times, 500 times, 1000 times, 2000 times, 5000 times, 10000 times, or more, higher than a control particle or a corresponding particle. In some cases, a particle described herein may pass through mucus or a mucosal barrier at a rate of diffusivity that is less than or equal to about 10000 times higher, less than or equal to about 5000 times higher, less than or equal to about 2000 times higher, less than or equal to about 1000 times higher, less than or equal to about 500 times higher, less than or equal to about 200 times higher, less than or equal to about 100 times higher, less than or equal to about 50 times higher, less than or equal to about 30 times higher, less than or equal to about 20 times higher, or less than or equal to about 10 times higher than a control particle or a corresponding particle. Combinations of the above-referenced ranges are also possible (*e.g.*, at least about 10 times and less than or equal to about 1000 times higher than a control particle or a corresponding particle). Other ranges are also possible.

[000234] For the purposes of the comparisons described herein, the corresponding particle may be approximately the same size, shape, and/or density as the test particle but lacking the coating that makes the test particle mobile in mucus. In some cases, the measurement is based on a time scale of about 1 second, or about 0.5 second, or about 2 seconds, or about 5 seconds, or about 10 seconds. Those of ordinary skill in the art will be aware of methods for determining the geometric mean square displacement and rate of diffusivity.

[000235] In addition, a particle described herein may pass through mucus or a mucosal barrier with a geometric mean squared displacement that is at least about 10 times, 20 times, 30 times, 50 times, 100 times, 200 times, 500 times, 1000 times, 2000 times, 5000 times, 10000 times, or more, higher than a corresponding particle or control particle. In some cases, a particle described herein may pass through mucus or a mucosal barrier with a geometric mean squared displacement that is less than or equal to about 10000 times higher, less than or equal to about 5000 times higher, less than or equal to about 2000 times higher, less than or equal to about 1000 times higher, less than or equal to about 500 times higher, less than or equal to about 200 times higher, less than or equal to about 100 times higher, less than or equal to about 50 times higher, less than or equal to about 30 times higher, less than or equal to about 20 times higher, or less than or equal to about 10 times higher than a control particle or a corresponding particle. Combinations of the above-referenced ranges are also possible

(*e.g.*, at least about 10 times and less than or equal to about 1000 times higher than a control particle or a corresponding particle). Other ranges are also possible.

[000236] In some embodiments, a particle described herein diffuses through a mucosal barrier at a rate approaching the rate or diffusivity at which said particles can diffuse through water. In some cases, a particle described herein may pass through a mucosal barrier at a rate or diffusivity that is less than or equal to about 1/100, less than or equal to about 1/200, less than or equal to about 1/300, less than or equal to about 1/400, less than or equal to about 1/500, less than or equal to about 1/600, less than or equal to about 1/700, less than or equal to about 1/800, less than or equal to about 1/900, less than or equal to about 1/1000, less than or equal to about 1/2000, less than or equal to about 1/5000, less than or equal to about 1/10,000 the diffusivity that the particle diffuse through water under identical conditions. In some cases, a particle described herein may pass through a mucosal barrier at a rate or diffusivity that is greater than or equal to about 1/10,000, greater than or equal to about 1/5000, greater than or equal to about 1/2000, greater than or equal to about 1/1000, greater than or equal to about 1/900, greater than or equal to about 1/800, greater than or equal to about 1/700, greater than or equal to about 1/600, greater than or equal to about 1/500, greater than or equal to about 1/400, greater than or equal to about 1/300, greater than or equal to about 1/200, or greater than or equal to about 1/100 the diffusivity that the particle diffuse through water under identical conditions. Combinations of the above-referenced ranges are also possible (*e.g.*, greater than or equal to about 1/5000 and less than 1/500 the diffusivity that the particle diffuse through water under identical conditions). Other ranges are also possible. The measurement may be based on a time scale of about 1 second, or about 0.5 second, or about 2 seconds, or about 5 seconds, or about 10 seconds.

[000237] In a particular embodiment, a particle described herein may diffuse through human cervicovaginal mucus at a diffusivity that is less than about 1/500 the diffusivity that the particle diffuses through water. In some cases, the measurement is based on a time scale of about 1 second, or about 0.5 second, or about 2 seconds, or about 5 seconds, or about 10 seconds.

[000238] In certain embodiments, the present invention provides particles that travel through mucus, such as human cervicovaginal mucus, at certain absolute diffusivities. For example, the particles of described herein may travel at diffusivities of at least about 1×10^{-4}

μm/s, 2 x 10^{-4} μm/s, 5 x 10^{-4} μm/s, 1 x 10^{-3}μm/s, 2 x 10^{-3} μm/s, 5 x 10^{-3} μm/s, 1 x 10^{-2} μm/s, 2 x 10^{-2} μm/s, 4 x 10^{-2} μm/s, 5 x 10^{-2}μm/s, 6 x 10^{-2} μm/s, 8 x 10^{-2} μm/s, 1 x 10^{-1} μm/s, 2 x 10^{-1} μm/s, 5 x 10^{-1} μm/s, 1 μm/s, or 2 μm/s. In some cases, the particles may travel at diffusivities of less than or equal to about 2 μm/s, less than or equal to about 1 μm/s, less than or equal to about 5 x 10^{-1} μm/s, less than or equal to about 2 x 10^{-1} μm/s, less than or equal to about 1 x 10^{-1} μm/s, less than or equal to about 8 x 10^{-2} μm/s, less than or equal to about 6 x 10^{-2} μm/s, less than or equal to about 5 x 10^{-2} μm/s, less than or equal to about 4 x 10^{-2} μm/s, less than or equal to about 2 x 10^{-2} μm/s, less than or equal to about 1 x 10^{-2} μm/s, less than or equal to about 5 x 10^{-3} μm/s, less than or equal to about 2 x 10^{-3} μm/s, less than or equal to about 1 x 10^{-3} μm/s, less than or equal to about 5 x 10^{-4} μm/s, less than or equal to about 2 x 10^{-4} μm/s, or less than or equal to about 1 x 10^{-4} μm/s. Combinations of the above-referenced ranges are also possible (*e.g.*, greater than or equal to about 2 x 10^{-4} μm/s and less than or equal to about 1 x 10^{-1} μm/s). Other ranges are also possible. In some cases, the measurement is based on a time scale of about 1 second, or about 0.5 second, or about 2 seconds, or about 5 seconds, or about 10 seconds.

[000239] It should be appreciated that while many of the mobilities (*e.g.*, relative velocities, diffusivities) described here may be measured in human cervicovaginal mucus, they may be measured in other types of mucus as well.

[000240] In certain embodiments, a particle described herein comprises surface-altering moieties at a given density. The surface-altering moieties may be the portions of a surface-altering agent that are, for example, exposed to the solvent containing the particle. As an example, the hydrolyzed units/blocks of PVA may be surface-altering moieties of the surface-altering agent PVA. In another example, the PEG segments may be surface-altering moieties of the surface-altering agent PEG-PPO-PEG. In some cases, the surface-altering moieties and/or surface-altering agents are present at a density of at least about 0.001 units or molecules per nm^2, at least about 0.002, at least about 0.005, at least about 0.01, at least about 0.02, at least about 0.05, at least about 0.1, at least about 0.2, at least about 0.5, at least about 1, at least about 2, at least about 5, at least about 10, at least about 20, at least about 50, at least about 100 units or molecules per nm^2, or more units or molecules per nm^2. In some cases, the surface-altering moieties and/or surface-altering agents are present at a density of less than or equal to about 100 units or molecules per nm^2, less than or equal to about 50, less

than or equal to about 20, less than or equal to about 10, less than or equal to about 5, less than or equal to about 2, less than or equal to about 1, less than or equal to about 0.5, less than or equal to about 0.2, less than or equal to about 0.1, less than or equal to about 0.05, less than or equal to about 0.02, or less than or equal to about 0.01 units or molecules per nm^2. Combinations of the above-referenced ranges are possible (*e.g.*, a density of at least about 0.01 and less than or equal to about 1 units or molecules per nm^2). Other ranges are also possible. In some embodiments, the density values described above may be an average density as the surface altering agent is in equilibrium with other components in solution.

[000241] Those of ordinary skill in the art will be aware of methods to estimate the average density of surface-altering moieties (see, for example, S.J. Budijono et al.,Colloids and Surfaces A: Physicochem. Eng. Aspects 360 (2010) 105–110 and Joshi, *et al.*,, *Anal. Chim. Acta* 104 (1979) 153–160, each of which is incorporated herein by reference). For example, as described herein, the average density of surface-altering moieties can be determined using HPLC quantitation and DLS analysis. A suspension of particles for which surface density determination is of interest is first sized using DLS: a small volume is diluted to an appropriate concentration (~100 μg/mL, for example), and the z-average diameter is taken as a representative measurement of particle size. The remaining suspension is then divided into two aliquots. Using HPLC, the first aliquot is assayed for the total concentration of core material and for the total concentration of surface-altering moiety. Again using HPLC the second aliquot is assayed for the concentration of free or unbound surface-altering moiety. In order to get only the free or unbound surface-altering moiety from the second aliquot, the particles, and therefore any bound surface-altering moiety, are removed by ultracentrifugation. By subtracting the concentration of the unbound surface-altering moiety from the total concentration of surface-altering moiety, the concentration of bound surface-altering moiety can be determined. Since the total concentration of core material was also determined from the first aliquot, the mass ratio between the core material and the surface-altering moiety can be determined. Using the molecular weight of the surface-altering moiety the number of surface-altering moiety to mass of core material can be calculated. To turn this number into a surface density measurement, the surface area per mass of core material needs to be calculated. The volume of the particle is approximated as that of a sphere with the diameter obtained from DLS allowing for the calculation of the surface area per mass of core

material. In this way the number of surface-altering moieties per surface area can be determined.

[000242] In certain embodiments, the particles described herein comprise surface-altering moieties and/or agents that affect the zeta-potential of the particle. The zeta potential of the coated particle may be, for example, at least about -100 mV, at least about -75 mV, at least about -50 mV, at least about -40 mV, at least about -30 mV, at least about -20 mV, at least about -10 mV, at least about -5 mV, at least about 5 mV, at least about 10 mV, at least about 20 mV, at least about 30 mV, at least about 40 mV, at least about 50 mV, at least about 75 mV, or at least about 100 mV. Combinations of the above-referenced ranges are possible (*e.g.*, a zeta-potential of at least about -50 mV and less than or equal to about 50 mV). Other ranges are also possible.

[000243] The coated particles described herein may have any suitable shape and/or size. In some embodiments, a coated particle has a shape substantially similar to the shape of the core. In some cases, a coated particle described herein may be a nanoparticle, *i.e.*, the particle has a characteristic dimension of less than about 1 micrometer, where the characteristic dimension of the particle is the diameter of a perfect sphere having the same volume as the particle. In other embodiments, larger sizes are possible (*e.g.*, about 1 – 10 microns). A plurality of particles, in some embodiments, may also be characterized by an average size (*e.g.*, an average largest cross-sectional dimension, or an average smallest cross-sectional dimension for the plurality of particles). A plurality of particles may have an average size of, for example, less than or equal to about 10 μm, less than or equal to about 5 μm, less than or equal to about 1 μm, less than or equal to about 800 nm, less than or equal to about 700 nm, less than or equal to about 500 nm, less than or equal to 400 nm, less than or equal to 300 nm, less than or equal to about 200 nm, less than or equal to about 100 nm, less than or equal to about 75 nm, less than or equal to about 50 nm, less than or equal to about 40 nm, less than or equal to about 35 nm, less than or equal to about 30 nm, less than or equal to about 25 nm, less than or equal to about 20 nm, less than or equal to about 15 nm, or less than or equal to about 5 nm. In some cases, a plurality of particles may have an average size of, for example, at least about 5 nm, at least about 20 nm, at least about 50 nm, at least about 100 nm, at least about 200 nm, at least about 300 nm, at least about 400 nm, at least about 500 nm, at least about 1 μm, at least or at least about 5 μm. Combinations of the above-referenced ranges are

also possible (*e.g.*, an average size of at least about 50 nm and less than or equal to about 500 nm). Other ranges are also possible. In some embodiments, the sizes of the cores formed by a process described herein have a Gaussian-type distribution.

Pharmaceutical Agents

[000244] In some embodiments, a coated particle comprises at least one pharmaceutical agent. The pharmaceutical agent may be present in the core of the particle and/or present in a coating of the particle (*e.g.*, dispersed throughout the core and/or coating). In some cases, a pharmaceutical agent may be disposed on the surface of the particle (*e.g.*, on an outer surface of a coating, the inner surface of a coating, on a surface of the core). The pharmaceutical agent may be contained within a particle and/or disposed in a portion of the particle using commonly known techniques (*e.g.*, by coating, adsorption, covalent linkage, encapsulation, or other process). In some cases, the pharmaceutical agent may be present in the core of the particle prior to or during coating of the particle. In some cases, the pharmaceutical agent is present during the formation of the core of the particle, as described herein.

[000245] Non-limiting examples of pharmaceutical agents include imaging agents, diagnostic agents, therapeutic agents, agents with a detectable label, nucleic acids, nucleic acid analogs, small molecules, peptidomimetics, proteins, peptides, lipids, vaccines, viral vectors, virus, and surfactants.

[000246] In some embodiments, a pharmaceutical agent contained in a particle described herein has a therapeutic, diagnostic, or imaging effect in a mucosal tissue to be targeted. Non-limiting examples of mucosal tissues include oral (*e.g.*, including the buccal and esophagal membranes and tonsil surface), ophthalmic, gastrointestinal (*e.g.*, including stomach, small intestine, large intestine, colon, rectum), nasal, respiratory (*e.g.*, including nasal, pharyngeal, tracheal and bronchial membranes), and genital (*e.g.*, including vaginal, cervical and urethral membranes) tissues.

[000247] Any suitable number of pharmaceutical agents may be present in a particle described herein. For example, at least 1, at least 2, at least 3, at least 4, at least 5, or more, but generally less than 10, pharmaceutical agents may be present in a particle described herein.

[000248] A number of drugs that are mucoadhesive are known in the art and may be used as pharmaceutical agents in the particles described herein (see, for example, Khanvilkar K, Donovan MD, Flanagan DR, Drug transfer through mucus, Advanced Drug Delivery Reviews 48 (2001) 173-193; Bhat PG, Flanagan DR, Donovan MD. Drug diffusion through cystic fibrotic mucus: steady-state permeation, rheologic properties, and glycoprotein morphology, J Pharm Sci, 1996 Jun;85(6):624-30). Additional non-limiting examples of pharmaceutical agents include imaging and diagnostic agents (such as radioopaque agents, labeled antibodies, labeled nucleic acid probes, dyes, such as colored or fluorescent dyes, *etc.*) and adjuvants (radiosensitizers, transfection-enhancing agents, chemotactic agents and chemoattractants, peptides that modulate cell adhesion and/or cell mobility, cell permeabilizing agents, vaccine potentiators, inhibitors of multidrug resistance and/or efflux pumps, *etc.*).

[000249] Additional non-limiting examples of pharmaceutical agents include pazopanib, sorafenib, lapatinib, fluocinolone acetonide, semaxanib, axitinib, tivozanib, cediranib, linifanib, regorafenib, telatinib, vatalanib, MGCD-265, OSI-930, KRN-633, bimatoprost, latanoprost, travoprost, aloxiprin, auranofin, azapropazone, benorylate, diflunisal, etodolac, fenbufen, fenoprofen calcim, flurbiprofen, furosemide, ibuprofen, indomethacin, ketoprofen, loteprednol etabonate, bromfenac beryllium, bromfenac magnesium, bromfenac calcium, bromfenac strontium, bromfenac barium, bromfenac zinc, bromfenac copper(II), diclofenac free acid, diclofenac beryllium, diclofenac magnesium, diclofenac calcium, diclofenac strontium, diclofenac barium, diclofenac zinc, diclofenac copper(II), ketorolac free acid, ketorolac beryllium, ketorolac magnesium, ketorolac calcium, ketorolac strontium, ketorolac barium, ketorolac zinc, ketorolac copper(II), meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxyphenbutazone, phenylbutazone, piroxicam, sulindac, albendazole, bephenium hydroxynaphthoate, cambendazole, dichlorophen, ivermectin, mebendazole, oxamniquine, oxfendazole, oxantel embonate, praziquantel, pyrantel embonate, thiabendazole, amiodarone HCl, disopyramide, flecainide acetate, quinidine sulphate. Anti-bacterial agents: benethamine penicillin, cinoxacin, ciprofloxacin HCl, clarithromycin, clofazimine, cloxacillin, demeclocycline, doxycycline, erythromycin, ethionamide, imipenem, nalidixic acid, nitrofurantoin, rifampicin, spiramycin, sulphabenzamide, sulphadoxine, sulphamerazine, sulphacetamide, sulphadiazine, sulphafurazole,

sulphamethoxazole, sulphapyridine, tetracycline, trimethoprim, dicoumarol, dipyridamole, nicoumalone, phenindione, amoxapine, maprotiline HCl, mianserin HCL, nortriptyline HCl, trazodone HCL, trimipramine maleate, acetohexamide, chlorpropamide, glibenclamide, gliclazide, glipizide, tolazamide, tolbutamide, beclamide, carbamazepine, clonazepam, ethotoin, methoin, methsuximide, methylphenobarbitone, oxcarbazepine, paramethadione, phenacemide, phenobarbitone, phenytoin, phensuximide, primidone, sulthiame, valproic acid, amphotericin, butoconazole nitrate, clotrimazole, econazole nitrate, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, miconazole, natamycin, nystatin, sulconazole nitrate, terbinafine HCl, terconazole, tioconazole, undecenoic acid, allopurinol, probenecid, sulphin-pyrazone, amlodipine, benidipine, darodipine, dilitazem HCl, diazoxide, felodipine, guanabenz acetate, isradipine, minoxidil, nicardipine HCl, nifedipine, nimodipine, phenoxybenzamine HCl, prazosin HCL, reserpine, terazosin HCL, amodiaquine, chloroquine, chlorproguanil HCl, halofantrine HCl, mefloquine HCl, roguanil HCl, pyrimethamine, quinine sulphate, dihydroergotamine mesylate, ergotamine tartrate, methysergide maleate, pizotifen maleate, sumatriptan succinate, atropine, benzhexol HCl, biperiden, ethopropazine HCl, hyoscyamine, mepenzolate bromide, oxyphencylcimine HCl, tropicamide, aminoglutethimide, amsacrine, azathioprine, busulphan, chlorambucil, cyclosporin, dacarbazine, estramustine, etoposide, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, mitozantrone, procarbazine HCl, tamoxifen citrate, testolactone, benznidazole, clioquinol, decoquinate, diiodohydroxyquinoline, diloxanide furoate, dinitolmide, furzolidone, metronidazole, nimorazole, nitrofurazone, ornidazole, tinidazole, carbimazole, propylthiouracil, alprazolam, amylobarbitone, barbitone, bentazepam, bromazepam, bromperidol, brotizolam, butobarbitone, carbromal, chlordiazepoxide, chlormethiazole, chlorpromazine, clobazam, clotiazepam, clozapine, diazepam, droperidol, ethinamate, flunanisone, flunitrazepam, fluopromazine, flupenthixol decanoate, fluphenazine decanoate, flurazepam, haloperidol, lorazepam, lormetazepam, medazepam, meprobamate, methaqualone, midazolam, nitrazepam, oxazepam, pentobarbitone, perphenazine pimozide, prochlorperazine, sulpiride, temazepam, thioridazine, triazolam, zopiclone, acebutolol, alprenolol, atenolol, labetalol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, amrinone, digitoxin, digoxin, enoximone, lanatoside C, medigoxin, beclomethasone, betamethasone, budesonide, cortisone acetate, desoxymethasone, dexamethasone,

fludrocortisone acetate, flunisolide, flucortolone, fluticasone propionate, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone, acetazolamide, amiloride, bendrofluazide, bumetanide, chlorothiazide, chlorthalidone, ethacrynic acid, frusemide, metolazone, spironolactone, triamterene, bromocriptine mesylate, lysuride maleate, bisacodyl, cimetidine, cisapride, diphenoxylate HCl, domperidone, famotidine, loperamide, mesalazine, nizatidine, omeprazole, ondansetron HCL, ranitidine HCl, sulphasalazine, acrivastine, astemizole, cinnarizine, cyclizine, cyproheptadie HCl, dimenhydrinate, flunarizine HCl, loratadine, meclozine HCl, oxatomide, terfenadine, bezafibrate, clofibrate, fenofibrate, gemfibrozil, probucol, amyl nitrate, glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate, pentaerythritol tetranitrate, betacarotene, vitamin A, vitamin B2, vitamin D, vitamin E, vitamin K, codeine, dextropropyoxyphene, diamorphine, dihydrocodeine, meptazinol, methadone, morphine, nalbuphine, pentazocine, clomiphene citrate, danazol, ethinyl estradiol, medroxyprogesterone acetate, mestranol, methyltestosterone, norethisterone, norgestrel, estradiol, conjugated oestrogens, progesterone, stanozolol, stibestrol, testosterone, tibolone, amphetamine, dexamphetamine, dexfenfluramine, fenfluramine, and mazindol.

[000250] In some embodiments, the pharmaceutical agent present in a particle described herein may be a corticosteroid, a non-steroidal anti-inflammatory drug (NSAID), a receptor tyrosine kinase (RTK) inhibitor, a cyclooxygenase (COX) inhibitor, an angiogenesis inhibitor, a glucocorticoid receptor agonist, a prostaglandin analog, a β-blocker, a carbonic anhydrase inhibitor, a mammalian target of rapamycin (mTOR) inhibitor, a calcineurin inhibitor, a Rho kinase inhibitor, a vitamin, a mineral, an antihistamine, a mast cell stabilizer, an immunosuppressant, an immunomodulator, an α-blocker, an antibacterial agent, an antiviral agent, an antifungal agent, a cholinergic agonist, an anticholinesterase agent, a muscarinic antagonist, a sympathomimetic agent, and combinations thereof.

[000251] In certain embodiments, the pharmaceutical agent present in a particle described herein is a corticosteroid. In certain embodiments, the corticosteroid present in a particle described herein is selected from loteprednol etabonate, hydrocortisone, cortisone, tixocortol, prednisolone, methylprednisolone, prednisone, triamcinolone, mometasone, amcinonide, budesonide, desonide, fluocinonide, fluocinolone, halcinonide, betamethasone, dexamethasone, fluocortolone, hydrocortisone, aclometasone, prednicarbate, clobetasone,

clobetasol, fluprednidene, glucocorticoid, mineralocorticoid, aldosterone, deoxycorticosterone, fludrocortisone, halobetasol, diflorasone, desoximetasone, fluticasone, flurandrenolide, alclometasone, diflucortolone, flunisolide, beclomethasone, difluprednate, prednisolone acetaterimexolone, dexamethasone, fluorometholone, or combinations thereof.

[000252] In certain embodiments, the pharmaceutical agent present in a particle described herein is an NSAID. In certain embodiments, the NSAID present in a particle described herein is selected from bromfenac, diclofenac, ketorolac, flurbiprofen, nepafenac, suprofen, salts thereof (e.g., alkaline earth metal salts thereof), and combinations thereof.

[000253] In certain embodiments, the pharmaceutical agent present in a particle described herein is a receptor tyrosine kinase (RTK) inhibitor. In certain embodiments, the RTK inhibitor present in a particle described herein is selected from sorafenib, linifanib, MGCD-265, pazopanib, cediranib, axitinib, TAK-285 (Takeda), TAK-593 (Takeda), AGN-199659 (Allergan), lestaurtinib, tivantinib, lapatinib, panitumumab, imatinib, nilotinib, afatinib, bevacizumab, regorafenib, vandetanib, sunitinib, and combinations thereof.

[000254] In certain embodiments, the pharmaceutical agent present in a particle described herein is a cyclooxygenase (COX) inhibitor. In certain embodiments, the COX inhibitor present in a particle described herein is selected from bromfenac, celecoxib, rofecoxib, valdecoxib, parecoxib, lumiracoxib, etoricoxib, firocoxib, suprofen, and combinations thereof.

[000255] In certain embodiments, the pharmaceutical agent present in a particle described herein is an angiogenesis inhibitor. In certain embodiments, the angiogenesis inhibitor present in a particle described herein is selected from sorafenib, linifanib, MGCD-265 (MethylGene), pazopanib, cediranib, axitinib, squalamine, squalamine lactate, tivozanib, semaxanib, lapatinib, regorafenib, telatinib, vatalanib, OSI-930 (Astellas), KRN-633 (Kirin Brewery), NRP-1, angiopoietin 2, TSP-1, TSP-2, angiostatin, endostatin, vasostatin, calreticulin, platelet factor-4, TIMP, CDAI, Meth-1, Meth-2, IFN-α, IFN-β, IFN-γ, CXCL10, IL-4, IL-12, IL-18, prothrombin, antithrombin III fragment, prolactin, VEGI, SPARC, osteopontin, maspin, canstatin, a proliferin-related protein, restin, TAK-285 (Takeda), TAK-593 (Takeda), AGN-199659 (Allergan), iSONEP (Lpath), MC-1101 (MacuCLEAR), ESBA1008 (Alcon), X-82 and ranibizumab, bevacizumab, vandetanib, ranibizumab, aflibercept, pegaptanib, cetuximab, and combinations thereof.

[000256] In certain embodiments, the pharmaceutical agent present in a particle described herein is a glucocorticoid receptor agonist. In certain embodiments, the glucocorticoid receptor agonist present in a particle described herein is selected from mapracorat, rimexolone, prednisone, dexamethasone, fluorometholone, medrysone, and combinations thereof.

[000257] In certain embodiments, the pharmaceutical agent present in a particle described herein is a prostaglandin analog. In certain embodiments, the prostaglandin analog present in a particle described herein is selected from latanoprost, travoprost, unoprostone, bimatoprost, and combinations thereof.

[000258] In certain embodiments, the pharmaceutical agent present in a particle described herein is a β-blocker. In certain embodiments, the β-blocker present in a particle described herein is selected from alprenolol, bucindolol, carteolol, carvedilol, labetalol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, timolol, timolol maleate, eucommia bark, acebutolol, atenolol, betaxolol, bisoprolol, celiprolol, esmolol, metoprolol, nebivolol, butaxamine, ICI-118,551 (Imperial Chemical Industries), SR 59230A (Sanofi Recherche), levobunolol, metipranolol, carteolol, betaxolol, and and combinations thereof.

[000259] In certain embodiments, the pharmaceutical agent present in a particle described herein is a carbonic anhydrase inhibitor. In certain embodiments, the carbonic anhydrase inhibitor present in a particle described herein is selected from acetazolamide, brinzolamide, dorzolamide, dorzolamide and timolol, methazolamide, and combinations thereof.

[000260] In certain embodiments, the pharmaceutical agent present in a particle described herein is a mammalian target of rapamycin (mTOR) inhibitor. In certain embodiments, the mTOR inhibitor present in a particle described herein is selected from tacrolimus, sirolimus, and combinations thereof.

[000261] In certain embodiments, the pharmaceutical agent present in a particle described herein is a calcineurin inhibitor. In certain embodiments, the calcineurin inhibitor present in a particle described herein is selected from voclosporin,cyclosporine, and combinations thereof.

[000262] In certain embodiments, the pharmaceutical agent present in a particle described herein is a Rho kinase inhibitor. In certain embodiments, the Rho kinase inhibitor present in a

particle described herein is selected from SNJ-1656 (Senju Pharmaceuticals), AR-12286 (Aerie Pharmaceuticals), AR-13324 (Aerie Pharmaceuticals), and combinations thereof.

[000263] In certain embodiments, the pharmaceutical agent present in a particle described herein is a vitamin. In certain embodiments, the vitamin present in a particle described herein is selected from vitamin A, vitamin B_1, vitamin B_2 (riboflavin), vitamin B_6, vitamin B_{12}, vitamin C, vitamin E, folic acid, vitamin K, and combinations thereof.

[000264] In certain embodiments, the pharmaceutical agent present in a particle described herein is a mineral. In certain embodiments, the mineral present in a particle described herein is zinc.

[000265] In certain embodiments, the pharmaceutical agent present in a particle described herein is an antihistamine. In certain embodiments, the antihistamine present in a particle described herein is selected from emedastine difumarate, levocabastine hydrochloride, cromolyn sodium, and combinations thereof.

[000266] In certain embodiments, the pharmaceutical agent present in a particle described herein is a mast cell stabilizer. In certain embodiments, the mast cell stabilizer present in a particle described herein is selected from lodoxamide tromethamine, pemirolast, nedocromil, olopatadine hydrochloride, ketotifen fumarate, azelastine, epinastine, and combinations thereof.

[000267] In certain embodiments, the pharmaceutical agent present in a particle described herein is an immunosuppressant. In certain embodiments, the immunosuppressant present in a particle described herein is selected from fluorouracil, mitomycin, and combinations thereof.

[000268] In certain embodiments, the pharmaceutical agent present in a particle described herein is an immunomodulator. In certain embodiments, the immunomodulator present in a particle described herein is ciclosporin.

[000269] In certain embodiments, the pharmaceutical agent present in a particle described herein is an α-blocker. In certain embodiments, the α-blocker present in a particle described herein is dapiprazole.

[000270] In certain embodiments, the pharmaceutical agent present in a particle described herein is an antibacterial agent. In certain embodiments, the antibacterial agent present in a particle described herein is selected from bacitracin zinc, chloramphenicol, ciprofloxacin

hydrochloride, erythromycin, gatifloxacin, gentamicin sulfate, levofloxacin, moxifloxacin, ofloxacin, sulfacetamide sodium, polymyxin B combinations, tobramycin sulfate, and combinations thereof.

[000271] In certain embodiments, the pharmaceutical agent present in a particle described herein is an antiviral agent. In certain embodiments, the antiviral agent present in a particle described herein is selected from trifluridine, vidarabine, acyclovir, valacyclovir, famciclovir, foscarnet, ganciclovir, formivirsen, cidofovir, and combinations thereof.

[000272] In certain embodiments, the pharmaceutical agent present in a particle described herein is an antifungal agent. In certain embodiments, the antifungal agent present in a particle described herein is selected from amphotericin B, natamycin, fluconazole, itraconazole, ketoconazole, miconazole, and combinations thereof.

[000273] In certain embodiments, the pharmaceutical agent present in a particle described herein is a cholinergic agonist. In certain embodiments, the cholinergic agonist present in a particle described herein is selected from acetylcholine, carbachol, pilocarpine, and combinations thereof.

[000274] In certain embodiments, the pharmaceutical agent present in a particle described herein is an anticholinesterase agent. In certain embodiments, the anticholinesterase agent present in a particle described herein is selected from physostigmine, echothiophate, and combinations thereof.

[000275] In certain embodiments, the pharmaceutical agent present in a particle described herein is a muscarinic antagonist. In certain embodiments, the muscarinic antagonist present in a particle described herein is selected from atropine, scopolamine, homatropine, cyclopentolate, tropicamide, and combinations thereof.

[000276] In certain embodiments, the pharmaceutical agent present in a particle described herein is a sympathomimetic agent. In certain embodiments, the sympathomimetic agent present in a particle described herein is selected from dipivefrin, epinephrine, phenylephrine, apraclonidine, brimonidine, cocaine, hydroxyamphetamine, naphazoline, tetrahydrozoline, and combinations thereof.

[000277] The pharmaceutical agents present in a particle described herein may also include other compounds described herein or known in the art. In certain embodiments, the

pharmaceutical agent present in a particle described herein is microplasmin or CLG561 (Alcon).

Uses and Pharmaceutical Compositions

[000278] The particles described herein may be employed in any suitable application. In some cases, the particles are part of pharmaceutical compositions (*e.g.*, as described herein), for example, those used to deliver a pharmaceutical agent (*e.g.*, a drug, therapeutic agent, diagnostic agent, imaging agent) through or to mucus or a mucosal surface. A pharmaceutical composition may comprise at least one particle described herein and one or more pharmaceutically acceptable excipients or carriers. The composition may be used in treating, preventing, and/or diagnosing a condition in a subject, wherein the method comprises administering to a subject the pharmaceutical composition. A subject or patient to be treated by the articles and methods described herein may mean either a human or non-human animal, such as primates, mammals, and vertebrates.

[000279] Methods involving treating a subject may include preventing a disease, disorder or condition from occurring in the subject which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it; inhibiting the disease, disorder or condition, *e.g.*, impeding its progress; and relieving the disease, disorder, or condition, *e.g.*, causing regression of the disease, disorder and/or condition. Treating the disease or condition includes ameliorating at least one symptom of the particular disease or condition, even if the underlying pathophysiology is not affected (*e.g.*, such treating the pain of a subject by administration of an analgesic agent even though such agent does not treat the cause of the pain).

[000280] In some embodiments, a pharmaceutical composition described herein is delivered to a mucosal surface in a subject and may pass through a mucosal barrier in the subject (*e.g.*, mucus), and/or may exhibit prolonged retention and/or increased uniform distribution of the particles at mucosal surfaces, *e.g.*, due to reduced mucoadhesion. Non-limiting examples of mucosal tissues include oral (*e.g.*, including the buccal and esophagal membranes and tonsil surface), ophthalmic, gastrointestinal (*e.g.*, including stomach, small intestine, large intestine, colon, rectum), nasal, respiratory (*e.g.*, including nasal, pharyngeal, tracheal and bronchial membranes), genital (*e.g.*, including vaginal, cervical and urethral membranes).

[000281] Pharmaceutical compositions described herein and for use in accordance with the articles and methods described herein may include a pharmaceutically acceptable excipient or carrier. A pharmaceutically acceptable excipient or pharmaceutically acceptable carrier may include a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any suitable type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose, and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; detergents such as Tween 80; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator. As would be appreciated by one of skill in this art, the excipients may be chosen based on the route of administration as described below, the pharmaceutical agent being delivered, time course of delivery of the agent, *etc.*

[000282] Pharmaceutical compositions containing the particles described herein may be administered to a subject via any route known in the art. These include, but are not limited to, oral, sublingual, nasal, intradermal, subcutaneous, intramuscular, rectal, vaginal, intravenous, intraarterial, intracisternally, intraperitoneal, intravitreal, periocular, topical (as by powders, creams, ointments, or drops), buccal and inhalational administration. In some embodiments, compositions described herein may be administered parenterally as injections (intravenous, intramuscular, or subcutaneous), drop infusion preparations, or suppositories. As would be appreciated by one of skill in this art, the route of administration and the effective dosage to achieve the desired biological effect may be determined by the agent being administered, the target organ, the preparation being administered, time course of administration, disease being treated, intended use, *etc.*

[000283] As an example, the particles may be included in a pharmaceutical composition to be formulated as a nasal spray, such that the pharmaceutical composition is delivered across a nasal mucus layer. As another example, the particles may be included in a pharmaceutical composition to be formulated as an inhaler, such that the pharmaceutical compositions is delivered across a pulmonary mucus layer. As another example, if compositions are to be administered orally, it may be formulated as tablets, capsules, granules, powders, or syrups. Similarly, the particles may be included in a pharmaceutical composition that is to be delivered via ophthalmic, gastrointestinal, nasal, respiratory, rectal, urethral and/or vaginal tissues.

[000284] For application by the ophthalmic mucous membrane route, subject compositions may be formulated as eye drops or eye ointments. These formulations may be prepared by conventional means, and, if desired, the subject compositions may be mixed with any conventional additive, such as a buffering or pH-adjusting agents, tonicity adjusting agents, viscosity modifiers, suspension stabilizers, preservatives, and other pharmaceutical excipients. In addition, in certain embodiments, subject compositions described herein may be lyophilized or subjected to another appropriate drying technique such as spray drying.

[000285] In some embodiments, particles described herein that may be administered in inhalant or aerosol formulations comprise one or more pharmaceutical agents, such as adjuvants, diagnostic agents, imaging agents, or therapeutic agents useful in inhalation therapy. The particle size of the particulate medicament should be such as to permit inhalation of substantially all of the medicament into the lungs upon administration of the aerosol formulation and may be, for example, less than about 20 microns, *e.g.*, in the range of about 1 to about 10 microns, *e.g.*, about 1 to about 5 microns, although other ranges are also possible. The particle size of the medicament may be reduced by conventional means, for example by milling or micronisation. Alternatively, the particulate medicament can be administered to the lungs via nebulization of a suspension. The final aerosol formulation may contain, for example, between 0.005-90% w/w, between 0.005-50%, between 0.005-10%, between about 0.005-5% w/w, or between 0.01-1.0% w/w, of medicament relative to the total weight of the formulation. Other ranges are also possible.

[000286] It is desirable, but by no means required, that the formulations described herein contain no components which may provoke the degradation of stratospheric ozone. In

particular, in some embodiments, propellants are selected that do not contain or do not consist essentially of chlorofluorocarbons such as CCl_3F, CCl_2F_2, and CF_3CCl_3.

[000287] The aerosol may comprise propellant. The propellant may optionally contain an adjuvant having a higher polarity and/or a higher boiling point than the propellant. Polar adjuvants which may be used include (*e.g.*, C_{2-6}) aliphatic alcohols and polyols such as ethanol, isopropanol, and propylene glycol, preferably ethanol. In general, only small quantities of polar adjuvants (*e.g.*, 0.05-3.0% w/w) may be required to improve the stability of the dispersion-the use of quantities in excess of 5% w/w may tend to dissolve the medicament. Formulations in accordance with the embodiments described herein may contain less than 1% w/w, *e.g.*, about 0.1% w/w, of polar adjuvant. However, the formulations described herein may be substantially free of polar adjuvants, especially ethanol. Suitable volatile adjuvants include saturated hydrocarbons such as propane, n-butane, isobutane, pentane and isopentane and alkyl ethers such as dimethyl ether. In general, up to 50% w/w of the propellant may comprise a volatile adjuvant, for example, up to 30% w/w of a volatile saturated C_1-C_6 hydrocarbon. Optionally, the aerosol formulations according to the invention may further comprise one or more surfactants. The surfactants can be physiologically acceptable upon administration by inhalation. Within this category are included surfactants such as L-α-phosphatidylcholine (PC), 1,2-dipalmitoylphosphatidycholine (DPPC), oleic acid, sorbitan trioleate, sorbitan mono-oleate, sorbitan monolaurate, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate, natural lecithin, oleyl polyoxyethylene ether, stearyl polyoxyethylene ether, lauryl polyoxyethylene ether, block copolymers of oxyethylene and oxypropylene, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl monooleate, glyceryl monostearate, glyceryl monoricinoleate, cetyl alcohol, stearyl alcohol, polyethylene glycol 400, cetyl pyridinium chloride, benzalkonium chloride, olive oil, glyceryl monolaurate, corn oil, cotton seed oil, and sunflower seed oil.

[000288] The formulations described herein may be prepared by dispersal of the particles in the selected propellant and/or co-propellant in an appropriate container, *e.g.*, with the aid of sonication. The particles may be suspended in co-propellant and filled into a suitable container. The valve of the container is then sealed into place and the propellant introduced by pressure filling through the valve in the conventional manner. The particles may be thus

suspended or dissolved in a liquified propellant, sealed in a container with a metering valve and fitted into an actuator. Such metered dose inhalers are well known in the art. The metering valve may meter 10 to 500 μL and preferably 25 to 150 μL. In certain embodiments, dispersal may be achieved using dry powder inhalers (*e.g.*, spinhaler) for the particles (which remain as dry powders). In other embodiments, nanospheres, may be suspended in an aqueous fluid and nebulized into fine droplets to be aerosolized into the lungs.

[000289] Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the particles. Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of the particles together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular composition, but typically include non-ionic surfactants (Tweens, Pluronic®, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars, or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[000290] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the active ingredients (*i.e.*, microparticles, nanoparticles, liposomes, micelles, polynucleotide/lipid complexes), the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[000291] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension, or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and

solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables. In certain embodiments, the particles are suspended in a carrier fluid comprising 1% (w/v) sodium carboxymethyl cellulose and 0.1% (v/v) Tween 80.

[000292] The injectable formulations can be sterilized, for example, by filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[000293] Compositions for rectal or vaginal administration can be suppositories which can be prepared by mixing the particles with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol, or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the particles.

[000294] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the particles are mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as 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, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, 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, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets, and pills, the dosage form may also comprise buffering agents.

[000295] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[000296] The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

[000297] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[000298] Dosage forms for topical or transdermal administration of an inventive pharmaceutical composition include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, or patches. The particles are admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention.

[000299] The ointments, pastes, creams, and gels may contain, in addition to the particles described herein, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc, and zinc oxide, or mixtures thereof.

[000300] Powders and sprays can contain, in addition to the particles described herein, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates, and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

[000301] Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the microparticles or nanoparticles in a proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the particles in a polymer matrix or gel.

[000302] The particles described herein comprising a pharmaceutical agent may be administered to a subject to be delivered in an amount sufficient to deliver to a subject a

therapeutically effective amount of an incorporated pharmaceutical agent as part of a diagnostic, prophylactic, or therapeutic treatment. In general, an effective amount of a pharmaceutical agent or component refers to the amount necessary to elicit the desired biological response. The desired concentration of pharmaceutical agent in the particle will depend on numerous factors, including, but not limited to, absorption, inactivation, and excretion rates of the drug as well as the delivery rate of the compound from the subject compositions, the desired biological endpoint, the agent to be delivered, the target tissue, *etc.* It is to be noted that dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. Typically, dosing will be determined using techniques known to one skilled in the art.

[000303] The concentration and/or amount of any pharmaceutical agent to be administered to a subject may be readily determined by one of ordinary skill in the art. Known methods are also available to assay local tissue concentrations, diffusion rates from particles and local blood flow before and after administration of the therapeutic formulation.

[000304] The compositions and/or formulations described herein may have any suitable osmolarity. In some embodiments, a composition and/or formulation described herein may have an osmolarity of at least about 0 mOsm/L, at least about 5 mOsm/L, at least about 25 mOsm/L, at least about 50 mOsm/L, at least about 75 mOsm/L, at least about 100 mOsm/L, at least about 150 mOsm/L, at least about 200 mOsm/L, at least about 250 mOsm/L, or at least about 310 mOsm/L. In certain embodiments, a composition and/or formulation described herein may have an osmolarity of less than or equal to about 310 mOsm/L, less than or equal to about 250 mOsm/L, less than or equal to about 200 mOsm/L, less than or equal to about 150 mOsm/L, less than or equal to about 100 mOsm/L, less than or equal to about 75 mOsm/L, less than or equal to about 50 mOsm/L, less than or equal to about 25 mOsm/L, or less than or equal to about 5 mOsm/L. Combinations of the above-referenced ranges are also possible (*e.g.*, an osmolarity of at least about 0 mOsm/L and less than or equal to about 50 mOsm/L). Other ranges are also possible. The osmolarity of the composition and/or formulation can be varied by changing, for example, the concentration of salts present in the solvent of the composition and/or formulation.

[000305] In one set of embodiments, a composition and/or formulation includes a core material comprises a drug, such as loteprednol etabonate, sorafenib, linifanib, MGCD-265, pazopanib, cediranib, axitinib, bromfenac calcium, diclofenac (*e.g.*, diclofenac free acid or a divalent or trivalent metal salt thereof), ketorolac (*e.g.*, ketorolac free acid or a divalent or trivalent metal salt thereof), or other suitable drug described herein. In some embodiments, the ratio of the weight of the drug to the weight of the one or more surface-altering agents (*e.g.*, Pluronic® F127) present in the composition and/or formulation is greater than or equal to about1:100,greater than or equal to about 1:30, greater than or equal to about 1:10, greater than or equal to about 1:3, greater than or equal to about 1:1, greater than or equal to about 3:1, greater than or equal to about 10:1, greater than or equal to about 30:1, or greater than or equal to about 100:1.In some embodiments, the ratio of the weight of the drug to the weight of the one or more surface-altering agents in a composition and/or formulation is less than or equal to about 100:1, less than or equal to about 30:1, less than or equal to about 10:1, less than or equal to about 3:1, less than or equal to about 1:1, less than or equal to about1:3: less than or equal to about1:10, less than or equal to about1:30, or less than or equal to about1:100.Combinations of the above-noted ranges are possible (*e.g.*, a ratio of greater than or equal to about 1:1 and less than or equal to about 10:1). Other ranges are also possible. In certain embodiments, the ratio is about 1:1. In certain embodiments, the ratio is about 2:1. In certain embodiments, the ratio is about 10:1.

[000306] In some embodiments, a composition and/or formulation may include the above-noted ranges for the ratio of the weight of the drug to the weight of the one or more surface-altering agents during a formation process and/or a dilution process described herein. In certain embodiments, a composition and/or formulation may include the above-noted ranges for the ratio of the weight of the drug to the weight of the one or more surface-altering agents in a final product.

[000307] The pharmaceutical agent may be present in the composition and/or formulation in any suitable amount, *e.g.*, at least about 0.01 wt%, at least about 0.1 wt%, at least about 1 wt%, at least about 5 wt%, at least about 10 wt%, at least about 20 wt% of the composition and/or formulation. In some cases, the pharmaceutical agent may be present in the composition and/or formulation at less than or equal to about 30 wt%, less than or equal to about 20 wt%, less than or equal to about 10 wt%, less than or equal to about 5 wt%, less

than or equal to about 2 wt%, or less than or equal to about 1 wt%. Combinations of the above-referenced ranges are also possible (*e.g.*, present in an amount of at least about 0.1 wt% and less than or equal to about 10 wt%). Other ranges are also possible. In certain embodiments, the pharmaceutical agent is about 0.1-2 wt% of the composition and/or formulation. In certain embodiments, the pharmaceutical agent is about 2-20 wt% of the composition and/or formulation. In certain embodiments, the pharmaceutical agent is about 0.2 wt% of the composition and/or formulation. In certain embodiments, the pharmaceutical agent is about 0.4 wt% of the composition and/or formulation. In certain embodiments, the pharmaceutical agent is about 1 wt% of the composition and/or formulation. In certain embodiments, the pharmaceutical agent is about 2 wt% of the composition and/or formulation. In certain embodiments, the pharmaceutical agent is about 5 wt% of the composition and/or formulation. In certain embodiments, the pharmaceutical agent is about 10 wt% of the composition and/or formulation.

[000308] In one set of embodiments, a composition and/or formulation includes one or more chelating agents. A chelating agent used herein refers to a chemical compound that has the ability to react with a metal ion to form a complex through one or more bonds. The one or more bonds are typically ionic or coordination bonds. The chelating agent can be an inorganic or an organic compound. A metal ion capable of catalyzing certain chemical reactions (*e.g.*, oxidation reactions) may lose its catalytic activity when the metal ion is bound to a chelating agent to form a complex. Therefore, a chelating agent may show preservative properties when it binds to a metal ion. Any suitable chelating agent that has preservative properties can be used, such as phosphonic acids, aminocarboxylic acids, hydroxycarboxylic acids, polyamines, aminoalcohols, and polymeric chelating agents. Specific examples of chelating agents include, but are not limited to, ethylenediaminetetraacetic acid (EDTA), nitrilotriacetic acid (NTA), diethylenetriaminepentacetic acid (DTPA), *N*-hydroxyethylethylene diaminetriacetic acid (HEDTA), tetraborates, triethylamine diamine, and salts and derivatives thereof. In certain embodiments, the chelating agent is EDTA. In certain embodiments, the chelating agent is a salt of EDTA. In certain embodiments, the chelating agent is disodium EDTA.

[000309] A chelating agent may be present at a suitable concentration in a composition and/or formulation including the coated particles described herein. In certain embodiments,

the concentration of the chelating agent is greater than or equal to about 0.0003 wt%, greater than or equal to about 0.001wt%, greater than or equal to about 0.003wt%, greater than or equal to about 0.01wt%, greater than or equal to about 0.03wt%, greater than or equal to about 0.05 wt%, greater than or equal to about 0.1wt%, greater than or equal to about 0.3wt%, greater than or equal to about 1wt%, or greater than or equal to about 3wt%. In certain embodiments, the concentration of the chelating agent is less than or equal to about 3wt%, less than or equal to about 1wt%, less than or equal to about 0.3wt%, less than or equal to about 0.1wt%, less than or equal to about 0.05 wt%, less than or equal to about 0.03wt%, less than or equal to about 0.01wt%, less than or equal to about 0.003wt%, less than or equal to about 0.001 wt%, or less than or equal to about 0.0003wt%. Combinations of the above-noted ranges are possible (*e.g.*, a concentration of greater than or equal to about 0.01 wt% and less than or equal to about 0.3wt%). Other ranges are also possible. In certain embodiments, the concentration of the chelating agent is about 0.001-0.1 wt%. In certain embodiments, the concentration of the chelating agent is about 0.005 wt%. In certain embodiments, the concentration of the chelating agent is about 0.01 wt%. In certain embodiments, the concentration of the chelating agent is about 0.05wt%. In certain embodiments, the concentration of the chelating agent is about 0.1 wt%.

[000310] In some embodiments, a chelating agent may be present in a composition and/or formulation in one or more of the above-noted ranges during a formation process and/or a dilution process described herein. In certain embodiments, a chelating agent may be present in a composition and/or formulation in one or more of the above-noted ranges in a final product.

[000311] In some embodiments, an antimicrobial agent may be included in a composition and/or formulation including the coated particles described herein. An antimicrobial agent used herein refers to a bioactive agent effective in the inhibition of, prevention of, or protection against microorganisms such as bacteria, microbes, fungi, viruses, spores, yeasts, molds, and others generally associated with infections. Examples of antimicrobial agents include cephaloporins, clindamycin, chlorampheanicol, carbapenems, minocyclines, rifampin, penicillins, monobactams, quinolones, tetracycline, macrolides, sulfa antibiotics, trimethoprim, fusidic acid, aminoglycosides, amphotericin B, azoles, flucytosine, cilofungin, bactericidal nitrofuran compounds, nanoparticles of metallic silver or an alloy of silver

containing about 2.5 wt % copper, silver citrate, silver acetate, silver benzoate, bismuth pyrithione, zinc pyrithione, zinc percarbonates, zinc perborates, bismuth salts, parabens (*e.g.*, methyl-, ethyl-, propyl-, butyl-, and octyl-benzoic acid esters), citric acid, benzalkonium chloride (BAC), rifamycin, and sodium percarbonate.

[000312] An antimicrobial agent may be present at a suitable concentration in a composition and/or formulation including the coated particles described herein. In certain embodiments, the concentration of the antimicrobial agent may begreater than or equal to about 0.0003wt%, greater than or equal to about 0.001wt%, greater than or equal to about 0.003wt%, greater than or equal to about 0.01wt%, greater than or equal to about 0.03wt%, greater than or equal to about 0.1wt%, greater than or equal to about 0.3wt%, greater than or equal to about 1wt%, or greater than or equal to about 3wt%. In certain embodiments, the concentration of the antimicrobial agent may be less than or equal to about 3wt%, less than or equal to about 1wt%, less than or equal to about 0.3wt%, less than or equal to about 0.1wt%, less than or equal to about 0.03wt%, less than or equal to about 0.01wt%, less than or equal to about 0.003wt%, less than or equal to about 0.001wt%, or less than or equal to about 0.0003wt%. Combinations of the above-noted ranges are possible (*e.g.*, a concentration of greater than or equal to about 0.001 wt% and less than or equal to about 0.1wt%). Other ranges are also possible. In certain embodiments, the concentration of the antimicrobial agent is about 0.001-0.05 wt%. In certain embodiments, the concentration of the antimicrobial agent is about 0.002 wt%. In certain embodiments, the concentration of the antimicrobial agent is about 0.005 wt%. In certain embodiments, the concentration of the antimicrobial agent is about 0.01wt%. In certain embodiments, the concentration of the antimicrobial agent is about 0.02 wt%. In certain embodiments, the concentration of the antimicrobial agent is about 0.05 wt%.

[000313] In some embodiments, an antimicrobial agent may be present in a composition and/or formulation in one or more of the above-noted ranges during a formation process and/or a dilution process described herein. In certain embodiments, an antimicrobial agent may be present in a composition and/or formulation in one or more of the above-noted ranges in a final product.

[000314] In some embodiments, a tonicity agent may be included in a composition and/or formulation including the coated particles described herein. A tonicity agent used herein

refers to a compound or substance that can be used to adjust the composition of a formulation to the desired osmolarity range. In certain embodiments, the desired osmolarity range is an isotonic range compatible with blood. In certain embodiments, the desired osmolarity range is hypotonic. In certain embodiments, the desired osmolarity range is hypertonic. Examples of tonicity agents include glycerin, lactose, mannitol, dextrose, sodium chloride, sodium sulfate, sorbitol, saline-sodium citrate (SSC), and the like. In certain embodiments, a combination of one or more tonicity agents may be used. In certain embodiments, the tonicity agent is glycerin. In certain embodiments, the tonicity agent is sodium chloride.

[000315] A tonicity agent (such as one described herein) may be present at a suitable concentration in a composition and/or formulation including the coated particles described herein. In certain embodiments, the concentration of the tonicity agent is greater than or equal to about 0.003wt%, greater than or equal to about 0.01wt%, greater than or equal to about 0.03wt%, greater than or equal to about 0.1wt%, greater than or equal to about 0.3wt%, greater than or equal to about 1wt%, greater than or equal to about 3wt%, greater than or equal to about 10wt%, greater than or equal to about 20 wt%, or greater than or equal to about 30wt%. In certain embodiments, the concentration of the tonicity agent is less than or equal to about 30 wt%, less than or equal to about 10 wt%, less than or equal to about 3 wt%, less than or equal to about 1 wt%, less than or equal to about 0.3wt%, less than or equal to about 0.1wt%, less than or equal to about 0.03wt%, less than or equal to about 0.01 wt%, or less than or equal to about 0.003 wt%. Combinations of the above-noted ranges are possible (*e.g.*, a concentration of greater than or equal to about 0.1wt% and less than or equal to about 10wt%). Other ranges are also possible. In certain embodiments, the concentration of the tonicity agent is about 0.1-1%. In certain embodiments, the concentration of the tonicity agent is about 0.5-3%. In certain embodiments, the concentration of the tonicity agent is about 0.25 wt%. In certain embodiments, the concentration of the tonicity agent is about 0.45wt%. In certain embodiments, the concentration of the tonicity agent is about 0.9wt%. In certain embodiments, the concentration of the tonicity agent is about 1.2wt%. In certain embodiments, the concentration of the tonicity agent is about 2.4wt%. In certain embodiments, the concentration of the tonicity agent is about 5 wt%.

[000316] In some embodiments, a tonicity agent may be present in a composition and/or formulation in one or more of the above-noted ranges during a formation process and/or a

dilution process described herein. In certain embodiments, a tonicity agent may be present in a composition and/or formulation in one or more of the above-noted ranges in a final product.

[000317] In some embodiments, a composition and/or formulation described herein may have an osmolarity of at least about 0 mOsm/L, at least about 5 mOsm/L, at least about 25 mOsm/L, at least about 50 mOsm/L, at least about 75 mOsm/L, at least about 100 mOsm/L, at least about 150 mOsm/L, at least about 200 mOsm/L, at least about 250 mOsm/L, at least about 310 mOsm/L, or at least about 450 mOsm/L. In certain embodiments, a composition and/or formulation described herein may have an osmolarity of less than or equal to about 450 mOsm/L, less than or equal to about 310 mOsm/L, less than or equal to about 250 mOsm/L, less than or equal to about 200 mOsm/L, less than or equal to about 150 mOsm/L, less than or equal to about 100 mOsm/L, less than or equal to about 75 mOsm/L, less than or equal to about 50 mOsm/L, less than or equal to about 25 mOsm/L, or less than or equal to about 5 mOsm/L. Combinations of the above-referenced ranges are also possible (*e.g.*, an osmolarity of at least about 0 mOsm/L and less than or equal to about 50 mOsm/L). Other ranges are also possible.

[000318] It is appreciated in the art that the ionic strength of a formulation comprising particles may affect the polydispersity of the particles. Polydispersity is a measure of the heterogeneity of sizes of particles in a formulation. Heterogeneity of particle sizes may be due to differences in individual particle sizes and/or to the presence of aggregation in the formulation. A formulation comprising particles is considered substantially homogeneous or "monodisperse" if the particles have essentially the same size, shape, and/or mass. A formulation comprising particles of various sizes, shapes, and/or masses is deemed heterogeneous or "polydisperse".

[000319] The ionic strength of a formulation comprising particles may also affect the colloidal stability of the particles. For example, a relatively high ionic strength of a formulation may cause the particles of the formulation to coagulate and therefore may destabilize the formulation. In some embodiments, a formulation comprising particles is stabilized by repulsive inter-particle forces. For example, the particles may be electrically or electrostatically charged. Two charged particles may repel each other, preventing collision and aggregation. When the repulsive inter-particle forces weaken or become attractive, particles may start to aggregate. For instance, when the ionic strength of the formulation is

increased to a certain level, the charges (*e.g.*, negative charges) of the particles may be neutralized by the oppositely charged ions present in the formulation (*e.g.*, Na^+ ions in solution). As a result, the particles may collide and bond to each other to form aggregates (*e.g.*, clusters or flocs) of larger sizes. The formed aggregates of particles may also differ in size, and thus the polydispersity of the formulation may also increase. For example, a formulation comprising similarly-sized particles may become a formulation comprising particles having various sizes (*e.g.*, due to aggregation) when the ionic strength of the formulation is increased beyond a certain level. In the course of aggregation, the aggregates may grow in size and eventually settle to the bottom of the container, and the formulation is considered colloidally unstable. Once the particles in a formulation form aggregates, it is usually difficult to disrupt the aggregates into individual particles.

[000320] Certain formulations described herein show unexpected properties in that, among other things, the presence of one or more ionic tonicity agents (*e.g.*, a salt such as NaCl) in the formulations at certain concentrations actually decreases or maintains the degree of aggregation of the particles present in the formulations, and/or does not significantly increase aggregation. See, for instance, Example 14. In certain embodiments, the polydispersity of a formulation decreases, is relatively constant, or does not change by an appreciable amount upon addition of one or more ionic tonicity agents into the formulation.

[000321] For example, in some embodiments, the polydispersity of a composition and/or formulation is relatively constant in the presence of added ionic strength and/or when the added ionic strength of the composition and/or formulation is kept relatively constant or increased (*e.g.*, during a formation and/or dilution process). In certain embodiments, when the ionic strength increases by at least 50%, the polydispersity increases by less than or equal to about 200%, less than or equal to about 150%, less than or equal to about 100%, less than or equal to about 75%, less than or equal to about 50%, less than or equal to about 30%, less than or equal to about 20%, less than or equal to about 10%, less than or equal to about 3%, or less than or equal to about 1%. In certain embodiments, when the ionic strength is increased by at least 50%, the polydispersity increases by greater than or equal to about 1%, greater than or equal to about 3%, greater than or equal to about 10%, greater than or equal to about 30%, or greater than or equal to about 100%. Combinations of the above-noted ranges

are possible (*e.g.*, an increase in polydispersity of less than or equal to 50% and greater than or equal to 1%). Other ranges are also possible.

[000322] The ionic strength of a formulation described herein may be controlled (*e.g.*, increased) through a variety of means, such as the addition of one or more ionic tonicity agents (*e.g.*, a salt such as NaCl) to the formulation. In certain embodiments, the ionic strength of a formulation described herein is greater than or equal to about 0.0005 M, greater than or equal to about 0.001 M, greater than or equal to about 0.003 M, greater than or equal to about 0.01 M, greater than or equal to about 0.03 M, greater than or equal to about 0.1 M, greater than or equal to about 0.3 M, greater than or equal to about 1 M, greater than or equal to about 3 M, or greater than or equal to about 10 M. In certain embodiments, the ionic strength of a formulation described herein is less than or equal to about 10 M, less than or equal to about 3 M, less than or equal to about 1 M, less than or equal to about 0.3 M, less than or equal to about 0.1 M, less than or equal to about 0.03 M, less than or equal to about 0.01 M, less than or equal to about 0.003 M, less than or equal to about 0.001 M, or less than or equal to about 0.0005 M. Combinations of the above-noted ranges are possible (*e.g.*, an ionic strength of greater than or equal to about 0.01 M and less than or equal to about 1 M). Other ranges are also possible. In certain embodiments, the ionic strength of a formulation described herein is about 0.1 M. In certain embodiments, the ionic strength of a formulation described herein is about 0.15 M. In certain embodiments, the ionic strength of a formulation described herein is about 0.3 M.

[000323] In certain embodiments, the polydispersity of a formulation does not change upon addition of one or more ionic tonicity agents into the formulation. In certain embodiments, the polydispersity does not significantly increase upon addition of one or more ionic tonicity agents into the formulation. In certain embodiments, the polydispersity increases to a level described herein upon addition of one or more ionic tonicity agents into the formulation.

[000324] The polydispersity of a formulation described herein may be measured by the polydispersity index (PDI).The PDI is used to describe the width of the particle size distribution and is often calculated from a cumulants analysis of the dynamic light scattering (DLS) measured intensity autocorrelation function. The calculations for these parameters are defined in the standards ISO 13321:1996 E and ISO 22412:2008. The PDI is dimensionless and, when measured by DLS, scaled such that values smaller than 0.05 indicate a highly

monodisperse sample while values greater than 0.7 indicate a very broad size distribution. In certain embodiments, the PDI of a formulation and/or composition described herein is less than or equal to about 1, less than or equal to about 0.9, less than or equal to about 0.8, less than or equal to about 0.7, less than or equal to about 0.6, less than or equal to about 0.5, less than or equal to about 0.4, less than or equal to about 0.3, less than or equal to about 0.2, less than or equal to about 0.15, less than or equal to about 0.1, less than or equal to about 0.05, less than or equal to about 0.01, or less than or equal to about 0.005. In certain embodiments, the PDI of a formulation and/or composition described herein is greater than or equal to about0.005, greater than or equal to about 0.01, greater than or equal to about 0.05, greater than or equal to about 0.1, greater than or equal to about 0.15, greater than or equal to about 0.2, greater than or equal to about 0.3, greater than or equal to about 0.4, greater than or equal to about 0.5, greater than or equal to about 0.6, greater than or equal to about 0.7, greater than or equal to about 0.8, greater than or equal to about 0.9, or greater than or equal to about 1.Combinations of the above-noted ranges are possible (*e.g.*, a PDI of greater than or equal to about0.1 and less than or equal to about 0.5). Other ranges are also possible. In certain embodiments, the PDI of a formulation is about 0.1. In certain embodiments, the PDI of a formulation is about 0.15. In certain embodiments, the PDI of a formulation is about 0.2.

[000325] In certain embodiments, the compositions and/or formulations described herein may be highly dispersible and do not tend to form aggregates. Even when the particles do form aggregates, the aggregates may be easily broken up into individual particles without rigorously agitating the compositions and/or formulations.

[000326] Generally, it is desired that a formulation is sterile before or upon administration to a subject. A sterile formulation is essentially free of pathogenic microorganisms, such as bacteria, microbes, fungi, viruses, spores, yeasts, molds, and others generally associated with infections. In some embodiments, compositions and/or formulations including the coated particles described herein may be subject to an aseptic process and/or other sterilization process. An aseptic process typically involves sterilizing the components of a formulation, final formulation, and/or container closure of a drug product through a process such as heat, gamma irradiation, ethylene oxide, or filtration and then combining in a sterile environment. In some cases, an aseptic process is preferred. In other embodiments, terminal sterilization is preferred..

[000327] Examples of other sterilization methods include radiation sterilization (*e.g.*, gamma, electron, or x-ray radiation), heat sterilization, sterile filtration, and ethylene oxide sterilization. The terms "radiation" and "irradiation" are used herein interchangeably. Unlike other sterilization methods, radiation sterilization has the advantage of high penetrating ability and instantaneous effects, without the need to control temperature, pressure, vacuum, or humidity in some instances. In certain embodiments, the radiation used to sterilize the coated particles described herein is gamma radiation. Gamma radiation may be applied in an amount sufficient to kill most or substantially all of the microbes in or on the coated particles. The temperature of the coated particles described herein and the rate of radiation may be relatively constant during the entire gamma radiation period. Gamma irradiation may be performed at any suitable temperature (*e.g.*, ambient temperature, about 40 ºC, between about 30 to about 50 ºC). Unless otherwise indicated, measurements of gamma irradiation described herein refer to ones performed at about 40 ºC.

[000328] In embodiments in which a sterilization process is used, it may be desired that the process does not: (1) significantly change the particle size of the coated particles described herein; (2) significantly change the integrity of the active ingredient (such as a drug) of the coated particles described herein; and (3) generate unacceptable concentrations of impurities during or following the process. In certain embodiments, the impurities generated during or following the process are degradants of the active ingredient of the coated particles described herein. For example, when the active ingredient is loteprednol etabonate (LE), degradants of LE may include 11β,17α-dihydroxy-3-oxoandrosta-1,4-diene-17-carboxylic acid (PJ-90), 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-1,4-diene-17β-carboxylic acid (PJ-91), 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-4-ene-17-carboxylic acid chloromethyl ester (tetradeca), and/or 17α-[(ethoxycarbonyl)oxy]-3,11-dioxoandrosta-1,4-diene-17-carboxylic acid chloromethyl ester (11-keto), as shown in FIG. 22.

[000329] In certain embodiments, a process used to sterilize a composition and/or formulation described herein results in the presence of one or more degradants in the formulation at less than or equal to about 10 wt% (relative to the weight of the undegraded drug), less than or equal to about 3 wt%, less than or equal to about 2 wt%, less than or equal to about 1.5 wt%, less than or equal to about 1 wt%, less than or equal to about 0.9 wt%, less than or equal to about 0.8 wt%, less than or equal to about 0.7 wt%, less than or equal to

about 0.6 wt%, less than or equal to about 0.5 wt%, less than or equal to about 0.4 wt%, less than or equal to about 0.3 wt%, less than or equal to about 0.2 wt%, less than or equal to about 0.15 wt%, less than or equal to about 0.1 wt%, less than or equal to about 0.03 wt%, less than or equal to about 0.01 wt%, less than or equal to about 0.003 wt%, or less than or equal to about 0.001 wt%. In some embodiments, the process results in a degradant in the formulation at greater than or equal to about 0.001wt%, greater than or equal to about 0.003wt%, greater than or equal to about 0.01wt%, greater than or equal to about 0.03wt%, greater than or equal to about 0.1wt%, greater than or equal to about 0.3wt%, greater than or equal to about 1wt%, greater than or equal to about 3wt%, or greater than or equal to about 10wt%.Combinations of the above-referenced ranges are also possible (*e.g.*, less than or equal to about 1 wt% and greater than or equal to about 0.01 wt%). Other ranges are also possible.

[000330] In some embodiments, a composition and/or formulation subjected to gamma irradiation includes a degradant having a concentration at one or more of the above-noted ranges. In one set of embodiments, the drug is loteprednol etabonate and the degradant is PJ-90,PJ-91, tetradeca, and/or 11-keto. In certain embodiments, one or more, or each, of the degradants is present in a composition and/or formulation at one or more of the above-noted ranges (*e.g.*, less than or equal to about1 wt%, less than or equal to about 0.9 wt%, less than or equal to about 0.8 wt%, less than or equal to about 0.7 wt%, less than or equal to about 0.6 wt%, less than or equal to about 0.5 wt%, less than or equal to about 0.4 wt%, less than or equal to about 0.3 wt%, less than or equal to about 0.2 wt%, or less than or equal to about 0.1 wt%). Other ranges are also possible.

[000331] In some embodiments, one or more additives are included in the composition and/or formulation to help achieve a relatively low amount of one or more degradants. For example, as described in Example 13, the presence of glycerin in a loteprednol etabonate formulation resulted in relatively low amounts of the degradant tetradeca after the formulation was sterilized with gamma irradiation, compared to a loteprednol etabonate formulation that did not include glycerin.

[000332] When gamma irradiation is used in a sterilization process, the cumulative amount of the gamma radiation used may vary. In certain embodiments, the cumulative amount of the gamma radiation is greater than or equal to about 0.1 kGy, greater than or equal to about 0.3

kGy, greater than or equal to about 1 kGy, greater than or equal to about 3 kGy, greater than or equal to about 10 kGy, greater than or equal to about 30 kGy, greater than or equal to about 100 kGy, or greater than or equal to about 300 kGy. In certain embodiments, the cumulative amount of the gamma radiation is less than or equal to about 0.1 kGy, less than or equal to about 0.3 kGy, less than or equal to about 1 kGy, less than or equal to about 3 kGy, less than or equal to about 10 kGy, less than or equal to about 30 kGy, less than or equal to about 100 kGy, or less than or equal to about 300 kGy. Combinations of the above-noted ranges are possible (*e.g.*, greater than or equal to about 1 kGy and less than or equal to about 30 kGy). Other ranges are also possible. In certain embodiments, multiple doses of radiation are utilized to achieve a desired cumulative radiation dosage.

[000333] The compositions and/or formulations described herein may have any suitable pH values. The term "pH," unless otherwise provided, refers to pH measured at ambient temperature (*e.g.*, about 20 °C, about 23 °C, or about 25 °C). The compositions and/or formulations have, for example, an acidic pH, a neutral pH, or a basic pH and may depend on, for example, where the compositions and/or formulations are to be delivered in the body. In certain embodiments, the compositions and/or formulations have a physiological pH. In certain embodiments, the pH value of the compositions and/or formulations is at least about 1, at least about 2, at least about 3, at least about 4, at least about 5, at least about 6, at least about 6.2, at least about 6.4, at least about 6.6, at least about 6.8, at least about 7, at least about 7.2, at least about 7.4, at least about 7.6, at least about 7.8, at least about 8, at least about 8.2, at least about 8.4, at least about 8.6, at least about 8.8, at least about 9, at least about 10, at least about 11, or at least about 12. In certain embodiments, the pH value of the compositions and/or formulations is less than or equal to about 12, less than or equal to about 11, less than or equal to about 10, less than or equal to about 9, less than or equal to about 8.8, less than or equal to about 8.6, less than or equal to about 8.4, less than or equal to about 8.2, less than or equal to about 8, less than or equal to about 7.8, less than or equal to about 7.6, less than or equal to about 7.4, less than or equal to about 7.2, less than or equal to about 7, less than or equal to about 6.8, less than or equal to about 6.6, less than or equal to about 6.4, less than or equal to about 6.2, less than or equal to about 6, less than or equal to about 5, less than or equal to about 4, less than or equal to about 3, less than or equal to about 2, or less than or equal to about 1. Combinations of the above-noted ranges are possible (*e.g.*, a pH

value of at least about 5 and less than or equal to about 8.2). Other ranges are also possible. In certain embodiments, the pH value of the compositions and/or formulations described herein is at least about 5 and less than or equal to about 8.

Methods, Compositions and Formulations for the Treatment of Ocular Conditions

[000334] The mammalian eye is a complex organ comprising an outer covering including the sclera (the tough white portion of the exterior of the eye) and the cornea (the clear outer portion covering the pupil and iris). An exemplary schematic diagram of an eye is shown in FIG. 15A. As shown illustratively in FIG. 15A in a medial cross section, from anterior to posterior, an eye 100comprises features including, without limitation: a cornea 105, an iris110 (a curtain-like feature that can open and close in response to ambient light), a conjunctiva 115 (composed of rare stratified columnar epithelium, covering the sclera, and lining the inside of the eyelids), a tear film 120 (which may include an oil layer, a water layer, and a mucous layer (where the mucous layer(s)has several functions such as serving as an anchor for the tear film and helping it adhere to the eye), a corneal epithelium 125 (several layers of cells covering the front of the cornea that act as a barrier to protect the cornea, resist the free flow of fluids from the tears, and prevent bacteria from entering), an anterior chamber 130 (a hollow feature filled with a watery, clear fluid called the aqueous humor 135 and bounded by the cornea in the front and the iris), a lens140 (a transparent, biconvex structure that, along with the cornea, which helps to refract light to be focused on the retina), a ciliary body 145 (a circumferential tissue composed of ciliary muscles and ciliary processes), a ciliary zonule 146 (a ring of fibrous strands connecting the ciliary body with the lens), a posterior chamber 148 (a narrow space bounded by the iris in front and by the ciliary zonule and the ciliary body in back and also contains the aqueous humor, a retina150, a macula 155, a sclera 160, an optic nerve 165 (also known as cranial nerve, transmitting visual information from the retina to the brain), a choroid170, and avitreous chamber 175 (filled with a viscous fluid called the vitreous humor 180). The vitreous chamber comprises approximately 2/3 of the inner volume of the eye, while the anterior chamber and posterior chamber comprise about 1/3 of the eye's inner volume.

[000335] As shown illustratively in FIG. 15B, there area number of mucus layers in the eye, present at a bulbar conjunctiva 116 (covering the eyeball, over the sclera, tightly bound to the

underlying sclera, and moving with the eyeball movements), a palpebral conjunctiva 117 (lining the eyelids), a fornix conjunctiva 118 (a loose and flexible tissue forming the junction between the bulbar and palpebral conjunctivas and allowing the free movement of the lids and eyeball), and the cornea. These mucus layers form a complete surface that a topically administered medication contacts. Therefore, the topically administered medication typically has to penetrate through these mucus layers in order to reach the various underneath eye tissues.

[000336] As shown illustratively in FIG. 15A, front of the eye, or anterior or anterior segment of the eye, depicted by a bracket 190, generally includes tissues or fluids that are located anterior to a posterior wall 142 of a lens capsule 144 (a clear, membrane-like structure that is elastic and keeps the lens under constant tension) or ciliary muscles. The front of the eye includes, for example, the conjunctiva, the cornea, the iris, the tear film, the anterior chamber, the posterior chamber, the lens and the lens capsule, as well as blood vessels, lymphatics and nerves which vascularize, maintain or innervate an anterior ocular region or site.

[000337] As shown illustratively FIG. 15A, the back of the eye, or posterior or posterior segment of the eye, depicted by a bracket 195, generally includes tissues or fluids that are located posterior to posterior wall of the lens capsule or ciliary muscles. The back of the eye includes, for example, the choroid, the sclera (in a position posterior to a plane through the posterior wall of the lens capsule), the vitreous humor, the vitreous chamber, the retina, the macula, the optic nerve, and the blood vessels and nerves which vascularize or innervate a posterior ocular region or site.

[000338] As described in more detail below, in some embodiments, the particles, compositions and/or formulations described herein may be used to diagnose, prevent, treat or manage diseases or conditions at the back of the eye, such as at the retina, macula, choroid, sclera and/or uvea.

[000339] The retina is a 10-layered, delicate nervous tissue membrane of the eye, continuous with the optic nerve, that receives images of external objects and transmits visual impulses through the optic nerve to the brain. The retina is soft and semitransparent and contains rhodopsin. It consists of the outer pigmented layer and the nine-layered retina proper. These nine layers, starting with the most internal, are the internal limiting membrane,

the stratum opticum, the ganglion cell layer, the inner plexiform layer, the inner nuclear layer, the outer plexiform layer, the outer nuclear layer, the external limiting membrane, and the layer of rods and cones. The outer surface of the retina is in contact with the choroid; the inner surface with the vitreous body. The retina is thinner anteriorly, where it extends nearly as far as the ciliary body, and thicker posteriorly, except for a thin spot in the exact center of the posterior surface where focus is best. The photoreceptors end anteriorly in the jagged ora serrata at the ciliary body, but the membrane of the retina extends over the back of the ciliary processes and the iris. The retina becomes clouded and opaque if exposed to direct sunlight.

[000340] The macula or macula lutea is an oval-shaped highly pigmented yellow spot near the center of the retina of the human eye. It has a diameter of around 5 mm and is often histologically defined as having two or more layers of ganglion cells. Near its center is the fovea, a small pit that contains the largest concentration of cone cells in the eye and is responsible for central, high resolution vision. The macula also contains the parafovea and perifovea. Because the macula is yellow in color it absorbs excess blue and ultraviolet light that enter the eye, and acts as a natural sunblock (analogous to sunglasses) for this area of the retina. The yellow color comes from its content of lutein and zeaxanthin, which are yellow xanthophyll carotenoids, derived from the diet. Zeaxanthin predominates at the macula, while lutein predominates elsewhere in the retina. There is some evidence that these carotenoids protect the pigmented region from some types of macular degeneration. Structures in the macula are specialized for high acuity vision. Within the macula are the fovea and foveola which contain a high density of cones (photoreceptors with high acuity).

[000341] The choroid, also known as the choroidea or choroid coat, is the vascular layer of the eye, containing connective tissue, and lying between the retina and the sclera. The human choroid is thickest at the far extreme rear of the eye (at 0.2 mm), while in the outlying areas it narrows to 0.1 mm. The choroid provides oxygen and nourishment to the outer layers of the retina. Along with the ciliary body and iris, the choroid forms the uveal tract.

[000342] The sclera refers to the tough inelastic opaque membrane covering the posterior five sixths of the eyebulb. It maintains the size and form of the bulb and attaches to muscles that move the bulb. Posteriorly it is pierced by the optic nerve and, with the transparent cornea, makes up the outermost of three tunics covering the eyebulb.

[000343] The uvea refers to the fibrous tunic beneath the sclera that includes the iris, the ciliary body, and the choroid of the eye.

[000344] Ophthalmic therapy may be performed by topically administering compositions, such as eye drops, to the exterior surface of the eye. Eye drops administration is by far the most desired route of drug delivery to the eye due to its convenience, non-invasive nature, localized action, and relative patient comfort. However, drugs administered to the eye topically as solutions (*e.g.,* ophthalmic solutions) may be rapidly cleared from the eye's surface by drainage and lachrymation. Drugs administered to the eye topically as particles (*e.g.,* ophthalmic suspensions) are typically trapped by the mucus layer or tear film in the eye. The eye's natural clearance mechanisms remove the species trapped in such a layer, and hence, drugs trapped in this layer are also rapidly cleared. As a result, achieving desired drug levels in the eye, especially in the posterior portions of the eye, such as the posterior sclera, the uveal tract (located in the vascular middle layer of the eye, constituting the iris, ciliary body, and choroids), the vitreous, the choroid, the retina, and the optic nerve head (ONH), or even the inner portions of the cornea, by topical route of administration is often difficult.

[000345] For example, cornea and conjunctiva are naturally covered by a 3–40 μm layer of mucus. As shown illustratively in FIG. 15C, the outer layer is comprised of secreted mucins 310 (cleared rapidly by mucin turnover and blinking), whose primary role is to trap and eliminate allergens, pathogens, and debris (including drug particles) from the aqueous layer 305 of the eye. The inner layer (thickness up to 500 nm) is formed by mucins tethered to epithelium 315 (glycocalyx), which protects the underlying tissue from abrasive stress and are cleared less rapidly. Without wishing to be bound by theory, it is believed that conventional particles (CP; *i.e.,* non-MPP) are trapped in the outer mucus layer and are readily cleared from the ocular surface. Thus, the conventional particles may be cleared before the drugs contained in the particles can be transported to other portions of the eye (*e.g.,* by diffusion or other mechanisms). In contrast, the particles described herein (*e.g.,* MPP) may avoid adhesion to secreted mucins, and thus may penetrate the peripheral mucus layer and reach the slow-clearing glycocalyx, thereby prolonging particle retention and sustaining drug release (FIG. 15C). This suggests that the particles described herein may deliver drugs to underlying tissues (cornea, conjunctiva, *etc.*) much more efficiently than CP trapped in outer mucus. Furthermore, the formulations described herein may create an even

coverage of particles and/or pharmaceutical agent over the whole surface of the eye, where a conventional formulation without the coatings described herein may not spread as evenly due to their immobilization in mucus. Therefore, the formulations described herein may enhance efficacy by more uniform coverage. This in turn, along with higher concentrations, may enhance penetration through mucus.

[000346] Moreover, the use of the particles described herein for topical administration may address some of the challenges associated with other modes of delivery to the eye, such as injection methods and the use of topical gels or inserts. Injection methods may be effective for delivering drugs to the posterior portions of the eye, but such methods are invasive and may not be desirable. Other methods of delivery, such as topical gels and/or various inserts, that may help to deliver drug to the eye are less desirable from the patient comfort perspective.

[000347] There are other challenges associated with topical administration to the eye. The absorption of pharmaceutical agents into the eye is severely limited by some protective mechanisms that ensure the proper functioning of the eye, and by other concomitant factors, for example: drainage of the instilled solutions; lacrimation and tear turnover; metabolism; tear evaporation; non-productive absorption/adsorption; limited corneal area and poor corneal permeability; and binding by the lacrimal proteins. Therefore, eye drops that can achieve and maintain a high concentration of the pharmaceutical agent for an extended duration at the eye's surface would be desirable.

[000348] For example, the drainage of the administered dose via the nasolacrimal system into the nasopharynx and the gastrointestinal tract takes place when the volume of fluid in the eye exceeds the normal lacrimal volume of seven to 10 microlitres. Thus, the portion of the instilled dose (one to two drops, corresponding to 50–100 microlitres) that is not eliminated by spillage from the palpebral fissure may be drained quickly and the contact time of the dose with the absorbing surfaces (cornea and sclera) may be reduced to, for example, a maximum of two minutes.

[000349] The lacrimation and the physiological tear turnover (*e.g.*, 16% per minute in humans in normal conditions) can be stimulated and increased by the instillation even of mildly irritating solutions. The net result is a dilution of the applied medication and an acceleration of the loss of the pharmaceutical agent.

[000350] Topically administered drug-loaded micro- and nanoparticles have the potential to prolong ocular retention and increase local bioavailability of drugs without causing the discomfort associated with other sustained release formulations such as gels, ointments and inserts. However, a major barrier for such particles is the mucus layer at ocular surfaces (*e.g.*, at the palpebral conjunctiva, bulbar conjunctiva, and cornea; FIG. 15B). This mucus, whose natural role is to clear debris and allergens, effectively traps and rapidly removes virtually all foreign particles, including drug-loaded nanoparticles, from the ocular surface. To prolong drug retention at the ocular surface and deliver the drug closer to the underlying tissue, drug carriers / particles may need to avoid adhesion to the rapidly-clearing mucus. Therefore, drug carriers / particles that can avoid or have reduced adhesion to mucus would be desirable.

[000351] For an effective amount of a pharmaceutical agent to be delivered into an eye, high doses and/or frequent dosages may be used. However, high doses of a pharmaceutical agent increase the risk of local and systemic side effects. Moreover, frequent administration is not desirable because of its inconvenience caused to the patient, often resulting in poor compliance. Therefore, improving the mucus penetration of the pharmaceutical agent by using appropriate formulations, such as those described herein, becomes advantageous because an effective concentration of the pharmaceutical agent in the eye can be achieved without the need to use high and/or frequent doses.

[000352] Moreover, without wishing to be bound by theory, it is believed that topically administered pharmaceutical agents may be transported to the back of the eye through one or more of three main pathways: 1) the trans-vitreous trans corneal diffusion followed by entry into vitreous and subsequent distribution to ocular tissues (FIG. 16, pathway 205); 2) the uvea-scleral route, *i.e.*, trans-corneal diffusion, passage through the anterior chamber, and drainage via the aqueous humor to the uvea-scleral tissue towards the posterior tissues (FIG. 16, pathway 210); and 3) the periocular route, *i.e.*, permeation through the conjunctiva to access the periocular fluid of the tenon, diffusion around the sclera followed by diffusion across the sclera, choroid, and retina (FIG. 16, pathway 215) (Uday B. Kompella and Henry F. Edelhauser; *Drug Product Development for the Back of the Eye*, 1st Ed.; Springer; 2011). Due to anatomic membrane barriers (*i.e.* cornea, conjunctiva and sclera) and the lachrymal drainage, it can be quite challenging to obtain therapeutic drug concentrations in the posterior parts of the eye after topical drug administration. Reaching the posterior part of the eye is

even more challenging task because of the anatomical and physiological barriers associated with this part of the eye. Since those barriers cannot be altered with non-invasive methods, improvements in ophthalmic compositions and formulations that would increase the ocular bioavailability and address other challenges of topical administration to the eye would be beneficial.

[000353] The urgency to develop such formulations can be inferred from the fact that the leading causes of vision impairment and blindness are conditions linked to the posterior segment of the eye. These conditions may include, without limitation, age-related ocular degenerative diseases such as, age-related macular degeneration (AMD), proliferative vitreoretinopathy (PVR), retinal ocular condition, retinal damage, macular edema (*e.g.*, cystoid macular edema (CME) or (diabetic macular edema (DME)), and endophthalmitis. Glaucoma, which is often thought of as a condition of the anterior chamber affecting the flow (and thus, the intraocular pressure (IOP)) of aqueous humor, also has a posterior segment component. In fact, certain forms of glaucoma are not characterized by high IOP, but mainly by retinal degeneration alone.

[000354] In certain embodiments, these and other conditions may be treated, diagnosed, prevented, or managed using the mucus-penetrating particles, compositions and formulations described herein. For example, topical administration of eye drops containing mucus-penetrating particles may be used to effectively deliver an anti-AMD drug to the back of the eye and treat AMD without subjecting the patient to an invasive procedure such as an intravetreal injection. Or, for example, topical administration of eye drops containing mucus-penetrating particles loaded with an anti-inflammatory drug (*e.g.* corticosteroid or NSIAD) can be used for the treatment of ocular inflammation at a reduced dosing frequency.

[000355] The particles, compositions, and methods described herein may address the challenges described herein associated with the delivery of pharmaceutical agents to the anterior and/or posterior portions of the eye at least in part due to the mucus-penetrating properties of the particles. Without wishing to be bound by theory, it is believed that the particles described herein having mucus-penetrating properties are able to avoid adhesion to, and effectively penetrate through, the mucus coating the eye. As the particles penetrate through the mucus layer of an eye tissue (*e.g.*, palpebral conjunctiva, bulbar conjunctiva, cornea, or tear film), they avoid rapid clearance by the body's natural clearance mechanisms

and achieve prolonged retention at the front of the eye. The particles may then be dissolved and/or may release a pharmaceutical agent as the particles and/or pharmaceutical agents are transported towards the back of the eye, *e.g.,* by one of the mechanisms described in FIG. 16. By contrast, particles or drugs that are not mucus penetrating may adhere to mucus, and may be rapidly cleared by the body's natural clearance mechanisms such that insufficient amounts of the particles or drugs remain at the front of the eye shortly after administration. Thus, relatively low amounts of the particles or drugs may be available for being transported to the back of the eye (*e.g.*, by diffusion or other mechanisms). For example, as described in more detail in Examples 3 and 8, the marketed ophthalmic suspension Lotemax®, which includes particles of the pharmaceutical agent loteprednol etabonate (LE) that do not effectively penetrate mucus, was compared with LE particles having a coating of Pluronic® F127. This drug is typically used for treating inflammation of tissues at the front of the eye. Surprisingly, when particles of the pharmaceutical agent LE were coated with a coating of Pluronic® F127, Tween 80®, or certain PVAs rendering them mucus-penetrating, not only was delivery to the ocular surface at the front of the eye (*e.g.,* cornea, iris/ciliary body, aqueous humor) enhanced markedly as described in Examples 3 and 34, but delivery to the middle and back of the eye (*e.g.,* retina, choroid, and sclera)was also enhanced as described in Example 8. These results were unexpected, in particular, because LE has not been previously shown to penetrate to the back of the eye when dosed topically as an eye drop. Moreover, conventional wisdom would suggest that LE particles coated with Pluronic ® F127 would be rapidly washed away from the ocular surface by lachrymation since many have previously reported that nanosized drug particles are highly soluble in the solution in which they are contained and, thus, are expected to behave more like a conventional solution incapable of sustained release. It should be appreciated that while much of the description herein refers to treating, diagnosing, preventing, or managing tissues in the posterior portions of the eye or the back of the eye, the methods, compositions and formulations described herein are not so limited, and that other portions of the eye may benefit from the methods, compositions and formulations described herein.

[000356] Additionally, described in Examples 21 and 29-33 are particles and compositions including an RTK inhibitor (*e.g.*, sorafenib, linifanib, MGCD-265, pazopanib, cediranib, and axitinib), which demonstrate enhanced exposure of the RTK inhibitor at the back of the eye.

[000357] Portions of the eye that may be targeted or treated by the methods, compositions, and formulations described herein are now described in more detail.

[000358] In some embodiments, the methods, particles, compositions, and/or formulations described herein may be used to target and/or treat the conjunctiva of a subject. The conjunctiva refers to the mucous membrane lining the inner surfaces of the eyelids and anterior part of the sclera. The palpebral conjunctiva lines the inner surface of the eyelids and is thick, opaque, and highly vascular. The bulbar conjunctiva is loosely connected, thin, and transparent, covering the sclera or the anterior third of the eye.

[000359] In certain embodiments, the methods, particles, compositions, and/or formulations described herein may be used to target and/or treat the all or portions of the cornea of a subject. The cornea refers to the convex, transparent anterior part of the eye, comprising one sixth of the outermost tunic of the eye bulb. It allows light to pass through it to the lens. The cornea is a fibrous structure with five layers: the anterior corneal epithelium, continuous with that of the conjunctiva; the anterior limiting layer (Bowman's membrane); the substantial propria; the posterior limiting layer (Descemet's membrane); and the endothelium of the anterior chamber (keratoderma). It is dense, uniform in thickness, and nonvascular, and it projects like a dome beyond the sclera, which forms the other five sixths of the eye's outermost tunic. The degree of corneal curvature varies among different individuals and in the same person at different ages; the curvature is more pronounced in youth than in advanced age.

[000360] In some embodiments, the methods, particles, compositions, and/or formulations described herein may be used to target and/or treat portions within the posterior portion or back of the eye, such as the retina, the choroid, and/or the sclera, of a subject. Starting from the inside of the eye and going towards the back, the three main layers at the back of the eye are the retina, which contains the nerves; the choroid, which contains the blood supply; and the sclera, which is the white of the eye.

[000361] In some embodiments, the methods, particles, compositions, and/or formulations described herein may be used to treat, diagnose, prevent, or manage an ocular condition, *i.e.*, a disease, ailment, or condition that affects or involves the eye or one or more of the parts or regions of the eye. Broadly speaking, the eye includes the eyeball and the tissues and fluids

which constitute the eyeball, the periocular muscles (such as the oblique and rectus muscles) and the portion of the optic nerve which is within or adjacent to the eyeball.

[000362] In some embodiments, the methods, particles, compositions, and/or formulations described herein may be used to treat, diagnose, prevent, or manage an ocular condition at the front of the eye of a subject. In general, a front of the eye (or anterior or anterior segment) ocular condition is a disease, ailment or condition which affects or involves a tissue or a fluid at the front of the eye, as described herein. A front of the eye ocular condition includes a disease, ailment or condition, such as for example, post-surgical inflammation; uveitis; infections; aphakia; pseudophakia; astigmatism; blepharospasm; cataract; conjunctival diseases; conjunctivitis; corneal diseases; corneal ulcer; dry eye syndromes; eyelid diseases; lacrimal apparatus diseases; lacrimal duct obstruction; myopia; presbyopia; pupil disorders; corneal neovascularization; refractive disorders and strabismus. Glaucoma can be considered to be a front of the eye ocular condition in some embodiments because a clinical goal of glaucoma treatment can be to reduce a hypertension of aqueous fluid in the anterior chamber of the eye (*i.e.*, reduce intraocular pressure).

[000363] In some embodiments, the methods, particles, compositions, and/or formulations described herein may be used to treat, diagnose, prevent, or manage an ocular condition at the back of the eye of a subject. In general, a back of the eye or posterior ocular condition is a disease, ailment, or condition which primarily affects or involves a tissue or fluid at the back of the eye, as described herein. A posterior ocular condition can include a disease, ailment, or condition, such as intraocular melanoma; acute macular neuroretinopathy; Behcet's disease; choroidal neovascularization; uveitis; diabetic uveitis; histoplasmosis; infections, such as fungal or viral-caused infections; macular degeneration, such as acute macular degeneration, non-exudative age related macular degeneration and exudative age related macular degeneration; edema, such as macular edema (*e.g.*, cystoid macular edema (CME) and diabetic macular edema (DME)); multifocal choroiditis; ocular trauma which affects a posterior ocular site or location; ocular tumors; retinal disorders, such as central retinal vein occlusion, diabetic retinopathy (including proliferative diabetic retinopathy), proliferative vitreoretinopathy (PVR), retinal arterial occlusive disease, retinal detachment, uveitic retinal disease; sympathetic opthalmia; Vogt Koyanagi-Harada (VKH) syndrome; uveal diffusion; a posterior ocular condition caused by or influenced by an ocular laser treatment; posterior

ocular conditions caused by or influenced by a photodynamic therapy, photocoagulation, radiation retinopathy, epiretinal membrane disorders, branch retinal vein occlusion, anterior ischemic optic neuropathy, non-retinopathy diabetic retinal dysfunction, retinitis pigmentosa, retinoblastoma, and glaucoma. Glaucoma can be considered a posterior ocular condition in some embodiments because the therapeutic goal is to prevent the loss of or reduce the occurrence of loss of vision due to damage to or loss of retinal cells or optic nerve cells (*i.e.*, neuroprotection).

[000364] In some embodiments, the methods, particles, compositions, and/or formulations described herein may be used to treat, diagnose, prevent, or manage dry eye in a subject. Dry eye is a condition in which there are insufficient tears to lubricate and nourish the eye. Tears are necessary for maintaining the health of the front surface of the eye and for providing clear vision. People with dry eyes either do not produce enough tears or have a poor quality of tears. Dry eye is a common and often chronic problem, particularly in older adults.

With each blink of the eyelids, tears are spread across the front surface of the eye, known as the cornea. Tears provide lubrication, reduce the risk of eye infection, wash away foreign matter in the eye, and keep the surface of the eyes smooth and clear. Excess tears in the eyes flow into small drainage ducts, in the inner corners of the eyelids, which drain in the back of the nose. Tears are produced by several glands (*e.g.*, lacrimal gland) in and around the eyelids. Tear production tends to diminish with age, with various medical conditions, or as a side effect of certain medicines. Environmental conditions such as wind and dry climates can also affect tear volume by increasing tear evaporation. When the normal amount of tear production decreases or tears evaporate too quickly from the eyes, symptoms of dry eye can develop.

[000365] The most common form of dry eyes is due to an inadequate amount of the water layer of tears. This condition, called keratoconjunctivitis sicca (KCS), is also referred to as dry eye syndrome.

[000366] Treatments for dry eyes aim to restore or maintain the normal amount of tears in the eye to minimize dryness and related discomfort and to maintain eye health. These goals may be achieved through different pathways, such as increasing the lacrimal glands' tear production, regulating conjunctiva's mucin production, and suppressing inflammation of eye tissues. For example, Restasis® (0.05% cyclosporine) is an immunosuppressant that lowers

the activity of T cells in the conjunctiva and lacrimal gland. Challenges in developing new treatment of dry eyes include identifying underlying diseases and causes, length of time to see results (3-6 months), and the fact that treatment may only work in 10-15% of dry eye population. Drug delivery may also be a challenge. Although the eye tissues targeted in the treatment of dry eyes are at the front of the eye, a fraction of a topically administered pharmaceutical agent may still be immobilized by the mucus in the conjunctiva, tear film, and cornea). In some embodiments, the particles, formulations, and compositions described herein may address these issues by facilitating effective delivery of pharmaceutical agents to the appropriate tissues, promoting more even and/or wide-spread coverage of the particles across the eye surface, and/or avoiding or minimizing clearance of the particle/pharmaceutical agent.

[000367] In some embodiments, the methods, particles, compositions, and/or formulations described herein may be used to treat, diagnose, prevent, or manage inflammation in the eye of a subject. Inflammation is associated with a variety of ocular disorders. Inflammation may also result from a number of ophthalmic surgical procedures, including cataract surgery. Corticosteroids are often used as ocular anti-inflammatory agents, however, theytypically require frequent dosing.

[000368] To prevent post-surgical inflammation, steroids or NSAIDs (non-steroidal anti-inflammatory drugs) may be given prophylactically. Current treatment of post-surgical inflammation includes steroids (*e.g.*, Lotemax® (0.5% loteprednol etabonate), Durezol® (0.05% difluprednate), Pred Mild® (0.12% prednisolone acetate), and Omnipred® (1% prednisolone acetate)) and NSAIDs (*e.g.*, Bromday® (0.09% bromfenac), Nevanac® (0.1% nepafenac), Acular LS® (0.4% ketorolac tromethamine), Acuvail® (0.45% ketorolac tromethamine)), Toradol® (ketorolac tromethamine), Sprix® (ketorolac tromethamine), Voltaren® (0.1% diclofenac), Aclonac® (diclofenac), and Cataflam® (diclofenac). One of the greatest challenges for the treatment of post-surgical inflammation is compliance inasmuch as, due to the rapid clearance of eye drops from the surface of the eye, most currently marketed steroid or NSAID eye drops must be administered multiple times a day to achieve and sustain therapeutic effect. In some embodiments, the particles, compositions, and/or formulations described herein may include one or more of these steroidal pharmaceutical agents. For example, as described in more detail in the Examples, particles of Loteprednol

Etabonate, the ingredient of Lotemax®, that included certain polymeric coatings described herein produced markedly higher drug levels in various ocular tissues in New Zealand white rabbits, compared to an equivalent dose of the commercial formulation that did not include a suitable polymeric coating. This data suggests that the coated particles may be administered fewer times a day to achieve and sustain therapeutic effect compared to commercial formulations.

[000369] A number of topical NSAID formulations (*e.g.*, Bromday® (0.09% bromfenac)) are available in the market. Table 17 provides a list of these formulations, their respective trade names, active pharmaceutical ingredients (APIs), dosing concentration, and dosing frequency. The majority of these formulations (*i.e.*, Bromday®, Flurbiprofen®, Acular®, and Voltaren®) are supplied as solutions in which the active ingredient is completely dissolved.

[000370] It has been found that bromfenac is susceptible to degradation in solution via lactam formation, especially below neutral pH (Table 18). Data in Table 18 show that more degradant of bromfenac was observed when the pH of an aqueous solution containing bromfenac sodium was lowered (*e.g.,* from pH 7.8 to 5.8).

[000371] To enhance topical delivery of bromfenac, which in turn may translate into a lower dose for improved safety or enhanced therapy for conditions in the middle and back of the eye, it may be desirable to formulate bromfenac as a suspension of MPPs comprising a bromfenac core. Additionally, formulating bromfenac as a suspension of MPPs may allow for an increase in the concentration of bromfenac in the formulation without substantially increasing the concentration of degradants (*e.g.*, compared to an aqueous solution of bromfenac). However, it is difficult to formulate bromfenac sodium as a solid or crystalline particle due to its relatively high water solubility. Bromfenac free acid (bromfenac FA) may also be difficult to develop into a shelf-stable MPP suspension formulation in some embodiments, *e.g.*, due to significant degradation of bromfenac FA in the presence of aqueous Pluronic® F127 (Table 19).

[000372] **Table 17.** Currently available products featuring topically-delivered NSAIDs.

Trade name	Manufacturer	API	Concentration of API (% w/v)	Treatment frequency (drops per day)	Dosage form

Bromday®	Bausch & Lomb	bromfenac sodium	0.09	1	solution
Ocufen®	Allergan	flurbiprofen	0.03	4	solution
Acular®, Acular LS®, Acuvail®	Allergan	ketorolac tromethamine	0.4-0.5	2-4	solution
Voltaren®	Novartis	diclofenac sodium	0.1	4	solution
Nevanac®	Alcon	nepafenac	0.1	3	suspension

The products listed are prescribed for administration post-surgery, with the exception of Ocufen® which is administered within 2 hr prior to surgery.

[000373] Table **18.** Chemical degradation of bromfenac sodium at various pH.*

pH	% peak area
5.8	3.16
6.8	0.05
7.8	0

*The chemical stability of bromfenac sodium was determined as % chromatographic peak area for the lactam degradant of bromfenac after 0.02% aqueous solutions of bromfenac sodium were stored for 5 days at room temperature.

[000374] **Table 19**. Chemical degradation of bromfenac free acid in unbuffered aqueous suspensions in the presence of Pluronic® F127.*

Concentration of Pluronic ® F127 (% w/v)	Concentration of Bromfenac FA (% w/v)	% peak area
0.50	0.5	12.0 (day 14)
5	5	10.2 (day 5)

*The chemical stability of bromfenac free acid was determined as % chromatographic peak area for the lactam degradant of bromfenac after an aqueous suspension of bromfenac free acid was stored for 5 or 14 days at room temperature.

[000375] As described herein, it is desirable to develop a composition comprising an NSAID (*e.g.*, bromfenac, diclofenac, ketorolac, or a salt thereof) that is stable at a suitable pH for topical administration to the eye. In some embodiments, such compositions include solid

or crystalline particles of bromfenac, diclofenac, ketorolac, or a salt thereof, that can effectively penetrate mucus. The particles may include one or more surface-altering agents described herein (*e.g.*, a poloxamer, a polysorbate (*e.g.*, Tween 80®), PVA) that can reduce mucoadhesion of the particles.

[000376] In some embodiments, the particles, compositions, and/or formulations described herein include a divalent metal salt of bromfenac, such as a divalent metal salt of bromfenac. For instance, the divalent metal salt of bromfenac may be relatively water insoluble and may include, for example, bromfenac beryllium, bromfenac magnesium, bromfenac calcium, bromfenac strontium, bromfenac barium, bromfenac zinc, or bromfenac copper(II). In some embodiments, the particles including a divalent metal salt of bromfenac may have an aqueous solubility in a range described herein (*e.g.*, at least about 0.001 mg/mL and less than or equal to about 1 mg/mL).

[000377] In certain embodiments, the particles, compositions, and/or formulations described herein include diclofenac FA. In certain embodiments, the particles, compositions, and/or formulations described herein include a metal salt of diclofenac, such as an alkaline earth metal salt of diclofenac. In certain embodiments, the particles, compositions, and/or formulations described herein include ketorolac FA. In certain embodiments, the particles, compositions, and/or formulations described herein include a metal salt of ketorolac, such as an alkaline earth metal salt of ketorolac. Trivalent metal salts of such compounds are also possible.

[000378] The divalent metal salts of bromfenac described herein (*e.g.*, bromfenac calcium) are less water soluble and more hydrophobic than bromfenac sodium and/or other monovalent salts of bromfenac. For example, the aqueous solubility of bromfenac calcium at 25 °C is about 0.15 mg/mL. Compared to the more water soluble and hydrophilic bromfenac sodium, the divalent metal salts of bromfenac may be more suitable to be processed into MPPs using the methods described herein (*e.g.*, milling and/or precipitation). The divalent metal salts of bromfenac are present in the MPPs mostly in solid (*e.g.*, crystalline) form and, therefore, may be less prone to degradation and more chemically stable. Additionally, relatively high concentrations of the divalent metal salts of bromfenac in a composition and/or formulation including MPPs of the divalent metal salts of bromfenac are not limited by the aqueous solubility and/or the formation of degradants of the divalent metal salts of

bromfenac. Therefore, the particles, compositions, and/or formulations described herein comprising a divalent metal salt of bromfenac may allow for higher concentrations of bromfenac in the compositions or formulations compared to the free acid form which is dissolved in solution. In some embodiments, such particles, compositions, and/or formulations allow for higher concentrations of bromfenac in ocular tissues after administration to the eye.

[000379] For similar reasons discussed herein with respect to bromfenac calcium and the free acid form of bromfenac, the less water soluble and hydrophilic diclofenac FA and a metal salt thereof (*e.g.*, divalent or trivalent metal salts) may be more suitable for being processed into particles, compositions, and/or formulations that are mucus penetrating compared to diclofenac sodium and/or other monovalent salts of diclofenac. Similarly, ketorolac FA and a metal salt thereof (*e.g.*, divalent or trivalent metal salts), which are less water soluble and hydrophilic than ketorolac tromethamine and/or other monovalent salts of ketorolac, may be formed into mucus penetrating particles, compositions, and/or formulations. Moreover, since diclofenac FA or ketorolac FA, or a divalent or trivalent metal salt thereof, may not be limited by their aqueous solubilities, these compounds may be present in a higher concentration in the particles, compositions, and/or formulations described herein compared to aqueous formulations of diclofenac sodium or ketorolac tromethamine, respectively.

[000380] In certain embodiments, a pharmaceutical agent described herein (*e.g.*, an NSAID such as a divalent metal salt of bromfenac (*e.g.*, bromfenac calcium), diclofenac FA, a metal salt of diclofenac (*e.g.*, divalent or trivalent metal salts), ketorolac FA, or a metal salt of ketorolac (*e.g.*, divalent or trivalent metal salts); a receptor tyrosine kinase (RTK) inhibitor, such as sorafenib, linifanib, MGCD-265, pazopanib, cediranib, and axitinib; or a corticosteroid, such as LE) is present in a composition and/or formulation described herein at at least about 0.001%, at least about 0.003%, at least about 0.01%, at least about 0.02%, at least about 0.05%, at least about 0.1%, at least about 0.2%, at least about 0.3%, at least about 0.4%, at least about 0.5%, at least about 0.6%, at least about 0.8%, at least about 1%, at least about 1.5%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 8%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, or at least about 50%, w/v. In certain embodiments, the pharmaceutical

agent is present in a composition and/or formulation described herein at less than or equal to about 50%, less than or equal to about 40%, less than or equal to about 30%, less than or equal to about 20%, less than or equal to about 10%, less than or equal to about 8%, less than or equal to about 6%, less than or equal to about 5%, less than or equal to about 4%, less than or equal to about 3%, less than or equal to about 2%, less than or equal to about 1.5%, less than or equal to about 1%, less than or equal to about 0.8%, less than or equal to about 0.6%, less than or equal to about 0.5%, less than or equal to about 0.4%, less than or equal to about 0.3%, less than or equal to about 0.2%, less than or equal to about 0.1% less than or equal to about 0.05%, less than or equal to about 0.02%, less than or equal to about 0.01%, less than or equal to about 0.003%, or less than or equal to about 0.001%, w/v. Combinations of the above-referenced ranges are also possible (*e.g.,* at least about 0.5% and less than or equal to 5% w/v). Other ranges are also possible.

[000381] In certain embodiments, a divalent metal salt of bromfenac (*e.g.*, bromfenac calcium) is present in a composition and/or formulation described herein at about 0.09% w/v or greater. In certain embodiments, the divalent metal salt of bromfenac (*e.g.*, bromfenac calcium) is present in a composition and/or formulation described herein at about 0.5% w/v or greater. In certain embodiments, diclofenac FA or ketorolac FA, or a metal salt thereof (*e.g.*, divalent or trivalent metal salt), is present in a composition and/or formulation described herein at about 0.5% w/v or greater.

[000382] In some embodiments, the compositions and/or formulations including MPPs of divalent metal salts of bromfenac or other pharmaceutical agents described herein may have a pH that is not irritating to the eye, such as a mildly basic pH (*e.g.*, pH 8), physiological pH (*i.e.*, about pH 7.4), a substantially neutral pH (*e.g.*, about pH 7), a mildly acidic pH (*e.g.*, about pH 5-6), or ranges thereof (*e.g.*, about pH 5-7, or 6-7). At these pHs, the MPPs, compositions, and/or formulations may be chemically and colloidally stable and may achieve therapeutically and/or prophylactically effective drug levels for a longer duration in ocular tissues compared to certain marketed formulations. The benefits described herein may further lead to a lower required dose for improved safety of this treatment and/or enhanced topical delivery for treating conditions in the middle and back of the eye compared to certain marketed formulations.

[000383] In some embodiments, the methods, particles, compositions, and/or formulations described herein may be used to treat, diagnose, prevent, or manage glaucoma in a subject. Glaucoma is an eye disease in which the optic nerve is damaged in a characteristic pattern. This can permanently damage vision in the affected eye and lead to blindness if left untreated. It is normally associated with increased fluid pressure in the eye (aqueous humour). The term ocular hypertension is used for people with consistently raised IOP without any associated optic nerve damage. Conversely, the term normal tension or low tension glaucoma is used for those with optic nerve damage and associated visual field loss but normal or low IOP.

[000384] The nerve damage involves loss of retinal ganglion cells in a characteristic pattern. There are many different subtypes of glaucoma, but they can all be considered to be a type of optic neuropathy. Raised intraocular pressure (*e.g.,* above 21 mmHg or 2.8 kPa) is the most important and only modifiable risk factor for glaucoma. However, some may have high eye pressure for years and never develop damage, while others can develop nerve damage at a relatively low pressure. Untreated glaucoma can lead to permanent damage of the optic nerve and resultant visual field loss, which over time can progress to blindness.

[000385] Current treatment of glaucoma may include the use of prostaglandin analogs which increase aqueous humor outflow (*e.g.*, Xalatan® (0.005% latanoprost), Lumigan® (0.03% and 0.01% bimatoprost), and Travatan Z® (0.004% travoprost)); beta-blockers which decreases aqueous humor production (*e.g.*, Timoptic® (0.5% and 0.25% timolol)); alpha agonists which both decrease aqueous humor production and increase outflow (*e.g.*, Alphagan® (0.1% and 0.15% brimonidine tartrate)); carbonic anhydrase inhibitors which decreases aqueous humor production (*e.g.*, Trusopt® (2% dorzolamide)); and cholinergics (miotic) which increase conventional outflow (*e.g.*, Isopto® (1%, 2%, and 4% pilocarpine)). In some embodiments, the particles, formulations, and compositions described herein may address the issues described above by facilitating effective delivery of pharmaceutical agents to the appropriate tissues and avoiding or minimizing clearance of the pharmaceutical agent. For example, the particles, compositions, and/or formulations described herein may include one or more of these or other prostaglandin analogs, beta-blockers, alpha agonists, carbonic anhydrase inhibitors and cholinergics, and may include a coating described herein to facilitate

penetration of the particle through mucus and allow effective delivery of the pharmaceutical agent.

[000386] In some embodiments, the methods, particles, compositions, and/or formulations described herein may be used to treat, diagnose, prevent, or manage uveitis in a subject. Uveitis is inflammation of the uvea, the vascular layer of the eye sandwiched between the retina and the white of the eye (sclera). The uvea extends toward the front of the eye and consists of the iris, choroid layer and ciliary body. The most common type of uveitis is an inflammation of the iris called iritis (anterior uveitis). Uveitis may also occur at the posterior segment of the eye (*e.g.*, at the choroid). Inflammation of the uvea can be recurring and can cause serious problems such as blindness if left untreated (accounts for 10% of blindness globally). Early diagnosis and treatment are important to prevent the complications of uveitis.

[000387] Current treatment of uveitis includes eye drops (*e.g.*, TobraDex® (0.1% dexamethasone / 0.3% tobramycin) and Zylet® (0.5% loteprednol etabonate / 0.3% tobramycin)); intravitreal injections of "gel suspension" in sodium hyaluronate (*e.g.*, Trivaris® (8% triamcinolone acetonide)); intravitreal injection of "aqueous suspension" in carboxymethylcellulose and Tween 80 (*e.g.*, Triesence® (4% triamcinolone acetonide)); and implants (*e.g.*, Retisert® (0.59mg fluocinolone acetonide) and Ozurdex® (0.7mg dexamethasone)). Oral steroids and NSAIDS are also employed. Challenges in developing new treatment of uveitis include non-invasive delivery for posterior uveitis, clearance due to high vascularization of the uvea, side effects of long term steroid use such as increased IOP and cataracts. In some embodiments, the particles, compositions, and/or formulations described herein may include one or more of these drugs, which may be administered topically to a subject.

[000388] In some embodiments, the methods, particles, compositions, and/or formulations described herein may be used to treat, diagnose, prevent, or manage age-related macular degeneration (AMD) in a subject. AMD is a medical condition which usually affects older adults and results in a loss of vision in the center of the visual field (the macula) because of damage to the retina. It occurs in "dry" and "wet" forms. It is a major cause of blindness and visual impairment in older adults (>50 years). Macular degeneration can make it difficult or impossible to read or recognize faces, although enough peripheral vision remains to allow other activities of daily life.The macula is the central area of the retina, which provides the

most detailed central vision.In the dry (nonexudative) form, cellular debris called drusen accumulate between the retina and the choroid, and the retina can become detached. In the wet (exudative) form, which is more severe, blood vessels grow up from the choroid behind the retina, and the retina can also become detached. It can be treated with laser coagulation, and with medication that stops and sometimes reverses the growth of blood vessels. Although some macular dystrophies affecting younger individuals are sometimes referred to as macular degeneration, the term generally refers to age-related macular degeneration (AMD or ARMD).

[000389] Age-related macular degeneration begins with characteristic yellow deposits (drusen) in the macula, between the retinal pigment epithelium and the underlying choroid. Most people with these early changes (referred to as age-related maculopathy) have good vision. People with drusen can go on to develop advanced AMD. The risk is considerably higher when the drusen are large and numerous and associated with disturbance in the pigmented cell layer under the macula. Recent research suggests that large and soft drusen are related to elevated cholesterol deposits and may respond to cholesterol-lowering agents.

[000390] Potential treatment of AMD includes used of pharmaceutical agents such as verteporfin (*e.g.*, Chlorin®, Visudyne®), thalidomide (*e.g.*, Ambiodry®, Synovir®, Thalomid®), talaporfin sodium (*e.g.*, Aptocine®, Laserphyrin®, Litx®), ranibizumab (*e.g.*, Lucentis®), pegaptanib octasodium (*e.g.*, Macugen®, Macuverse®), isopropyl unoprostone (*e.g.*, Ocuseva®, Rescula®), interferon beta (*e.g.*, Feron®), fluocinolone acetonide (*e.g.*, Envision TD®, Retisert®), everolimus (*e.g.*, Afinitor®, Certican®, Votubia®, Zortress®), eculizumab (*e.g.*, Solaris®, Soliris®), dexamethasone (*e.g.*, Osurdex®, Ozurdex®, Posurdex®, Surodex®), canakinumab (*e.g.*, Ilaris ®), bromfenac (Bromday®), ophthalmic (*e.g.*, Bronac®, Bronuck®, Xibrom®, Yellox®), brimonidine (*e.g.*, Alphagan®, Bromoxidine®, Enidin®), anecortave acetate (*e.g.*, Retaane®, Edex®, Prostavasin®, Rigidur®, Vasoprost®, Viridal®), aflibercept ophthalmic solution (*e.g.*, Eyelea®, Eylea®, VEGF-Trap-Eye®), ocriplasmin (*e.g.*, Iluvien®, Medidur®, Medidur FA®), sirolimus (*e.g.*, Perceiva®), NT-501, KH-902, fosbretabulin tromethamine (*e.g.*, Zybrestat®), AL-8309, aganirsen (*e.g.*, Norvess®), volociximab (*e.g.*, Opthotec®), triamcinolone (*e.g.*, Icon Bioscience), TRC-105, Burixafor (*e.g.*, TG-0054), TB-403 (*e.g.*, R-7334), squalamine (*e.g.*, Evizon®), SB-623, S-646240, RTP-801i-14 (*e.g.*, PF-4523655), RG-7417 (*e.g.*, FCFD-4514S), AL-78898A (*e.g.*, POT-4), PG-

11047 (*e.g.*, CGC-11047), pazopanib hydrochloride, sonepcizumab (*e.g.*, Asonep®, Sphingomab®), padeliporfin (*e.g.*, Stakel®), OT-551, ontecizumab, NOX-A12, hCNS-SC, Neu-2000, NAFB001, MA09-hRPE, LFG-316, iCo-007 (*e.g.*, ISIS-13650), hI-con1, GSK-933776A, GS-6624 (*e.g.*, AB-0024), ESBA-1008, epitalon, E-10030 (*e.g.*, ARC-127), dalantercept, MP-0112, CNTO-2476, CERE-120, AAV-NTN, CCX-168, Brimonidine-DDS, bevasiranib sodium (*e.g.*, Cand5), bertilimumab, AVA-101, ALG-1001, AL-39324, AGN-150998, ACU-4429, A6 (*e.g.*, Paralit®), TT-30, sFLT-01 gene therapy, RetinoStat®, PRS-050 (*e.g.*, Angiocal®), PF-4382923, Palomid-529, MC-1101, GW-824575, Dz13 (*e.g.*, TRC-093), D93, CDX-1135 (*e.g.*, TP10), ATL-1103, ARC-1905, XV-615, wet-AMD antibodies (*e.g.*, pSivida), VEGF/rGel, VAR-10200, VAL-566-620-MULTI, TKI, TK-001, STP-601, dry AMD stem cell therapy (*e.g.*, EyeCyte), OpRegen, SMT-D004, SAR-397769, RTU-007, RST-001, RGNX-004, RFE-007-CAI, retinal degeneraton programme (*e.g.*, Orphagen), retinal cells (*e.g.*, ISCO), ReN003, PRM-167, ProDex, Photoswitches (*e.g.*, Photoswitch Biosciences), Parkinson's therapy, OMS-721, OC-10X, NV. AT.08, NT-503, NAFB002, NADPH oxidase inhibitors (*e.g.*, Alimera Sciences), MC-2002, lycium anti-angiogenic proteoglycan, IXSVEGF, integrin inhibitors, GW-771806, GBS-007, Eos-013, EC-400, dry-AMD therapy (*e.g.*, Neuron Systems), CGEN-25017, CERE-140, AP-202, AMD therapy (*e.g.*, Valens Therapeutics), AMD therapy (*e.g.*, Amarna Therapeutics), AMD RNAi therapy (*e.g.*, RXi), ALK-001, AMD therapy (*e.g.*, Aciont), AC-301, 4-IPP, zinc-monocysteine complexes (*e.g.*, Adeona), vatalanib, TG-100-344, prinomastat, PMX-53, Neovastat, mecamylamine, JSM-6427, JPE-1375, CereCRIB, BA-285, ATX-S10, AG-13958, verteporfin/alphavß3 conjugate, VEGF/rGel, VEGF-saporin, VEGF-R2 antagonist (*e.g.*, Allostera), VEGF inhibitors (*e.g.*, Santen), VEGF antagonists (*e.g.*, Ark), Vangiolux®, Triphenylmethanes (*e.g.*, Alimera), TG-100-801, TG-100-572, TA-106, T2-TrpRS, SU-0879, stem cell therapy (*e.g.*, Pfizer and UCL), SOD mimetics (*e.g.*, Inotek), SHEF-1, rostaporfin (*e.g.*, Photrex®, Purlytin®, SnET2), RNA interference (*e.g.*, Idera and Merck), rhCFHp (*e.g.*, Optherion), retino-NPY, retinitis pigmentosa therapy (*e.g.*, Mimetogen), AMD gene therapy (*e.g.*, Novartis), retinal gene therapy (*e.g.*, Genzyme), AMD gene therapy (*e.g.*, Copernicus), retinal dystrophy ther (*e.g.*, Fovea and Genzyme), Ramot project No. K-734B, PRS-055, porcine RPE cells (*e.g.*, GenVec), PMI-002, PLG-101 (*e.g.*, BiCentis®), PJ-34, PI3K conjugates (*e.g.*, Semafore), PhotoPoint, Pharmaprojects No. 6526, pegaptanib sodium (*e.g.*,

SurModics®), PEDF ZFP TF, PEDF gene therapy (*e.g.*, GenVec), PDS-1.0, PAN-90806, Opt-21, OPK-HVB-010, OPK-HVB-004, Ophthalmologicals (*e.g.*, Cell NetwoRx), ophthalmic compounds (*e.g.*, AstraZenca and Alcon), OcuXan, NTC-200, NT-502, NOVA-21012, Neurosolve®, neuroprotective (*e.g.*, BDSI), MEDI-548, MCT-355, McEye®, LentiVue®, LYN-002, LX-213, lutetium texaphyrin (*e.g.*, Antrin®), LG-339 inhibitors (*e.g.*, Lexicon), KDR kinase inhibitors (*e.g.*, Merck), ISV-616, INDUS-815C, ICAM-1 aptamer (*e.g.*, Eyetech), hedgehog antagonists (*e.g.*, Opthalmo), GTx-822, GS-102, Granzyme B/VEGF®, gene therapy (*e.g.*, EyeGate), GCS-100 analogue programme, FOV-RD-27, fibroblast growth factor (*e.g.*, Ramot), fenretinide, F-200 (*e.g.*, Eos-200-F), Panzem SR®, ETX-6991, ETX-6201, EG-3306, Dz-13, disulfiram (*e.g.*, ORA-102), Diclofenac (*e.g.*, Ophthalmopharma), ACU-02, CLT-010, CLT-009, CLT-008, CLT-007, CLT-006, CLT-005, CLT-004, CLT-003 (*e.g.*, Chirovis®), CLT-001, Cethrin® (*e.g.*, BA-210), celecoxib, CD91 antagonist (*e.g.*, Ophthalmophar), CB-42, BNC-4, bestrophin, batimastat, BA-1049, AVT-2, AVT-1, atu012, Ape1 programme (*e.g.*, ApeX-2), anti-VEGF (*e.g.*, Gryphon), AMD ZFPs (*e.g.*, ToolGen), AMD therapy (*e.g.*, Optherion), AMD therapy (*e.g.*, ItherX), dry AMD therapy (*e.g.*, Opko), AMD therapy (*e.g.*, CSL), AMD therapies (*e.g.*, Pharmacopeia and Allergan), AMD therapeutic protein (*e.g.*, ItherX), AMD RNAi therapy (*e.g.*, BioMolecular Therapeutics), AM-1101, ALN-VEG01, AK-1003, AGN-211745, ACU-XSP-001 (*e.g.*, Excellair®), ACU-HTR-028, ACU-HHY-011, ACT-MD (*e.g.*, NewNeural), ABCA4 modulators (*e.g.*, Active Pass), A36 (*e.g.*, Angstrom), 267268 (*e.g.*, SB-267268), bevacizumab (*e.g.*, Avastin®), aflibercept (*e.g.*, Eylea®), 131-I-TM-601, vandetanib (*e.g.*, Caprelsa®, Zactima®, Zictifa®), sunitinib malate (*e.g.*, Sutene®, Sutent®), sorafenib (*e.g.*, Nexavar®), pazopanib (*e.g.*, Armala®, Patorma®, Votrient®), axitinib (*e.g.*, Inlyta®), tivozanib, XL-647, RAF-265, pegdinetanib (*e.g.*, Angiocept®), pazopanib, MGCD-265, icrucumab, foretinib, ENMD-2076, BMS-690514, regorafenib, ramucirumab, plitidepsin (*e.g.*, Aplidin®), orantinib, nintedanib (*e.g.*, Vargatef®), motesanib, midostaurin, linifanib, telatinib, lenvatinib, elpamotide, dovitinib, cediranib (*e.g.*, Recentin®), JI-101, cabozantinib, brivanib, apatinib, Angiozyme®, X-82, SSR-106462, rebastinib, PF-337210, IMC-3C5, CYC116, AL-3818, VEGFR2 inhibitor (*e.g.*, AB Science), VEGF/rGel (*e.g.*, Clayton Biotechnologies), TLK-60596, TLK-60404, R84 antibody (*e.g.*, Peregrine), MG-516, FLT4 kinase inhibitors (*e.g.*, Sareum), flt-4 kinase inhibitors, Sareum, DCC-2618, CH-330331, XL-999, XL-820, vatalanib, SU-14813,

semaxanib, KRN-633, CEP-7055, CEP-5214, ZK-CDK, ZK-261991, YM-359445, YM-231146, VEGFR2 kinase inhibitors (*e.g.*, Takeda), VEGFR-2 kinase inhibitors (*e.g.*, Hanmi), VEGFR-2 antagonist (*e.g.*, Affymax), VEGF/rGel (*e.g.*, Targa), VEGF-TK inhibitors (*e.g.*, AstraZeneca), tyrosine kinase inhibitors (*e.g.*, Abbott), tyrosine kinase inhibitors (*e.g.*, Abbott), Tie-2 kinase inhibitors (*e.g.*, GSK), SU-0879, SP-5.2, sorafenib bead (*e.g.*, Nexavar® bead), SAR-131675, Ro-4383596, R-1530, Pharmaprojects No. 6059, OSI-930, OSI-817, OSI-632, MED-A300, L-000021649, KM-2550, kinase inhibitors (*e.g.*, MethylGene), kinase inhibitors (*e.g.*, Amgen), Ki-8751, KDR kinase inhibitors (*e.g.*, Celltech), KDR kinase inhibitors (*e.g.*, Merck), KDR kinase inhibitors (*e.g.*, Amgen), KDR inhibitors (*e.g.*, Abbott), KDR inhibitor (*e.g.*, LGLS), JNJ-17029259, IMC-1C11, Flt 3/4 anticancer (*e.g.*, Sentinel), EG-3306, DP-2514, DCC-2157, CDP-791, CB-173, c-kit inhibitors (*e.g.*, Deciphera), BIW-8556, anticancers (*e.g.*, Bracco and Dyax), anti-Flt-1 MAbs (*e.g.*, ImClone), AGN-211745, AEE-788, and AB-434.

[000391] Laser therapy is also available for wet AMD. Small molecule anti-VEGF therapies are being investigated, but none are currently approved. Challenges in developing new treatment of AMD include identifying treatments, delivery to the macula, side effects and patient compliance with intravitreal injection.

[000392] In addition to other bodily conditions described herein, in some embodiments, the methods, particles, compositions, and/or formulations described herein may be used to treat, diagnose, prevent, or manage macular edema (*e.g.*, cystoid macular edema (CME) or (diabetic macular edema (DME)) in a subject. CME is a disorder which affects the central retina or macula of the eye. When this condition is present, multiple cyst-like (cystoid) areas of fluid appear in the macula and cause retinal swelling or edema. CME may accompany a variety of diseases such as retinal vein occlusion, uveitis, and/or diabetes. CME commonly occurs after cataract surgery.

[000393] Currently treatment of CME includes administration of an NSAID (such as bromfenac (*e.g.*, Bromday®)). The NSAID may be co-administered topically or intravitreally with a corticosteroid. Severe and persistent cases of CME are usually treated by intravitreal injection of corticosteroids, which is an invasive and costly procedure.

[000394] DME occurs when blood vessels in the retina of patients with diabetes begin to leak into the macula, the part of the eye responsible for detailed central vision. These leaks

cause the macula to thicken and swell, progressively distorting acute vision. While the swelling may not lead to blindness, the effect can cause a severe loss in central vision.

[000395] Currently treatment of DME includes Lucentis® (ranibizumab) injections that are inconvenient and invasive. Another treatment of DME is laser photocoagulation. Laser photocoagulation is a retinal procedure in which a laser is used to cauterize leaky blood vessels or to apply a pattern of burns to reduce edema. This procedure has undesirable side effects including partial loss of peripheral and night vision.

[000396] Due to the drawbacks described above, there is a need for an improved formulation for the treatment and/or prevention of macular edema (*e.g.*, CME or DME). The particles, compositions, and/or formulations described herein including an NSAID (*e.g.*, bromfenac calcium) are stable at a pH suitable for topical administration to the eye and may address the issues described above with respect to current methods of treatment for macular edema. (See, for example, Examples 27-28).

[000397] The particles, compositions, and/or formulations described herein may be delivered into the eye by a variety of routes including, without limitation, orally in any acceptable form (*e.g.*, tablet, liquid, capsule, powder, and the like); topically in any acceptable form (*e.g.*, patch, eye drops, creams, gels, nebulization, punctal plug, drug eluting contact, iontophoresis, and ointments); by injection in any acceptable form (*e.g.*, intravenous, intraperitoneal, intramuscular, subcutaneous, parenteral, and epidural); and by implant or the use of reservoirs (*e.g.*, subcutaneous pump, intrathecal pump, suppository, biodegradable delivery system, non-biodegradable delivery system and other implanted extended or slow release device or formulation).

[000398] Partly because the administration of particles, compositions, and/or formulations into the eye by injections is invasive (causing discomfort for the patient and can also lead to complications that are even more serious than the disease being treated) and oral doses often lead to low distribution of the particles, compositions, and/or formulations into the eye, topical delivery may be preferred in some embodiments. The key benefits of topical delivery include non-invasive character, localized action with reduced systemic exposure, relative patient comfort, and ease of administration.

[000399] Compliance is an issue which stems from a wide variety of factors, from patients' difficulty remembering to take drops, to trouble in physically administering drops, to unpleasant side effects. Other issues include rapid clearance of drug and systemic exposure.

[000400] As described herein, in some embodiments, the particles, compositions, and/or formulations may be administered topically to an eye of the subject, and a pharmaceutical agent may be delivered to a posterior part of the eye (*e.g.* to retina, choroid, vitreous, and optic nerve). The particles, compositions, and/or formulations may be used to treat, diagnose, prevent, or manage a disorder such as age-related macular degeneration, diabetic retinopathy, retinal venous occlusions, retinal arterial occlusion, macular edema, postoperative inflammation, uveitis retinitis, proliferative vitreoretinopathy and glaucoma.

[000401] In certain embodiments, the particles, compositions, and methods described herein are useful in the imaging of the eye. In certain embodiments, the particles, compositions, and methods described herein are useful in the diagnosis of an ocular condition.

[000402] In some embodiments, ophthalmic delivery of a pharmaceutical composition described herein includes delivery to an ocular surface, to the lacrimal glands or lacrimal drainage system, to the eyelids, to the anterior segment of the eye, to the posterior segment of the eye, and/or to the periocular space. In certain embodiments, a pharmaceutical composition described herein can be delivered to the cornea, iris/ciliary body, aqueous humor, vitreous humor, retina, choroid and/or sclera. The therapeutic effect of delivering a pharmaceutical composition described herein may be improved compared to the effect of delivering of particles that are not identified herein as mucus penetrating.

[000403] In some embodiments, the pharmaceutical agent that is delivered into the eye by the particles, compositions, and/ormethods described herein may be a corticosteroid. In certain embodiments, the pharmaceutical agent is loteprednol etabonate. In certain embodiments, thepharmaceutical agent includes one or more of hydrocortisone, cortisone, tixocortol, prednisolone, methylprednisolone, prednisone, triamcinolone, mometasone, amcinonide, budesonide, desonide, fluocinonide, fluocinolone, halcinonide, betamethasone, dexamethasone, fluocortolone, hydrocortisone, aclometasone, prednicarbate, clobetasone, clobetasol, fluprednidene, glucocorticoid, mineralocorticoid, aldosterone, deoxycorticosterone, fludrocortisone, halobetasol, diflorasone, desoximetasone, fluticasone, flurandrenolide, alclometasone, diflucortolone, flunisolide, and beclomethasone.

[000404] In certain embodiments, the particles, compositions, and methods described herein are useful in the delivery of a corticosteroid, such as one described above, into the eye for the treatment of inflammation of the eye. In certain embodiments, the particles, compositions, and methods are useful in the delivery of a corticosteroid into the eye for the treatment of macular degeneration, macular edema, other retinal disorders, or other conditions described herein.

[000405] In some embodiments, the pharmaceutical agent that is delivered into the eye by the particles, compositions, and methods described herein may be a non-steroidal anti-inflammatory drug (NSAID). In certain embodiments, the pharmaceutical agent is a divalent metal salt of bromfenac (*e.g.*, bromfenac calcium). In certain embodiments, the pharmaceutical agent is diclofenac (*e.g.*, diclofenac free acid or a divalent or trivalent metal salt thereof). In certain embodiments, the pharmaceutical agent is ketorolac (*e.g.*, ketorolac free acid or a divalent or trivalent metal salt thereof). In certain embodiments, the pharmaceutical agent is a salicylate (*e.g.*, aspirin (acetylsalicylic acid), diflunisal, or salsalate). In certain embodiments, the pharmaceutical agent is a propionic acid derivative (*e.g.*, ibuprofen, naproxen, fenoprofen, ketoprofen,dexketoprofen,flurbiprofen,oxaprozin, and loxoprofen). In certain embodiments, the pharmaceutical agent is an acetic acid derivative (*e.g.*, indomethacin, sulindac, etodolac, ketorolac, diclofenac, and nabumetone). In certain embodiments, the pharmaceutical agent is an enolic acid (oxicam) derivative (*e.g.*, piroxicam,meloxicam,tenoxicam, droxicam, lornoxicam, and isoxicam). In certain embodiments, the pharmaceutical agent is a fenamic acid derivative (fenamate) (*e.g.*, mefenamic acid, meclofenamic acid, flufenamic acid, and tolfenamic acid). In certain embodiments, the pharmaceutical agent is a cyclooxygenase (cox) inhibitor, such as a cox-1 or cox-2 inhibitor (*e.g.*, bromfenac calcium). In certain embodiments, the pharmaceutical agent is a selective cox-2 inhibitor (coxib) (*e.g.*, celecoxib, rofecoxib, valdecoxib, parecoxib, lumiracoxib, etoricoxib,and firocoxib). In certain embodiments, the pharmaceutical agent is a sulphonanilide (*e.g.*, nimesulide). In certain embodiments, the pharmaceutical agent is licofelone.

[000406] In certain embodiments, the particles, compositions, and methods described herein are useful in the delivery of an NSAID, such as one described above, into the eye for the treatment of inflammation of the eye or other conditions described herein. In some

embodiments, the pharmaceutical agent that is delivered into the eye by the particles, compositions, and methods described herein may be an angiogenesis inhibitor. In certain embodiments, the pharmaceutical agent is an endogenous angiogenesis inhibitor (*e.g.*, VEGFR-1 (*e.g.*, pazopanib (Votrient®), cediranib (Recentin®), tivozanib (AV-951), axitinib (Inlyta®), semaxanib), HER2 (lapatinib (Tykerb®, Tyverb®), linifanib(ABT-869), MGCD-265, and KRN-633), VEGFR-2 (*e.g.*, regorafenib(BAY 73-4506), telatinib (BAY 57-9352), vatalanib (PTK787, PTK/ZK), MGCD-265, OSI-930, and KRN-633), NRP-1, angiopoietin 2, TSP-1, TSP-2, angiostatin, endostatin, vasostatin, calreticulin, platelet factor-4, TIMP, CDAI, Meth-1, Meth-2, IFN-α, IFN-β, IFN-γ, CXCL10, IL-4, IL -12, IL -18, prothrombin (kringle domain-2), antithrombin III fragment, prolactin, VEGI, SPARC, osteopontin, maspin, canstatin, a proliferin-related protein, sorafenib (Nexavar®)), and restin). In certain embodiments, the pharmaceutical agent is an exogenous angiogenesis inhibitor (*e.g.*, bevacizumab, itraconazole, carboxyamidotriazole, TNP-470, CM101, IFN-α, IL-12, platelet factor-4, suramin, SU5416, thrombospondin, VEGFR antagonist, an angiostatic steroid + heparin, a cartilage-derived angiogenesis inhibitory factor, a matrix metalloproteinase inhibitor, angiostatin, endostatin, 2-methoxyestradiol, tecogalan, tetrathiomolybdate, thalidomide, thrombospondin, prolactin, a $\alpha_V\beta_3$ inhibitor, linomide, and tasquinimod).

[000407] In certain embodiments, the particles, compositions, and methods described herein are useful in the delivery of an angiogenesis inhibitor, such as those described above, into the eye for the treatment of macular degeneration, other retinal disorders, or other conditions described herein. In some embodiments, the pharmaceutical agent that is delivered into the eye by the particles, compositions, and methods described herein may be a prostaglandin analog. In certain embodiments, the pharmaceutical agent is latanoprost, travoprost, unoprostone, or bimatoprost.

[000408] In some embodiments, the pharmaceutical agent in a particle, composition and/or formulation described herein is an RTK inhibitor. In certain embodiments, the pharmaceutical agent is sorafenib. For example, as described in more detail in Examples 21, 25, and 29, administration of particles of sorafenib that included certain surface-altering agents described herein resulted in markedly higher sorafenib levels in various ocular tissues (*e.g.*, tissues at the back of the eye) in rabbits, compared to an equivalent dose of particles of sorafenib that do not include a suitable surface-altering agent.

[000409] In certain embodiments, the pharmaceutical agent in a particle, composition and/or formulation described herein is linifanib. For example, as described in more detail in the Example 29, administration of MPPs containing linifanib enhanced the exposure of linifanib at the back of the eye of rabbits.

[000410] In certain embodiments, the pharmaceutical agent in a particle, composition and/or formulation described hereinisMGCD-265. For example, as described in more detail in the Example 30, administration of MPPs containing MGCD-265 resulted in therapeutically-relevant levels of MGCD-265 at the back of the eye of rabbits.

[000411] In certain embodiments, the pharmaceutical agent in a particle, composition and/or formulation described herein is pazopanib. For example, as described in more detail in the Example 30, administration of MPPs containing pazopanib generated therapeutically relevant levels of pazopanib at the back of the eye of rabbits.

[000412] In certain embodiments, the pharmaceutical agent in a particle, composition and/or formulation described herein is cediranib. For example, as described in more detail in the Example 31, a single topical administration of cediranib-MPPs produced therapeutically relevant cediranib levels at the back of the eye of rabbits for 24 hours.

[000413] In certain embodiments, the pharmaceutical agent in a particle, composition and/or formulation described herein is axitinib. For example, as described in more detail in the Examples 32 and 33, a single topical administration of axitinib-MPP resulted in therapeutically relevant axitinib levels at the back of the eye of rabbits for 24 hours, and axitinib-MPP reduced vascular leakage in a rabbit VEGF (vascular endothelial growth factor receptor)-challenge model.

[000414] The results described above and herein suggest that the particles, compositions, and/or formulations described herein may be administered topically to achieve and sustain therapeutic effect in treating AMD, other retinal disorders, or other conditions described herein, compared to certain marketed formulations such as those which must be injected into the eye.

[000415] In certain embodiments, the particles, compositions, and methods described herein are useful in the delivery of a prostaglandin analog, such as one described above, into the eye for the treatment of glaucoma or other condition described herein.

[000416] In some embodiments, the pharmaceutical agent that is delivered into the eye by the particles, compositions, and methods described herein may be a beta blocker. In certain embodiments, the pharmaceutical agent is a non-selective beta blocker (*e.g.*, alprenolol, bucindolol, carteolol, carvedilol, labetalol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, timolol, and eucommia bark). In certain embodiments, the pharmaceutical agent is a β_1-selective blocker (*e.g.*, acebutolol, atenolol, betaxolol, bisoprolol, celiprolol, esmolol, metoprolol, and nebivolol). In certain embodiments, the pharmaceutical agent is a β_2-selective blocker (*e.g.*, butaxamine and ICI-118,551). In certain embodiments, the pharmaceutical agent is a β_3-selective blocker (*e.g.*, SR 59230A).

[000417] In certain embodiments, the particles, compositions, and methods described herein are useful in the delivery of a beta blocker, such as one described above, into the eye for the treatment of glaucoma or other condition described herein.

[000418] In certain embodiments, the pharmaceutical agent that is delivered into the eye by the particles, compositions, and methods of the present invention may be a carbonic anhydrase inhibitor. In certain embodiments, the pharmaceutical agent is acetazolamide, brinzolamide, dorzolamide, dorzolamide and timolol, or methazolamide.

[000419] In certain embodiments, the particles, compositions, and methods described herein are useful in the delivery of a carbonic anhydrase inhibitor, such as those described above, into the eye for the treatment of glaucoma or other conditions described herein. As described herein, in some embodiments, the particles, compositions, and/or formulations described herein can improve or increase ocular bioavailability, defined as the area under the curve (AUC) of drug concentration in an ocular tissue of interest against time after administration, of a pharmaceutical agent that is administered topically to an eye of a subject compared to certain existing particles, compositions, and/or formulations. In some embodiments, the ocular bioavailability of the pharmaceutical agent may increase due to, at least in part, a coating on core particles comprising the pharmaceutical agent that renders the particles mucus penetrating, compared to particles of the pharmaceutical agent of similar size as the coated particle in question, but which does not include the coating.

[000420] In some embodiments, the particles, compositions, and/or formulations described herein increase the ocular bioavailability of a pharmaceutical agent by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about

60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 150%, at least about 200%, at least about 5 fold, at least about 10 fold, at least about 20 fold, at least about 50 fold, at least about 100 fold, at least about 500 fold, or at least about 1000 fold. In certain the particles, compositions, and/or formulations described herein increase the ocular bioavailability of a pharmaceutical agent by less than or equal to about 1000 fold, less than or equal to about 500 fold, less than or equal to about 100 fold, less than or equal to about 50 fold, less than or equal to about 20 fold, less than or equal to about 10 fold, less than or equal to about 5 fold, less than or equal to about 200%, less than or equal to about 150%, less than or equal to about 100%, less than or equal to about 90%, less than or equal to about 80%, less than or equal to about 70%, less than or equal to about 60%, less than or equal to about 50%, less than or equal to about 40%, less than or equal to about 30%, less than or equal to about 20%, or less than or equal to about 10%. Combinations of the above-referenced ranges are also possible (*e.g.,* an increase of at least about 10% and less than or equal to about 10 fold). Other ranges are also possible. In some instances, the AUC of a pharmaceutical agent increases at a tissue and/or fluid in the front of the eye. In other instances, the AUC of a pharmaceutical agent increases at a tissue and/or fluid in the back of the eye.

[000421] In general, an increase in ocular bioavailability may be calculated by taking the difference in the AUC measured in an ocular tissue of interest (*e.g.,* in aqueous humor) between those of a test composition and a control composition, and dividing the difference by the bioavailability of the control composition. A test composition may include particles comprising a pharmaceutical agent, and the particles may be characterized as being mucus penetrating (*e.g.,* having a relative velocity in mucus of greater than about 0.5, or another other relative velocity described herein). A control composition may include particles comprising the same pharmaceutical agent as that present in the test composition, the particles having a substantially similar size as those of the test composition, but which are not mucus penetrating (*e.g.,* having a relative velocity in mucus of less than or equal to about 0.5, or another other relative velocity described herein).

[000422] Ocular bioavailability of a pharmaceutical agent may be measured in an appropriate animal model (*e.g.* in a New Zealand white rabbit model). The concentration of a

pharmaceutical agent and, when appropriate, its metabolite(s), in appropriate ocular tissues or fluids is measured as a function of time after administration.

[000423] Other methods of measuring ocular bioavailability of a pharmaceutical agent are possible.

[000424] As described herein, in some embodiments, the concentration of a pharmaceutical agent in an ocular tissue and/or fluid may be increased when the pharmaceutical agent is delivered (*e.g.*, via topical administration to the eye) using the particles, compositions, and/or formulations described herein compared to when the pharmaceutical agent is delivered using certain existing particles, compositions, and/or formulations that contain the same the pharmaceutical agent (or compared to the delivery of the same pharmaceutical agent (*e.g.,* of similar size) as the coated particle in question, but which does not include the coating). In certain embodiments, a dose of the particles, compositions, and/or formulations is administered, followed by the measurement of the concentration of the pharmaceutical agent in a tissue and/or fluid of the eye. For purposes of comparison, the amount of the pharmaceutical agent included in the administered dose of the particles, compositions, and/or formulations described herein may be similar or substantially equal to the amount of the pharmaceutical agent included in the administered dose of the existing particles, compositions, and/or formulations. In certain embodiments, the concentration of the pharmaceutical agent in a tissue and/or fluid of the eye is measured at a certain time subsequent to the administration ("time post-dose") of a dose of the particles, compositions, and/or formulations described herein or of the existing particles, compositions, and/or formulations. In certain embodiments, the time when the concentration is measured is about 1 min, about 10 min, about 30 min, about 1 h, about 2 h, about 3 h, about 4 h, about 5 h, about 6 h, about 7 h, about 8 h, about 9 h, about 10 h, about 11 h, about 12 h, about 18 h, about 24 h, about 36 h, or about 48 h, post-dose.

[000425] In some embodiments, the concentration of the pharmaceutical agent in a tissue and/or fluid may increase due to, at least in part, a coating on core particles comprising the pharmaceutical agent that renders the particles mucus penetrating, compared to particles of the same pharmaceutical agent (*e.g.,* of similar size) as the coated particle in question, but which does not include the coating. In some embodiments, the particles, compositions, and/or formulations described herein increases the concentration of a pharmaceutical agent in a

tissue and/or fluid by at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 200%, at least about 300%, at least about 400%, at least about 500%, or at least about 10 fold, at least about 20 fold, at least about 50 fold, at least about 100 fold, at least about 1000 fold, at least about 10^4 fold, at least about 10^5 fold, or at least about 10^6 fold. In some cases, the particles, compositions, and/or formulations described herein increases the concentration of a pharmaceutical agent in a tissue and/or fluid by less than or equal to about 10^6 fold, less than or equal to about 10^5 fold, less than or equal to about 10^4 fold, 1000 fold, less than or equal to about 100 fold, less than or equal to about 10 fold, less than or equal to about 500%, less than or equal to about 400%, less than or equal to about 300%, less than or equal to about 200%, less than or equal to about 100%, less than or equal to about 90%, less than or equal to about 80%, less than or equal to about 70%, less than or equal to about 60%, less than or equal to about 50%, less than or equal to about 40%, less than or equal to about 30%, less than or equal to about 20%, or less than or equal to about 10%. Combinations of the above-referenced ranges are also possible (*e.g.,* an increase of greater than or equal to about 10% and less than or equal to about 90%). Other ranges are also possible. In some instances, the concentration of a pharmaceutical agent increases at a tissue and/or fluid in the front of the eye. In other instances, the concentration of a pharmaceutical agent increases at a tissue and/or fluid in the back of the eye.

[000426] The ocular concentration of a pharmaceutical agent, and, when appropriate, its metabolite(s), in appropriate ocular fluids or tissues may be measured as a function of time *in vivo* using an appropriate animal model. One method of determining the ocular concentration of a pharmaceutical agent involves dissecting of the eye to isolate tissues of interest (*e.g.*, in a animal model comparable to the subject). The concentration of the pharmaceutical agent in the tissues of interest is then determined by HPLC or LC/MS analysis.

[000427] In certain embodiments, the period of time between administration of the particles described herein and obtaining a sample for measurement of concentration or AUC is less than about 1 hour, less than or equal to about 2 hours, less than or equal to about 3 hours, less than or equal to about 4 hours, less than or equal to about 6 hours, less than or equal to about 12 hours, less than or equal to about 36 hours, or less than or equal to about 48 hours. In certain embodiments, the period of time is at least about 1 hour, at least about 2 hours, at least

about 3 hours, at least about 4 hours, at least about 6 hours, at least about 8 hours, at least about 12 hours, at least about 36 hours, or at least about 48 hours. Combinations of the above-referenced ranges are also possible (*e.g.,* a period of time between consecutive doses of greater than or equal to about 3 hours and less than or equal to about 12 hours). Other ranges are also possible.

[000428] Other methods of measuring the concentration of a pharmaceutical agent in an eye of a subject or an animal model are also possible. In some embodiments, the concentration of a pharmaceutical agent may be measured in the eye of the subject directly or indirectly (*e.g.,* taking a sample of fluid, such as vitreous humor, from an eye of the subject).

[000429] In general, an increase in concentration of a pharmaceutical agent in an ocular site may be calculated by taking the difference in concentration measured between those of a test composition and a control composition, and dividing the difference by the concentration of the control composition. A test composition may include particles comprising a pharmaceutical agent, and the particles may be characterized as being mucus penetrating (*e.g.,* having a relative velocity of greater than about 0.5, or another other relative velocity described herein). A control composition may include particles comprising the same pharmaceutical agent as that present in the test composition, the particles having a substantially similar size as those of the test composition, but which are not mucus penetrating (*e.g.,* having a relative velocity of less than about 0.5, or another other relative velocity described herein).

[000430] As described herein, in some embodiments, the particles, compositions, and/or formulations described herein, or a component thereof, is present in a sufficient amount to increase the bioavailability and/or concentration of a pharmaceutical agent in an ocular tissue, compared to the pharmaceutical agent administered to the ocular tissue in the absence of the particles, compositions, and formulations described herein, or a component thereof.

[000431] The ocular tissue may be an ocular tissue described herein, such as an anterior ocular tissue (*e.g.*, a palpebral conjunctiva, a bulbar conjunctiva, or a cornea). The pharmaceutical agent may be any suitable agent as described herein, such as a corticosteroid (*e.g.*, loteprednol etabonate), an RTK inhibitor (*e.g.*, sorafenib, linifanib, MGCD-265, pazopanib, cediranib, and axitinib), an NSAID (*e.g.*, bromfenac calcium), or a cox inhibitor (*e.g.*, bromfenac calcium).In certain embodiments, the core particle of a formulation

comprising a pharmaceutical agent is present in a sufficient amount to increase the bioavailability and/or concentration of the pharmaceutical agent in an ocular tissue. In certain embodiments, the coating on the core particle of a formulation comprising a pharmaceutical agent is present in a sufficient amount to increase the bioavailability and/or concentration of the pharmaceutical agent in an ocular tissue. In certain embodiments, the coating on the core particle of a formulation comprising a pharmaceutical agent is present in a sufficient amount to increase the concentration of the pharmaceutical agent in an ocular tissue after at least 10 minutes, at least 20 minutes, at least 30 minutes, at least 1 hour, at least 2 hours, at least 3 hours, at least 4 hours, at least 6 hours, at least 9 hours, at least 12 hours, at least 18 hours, or at least 24 hours after administration of the formulation to the ocular tissue. In certain embodiments, the coating on the core particle of a formulation comprising a pharmaceutical agent is present in a sufficient amount to increase the concentration of the pharmaceutical agent in an ocular tissue after less than or equal to 24 hours, less than or equal to 18 hours, less than or equal to 12 hours, less than or equal to 9 hours, less than or equal to 6 hours, less than or equal to 4 hours, less than or equal to 3 hours, less than or equal to 2 hours, less than or equal to 1 hour, less than or equal to 30 minutes, less than or equal to 20 minutes, or less than or equal to 10 minutes after administration of the formulation to the ocular tissue. Combinations of the above-referenced ranges are also possible (*e.g.*, the concentration of the pharmaceutical agent increases after at least 10 minutes and less than or equal to 2 hours). Other ranges are also possible. In certain embodiments, the coating on the core particle of a formulation comprising a pharmaceutical agent is present in a sufficient amount to increase the concentration of the pharmaceutical agent in an ocular tissue after about 30 minutes after administration of the formulation to the ocular tissue.

[000432] As described herein, in some embodiments, the particles, compositions, and/or formulations described herein can be administered topically to an eye of a subject in various forms of doses. For example, the particles, compositions, and/or formulations described herein may be administered in a single unit dose or repeatedly administered in a plurality of single unit doses. A unit dose is a discrete amount of the particles, compositions, and/or formulations described herein comprising a predetermined amount of a pharmaceutical agent. In some embodiments, fewer numbers of doses (*e.g.*, 1/2, 1/3, or 1/4 the number doses) are

required using the particles described herein having a mucus-penetrating coating compared to particles that do not have such a coating.

[000433] The exact amount of the particles, compositions, and/or formulations described herein required to achieve a therapeutically or prophylactically effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound, mode of administration, and the like. The particles, compositions, and/or formulations described herein can be delivered using repeated administrations where there is a period of time between consecutive doses. Repeated administration may be advantageous because it may allow the eye to be exposed to a therapeutically or prophylactically effective amount of a pharmaceutical agent for a period of time that is sufficiently long for the ocular condition to be treated, prevented, or managed. In certain embodiments, the period of time between consecutive doses is less than or equal to about 1 hour, less than or equal to about 2 hours, less than or equal to about 3 hours, less than or equal to about 4 hours, less than or equal to about 6 hours, less than or equal to about 12 hours, less than or equal to about 36 hours, or less than or equal to about 48 hours. In certain embodiments, the period of time between consecutive doses is at least about 1 hour, at least about 2 hours, at least about 3 hours, at least about 4 hours, at least about 6 hours, at least about 12 hours, at least about 36 hours, or at least about 48 hours. Combinations of the above-referenced ranges are also possible (*e.g.*, a period of time between consecutive doses of greater than or equal to about3 hours and less than or equal to about 12 hours). Other ranges are also possible.

[000434] Delivery of the particles, compositions, and/or formulations described herein to an ocular tissue may result in ophthalmically efficacious drug levels in the ocular tissue for an extended period of time after administration (*e.g.*, topical administration or administration by direct injection). An ophthalmically efficacious level of a drug refers to an amount sufficient to elicit the desired biological response of an ocular tissue, *i.e.*, treating an ocular disease. As will be appreciated by those skilled in this art, the ophthalmically efficacious level of a drug may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the drug, the ocular disease being treated, the mode of administration, and the age and health of the subject. In certain embodiments, the ophthalmically efficacious level of a drug is an amount of the drug, alone or in combination with other therapies, which provides a

therapeutic benefit in the treatment of the ocular condition. The ophthalmically efficacious level of a drug can encompass a level that improves overall therapy, reduces or avoids symptoms or causes of the ocular condition, or enhances the therapeutic efficacy of another therapeutic agent.

[000435] In some embodiments, an ophthalmically efficacious drug level may be gauged, at least in part, by the maximum concentration (C_{max}) of the pharmaceutical agent in the ocular tissue after administration. In some cases, delivery of the particles, compositions, and/or formulations comprising a pharmaceutical agent as described herein to an ocular tissue may result in a higher C_{max} of the pharmaceutical agent in the ocular tissue after administration, compared to marketed particles, compositions, and formulations at similar doses. In certain embodiments, the C_{max} obtained from an administration of the particles, compositions, and/or formulations described herein is at least about 3%, at least about 10%, at least about 30%, at least about 100%, at least about 200%, at least about 300%, at least about 400%, at least about 500%, at least about 1000%, or at least about 3000%, higher than the C_{max} obtained from an administration of the marketed particles, compositions, and/or formulations. In certain embodiments, the C_{max} obtained from an administration of the particles, compositions, and/or formulations described herein is less than or equal to about 3000%, less than or equal to about 1000%, less than or equal to about 500%, less than or equal to about 400%, less than or equal to about 300%, less than or equal to about 200%, less than or equal to about 100%, less than or equal to about 30%, less than or equal to about 10%, or less than or equal to about 3%, higher than the C_{max} obtained from an administration of the marketed particles, compositions, and/or formulations. Combinations of the above-referenced ranges are also possible (*e.g.*, an increase in C_{max} at least about 30% and less than or equal to about 500%). Other ranges are also possible.

[000436] In some embodiments, the ophthalmically efficacious drug levels are gauged, at least in part, by minimally efficacious concentrations of the drug, *e.g.*, IC_{50}or IC_{90}, as known in the art.

[000437] In certain embodiments in which ophthalmically efficacious drug levels (or C_{max}, IC_{50}, or IC_{90}) are present in the ocular tissue for an extended period of time after administration, the extended period of time after administration can range from hours to days. In certain embodiments, the extended period of time after administration is at least 1 hour, at

least 2 hours, at least 4 hours, at least 6 hours, at least 9 hours, at least 12 hours, at least 1 day, at least 2 days, at least 3 days, at least 4 days, at least 5 days, at least 6 days, or at least 1 week. In certain embodiments, the extended period of time after administration is less than or equal to 1 week, less than or equal to 6 days, less than or equal to 5 days, less than or equal to 4 days, less than or equal to 3 days, less than or equal to 2 days, less than or equal to 1 day, less than or equal to 12 hours, less than or equal to 9 hours, less than or equal to 6 hours, less than or equal to 4 hours, less than or equal to 2 hours, less than or equal to 1 hour. Combinations of the above-referenced ranges are also possible (*e.g.*, an extended period of time of at least about 4 hours and less than or equal to about 1 week). Other ranges are also possible.

[000438] In certain embodiments, the particles, compositions, and/or formulations described herein may be at dosage levels sufficient to deliver an effective amount of a pharmaceutical agent to an eye of a subject to obtain a desired therapeutic or prophylactic effect. In certain embodiments, an effective amount of a pharmaceutical agent that is delivered to an appropriate eye tissue is at least about 10^{-3} ng/g, at least about 10^{-2} ng/g, at least about 10^{-1} ng/g, at least about 1 ng/g, at least about 10^{1} ng/g, at least about 10^{2} ng/g, at least about 10^{3} ng/g, at least about 10^{4} ng/g, at least about 10^{5} ng/g, or at least about 10^{6} ng/g of tissue weight. In certain embodiments, an effective amount of a pharmaceutical agent that is delivered to the eye is less than or equal to about 10^{6} ng/g, less than or equal to about 10^{5} ng/g, less than or equal to about 10^{4} ng/g, less than or equal to about 10^{3} ng/g, less than or equal to about 10^{2} ng/g, less than or equal to about 10^{1} ng/g, less than or equal to about 1 ng/g, less than or equal to about 10^{-1} ng/g, less than or equal to about 10^{-2} ng/g, or less than or equal to about 10^{-3} ng/g of tissue weight. Combinations of the above-referenced ranges are also possible (*e.g.*, an effective amount of a pharmaceutical agent of at least about 10^{-2} ng/g and less than or equal to about 10^{3} ng/g of tissue weight). Other ranges are also possible. In certain embodiments, the particles, compositions, and/or formulations described herein may be at dosage levels sufficient to deliver an effective amount of a pharmaceutical agent to the back of an eye of a subject to obtain a desired therapeutic or prophylactic effect.

[000439] It will be appreciated that dose ranges as described herein provide guidance for the administration of provided particles, compositions, and/or formulations to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a

medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[000440] The particles, compositions, and/or formulations described herein may be topically administered by any method, for example, as by drops, powders, ointments, or creams. Other topical administration approaches or forms are also possible.

[000441] In certain embodiments, the compositions and/or formulations described herein are packaged as a ready to use shelf stable suspension. Eye drop formulations are traditionally liquid formulations (solutions or suspensions) which can be packaged in dropper bottles (which dispense a standard drop volume of liquid) or in individual use droppers (typically used for preservative free drops; used once and disposed). These formulations are ready to use and can be self-administered. In some cases the bottle should be shaken before use to ensure homogeneity of the formulation, but no other preparation may be necessary. This may be the simplest and most convenient method of ocular delivery. The compositions and/or formulations described herein can be packaged in the same way as traditional eye drop formulations. They can be stored in suspension and may retain the characteristics which allow the particles to avoid adhesion to mucus.

[000442] The pharmaceutical agent may be one of those pharmaceutical agents described herein. In certain embodiments, the pharmaceutical agent is an NSAID, an RTK inhibitor, a cox inhibitor, a corticosteroid, an angiogenesis inhibitor, a prostaglandin analog, a beta blocker, or a carbonic anhydrase inhibitor. In certain embodiments, the pharmaceutical agent is loteprednol etabonate. In certain embodiments, the pharmaceutical agent is sorafenib. In certain embodiments, the pharmaceutical agent is linifanib. In certain embodiments, the pharmaceutical agent is MGCD-265. In certain embodiments, the pharmaceutical agent is pazopanib. In certain embodiments, the pharmaceutical agent is cediranib. In certain embodiments, the pharmaceutical agent is axitinib. In certain embodiments, the pharmaceutical agent is a divalent metal salt of bromfenac (*e.g.*, bromfenac calcium). In certain embodiments, the pharmaceutical agent is bromfenac beryllium, bromfenac magnesium, bromfenac strontium, or bromfenac barium, bromfenac zinc, or bromfenac copper(II). Other pharmaceutical agents are also possible.

[000443] In one set of embodiments, a pharmaceutical composition suitable for administration to an eye is provided. The pharmaceutical composition comprises a plurality

of coated particles, comprising a core particle comprising or formed of A) a pharmaceutical agent or a salt thereof, wherein A) the pharmaceutical agent or a salt thereof constitutes at least about 80 wt% of the core particle, and a coating comprising or formed of one or more B) surface-altering agents surrounding the core particle. The one or more surface altering agents is present on the outer surface of the core particle at C) a density of at least 0.01 molecules/nm^2. The one or more surface altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight. The plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron. The pharmaceutical composition also includes one or more ophthalmically acceptable carriers, additives, and/or diluents. Methods of use and administration of such pharmaceutical compositions to the eye are also provided.

[000444] In some embodiments, A) a pharmaceutical agent or a salt thereof can be selected from: A1) a corticosteroid, A2) a glucocorticoid receptor agonist (SEGRAs), A3) an RTK inhibitor, A4) an NSAID, A5) an mTOR inhibitor, A6) a calcineurin inhibitor, A7) a prostanoid, A8) a rho kinase inhibitor, A9) a riboflavin, A10) a Cox-2 inhibitor, A11) an angiogenesis inhibitor, A12) a prostaglandin analog, A13) a beta blocker, A14) a carbonic anhydrase inhibitor, A15) an antihistamine, A16) a mast cell stabilizer, A17) an immunosuppressant, A18) an alpha-blocker, A19) an antibiotic, and combinations thereof.

[000445] In some embodiments, B) a surface-altering agent can be selected from: B1) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer (e.g., certain poloxamers), B2) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed (e.g., poly(vinyl alcohol), a partially hydrolyzed poly(vinyl acetate) or a copolymer of vinyl alcohol and vinyl acetate), B3) a polysorbate, B4) an octylphenol ethoxylate surfactant, B5) a polyoxyethylene hydroxystearate, B6) a polyoxyethylene castor oil derivative, B7) an alkyl aryl polyether alcohol, B8) a polyethylene glycol succinate, B9) a polyoxyethylene alkyl ether, and combinations thereof.

[000446] In certain embodiments, A1) a corticosteroid can be selected from: A1a) loteprednol etabonate, A1b) dexamethasone, A1c) triamcinolone, A1d) flucinolide, A1e) prednisolone, A1f) fluormethalone, A1g) difluprednate, A1h) fluticasone, and combinations thereof.

[000447] In certain embodiments, A2) a glucocorticoid receptor agonist can be selected from: A2a) mapracorat, A2b) rimexolone, and combinations thereof.

[000448] In certain embodiments, A3) an RTK inhibitor can be selected from: A3a) sorafenib, A3b) linifanib, A3c) MGCD-265 (MethylGene), A3d) pazopanib, A3e) cediranib, A3f) axitinib, and combinations thereof.

[000449] In certain embodiments, A4) an NSAID can be selected from: A4a) nepafanac, A4b) bromfenac (e.g., bromfenac calcium), A4c) diclofenac (e.g., diclofenac free acid), A4d) ketorolac (e.g., ketorolac free acid), and combinations thereof.

[000450] In certain embodiments, A5) an mTOR inhibitor can be selected from: A5a) tacrolimus, A5b) sirolimus, and combinations thereof.

[000451] In certain embodiments, A6) a calcineurin inhibitor can be selected from: A6a) cyclosporine, A6b) voclosporin, and combinations thereof.

[000452] In certain embodiments, A7) a prostanoid can be selected from: A7a) latanoprost, A7b) bimatoprost, A7c) travoprost, and combinations thereof.

[000453] In certain embodiments, A8) a rho kinase inhibitor can be selected from: A8a) SNJ-1656, A8b) AR-12286, A8c) AR-13324, and combinations thereof.

[000454] In certain embodiments, A10) a Cox-2 inhibitor can be selected from: A10a) celecoxib, A10b) valdecoxib, and combinations thereof.

[000455] In certain embodiments, B1) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer, can be selected from: B1a) a poloxamer, B1b) Pluronic F127, B1c) Pluronic P123, B1d) Pluronic P103, B1e) Pluronic P105, B1f) Pluronic F108, and combinations thereof.

[000456] In certain embodiments, B2) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30%

hydrolyzed and less than about 95% hydrolyzed, can be selected from: B2a) a polyvinyl alcohol, B2b) PVA 13K87, B2c) PVA 31K98, B2d) PVA 31K87, B2e) PVA 9K80, B2f) PVA 2K75, B2g) PVA 57K87, B2h) PVA 85K87, B2i) PVA105K80, B2j) PVA130K87, and combinations thereof.

[000457] In certain embodiments, B3) a polysorbate can be selected from: B3a) Tween 20, B3b) Tween 80, and combinations thereof.

[000458] In certain embodiments, B4) an octylphenol ethoxylate surfactant can be: B4a) Triton X100.

[000459] In certain embodiments, B5) a polyoxyethylene hydroxystearate can be: B5a) Solutol HS 15.

[000460] In certain embodiments, B6) a polyoxyethylene castor oil derivative can be selected from: B6a) Cremophor EL, B6b) Cremophor RH 40, and combinations thereof.

[000461] In certain embodiments, B7) an alkyl aryl polyether alcohol can be: B7a) Tyloxapol.

[000462] In certain embodiments, B8) a polyethylene glycol succinate can be: B8a) Vitamin E-TPGS.

[000463] In certain embodiments, B9) a polyoxyethylene alkyl ether can be selected from: B9a) Brij 35, B9b) Brij 98, B9c) Brij S100, and combinations thereof.

[000464] In certain embodiments, C) the density of the one or more surface altering agents present on the outer surface of the core particle can be selected from: C1) a density of at least 0.01 molecules/nm^2, C2) a density of at least 0.05 molecules/nm^2, C3) a density of at least 0.1 molecules/nm^2, C4) a density of at least 0.15 molecules/nm^2, or C5) a density of at least 0.2 molecules/nm^2.

[000465] It should be appreciated that any combination of the herein-disclosed A) pharmaceutical agent or a salt thereof (e.g., A1-A19 and species thereof identified herein), B) surface-altering agent (e.g., B1-B9 and species thereof identified herein), and/or C) density of the one or more surface altering agents present on the outer surface of the core particle (e.g., C1-C5), may be present in a composition and/of formulation described herein. In addition, such combinations may be present in conjunction with parameters described herein such as particular ranges or values of wt% of surface-altering agent, average size or smallest cross-

sectional dimension of the coated particles, pH, thickness of coating, PDI, types of carriers and diluents, etc.

[000466] In some embodiments, the combination of A) pharmaceutical agent or a salt thereof and B) surface-altering agent in the pharmaceutical composition may be selected from: A1, B1 (i.e., A1 and B1); A1, B2; A1, B3; A1, B4; A1, B5; A1, B6; A1, B7; A1, B8; A1, B9; A2, B1; A2, B2; A2, B3; A2, B4; A2, B5; A2, B6; A2, B7; A2, B8; A2, B9; A3, B1; A3, B2; A3, B3; A3, B4; A3, B5; A3, B6; A3, B7; A3, B8; A3, B9; A4, B1; A4, B2; A4, B3; A4, B4; A4, B5; A4, B6; A4, B7; A4, B8; A4, B9; A5, B1; A5, B2; A5, B3; A5, B4; A5, B5; A5, B6; A5, B7; A5, B8; A5, B9; A6, B1; A6, B2; A6, B3; A6, B4; A6, B5; A6, B6; A6, B7; A6, B8; A6, B9; A7, B1; A7, B2; A7, B3; A7, B4; A7, B5; A7, B6; A7, B7; A7, B8; A7, B9; A8, B1; A8, B2; A8, B3; A8, B4; A8, B5; A8, B6; A8, B7; A8, B8; A8, B9; A9, B1; A9, B2; A9, B3; A9, B4; A9, B5; A9, B6; A9, B7; A9, B8; A9, B9; A10, B1; A10, B2; A10, B3; A10, B4; A10, B5; A10, B6; A10, B7; A10, B8; A10, B9; A11, B1; A11, B2; A11, B3; A11, B4; A11, B5; A11, B6; A11, B7; A11, B8; A11, B9; A12, B1; A12, B2; A12, B3; A12, B4; A12, B5; A12, B6; A12, B7; A12, B8; A12, B9; A13, B1; A13, B2; A13, B3; A13, B4; A13, B5; A13, B6; A13, B7; A13, B8; A13, B9; A14, B1; A14, B2; A14, B3; A14, B4; A14, B5; A14, B6; A14, B7; A14, B8; A14, B9; A15, B1; A15, B2; A15, B3; A15, B4; A15, B5; A15, B6; A15, B7; A15, B8; A15, B9; A16, B1; A16, B2; A16, B3; A16, B4; A16, B5; A16, B6; A16, B7; A16, B8; A16, B9; A17, B1; A17, B2; A17, B3; A17, B4; A17, B5; A17, B6; A17, B7; A17, B8; A17, B9; A18, B1; A18, B2; A18, B3; A18, B4; A18, B5; A18, B6; A18, B7; A18, B8; A18, B9; A19, B1; A19, B2; A19, B3; A19, B4; A19, B5; A19, B6; A19, B7; A19, B8; A19, B9; and combinations thereof.

[000467] In some embodiments, the combination of A) pharmaceutical agent or a salt thereof and B) surface-altering agent in the pharmaceutical composition may be selected from: A1, B1a; A1, B1b; A1, B1c; A1, B1d; A1, B1e; A1, B1f; A1, B2a; A1, B2b; A1, B2c; A1, B2d; A1, B2e; A1, B2f; A1, B2g; A1, B2h; A1, B2i; A1, B2j; A1, B3a; A1, B3b; A1, B4a; A1, B5a; A1, B6a; A1, B6b; A1, B7a; A1, B8a; A1, B9a; A1, B9b; A1, B9c; A2, B1a; A2, B1b; A2, B1c; A2, B1d; A2, B1e; A2, B1f; A2, B2a; A2, B2b; A2, B2c; A2, B2d; A2, B2e; A2, B2f; A2, B2g; A2, B2h; A2, B2i; A2, B2j; A2, B3a; A2, B3b; A2, B4a; A2, B5a; A2, B6a; A2, B6b; A2, B7a; A2, B8a; A2, B9a; A2, B9b; A2, B9c; A3, B1a; A3, B1b; A3, B1c; A3, B1d; A3, B1e; A3, B1f; A3, B2a; A3, B2b; A3, B2c; A3, B2d; A3, B2e; A3, B2f;

A3, B2g; A3, B2h; A3, B2i; A3, B2j; A3, B3a; A3, B3b; A3, B4a; A3, B5a; A3, B6a; A3, B6b; A3, B7a; A3, B8a; A3, B9a; A3, B9b; A3, B9c; A4, B1a; A4, B1b; A4, B1c; A4, B1d; A4, B1e; A4, B1f; A4, B2a; A4, B2b; A4, B2c; A4, B2d; A4, B2e; A4, B2f; A4, B2g; A4, B2h; A4, B2i; A4, B2j; A4, B3a; A4, B3b; A4, B4a; A4, B5a; A4, B6a; A4, B6b; A4, B7a; A4, B8a; A4, B9a; A4, B9b; A4, B9c; A5, B1a; A5, B1b; A5, B1c; A5, B1d; A5, B1e; A5, B1f; A5, B2a; A5, B2b; A5, B2c; A5, B2d; A5, B2e; A5, B2f; A5, B2g; A5, B2h; A5, B2i; A5, B2j; A5, B3a; A5, B3b; A5, B4a; A5, B5a; A5, B6a; A5, B6b; A5, B7a; A5, B8a; A5, B9a; A5, B9b; A5, B9c; A6, B1a; A6, B1b; A6, B1c; A6, B1d; A6, B1e; A6, B1f; A6, B2a; A6, B2b; A6, B2c; A6, B2d; A6, B2e; A6, B2f; A6, B2g; A6, B2h; A6, B2i; A6, B2j; A6, B3a; A6, B3b; A6, B4a; A6, B5a; A6, B6a; A6, B6b; A6, B7a; A6, B8a; A6, B9a; A6, B9b; A6, B9c; A7, B1a; A7, B1b; A7, B1c; A7, B1d; A7, B1e; A7, B1f; A7, B2a; A7, B2b; A7, B2c; A7, B2d; A7, B2e; A7, B2f; A7, B2g; A7, B2h; A7, B2i; A7, B2j; A7, B3a; A7, B3b; A7, B4a; A7, B5a; A7, B6a; A7, B6b; A7, B7a; A7, B8a; A7, B9a; A7, B9b; A7, B9c; A8, B1a; A8, B1b; A8, B1c; A8, B1d; A8, B1e; A8, B1f; A8, B2a; A8, B2b; A8, B2c; A8, B2d; A8, B2e; A8, B2f; A8, B2g; A8, B2h; A8, B2i; A8, B2j; A8, B3a; A8, B3b; A8, B4a; A8, B5a; A8, B6a; A8, B6b; A8, B7a; A8, B8a; A8, B9a; A8, B9b; A8, B9c; A9, B1a; A9, B1b; A9, B1c; A9, B1d; A9, B1e; A9, B1f; A9, B2a; A9, B2b; A9, B2c; A9, B2d; A9, B2e; A9, B2f; A9, B2g; A9, B2h; A9, B2i; A9, B2j; A9, B3a; A9, B3b; A9, B4a; A9, B5a; A9, B6a; A9, B6b; A9, B7a; A9, B8a; A9, B9a; A9, B9b; A9, B9c; A10, B1a; A10, B1b; A10, B1c; A10, B1d; A10, B1e; A10, B1f; A10, B2a; A10, B2b; A10, B2c; A10, B2d; A10, B2e; A10, B2f; A10, B2g; A10, B2h; A10, B2i; A10, B2j; A10, B3a; A10, B3b; A10, B4a; A10, B5a; A10, B6a; A10, B6b; A10, B7a; A10, B8a; A10, B9a; A10, B9b; A10, B9c; A11, B1a; A11, B1b; A11, B1c; A11, B1d; A11, B1e; A11, B1f; A11, B2a; A11, B2b; A11, B2c; A11, B2d; A11, B2e; A11, B2f; A11, B2g; A11, B2h; A11, B2i; A11, B2j; A11, B3a; A11, B3b; A11, B4a; A11, B5a; A11, B6a; A11, B6b; A11, B7a; A11, B8a; A11, B9a; A11, B9b; A11, B9c; A12, B1a; A12, B1b; A12, B1c; A12, B1d; A12, B1e; A12, B1f; A12, B2a; A12, B2b; A12, B2c; A12, B2d; A12, B2e; A12, B2f; A12, B2g; A12, B2h; A12, B2i; A12, B2j; A12, B3a; A12, B3b; A12, B4a; A12, B5a; A12, B6a; A12, B6b; A12, B7a; A12, B8a; A12, B9a; A12, B9b; A12, B9c; A13, B1a; A13, B1b; A13, B1c; A13, B1d; A13, B1e; A13, B1f; A13, B2a; A13, B2b; A13, B2c; A13, B2d; A13, B2e; A13, B2f; A13, B2g; A13, B2h; A13, B2i; A13, B2j; A13, B3a; A13, B3b; A13, B4a; A13, B5a; A13, B6a; A13, B6b; A13, B7a; A13, B8a;

A13, B9a; A13, B9b; A13, B9c; A14, B1a; A14, B1b; A14, B1c; A14, B1d; A14, B1e; A14, B1f; A14, B2a; A14, B2b; A14, B2c; A14, B2d; A14, B2e; A14, B2f; A14, B2g; A14, B2h; A14, B2i; A14, B2j; A14, B3a; A14, B3b; A14, B4a; A14, B5a; A14, B6a; A14, B6b; A14, B7a; A14, B8a; A14, B9a; A14, B9b; A14, B9c; A15, B1a; A15, B1b; A15, B1c; A15, B1d; A15, B1e; A15, B1f; A15, B2a; A15, B2b; A15, B2c; A15, B2d; A15, B2e; A15, B2f; A15, B2g; A15, B2h; A15, B2i; A15, B2j; A15, B3a; A15, B3b; A15, B4a; A15, B5a; A15, B6a; A15, B6b; A15, B7a; A15, B8a; A15, B9a; A15, B9b; A15, B9c; A16, B1a; A16, B1b; A16, B1c; A16, B1d; A16, B1e; A16, B1f; A16, B2a; A16, B2b; A16, B2c; A16, B2d; A16, B2e; A16, B2f; A16, B2g; A16, B2h; A16, B2i; A16, B2j; A16, B3a; A16, B3b; A16, B4a; A16, B5a; A16, B6a; A16, B6b; A16, B7a; A16, B8a; A16, B9a; A16, B9b; A16, B9c; A17, B1a; A17, B1b; A17, B1c; A17, B1d; A17, B1e; A17, B1f; A17, B2a; A17, B2b; A17, B2c; A17, B2d; A17, B2e; A17, B2f; A17, B2g; A17, B2h; A17, B2i; A17, B2j; A17, B3a; A17, B3b; A17, B4a; A17, B5a; A17, B6a; A17, B6b; A17, B7a; A17, B8a; A17, B9a; A17, B9b; A17, B9c; A18, B1a; A18, B1b; A18, B1c; A18, B1d; A18, B1e; A18, B1f; A18, B2a; A18, B2b; A18, B2c; A18, B2d; A18, B2e; A18, B2f; A18, B2g; A18, B2h; A18, B2i; A18, B2j; A18, B3a; A18, B3b; A18, B4a; A18, B5a; A18, B6a; A18, B6b; A18, B7a; A18, B8a; A18, B9a; A18, B9b; A18, B9c; A19, B1a; A19, B1b; A19, B1c; A19, B1d; A19, B1e; A19, B1f; A19, B2a; A19, B2b; A19, B2c; A19, B2d; A19, B2e; A19, B2f; A19, B2g; A19, B2h; A19, B2i; A19, B2j; A19, B3a; A19, B3b; A19, B4a; A19, B5a; A19, B6a; A19, B6b; A19, B7a; A19, B8a; A19, B9a; A19, B9b; A19, B9c; and combinations thereof.

[000468] In some embodiments, the combination of A) pharmaceutical agent or a salt thereof and B) surface-altering agent in the pharmaceutical composition may be selected from: A1a, B1; A1b, B1; A1c, B1; A1d, B1; A1e, B1; A1f, B1, A1g, B1; A1h, B1; A2a, B1; A2b, B1; A3a, B1; A3b, B1; A3c, B1; A3d, B1; A3e, B1, A3f, B1; A4a, B1; A4b, B1; A4c, B1; A4d, B1; A5a, B1; A5b, B1; A6a, B1; A6b, B1; A7a, B1; A7b, B1; A7c, B1; A8a, B1; A8b, B1; A8c, B1; A10a, B1; A10b, B1; A1a, B2; A1b, B2; A1c, B2; A1d, B2; A1e, B2; A1f, B2, A1g, B2; A1h, B2; A2a, B2; A2b, B2; A3a, B2; A3b, B2; A3c, B2; A3d, B2; A3e, B2, A3f, B2; A4a, B2; A4b, B2; A4c, B2; A4d, B2; A5a, B2; A5b, B2; A6a, B2; A6b, B2; A7a, B2; A7b, B2; A7c, B2; A8a, B2; A8b, B2; A8c, B2; A10a, B2; A10b, B2; A1a, B3; A1b, B3; A1c, B3; A1d, B3; A1e, B3; A1f, B3, A1g, B3; A1h, B3; A2a, B3; A2b, B3; A3a, B3; A3b, B3; A3c, B3; A3d, B3; A3e, B3, A3f, B3; A4a, B3; A4b, B3; A4c, B3; A4d, B3;

A5a, B3; A5b, B3; A6a, B3; A6b, B3; A7a, B3; A7b, B3; A7c, B3; A8a, B3; A8b, B3; A8c, B3; A10a, B3; A10b, B3; A1a, B4; A1b, B4; A1c, B4; A1d, B4; A1e, B4; A1f, B4, A1g, B4; A1h, B4; A2a, B4; A2b, B4; A3a, B4; A3b, B4; A3c, B4; A3d, B4; A3e, B4, A3f, B4; A4a, B4; A4b, B4; A4c, B4; A4d, B4; A5a, B4; A5b, B4; A6a, B4; A6b, B4; A7a, B4; A7b, B4; A7c, B4; A8a, B4; A8b, B4; A8c, B4; A10a, B4; A10b, B4; A1a, B5; A1b, B5; A1c, B5; A1d, B5; A1e, B5; A1f, B5, A1g, B5; A1h, B5; A2a, B5; A2b, B5; A3a, B5; A3b, B5; A3c, B5; A3d, B5; A3e, B5, A3f, B5; A4a, B5; A4b, B5; A4c, B5; A4d, B5; A5a, B5; A5b, B5; A6a, B5; A6b, B5; A7a, B5; A7b, B5; A7c, B5; A8a, B5; A8b, B5; A8c, B5; A10a, B5; A10b, B5; A1a, B6; A1b, B6; A1c, B6; A1d, B6; A1e, B6; A1f, B6, A1g, B6; A1h, B6; A2a, B6; A2b, B6; A3a, B6; A3b, B6; A3c, B6; A3d, B6; A3e, B6, A3f, B6; A4a, B6; A4b, B6; A4c, B6; A4d, B6; A5a, B6; A5b, B6; A6a, B6; A6b, B6; A7a, B6; A7b, B6; A7c, B6; A8a, B6; A8b, B6; A8c, B6; A10a, B6; A10b, B6; A1a, B7; A1b, B7; A1c, B7; A1d, B7; A1e, B7; A1f, B7, A1g, B7; A1h, B7; A2a, B7; A2b, B7; A3a, B7; A3b, B7; A3c, B7; A3d, B7; A3e, B7, A3f, B7; A4a, B7; A4b, B7; A4c, B7; A4d, B7; A5a, B7; A5b, B7; A6a, B7; A6b, B7; A7a, B7; A7b, B7; A7c, B7; A8a, B7; A8b, B7; A8c, B7; A10a, B7; A10b, B7; A1a, B8; A1b, B8; A1c, B8; A1d, B8; A1e, B8; A1f, B8, A1g, B8; A1h, B8; A2a, B8; A2b, B8; A3a, B8; A3b, B8; A3c, B8; A3d, B8; A3e, B8, A3f, B8; A4a, B8; A4b, B8; A4c, B8; A4d, B8; A5a, B8; A5b, B8; A6a, B8; A6b, B8; A7a, B8; A7b, B8; A7c, B8; A8a, B8; A8b, B8; A8c, B8; A10a, B8; A10b, B8; A1a, B9; A1b, B9; A1c, B9; A1d, B9; A1e, B9; A1f, B9, A1g, B9; A1h, B9; A2a, B9; A2b, B9; A3a, B9; A3b, B9; A3c, B9; A3d, B9; A3e, B9, A3f, B9; A4a, B9; A4b, B9; A4c, B9; A4d, B9; A5a, B9; A5b, B9; A6a, B9; A6b, B9; A7a, B9; A7b, B9; A7c, B9; A8a, B9; A8b, B9; A8c, B9; A10a, B9; A10b, B9; and combinations thereof.

[000469] In some embodiments, the combination of A) pharmaceutical agent or a salt thereof and B) surface-altering agent in the pharmaceutical composition may be selected from: A1a, B1a; A1a, B1b; A1a, B1c; A1a, B1d; A1a, B1e; A1a, B1f; A1a, B2a; A1a, B2b; A1a, B2c; A1a, B2d; A1a, B2e; A1a, B2f; A1a, B2g; A1a, B2h; A1a, B2i; A1a, B2j; A1a, B3a; A1a, B3b; A1a, B4a; A1a, B5a; A1a, B6a; A1a, B6b; A1a, B7a; A1a, B8a; A1a, B9a; A1a, B9b; A1a, B9c; A1b, B1a; A1b, B1b; A1b, B1c; A1b, B1d; A1b, B1e; A1b, B1f; A1b, B2a; A1b, B2b; A1b, B2c; A1b, B2d; A1b, B2e; A1b, B2f; A1b, B2g; A1b, B2h; A1b, B2i; A1b, B2j; A1b, B3a; A1b, B3b; A1b, B4a; A1b, B5a; A1b, B6a; A1b, B6b; A1b, B7a; A1b, B8a; A1b, B9a; A1b, B9b; A1b, B9c; A1c, B1a; A1c, B1b; A1c, B1c; A1c, B1d; A1c, B1e;

A1c, B1f; A1c, B2a; A1c, B2b; A1c, B2c; A1c, B2d; A1c, B2e; A1c, B2f; A1c, B2g; A1c, B2h; A1c, B2i; A1c, B2j; A1c, B3a; A1c, B3b; A1c, B4a; A1c, B5a; A1c, B6a; A1c, B6b; A1c, B7a; A1c, B8a; A1c, B9a; A1c, B9b; A1c, B9c; A1d, B1a; A1d, B1b; A1d, B1c; A1d, B1d; A1d, B1e; A1d, B1f; A1d, B2a; A1d, B2b; A1d, B2c; A1d, B2d; A1d, B2e; A1d, B2f; A1d, B2g; A1d, B2h; A1d, B2i; A1d, B2j; A1d, B3a; A1d, B3b; A1d, B4a; A1d, B5a; A1d, B6a; A1d, B6b; A1d, B7a; A1d, B8a; A1d, B9a; A1d, B9b; A1d, B9c; A1e, B1a; A1e, B1b; A1e, B1c; A1e, B1d; A1e, B1e; A1e, B1f; A1e, B2a; A1e, B2b; A1e, B2c; A1e, B2d; A1e, B2e; A1e, B2f; A1e, B2g; A1e, B2h; A1e, B2i; A1e, B2j; A1e, B3a; A1e, B3b; A1e, B4a; A1e, B5a; A1e, B6a; A1e, B6b; A1e, B7a; A1e, B8a; A1e, B9a; A1e, B9b; A1e, B9c; A1f, B1a; A1f, B1b; A1f, B1c; A1f, B1d; A1f, B1e; A1f, B1f; A1f, B2a; A1f, B2b; A1f, B2c; A1f, B2d; A1f, B2e; A1f, B2f; A1f, B2g; A1f, B2h; A1f, B2i; A1f, B2j; A1f, B3a; A1f, B3b; A1f, B4a; A1f, B5a; A1f, B6a; A1f, B6b; A1f, B7a; A1f, B8a; A1f, B9a; A1f, B9b; A1f, B9c; A1g, B1a; A1g, B1b; A1g, B1c; A1g, B1d; A1g, B1e; A1g, B1f; A1g, B2a; A1g, B2b; A1g, B2c; A1g, B2d; A1g, B2e; A1g, B2f; A1g, B2g; A1g, B2h; A1g, B2i; A1g, B2j; A1g, B3a; A1g, B3b; A1g, B4a; A1g, B5a; A1g, B6a; A1g, B6b; A1g, B7a; A1g, B8a; A1g, B9a; A1g, B9b; A1g, B9c; A1h, B1a; A1h, B1b; A1h, B1c; A1h, B1d; A1h, B1e; A1h, B1f; A1h, B2a; A1h, B2b; A1h, B2c; A1h, B2d; A1h, B2e; A1h, B2f; A1h, B2g; A1h, B2h; A1h, B2i; A1h, B2j; A1h, B3a; A1h, B3b; A1h, B4a; A1h, B5a; A1h, B6a; A1h, B6b; A1h, B7a; A1h, B8a; A1h, B9a; A1h, B9b; A1h, B9c; A2a, B1a; A2a, B1b; A2a, B1c; A2a, B1d; A2a, B1e; A2a, B1f; A2a, B2a; A2a, B2b; A2a, B2c; A2a, B2d; A2a, B2e; A2a, B2f; A2a, B2g; A2a, B2h; A2a, B2i; A2a, B2j; A2a, B3a; A2a, B3b; A2a, B4a; A2a, B5a; A2a, B6a; A2a, B6b; A2a, B7a; A2a, B8a; A2a, B9a; A2a, B9b; A2a, B9c; A2b, B1a; A2b, B1b; A2b, B1c; A2b, B1d; A2b, B1e; A2b, B1f; A2b, B2a; A2b, B2b; A2b, B2c; A2b, B2d; A2b, B2e; A2b, B2f; A2b, B2g; A2b, B2h; A2b, B2i; A2b, B2j; A2b, B3a; A2b, B3b; A2b, B4a; A2b, B5a; A2b, B6a; A2b, B6b; A2b, B7a; A2b, B8a; A2b, B9a; A2b, B9b; A2b, B9c; A3a, B1a; A3a, B1b; A3a, B1c; A3a, B1d; A3a, B1e; A3a, B1f; A3a, B2a; A3a, B2b; A3a, B2c; A3a, B2d; A3a, B2e; A3a, B2f; A3a, B2g; A3a, B2h; A3a, B2i; A3a, B2j; A3a, B3a; A3a, B3b; A3a, B4a; A3a, B5a; A3a, B6a; A3a, B6b; A3a, B7a; A3a, B8a; A3a, B9a; A3a, B9b; A3a, B9c; A3b, B1a; A3b, B1b; A3b, B1c; A3b, B1d; A3b, B1e; A3b, B1f; A3b, B2a; A3b, B2b; A3b, B2c; A3b, B2d; A3b, B2e; A3b, B2f; A3b, B2g; A3b, B2h; A3b, B2i; A3b, B2j; A3b, B3a; A3b, B3b; A3b, B4a; A3b, B5a; A3b, B6a; A3b, B6b; A3b, B7a; A3b, B8a; A3b, B9a; A3b, B9b; A3b,

B9c; A3c, B1a; A3c, B1b; A3c, B1c; A3c, B1d; A3c, B1e; A3c, B1f; A3c, B2a; A3c, B2b; A3c, B2c; A3c, B2d; A3c, B2e; A3c, B2f; A3c, B2g; A3c, B2h; A3c, B2i; A3c, B2j; A3c, B3a; A3c, B3b; A3c, B4a; A3c, B5a; A3c, B6a; A3c, B6b; A3c, B7a; A3c, B8a; A3c, B9a; A3c, B9b; A3c, B9c; A3d, B1a; A3d, B1b; A3d, B1c; A3d, B1d; A3d, B1e; A3d, B1f; A3d, B2a; A3d, B2b; A3d, B2c; A3d, B2d; A3d, B2e; A3d, B2f; A3d, B2g; A3d, B2h; A3d, B2i; A3d, B2j; A3d, B3a; A3d, B3b; A3d, B4a; A3d, B5a; A3d, B6a; A3d, B6b; A3d, B7a; A3d, B8a; A3d, B9a; A3d, B9b; A3d, B9c; A3e, B1a; A3e, B1b; A3e, B1c; A3e, B1d; A3e, B1e; A3e, B1f; A3e, B2a; A3e, B2b; A3e, B2c; A3e, B2d; A3e, B2e; A3e, B2f; A3e, B2g; A3e, B2h; A3e, B2i; A3e, B2j; A3e, B3a; A3e, B3b; A3e, B4a; A3e, B5a; A3e, B6a; A3e, B6b; A3e, B7a; A3e, B8a; A3e, B9a; A3e, B9b; A3e, B9c; A3f, B1a; A3f, B1b; A3f, B1c; A3f, B1d; A3f, B1e; A3f, B1f; A3f, B2a; A3f, B2b; A3f, B2c; A3f, B2d; A3f, B2e; A3f, B2f; A3f, B2g; A3f, B2h; A3f, B2i; A3f, B2j; A3f, B3a; A3f, B3b; A3f, B4a; A3f, B5a; A3f, B6a; A3f, B6b; A3f, B7a; A3f, B8a; A3f, B9a; A3f, B9b; A3f, B9c; A4a, B1a; A4a, B1b; A4a, B1c; A4a, B1d; A4a, B1e; A4a, B1f; A4a, B2a; A4a, B2b; A4a, B2c; A4a, B2d; A4a, B2e; A4a, B2f; A4a, B2g; A4a, B2h; A4a, B2i; A4a, B2j; A4a, B3a; A4a, B3b; A4a, B4a; A4a, B5a; A4a, B6a; A4a, B6b; A4a, B7a; A4a, B8a; A4a, B9a; A4a, B9b; A4a, B9c; A4b, B1a; A4b, B1b; A4b, B1c; A4b, B1d; A4b, B1e; A4b, B1f; A4b, B2a; A4b, B2b; A4b, B2c; A4b, B2d; A4b, B2e; A4b, B2f; A4b, B2g; A4b, B2h; A4b, B2i; A4b, B2j; A4b, B3a; A4b, B3b; A4b, B4a; A4b, B5a; A4b, B6a; A4b, B6b; A4b, B7a; A4b, B8a; A4b, B9a; A4b, B9b; A4b, B9c; A4c, B1a; A4c, B1b; A4c, B1c; A4c, B1d; A4c, B1e; A4c, B1f; A4c, B2a; A4c, B2b; A4c, B2c; A4c, B2d; A4c, B2e; A4c, B2f; A4c, B2g; A4c, B2h; A4c, B2i; A4c, B2j; A4c, B3a; A4c, B3b; A4c, B4a; A4c, B5a; A4c, B6a; A4c, B6b; A4c, B7a; A4c, B8a; A4c, B9a; A4c, B9b; A4c, B9c; A4d, B1a; A4d, B1b; A4d, B1c; A4d, B1d; A4d, B1e; A4d, B1f; A4d, B2a; A4d, B2b; A4d, B2c; A4d, B2d; A4d, B2e; A4d, B2f; A4d, B2g; A4d, B2h; A4d, B2i; A4d, B2j; A4d, B3a; A4d, B3b; A4d, B4a; A4d, B5a; A4d, B6a; A4d, B6b; A4d, B7a; A4d, B8a; A4d, B9a; A4d, B9b; A4d, B9c; A5a, B1a; A5a, B1b; A5a, B1c; A5a, B1d; A5a, B1e; A5a, B1f; A5a, B2a; A5a, B2b; A5a, B2c; A5a, B2d; A5a, B2e; A5a, B2f; A5a, B2g; A5a, B2h; A5a, B2i; A5a, B2j; A5a, B3a; A5a, B3b; A5a, B4a; A5a, B5a; A5a, B6a; A5a, B6b; A5a, B7a; A5a, B8a; A5a, B9a; A5a, B9b; A5a, B9c; A5b, B1a; A5b, B1b; A5b, B1c; A5b, B1d; A5b, B1e; A5b, B1f; A5b, B2a; A5b, B2b; A5b, B2c; A5b, B2d; A5b, B2e; A5b, B2f; A5b, B2g; A5b, B2h; A5b, B2i; A5b, B2j; A5b, B3a; A5b, B3b; A5b, B4a; A5b, B5a; A5b, B6a;

A5b, B6b; A5b, B7a; A5b, B8a; A5b, B9a; A5b, B9b; A5b, B9c; A6a, B1a; A6a, B1b; A6a, B1c; A6a, B1d; A6a, B1e; A6a, B1f; A6a, B2a; A6a, B2b; A6a, B2c; A6a, B2d; A6a, B2e; A6a, B2f; A6a, B2g; A6a, B2h; A6a, B2i; A6a, B2j; A6a, B3a; A6a, B3b; A6a, B4a; A6a, B5a; A6a, B6a; A6a, B6b; A6a, B7a; A6a, B8a; A6a, B9a; A6a, B9b; A6a, B9c; A6b, B1a; A6b, B1b; A6b, B1c; A6b, B1d; A6b, B1e; A6b, B1f; A6b, B2a; A6b, B2b; A6b, B2c; A6b, B2d; A6b, B2e; A6b, B2f; A6b, B2g; A6b, B2h; A6b, B2i; A6b, B2j; A6b, B3a; A6b, B3b; A6b, B4a; A6b, B5a; A6b, B6a; A6b, B6b; A6b, B7a; A6b, B8a; A6b, B9a; A6b, B9b; A6b, B9c; A7a, B1a; A7a, B1b; A7a, B1c; A7a, B1d; A7a, B1e; A7a, B1f; A7a, B2a; A7a, B2b; A7a, B2c; A7a, B2d; A7a, B2e; A7a, B2f; A7a, B2g; A7a, B2h; A7a, B2i; A7a, B2j; A7a, B3a; A7a, B3b; A7a, B4a; A7a, B5a; A7a, B6a; A7a, B6b; A7a, B7a; A7a, B8a; A7a, B9a; A7a, B9b; A7a, B9c; A7b, B1a; A7b, B1b; A7b, B1c; A7b, B1d; A7b, B1e; A7b, B1f; A7b, B2a; A7b, B2b; A7b, B2c; A7b, B2d; A7b, B2e; A7b, B2f; A7b, B2g; A7b, B2h; A7b, B2i; A7b, B2j; A7b, B3a; A7b, B3b; A7b, B4a; A7b, B5a; A7b, B6a; A7b, B6b; A7b, B7a; A7b, B8a; A7b, B9a; A7b, B9b; A7b, B9c; A7c, B1a; A7c, B1b; A7c, B1c; A7c, B1d; A7c, B1e; A7c, B1f; A7c, B2a; A7c, B2b; A7c, B2c; A7c, B2d; A7c, B2e; A7c, B2f; A7c, B2g; A7c, B2h; A7c, B2i; A7c, B2j; A7c, B3a; A7c, B3b; A7c, B4a; A7c, B5a; A7c, B6a; A7c, B6b; A7c, B7a; A7c, B8a; A7c, B9a; A7c, B9b; A7c, B9c; A8a, B1a; A8a, B1b; A8a, B1c; A8a, B1d; A8a, B1e; A8a, B1f; A8a, B2a; A8a, B2b; A8a, B2c; A8a, B2d; A8a, B2e; A8a, B2f; A8a, B2g; A8a, B2h; A8a, B2i; A8a, B2j; A8a, B3a; A8a, B3b; A8a, B4a; A8a, B5a; A8a, B6a; A8a, B6b; A8a, B7a; A8a, B8a; A8a, B9a; A8a, B9b; A8a, B9c; A8b, B1a; A8b, B1b; A8b, B1c; A8b, B1d; A8b, B1e; A8b, B1f; A8b, B2a; A8b, B2b; A8b, B2c; A8b, B2d; A8b, B2e; A8b, B2f; A8b, B2g; A8b, B2h; A8b, B2i; A8b, B2j; A8b, B3a; A8b, B3b; A8b, B4a; A8b, B5a; A8b, B6a; A8b, B6b; A8b, B7a; A8b, B8a; A8b, B9a; A8b, B9b; A8b, B9c; A8c, B1a; A8c, B1b; A8c, B1c; A8c, B1d; A8c, B1e; A8c, B1f; A8c, B2a; A8c, B2b; A8c, B2c; A8c, B2d; A8c, B2e; A8c, B2f; A8c, B2g; A8c, B2h; A8c, B2i; A8c, B2j; A8c, B3a; A8c, B3b; A8c, B4a; A8c, B5a; A8c, B6a; A8c, B6b; A8c, B7a; A8c, B8a; A8c, B9a; A8c, B9b; A8c, B9c; A10a, B1a; A10a, B1b; A10a, B1c; A10a, B1d; A10a, B1e; A10a, B1f; A10a, B2a; A10a, B2b; A10a, B2c; A10a, B2d; A10a, B2e; A10a, B2f; A10a, B2g; A10a, B2h; A10a, B2i; A10a, B2j; A10a, B3a; A10a, B3b; A10a, B4a; A10a, B5a; A10a, B6a; A10a, B6b; A10a, B7a; A10a, B8a; A10a, B9a; A10a, B9b; A10a, B9c; A10b, B1a; A10b, B1b; A10b, B1c; A10b, B1d; A10b, B1e; A10b, B1f; A10b, B2a; A10b, B2b; A10b, B2c; A10b,

B2d; A10b, B2e; A10b, B2f; A10b, B2g; A10b, B2h; A10b, B2i; A10b, B2j; A10b, B3a; A10b, B3b; A10b, B4a; A10b, B5a; A10b, B6a; A10b, B6b; A10b, B7a; A10b, B8a; A10b, B9a; A10b, B9b; A10b, B9c; and combinations thereof.

[000470] In some embodiments, the combination of A) pharmaceutical agent or a salt thereof, B) surface-altering agent in the pharmaceutical composition, and C) density of the one or more surface altering agents is present on the outer surface of the core particle, may be selected from: A1, B1, C1; A1, B1, C2; A1, B1, C3; A1, B1, C4; A1, B1, C5; A1, B2, C1; A1, B2, C2; A1, B2, C3; A1, B2, C4; A1, B2, C5; A1, B3, C1; A1, B3, C2; A1, B3, C3; A1, B3, C4; A1, B3, C5; A1, B4, C1; A1, B4, C2; A1, B4, C3; A1, B4, C4; A1, B4, C5; A1, B5, C1; A1, B5, C2; A1, B5, C3; A1, B5, C4; A1, B5, C5; A1, B6, C1; A1, B6, C2; A1, B6, C3; A1, B6, C4; A1, B6, C5; A1, B7, C1; A1, B7, C2; A1, B7, C3; A1, B7, C4; A1, B7, C5; A1, B8, C1; A1, B8, C2; A1, B8, C3; A1, B8, C4; A1, B8, C5; A1, B9, C1; A1, B9, C2; A1, B9, C3; A1, B9, C4; A1, B9, C5; A2, B1, C1; A2, B1, C2; A2, B1, C3; A2, B1, C4; A2, B1, C5; A2, B2, C1; A2, B2, C2; A2, B2, C3; A2, B2, C4; A2, B2, C5; A2, B3, C1; A2, B3, C2; A2, B3, C3; A2, B3, C4; A2, B3, C5; A2, B4, C1; A2, B4, C2; A2, B4, C3; A2, B4, C4; A2, B4, C5; A2, B5, C1; A2, B5, C2; A2, B5, C3; A2, B5, C4; A2, B5, C5; A2, B6, C1; A2, B6, C2; A2, B6, C3; A2, B6, C4; A2, B6, C5; A2, B7, C1; A2, B7, C2; A2, B7, C3; A2, B7, C4; A2, B7, C5; A2, B8, C1; A2, B8, C2; A2, B8, C3; A2, B8, C4; A2, B8, C5; A2, B9, C1; A2, B9, C2; A2, B9, C3; A2, B9, C4; A2, B9, C5; A3, B1, C1; A3, B1, C2; A3, B1, C3; A3, B1, C4; A3, B1, C5; A3, B2, C1; A3, B2, C2; A3, B2, C3; A3, B2, C4; A3, B2, C5; A3, B3, C1; A3, B3, C2; A3, B3, C3; A3, B3, C4; A3, B3, C5; A3, B4, C1; A3, B4, C2; A3, B4, C3; A3, B4, C4; A3, B4, C5; A3, B5, C1; A3, B5, C2; A3, B5, C3; A3, B5, C4; A3, B5, C5; A3, B6, C1; A3, B6, C2; A3, B6, C3; A3, B6, C4; A3, B6, C5; A3, B7, C1; A3, B7, C2; A3, B7, C3; A3, B7, C4; A3, B7, C5; A3, B8, C1; A3, B8, C2; A3, B8, C3; A3, B8, C4; A3, B8, C5; A3, B9, C1; A3, B9, C2; A3, B9, C3; A3, B9, C4; A3, B9, C5; A4, B1, C1; A4, B1, C2; A4, B1, C3; A4, B1, C4; A4, B1, C5; A4, B2, C1; A4, B2, C2; A4, B2, C3; A4, B2, C4; A4, B2, C5; A4, B3, C1; A4, B3, C2; A4, B3, C3; A4, B3, C4; A4, B3, C5; A4, B4, C1; A4, B4, C2; A4, B4, C3; A4, B4, C4; A4, B4, C5; A4, B5, C1; A4, B5, C2; A4, B5, C3; A4, B5, C4; A4, B5, C5; A4, B6, C1; A4, B6, C2; A4, B6, C3; A4, B6, C4; A4, B6, C5; A4, B7, C1; A4, B7, C2; A4, B7, C3; A4, B7, C4; A4, B7, C5; A4, B8, C1; A4, B8, C2; A4, B8, C3; A4, B8, C4; A4, B8, C5; A4, B9, C1; A4, B9, C2; A4, B9, C3; A4, B9, C4; A4, B9, C5; A5, B1, C1; A5, B1, C2;

A5, B1, C3; A5, B1, C4; A5, B1, C5; A5, B2, C1; A5, B2, C2; A5, B2, C3; A5, B2, C4; A5, B2, C5; A5, B3, C1; A5, B3, C2; A5, B3, C3; A5, B3, C4; A5, B3, C5; A5, B4, C1; A5, B4, C2; A5, B4, C3; A5, B4, C4; A5, B4, C5; A5, B5, C1; A5, B5, C2; A5, B5, C3; A5, B5, C4; A5, B5, C5; A5, B6, C1; A5, B6, C2; A5, B6, C3; A5, B6, C4; A5, B6, C5; A5, B7, C1; A5, B7, C2; A5, B7, C3; A5, B7, C4; A5, B7, C5; A5, B8, C1; A5, B8, C2; A5, B8, C3; A5, B8, C4; A5, B8, C5; A5, B9, C1; A5, B9, C2; A5, B9, C3; A5, B9, C4; A5, B9, C5; A6, B1, C1; A6, B1, C2; A6, B1, C3; A6, B1, C4; A6, B1, C5; A6, B2, C1; A6, B2, C2; A6, B2, C3; A6, B2, C4; A6, B2, C5; A6, B3, C1; A6, B3, C2; A6, B3, C3; A6, B3, C4; A6, B3, C5; A6, B4, C1; A6, B4, C2; A6, B4, C3; A6, B4, C4; A6, B4, C5; A6, B5, C1; A6, B5, C2; A6, B5, C3; A6, B5, C4; A6, B5, C5; A6, B6, C1; A6, B6, C2; A6, B6, C3; A6, B6, C4; A6, B6, C5; A6, B7, C1; A6, B7, C2; A6, B7, C3; A6, B7, C4; A6, B7, C5; A6, B8, C1; A6, B8, C2; A6, B8, C3; A6, B8, C4; A6, B8, C5; A6, B9, C1; A6, B9, C2; A6, B9, C3; A6, B9, C4; A6, B9, C5; A7, B1, C1; A7, B1, C2; A7, B1, C3; A7, B1, C4; A7, B1, C5; A7, B2, C1; A7, B2, C2; A7, B2, C3; A7, B2, C4; A7, B2, C5; A7, B3, C1; A7, B3, C2; A7, B3, C3; A7, B3, C4; A7, B3, C5; A7, B4, C1; A7, B4, C2; A7, B4, C3; A7, B4, C4; A7, B4, C5; A7, B5, C1; A7, B5, C2; A7, B5, C3; A7, B5, C4; A7, B5, C5; A7, B6, C1; A7, B6, C2; A7, B6, C3; A7, B6, C4; A7, B6, C5; A7, B7, C1; A7, B7, C2; A7, B7, C3; A7, B7, C4; A7, B7, C5; A7, B8, C1; A7, B8, C2; A7, B8, C3; A7, B8, C4; A7, B8, C5; A7, B9, C1; A7, B9, C2; A7, B9, C3; A7, B9, C4; A7, B9, C5; A8, B1, C1; A8, B1, C2; A8, B1, C3; A8, B1, C4; A8, B1, C5; A8, B2, C1; A8, B2, C2; A8, B2, C3; A8, B2, C4; A8, B2, C5; A8, B3, C1; A8, B3, C2; A8, B3, C3; A8, B3, C4; A8, B3, C5; A8, B4, C1; A8, B4, C2; A8, B4, C3; A8, B4, C4; A8, B4, C5; A8, B5, C1; A8, B5, C2; A8, B5, C3; A8, B5, C4; A8, B5, C5; A8, B6, C1; A8, B6, C2; A8, B6, C3; A8, B6, C4; A8, B6, C5; A8, B7, C1; A8, B7, C2; A8, B7, C3; A8, B7, C4; A8, B7, C5; A8, B8, C1; A8, B8, C2; A8, B8, C3; A8, B8, C4; A8, B8, C5; A8, B9, C1; A8, B9, C2; A8, B9, C3; A8, B9, C4; A8, B9, C5; A9, B1, C1; A9, B1, C2; A9, B1, C3; A9, B1, C4; A9, B1, C5; A9, B2, C1; A9, B2, C2; A9, B2, C3; A9, B2, C4; A9, B2, C5; A9, B3, C1; A9, B3, C2; A9, B3, C3; A9, B3, C4; A9, B3, C5; A9, B4, C1; A9, B4, C2; A9, B4, C3; A9, B4, C4; A9, B4, C5; A9, B5, C1; A9, B5, C2; A9, B5, C3; A9, B5, C4; A9, B5, C5; A9, B6, C1; A9, B6, C2; A9, B6, C3; A9, B6, C4; A9, B6, C5; A9, B7, C1; A9, B7, C2; A9, B7, C3; A9, B7, C4; A9, B7, C5; A9, B8, C1; A9, B8, C2; A9, B8, C3; A9, B8, C4; A9, B8, C5; A9, B9, C1; A9, B9, C2; A9, B9, C3; A9, B9, C4; A9, B9, C5; A10, B1, C1; A10, B1, C2; A10, B1, C3; A10, B1, C4;

A10, B1, C5; A10, B2, C1; A10, B2, C2; A10, B2, C3; A10, B2, C4; A10, B2, C5; A10, B3, C1; A10, B3, C2; A10, B3, C3; A10, B3, C4; A10, B3, C5; A10, B4, C1; A10, B4, C2; A10, B4, C3; A10, B4, C4; A10, B4, C5; A10, B5, C1; A10, B5, C2; A10, B5, C3; A10, B5, C4; A10, B5, C5; A10, B6, C1; A10, B6, C2; A10, B6, C3; A10, B6, C4; A10, B6, C5; A10, B7, C1; A10, B7, C2; A10, B7, C3; A10, B7, C4; A10, B7, C5; A10, B8, C1; A10, B8, C2; A10, B8, C3; A10, B8, C4; A10, B8, C5; A10, B9, C1; A10, B9, C2; A10, B9, C3; A10, B9, C4; A10, B9, C5; A11, B1, C1; A11, B1, C2; A11, B1, C3; A11, B1, C4; A11, B1, C5; A11, B2, C1; A11, B2, C2; A11, B2, C3; A11, B2, C4; A11, B2, C5; A11, B3, C1; A11, B3, C2; A11, B3, C3; A11, B3, C4; A11, B3, C5; A11, B4, C1; A11, B4, C2; A11, B4, C3; A11, B4, C4; A11, B4, C5; A11, B5, C1; A11, B5, C2; A11, B5, C3; A11, B5, C4; A11, B5, C5; A11, B6, C1; A11, B6, C2; A11, B6, C3; A11, B6, C4; A11, B6, C5; A11, B7, C1; A11, B7, C2; A11, B7, C3; A11, B7, C4; A11, B7, C5; A11, B8, C1; A11, B8, C2; A11, B8, C3; A11, B8, C4; A11, B8, C5; A11, B9, C1; A11, B9, C2; A11, B9, C3; A11, B9, C4; A11, B9, C5; A12, B1, C1; A12, B1, C2; A12, B1, C3; A12, B1, C4; A12, B1, C5; A12, B2, C1; A12, B2, C2; A12, B2, C3; A12, B2, C4; A12, B2, C5; A12, B3, C1; A12, B3, C2; A12, B3, C3; A12, B3, C4; A12, B3, C5; A12, B4, C1; A12, B4, C2; A12, B4, C3; A12, B4, C4; A12, B4, C5; A12, B5, C1; A12, B5, C2; A12, B5, C3; A12, B5, C4; A12, B5, C5; A12, B6, C1; A12, B6, C2; A12, B6, C3; A12, B6, C4; A12, B6, C5; A12, B7, C1; A12, B7, C2; A12, B7, C3; A12, B7, C4; A12, B7, C5; A12, B8, C1; A12, B8, C2; A12, B8, C3; A12, B8, C4; A12, B8, C5; A12, B9, C1; A12, B9, C2; A12, B9, C3; A12, B9, C4; A12, B9, C5; A13, B1, C1; A13, B1, C2; A13, B1, C3; A13, B1, C4; A13, B1, C5; A13, B2, C1; A13, B2, C2; A13, B2, C3; A13, B2, C4; A13, B2, C5; A13, B3, C1; A13, B3, C2; A13, B3, C3; A13, B3, C4; A13, B3, C5; A13, B4, C1; A13, B4, C2; A13, B4, C3; A13, B4, C4; A13, B4, C5; A13, B5, C1; A13, B5, C2; A13, B5, C3; A13, B5, C4; A13, B5, C5; A13, B6, C1; A13, B6, C2; A13, B6, C3; A13, B6, C4; A13, B6, C5; A13, B7, C1; A13, B7, C2; A13, B7, C3; A13, B7, C4; A13, B7, C5; A13, B8, C1; A13, B8, C2; A13, B8, C3; A13, B8, C4; A13, B8, C5; A13, B9, C1; A13, B9, C2; A13, B9, C3; A13, B9, C4; A13, B9, C5; A14, B1, C1; A14, B1, C2; A14, B1, C3; A14, B1, C4; A14, B1, C5; A14, B2, C1; A14, B2, C2; A14, B2, C3; A14, B2, C4; A14, B2, C5; A14, B3, C1; A14, B3, C2; A14, B3, C3; A14, B3, C4; A14, B3, C5; A14, B4, C1; A14, B4, C2; A14, B4, C3; A14, B4, C4; A14, B4, C5; A14, B5, C1; A14, B5, C2; A14, B5, C3; A14, B5, C4; A14, B5, C5; A14, B6, C1; A14, B6, C2; A14, B6, C3; A14, B6, C4; A14, B6, C5; A14, B7,

C1; A14, B7, C2; A14, B7, C3; A14, B7, C4; A14, B7, C5; A14, B8, C1; A14, B8, C2; A14, B8, C3; A14, B8, C4; A14, B8, C5; A14, B9, C1; A14, B9, C2; A14, B9, C3; A14, B9, C4; A14, B9, C5; A15, B1, C1; A15, B1, C2; A15, B1, C3; A15, B1, C4; A15, B1, C5; A15, B2, C1; A15, B2, C2; A15, B2, C3; A15, B2, C4; A15, B2, C5; A15, B3, C1; A15, B3, C2; A15, B3, C3; A15, B3, C4; A15, B3, C5; A15, B4, C1; A15, B4, C2; A15, B4, C3; A15, B4, C4; A15, B4, C5; A15, B5, C1; A15, B5, C2; A15, B5, C3; A15, B5, C4; A15, B5, C5; A15, B6, C1; A15, B6, C2; A15, B6, C3; A15, B6, C4; A15, B6, C5; A15, B7, C1; A15, B7, C2; A15, B7, C3; A15, B7, C4; A15, B7, C5; A15, B8, C1; A15, B8, C2; A15, B8, C3; A15, B8, C4; A15, B8, C5; A15, B9, C1; A15, B9, C2; A15, B9, C3; A15, B9, C4; A15, B9, C5; A16, B1, C1; A16, B1, C2; A16, B1, C3; A16, B1, C4; A16, B1, C5; A16, B2, C1; A16, B2, C2; A16, B2, C3; A16, B2, C4; A16, B2, C5; A16, B3, C1; A16, B3, C2; A16, B3, C3; A16, B3, C4; A16, B3, C5; A16, B4, C1; A16, B4, C2; A16, B4, C3; A16, B4, C4; A16, B4, C5; A16, B5, C1; A16, B5, C2; A16, B5, C3; A16, B5, C4; A16, B5, C5; A16, B6, C1; A16, B6, C2; A16, B6, C3; A16, B6, C4; A16, B6, C5; A16, B7, C1; A16, B7, C2; A16, B7, C3; A16, B7, C4; A16, B7, C5; A16, B8, C1; A16, B8, C2; A16, B8, C3; A16, B8, C4; A16, B8, C5; A16, B9, C1; A16, B9, C2; A16, B9, C3; A16, B9, C4; A16, B9, C5; A17, B1, C1; A17, B1, C2; A17, B1, C3; A17, B1, C4; A17, B1, C5; A17, B2, C1; A17, B2, C2; A17, B2, C3; A17, B2, C4; A17, B2, C5; A17, B3, C1; A17, B3, C2; A17, B3, C3; A17, B3, C4; A17, B3, C5; A17, B4, C1; A17, B4, C2; A17, B4, C3; A17, B4, C4; A17, B4, C5; A17, B5, C1; A17, B5, C2; A17, B5, C3; A17, B5, C4; A17, B5, C5; A17, B6, C1; A17, B6, C2; A17, B6, C3; A17, B6, C4; A17, B6, C5; A17, B7, C1; A17, B7, C2; A17, B7, C3; A17, B7, C4; A17, B7, C5; A17, B8, C1; A17, B8, C2; A17, B8, C3; A17, B8, C4; A17, B8, C5; A17, B9, C1; A17, B9, C2; A17, B9, C3; A17, B9, C4; A17, B9, C5; A18, B1, C1; A18, B1, C2; A18, B1, C3; A18, B1, C4; A18, B1, C5; A18, B2, C1; A18, B2, C2; A18, B2, C3; A18, B2, C4; A18, B2, C5; A18, B3, C1; A18, B3, C2; A18, B3, C3; A18, B3, C4; A18, B3, C5; A18, B4, C1; A18, B4, C2; A18, B4, C3; A18, B4, C4; A18, B4, C5; A18, B5, C1; A18, B5, C2; A18, B5, C3; A18, B5, C4; A18, B5, C5; A18, B6, C1; A18, B6, C2; A18, B6, C3; A18, B6, C4; A18, B6, C5; A18, B7, C1; A18, B7, C2; A18, B7, C3; A18, B7, C4; A18, B7, C5; A18, B8, C1; A18, B8, C2; A18, B8, C3; A18, B8, C4; A18, B8, C5; A18, B9, C1; A18, B9, C2; A18, B9, C3; A18, B9, C4; A18, B9, C5; A19, B1, C1; A19, B1, C2; A19, B1, C3; A19, B1, C4; A19, B1, C5; A19, B2, C1; A19, B2, C2; A19, B2, C3; A19, B2, C4; A19, B2, C5; A19, B3, C1; A19, B3, C2; A19,

B3, C3; A19, B3, C4; A19, B3, C5; A19, B4, C1; A19, B4, C2; A19, B4, C3; A19, B4, C4; A19, B4, C5; A19, B5, C1; A19, B5, C2; A19, B5, C3; A19, B5, C4; A19, B5, C5; A19, B6, C1; A19, B6, C2; A19, B6, C3; A19, B6, C4; A19, B6, C5; A19, B7, C1; A19, B7, C2; A19, B7, C3; A19, B7, C4; A19, B7, C5; A19, B8, C1; A19, B8, C2; A19, B8, C3; A19, B8, C4; A19, B8, C5; A19, B9, C1; A19, B9, C2; A19, B9, C3; A19, B9, C4; A19, B9, C5; and combinations thereof.

[000471] In the above-described pharmaceutical compositions comprising the plurality of coated particles having a sutiable combination of features A) (e.g., A1-A19 and species identified therein), in combination with B) (e.g., B1-B9 and species identified therein) and C) (e.g., C1-C5), in some embodiments the coated particle includes a core particle comprising or formed of a solid pharmaceutical agent or a salt thereof, wherein the agent or salt has an aqueous solubility of less than or equal to about 1 mg/mL at 25 ºC (e.g., less than or equal to about 0.1 mg/mL at 25 ºC) at any point throughout the pH range, wherein the pharmaceutical agent or salt thereof constitutes at least about 80 wt% (e.g., at least about 90 wt%, at least about 95 wt%, at least about 99 wt%) of the core particle. The surface-altering agent may be adsorbed to the surface of the core particle. The coated particles may have a relative velocity of greater than 0.5 in mucus. The coated particles may have an average size of at least about 20 nm and less than or equal to about 1 μm (e.g., less than or equal to about 500 nm). The thickness of the coating may be, for example, less than or equal to about 50 nm (e.g., less than or equal to about 30 nm, less than or equal to about 10 nm). The pharmaceutical composition may include one or more pharmaceutically acceptable carriers, additives, and/or diluents. Optionally, the one or more ophthalmically acceptable carriers, additives, and/or diluents comprises glycerin. In some embodiments, the plurality of coated particles are in solution (e.g., an aqueous solution) with one or more free surface-altering agents (e.g., surface-altering agents that are not attached to a particle) in the composition. The free surface-altering agent(s) in solution and surface-altering agent B) on the surface of the particle may be the same surface-altering agent(s) and may be in equilibrium with each other in the composition. The total amount of surface-altering agent present in the composition may be, for example, between about 0.001% to about 5% by weight (e.g., between about 0.01% to about 5% by weight, or between about 0.1% to about 5% by weight). In some embodiments, the PDI of the composition is less than or equal to about 0.5 (e.g., less than or

equal to about 0.3, or less than or equal to about 0.2), and optionally, greater than or equal to about 0.1. In some embodiments, the pharmaceutical composition comprises one or more degradants of the pharmaceutical agent, and the concentration of each degradant in the composition is less than or equal to about 1 wt% relative to the weight of the pharmaceutical agent. Methods of use and/or delivery of such compositions to a patient or subject (e.g., to the eye, mucus, or a mucus membrane) are also provided.

[000472] In one particular set of embodiments involving the above-described pharmaceutical compositions, the surface-altering agent B) is or comprises a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 3 kDa, the hydrophilic blocks constitute at least about 30 wt% of the triblock, wherein the hydrophilic blocks comprise or are poly(ethylene oxide) having a molecular weight of at least about 2 kDa, wherein the hydrophobic block associates with the surface of the core particle (e.g., by adsorption), and wherein the hydrophilic block is present at the surface of the coated particle and renders the coated particle hydrophilic.

[000473] In certain of the embodiments described above, in which the B) surface-altering is a poloxamer, the poloxamer is selected from Pluronic® P123, Pluronic® P103, Pluronic® P105, Pluronic® F127, and combinations thereof. In some embodiments, the poloxamer is not Pluronic® F68 or Pluronic® F108.

[000474] In another particular set of embodiments involving the above-described pharmaceutical compositions, the surface-altering agent B) is or comprises a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer. The polymer has a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa (e.g., less than or equal to about 200 kDa), and may be least about 30% hydrolyzed (e.g., at least about 70% hydrolyzed) and less than or equal to about 98% hydrolyzed (e.g., less than about 95% hydrolyzed). The synthetic polymer may be, for example, poly(vinyl alcohol), a partially hydrolyzed poly(vinyl acetate) or a copolymer of vinyl alcohol and vinyl acetate. (In certain embodiments, the polymer is a PVA that is less than or equal to about 98% hydrolyzed and has a molecular weight of less than or equal to about 75 kDa, or a PVA that is less than about 95% hydrolyzed.) The surface-altering agent may be adsorbed to the surface of the core particle.

[000475] In certain of the embodiments described above, in which the B) surface-altering is PVA, the PVA is selected from PVA 13K87, PVA 31K98, PVA 31K87, PVA 9K80, PVA 2K75, PVA 57K87, PVA 85K87, PVA105K80, PVA130K87, and combinations thereof.

[000476] As described herein, such pharmaceutical compositions described above may include any suitable pharmaceutical agent A) and density C) of surface-altering agent.

[000477] These and other aspects of the present invention will be further appreciated upon consideration of the following Examples, which are intended to illustrate certain particular embodiments of the invention but are not intended to limit its scope, as defined by the claims.

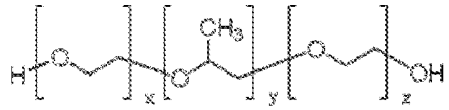
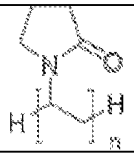
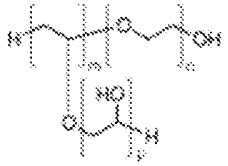
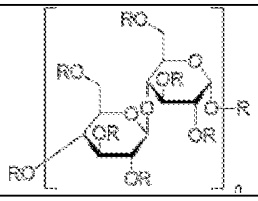
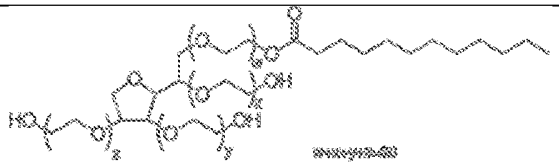
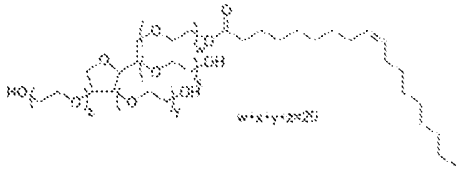
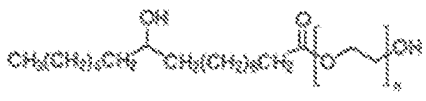
Examples

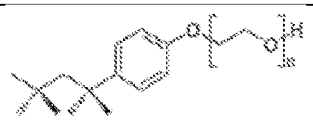
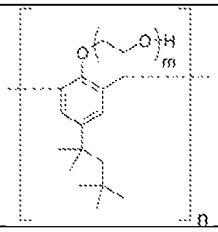
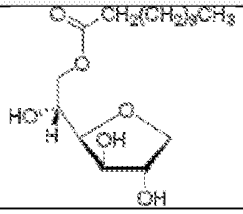
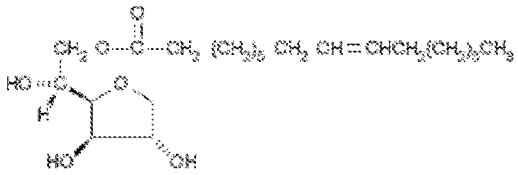
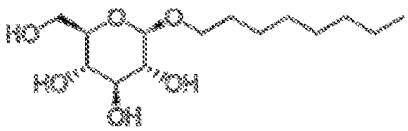
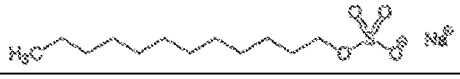
Example 1

[000478] The following describes a non-limiting example of a method of forming non-polymeric solid particles into mucus-penetrating particles. Pyrene, a hydrophobic naturally fluorescent compound, was used as the core particle and was prepared by a milling process in the presence of various surface-altering agents. The surface-altering agents formed coatings around the core particles. Different surface-altering agents were evaluated to determine effectiveness of the coated particles in penetrating mucus.

[000479] Pyrene was milled in aqueous dispersions in the presence of various surface-altering agents to determine whether certain surface-altering agents can: 1) aid particle size reduction to several hundreds of nanometers and 2) physically (non-covalently) coat the surface of generated nanoparticles with a mucoinert coating that would minimize particle interactions with mucus constituents and prevent mucus adhesion. In these experiments, the surface-altering agents acted as a coating around the core particles, and the resulting particles were tested for their mobility in mucus, although in other embodiments, the surface-altering agents may be exchanged with other surface-altering agents that can increase mobility of the particles in mucus. The surface-altering agents tested included a variety of polymers, oligomers, and small molecules listed in Table2, including pharmaceutically relevant excipients such as poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) block copolymers (Pluronics®), polyvinylpyrrolidones (Kollidon), and hydroxypropyl methylcellulose (Methocel), *etc.*

[000480] Table 2. Surface-altering agents tested with Pyrene as a model compound.

Polymeric surface-altering agents			
Stabilizer	Acronym or Trade Name	Grade or Molecular Weight	Chemical Structure
Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) block copolymers	Pluronic®	F127, F108, F68, F87, F38, P123, P105, P103, P65, L121, L101, L81, L44, L31	
Polyvinylpyrrolidone	PVP	Kollidon 17 (9K), Kollidon 25 (26K), Kollindon 30 (43K)	
PVA-poly(ethylene glycol) graft-copolymer		Kollicoat IR	
Hydroxypropyl methylcellulose	HPMC	Methocel E50, Methocel K100	
Oligomeric surface-altering agents			
Tween 20			
Tween 80			
Solutol HS 15			

Triton X100	
Tyloxapol	
Cremophor RH 40	
Small molecule surface-altering agents	
Span 20	
Span 80	
Octyl glucoside	
Cetytrimethylammonium bromide (CTAB)	
Sodium dodecyl sulfate (SDS)	

[000481] An aqueous dispersion containing pyrene and one of the surface-altering agents listed above was milled with milling media until particle size was reduced below 500 nm. Table3 lists particle size characteristics of pyrene particles obtained by milling in the presence of the various surface-altering agents. Particle size was measured by dynamic light scattering. When Pluronics® L101, L81, L44, L31, Span 20, Span 80, or Octyl glucoside were used as surface-altering agents, stable nanosuspensions could not be obtained. Therefore, these surface-altering agents were excluded from further investigation due to their inability to effectively aid particle size reduction.

[000482] **Table 3.** Particle size measured by DLS in nanosuspensions obtained by milling of Pyrene with various surface-altering agents.

Stabilizer	N-Ave. D (nm)
Pluronic® F127	239
Pluronic® F108	267
Pluronic® P105	303
Pluronic® P103	319
Pluronic® P123	348
Pluronic® L121	418
Pluronic® F68	353
Pluronic® P65	329
Pluronic® F87	342
Pluronic® F38	298
Pluronic® L101	not measurable*
Pluronic® L81	not measurable*
Pluronic® L44	not measurable*
Pluronic® L31	not measurable*
PVA 13K	314
PVA 31K	220
PVA 85K	236
Kollicoat IR	192
Kollidon 17 (PVP 9K)	163
Kollidon 25 (PVP 26K)	210
Kollindon 30 (PVP 43K)	185
Methocel E50	160
Methocel K100	216
Tween 20	381
Tween 80	322
Solutol HS	378

Triton X100	305
Tyloxapol	234
Cremophor RH40	373
SDS	377
CTAB	354
Span 20	not measurable*
Span 80	not measurable*
Octyl glucoside	not measurable*

* milling with Pluronics® L101, L81, L44, L31, Span 20, Span 80, Octyl glucoside failed to effectively reduce pyrene particle size and produce stable nanosuspensions.

[000483] The mobility and distribution of pyrene nanoparticles from the produced nanosuspensions in human cervicovaginal mucus (CVM) were characterized using fluorescence microscopy and multiple particle tracking software. In a typical experiment, ≤0.5uL of a nanosuspension (diluted if necessary to the surfactant concentration of ~1%) was added to 20 µl of fresh CVM along with controls. Conventional nanoparticles (200 nm yellow-green fluorescent carboxylate-modified polystyrene microspheres from Invitrogen) were used as a negative control to confirm the barrier properties of the CVM samples. Red fluorescent polystyrene nanoparticles covalently coated with PEG 5 kDa were used as a positive control with well-established MPP behavior. Using a fluorescent microscope equipped with a CCD camera, 15 s movies were captured at a temporal resolution of 66.7 ms (15 frames/s) under 100x magnification from several areas within each sample for each type of particles: sample (pyrene), negative control, and positive control (natural blue fluorescence of pyrene allowed observing of pyrene nanoparticles separately from the controls). Next, using an advanced image processing software, individual trajectories of multiple particles were measured over a time-scale of at least 3.335 s (50 frames). Resulting transport data are presented here in the form of trajectory-mean velocity V_{mean}, *i.e.*, velocity of an individual particle averaged over its trajectory, and ensemble-average velocity $\langle V_{mean} \rangle$, *i.e.*, V_{mean} averaged over an ensemble of particles. To enable easy comparison between different samples and normalize velocity data with respect to natural variability in penetrability of CVM samples, relative sample velocity $\langle V_{mean} \rangle_{rel}$, was determined according to the formula shown in Equation 1.

[000484] Prior to quantifying mobility of the produced pyrene nanoparticles, their spatial distribution in the mucus sample was assessed by microscopy at low magnifications (10x, 40x). It was found that pyrene/Methocel nanosuspensions did not achieve uniform distribution in CVM and strongly aggregated into domains much larger than the mucus mesh size (data not shown). Such aggregation is indicative of mucoadhesive behavior and effectively prevents mucus penetration. Therefore, further quantitative analysis of particle mobility was deemed unnecessary. Similarly to the positive control, all other tested pyrene/stabilizer systems achieved a fairly uniform distribution in CVM. Multiple particle tracking confirmed that in all tested samples the negative controls were highly constrained, while the positive controls were highly mobile as demonstrated by $\langle V_{mean} \rangle$ for the positive controls being significantly greater than those for the negative controls (Table 4).

[000485] **Table 4.** Ensemble-average velocity $\langle V_{mean} \rangle$ (um/s) and relative sample velocity $\langle V_{mean} \rangle_{rel}$ for pyrene/stabilizer nanoparticles (sample) and controls in CVM.

	Negative Control		Positive Control		Sample		Sample (relative)	
Stabilizer	$\langle V_{mean} \rangle$	SD	$\langle V_{mean} \rangle$	SD	$\langle V_{mean} \rangle$	SD	$\langle V_{mean} \rangle_{rel}$	SD
Pluronic F127	0.58	0.18	5.97	0.54	6.25	0.72	1.05	0.18
Pluronic F108	0.43	0.64	5.04	1.88	4.99	1.47	0.99	0.55
Pluronic P105	0.56	0.52	4.38	1.36	4.47	2.11	1.02	0.69
Pluronic P103	0.58	0.77	4.5	2.01	4.24	1.95	0.93	0.74
Pluronic P123	0.56	0.44	4.56	1.44	3.99	1.66	0.86	0.54
Pluronic L121	0.42	0.3	4.27	2.04	0.81	0.51	0.10	0.16
Pluronic F68	0.56	0.52	4.38	1.36	0.81	0.7	0.07	0.23
Pluronic P65	0.26	0.25	4.52	2.15	0.53	0.56	0.06	0.15
Pluronic F87	0.95	1.6	5.06	1.34	0.74	0.78	-0.05	-0.43
Pluronic F38	0.26	0.1	5.73	0.84	0.54	0.29	0.05	0.06
Kollicoat IR	0.62	0.62	5.39	0.55	0.92	0.81	0.06	0.22
Kollidon 17	1.69	1.8	5.43	0.98	0.82	0.59	-0.23	-0.52
Kollidon 25	0.41	0.34	5.04	0.64	1.29	1.09	0.19	0.25
Kollindon 30	0.4	0.2	4.28	0.57	0.35	0.11	-0.01	0.06
Methocel E50**								
Methocel K100**								
Tween 20	0.77	0.93	5.35	1.76	1.58	2.02	0.18	0.49
Tween 80	0.46	0.34	3.35	1.89	0.94	0.5	0.17	0.24
Solutol HS	0.42	0.13	3.49	0.5	0.8	0.6	0.12	0.20
Triton X100	0.26	0.13	4.06	1.11	0.61	0.19	0.09	0.07
Tyloxapol	0.5	0.5	3.94	0.58	0.42	0.23	-0.02	-0.16

Cremophor RH40	0.48	0.21	3.2	0.97	0.49	0.24	0.00	0.12
SDS	0.3	0.12	5.99	0.84	0.34	0.15	0.01	0.03
CTAB	0.39	0.09	4.75	1.79	0.32	0.31	-0.02	-0.07

* Did not produce stable nanosuspensions, hence not mucus-penetrating (velocity in CVM not measured)
** Aggregated in CVM, hence not mucus-penetrating (velocity in CVM not measured)

[000486] It was discovered that nanoparticles obtained in the presence of certain (but, importantly, not all) surface-altering agents migrate through CVM at the same rate or nearly the same velocity as the positive control. Specifically, pyrene nanoparticles stabilized with Pluronics® F127, F108, P123, P105, and P103 exhibited$\langle V_{mean} \rangle$ that exceeded those of the negative controls by approximately an order of magnitude and were indistinguishable, within experimental error, from those of the positive controls, as shown in Table 4 and FIG. 2A. For these samples, $\langle V_{mean} \rangle_{rel}$ values exceeded 0.5, as shown in FIG. 2B.

[000487] On the other hand, pyrene nanoparticles obtained with the other surface-altering agents were predominantly or completely immobilized as demonstrated by respective $\langle V_{mean} \rangle_{rel}$ values of no greater than 0.4 and, with most surface-altering agents, no greater than 0.1 (Table 4 and FIG. 2B). Additionally, FIGs. 3A-3D are histograms showing distribution of V_{mean} within an ensemble of particles. These histograms illustrate muco-diffusive behavior of samples stabilized with Pluronic® F127 and Pluronic® F108 (similar histograms were obtained for samples stabilized with Pluronic® P123, P105, and P103, but are not shown here) as opposed to muco-adhesive behavior of samples stabilized with Pluronic® 87, and Kollidon 25 (chosen as representative muco-adhesive samples).

[000488] To identify the characteristics of Pluronics® that render pyrene nanocrystals mucus penetrating, $\langle V_{mean} \rangle_{rel}$ of the Pyrene/ Pluronic® nanocrystals was mapped with respect to molecular weight of the PPO block and the PEO weight content (%) of the Pluronics® used (FIG. 4). It was concluded that at least those Pluronics® that have the PPO block of at least 3 kDa and the PEO content of at least about 30 wt% rendered the nanocrystals mucus-penetrating. Without wishing to be bound by any theory, it is believed that the hydrophobic PPO block can provide effective association with the surface of the core particles if the molecular weight of that block is sufficient (*e.g.*, at least about 3 kDa in some embodiments); while the hydrophilic PEO blocks are present at the surface of the coated particles and can shield the coated particles from adhesive interactions with mucin fibers if the PEO content of

the Pluronic® is sufficient (*e.g.*, at least 30 wt% in some embodiments). As described herein, in some embodiments the PEO content of the surface-altering agent may be chosen to be greater than or equal to about 10 wt% (*e.g.*, at least about 15 wt%, or at least about 20 wt%), as a 10 wt% PEO portion rendered the particles mucoadhesive.

Example 2

[000489] This example describes the formation of mucus-penetrating particles using various non-polymeric solid particles.

[000490] The technique described in Example 1 was applied to other non-polymeric solid particles to show the versatility of the approach. F127 was used as the surface-altering agent for coating a variety of active pharmaceuticals used as core particles. Sodium dodecyl sulfate (SDS) was chosen as a negative control so that each drug was compared to a similarly sized nanoparticle of the same compound. An aqueous dispersion containing the pharmaceutical agent and Pluronic® F127 or SDS was milled with milling media until particle size was reduced below 300nm. Table 5 lists the particle sizes for a representative selection of drugs that were milled using this method.

[000491] **Table 5.** Particle sizes for a representative selection of drugs milled in the presence of SDS and F127.

Drug	Stabilizer	Z-Ave D (nm)	PDI
Fluticasone propionate	F127	203	0.114
	SDS	202	0.193
Furosemide	F127	217	0.119
	SDS	200	0.146
Itraconazole	F127	155	0.158
	SDS	168	0.163
Prednisolone	F127	273	0.090
	SDS	245	0.120
Loteprednol etabonate	F127	241	0.123
	SDS	241	0.130
Budesonide	F127	173	0.112
	SDS	194	0.135
Indomethacin	F127	225	0.123
	SDS	216	0.154

[000492] In order to measure the ability of drug nanoparticles to penetrate mucus a new assay was developed which measures the mass transport of nanoparticles into a mucus sample. Most drugs are not naturally fluorescent and are therefore difficult to measure with particle tracking microscopy techniques. The newly-developed bulk transport assay does not require the analyzed particles to be fluorescent or labeled with dye. In this method, 20 μL of CVM is collected in a capillary tube and one end is sealed with clay. The open end of the capillary tube is then submerged in 20 μL of an aqueous suspension of particles which is 0.5% w/v drug. After the desired time, typically 18 hours, the capillary tube is removed from the suspension and the outside is wiped clean. The capillary containing the mucus sample is placed in an ultracentrifuge tube. Extraction media is added to the tube and incubated for 1 hour while mixing which removes the mucus from the capillary tube and extracts the drug from the mucus. The sample is then spun to remove mucins and other non-soluble components. The amount of drug in the extracted sample can then be quantified using HPLC. The results of these experiments are in good agreement with those of the microscopy method, showing clear differentiation in transport between mucus penetrating particles and conventional particles. The transport results for a representative selection of drugs are shown in FIG. 5. These results corroborate microscopy / particle tracking findings with Pyrene and demonstrate the extension to common active pharmaceutical compounds; coating non-polymeric solid nanoparticles with F127 enhances mucus penetration.

[000493] In Examples 1-2, 4-6, and 10, cervicovaginal mucus (CVM) samples were obtained from healthy females volunteers age 18 years or older. CVM was collected by inserting a Softcup® menstrual collection cup into the vaginal tract as described by the product literature for between 30 seconds and 2 minutes. After removal the CVM was then collected from the Softcup® by gentle centrifugation at ~30xG to ~120xG in a 50 mL centrifuge tube. In Example 1, CVM was used undiluted and fresh (stored for no longer than 7 days under refrigerated conditions). Barrier and transport of all CVM samples used in Example 1 were verified with negative (200nm carboxylated polystyrene particles) and positive (200nm polystyrene particles modified with PEG 5K) controls. In Example 2, CVM was lyophilized and reconstituted. In Example 2, mucus was frozen at -50 °C and then lyophilized to dryness. Samples were then stored at -50°C. Before use, the mucus was reconstituted by grinding the solid into a fine powder using a mortar and pestle followed by

water addition to a final volume equal to the original volume to 2 times the original volume. The reconstituted mucus was then incubated at 4°C for 12 hours and used as described in Example 2. Barrier and transport of all CVM samples used in Example 2 were verified with negative (200nm carboxylated polystyrene particles) and positive (F127 coated 200nm polystyrene particles) controls.

Example 3

[000494] This example describes the formation of mucus-penetrating particles using a core comprising the drug loteprednol etabonate (LE).

[000495] In order to demonstrate the value of enhanced mucus penetration in the delivery of non-polymeric solid particles, an MPP formulation of loteprednol etabonate (LE MPP; LE particles coated with Pluronic® F127 made by the method described in Example 2) was compared to the currently marketed formulation, Lotemax®. Lotemax® is a steroid eye drop approved for the treatment of surface ocular inflammation. Conventional particles, such as those in Lotemax®, are extensively trapped by the peripheral rapidly-cleared mucus layer in the eye and, hence, are also rapidly cleared. LE MPPs are able to avoid adhesion to, and effectively penetrate through, mucus to facilitate sustained drug release directly to underlying tissues. Enhancing drug exposure at the target site would allow the overall dose to be reduced, increasing patient compliance and safety. *In vivo*, a single topical instillation of LE MPP to New Zealand white rabbits produced significantly higher drug levels in palpebral conjunctiva, bulbar conjunctiva, and cornea compared to an equivalent dose of Lotemax® (FIGs. 6A-6C). At 2 hours LE levels from MPP are 6, 3, and 8 times higher than from Lotemax® (palpebral, bulbar, and cornea, respectively). Notably, LE levels from MPP are approximately 2 times higher at 2 hours than levels from Lotemax® at 30 minutes. These results demonstrate the enhanced exposure achievable with the MPP technology over the commercial formulation.

Example 4

[000496] The following describes a non-limiting example of a method of forming mucus-penetrating particles from pre-fabricated polymeric particles by physical adsorption of certain poly(vinyl alcohol) polymers (PVA). Carboxylated polystyrene nanoparticles (PSCOO) were

used as the prefabricated particle / core particle with a well-established strongly mucoadhesive behavior. The PVAs acted as surface-altering agents forming coatings around the core particles. PVA of various molecular weights (MW) and hydrolysis degrees were evaluated to determine effectiveness of the coated particles in penetrating mucus.

[000497] PSCOO particles were incubated in aqueous solution in the presence of various PVA polymers to determine whether certain PVAs can physically (non-covalently) coat the core particle with a mucoinert coating that would minimize particle interactions with mucus constituents and lead to rapid particle penetration in mucus. In these experiments, the PVA acted as a coating around the core particles, and the resulting particles were tested for their mobility in mucus, although in other embodiments, PVA may be exchanged with other surface-altering agents that can increase mobility of the particles in mucus. The PVAs tested ranged in the average molecular weight from 2 kDa to 130 kDa and in the average hydrolysis degree from 75% to 99+%. The PVAs that were tested are listed in Table 1, shown above.

[000498] The particle modification process was as follows: 200nm carboxylated-modified red fluorescent polystyrene nanoparticles (PSCOO) were purchased from Invitrogen. The PSCOO particles (0.4 - 0.5 wt%) were incubated in an aqueous PVA solution (0.4 – 0.5 wt%) for at least 1 hour at room temperature.

[000499] The mobility and distribution of the modified nanoparticles in human cervicovaginal mucus (CVM) were characterized using fluorescence microscopy and multiple particle tracking software. In a typical experiment, ≤0.5 μL of an incubated nanosuspension (diluted ~10x with 0.5 wt% aqueous solution of a corresponding PVA) was added to 20 μl of fresh CVM along with controls. Conventional nanoparticles (200 nm blue fluorescent carboxylate-modified polystyrene microspheres from Invitrogen) were used as a negative control to confirm the barrier properties of the CVM samples. Yellow-green fluorescent polystyrene nanoparticles covalently coated with PEG 2 kDa were used as a positive control with well-established MPP behavior. Using a fluorescent microscope equipped with a CCD camera, 15 s movies were captured at a temporal resolution of 66.7 ms (15 frames/s) under 100x magnification from several areas within each sample for each type of particles: sample (observed through a Texas Red filter set), negative control (observed through a DAPI filter set), and positive control (observed through a FITC filter set). Next, using an advanced image processing software, individual trajectories of multiple particles

were measured over a time-scale of at least 3.335 s (50 frames). Resulting transport data are presented here in the form of trajectory-mean velocity V_{mean}, *i.e.*, velocity of an individual particle averaged over its trajectory, and ensemble-average velocity $\langle V_{mean} \rangle$, *i.e.*, V_{mean} averaged over an ensemble of particles. To enable easy comparison between different samples and normalize velocity data with respect to natural variability in penetrability of CVM samples, ensemble-average (absolute) velocity is then converted to relative sample velocity $\langle V_{mean} \rangle_{rel}$ according to the formula shown in Equation 1. Multiple particle tracking confirmed that in all tested CVM samples the negative controls were constrained, while the positive controls were mobile as demonstrated by the differences in $\langle V_{mean} \rangle$ for the positive and negative controls (Table 6).

[000500] **Table 6.** Transport of nanoparticles incubated with various PVA (sample) and controls in CVM: Ensemble-average velocity $\langle V_{mean} \rangle$ (μm/s) and relative sample velocity $\langle V_{mean} \rangle_{rel}$.

Stabilizer	Negative Control		Positive Control		Sample		Sample (relative)	
	$\langle V_{mean} \rangle$	SD	$\langle V_{mean} \rangle$	SD	$\langle V_{mean} \rangle$	SD	$\langle V_{mean} \rangle_{rel}$	SD
PVA2K75	1.39	0.33	3.3	0.68	3.44	0.7	1.07	0.59
PVA9K80	0.4	0.08	5.13	1.16	4.88	1.74	0.95	0.44
PVA13K87	0.56	0.61	5.23	1.24	4.92	1.77	0.93	0.49
PVA31K87	0.53	0.63	4.48	1.38	3.69	1.94	0.80	0.60
PVA57K86	0.5	0.25	5.74	1.11	4.76	0.91	0.81	0.25
PVA85K87	0.29	0.28	4.25	0.97	4.01	0.71	0.94	0.31
PVA105K80	0.98	0.52	5.44	0.86	4.93	0.66	0.89	0.27
PVA130K87	1.41	0.56	3.75	0.82	3.57	0.6	0.92	0.53
PVA95K95	0.51	0.36	3.19	0.68	0.45	0.19	-0.02	-0.15
PVA13K98	0.43	0.17	3.42	1.65	0.5	0.76	0.02	0.26
PVA31K98	0.41	0.23	6.03	1.19	0.26	0.14	-0.03	-0.05
PVA85K99	0.28	0.1	4.7	0.82	0.53	0.77	0.06	0.18

[000501] It was discovered that nanoparticles incubated in the presence of certain (but, interestingly, not all) PVA transported through CVM at the same rate or nearly the same velocity as the positive control. Specifically, the particles stabilized with PVA2K75, PVA9K80, PVA13K87, PVA31K87, PVA57K86, PVA85K87, PVA105K80, and PVA130K87 exhibited $\langle V_{mean} \rangle$ that significantly exceeded those of the negative controls and were indistinguishable, within experimental error, from those of the positive controls. The

results are shown in Table 6 and FIG. 7A. For these samples, $\langle V_{mean} \rangle_{rel}$ values exceeded 0.5, as shown in FIG. 7B.

[000502] On the other hand, nanoparticles incubated with PVA95K95, PVA13K98, PVA31K98, and PVA85K99 were predominantly or completely immobilized as demonstrated by respective $\langle V_{mean} \rangle_{rel}$ values of no greater than 0.1 (Table 6 and FIG. 7B).

[000503] To identify the characteristics of the PVA that render particles mucus penetrating, $\langle V_{mean} \rangle_{rel}$ of the nanoparticles prepared by incubation with the various PVAs was mapped with respect to MW and hydrolysis degree of the PVAs used (FIG. 8). It was concluded that at least those PVAs that have the hydrolysis degree of less than 95% rendered the nanocrystals mucus-penetrating. Without wishing to be bound by any theory, it is believed that the unhydrolyzed (vinyl acetate) units of PVA can provide effective hydrophobic association with the surface of the core particles if the content of these segments in the PVA is sufficient (*e.g.*, greater than 5% in some embodiments); while the hydrophilic (vinyl alcohol) units of PVA present at the surface of the coated particles render them hydrophilic and can shield the coated particles from adhesive interactions with mucus.

[000504] To further confirm the ability of the specific PVA grades to convert mucoadhesive particles into mucus-penetrating particles by physical adsorption, PSCOO nanoparticles incubated with the various PVAs were tested using the bulk transport assay. In this method, 20 μL of CVM was collected in a capillary tube and one end is sealed with clay. The open end of the capillary tube is then submerged in 20 μL of an aqueous suspension of particles which is 0.5% w/v drug. After the desired time, typically 18 hours, the capillary tube is removed from the suspension and the outside is wiped clean. The capillary containing the mucus sample is placed in an ultracentrifuge tube. Extraction media is added to the tube and incubated for 1 hour while mixing which removes the mucus from the capillary tube and extracts the drug from the mucus. The sample is then spun to remove mucins and other non-soluble components. The amount of drug in the extracted sample can then be quantified using HPLC. The results of these experiments are in good agreement with those of the microscopy method, showing clear differentiation in transport between positive (mucus-penetrating particles) and negative controls (conventional particles). The bulk transport results for PSCOO nanoparticles incubated with the various PVAs are shown in FIG. 9. These results corroborate microscopy / particle tracking findings with PSCOO nanoparticles incubated with

the various PVAs and demonstrate the incubating nanoparticles with partially hydrolyzed PVAs enhances mucus penetration.

Example 5

[000505] The following describes a non-limiting example of a method of forming mucus-penetrating particles by an emulsification process in the presence of certain poly(vinyl alcohol) polymers (PVA). Polylactide (PLA), a biodegradable pharmaceutically relevant polymer was used as a material to form the core particle via an oil-in-water emulsification process. The PVAs acted as emulsion surface-altering agents and surface-altering agents forming coatings around the produced core particles. PVA of various molecular weights (MW) and hydrolysis degrees were evaluated to determine effectiveness of the formed particles in penetrating mucus.

[000506] PLA solution in dichloromethane was emulsified in aqueous solution in the presence of various PVA to determine whether certain PVAs can physically (non-covalently) coat the surface of generated nanoparticles with a coating that would lead to rapid particle penetration in mucus. In these experiments, the PVA acted as an surfactant that forms a stabilizing coating around droplets of emulsified organic phase that, upon solidification, form the core particles The resulting particles were tested for their mobility in mucus, although in other embodiments, PVA may be exchanged with other surface-altering agents that can increase mobility of the particles in mucus. The PVAs tested ranged in the average molecular weight from 2 kDa to 130 kDa and in the average hydrolysis degree from 75% to 99+%. The PVAs that were tested are listed in Table 1, shown above.

[000507] The emulsification-solvent evaporation process was as follows: Approximately 0.5 mL of 20-40 mg/ml solution of PLA (Polylactide grade 100DL7A, purchased from Surmodics) in dichloromethane was emulsified in approximately 4mL of an aqueous PVA solution (0.5 – 2 wt%) by sonication to obtain a stable emulsion with the target number-average particle size of <500 nm. Obtained emulsions were immediately subjected to exhaustive rotary evaporation under reduced pressure at room temperature to remove the organic solvent. Obtained suspensions were filtered through 1 micron glass fiber filters to remove any agglomerates. Table 7Table lists the particle size characteristics of the nanosuspensions obtained by this emulsification procedure with the various PVA. In all

cases, a fluorescent organic dye Nile Red was added to the emulsified organic phase to fluorescently label the resulting particles.

[000508] **Table 7.** Particle size measured by DLS in nanosuspensions obtained by the emulsification process with various PVA.

PVA Grade	Z-Ave D (nm)	N-Ave D (nm)
PVA2K75	186	156
PVA10K80	208	173
PVA13K98	245	205
PVA31K87	266	214
PVA31K98	245	228
PVA85K87	356	301
PVA85K99	446	277
PVA95K95	354	301
PVA105K80	361	300
PVA130K87	293	243

[000509] The mobility and distribution of the produced nanoparticles in human cervicovaginal mucus (CVM) were characterized using fluorescence microscopy and multiple particle tracking software. In a typical experiment, ≤0.5uL of a nanosuspension (diluted if necessary to the PVA concentration of ~0.5%) was added to 20 μl of fresh CVM along with controls. Conventional nanoparticles (200 nm blue fluorescent carboxylate-modified polystyrene microspheres from Invitrogen) were used as a negative control to confirm the barrier properties of the CVM samples. Yellow-green fluorescent polystyrene nanoparticles covalently coated with PEG 2 kDa were used as a positive control with well-established MPP behavior. Using a fluorescent microscope equipped with a CCD camera, 15 s movies were captured at a temporal resolution of 66.7 ms (15 frames/s) under 100x magnification from several areas within each sample for each type of particles: sample (observed through a Texas Red filter set due to the encapsulated Nile Red), negative control (observed through a DAPI filter set), and positive control (observed through a FITC filter

set). Next, using an advanced image processing software, individual trajectories of multiple particles were measured over a time-scale of at least 3.335 s (50 frames). Resulting transport data are presented here in the form of trajectory-mean velocity V_{mean}, *i.e.*, velocity of an individual particle averaged over its trajectory, and ensemble-average velocity $\langle V_{mean} \rangle$, *i.e.*, V_{mean} averaged over an ensemble of particles. To enable easy comparison between different samples and normalize velocity data with respect to natural variability in penetrability of CVM samples, ensemble-average (absolute) velocity is then converted to relative sample velocity $\langle V_{mean} \rangle_{rel}$ according to the formula shown in Equation 1. Multiple particle tracking confirmed that in all tested CVM samples the negative controls were constrained, while the positive controls were mobile as demonstrated by the differences in $\langle V_{mean} \rangle$ for the positive and negative controls (Table 8).

[000510] Table 8. Transport of PLA nanoparticles obtained by the emulsification process with various PVAs (sample) and controls in CVM: Ensemble-average velocity $\langle V_{mean} \rangle$ (um/s) and relative sample velocity $\langle V_{mean} \rangle_{rel}$.

Stabilizer	Negative Control		Positive Control		Sample		Sample (relative)	
	$\langle V_{mean} \rangle$	SD	$\langle V_{mean} \rangle$	SD	$\langle V_{mean} \rangle$	SD	$\langle V_{mean} \rangle_{rel}$	SD
PVA2K75	0.95	0.64	5.5	0.92	5.51	1.2	1.00	0.39
PVA9K80	0.72	0.47	5.61	0.79	4.6	1.5	0.79	0.35
PVA31K87	0.63	0.60	4.94	1.50	3.36	1.84	0.63	0.51
PVA85K87	0.57	0.4	4.49	1.21	2.9	1.56	0.59	0.45
PVA105K80	0.69	0.56	4.85	1.54	3.55	1.26	0.69	0.43
PVA130K87	0.95	0.54	4.98	1.25	3.46	1.23	0.62	0.39
PVA95K95	1.39	1.28	5.72	1.57	1.63	1.5	0.06	0.46
PVA13K98	1.02	0.49	5.09	0.99	2.61	1.54	0.39	0.41
PVA31K98	1.09	0.6	5.09	0.9	2.6	1.13	0.38	0.34
PVA85K99	0.47	0.33	5.04	2.2	0.81	0.77	0.07	0.19

[000511] It was discovered that nanoparticles prepared in the presence of certain (but, interestingly, not all) PVA transported through CVM at the same rate or nearly the same velocity as the positive control. Specifically, the particles stabilized with PVA2K75, PVA9K80, PVA13K87, PVA31K87, PVA85K87, PVA105K80, and PVA130K87 exhibited $\langle V_{mean} \rangle$ that significantly exceeded those of the negative controls and were indistinguishable,

within experimental error, from those of the positive controls, as shown in Table 8 and FIG. 10A. For these samples, $<V_{mean}>_{rel}$ values exceeded 0.5, as shown in FIG. 10B.

[000512] On the other hand, pyrene nanoparticles obtained with PVA95K95, PVA13K98, PVA31K98, and PVA85K99 were predominantly or completely immobilized as demonstrated by respective $<V_{mean}>_{rel}$ values of no greater than 0.4 (Table 8 and FIG. 10B). To identify the characteristics of the PVA that render particles mucus penetrating, $<V_{mean}>_{rel}$ of the nanoparticles prepared with the various PVAs was mapped with respect to MW and hydrolysis degree of the PVAs used (Table 6 and FIG. 7B). It was concluded that at least those PVAs that have the hydrolysis degree of less than 95% rendered the nanocrystals mucus-penetrating. Without wishing to be bound by any theory, it is believed that the unhydrolyzed (vinyl acetate) units of PVA can provide effective hydrophobic association with the surface of the core particles if the content of these segments in the PVA is sufficient (*e.g.*, greater than 5% in some embodiments); while the hydrophilic (vinyl alcohol) units of PVA present at the surface of the coated particles render them hydrophilic and can shield the coated particles from adhesive interactions with mucus.

Example 6

[000513] The following describes a non-limiting example of a method of forming mucus-penetrating non-polymeric solid particles by milling in the presence of certain poly(vinyl alcohol) polymers (PVA). Pyrene, a model hydrophobic compound, was used as the core particle processed by a milling. The PVA acted as milling aids facilitating particle size reduction of the core particles and surface-altering agents forming coatings around the core particles. PVA of various molecular weights (MW) and hydrolysis degrees were evaluated to determine effectiveness of the milled particles in penetrating mucus.

[000514] Pyrene was milled in aqueous dispersions in the presence of various PVA to determine whether PVAs of certain MW and hydrolysis degree can: 1) aid particle size reduction to several hundreds of nanometers and 2) physically (non-covalently) coat the surface of generated nanoparticles with a mucoinert coating that would minimize particle interactions with mucus constituents and prevent mucus adhesion. In these experiments, the PVA acted as a coating around the core particles, and the resulting particles were tested for their mobility in mucus. The PVAs tested ranged in the average molecular weight from 2 kDa

to 130 kDa and in the average hydrolysis degree from 75% to 99+%. The PVAs that were tested are listed in Table 1, shown above. A variety of other polymers, oligomers, and small molecules listed in Table , including pharmaceutically relevant excipients such as polyvinylpyrrolidones (Kollidon), hydroxypropyl methylcellulose (Methocel), Tween, Span, *etc.*, were tested in a similar manner.

[000515] **Table 9.** Other surface-altering agents tested with pyrene as a model compound.

Chemical Family	Grades
Polyvinylpyrrolidone (PVP)	Kollidon 17 Kollidon 25 Kollindon 30
PVA-poly(ethylene glycol) graft-copolymer	Kollicoat IR
Hydroxypropyl methylcellulose (HPMC)	Methocel E50 Methocel K100
Non-ionic polyoxyethylene surfactants	Solutol HS 15 Span 20 Span 80 Triton X100 Tween 20 Tween 80 Tyloxapol
Non-ionic small molecule surfactants	Octyl glucoside
Ionic small molecule surfactants	Cetytrimethylammonium bromide (CTAB) Sodium dodecyl sulfate (SDS)

[000516] An aqueous dispersion containing pyrene and one of the surface-altering agents listed above was stirred with milling media until particle size was reduced below 500 nm (as measured by dynamic light scattering). Table 10 lists particle size characteristics of pyrene particles obtained by milling in the presence of the various surface-altering agents. When Span 20, Span 80, or Octyl glucoside was used as surface-altering agents, stable nanosuspensions could not be obtained. Therefore, these surface-altering agents were excluded from further investigation due to their inability to effectively aid particle size reduction.

[000517] Table 10. Particle size measured by DLS in nanosuspensions obtained by milling of pyrene with various surface-altering agents.

Stabilizer	Z-Ave D (nm)	N-Ave D (nm)
PVA2K75	340	301
PVA9K80	380	337
PVA13K87	375	326
PVA13K98	396	314
PVA31K87	430	373
PVA31K98	344	220
PVA85K87	543	434
PVA85K99	381	236
PVA95K95	534	392
PVA130K87	496	450
Kollidon 17	237	163
Kollidon 25	307	210
Kollindon 30	255	185
Kollicoat IR	364	192
Methocel E50	244	160
Methocel K100	375	216
Tween 20	567	381
Tween 80	553	322
Solutol HS	576	378
Triton X100	410	305
Tyloxapol	334	234
Cremophor RH40	404	373
Span 20	not measurable*	
Span 80	not measurable*	
Octyl glucoside	not measurable*	
SDS	603	377
CTAB	432	354

* milling with Span 20, Span 80, Octyl glucoside failed to effectively reduce pyrene particle size and produce stable nanosuspensions.

[000518] The mobility and distribution of the produced pyrene nanoparticles in human cervicovaginal mucus (CVM) were characterized using fluorescence microscopy and multiple particle tracking software. In a typical experiment, ≤0.5uL of a nanosuspension (diluted if necessary to the surfactant concentration of ~1%) was added to 20 μl of fresh CVM along with controls. Conventional nanoparticles (200 nm yellow-green fluorescent carboxylate-modified polystyrene microspheres from Invitrogen) were used as a negative control to confirm the barrier properties of the CVM samples. Red fluorescent polystyrene nanoparticles covalently coated with PEG 5 kDa were used as a positive control with well-established MPP behavior. Using a fluorescent microscope equipped with a CCD camera, 15 s movies were captured at a temporal resolution of 66.7 ms (15 frames/s) under 100 × magnification from several areas within each sample for each type of particles: sample (pyrene), negative control, and positive control (natural blue fluorescence of pyrene allowed observing of pyrene nanoparticles separately from the controls). Next, using an advanced image processing software, individual trajectories of multiple particles were measured over a time-scale of at least 3.335 s (50 frames). Resulting transport data are presented here in the form of trajectory-mean velocity V_{mean}, *i.e.*, velocity of an individual particle averaged over its trajectory, and ensemble-average velocity $\langle V_{mean} \rangle$, *i.e.*, V_{mean} averaged over an ensemble of particles. To enable easy comparison between different samples and normalize velocity data with respect to natural variability in penetrability of CVM samples, ensemble-average (absolute) velocity is then converted to relative sample velocity $\langle V_{mean} \rangle_{rel}$ according to the formula shown in Equation 1.

[000519] Prior to quantifying mobility of pyrene particles, their spatial distribution in the mucus sample was assessed visually. It was found that pyrene/Methocel nanosuspensions did not achieve uniform distribution in CVM and strongly aggregated into domains much larger than the mucus mesh size (data not shown). Such aggregation is indicative of mucoadhesive behavior and effectively prevents mucus penetration. Therefore, further quantitative analysis of particle mobility was deemed unnecessary. Similarly to the positive control, all other tested pyrene/stabilizer systems achieved a fairly uniform distribution in CVM. Multiple particle tracking confirmed that in all tested CVM samples the negative controls were

constrained, while the positive controls were mobile as demonstrated by the differences in $\langle V_{mean} \rangle$ for the positive and negative controls (Table).

[000520] Table 11. Transport of pyrene nanoparticles (sample) obtained with various surface-altering agents and controls in CVM: Ensemble-average velocity $\langle V_{mean} \rangle$ (um/s) and relative sample velocity $\langle V_{mean} \rangle_{rel}$.

Stabilizer	Negative Control		Positive Control		Sample		Sample (relative)	
	$\langle V_{mean} \rangle$	SD	$\langle V_{mean} \rangle$	SD	$\langle V_{mean} \rangle$	SD	$\langle V_{mean} \rangle_{rel}$	SD
PVA2K75	0.4	0.24	5.73	0.73	4.73	1.08	0.81	0.24
PVA9K80	0.36	0.20	6.00	0.70	6.19	1.13	1.03	0.24
PVA13K87	1.01	1.21	5.09	0.98	4.54	1.03	0.87	0.51
PVA31K87	1.28	1.14	4.88	0.6	4.57	1.123	0.91	0.55
PVA85K87	1.05	0.9	4.1	0.57	3.3	0.98	0.74	0.51
PVA130K87	0.51	0.82	5.29	0.73	4.12	1.49	0.76	0.40
PVA95K95	0.4	0.27	4.53	1.03	0.67	0.6	0.07	0.16
PVA13K98	0.61	0.42	2.13	0.99	1.29	0.57	0.45	0.56
PVA31K98	0.68	0.87	5.77	1.24	2.69	2.02	0.39	0.45
PVA85K99	0.43	0.23	5.42	0.97	2.23	1.60	0.36	0.33
Kollicoat IR	0.62	0.62	5.39	0.55	0.92	0.81	0.06	0.22
Kollidon 17	1.69	1.8	5.43	0.98	0.82	0.59	-0.23	-0.52
Kollidon 25	0.41	0.34	5.04	0.64	1.29	1.09	0.19	0.25
Kollindon 30	0.4	0.2	4.28	0.57	0.35	0.11	-0.01	0.06
Methocel E50*								
Methocel K100*								
Tween 20	0.77	0.93	5.35	1.76	1.58	2.02	0.18	0.49
Tween 80	0.46	0.34	3.35	1.89	0.94	0.5	0.17	0.24
Solutol HS	0.42	0.13	3.49	0.5	0.8	0.6	0.12	0.20
Triton X100	0.26	0.13	4.06	1.11	0.61	0.19	0.09	0.07
Tyloxapol	0.5	0.5	3.94	0.58	0.42	0.23	-0.02	-0.16
Cremophor RH40	0.48	0.21	3.2	0.97	0.49	0.24	0.00	0.12
SDS	0.3	0.12	5.99	0.84	0.34	0.15	0.01	0.03
CTAB	0.39	0.09	4.75	1.79	0.32	0.31	-0.02	-0.07

* Aggregated in CVM, hence not mucus-penetrating (velocity in CVM not measured)

[000521] It was discovered that nanoparticles obtained in the presence of certain (but, interestingly, not all) PVA transported through CVM at the same rate or nearly the same velocity as the positive control. Specifically, pyrene nanoparticles stabilized with PVA2K75, PVA9K80, PVA13K87, PVA31K87, PVA85K87, and PVA130K87 exhibited $\langle V_{mean} \rangle$ that significantly exceeded those of the negative controls and were indistinguishable, within

experimental error, from those of the positive controls, as shown in Table 11and FIG. 12A. For these samples, $<V_{mean}>_{rel}$ values exceeded 0.5, as shown in FIG. 12B.

[000522] On the other hand, pyrene nanoparticles obtained with the other surface-altering agents, including PVA95K95, PVA13K98, PVA31K98, and PVA85K99, were predominantly or completely immobilized as demonstrated by respective $<V_{mean}>_{rel}$ values of no greater than 0.5 and, with most surface-altering agents, no greater than 0.4 (Table 11 and FIG. 12 B). Additionally, FIGs. 13A-13F are histograms showing distribution of V_{mean} within an ensemble of particles. These histograms illustrate muco-diffusive behavior of samples stabilized with PVA2K75 and PVA9K80 (similar histograms were obtained for samples stabilized with PVA13K87, PVA31K87, PVA85K87, and PVA130K87, but are not shown here) as opposed to muco-adhesive behavior of samples stabilized with PVA31K98, PVA85K99, Kollidon 25, and Kollicoat IR (chosen as representative muco-adhesive samples).

[000523] To identify the characteristics of the PVA that render pyrene nanocrystals mucus penetrating, $<V_{mean}>_{rel}$ of the pyrene nanocrystals stabilized with various PVAs was mapped with respect to MW and hydrolysis degree of the PVAs used (FIG. 14). It was concluded that at least those PVAs that have the hydrolysis degree of less than 95% rendered the nanocrystals mucus-penetrating. Without wishing to be bound by any theory, it is believed that the unhydrolyzed (vinyl acetate) segments of PVA can provide effective hydrophobic association with the surface of the core particles if the content of these segments in the PVA is sufficient (*e.g.*, greater than 5% in some embodiments); while the hydrophilic (vinyl alcohol) segments of PVA present at the surface of the coated particles render them hydrophilic and can shield the coated particles from adhesive interactions with mucus.

Example 7

[000524] This example shows an improved ophthalmic delivery of a pharmaceutical agent from mucus-penetrating particles comprised of a polymeric core encapsulating the pharmaceutical agent and mucus-penetrating particles comprised of a drug core without any polymeric carrier.

[000525] In order to demonstrate the value of enhanced mucus penetration in the delivery of pharmaceutical agents to the eye, concentrations of loteprednol etabonate in the cornea of

New Zealand White Rabbits were measured following a single equivalent dose of Lotemax® (the currently marketed ophthalmic suspension of loteprednol etabonate (LE), a soft steroid indicated for the treatment of ocular inflammation), MPP1 (mucus-penetrating particles comprised of a polymeric core encapsulating LE), and MPP2 (mucus-penetrating particles comprised of the LE core). MPP1 particles were made by nanoprecipitation of loteprednol etabonate with poly(lactide) (100DL2A from Surmodics) from a solution in acetone into an aqueous solution. MPP2 particles were made by the method described in Example 2. Both MPP1 and MPP2 particles were coated with Pluronic® F127. As shown in FIG. 17A and FIG. 17B, MPP1 and MPP2 formulations resulted in higher drug levels in the cornea compared to those from the commercial drop having the same concentration of particles as that of the MPP formulations. Without wishing to be bound by any theory, it is believed that conventional particles, such as those in Lotemax®, are extensively trapped by the peripheral rapidly-cleared mucus layer in the eye and, hence, are rapidly cleared; while the MPP particles are able to avoid adhesion to mucus and, hence, achieve prolonged residence at the ocular surface and facilitate sustained drug release directly to underlying tissues.

Example 8

[000526] This example shows an improved delivery of a pharmaceutical agent from mucus-penetrating particles coated with Pluronic® F127 to the back of the eye, including the retina, choroid and sclera, which is not seen with conventional particles. Delivery to the cornea and iris was also improved for particles coated with Pluronic® F127 compared conventional particles.

[000527] In order to demonstrate the value of enhanced mucus penetration in the delivery of non-polymeric solid particles, an MPP formulation of loteprednol etabonate (LE MPP; LE particles coated with Pluronic® F127 made by the method described in Example 2) was compared to the currently marketed formulation, Lotemax®. Lotemax® is a steroid eye drop approved for the treatment of ocular inflammation. Conventional particles, such as those in Lotemax®, are extensively trapped by the peripheral rapidly-cleared mucus layer in the eye and, hence, are rapidly cleared. LE MPP are able to avoid adhesion to, and effectively penetrate through, mucus to facilitate sustained drug release directly to underlying tissues. Not only is delivery to the ocular surface enhanced as described in Example 3, but delivery to

the middle and back of the eye is also enhanced. In vivo, a single topical instillation of LE MPP to New Zealand white rabbits produced significantly higher drug levels in cornea, iris/ciliary body, aqueous humor, retina, choroid, and sclera compared to an equivalent dose of Lotemax® (FIG. 18). Current commercial eye drops are used in the treatment of anterior ocular disorders, but are not effective in treating posterior disorders because drug does not reach the back of the eye. Here the retina, choroid and sclera are sampled using an 8mm punch where the human macula would be located. In the back of the eye LE levels are below the limit of detection for Lotemax®, while LE MPP deliver detectable levels of LE to retina, choroid, and sclera. These results demonstrate the utility of the non-polymeric solid MPP approach over conventional approaches.

Example 9

[000528] This example describes the measurement of the density of Pluronic® F127 on the surface of particles comprising a nanocrystal core of a pharmaceutical agent.

[000529] An aqueous dispersion containing a pharmaceutical agent and Pluronic® F127 was milled with milling media until particle size was reduced below 300nm. A small volume from the milled suspension was diluted to an appropriate concentration (~100μg/mL, for example) and the z-average diameter was taken as a representative measurement of particle size. The remaining suspension was then divided into two aliquots. Using HPLC, the first aliquot was assayed for the total concentration of drug (here, loteprednol eltabonate or fluticasone propionate) and for the total concentration of surface-altering moiety (here, Pluronic® F127). Again using HPLC the second aliquot was assayed for the concentration of free or unbound surface-altering moiety. In order to get only the free or unbound surface-altering moiety from the second aliquot, the particles, and therefore any bound surface-altering moiety, were removed by ultracentrifugation. By subtracting the concentration of the unbound surface-altering moiety from the total concentration of surface-altering moiety, the concentration of bound surface-altering moiety was determined. Since the total concentration of drug was also determined from the first aliquot, the mass ratio between the core material and the surface-altering moiety can be determined. Using the molecular weight of the surface-altering moiety, the number of surface-altering moiety to mass of core material can be calculated. To turn this number into a surface density measurement, the surface area per mass of core material needs

to be calculated. The volume of the particle is approximated as that of a sphere with the diameter obtained from DLS allowing for the calculation of the surface area per mass of core material. In this way the number of surface-altering moieties per surface area is determined. FIG. 19 shows the results of surface-moiety density determination for loteprednol ltabonate and fluticasone propionate.

Example 10

[000530] The following describes a non-limiting example of a method of formingmucus-penetrating particles using a core comprising the drug loteprednol etabonate (LE) by milling in the presence of various Pluronic® surface-altering agents.

[000531] LE was milled as an aqueous suspension with milling media and in the presence of a stabilizer. Pluronics of various grades (listed in Table 12) were tested as surface-altering agents in order to determine whether certain Pluronic grades can: 1) aid reduction of particle size of LE to the submicron range and 2) physically (non-covalently) coat the surface of generated LE nanoparticles with a mucoinert coating that would minimize particle interactions with mucus constituents and prevent mucus adhesion. In these experiments, the Pluronics acted as a coating around the core particles, and the resulting particles were tested for their mobility in mucus, although in other embodiments, the surface-altering agents may be exchanged with other surface-altering agents that can increase mobility of the particles in mucus.

[000532] The milling process was carried out until LE particles were small and polydispersity was low (*i.e.*, z-average particle diameter below 500 nm and polydispersity index <0.20 as measured by dynamic light scattering). Table 12 lists particle size characteristics of LE particles obtained by milling in the presence of the various Pluronics®. Particle size was measured by dynamic light scattering. Milling of LE in the presence of Pluronic® L31, L35, L44 or L81 failed to produce stable nanosuspensions. Therefore, these Pluronics were excluded from further investigation due to their inability to effectively aid particle size reduction.

[000533] The mobility of LE nanoparticles from the produced nanosuspensions in fresh undiluted human cervicovaginal mucus (CVM) was characterized by dark-field microscopy using a CytoViva® High Resolution Illumination System which allows visualization of

fluorescent and non-fluorescent nano-sized objects. In a typical experiment, 0.5 μL of a nanosuspension was added to 20 μL of undiluted CVM pre-deposited into a 20 μL well on a microscope slide. Using a CCD camera, 15 s movies were captured at a temporal resolution of 66.7 ms (15 frames/s) under 100 × magnification from several randomly selected areas within each sample. Mobility of particles in the movies was scored on a scale from 0 to 3 in order of increasing mobility, in a single-blind experiment by independent observers. The scoring criterion is as follows: 0-0.5 immobile; 0.51-1.5 slightly mobile; 1.51-2.5 moderately mobile; and 2.51-3.0 very mobile.

[000534] The average mobility scores for each LE/Pluronic sample are plotted in FIG.20 as a function of the molecular weight of the PPO component (MW PPO) and the weight percentage of the PEO component (%PEO) of the Pluronic® polymer. It was discovered that LE milled in the presence of Pluronic® F87, F108, and F127 resulted in particles that are very mobile in CVM (mobility score >2.51). This corresponds to Pluronic® polymers with physical properties of MW PPO ≥ 2.3kDa and %PEO ≥ 70%. LE nanocrystals milled in Pluronic® P103, P105, and P123 are moderately mobile (mobility score 1.51.-2.50). The corresponding physical properties of this Pluronic® class is MW PPO ≥ 3.3kDa and 30% ≤ %PEO ≤ 70%. Pluronic® L121, P65, F38, and F68 produced LE nanocrystals that were not mobile (mobility score <0.50). This group of Pluronic® polymers constitutes those with MW PPO ≤ 1.9kDa and %PEO ≤ 10%. Pluronic® L31, L35, L44, or L81, whose physical properties also fall into the previous-mentioned MW PPO and %PEO categories, failed to produce small and monodisperse particles and are considered immobile (mobility score <0.50) in the analysis.

[000535] Without wishing to be bound by any theory, it is believed that the hydrophobic PPO block can provide effective association with the surface of the core LE particles if the molecular weight of that block is sufficient (*e.g.*, at least about 2.3 kDa in some embodiments); while the hydrophilic PEO blocks are present at the surface of the coated LE particles and can shield the coated LE particles from adhesive interactions with mucin fibers if the PEO content of the Pluronic® is sufficient (*e.g.*, at least 30 wt% in some embodiments). As described herein, in some embodiments the PEO content of the surface-altering agent may be chosen to be greater than or equal to about 10 wt% (*e.g.*, at least about 15 wt% or at least about 20 wt%), as a 10 wt% PEO portion rendered the particles mucoadhesive.

[000536] Interestingly, the molecular weight of the PPO block needed to provide high mobility (mobility score >2.51) when LE was used as the core was at least about 2.3 kDa, compared to 3 kDa for when pyrene was used as the core. This data suggests that the surface altering agent (*e.g.*, the molecular weight of the PPO block) may be varied, depending on the core to be coated, to tailor the mobility of the particle.

[000537] **Table 12.** Particle size measured by Dynamic Light Scattering (DLS) in nanosuspensions obtained by milling of LE with various Pluronic® surface-altering agents.

Pluronic® grade	Z-average diameter (nm)	Polydispersity index
L31 *	not measurable*	not measurable*
L35 *	not measurable*	not measurable*
L44 *	not measurable*	not measurable*
L81 *	not measurable*	not measurable*
L101 *	not measurable*	not measurable*
L121	343	0.18
P65	224	0.06
P103	251	0.08
P105	356	0.19
P123	281	0.12
F38	233	0.10
F68	404	0.13
F87	316	0.07
F108	294	0.12
F127	404	0.13

* denotes samples that failed to effectively reduce LE particle size and produce stable nanosuspensions. For these samples, Z-Ave diameter was greater than at least 1 μm and not measurable with DLS.

Example 11

[000538] The following describes a non-limiting example of a method of forming mucus-penetrating particles (MPP) using a core comprising the drug loteprednol etabonate (LE) in the presence of other components, such as Pluronic®, glycerin, sodium chloride (NaCl), disodium ethylenediaminetetraacetic acid (Na_2EDTA), and benzalkonium chloride (BAC).

[000539] The method of forming the loteprednol etabonate mucus-penetrating particles (LE MPP) involved two consecutive steps: milling and dilution. In the milling step, a coarse aqueous suspension containing about 2-20% loteprednol etabonate (coarse or micronized

crystals), about 0.2-20% Pluronic® F127, about 0.5-3% glycerin, about 0.1-1% sodium chloride, and about 0.001-0.1% EDTA was milled in the presence of milling media to produce a nanosuspension of loteprednol etabonate particles sized in the range of 200 - 300 nm.

[000540] In the subsequent dilution step, the obtained nanocrystalline suspension separated from the milling media was mixed in a product vessel with post-milling diluent containing about 0.5-3% glycerin, about 0.1-1% sodium chloride, about 0.001-0.1% EDTA, and about 0.001-0.05% BAC. This method produced a composition including about 0.1-2% loteprednol etabonate, about 0.01-2% Pluronic® F127, about 0.5-3% glycerin, about 0.1-1%sodium chloride, about 0.001-0.1%EDTA, and about 0.001-0.05%BAC.

Example 12

[000541] The following describes a non-limiting example of the effect of Pluronic® F127 on the mucus penetrating properties of the formulations.

[000542] The formulations were formed using methods similar to the method described in Example 10.FIG. 21 shows mass-transport-into-mucus data of the following formulations: particles comprising loteprednol etabonate and Pluronic® F127 (LE F127), particles comprising loteprednol etabonate and sodium dodecyl sulfate but not Pluronic® F127 (LE SDS), and marketed formulation Lotemax®.The ratio of loteprednol etabonate to Pluronic® F127 1:1 wt% and the ratio of loteprednol etabonate to SDS is 50:1 wt%. The mass transport was measured according to the procedure described in Example 2. The results shown in FIG. 21 indicate that the mucus penetrating properties of LE F127 were approximately 20 times greater compared to LE SDS and approximately 40 times greater compared to Lotemax®.It is believed that an ophthalmic formulation of a drug including a loteprednol etabonate core and a coating ofF127 may enhance the ocular exposure of the drug.

Example 13

[000543] This non-limiting example shows that loteprednol etabonate (LE) MPPs may be gamma-irradiated for terminal sterilization without adversely affecting the LE MPPs' particle stability, chemical stability, and pharmacokinetics and that glycerin gives chemical protection to the LE MPPs against gamma irradiation.

[000544] Gamma irradiation of a formulation can cause chemical degradation and free radical generation and is a concern especially in aqueous formulations. LE is a soft steroid designed to metabolize via the hydrolytic or enzymatic cleavage of two ester bonds into PJ-91 and PJ-90. When LE is exposed to gamma irradiation, 17α-[(ethoxycarbonyl)oxy]-11β-hydroxy-3-oxoandrosta-4-ene-17-carboxylic acid chloromethyl ester (tetradeca) and 17α-[(ethoxycarbonyl)oxy]-3,11-dioxoandrosta-1,4-diene-17-carboxylic acid chloromethyl ester (11-keto) are formed. When LE is gamma-irradiated, 11-keto appears in small amounts, whereas the amount of tetradeca rapidly increases to above 1%.

[000545] The formulations comprising LE and different concentrations of glycerin were formed using methods similar to the methods described in Examples 10-11. Table 13 shows the concentrations of certain degradants of LE after the formulations were exposed to gamma radiation. The concentrations of the degradants were measured immediately after being subjected to gamma irradiation ("Gamma irradiated initial") and 4 weeks after being subjected to gamma irradiation ("gamma irradiated after 4 weeks") using a Cobalt 60 gamma irradiation source at a dose of 25 kGy. In LE MPPs with no glycerin, the amount of tetradeca increased by 18-fold after the gamma irradiation of the LE MPPs. In contrast, after gamma irradiation little tetradeca was formed in the LE MPPs with 1.2% or 2.4% glycerin. Surprisingly, the levels of PJ-91 and PJ-90 were decreased in all cases. Although 11-keto was observed after the gamma irradiation, the level of 11-keto did not exceed 0.2%. The results show that much less tetradeca is produced upon gamma radiation when glycerin is present in the formulations. Different concentrations of glycerin were used (*e.g.*, 1.2wt% and 2.4wt%), and the resulting formulations generated similar levels of tetradeca after exposure to gamma radiation. These results are unexpected and suggest that glycerin, commonly used as a tonicity agent, may give chemical protection to the formulations during gamma radiation.

[000546] **Table 13.** Concentrations of LE and certain degradants of LE after LE formulations were exposed to 25 kGy of gamma radiation.*

Formulation composition	Time of gamma radiation	Concentration (wt%)				
		PJ-90	PJ-91	LE	Tetradeca	11-keto
LE, F127, NaCl, EDTA, BAC	Not irradiated	0.48	0.97	97.22	0.08	0.04
	Gamma irradiated initial	0.07	0.45	96.51	1.45	0.13
	Gamma irradiated after 4 weeks	0.07	0.46	96.55	1.49	0.16
LE, F127, 2.4% Glycerin, EDTA, BAC	Not irradiated	0.48	0.87	97.21	0.08	0.05
	Gamma irradiated initial	0.31	0.70	97.28	0.10	0.15
	Gamma irradiated after 4 weeks	0.36	0.81	97.24	0.11	0.16
LE, F127, 1.2% Glycerin, NaCl, EDTA, BAC	Not irradiated	0.38	0.78	97.93	0.06	0.09
	Gamma irradiated initial	0.29	0.48	98.04	0.09	0.16
	Gamma irradiated after 2 weeks	0.28	0.50	97.80	0.15	0.20

*LE MPPs employed in this Example were lab scale batches and may be less pure than batches used in other Examples described herein.

[000547] In addition to the chemical stability of a particle formulation, the physical stability of the formulation is also of high importance. As shown in FIG. 33A, LE MPP formulations containing sodium chloride and glycerin showed no change in particle size over a month after exposure to 25 kGy of gamma irradiation.

[000548] The effects of gamma irradiation on the pharmacokinetics (PK) of LE MPPs was also studied to investigate whether the performance of the LE MPPs was unaffected by gamma irradiation. *In vivo*, a single topical instillation of LE MPPs, which had been gamma irradiated at 25 kGy (Formulation 1 GAMMA, Formulation 2 GAMMA), to New Zealand white rabbits produced the same LE levels in the cornea of the rabbits as did LE MPPs that had not been exposed to gamma irradiation (Formulation 1, Formulation 2; FIG. 33B). In FIG. 33B, Formulation 1 (and Formulation 1 GAMMA) included a higher level of Pluronic® F127 than Formulation 2 (and Formulation 2 GAMMA). These results demonstrate that LE MPPs can be terminally sterilized by gamma irradiation without adverse effects on the particle stability, API (active pharmaceutical ingredient) chemical stability, or PK of the LE MPPs.

Example 14

[000549] This non-limiting example shows that NaCl is beneficial to the stability of an LE MPP formulation described herein during dilution of the formulation with water.

[000550] The formulations comprising LE and one or more tonicity agents (*e.g.*, NaCl, Tyloxapol, glycerin, and SSC (an aqueous solution of sodium citrate and about 1% NaCl)) were formed using methods similar to the method described in Examples 10-11. Table 14 shows the particle size and polydispersity index (PDI) of the LE formulations measured by Dynamic Light Scattering (DLS) before and after a 10-fold dilution of the formulations with water. In entries 1, 4, and 5, where the formulations do not include NaCl, the particle size (measured by diameter) increased by about 2-3 fold upon dilution of the formulation with water, most likely due to aggregation of the particles. In entries 4 and 5, the PDI also increased by about 2-3 fold. In contrast, in entries 2, 3, 6, and 7, where the formulations included NaCl, the particle size remained relatively constant upon dilution of the formulation with water. In entries 2, 3, and 7, there was also no significant increase in PDI. These results were unexpected because the addition of NaCl (a tonicity agent) to a particle formulation increases the ionic strength of the formulation, and is generally known to destabilize the particle formulation by causing aggregation of particles. The opposite effect was observed here.

[000551] **Table 14.** Particle size and polydispersity index (PDI) of LE formulations measured by Dynamic Light Scattering (DLS) before and after a 10-fold dilution with water.

Entry	Formulation composition	Before dilution		After dilution	
		Diameter (nm)	PDI	Diameter (nm)	PDI
1	1-5% LE, 1-5% F127	208	0.148	395	0.156
2	1-5% LE, 1-5% F127, 0.9% NaCl, 0.05% EDTA, 0.01% BAC	188	0.102	187	0.122
3	1-5% LE, 1-5% F127, 0.9% NaCl, 0.1% Tyloxapol, 0.05% EDTA, 0.01% BAC	190	0.128	193	0.139
4	1-5% LE, 1-5% F127, 2.4% Glycerin, 0.05% EDTA, 0.01% BAC	197	0.133	514	0.409
5	1-5% LE, 1-5% F127, 2.4% Glycerin, 0.1% Tyloxapol, 0.05% EDTA, 0.01% BAC	191	0.116	389	0.337
6	1-5% LE, 1-5% F127, SSC, 0.05% EDTA, 0.01% BAC	212	0.096	244	0.176
7	1-5% LE, 1-5% F127, SSC, 0.1% Tyloxapol, 0.05% EDTA, 0.01% BAC	212	0.100	246	0.095

Example 15

[000552] This non-limiting example shows that LE MPPs resulted in increased exposure when administered topically to an eye, compared to similarly sized non-MPPs.

[000553] LE MPPs were compared to LE SDS particles, similarly sized non-MPPs (Table 15). LE SDS particles are produced using methods similar to the methods described in Examples 10-11, except that the particles are coated with sodium dodecyl sulfate (SDS). Conventional particles, such as those coated in SDS, are extensively trapped by the peripheral rapidly-cleared mucus layer in the eye and are rapidly cleared. LE MPPs are able to avoid adhesion to, and effectively penetrate through, mucus to facilitate sustained drug release directly to underlying tissues. *In vivo*, a single topical instillation of LE MPPs to New Zealand white rabbits produced a 4.4-fold enhancement in the AUC of LE concentration in the cornea, compared to an equivalent dose of LE SDS, despite both being similarly sized nanoparticles (FIG. 23A). Additionally, despite the different particle sizes of LE SDS and Lotemax®, which is a commercially available microparticle, the concentrations of LE obtained from rabbits dosed with LE SDS were statistically equivalent to the concentrations of LE obtained from rabbits dosed with Lotemax® (FIG. 23B). These results demonstrate that

the MPP's capability to enhance the exposure, in the eye, of a drug that is formulated with the MPP is not solely due to the small particle size of the MPP.

[000554] **Table 15.** Particle size and polydispersity index (PDI) of LE SDS and LE MPP measured by Dynamic Light Scattering (DLS).

Sample	Diameter (nm)	PDI
LE SDS	240	0.143
LE MPP	241	0.096

Example 16

[000555] This non-limiting example shows that LE MPPs resulted in increased exposure when administered topically to an eye, compared to Lotemax® coated with Pluronic® F127.

[000556] LE MPPs were compared to Lotemax® + F127, a formulation in which F127 (0.5 wt%) was added to Lotemax®. *In vivo*, a single topical instillation of LE MPPs to New Zealand white rabbits produced significantly higher exposure of LE in cornea, compared to an equivalent dose of Lotemax® or Lotemax®+F127 (FIG.24). LE MPPs result in a4.4- and 2.3-fold enhancement of AUC of LE concentration in cornea over Lotemax® and Lotemax®+F127, respectively. While Lotemax®+F127 does result a 2-fold increase of AUC of LE concentration in cornea as compared to Lotemax® alone, these results demonstrate that the MPP's capability to enhance the exposure, in the eye, of a drug that is formulated with the MPP is not solely due to the presence of Pluronic® F127 in the formulation.

Example 17

[000557] This non-limiting example shows that a formulation including LE MPP enhances exposure of LE in the anterior chamber of the eye compared to Lotemax®.

[000558] In order to demonstrate that the enhanced exposure of LE from LE MPPs translates not only to the surface of the eye, but penetrates within the ocular globe, levels of LE in the aqueous humor obtained from LE MPPs and Lotemax® formulations were compared. *In vivo*, a single topical instillation of LE MPPs to New Zealand white rabbits produced significantly higher LE levels in the aqueous humor compared to a dose of

Lotemax® despite the fact that the Lotemax® dose is 20% larger (FIG. 25). LE MPPs (containing 0.4% LE) result in an $AUC_{0\text{-}3hr}$ enhancement of 3 fold over Lotemax® (containing 0.5% LE). These results demonstrate the enhanced exposure achievable with the MPP technology is not limited to the surface of the eye but extends into the anterior chamber. In addition, the dose of LE can be lowered by 20% with the LE MPP formulation and can still achieve enhanced exposure compared to Lotemax®.

Example 18

[000559] This non-limiting example demonstrates that a formulation including LE MPP that contains 20% less LE showed improved exposure in rabbit eye and plasma compared to Lotemax®.

[000560] In order to demonstrate the enhanced exposure from LE MPP can be sustained at lower doses than currently marketed formulations, such as Lotemax®, LE MPP was given at a dose 20% lower than Lotemax®. Levels of LE and two of its main metabolites, PJ-91 and PJ-90, from LE MPP and Lotemax® were determined. *In vivo*, a single topical instillation of LE MPP containing 0.4 wt% LE to New Zealand white rabbits produced significantly higher levels of LE in all tissues/fluids tested (*e.g.*, conjunctiva, cornea, aqueous humor, iris and ciliary body (ICB), central retina, and plasma) compared to a dose of Lotemax® containing 0.5 wt% LE, despite the fact that the Lotemax® dose is 20% larger than the LE MPP dose (FIGs. 26A-26R). Pharmacokinetic parameters are listed in Table 16. These results demonstrate the dose of LE can be lowered by 20% with the LE MPP formulation and still achieve enhanced exposure over Lotemax®.

[000561] **Table 16.** Pharmacokinetic parameters of Loteprednol Etabonate (LE) in ocular tissues *in vivo*. Rabbits were given one 50 µL dose of 0.5% Lotemax® or 0.4% LE MPP in each eye.

		Plasma	Aqueous Humor	Conjunctiva	Cornea	Iris Ciliary Body (ICB)	Retina (center-punch)
Lotemax®	T_{max} (h)	0.25	0.50	0.083	0.083	0.50	0.50
	C_{max} (nM)	0.704	14.0	2430	1330	105	4.47
	$t_{1/2\ elimination}$ (h)	1.88	2.31	4.26	3.75	3.04	9.18
	$AUC_{0\text{-}last}$ (nM·h)	1.62	30.0	3450	2420	194	14.8
	$AUC_{0\text{-}inf}$ (nM·h)	1.69	30.5	4070	2710	200	22.4
LE MPP	T_{max} (h)	0.50	0.50	0.083	0.083	0.25	0.50
	C_{max} (nM)	2.55	43.7	6280	4850	293	14.5
	$t_{1/2\ elimination}$ (h)	1.71	1.57	1.92	1.89	1.49	1.55
	$AUC_{0\text{-}last}$ (nM·h)	4.55	66.0	3450	3570	442	31.5
	$AUC_{0\text{-}inf}$ (nM·h)	4.71	66.4	3490	3610	445	31.9

Example 19

[000562] This non-limiting example demonstrates the fluticasone release profile of fluticasone-loaded MPPs containing a PEGylated copolymer and a non-PEGylated core-forming polymer.

[000563] Fluticasone-loaded MPPs were prepared according to methods similar to the ones described herein (*e.g.*, methods described in Example 21) by co-precipitating fluticasone with PLA7A (Surmodics 100DLA7A, MW = 108 KDa) as the main polymer and a PEGylated copolymer (*e.g.*, 100DL9K-PEG2K or 8515PLGA54K-PEG2K) as the secondary polymer. The ratios of the polymeric components tested were 10/90, 20/80, and 30/70 (with PLA7A being the main component in all cases). Various PEGylated copolymers were tested in order to explore the impact of the block composition (*i.e.*, MW of the PEG block vs. MW of the

hydrophobic block) on properties of resulting particles. In particular, the ability of resulting particles to penetrate mucus, control drug release, and maintain colloidal stability throughout the formulation process was assessed.

[000564] It was found that, while many compositions led to satisfactory drug release and mucus-penetration, good colloidal stability could not be achieved with most of them (see FIG. 27). Colloidal stability is especially important since the current formulation process involves isolation and purification of the MPPs by centrifugation and resuspenion. The poor colloidal stability of many compositions was manifested, in part, by the inability to resuspend product obtained after the centrifugation step. The compositions that resulted in MPPs with good colloidal stability as well as good control over drug release (*e.g.*, a continuous release over 24 hours *in vitro* as in this Example) appear to have a relatively high surface coverage of PEG on the particle (*e.g.*, at least about 0.18 PEG chains per nm^2) at a relatively low overall PEG content in the particle (*e.g.*, less than about 3 wt% of the total polymer content). In other words, combinations of PLA7A with PEG-copolymers with a relatively short hydrophobic block (*e.g.*, 100DL9K-PEG2K) result in MPPs that are more colloidally stable than similar combinations of PEG-copolymers with a relatively long hydrophobic block (*e.g.*, 8515PLGA54K-PEG2K) (see FIG. 27).

Example 20

[000565] This non-limiting example demonstrates that MPPs comprising sorafenib avoided entrapment in human cervicovaginal mucus and were able to diffuse through mucus.

[000566] MPPs comprising sorafenib may be prepared according to methods described herein (*e.g.*, methods described in Examples 21 and 29). Mobility of conventional nanoparticles and the MPPs described herein in human cervicovaginal mucus was characterized by bulk transport and/or microscopy as described in Examples 2 and 10, respectively. The results are shown in FIGs. 28A-28B. The conventional nanoparticles were trapped in human cervicovaginal mucus, whereas the MPPs described herein avoided entrapment and were able to diffuse through mucus.

Example 21

[000567] This non-limiting example demonstrates that topical delivery of sorafenib, (a small molecule receptor tyrosine kinase (RTK) inhibitor) formulated as MPP greatly enhances sorafenib levels in the retina and choroid of the eye. This example also shows that sorafenib levels in anterior segment tissues of the eye depend on the MPP release rate and can be reduced without significantly affecting sorafenib levels at the back of the eye.

[000568] Sorafenib-loaded MPPs with relatively fast drug release (MPP1) were prepared by a milling procedure: an aqueous dispersion containing drug and Pluronic F127 (F127) was stirred with zirconium oxide beads, as grinding medium, until particle size was reduced below 300 nm as measured by dynamic light scattering. This method employs excipients approved by the FDA for use in ophthalmic products and produced a stable aqueous nanosuspension of MPPs.

[000569] Sorafenib-loaded MPPs with relatively slow drug release kinetics (MPP2) were prepared by encapsulating sorafenib into a biodegradable polymeric nanoparticle decorated with a coating described herein. For example, a solution containing sorafenib free base (LC Labs), PLA (Polylactide, 100DL7A, Surmodics), and PLA-PEG (poly(ethylene glycol)-co-polylactide, 100DL-mPEG2K, Surmodics) in tetrahydrofuran was added at a controlled rate to an excess of aqueous solution of Pluronic® F127 with stirring. The produced particles were stirred at room temperature to let the volatiles evaporate and to crystallize out sorafenib that was unencapsulated. The crystals of unencapsulated sorafenib were removed by filtration through a suitable sized glass fiber filter. The nanoparticles were isolated from the filtrate by centrifugation and washed once with aqueous Pluronic® F127. The final product of nanoparticles was resuspended in Pluronic® F127.

[000570] Sorafenib concentrations in the MPP formulations were confirmed by HPLC. The size of the MPPs was measured by dynamic light scattering, using a Zetasizer Nano ZS90 (Malvern Instruments). *In vitro* drug release was evaluated at 37°C in 50mM phosphate buffer (pH 7.4) in the presence of 0.5% Tween 80 to ensure sink conditions, such as experimental conditions that are well-below saturation solubility.

[000571] The pharmacokinetics of sorafenib following a single topical administration of the MPPs or a non-MPP comparator was evaluated in New Zealand white rabbits (NZW) at a contract research organization. An aqueous suspension of sorafenib was used as the non-MPP

comparator. Each animal received a 50 μL topical instillation containing 5 mg/mL sorafenib in both eyes (n = 6). Ocular tissues, including cornea and an 8mm punch of choroid and of retina from the back of the eye, were harvested at various time points. The punch was used to target the area at the back of the eye where the human macula would be as this is the target for AMD therapy. Sorafenib levels were determined by LC/MS.

[000572] MPP1 and MPP2 formulated as described above formed stable nanosuspensions with a Z-average diameter of 187 nm (PDI = 0.172) and 222 nm (PDI = 0.058), respectively. Since MPP1 was essentially a suspension of the pure drug sorafenib, the drug release was driven largely by drug dissolution, which is relatively rapid. In the case of MPP2, the drug sorafenib was encapsulated in PLA polymers, and the drug loading was 20%. The polymeric composition of MPP2, including the molecular weight of PLA, the ratio of PLA to PLA-PEG, and the composition of PLA-PEG, was systematically varied in order to achieve a release rate well-differentiated from MPP1. The MPP2 formulation demonstrated continuous drug release over about 24 hrs *in vitro*.

[000573] In the cornea, a single dose of the fast-releasing MPP1 formulation produced sorafenib levels up to 18-fold higher than those from the comparator and sustained an at least 7-fold enhancement over the comparator for at least 6 hours. In contrast, the slow-releasing MPP2 formulation produced only an approximately 3-fold enhancement over the comparator steadily sustained over the course of 6 hours. However, in posterior segment tissues (*e.g.*, retina and choroid), both MPP1 and MPP2 produced similarly high sorafenib levels, well-outperforming the comparator (FIGs. 29A-29B). In fact, the levels of sorafenib in the retina produced by the MPP formulations approached or exceeded reported cellular IC_{50} values against VEGFR-2 (37 ng/g) and PDGFR-β (14 ng/g) for sorafenib, a relatively low potency, first-generation RTK inhibitor. Furthermore, both MPP formulations were well tolerated as assessed by Draize scoring.

[000574] These results not only demonstrate a proof-of-concept that the MPPs described herein, and compositions thereof, can greatly enhance delivery of a pharmaceutical agent to the back of the eye via topical administration but also suggest that topical delivery of a small molecule RTK inhibitor formulated as MPPs may have a potential in the treatment of a broad range of ocular diseases, such as AMD.

Example 22

[000575] This non-limiting example demonstrates that a formulation including LE MPPs improved the exposure of LE in the aqueous humor of the rabbit eye compared to Lotemax® gel.

[000576] In order to demonstrate that enhanced exposure of LE from LE MPPs can be sustained at lower doses compared not only to marketed suspension formulations, but also to marketed gel formulations, levels of LE were determined when LE MPPs (dosed at 0.4% LE) and Lotemax® gel (dosed at 0.5% LE) were used. Gel and ointment formulations are popularly used in an attempt to increase exposure in the eye by delivering LE in a viscous matrix. Gel and ointment formulations often blur vision and are less comfortable and harder to install than a liquid eye drop.

[000577] To generate LE MPPs, a milling procedure was employed according to the methods described herein. For example, an aqueous dispersion containing LE and Pluronic® F127 (F127) was milled with a grinding medium until the particle size was reduced to below about 300nm as measured by dynamic light scattering. Mucus mobility was characterized in human cervicovaginal mucus based on the previously described characterization methods.

[000578] *In vivo*, a single topical instillation of LE MPPs(KPI-121) to New Zealand white rabbits produced higher LE levels in aqueous humor compared to a dose of Lotemax® gel despite the fact that the Lotemax® gel dose was 20% higher and in a viscous matrix (FIG. 30). The AUC_{0-3} of the LE MPPs was 1.5 times higher than that of Lotemax® gel. The C_{max} of the LE MPPs was 2.4 times higher than that of Lotemax® gel. These results indicate that the MPPs described herein outperform the viscous matrix used in Lotemax® gel and that the dose of LE may be lowered by 20% with the LE MPP formulation and may still achieve similar or enhanced exposure compared to Lotemax® gel.

Example 23

[000579] This non-limiting example demonstrates that LE MPPs show dose-dependent exposure in the aqueous humor of New Zealand white rabbits.

[000580] In order to demonstrate that the exposure of LE from an LE MPP formulation is dose dependent, a dose ranging study was performed. To generate LE MPPs, a milling process according to the methods described herein was employed. For example, an aqueous

dispersion containing drug and Pluronic® F127 (F127) was milled with a grinding medium until the particle size was reduced to below about 300nm as measured by dynamic light scattering. Mucus mobility was characterized in human cervicovaginal mucus based on the previously described characterization methods. Dilutions were performed to give LE MPP suspensions that included 0.4%, 0.5%, 0.6%, or 1% LE. *In vivo*, a single topical instillation of LE MPPs to New Zealand white rabbits produced LE levels in the aqueous humor of the rabbits which were dependent on the dose given (FIGs. 31A-31B). These results demonstrate the LE MPPs exhibit dose-dependent pharmacokinetics (PK).

Example 24

[000581] This non-limiting example demonstrates that LE MPPs may be stably formulated in the presence of one or more ionic components, such as sodium chloride.

[000582] In order to demonstrate that LE MPPs may be formulated with ionic components, such as ionic salts, and can remain physically stable in such a formulation, sodium chloride, a tonicity agent with a well-known safety profiles in humans, was introduced into the LE MPPs. It is commonly known in the art that ionic components should not be added to particle suspensions as the ionic components tend to destabilize the particle suspensions. Surprisingly, this is not the case with LE MPPs.

[000583] It is known that, to achieve a formulation of an osmolarity of about 300 mOsm/kg, the concentration of sodium chloride in the formulation is typically about 0.9%. A combination of 1.2% glycerin and 0.45% sodium chloride generally also yields an isotonic solution and was tested to compare different levels of sodium chloride.

[000584] To generate nanoparticles, a milling process according to the methods described herein was employed. For example, an aqueous dispersion containing LE and Pluronic® F127 (F127) was milled with a grinding medium until the particle size was reduced to below about 300 nm as measured by dynamic light scattering. The physical stability of the resulted isotonic formulations was tested by monitoring the size of the particles in the formulations using dynamic light scattering (DLS). It was discovered that the particles in the formulations containing two different concentrations of sodium chloride were very stable in size as shown in FIG. 32. In FIG. 32, the data depicted with the triangular markers had a higher percentage of NaCl in the formulation than the data depicted with the circular markers. These results

demonstrate that LE MPPs can be formulated into stable compositions in the present of ionic components, such as sodium chloride.

Example 25

[000585] This non-limiting example demonstrates that particles containing Pluronic® F127 and diclofenac or ketorolac may be mucus penetrating.

[000586] In order to demonstrate that particles comprising a core containing an NSAID and comprising a surface-altering agent (*e.g.*, Pluronic® F127) may be mucus penetrating, two NSAIDs, *i.e.*, diclofenac and ketorolac, were studied.

[000587] To form particles containing diclofenac or ketorolac, a milling procedure was employed according to methods described herein. In one set of experiments, an aqueous dispersion containing Pluronic® F127 and one of ketorolac free acid and diclofenac free acid was milled with a grinding medium until the particle size was reduced to below about 300 nm as measured by dynamic light scattering. To generate similarly sized non-MPP comparators, a similar milling procedure was employed except that SDS was used as the surface-altering agent instead of Pluronic® F127. The mucus mobility of the produced particles was characterized in human cervicovaginal mucus based on the previously described microscopy methods. In the case of diclofenac, the mucus mobility was additionally characterized by the previously described bulk transport method. The results are shown in FIG. 41. The data demonstrate that the particles containing Pluronic® F127 and one of ketorolac and diclofenac were mucus penetrating, whereas the particles containing SDS and one of ketorolac and diclofenac were not mucus penetrating.

Example 26

[000588] This non-limiting example demonstrates a method of forming MPPs including bromfenac calcium, and compositions and/or formulations thereof.

[000589] MPPs including bromfenac calcium as the core and Pluronic® F127 (F127) as a muco-inert surface-altering agent, and compositions and/or formulations including these MPPs, were prepared using a method similar to the methods described in Example 2. In one set of experiments, bromfenac calcium was nanomilled in an aqueous dispersion containing bromfenac calcium and Pluronic® F127 using zirconium oxide beads as grinding medium,

until the particle size was reduced below 300 nm as measured by dynamic light scattering. The resulted nanomilled suspension can be diluted to a lower concentration if desired. In some experiments, bromfenac calcium was milled in water, 125 mM of $CaCl_2$, or 50mM of Tris buffer to give three formulations. The particle size of the obtained MPPs in the three formulations was measured by dynamic light scattering, and the results are shown in FIG 34. All three formulations had a Z-average diameter of about 200 nm and a polydispersity index < 0.2. These data demonstrate that the bromfenac calcium MPPs are small and uniform in size and thus are suitable for ocular applications.

Example 27

[000590] This non-limiting example demonstrates that MPPs including bromfenac calcium, and compositions and/or formulations thereof, are stable when stored at room temperature.

[000591] MPPs including bromfenac calcium, and compositions and/or formulations thereof, may be prepared according to methods in Example 26. The MPPs, compositions, and/or formulations were stored at room temperature for days, and the particle Z-average size and polydispersity index of the MPPs were determined by dynamic light scattering. The results are shown in FIGs. 35A-35D. These data demonstrate that the bromfenac calcium MPPs maintained good particle size stability over extended period of time when stored at room temperature.

[000592] Enhanced mucus mobility of bromfenac calcium MPPs in human cervicovaginal mucus was confirmed by fluorescent microscopy and high resolution dark field microscopy (data not shown).

Example 28

[000593] This non-limiting example demonstrates that excipients in compositions and/or formulations containing bromfenac calcium MPPs may improve the chemical stability of bromfenac calcium MPPs.

[000594] To improve the chemical stability of bromfenac calcium in MPPs, different excipient compositions were explored for the milling step and the final formulation that either (1) lower the solubility of bromfenac or (2) maintain a pH range at which bromfenac is most stable. Table 20 shows the pH and solubility of bromfenac calcium MPPs in two buffers (125

mM $CaCl_2$ and 50 mM Tris) and, for comparison, in unbuffered water. The chemical stability of bromfenac calcium MPPs in 125mM $CaCl_2$, which reduced the drug solubility, and in 50 mM Tris, which maintained the pH of the solution at about 8, was markedly enhanced compared to that in in water.

Table 20. pH, solubility, and chemical stability of bromfenac calcium MPP suspensions containing 0.09% w/v bromfenac in the presence of various excipient compositions at room temperature.*

Formulation: bromfenac calcium suspension (0.09% w/v bromfenac)				
Vehicle		Formulation Properties		
Buffer	Concentration of Pluronic®F127 (% w/v)	pH	Solubility (mg/mL)	% peak area*
None (water)	0.5	6.87	0.21	0.13 (day 7)
	0.09	6.75	0.20	0.09 (day 23)
125 mM $CaCl_2$	0.5	6.48	0.03	0 (day 7)
	0.09	6.60	0.07	0 (day 23)
50mM Tris buffer	0.5	8.03	0.25	0 (day 7)
	0.09	7.98	0.27	0 (day 23)

*The chemical stability of bromfenaccalcium was determined as % chromatographic peak area for the lactam degradant of bromfenac.

Example 29

[000595] This non-limiting example demonstrates that MPPs containing sorafenib or linifanib enhanced the exposure of sorafenib or linifanib at the back of the eye of rabbits.

[000596] In order to demonstrate that enhanced mucus penetration is useful not only at the front of the eye, but can lead to enhanced exposure at the back of the eye as well, sorafenib and linifanib, two receptor tyrosine kinase inhibitors, were formulated as MPPs. Small molecule RTK inhibitors that act on vascular endothelial growth factor receptor (VEGFR) have potential as therapy for age-related macular degeneration (AMD). If topical delivery of an RTK inhibitor could provide sufficient levels of the RTK inhibitor at the back of the eye then repeated intravitreal injections, used by current therapies, could be avoided. Delivery of

an RTK inhibitor to the back of the eye would also be beneficial in a number of other diseases which affect posterior segment tissues.

[000597] To generate MPPs containing an RTK inhibitor (*e.g.*, sorafenib and linifanib), a milling procedure similar to that used for Loteprednol Etabonate was employed: an aqueous dispersion containing the RTK inhibitor and F127 or sodium dodecyl sulfate (SDS) was milled with a grinding medium until the particle size was reduced to below about 300nm as measured by dynamic light scattering. Mucus mobility was characterized in human cervicovaginal mucus based on the previously described characterization methods. Sorafenib and linifanib were processed into MPPs when milled with F127 and into non-MPPs when milled with SDS.

[000598] *In vivo*, a single 50 μL topical instillation of 0.5%sorafenib-MPP to New Zealand White rabbits produced sorafenib levels in the retina of the rabbit which were 45 times higher than sorafenib levels from the non-MPP control at 2 hours and 96 fold above cellular IC_{50} (FIG.36A). A central punch of 8 mm in diameter was taken from the retina where the human macula would be in order to measure sorafenib levels at the back of the eye where AMD therapies would be targeted. The sorafenib-MPP outperforms the sorafenib non-MPP by a statistically significant amount.

[000599] *In vivo*, a single 50 μL topical instillation of 2% linifanib-MPP to New Zealand White rabbits produced linifanib levels in the center punch retina which were approximately 2 fold higher than linifanib levels from the non-MPP control over the full 4 hours examined and 777 fold above cellular IC_{50} at 4 hours (FIG.36B). Again the difference between MPP and non-MPP was statistically significant.

[000600] These results demonstrate that enhanced mucus penetration can enable higher drug exposure at the back of the eye. The application of this technology can be used to improve drug exposure in any tissue of the eye, whether at the ocular surface or the back of the eye.

Example 30

[000601] This non-limiting example demonstrates that MPPs containing MGCD-265 or pazopanib generated therapeutically relevant levels of MGCD-265 or pazopanib at the back of the eye of rabbits.

[000602] In order to demonstrate the wide applicability of the MPP technology to the delivery of small molecule RTK inhibitors in therapeutically relevant (*e.g.*, therapeutically effective)levels to the back of the eye, two additional compounds were studied: MGCD-265 and pazopanib.

[000603] To generate the MPPs, a milling procedure similar to that used for loteprednol etabonate was employed: an aqueous dispersion containing MGCD-265 or pazopanib and F127 was milled with a grinding medium until the particle size was reduced to below about 300nm as measured by dynamic light scattering. Mucus mobility was characterized in human cervicovaginal mucus based on the previously described characterization methods. Both MGCD-265 and pazopanib were processed into MPPs when milled with F127.

[000604] *In vivo*, a single 50 μL topical instillation of 0.5% pazopanib-MPP to New Zealand White rabbits produced pazopanib levels in the center punch retina which were 9 fold higher than the cellular IC_{50} at 4 hours (FIG. 37A).

[000605] *In vivo*, a single 50 μL topical instillation of 2% MGCD-265-MPP to New Zealand White rabbits produced MGCD-265levels in the retina which were 37 fold higher than the cellular IC_{50} at 30 minutes and 116 fold higher than the cellular IC_{50} at 4 hours (FIG. 37B).

[000606] These results, along with Example 29, demonstrate that a variety of RTK inhibitors can be formulated as MPPs and the levels of the RTK inhibitors achieved at the back of the eye with topical administration are relevant to the active concentrations (cellular IC_{50}) of the RTK inhibitors.

Example 31

[000607] This non-limiting example demonstrates that a single topical administration of cediranib-MPPs produced therapeutically relevant drug levels at the back of the eye of rabbits for 24 hours.

[000608] In order to demonstrate the potential for MPPs containing a drug to sustain therapeutically relevant drug levels at the back of the eye of rabbits over a 24 hour period, cediranib, an RTK inhibitor, was formulated as MPPs. If topical delivery of a drug could provide therapeutically relevant levels of the drug at the back of the eye, repeated intravitreal injections, which are used in current AMD therapies, could be avoided. Ideally, this topical therapy would sustain drug levels at the back of the eye to provide less frequent dosing.

[000609] To generate the MPPs, a milling procedure similar to that used for Loteprednol Etabonate was employed: an aqueous dispersion containing cediranib and Pluronic® F127 was milled with a grinding medium until the particle size was reduced to below about 300 nm as measured by dynamic light scattering. Mucus mobility was characterized in human cervicovaginal mucus based on the previously described characterization methods. Cediranib was processed into MPPs when milled with F127.

[000610] *In vivo*, a single 50 μL topical instillation of 2% cediranib-MPP to HY79b pigmented rabbits produced cediranib levels in the choroid of the rabbit which were 4,800 fold over cellular IC_{50} at 24 hours (FIG. 38A) and cediranib levels in the retina of the rabbit which were 1,000 fold over cellular IC_{50} at 24 hours (FIG. 38B). These results demonstrate the exposure achievable at the back of the eye with the MPP technology can be in therapeutically relevant ranges and that relevant drug exposure can be maintained over a long period of time (*e.g.*, at least 24 hours).

Example 32

[000611] This non-limiting example demonstrates that a single topical administration of axitinib-MPP produced therapeutically relevant axitinib levels at the back of the eye of Dutch belted rabbits for 24 hours.

[000612] In order to demonstrate the potential for MPPs to sustain therapeutically relevant drug levels at the back of the eye of rabbits over a 24 hour period, axitinib, an RTK inhititor, was formulated as MPPs. If topical delivery of a drug could provide therapeutically relevant levels of the drug at the back of the eye, repeated intravitreal injections, which are used by current AMD therapies, could be avoided. Ideally, this topical therapy would sustain drug levels at the back of the eye to provide less frequent dosing.

[000613] To generate nanoparticles, a milling procedure similar to that used for loteprednol etabonate was employed: an aqueous dispersion containing axitinib and F127 was milled with a grinding medium until the particle size was reduced to below about 300 nm as measured by dynamic light scattering. Mucus mobility was characterized in human cervicovaginal mucus based on the previously described characterization methods. Axitinib was processed into MPPs when milled with F127.

[000614] *In vivo*, a single 50 μL topical instillation of 2%axitinib-MPP to Dutch belted rabbits produced therapeutically relevant drug levels in the choroid of the rabbit 1,100 fold over cellular IC_{50} at 24 hours (FIG. 39A) and levels in the retina of the rabbit which were 37 fold over cellular IC_{50} at 24 hours (FIG. 39B). These results demonstrate the exposure achievable at the back of the eye with the MPP technology can be in therapeutically relevant ranges and that relevant drug exposure can be maintained over a long period of time (*e.g.*, at least 24 hours).

Example 33

[000615] This non-limiting example demonstrates that axitinib-MPP reduced vascular leakage in a rabbit VEGF (vascular endothelial growth factor receptor)-challenge model.

[000616] In order to demonstrate the therapeutic potential of the MPP technology in the treatment of an eye disease of the back of the eye, axitinib-MPPs were studied in an acute VEGF-challenge model. In this model, Dutch belted rabbits were given an intravitreal injection of VEGF to stimulate vascular growth. Fluorescein angiography was used to determine the degree to which the rabbits developed abnormal vascular and leakage. Representative images from fluorescein angiography after treatment with vehicle, axitinib-MPP, or Avastin® are shown in FIGs. 40A-40C. Rabbits which were dosed with vehicle showed a large amount of vessel growth, tortuosity, and leakage. Rabbits treated with Avastin®, commonly used off-label to treat AMD in humans and with a different mechanism of action than axitinib, showed no change in retinal vasculature. Rabbits treated with axitinib-MPP showed some vessel growth but significantly less leakage than the vehicle group. These results demonstrate the exposure achievable at the back of the eye using the MPP technology is sufficient to significantly reduce vascular leakage in an acute challenge model and has potential as an effective therapy in AMD and other back-of-the-eye diseases.

Example 34

[000617] This non-limiting example demonstrates that LE MPPs containing Pluronic® F127, Tween 80®, or PVA as the surface-altering agent showed improved exposure of LE in rabbits compared to Lotemax®.

[000618] In order to demonstrate that the LE MPPs' ability to enhance the exposure of LE is not limited to the inclusion of F127 as the surface-altering agent in the LE MPPs, two additional surface-altering agents were studied: Tween 80® and polyvinyl alcohol (PVA). Tween 80® is an FDA approved surface-altering agent which consists of PEGylated sorbitan forming a head group and an alkyl tail. Tween 80® is different from a range of other surface-altering agents (*e.g.*, F127 and PVA) in that, among other things, it is oligomeric and thus significantly lower in molecular weight. PVA is an FDA approved polymer produced by, *e.g.*, partially hydrolyzing polyvinyl acetate, creating a random copolymer of polyvinyl acetate and polyvinyl alcohol. PVA is different from a range of other surface-altering agents (*e.g.*, F127 and Tween 80®) in that, among other things, it contains no PEG. In Examples 4-6, it is shown that some PVAs enable mucus penetration while other PVAs do not. This differentiated mucus penetration behavior may be controlled by the molecular weight and degree of hydrolysis of PVA. Based on the results from these Examples, a PVA that has a molecular weight of about 2 kDa and is about 75% hydrolyzed was selected for the study of mucus penetration properties of LE MPPs.

[000619] To form the LE MPPs, a milling procedure was employed as described herein. In one set of experiments, an aqueous dispersion containing LE and one surface-altering agent selected from F127, Tween 80®, and PVA (2 kDa, 75% hydrolyzed) was milled with a grinding medium until the particle size was reduced to below about 300 nm as measured by dynamic light scattering. Mucus mobility was characterized in human cervicovaginal mucus based on the previously described characterization methods. All three LE MPPs (*i.e.*, LE-F127, LE-Tween80, and LE-PVA) showed mucus penetrating properties (FIG. 42).

[000620] *In vivo*, a single topical instillation of each one of the three LE MPPs to New Zealand white rabbits produced LE levels in the cornea of the rabbit which were significantly higher than the LE levels from a similarly administered dose of Lotemax® (FIG. 42). These

results demonstrate that the MPPs, compositions, and/or formulations containing a drug enhance exposure of the drug based on the mucus penetrating properties of the particles.

Example 35

[000621] The following non-limiting example describes the assessment of different surface-altering agents in producing mucus-penetrating particles comprising loteprednol etabonate (LE) as the core material.

[000622] In this example, LE, a relatively hydrophobic pharmaceutical agent, was milled as aqueous suspensions with milling media in the presence of various surfactants or stabilizers. The characteristics of the surfactants and stabilizers tested, including the molecular weight (MW), HLB value (for surfactants) and degree of hydrolysis (for PVA), are listed in Table 21. The milling process was carried out until LE particles were uniformly small, *i.e.*, Z-average diameter (D) $\leq$500 nm and polydispersity index (PDI) <0.20 as measured by dynamic light scattering (DLS). The resulting particle size and polydispersity index for LE nanoparticles as measured by DLS are also listed in Table 21.

[000623] Not all surface-altering agents were able to effectively aid particle size reduction during milling and produce stable nanosuspensions of LE. When Span® 20, Span® 80, Kollidon® 12PF, Kollidon® 17PF were used as surface-altering agents, stable nanosuspensions of LE could not be obtained.

[000624] Table 21. Characteristics of surface-altering agents tested (molecular weight (MW), HLB value (for surfactants), degree of hydrolysis (for PVAs)), and particle size (D and PDI) measured by DLS of nanosuspensions obtained by milling of loteprednol etabonate (LE) with the surface-altering agents.

Surface-altering agent		MW (Da)	HLB	D (nm)	PDI
Surfactant	Brij® 35	1200	16.9[1]	332	0.155
	Brij® 98	1150	15[+]	324	0.148
	Brij® S100	4670	18.8[+]	404	0.103
	Cremophor® EL	2650	13[1]	200	0.099
	Cremophor® RH 40	3,090	15[1]	301	0.102
	Vitamin E-TPGS	1513	13[+]	252	0.151
	Triton® X-100	647	13.5[+]	203	0.126
	SDS	288	8.3[#]	266	0.073
	Tween® 20	1228	16.7[1]	228	0.119
	Tween® 80	1310	15[1]	206	0.129
	Span® 20	346	8.6[1]	>1000	>0.2
	Span® 85	957	1.8[1]	>1000	NM
	Solutol® HS 15	345	15[+]	284	0.131
	DPPC	734	8.5[#]	248	0.148
	DPPC + PEG2K-PE	734 (DPPC) 2804 (PEG2K-DSPE)	9.85[#]	188	0.092
	Tyloxapol	280	13[2]	271	0.087
Stabilizer	Kollidon® 12PF	2500	NA	>1000	>0.2
	Kollidon® 17PF	9000	NA	>1000	>0.2
	Kollidon® 30	50000	NA	211	0.104
	PVA	**MW (kDa)**	**% Hydrolysis**	**D (nm)**	**PDI**
	PVA 2K75	2	75 - 79	172	0.105
	PVA 13K87	13 - 23	87 - 89	333	0.112
	PVA 31K87	31 - 50	87 - 89	253	0.085
	PVA 31K98	31 - 50	98 - 99	281	0.105
	PVA 85K87	85 - 124	87 - 89	323	0.136
	PVA 85K99	85 - 124	≥99	>500	>0.2
	PVA 95K95	95	95	366	0.136
	PVA 130K87	130	87 - 89	388	0.131

NA denotes not applicable; NM denotes not measurable.
[+] denotes HLB value as obtained from supplier.
denotes HLB value calculated using the Griffin approach, as shown in Equation 2.
[1] Handbook of Pharmaceutical Excipients, 4th Edition, Rowe, Sheskey, and Weller, Pharmaceutical Press, 2003.
[2] Pharmaceutical Suspensions, Kulshreshtha, Singh, Wall, Springer, 2010

[000625] The mucus-penetrating ability of LE nanoparticles from the produced nanosuspensions was characterized in reconstituted cervicovaginal mucus (CVM) (as described in Example 2) by high resolution dark-field microscopy. In a typical sample preparation, 20 μL of rehydrated CVM and 0.5 μL of a nanosuspension at a nanoparticle concentration of 5% w/v LE were deposited onto a microscope slide. In the case of LE milled in DPPC or DPPC+2PEG-PE, 1 μL of nanosuspensions at a concentration of 1% w/v LE was used. Videos at 15s length and temporal resolution of 66.7 ms (15 frames/s) were acquired of randomized regions within the mucus sample under dark-field microscopy at high magnification (100×). Mobility of LE nanoparticles in the videos was determined visually by comparing the degree particles' motion (i.e., overall particles' velocity and the amount of particles that appear mobile) in recorded videos against a well-established positive control (LE nanoparticles milled in Pluronic® F127, "mobile" or "mucus-penetrating") and negative control (LE nanoparticles milled in SDS, "not mobile" or "not mucus-penetrating"), and classified as "mobile" and "not mobile," respectively.

[000626] The results suggest that the following surface-altering agents render LE nanoparticles mucus-penetrating: Brij® 35, Brij® 98, Brij® S100, Cremophor® EL, Cremophor® RH 40, TPGS, Triton® X-100, Tween® 20, Tween® 80, Solutol® HS, Tyloxapol, PVA 2K75, PVA 13K87, PVA 31K87, PVA 31K98, PVA 85K87, and PVA 130K87.

[000627] To identify the characteristics of the surfactants that render LE nanocrystals mucus penetrating, the mobility for LE nanoparticles obtained by milling with various surfactants was mapped with respect to MW and HLB values of the surfactant used (FIG. 43). Without wishing to be bound by any theory, the results suggest that surfactants with HLB > 10 can produce LE nanocrystals that are mobile in CVM, whereas those with HLB below 10 either produce nanocrystals that are immobile in CVM (*e.g.*, SDS, DPPC, DPPC+PEG2K-PE) or does not have the ability to form stable nanocrystal suspensions (*e.g.*, Span® 20 and Span® 85).

[000628] To identify the characteristics of the PVA that render LE nanocrystals mucus penetrating, the mobility for LE nanoparticles obtained by milling with various PVAs was mapped with respect to MW and hydrolysis degree of the PVAs used (FIG. 44). It was observed that those PVAs that have both properties of hydrolysis degree > 95% and

molecular weight > 31 kDa failed to produce stable nanocrystals or those that were mucus-penetrating. Without wishing to be bound by any theory, it is believed that the unhydrolyzed segments (vinyl acetate) of PVA can provide effective hydrophobic association with the surface of the core particles if the content of these segments in the PVA is sufficient (e.g., equal or greater than 2% in some embodiments); while the hydrophilic segments (vinyl alcohol) of PVA present at the surface of the coated particles render the coated particles hydrophilic and can shield the coated particles from adhesive interactions with mucus.

Example 36

[000629] In order to demonstrate enhanced mucus penetration is useful not only at the front of the eye, but can lead to enhanced exposure at the back of the eye as well, axitinib, a receptor tyrosine kinase inhibitor (RTKi), were formulated as MPP. Small molecule RTKi which act on vascular endothelial growth factor receptor (VEGFR) have potential as therapy for age-related macular degeneration (AMD). If topical delivery could provide sufficient levels of drug at the back of the eye then repeated intravitreal injections, used by current therapies, could be avoided. Delivery to the back of the eye would also be beneficial in a number of other diseases which affect posterior segment tissues.

[000630] To generate nanoparticles, a milling procedure similar to that used for Loteprednol Etabonate was employed: an aqueous dispersion containing drug and Pluronic F127 (F127) or sodium dodecyl sulfate (SDS) was milled with grinding medium until particle size was reduced below 300 nm as measured by dynamic light scattering. Mucus mobility was characterized in human cervicovaginal mucus based on the previously described characterization methods. Axitinib was characterized as mucus penetrating (i.e., generating MPP) when milled with F127, and non-mucus penetrating when milled with SDS.

[000631] *In vivo*, a single 50 μL topical instillation of 0.5% Axitinib-MPP to New Zealand White rabbits produced therapeutically relevant drug levels in the retina 100 fold over cellular IC_{50} (FIG. 45). These results demonstrate that enhanced exposure is achievable at the back of the eye with the MPP technology and reaches therapeutically relevant ranges.

Example 37

[000632] This non-limiting example shows *in vivo* imaging data illustrating the differences in ocular residence time of conventional particles (CPs) and mucus-penetrating particles (MPPs) following a single topical dose of the particles to Long Evans pigmented rats.

[000633] CPs (Near-Infrared fluorescent (780 nm/820 nm) carboxylated polystyrene particles, 200nm in diameter) were purchased from Phosphorex, Inc., and used without further modification (except dilution with DI water to 0.9 % w/w particle concentration). MPPs were prepared from the aforementioned CPs by combining the CPs with Pluronic® F127 to produce 0.9% w/w particle concentration and 0.9% w/w Pluronic® F127 concentration. In *in vivo* imaging studies, Long Evans pigmented rats (n = 8) were given a 5 µl dose of CPs in the left eye and MPPs in the right eye at equivalent particle concentrations. Images were captured at 2, 4, and 6 hours post dose (n = 2/time point) using a Heidelberg camera at a fixed sensitivity providing uniform image amplification.

[000634] A more even distribution and greater corneal staining were observed in the eyes receiving MPPs (FIG. 46), confirming that MPPs provide longer residence at the ocular surface. Differences were also apparent, although not as great, with staining of the conjunctiva (data not shown).

Example 38

[000635] This non-limiting example shows the relationship between the relative velocity of polystyrene (PS) particles coated with Pluronic® F127 in mucus and the density of the Pluronic® F127 on the particle surface.

[000636] In one set of experiments, aqueous dispersions of carboxylated PS nanoparticles (200 nm, 0.5% w/v) were equilibrated in the presence of various concentrations of Pluronic® F127 at room temperature for at least 24 hrs. The density of Pluronic® F127 molecules on the surface of the obtained PS/Pluronic® F127 nanoparticles was quantified as follows. The PS/Pluronic® F127 mixtures were ultracentrifuged to a complete sedimentation of the particles. As a result, Pluronic® F127 that was bound to PS was sedimented along with the particles; Pluronic® F127 that was not bound to PS remained in the supernatant. The concentration of Pluronic® F127 in the obtained supernatants ($C_{F127,\,free}$) was measured by gel permeation chromatography (GPC). In this experiment, an Agilent 1100 HPLC system outfitted with a G1362A refractive index detector and the Agilent PLgel 5 µm Mixed-C

column for the analysis were employed. Concentration of the bound Pluronic® F127 ($C_{F127,\ bound}$) was calculated as:

$$C_{F127,\ bound} = C_{F127} - C_{F127,\ free}$$

where C_{F127} is the total concentration Pluronic® F127 present in the mixture. The number of Pluronic® F127 molecules per PS surface area (F127/nm^2) was then calculated as:

$$F127/nm^2 = \frac{N_A \times C_{F127,bound}}{SA \times C_{PS}}$$

where N_A is the Avogadro number, $C_{F127,\ bound}$ is the molar concentration of bound Pluronic® F127 (in moles/L), *SA* is the specific surface area of PS particle (in nm^2/g) calculated from the manufacturer (Invitrogen) specifications, and C_{PS} is the mass concentration of PS in the mixture (in g/L). The number average molecular weight of Pluronic® F127 specified by the manufacturer (BASF) was used in the calculation.

[000637] The ability of PS/Pluronic® F127 particles to penetrate mucus was measured as relative velocity in human cervicovaginal mucus using fluorescence microscopy and multiple particle tracking software as described in Examples 1 and 4-6. In particular, the sample was the particle of interest, the negative control was a 200 nm fluorescent carboxylate-modified polystyrene particle without a polymer coating, and the positive control was a 200 nm fluorescent polystyrene particle having a dense coating of 2 or 5 kDa PEG (which have well-established reduced mucoadhesion behavior). The sample, negative control, and positive control were differentiated from each other by their fluorescence colors. In a typical experiment, ≤0.5 μL of a particle suspension was added to 20 μL of fresh cervicovaginal mucus along with the positive and negative controls. Using a fluorescent microscope equipped with a CCD camera, 15 second (s) movies were captured at a temporal resolution of 66.7 milliseconds (15 frames/s) under 100× magnification from several areas within each sample for each type of particles: sample, negative control, and positive control. Next, using an advanced image processing software, individual trajectories of multiple particles were measured over a time-scale of at least 3.335 s (50 frames).

[000638] The results, shown in FIG. 47, indicted that the relative velocity of PS particles coated with Pluronic® F127 in mucus increased when the density of Pluronic® F127 molecules on the particle surface increased.

Other Embodiments

[000639] While several embodiments of the present invention have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the present invention. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the teachings of the present invention is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, the invention may be practiced otherwise than as specifically described and claimed. The present invention is directed to each individual feature, system, article, material, kit, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the scope of the present invention.

[000640] The indefinite articles "a" and "an," as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to mean "at least one."

[000641] The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, *i.e.*, elements that are conjunctively present in some cases and disjunctively present in other cases. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified unless clearly indicated to the contrary. Thus, as a non-limiting example, a reference to "A and/or B," when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A without B (optionally including elements other than B); in another embodiment, to B without A (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); *etc.*

[000642] As used herein in the specification and in the claims, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list, "or" or "and/or" shall be interpreted as being inclusive, *i.e.*, the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of" or "exactly one of," or, when used in the claims, "consisting of," will refer to the inclusion of exactly one element of a number or list of elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (*i.e.* "one or the other but not both") when preceded by terms of exclusivity, such as "either," "one of," "only one of," or "exactly one of." "Consisting essentially of," when used in the claims, shall have its ordinary meaning as used in the field of patent law.

[000643] As used herein in the specification and in the claims, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, "at least one of A and B" (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); *etc.*

[000644] In the claims, as well as in the specification above, all transitional phrases such as "comprising," "including," "carrying," "having," "containing," "involving," "holding," and the like are to be understood to be open-ended, *i.e.*, to mean including but not limited to. Only the transitional phrases "consisting of" and "consisting essentially of" shall be closed or

semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

What is claimed is:

Claims

1. A pharmaceutical composition suitable for administration to an eye, comprising:

a plurality of coated particles, comprising:

a core particle comprising loteprednol etabonate, wherein the loteprednol etabonate constitutes at least about 80 wt% of the core particle; and

a coating comprising one or more surface-altering agents surrounding the core particle,

wherein the one or more surface-altering agents comprises at least one of:

a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer,

b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or

c) a polysorbate,

wherein the one or more surface altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2,

wherein the one or more surface altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight,

wherein the plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron; and

one or more ophthalmically acceptable carriers, additives, and/or diluents.

2. A pharmaceutical composition suitable for topical administration to an eye, comprising:

a plurality of coated particles, comprising:

a core particle comprising loteprednol etabonate, wherein the loteprednol etabonate constitutes at least about 80 wt% of the core particle; and

a coating comprising one or more surface-altering agents, wherein the one or more surface-altering agents comprise at least one of a poloxamer, a poly(vinyl alcohol), or a polysorbate,

wherein the one or more surface-altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2,

wherein the one or more surface-altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight,

wherein the plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron; and

one or more ophthalmically acceptable carriers, additives, and/or diluents.

3. A method for treating inflammation, macular degeneration, macular edema, uveitis, dry eye, and/or other disorder in an eye of a patient, comprising:

administering to an eye of the patient, a pharmaceutical composition comprising:

a plurality of coated particles, comprising:

a core particle comprising loteprednol etabonate, wherein the loteprednol etabonate constitutes at least about 80 wt% of the core particle; and

a coating comprising one or more surface-altering agents surrounding the core particle,

wherein the one or more surface-altering agents comprises at least one of:

a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer,

b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or

c) a polysorbate,

wherein the one or more surface altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2,

wherein the one or more surface altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight,

wherein the plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron; and

one or more ophthalmically acceptable carriers, additives, and/or diluents.

4. A method for treating inflammation, macular degeneration, macular edema, uveitis, dry eye, and/or other disorder in an eye of a patient, comprising:

administering to an eye of the patient, a pharmaceutical composition comprising:

a plurality of coated particles, comprising:

a core particle comprising loteprednol etabonate, wherein the loteprednol etabonate constitutes at least about 80 wt% of the core particle; and

a coating comprising one or more surface-altering agents, wherein the one or more surface-altering agents comprise at least one of a poloxamer, poly(vinyl alcohol), or a polysorbate,

wherein the one or more surface-altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2,

wherein the one or more surface-altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight,

wherein the plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron; and

one or more ophthalmically acceptable carriers, additives, and/or diluents.

5. A pharmaceutical composition suitable for administration to an eye, comprising:

a plurality of coated particles, comprising:

a core particle comprising a pharmaceutical agent or a salt thereof, wherein the pharmaceutical agent or salt thereof constitutes at least about 80 wt% of the core particle, and wherein the pharmaceutical agent or salt thereof comprises a receptor tyrosine kinase (RTK) inhibitor; and

a coating comprising one or more surface-altering agents surrounding the core particle,

wherein the one or more surface-altering agents comprises at least one of:

a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer,

b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or

c) a polysorbate,

wherein the one or more surface altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2,

wherein the one or more surface altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight,

wherein the plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron; and

one or more ophthalmically acceptable carriers, additives, and/or diluents.

6. A method for treating macular degeneration, macular edema and/or another disorder in an eye of a patient, comprising:

administering to an eye of the patient, a pharmaceutical composition comprising:

a plurality of coated particles, comprising:

a core particle comprising a pharmaceutical agent or a salt thereof, wherein the pharmaceutical agent or salt thereof constitutes at least about 80 wt% of the core particle, and wherein the pharmaceutical agent or salt thereof comprises a receptor tyrosine kinase (RTK) inhibitor; and

a coating comprising one or more surface-altering agents surrounding the core particle,

wherein the one or more surface-altering agents comprises at least one of:

a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at

least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer,

b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or

c) a polysorbate,

wherein the one or more surface altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2,

wherein the one or more surface altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight,

wherein the plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron; and

one or more ophthalmically acceptable carriers, additives, and/or diluents.

7. A pharmaceutical composition suitable for administration to an eye, comprising:

a plurality of coated particles, comprising:

a core particle comprising a pharmaceutical agent or a salt thereof, wherein the pharmaceutical agent or salt thereof constitutes at least about 80 wt% of the core particle, and wherein the pharmaceutical agent or salt thereof comprises bromfenac calcium, diclofenac free acid, or ketorolac free acid; and

a coating comprising one or more surface-altering agents surrounding the core particle,

wherein the one or more surface-altering agents comprises at least one of:

a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer,

b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or

equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or

c) a polysorbate,

wherein the one or more surface altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2,

wherein the one or more surface altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight,

wherein the plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron; and

one or more ophthalmically acceptable carriers, additives, and/or diluents.

8. A method for treating inflammation, macular degeneration, macular edema, uveitis, dry eye, glaucoma, and/or other disorder in an eye of a patient, comprising:

administering to an eye of the patient, a pharmaceutical composition comprising:

a plurality of coated particles, comprising:

a core particle comprising a pharmaceutical agent or a salt thereof, wherein the pharmaceutical agent or salt thereof constitutes at least about 80 wt% of the core particle, and wherein the pharmaceutical agent or salt thereof comprises bromfenac calcium, diclofenac free acid, or ketorolac free acid; and

a coating comprising one or more surface-altering agents surrounding the core particle,

wherein the one or more surface-altering agents comprises at least one of:

a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer,

b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or

c) a polysorbate,

wherein the one or more surface altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2,

wherein the one or more surface altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight,

wherein the plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron; and

one or more ophthalmically acceptable carriers, additives, and/or diluents.

9. A pharmaceutical composition suitable for administration to an eye, comprising:

a plurality of coated particles, comprising:

a core particle comprising a pharmaceutical agent or a salt thereof selected from the group consisting of a corticosteroid, a receptor tyrosine kinase (RTK) inhibitor, a cyclooxygenase (COX) inhibitor, an angiogenesis inhibitor, a prostaglandin analog, an NSAID, a beta blocker, and a carbonic anhydrase inhibitor; and

a coating comprising one or more surface-altering agents surrounding the core particle,

wherein the one or more surface-altering agents comprises at least one of:

a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer, wherein the hydrophobic block associates with the surface of the core particle, and wherein the hydrophilic block is present at the surface of the coated particle and renders the coated particle hydrophilic,

b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or

c) a polysorbate,

wherein the one or more surface altering agents is present on the outer surface of the core particle at a density of at least 0.01 molecules/nm^2,

wherein the one or more surface altering agents is present in the pharmaceutical composition in an amount of between about 0.001% to about 5% by weight; and

one or more ophthalmically acceptable carriers, additives, and/or diluents.

10. A method of treating, diagnosing, preventing, or managing an ocular condition in a subject, the method comprising:

administering a composition to an eye of a subject, wherein the composition comprises a plurality of coated particles, the coated particles comprising:

a core particle comprising a pharmaceutical agent or a salt thereof selected from the group consisting of a corticosteroid, a receptor tyrosine kinase (RTK) inhibitor, a cyclooxygenase (COX) inhibitor, an angiogenesis inhibitor, a prostaglandin analog, an NSAID, a beta blocker, and a carbonic anhydrase inhibitor; and

a coating comprising one or more surface-altering agents surrounding the core particle,

wherein the one or more surface-altering agents comprises at least one of:

a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer, wherein the hydrophobic block associates with the surface of the core particle, and wherein the hydrophilic block is present at the surface of the coated particle and renders the coated particle hydrophilic, or

b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or

c) a polysorbate; and

delivering the pharmaceutical agent to a tissue in the eye of the subject.

11. A method of improving the ocular bioavailability of a pharmaceutical agent in a subject, the method comprising:

administering a composition to an eye of the subject, wherein the composition comprises a plurality of coated particles, the coated particles comprising:

a core particle comprising a pharmaceutical agent or a salt thereof selected from the group consisting of a corticosteroid, a receptor tyrosine kinase (RTK) inhibitor, a cyclooxygenase (COX) inhibitor, an angiogenesis inhibitor, a prostaglandin analog, an NSAID, a beta blocker, and a carbonic anhydrase inhibitor; and

a coating comprising a surface-altering agent surrounding the core particle,

wherein the coating on the core particle is present in a sufficient amount to improve the ocular bioavailability of the pharmaceutical agent when administered in the composition, compared to the ocular bioavailability of the pharmaceutical agent when administered as a core particle without the coating.

12. A method of improving the concentration of a pharmaceutical agent in a tissue of a subject, the method comprising:

administering a composition to an eye of the subject, wherein the composition comprises a plurality of coated particles, the coated particles comprising:

a core particle comprising the pharmaceutical agent or a salt thereof, wherein the pharmaceutical agent is selected from the group consisting of a corticosteroid, a receptor tyrosine kinase (RTK) inhibitor, a cyclooxygenase (COX) inhibitor, an angiogenesis inhibitor, a prostaglandin analog, an NSAID, a beta blocker, and a carbonic anhydrase inhibitor; and

a coating comprising a surface-altering agent surrounding the core particle,

wherein the tissue is selected from the group consisting of a retina, a macula, a sclera, or a choroid; and

wherein the coating on the core particle is present in a sufficient amount to increase the concentration of the pharmaceutical agent by at least 10% in the tissue when administered in the composition, compared to the concentration of the pharmaceutical agent in the tissue when administered as a core particle without the coating.

13. A method of treating an ocular condition in a subject by repeated administration of a pharmaceutical composition, the method comprising:

administering two or more doses of a pharmaceutical composition comprising loteprednol etabonate to an eye of a subject, wherein the period between consecutive doses is at least about 4 hours, at least about 6 hours, at least about 8 hours, at least about 12 hours, at least about 36 hours, or at least about 48 hours,

wherein the amount of loteprednol etabonate delivered to a tissue of an eye is effective to treat an ocular condition in the subject.

14. A method of treating an ocular condition in a subject by repeated administration of a pharmaceutical composition, the method comprising:

administering two or more doses of a pharmaceutical composition comprising one or more pharmaceutical agents to an eye of a subject, wherein the period between consecutive doses is at least about 4 hours, at least about 6 hours, at least about 8 hours, at least about 12 hours, at least about 36 hours, or at least about 48 hours,

wherein the one or more pharmaceutical agents is selected from the group consisting of loteprednol etabonate, sorafenib, linifanib, MGCD-265, pazopanib, cediranib, axitinib, bromfenac calcium, diclofenac free acid, ketorolac free acid and a combination thereof,

wherein the amount of the pharmaceutical agent delivered to a tissue of an eye is effective to treat an ocular condition in the subject.

15. A pharmaceutical composition suitable for treating an anterior ocular disorder by administration to an eye, comprising:

a plurality of coated particles, comprising:

a core particle comprising a corticosteroid; and

a coating comprising one or more surface-altering agents surrounding the core particle,

wherein the one or more surface-altering agents comprises at least one of:

a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at

least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer,

b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or

c) a polysorbate,

wherein the plurality of coated particles have an average smallest cross-sectional dimension of less than about 1 micron; and

wherein the coating on the core particle is present in a sufficient amount to increase the concentration of the corticosteroid by at least 50% in an anterior component of the eye selected from the group consisting of a cornea or aqueous humor 30 minutes after administration when administered to the eye, compared to the concentration of the corticosteroid in the tissue when administered as a core particle without the coating.

16. A method of treating an anterior ocular disorder by administration to an eye, comprising:

administering a composition to an eye of a subject, wherein the composition comprises:

a plurality of coated particles, comprising:

a core particle comprising a corticosteroid; and

a coating comprising one or more surface-altering agents surrounding the core particle,

wherein the one or more surface-altering agents comprises at least one of:

a) a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer,

b) a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or

equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed, or

c) a polysorbate; and

sustaining an ophthalmically efficacious level of the corticosteroid in an anterior ocular tissue selected from the group consisting of a palpebral conjunctiva, a bulbar conjunctiva, or a cornea for at least 12 hours after administration.

17. The composition or method of any preceding claim, wherein the poloxamer includes a hydrophobic block having a molecular weight of at least about 2 kDa, and wherein the poloxamer includes hydrophilic blocks constituting at least about 15 wt% of the poloxamer.

18. The composition or method of any preceding claim, wherein the surface-altering agent comprises a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer, wherein the hydrophobic block associates with the surface of the core particle, and

wherein the hydrophilic block is present at the surface of the coated particle and renders the coated particle hydrophilic.

19. The method of any preceding claim, comprising delivering the pharmaceutical agent to a tissue in the front of the eye of the subject.

20. The method of any preceding claim, comprising delivering the pharmaceutical agent to a tissue in the back of the eye of the subject.

21. The composition or method of any preceding claim, wherein the surface-altering agent is covalently attached to the core particles.

22. The composition or method of any preceding claim, wherein the surface-altering agent is non-covalently adsorbed to the core particles.

23. The composition or method of any preceding claim, wherein the surface-altering agent is present on the surfaces of the coated particles at a density of at least about 0.01, at least about 0.02, at least about 0.05, at least about 0.1, at least about 0.2, at least about 0.5, at least about 1, at least about 2, at least about 5, at least about 10, or at least about 20 molecules per nanometer squared.

24. The composition or method of any preceding claim, wherein the surface-altering agent comprises a linear polymer having pendant hydroxyl groups on the backbone of the polymer.

25. The composition or method of any preceding claim, wherein the hydrophilic blocks of the triblock copolymer constitute at least about 20 wt%, at least about 30 wt%, at least about 40 wt%, at least about 50 wt%, or at least about 60 wt% of the triblock polymer, and/or less than or equal to about 80 wt% of the triblock copolymer.

26. The composition or method of any preceding claim, wherein the hydrophobic block portion of the triblock copolymer has a molecular weight of at least about 3 kDa, at least about 4 kDa, or at least about 6 kDa, and/or less than or equal to about 20 kDa, less than or equal to about 10 kDa, or less than or equal to about 8 kDa.

27. The composition or method of any preceding claim, wherein the triblock copolymer is poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) or poly(ethylene glycol)-poly(propylene oxide)-poly(ethylene glycol).

28. The composition or method of any preceding claim, wherein the hydrophilic block of the triblock copolymer comprises poly(ethylene oxide) or poly(ethylene glycol) or a derivative thereof.

29. The composition or method of any preceding claim, wherein the poly(ethylene oxide) or poly(ethylene glycol) block has a molecular weight of at least about 2 kDa, at least about 3 kDa, or at least about 4 kDa.

30. The composition or method of any preceding claim, wherein the hydrophobic block of the triblock copolymer is poly(propylene oxide).

31. The composition or method of any preceding claim, wherein the poly(propylene oxide) block has a molecular weight of at least about 1.8 kDa, at least about 2 kDa, at least about 2.5 kDa, at least about 3 kDa, at least about 4 kDa, or at least about 5 kDa.

32. The composition or method of any preceding claim, wherein the surface-altering agent and/or polymer has a molecular weight of at least about 2 kDa, at least about 5 kDa, at least about 10 kDa, at least about 20 kDa, at least about 50 kDa, at least about 80 kDa, at least about 100 kDa, or at least about 120 kDa.

33. The composition or method of any preceding claim, wherein the polymer has a molecular weight of less than or equal to about 200 kDa, less than or equal to about 180 kDa, less than or equal to about 150 kDa, less than or equal to about 130 kDa, less than or equal to about 100 kDa, less than or equal to about 80 kDa, less than or equal to about 50 kDa, or less than or equal to about 30 kDa.

34. The composition or method of any preceding claim, wherein the polymer is at least about 40% hydrolyzed, at least about 50% hydrolyzed, at least about 60% hydrolyzed, at least about 70% hydrolyzed, at least about 80% hydrolyzed, or at least about 90% hydrolyzed.

35. The composition or method of any preceding claim, wherein the polymer is less than or equal to about 94%, less than or equal to about 90%, less than or equal to about 85%, or less than or equal to about 80% hydrolyzed.

36. The composition or method of any preceding claim, wherein the synthetic polymer is polyvinyl alcohol.

37. The composition or method of any preceding claim, wherein each of the core particles comprises a crystalline pharmaceutical agent or a salt thereof.

38. The composition or method of any preceding claim, wherein each of the core particles comprises an amorphous pharmaceutical agent or a salt thereof.

39. The composition or method of any preceding claim, wherein each of the core particles comprises a salt of the solid pharmaceutical agent.

40. The composition or method of any preceding claim, wherein each of the core particles comprises a pharmaceutical agent or a salt thereof that is encapsulated in a polymer, a lipid, a protein, or a combination thereof.

41. The composition or method of any preceding claim, wherein the pharmaceutical agent is at least one of a therapeutic agent or a diagnostic agent.

42. The composition or method of any preceding claim, wherein the pharmaceutical agent is at least one of a small molecule, a peptide, a peptidomimetic, a protein, a nucleic acid, or a lipid.

43. The composition or method of any preceding claim, wherein the pharmaceutical agent or a salt thereof is a corticosteroid.

44. The composition or method of any preceding claim, wherein the pharmaceutical agent or a salt thereof is loteprednol etabonate.

45. The composition or method of any preceding claim, wherein the pharmaceutical agent or a salt thereof comprises an anti-VEGF agent.

46. The composition or method of any preceding claim, wherein the pharmaceutical agent or a salt thereof comprises a tyrosine kinase inhibitor.

47. The composition or method of any preceding claim, wherein the pharmaceutical agent or a salt thereof has an aqueous solubility of less than or equal to about 1 mg/mL, less than or equal to about 0.1 mg/mL, or less than or equal to about 0.01 mg/mL at 25 ℃.

48. The composition or method of any preceding claim, wherein the pharmaceutical agent constitutes at least about 50 wt% of the core particle, at least about 80 wt% of the core particle, at least about 85 wt% of the core particle, at least about 90 wt% of the core particle, at least about 95 wt% of the core particle, or at least about 99 wt% of the core particle.

49. The composition or method of any preceding claim, wherein the core particle has an average size of at least about 10 nm, at least about 50 nm, or at least about 100 nm, and less than or equal to about 1 μm.

50. The composition or method of any preceding claim, wherein the coated particles have an average size of at least about 10 nm, at least about 50 nm or at least about 100 nm, and less than or equal to about1 μm.

51. The composition or method of any preceding claim, wherein the coated particles have a relative velocity of greater than 0.5, 0.6, 0.7, 0.8, 0.9, or 1.0.

52. A pharmaceutical composition comprising the composition of any preceding claim and one or more pharmaceutically acceptable carriers.

53. A pharmaceutical preparation suitable for topical administration to an eye of a subject, the pharmaceutical preparation comprising the composition of any preceding claim.

54. The composition or method of any preceding claim, wherein the coating on the core particle is present in a sufficient amount to increase the concentration of the pharmaceutical agent in the tissue by at least about 10%, by at least about 20%, by at least about 30%, by at least about 40%, by at least about 50%, by at least about 60%, by at least about 70%, by at least about 80%, by at least about 90%, or by at least about 100% when administered in the composition, compared to the concentration of the pharmaceutical agent in the tissue when administered as a core particle without the coating.

55. The composition or method of any preceding claim, wherein the ocular condition is a posterior ocular condition.

56. The composition or method of any preceding claim, wherein the ocular condition is a retinal disorder.

57. The composition or method of any preceding claim, wherein the ocular condition is inflammation, macular degeneration, macular edema, uveitis, dry eye, or glaucoma.

58. The composition or method of any preceding claim, wherein the subject is human.

59. The composition or method of any preceding claim, wherein the tissue is a retina, a macula, a sclera, or a choroid.

60. The composition or method of any preceding claim, wherein the composition comprises one or more degradants of the pharmaceutical agent, and wherein the concentration of each or at least one degradant is less than or equal to about 2 wt%, less than or equal to about 1 wt%, less than or equal to about 0.8 wt, less than or equal to about 0.6 wt%, less than or equal to about 0.4 wt%, less than or equal to about 0.2 wt%, less than or equal to about 0.15 wt%, or less than or equal to about 0.1 wt%, relative to the weight of the pharmaceutical agent.

61. The composition or method of any preceding claim, wherein the polydispersity index of the composition is less than or equal to about 0.5, less than or equal to about 0.4, less than or equal to about 0.3, less than or equal to about 0.2, less than or equal to about 0.15, less than or equal to about 0.1, or less than or equal to about 0.05.

62. The composition of any preceding claim, wherein the pharmaceutical composition is suitable for topical administration to the eye.

63. The composition of any preceding claim, wherein the pharmaceutical composition is suitable for direct injection into the eye.

64. The method of any preceding claim, comprising topically administrating the pharmaceutical composition to the eye.

65. The method of any preceding claim, comprising administrating the pharmaceutical composition by direct injection into the eye.

66. The method of any preceding claim, wherein the ophthalmically efficacious level is an IC50 or IC90 value.

67. A pharmaceutical composition or method of any preceding claim, wherein the pharmaceutical agent or a salt thereof is a corticosteroid.

68. A pharmaceutical composition or method of any preceding claim, wherein the pharmaceutical agent or a salt thereof is a receptor tyrosine kinase (RTK) inhibitor.

69. A pharmaceutical composition or method of any preceding claim, wherein the RTK inhibitor is sorafenib, linifanib, MGCD-265, pazopanib, cediranib, axitinib, or a combination thereof.

70. A pharmaceutical composition or method of any preceding claim, wherein the pharmaceutical agent or a salt thereof is a cyclooxygenase (COX) inhibitor.

71. A pharmaceutical composition or method of any preceding claim, wherein the cyclooxygenase (COX) inhibitor is a COX-2 inhibitor.

72. A pharmaceutical composition or method of any preceding claim, wherein the pharmaceutical agent or a salt thereof is an angiogenesis inhibitor.

73. A pharmaceutical composition or method of any preceding claim, wherein the pharmaceutical agent or a salt thereof is a prostaglandin analog.

74. A pharmaceutical composition or method of any preceding claim, wherein the pharmaceutical agent or a salt thereof is an NSAID.

75. A pharmaceutical composition or method of any preceding claim, wherein the pharmaceutical agent or a salt thereof is a beta blocker.

76. A pharmaceutical composition or method of any preceding claim, wherein the pharmaceutical agent or a salt thereof is a carbonic anhydrase inhibitor.

77. A pharmaceutical composition or method of any preceding claim, wherein the pharmaceutical agent or a salt thereof is loteprednol etabonate.

78. A pharmaceutical composition or method of any preceding claim, wherein the pharmaceutical agent or a salt thereof is bromfenac calcium.

79. A pharmaceutical composition or method of any preceding claim, wherein the surface-altering agent is a triblock copolymer comprising a hydrophilic block – hydrophobic block – hydrophilic block configuration, wherein the hydrophobic block has a molecular weight of at least about 2 kDa, and the hydrophilic blocks constitute at least about 15 wt% of the triblock copolymer.

80. A pharmaceutical composition or method of any preceding claim, wherein the surface-altering agent is a synthetic polymer having pendant hydroxyl groups on the backbone of the polymer, the polymer having a molecular weight of at least about 1 kDa and less than or equal to about 1000 kDa, wherein the polymer is at least about 30% hydrolyzed and less than about 95% hydrolyzed.

81. A pharmaceutical composition or method of any preceding claim, wherein the surface-altering agent is a polysorbate.

82. A pharmaceutical composition or method of any preceding claim, wherein the surface-altering agent is a poly(vinyl alcohol).

83. A pharmaceutical composition or method of any preceding claim, wherein the composition has a PDI of less than or equal to about 0.5, less than or equal to about 0.3, or less than or equal to about 0.2.

84. A pharmaceutical composition or method of any preceding claim, wherein the composition has a PDI of greater than or equal to about 0.1 and less than or equal to about 0.5, greater than or equal to about 0.1 and less than or equal to about 0.3, or greater than or equal to about 0.1 and less than or equal to about 0.2.

85. A pharmaceutical composition or method of any preceding claim, wherein coating has a thickness of less than or equal to about 100 nm, less than or equal to about 50 nm, less than or equal to about 30 nm, or less than or equal to about 10 nm.

86. A pharmaceutical composition or method of any preceding claim, wherein the total amount of the surface-altering agent present in the composition is between about 0.001% to about 5% by weight, between about 0.01% to about 5% by weight, or between about 0.1% to about 5% by weight.

87. A pharmaceutical composition or method of any preceding claim, wherein the composition comprises one or more free surface-altering agents; optionally, wherein the free surface-altering agent(s) in solution and surface-altering agent on the surface of the particle is/are the same surface-altering agent(s); optionally, wherein the free surface-altering agent(s) in solution and surface-altering agent on the surface of the particle are in equilibrium with each other in the composition.

88. A pharmaceutical composition or method of any preceding claim, wherein the pharmaceutical agent or salt thereof (A) is selected from A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13, A14, A15, A16, A17, A18, or A19, or a species of A1, A2, A3, A4, A5, A6, A7, A8, A9, A10, A11, A12, A13, A14, A15, A16, A17, A18, or A19 as identified herein.

89. A pharmaceutical composition or method of any preceding claim, wherein the surface altering agent (B) is selected from B1, B2, B3, B4, B5, B6, B7, B8, or B9, or a species of B1, B2, B3, B4, B5, B6, B7, B8, or B9 as identified herein.

90. A pharmaceutical composition or method of any preceding claim, wherein the one or more ophthalmically acceptable carriers, additives, and/or diluents comprises glycerin.

91. A pharmaceutical composition or method of any preceding claim, wherein the pharmaceutical composition comprises one or more degradants of the pharmaceutical agent, and wherein the concentration of each degradant is less than or equal to about 1 wt% relative to the weight of the pharmaceutical agent.

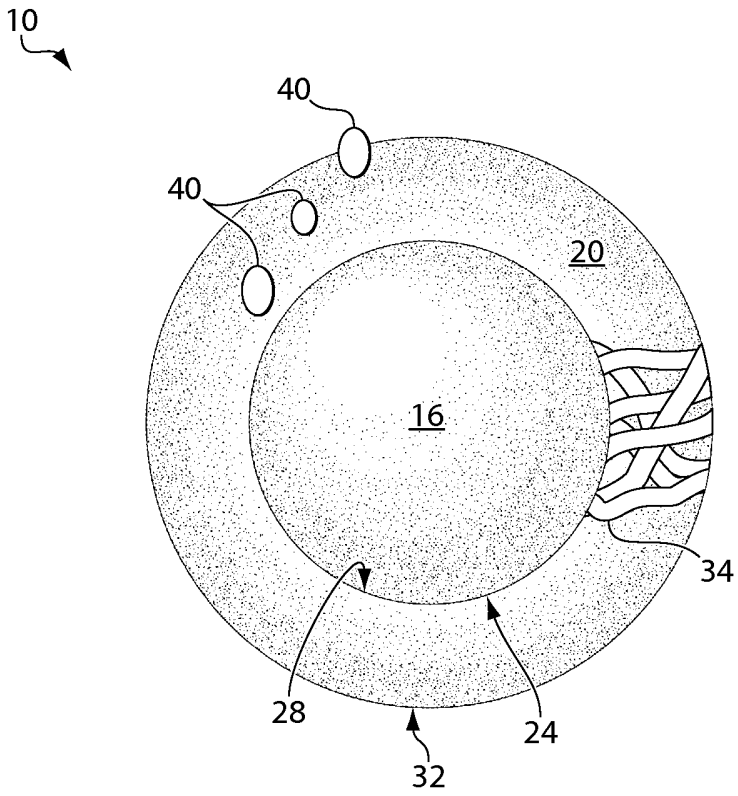


Fig. 1

FIG. 2A

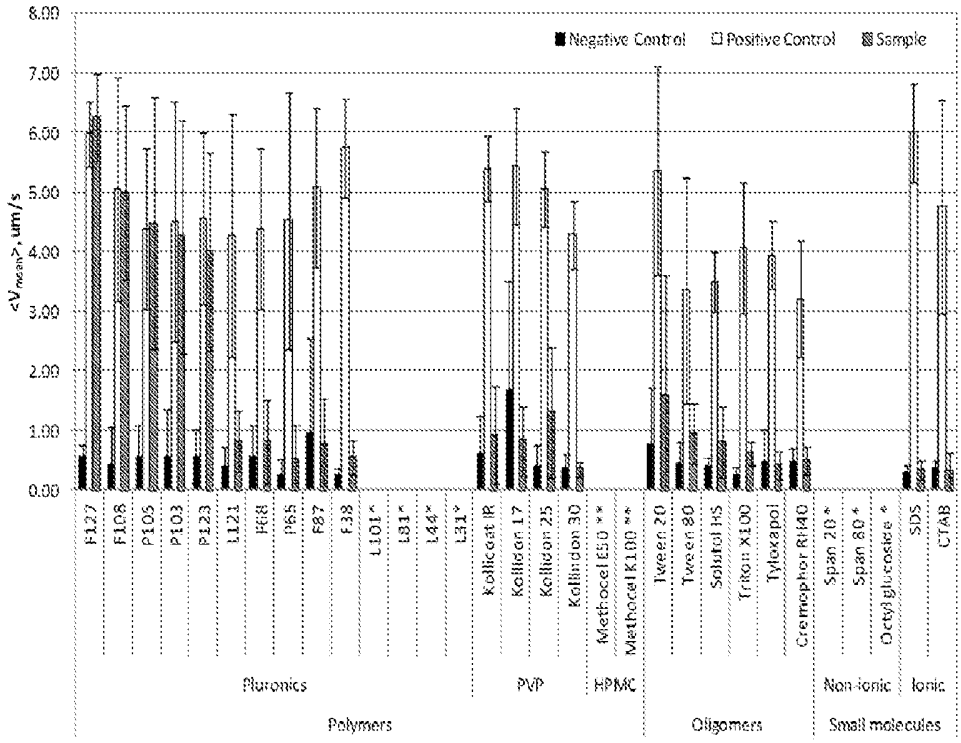

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Positive Control
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6.00
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4.00
3.00
2.00
1.00
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P103
P123
L121
F68
P65
F87
F38
L101*
L81*
L44*
L31*
Kollicoat IR
Kollidon 17
Kollidon 25
Kollidon 30
Methocel E50 **
Methocel K100 **
Tween 20
Tween 80
Solutol HS
Triton X100
Tyloxapol
Cremophor RH40
Span 20 *
Span 80 *
Octylglucoside *
SDS
CTAB
Pluronics
PVP
HPMC
Non-ionic
Ionic
Polymers
Oligomers
Small molecules

FIG. 2B

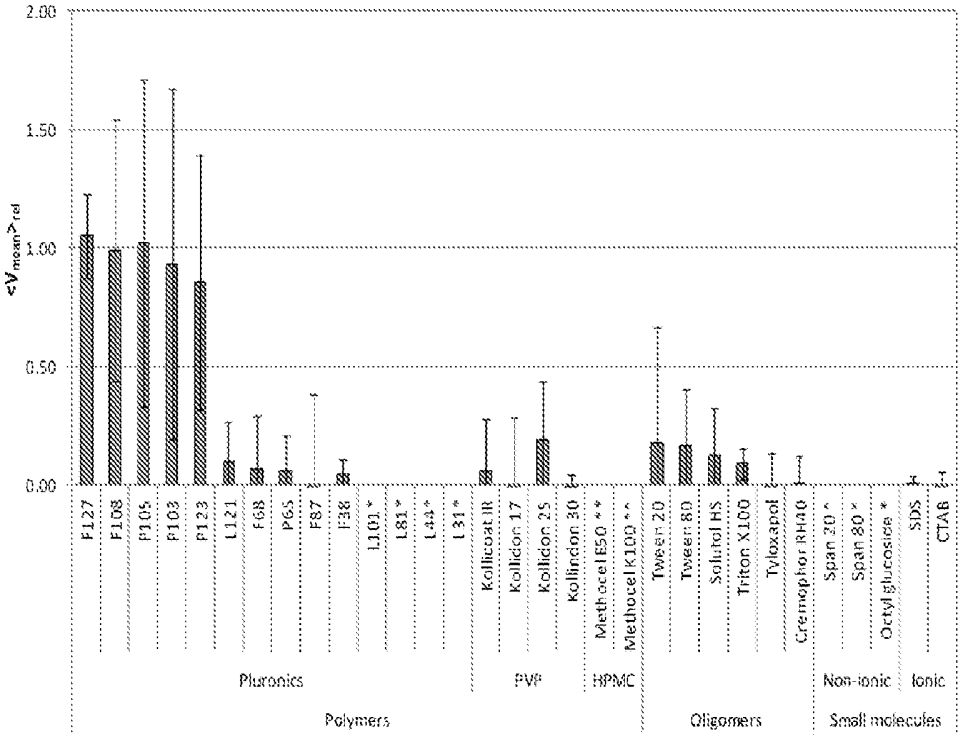

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1.00
0.50
0.00
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F108
P105
P103
P123
L121
F68
P65
F87
F38
L101*
L81*
L44*
L31*
Kollicoat IR
Kollidon 17
Kollidon 25
Kollidon 30
Methocel E50 **
Methocel K100 **
Tween 20
Tween 80
Solutol HS
Triton X100
Tyloxapol
Cremophor RH40
Span 20 *
Span 80 *
Octylglucoside *
SDS
CTAB
Pluronics
PVP
HPMC
Non-ionic
Ionic
Polymers
Oligomers
Small molecules

FIG. 3A Pluronic F127

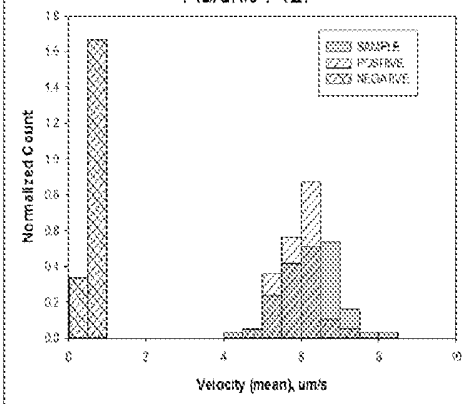


FIG. 3C Pluronic F108

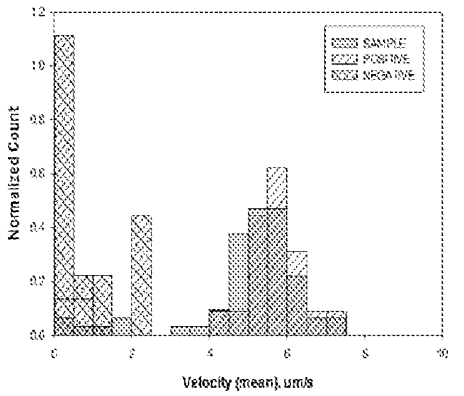


FIG. 3B Pluronic F87

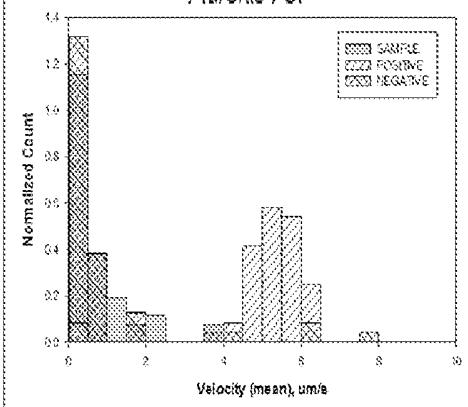
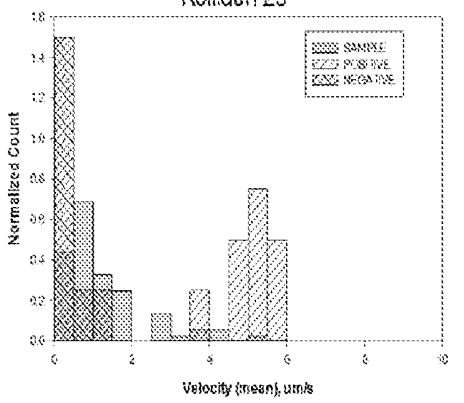


FIG. 3D Kollidon 25



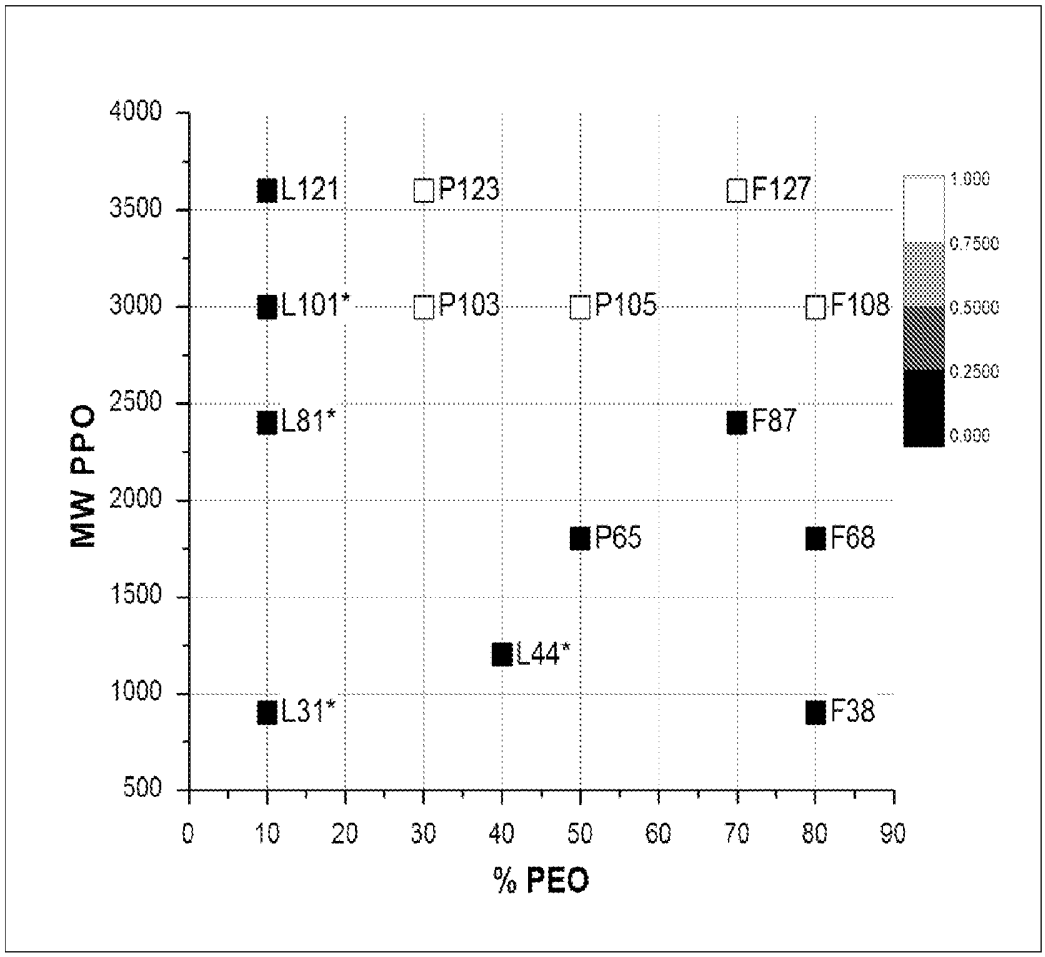

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3000
2500
2000
1500
1000
500
MW PPO
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10
20
30
40
50
60
70
80
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% PEO
L121
P123
F127
L101*
P103
P105
F108
L81*
F87
P65
F68
L44*
L31*
F38
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0.5000
0.2500
0.000

FIG. 4

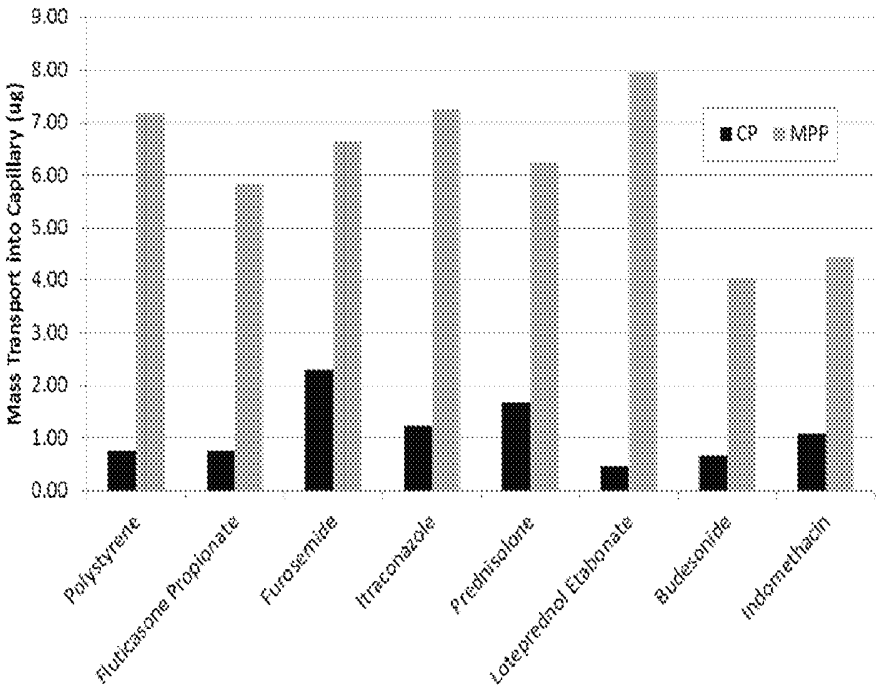

Mass Transport into Capillary (ug)
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7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
CP
MPP
Polystyrene
Fluticasone Propionate
Furosemide
Itraconazole
Prednisolone
Loteprednol Etabonate
Budesonide
Indomethacin

FIG. 5

FIG. 6A

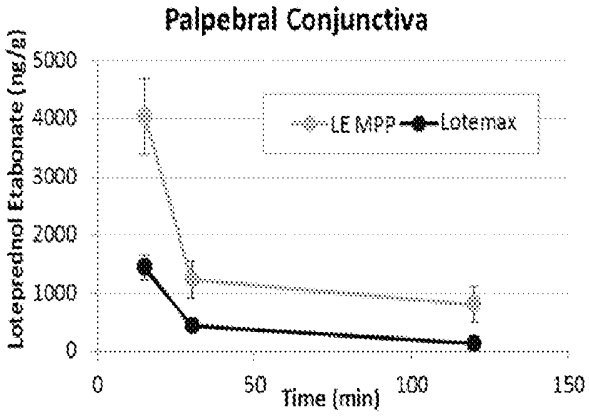


FIG. 6B

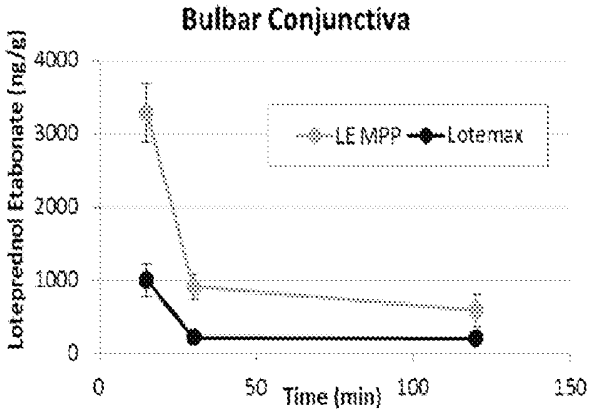
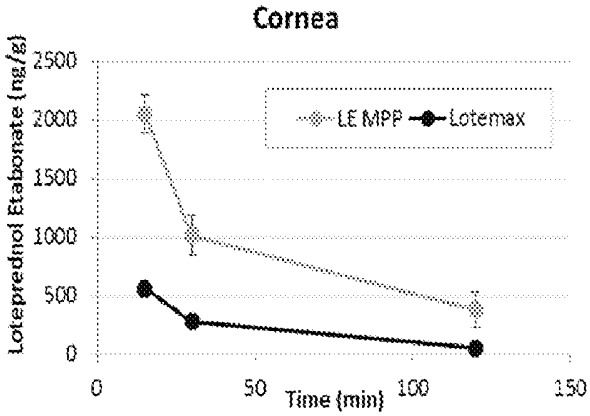


FIG. 6C



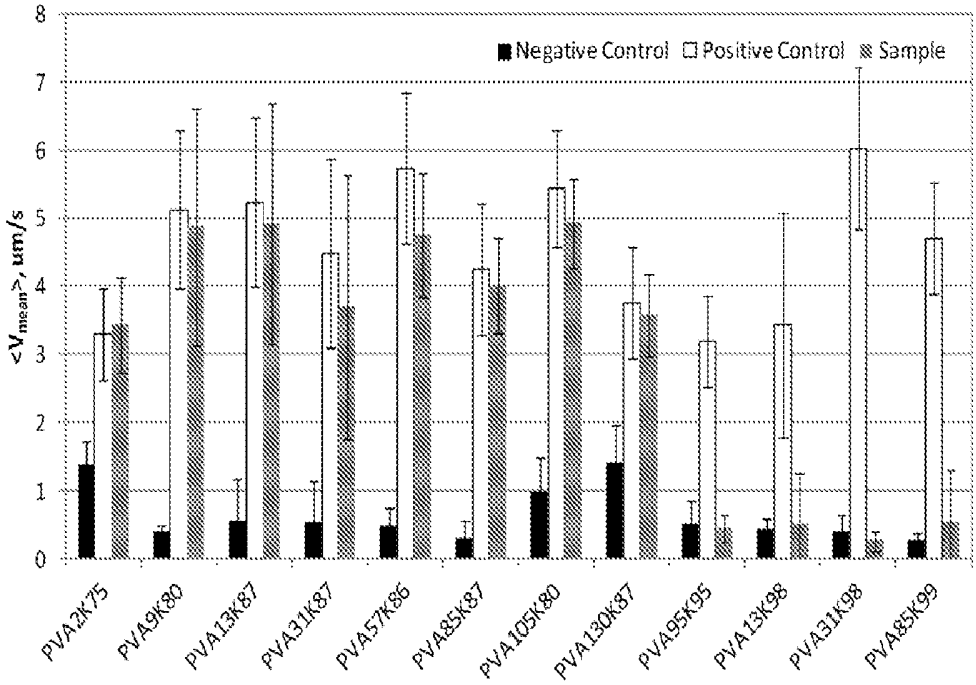

Negative Control
Positive Control
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3
4
5
6
7
8
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PVA9K80
PVA13K87
PVA31K87
PVA57K86
PVA85K87
PVA105K80
PVA130K87
PVA95K95
PVA13K98
PVA31K98
PVA85K99

FIG. 7A

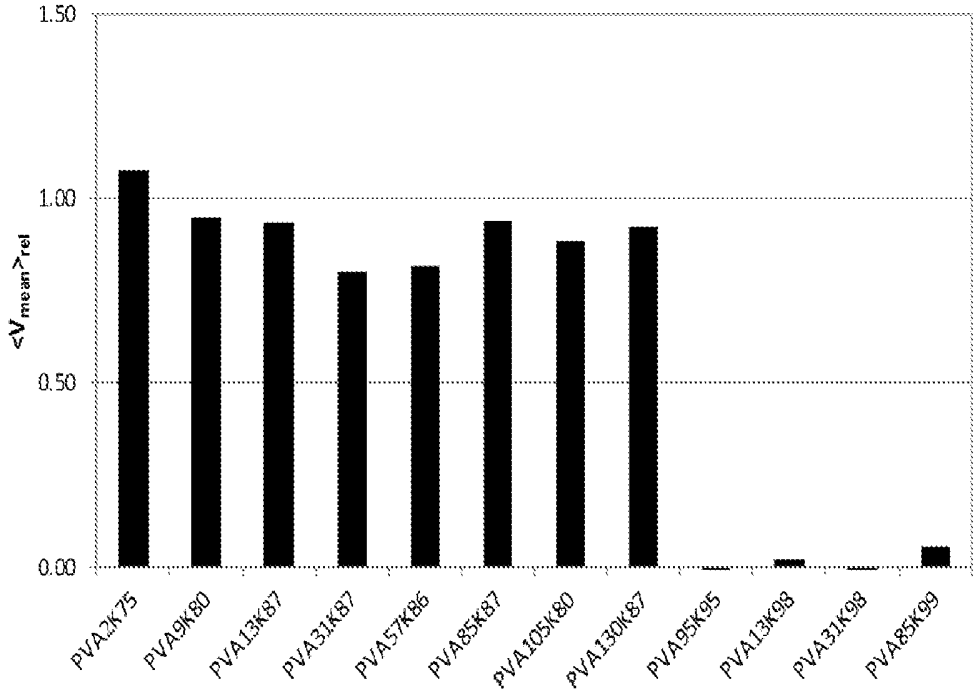

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PVA31K87
PVA57K86
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PVA95K95
PVA13K98
PVA31K98
PVA85K99

FIG. 7B

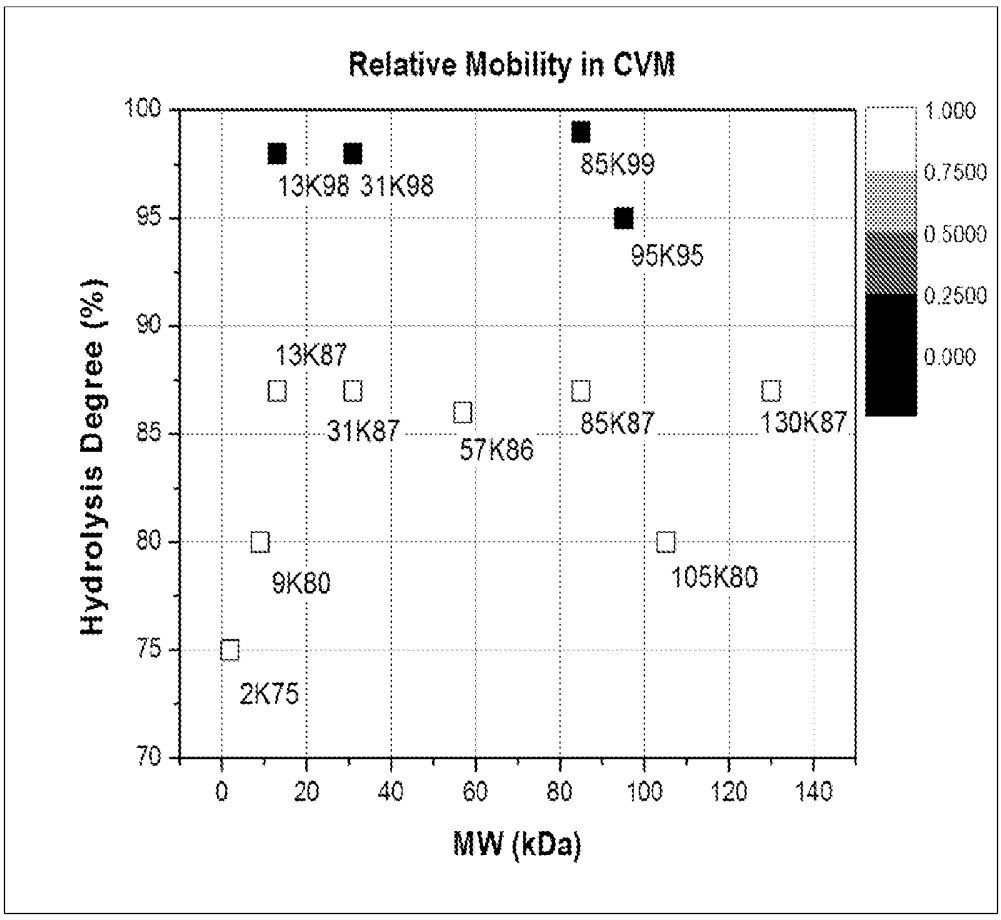

Relative Mobility in CVM
Hydrolysis Degree (%)
MW (kDa)
100
95
90
85
80
75
70
0
20
40
60
80
100
120
140
13K98
31K98
85K99
95K95
13K87
31K87
57K86
85K87
130K87
9K80
105K80
2K75
1.000
0.7500
0.5000
0.2500
0.000

FIG. 8

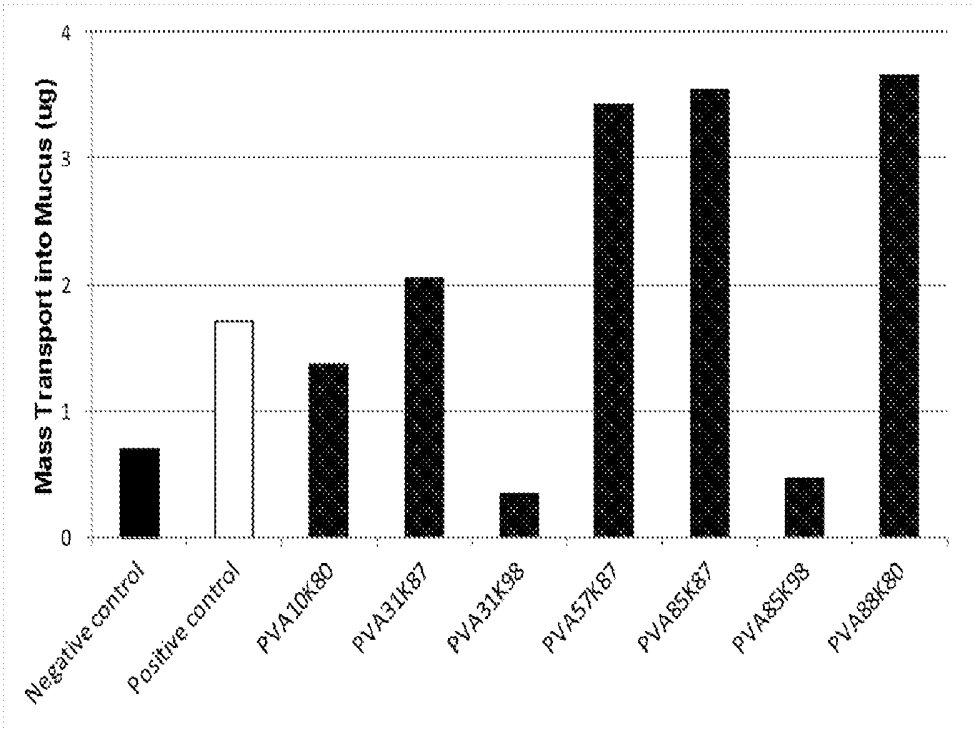

Mass Transport into Mucus (ug)
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1
2
3
4
Negative control
Positive control
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PVA57K87
PVA85K87
PVA85K98
PVA88K80

FIG. 9A

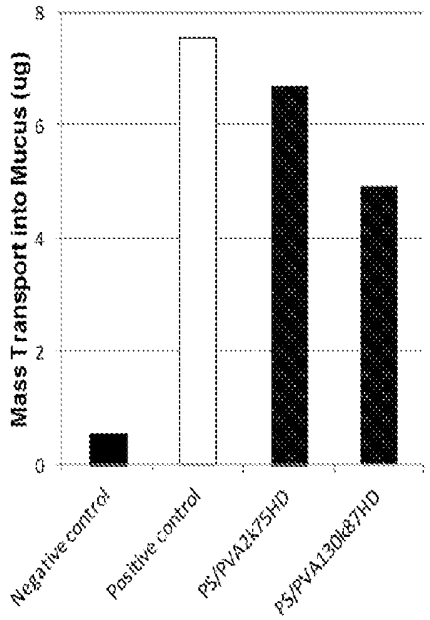

Mass Transport into Mucus (ug)
0
2
4
6
8
Negative control
Positive control
PS/PVA1K75HD
PS/PVA130k87HD

FIG. 9B

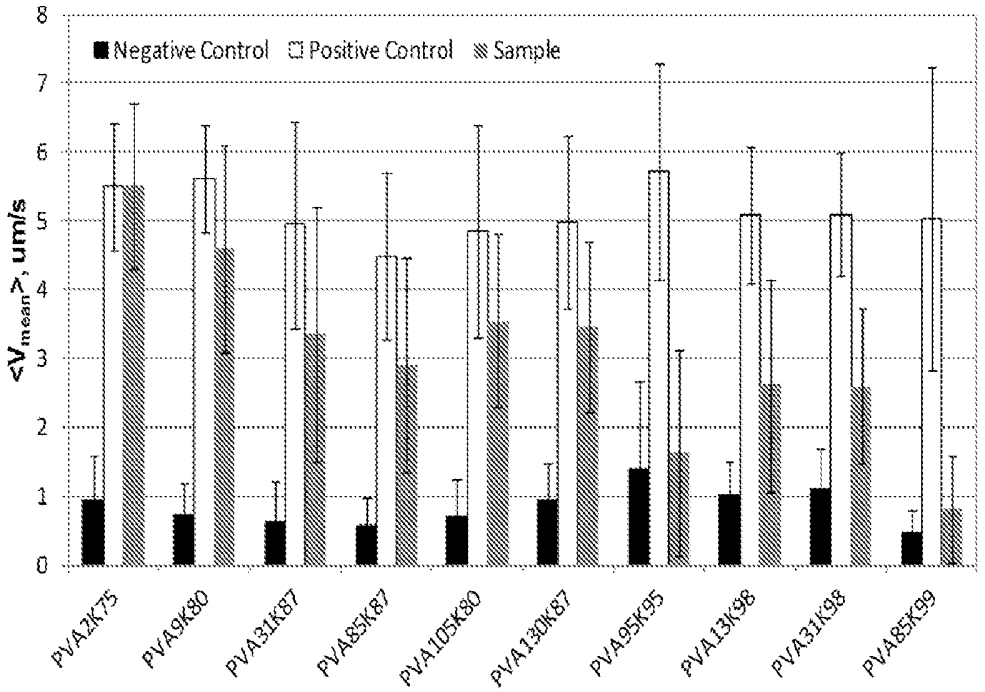


FIG. 10A

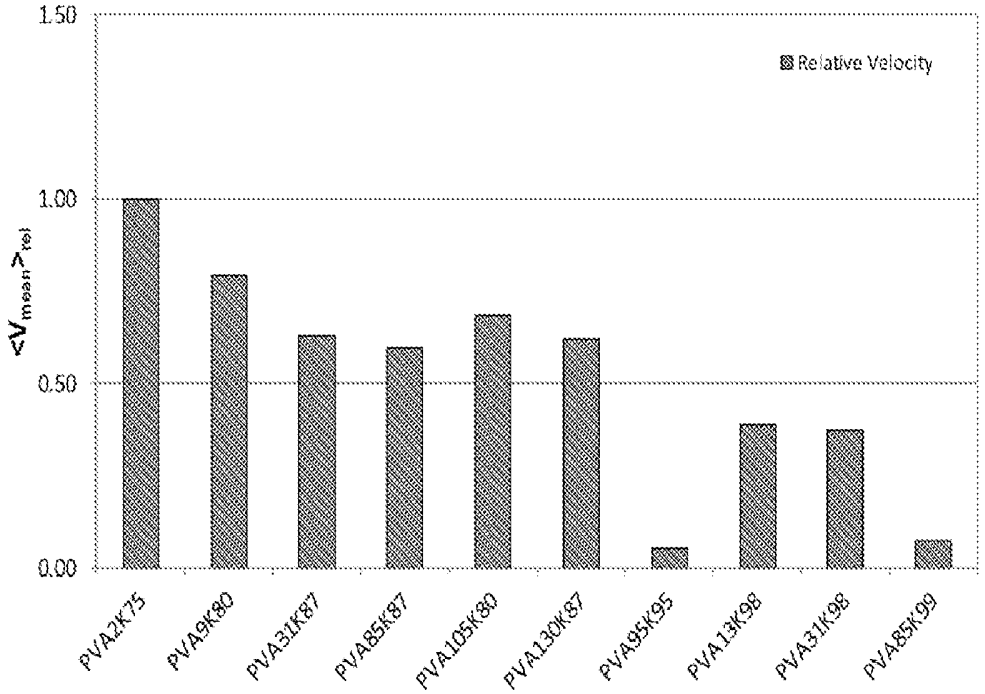


FIG. 10B

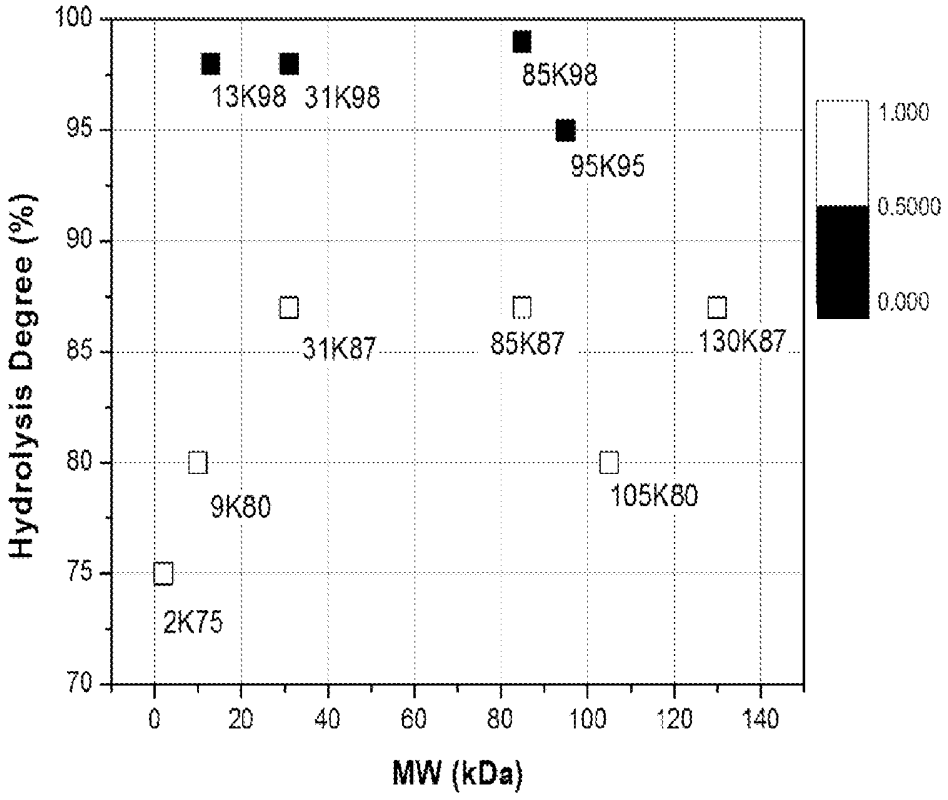

Hydrolysis Degree (%)
MW (kDa)
13K98
31K98
85K98
95K95
31K87
85K87
130K87
9K80
105K80
2K75
1.000
0.5000
0.000

FIG. 11

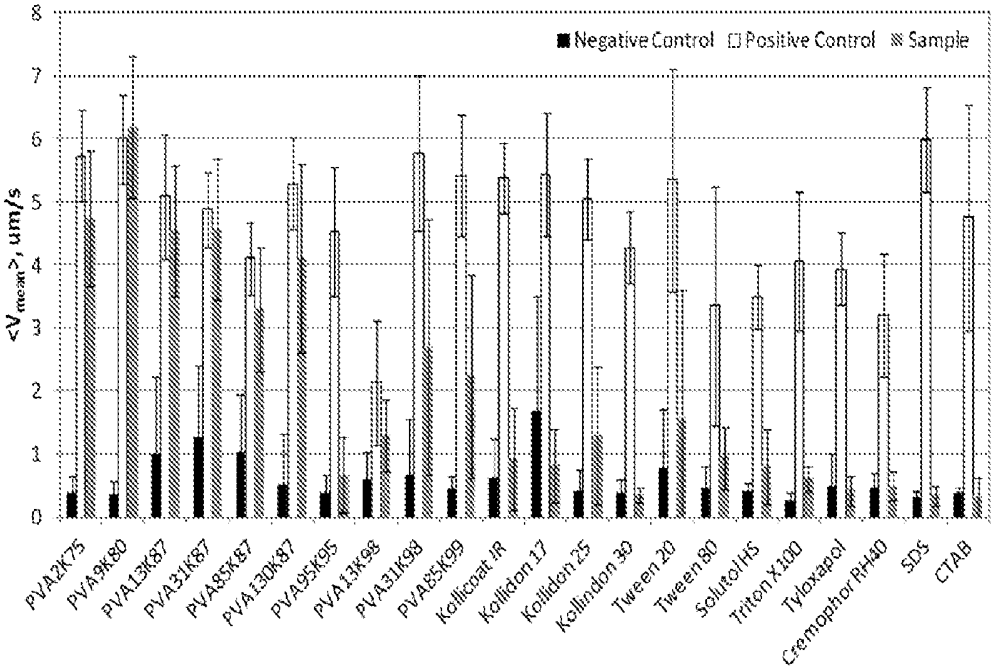


FIG. 12A

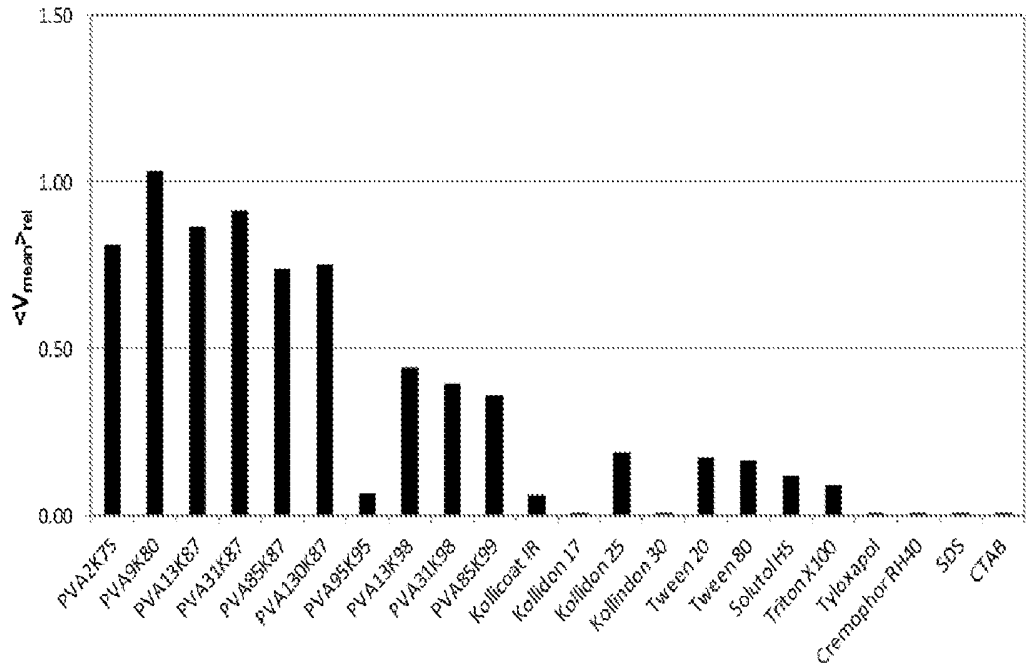


FIG. 12B

FIG. 13A PVA2K75

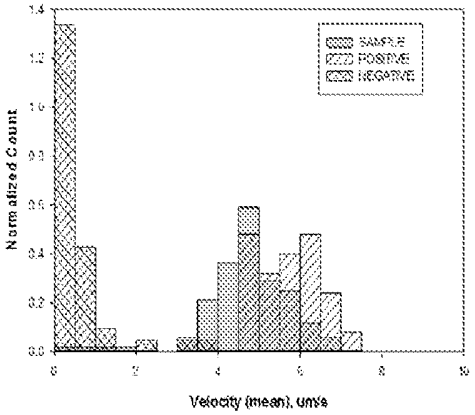


FIG. 13B PVA9K80

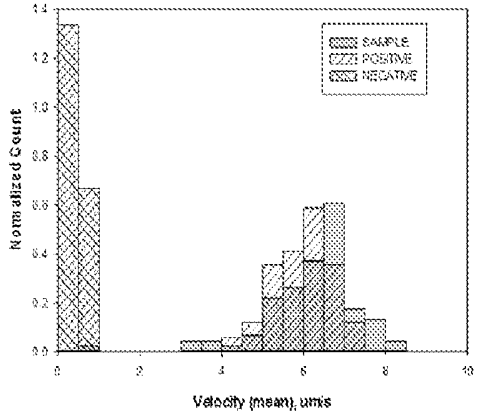


FIG. 13C PVA31K98

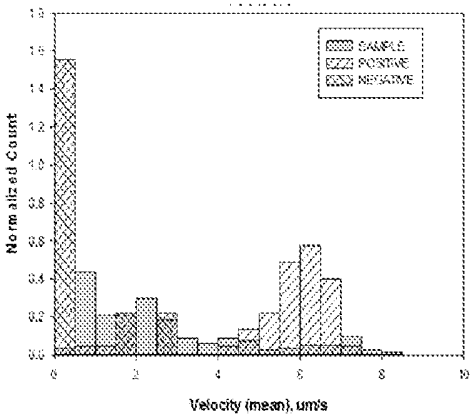


FIG. 13D PVA85K99

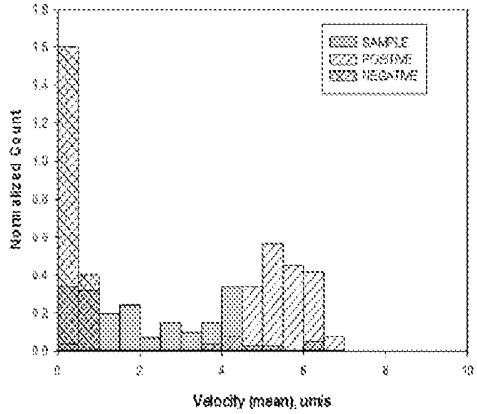


FIG. 13E Kollidon 25

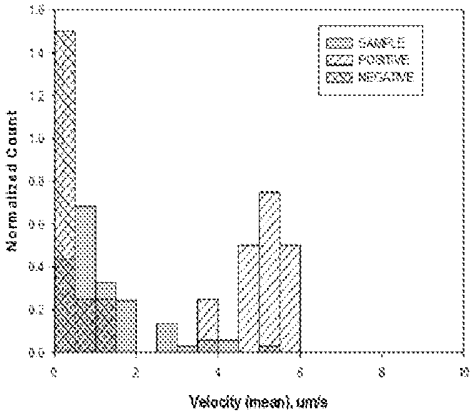
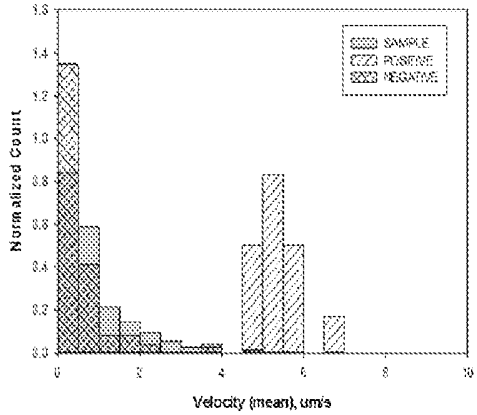


FIG. 13F Kollicoat IR



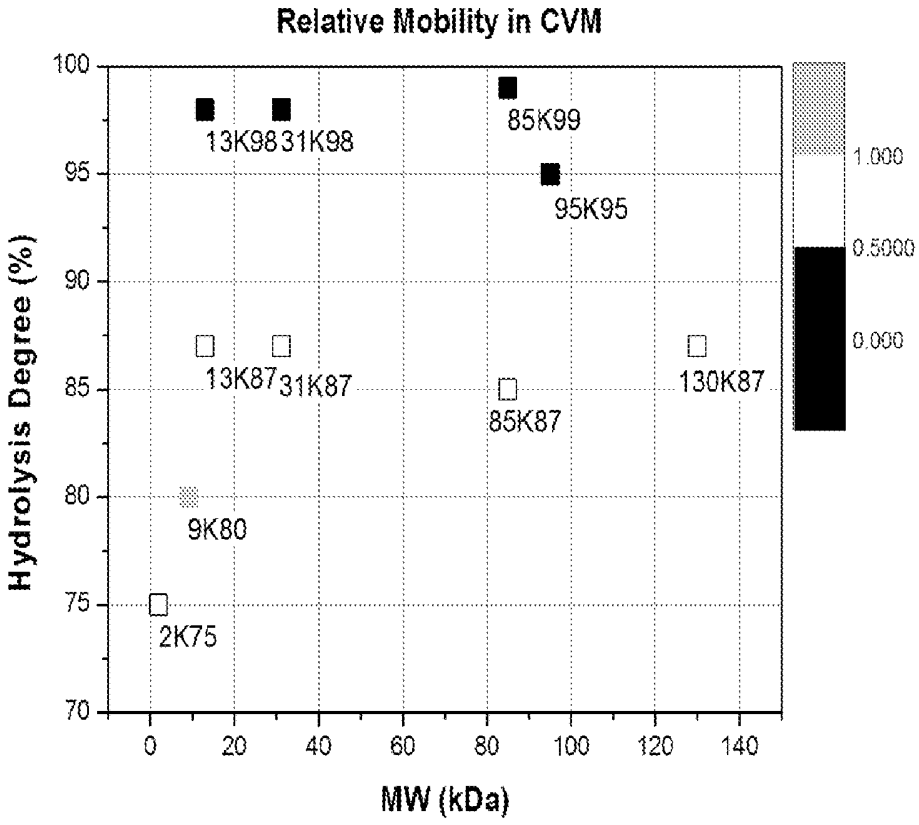

Relative Mobility in CVM
Hydrolysis Degree (%)
MW (kDa)
100
95
90
85
80
75
70
0
20
40
60
80
100
120
140
13K98
31K98
85K99
95K95
13K87
31K87
85K87
130K87
9K80
2K75
1.000
0.5000
0.000

FIG. 14

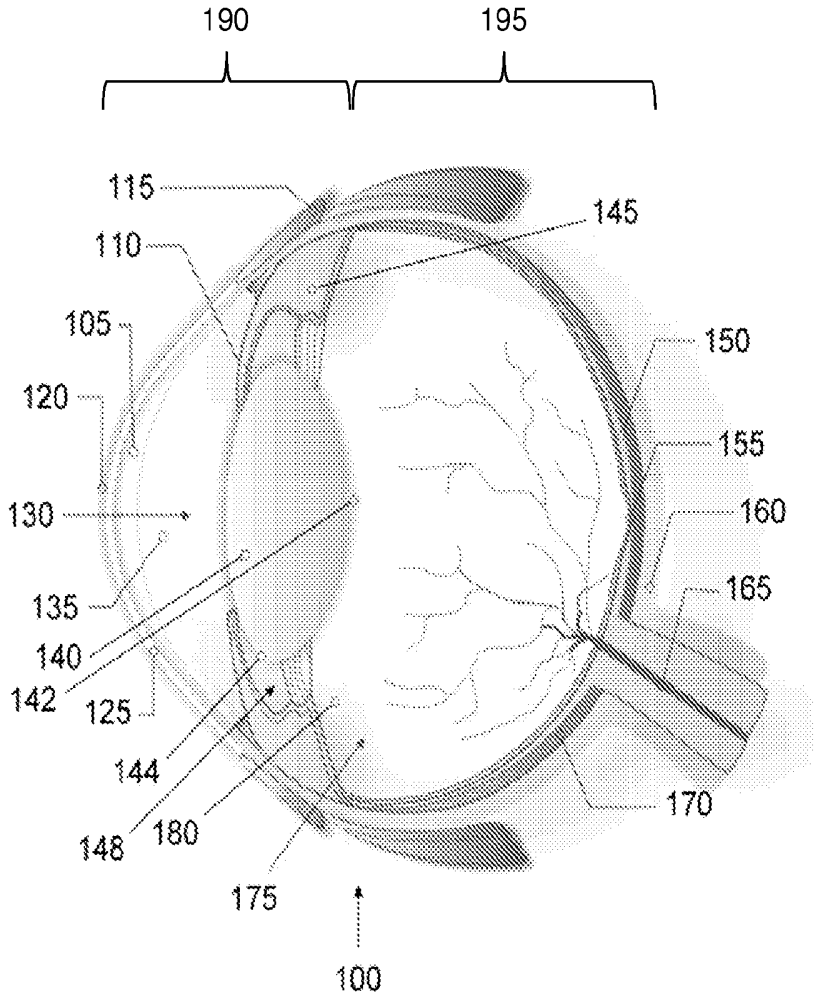

190
195
115
110
105
120
130
135
140
142
125
144
148
180
175
100
145
150
155
160
165
170

FIG. 15A

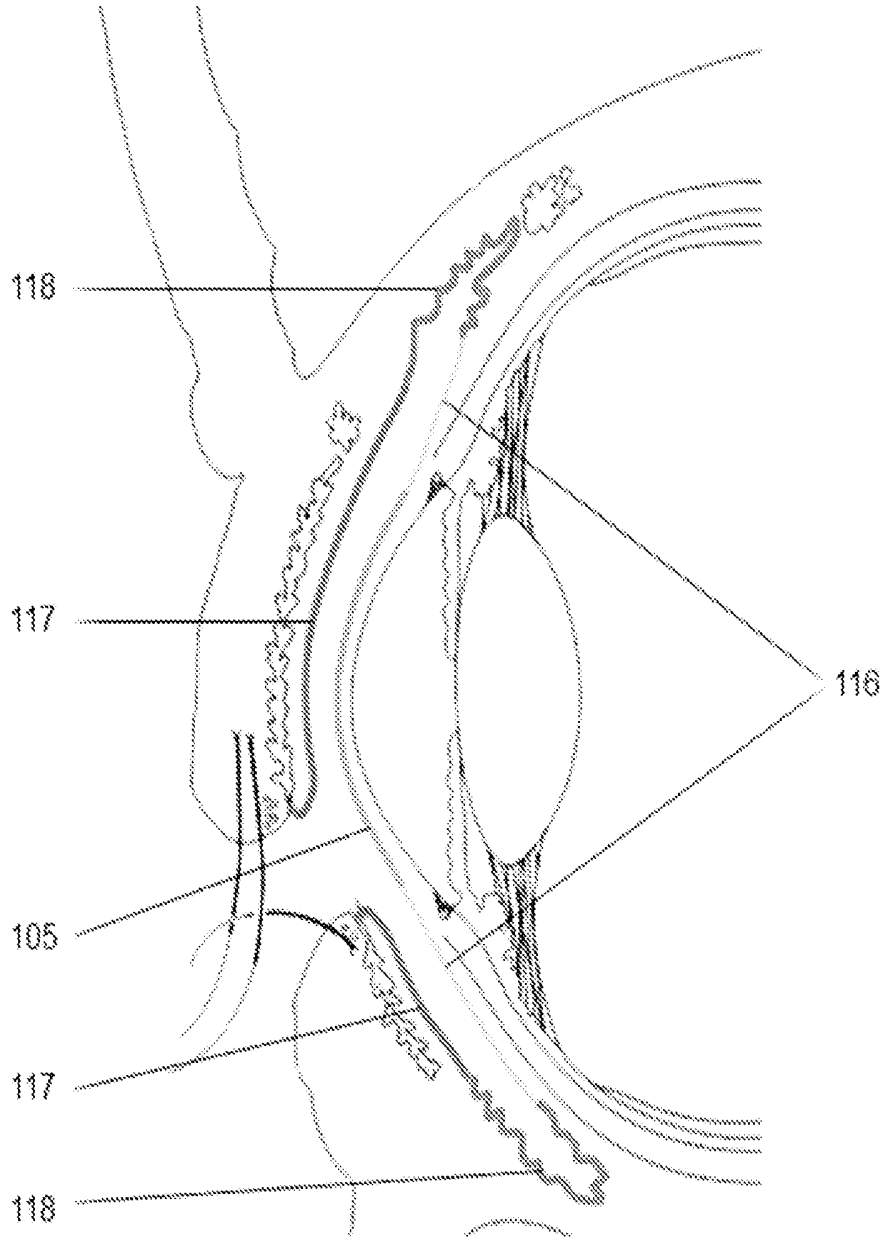


FIG. 15B

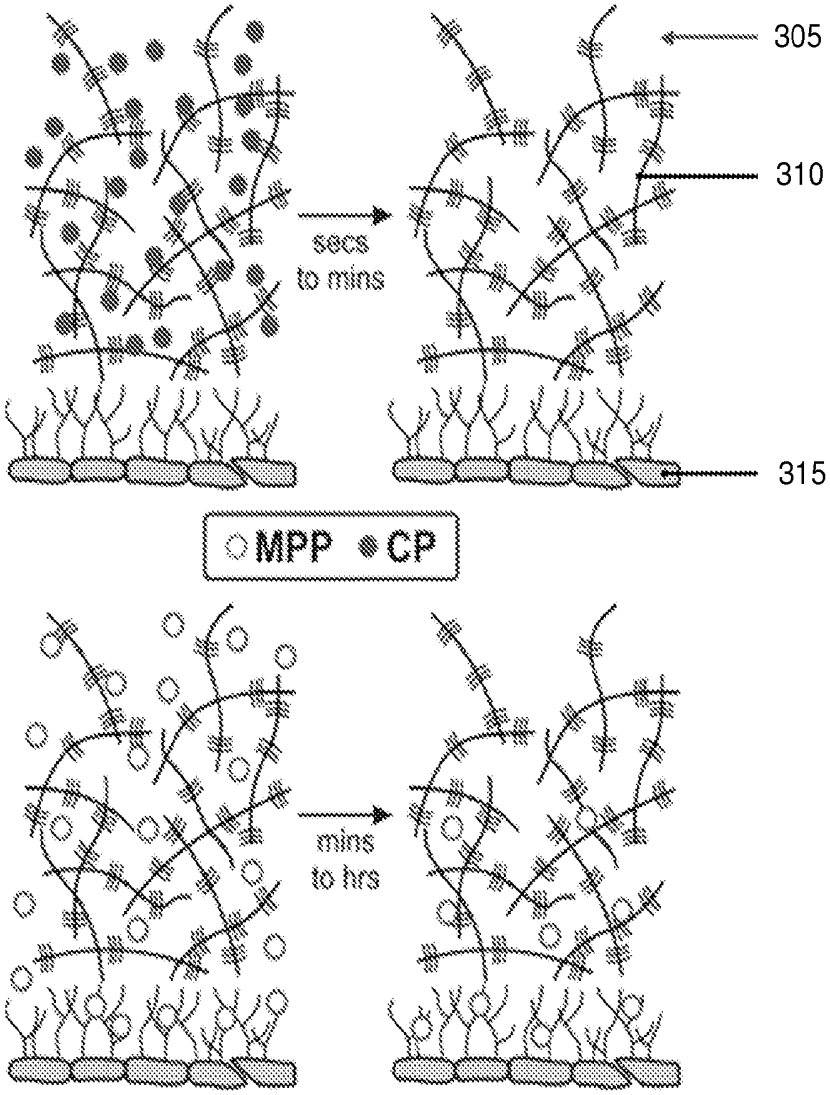


FIG. 15C

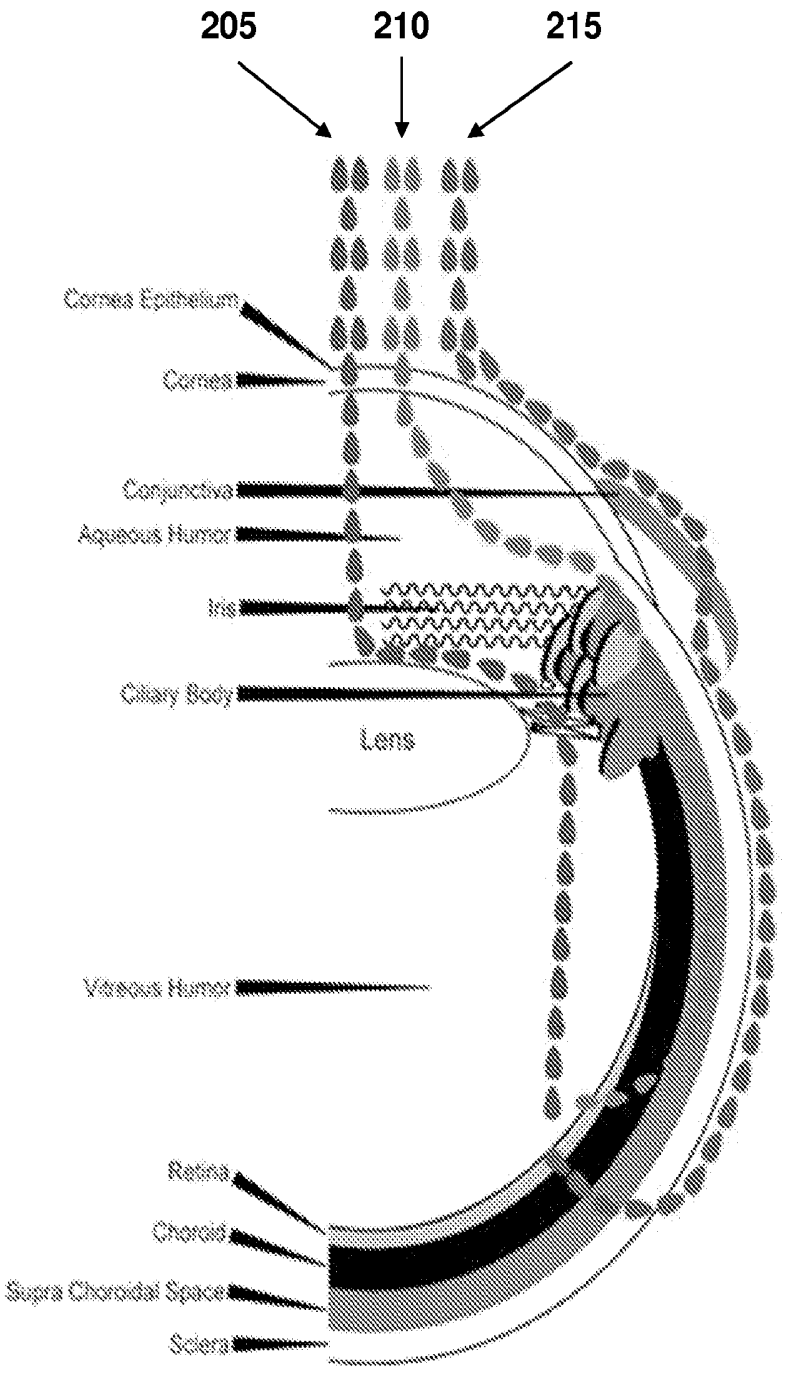

205
210
215
Cornea Epithelium
Cornea
Conjunctiva
Aqueous Humor
Iris
Ciliary Body
Lens
Vitreous Humor
Retina
Choroid
Supra Choroidal Space
Sclera

FIG. 16

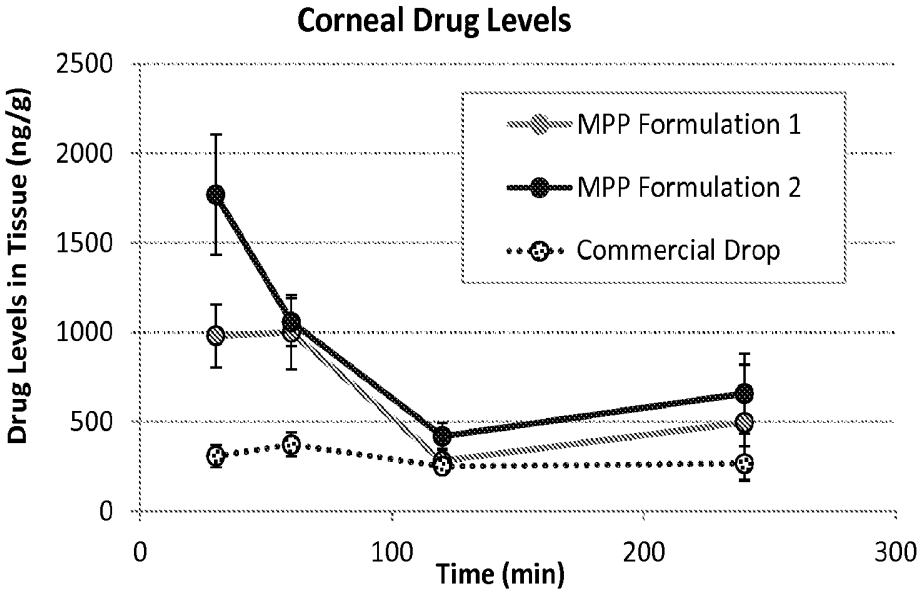


FIG. 17A

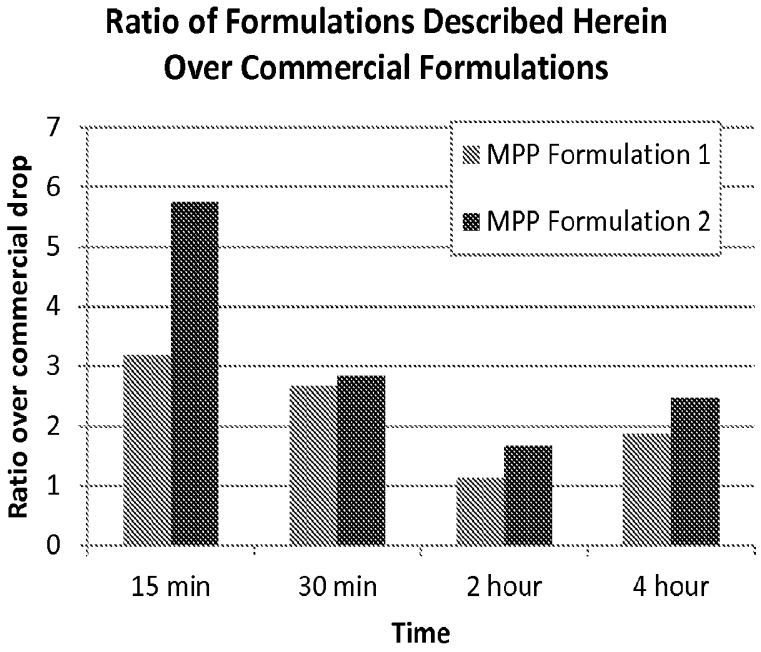


FIG. 17B

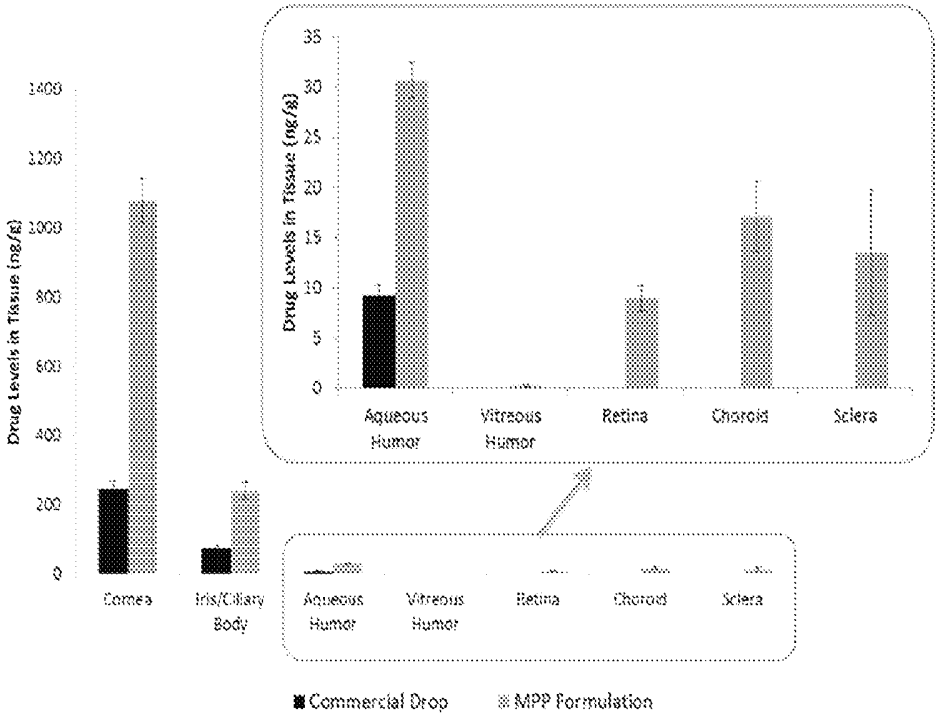

Drug Levels in Tissue (ng/g)
1400
1200
1000
800
600
400
200
0
Cornea
Iris/Ciliary Body
Drug Levels in Tissue (ng/g)
35
30
25
20
15
10
5
0
Aqueous Humor
Vitreous Humor
Retina
Choroid
Sclera
Commercial Drop
MPP Formulation

FIG. 18

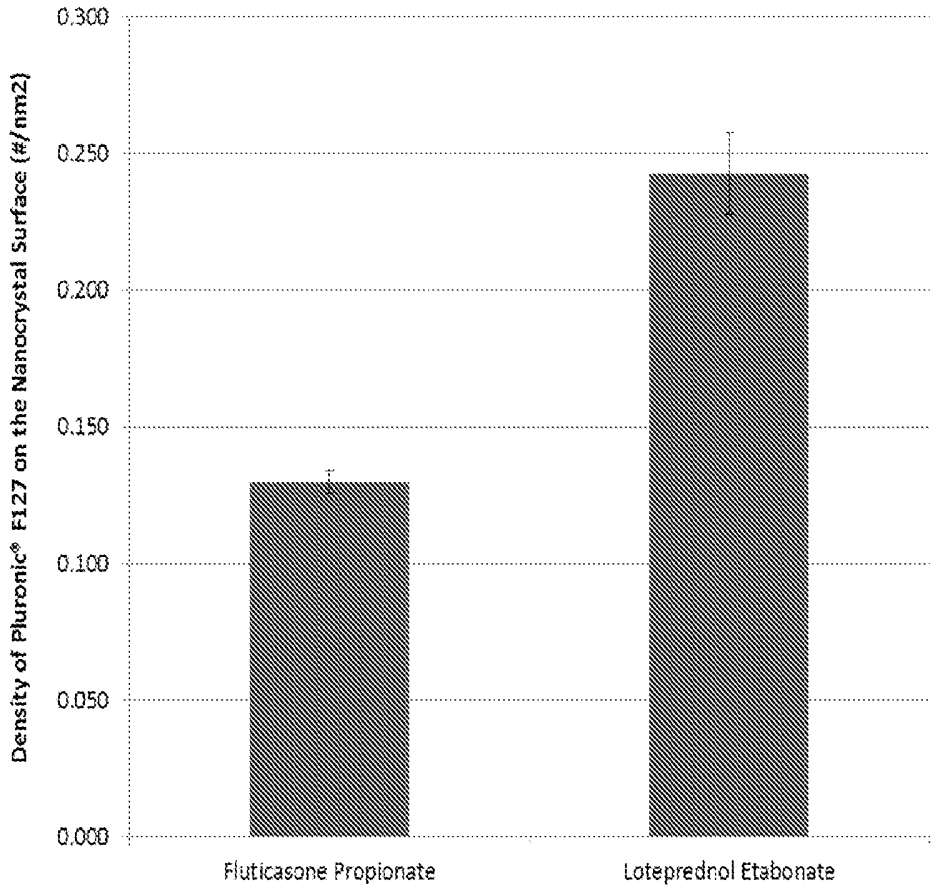

0.300
0.250
0.200
0.150
0.100
0.050
0.000
Density of Pluronic® F127 on the Nanocrystal Surface (#/nm2)
Fluticasone Propionate
Lotepredrol Etabonate

FIG. 19

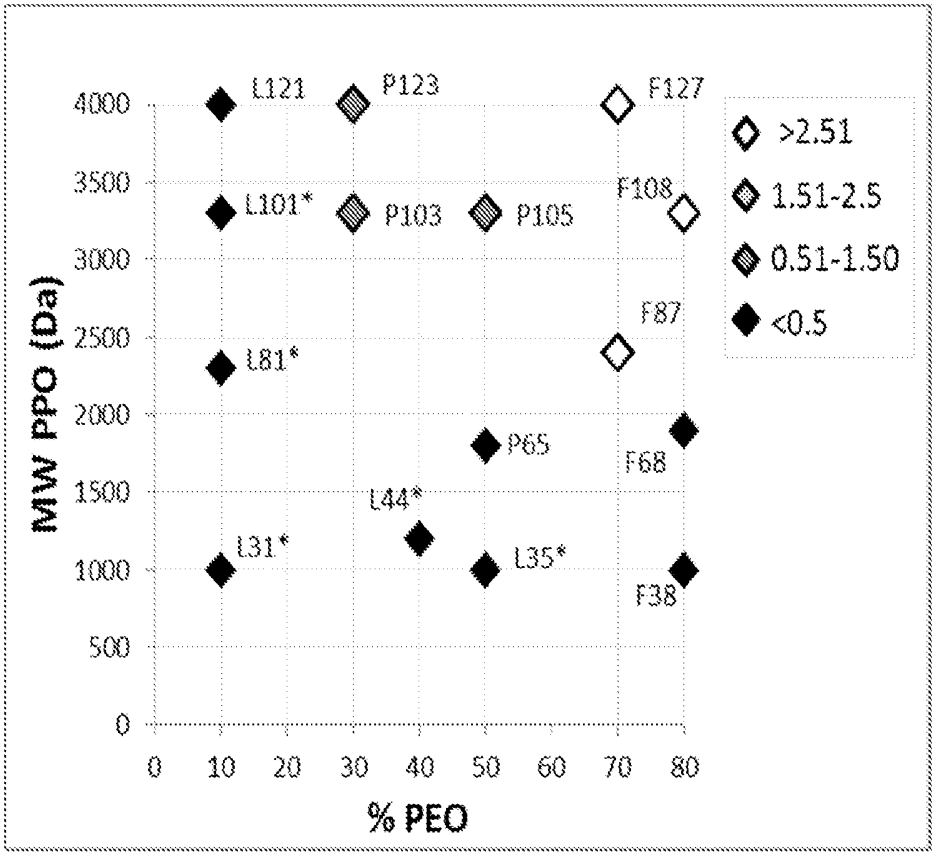

MW PPO (Da)
% PEO
4000
3500
3000
2500
2000
1500
1000
500
0
0
10
20
30
40
50
60
70
80
L121
P123
F127
L101*
P103
P105
F108
F87
L81*
P65
F68
L44*
L31*
L35*
F38
>2.51
1.51-2.5
0.51-1.50
<0.5

FIG. 20

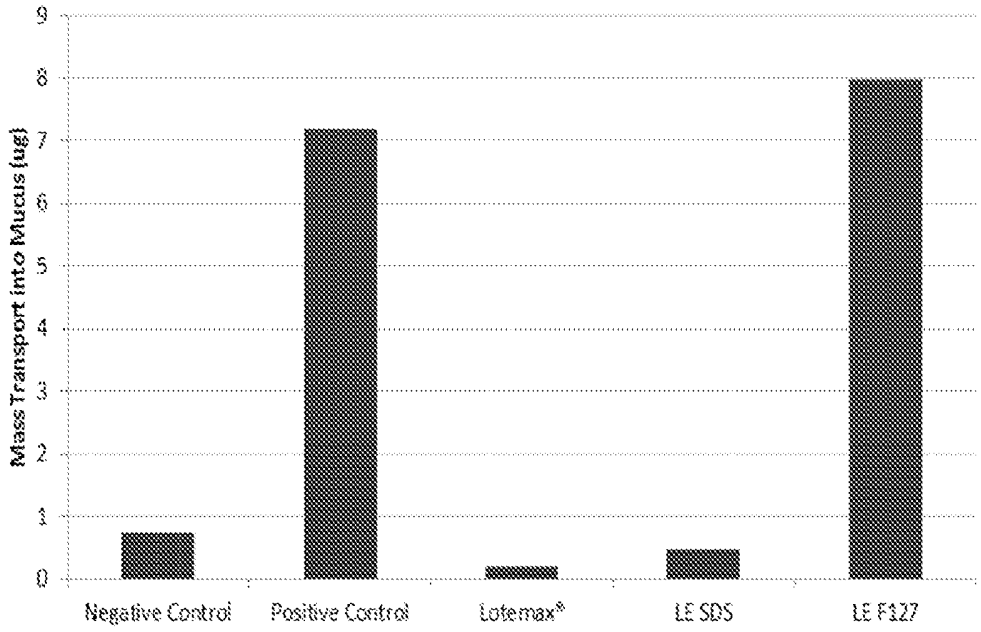
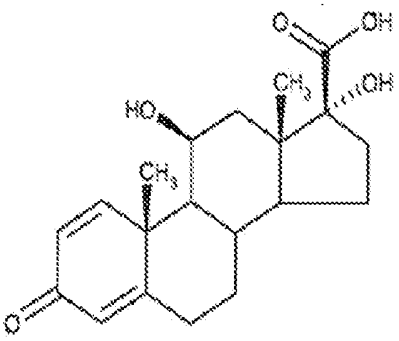
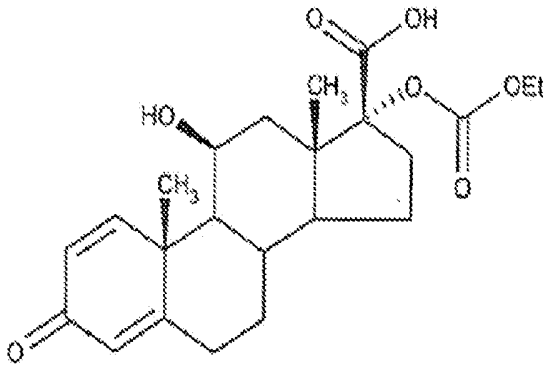

Mass Transport into Mucus (ug)
0
1
2
3
4
5
6
7
8
9
Negative Control
Positive Control
Lotemax®
LE SDS
LE F127

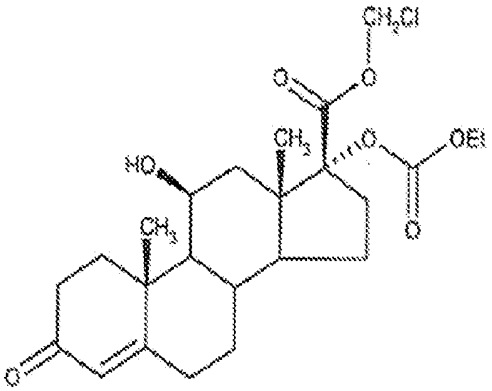
FIG. 21



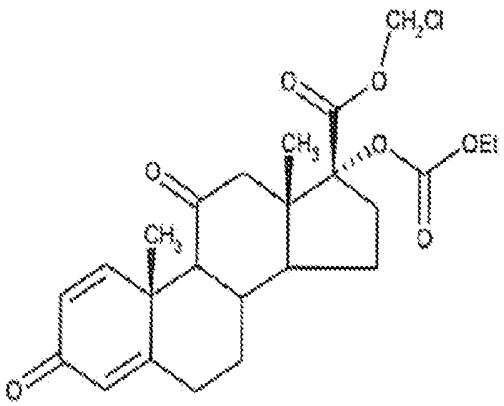
PJ90



PJ91



tetradeca



11-keto

FIG. 22

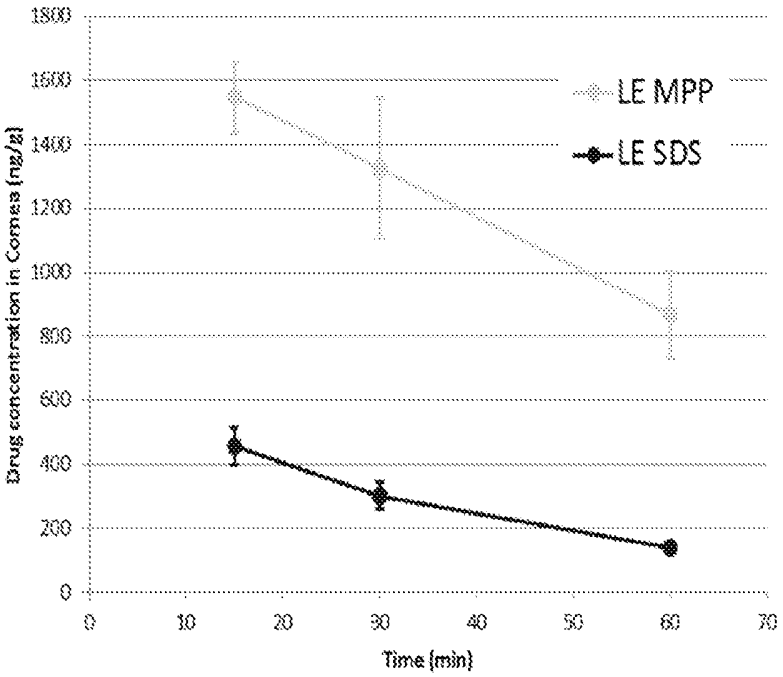


FIG. 23A

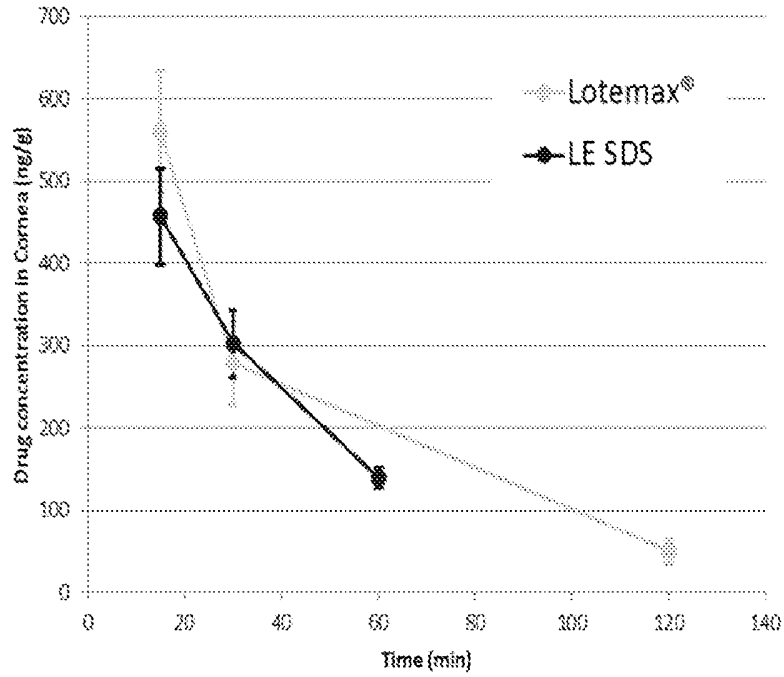


FIG. 23B

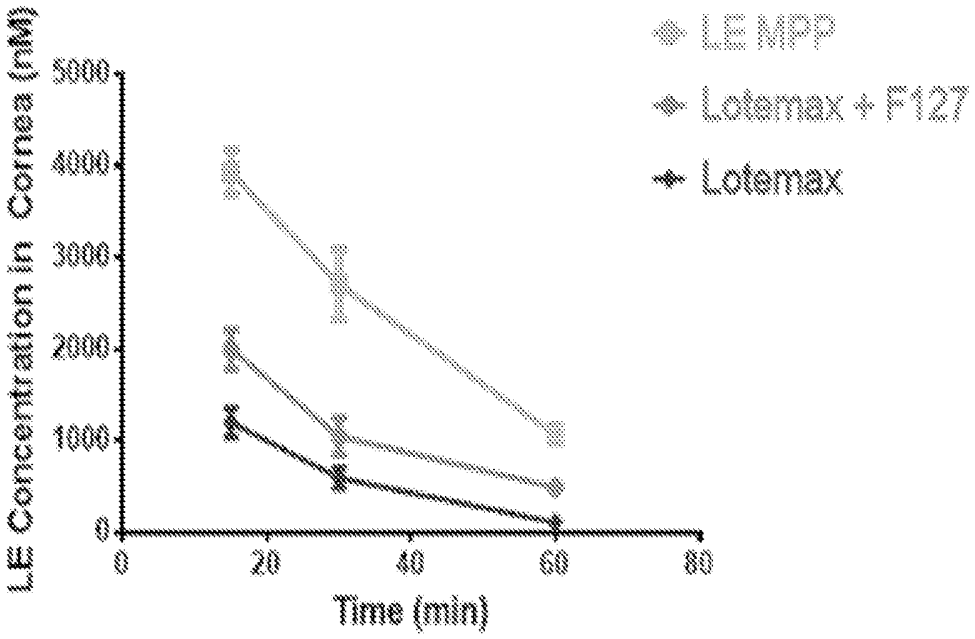

LE MPP
Lotemax + F127
Lotemax
LE Concentration in Cornea (nM)
5000
4000
3000
2000
1000
0
0
20
40
60
80
Time (min)

FIG. 24

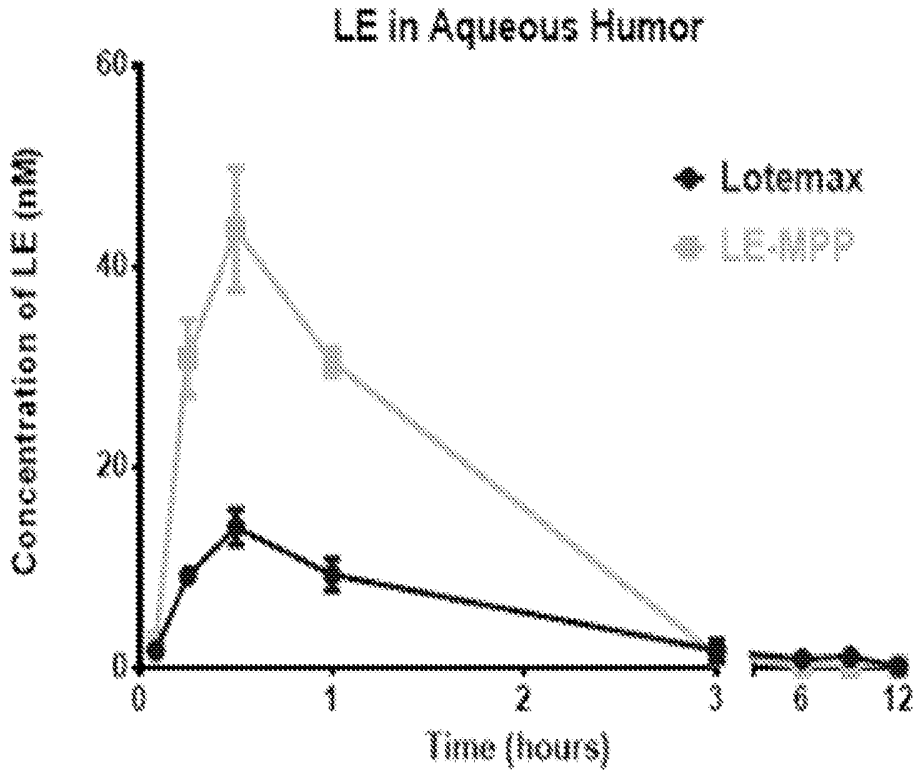

LE in Aqueous Humor
Concentration of LE (nM)
60
40
20
0
0
1
2
3
6
12
Time (hours)
Lotemax
LE-MPP

FIG. 25

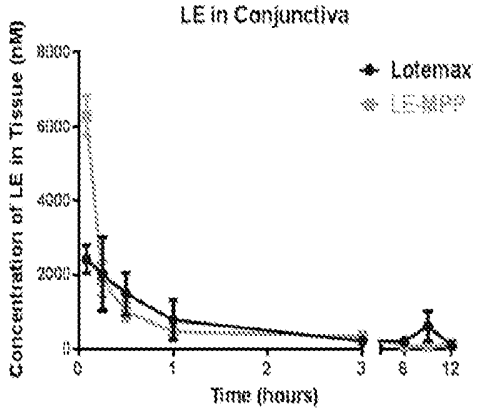


FIG. 26A

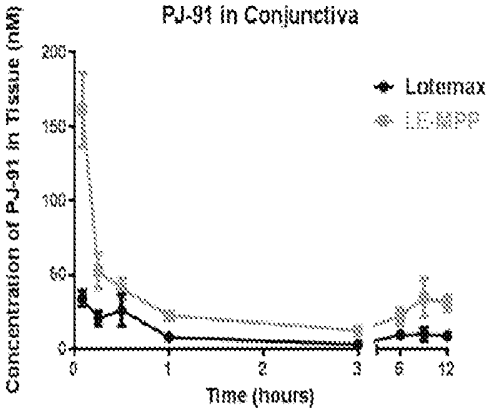


FIG. 26B

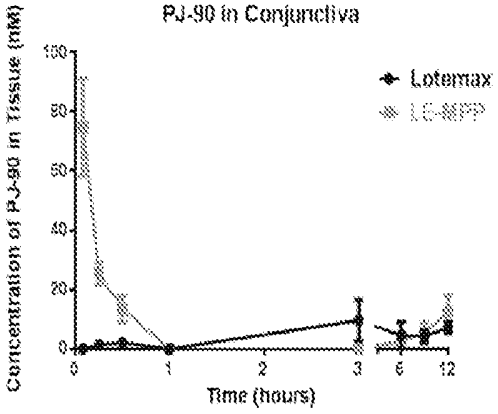


FIG. 26C

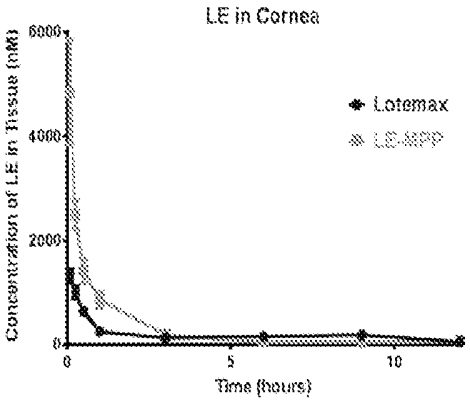


FIG. 26D

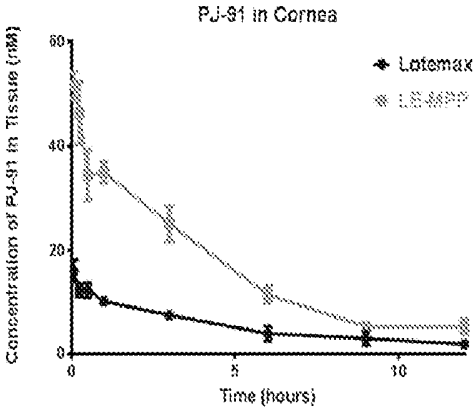


FIG. 26E

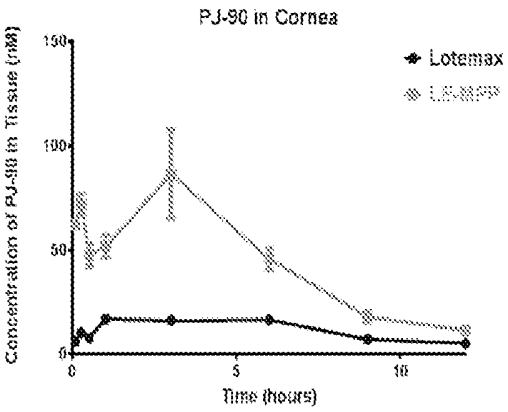


FIG. 26F

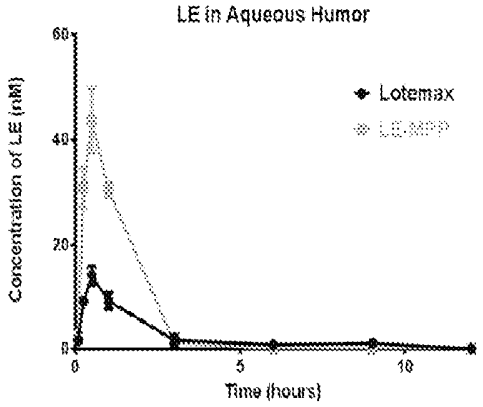


FIG. 26G

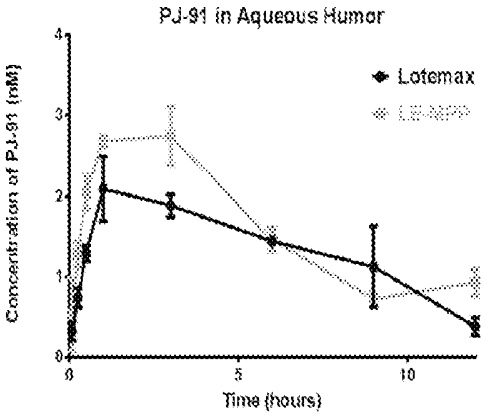


FIG. 26H

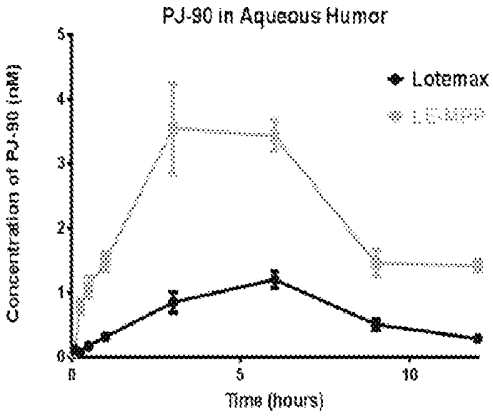


FIG. 26I

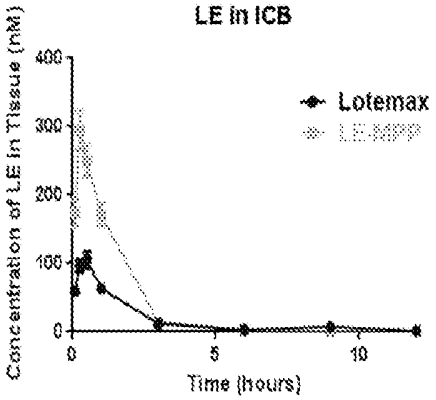


FIG. 26J

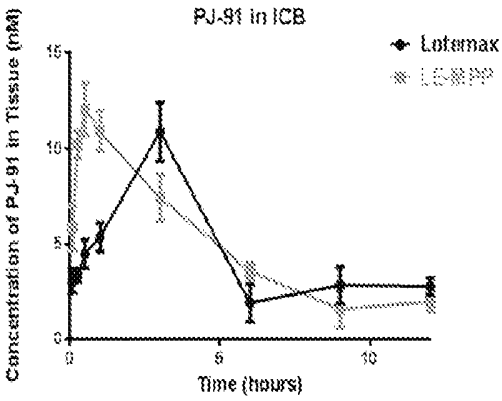


FIG. 26K

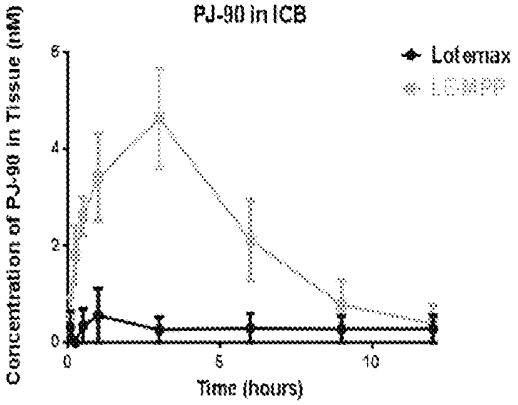


FIG. 26L

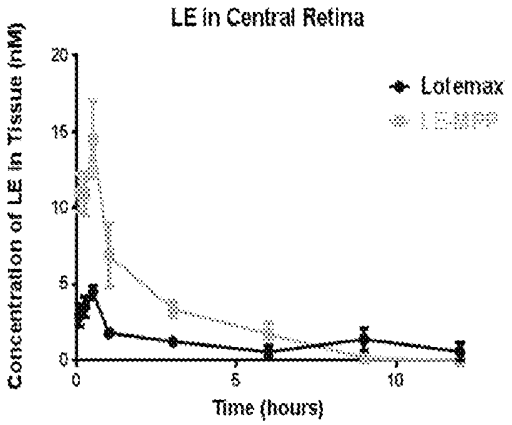


FIG. 26M

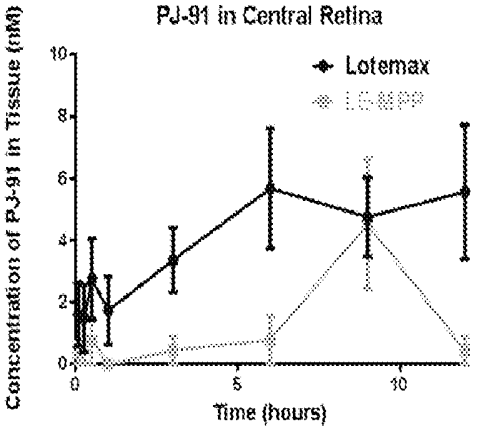


FIG. 26N

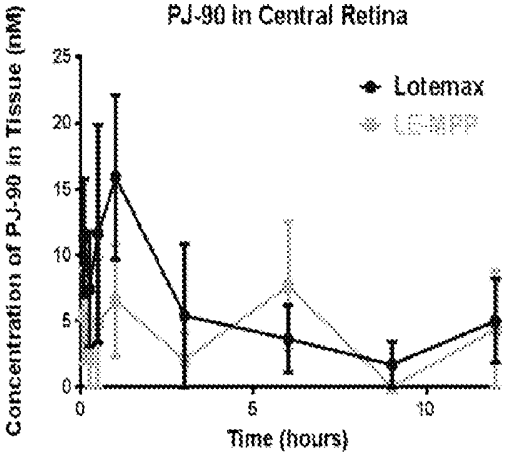


FIG. 26O

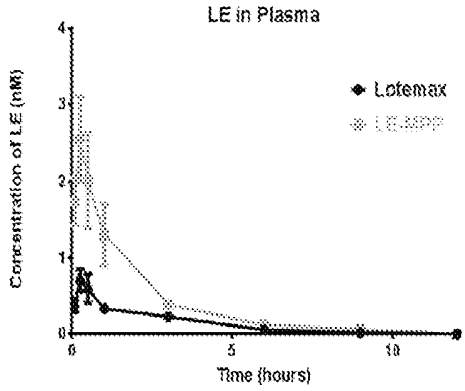


FIG. 26P

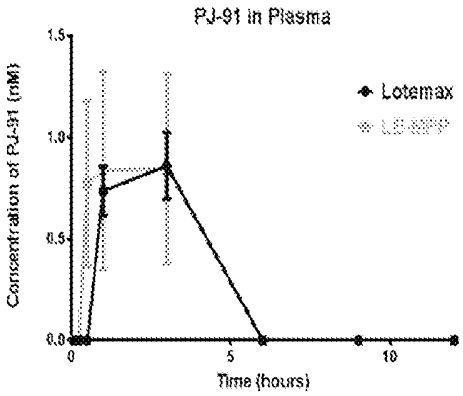


FIG. 26Q

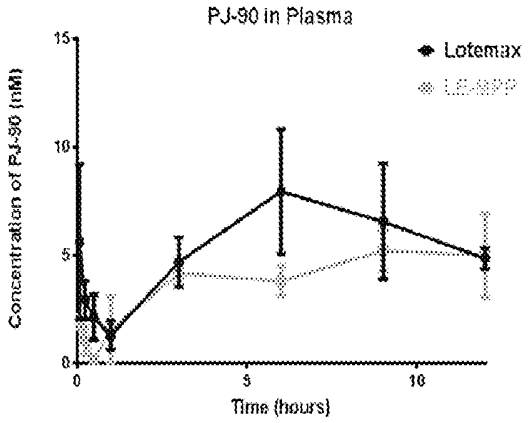


FIG. 26R

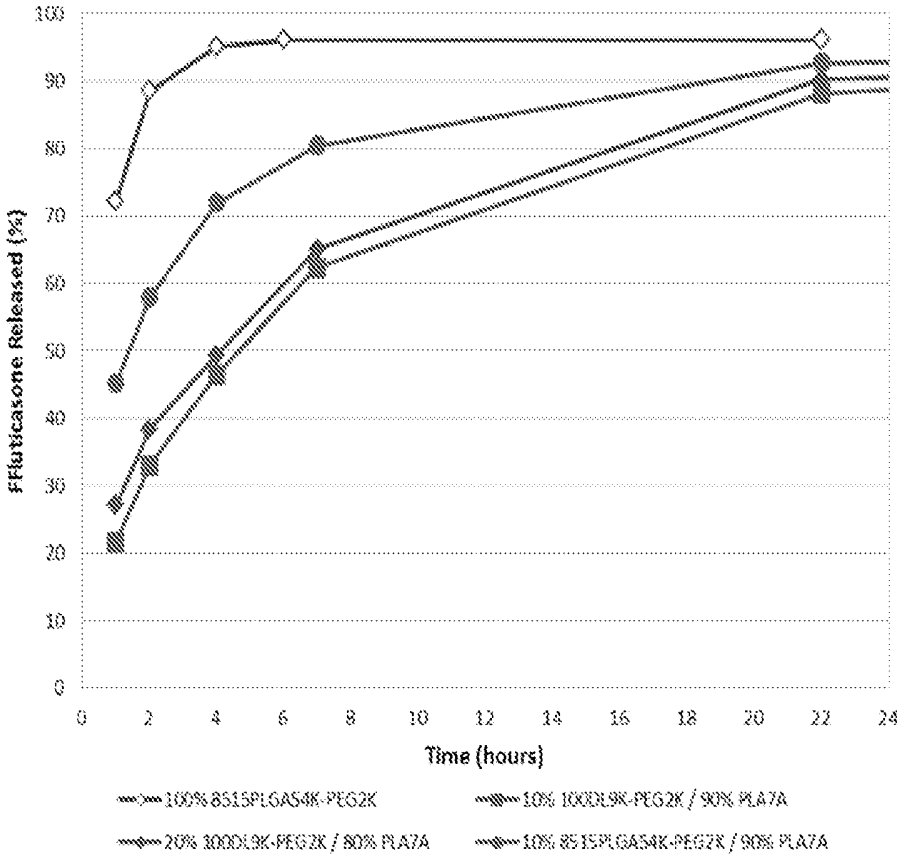

100
90
80
70
60
50
40
30
20
10
0
% Fluticasone Released (%)
0
2
4
6
8
10
12
14
16
18
20
22
24
Time (hours)
100% 8515PLGA54K-PEG2K
10% 1000L9K-PEG2K / 90% PLA7A
20% 1000L9K-PEG2K / 80% PLA7A
10% 8515PLGA54K-PEG2K / 90% PLA7A

FIG. 27

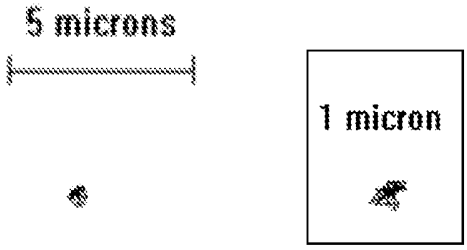


FIG. 28A

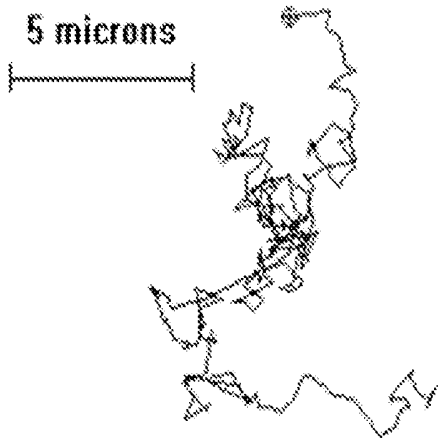


FIG. 28B

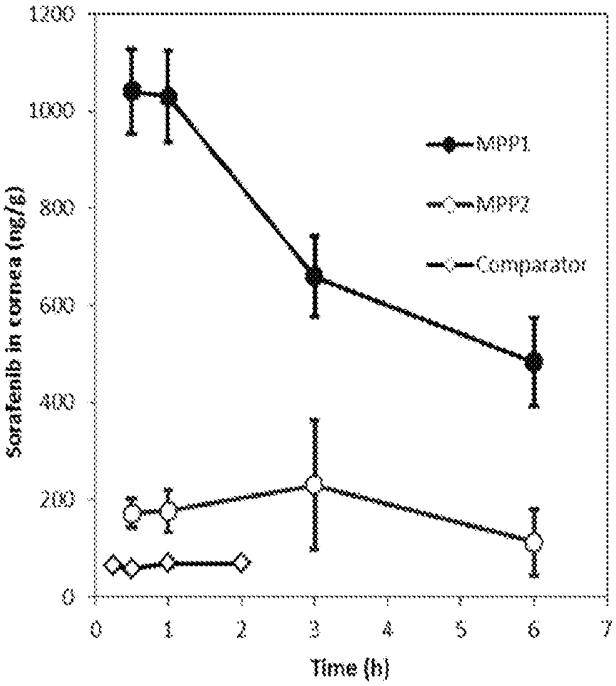


FIG. 29A

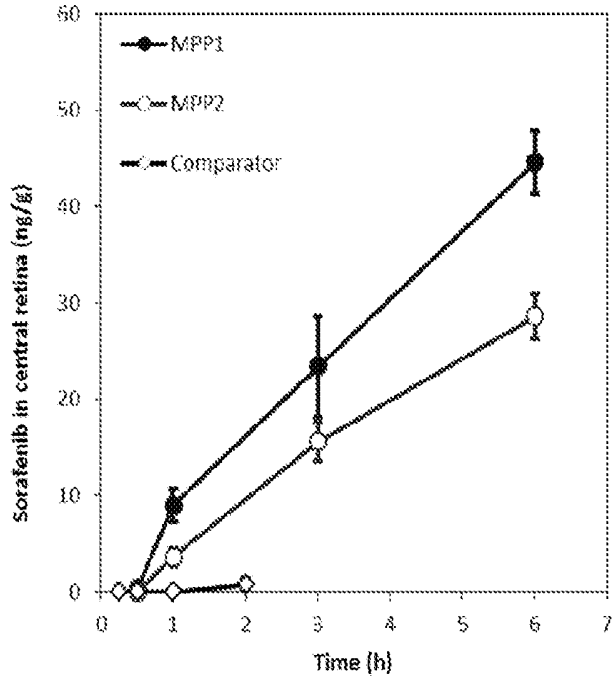


FIG. 29B

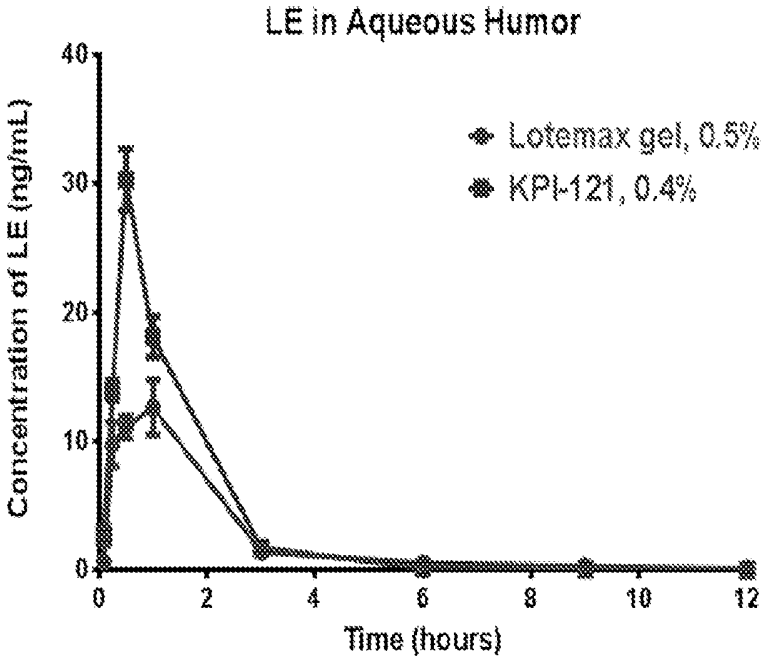

LE in Aqueous Humor
Concentration of LE (ng/mL)
40
30
20
10
0
0
2
4
6
8
10
12
Time (hours)
Lotemax gel, 0.5%
KPI-121, 0.4%

FIG. 30

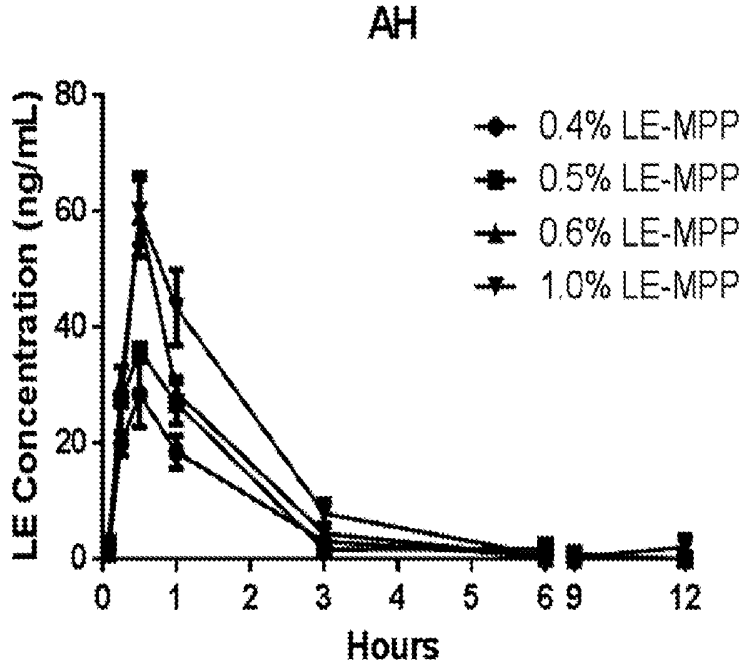


FIG. 31A

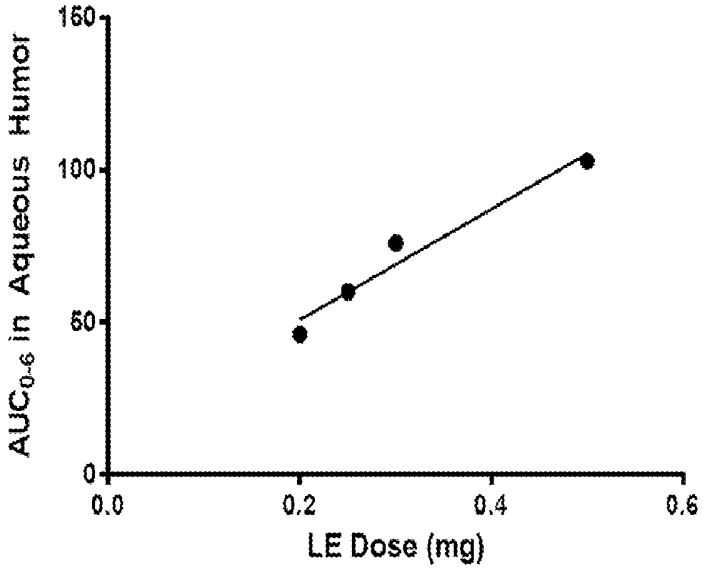


FIG. 31B

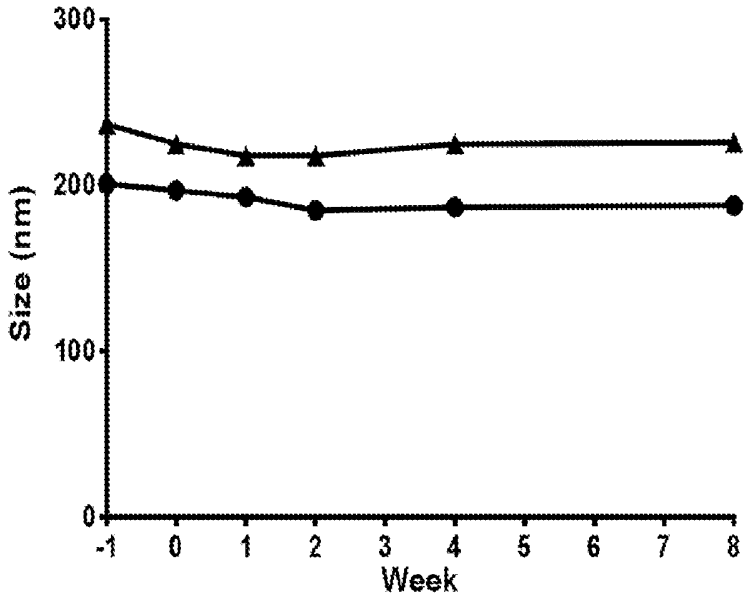


FIG. 32

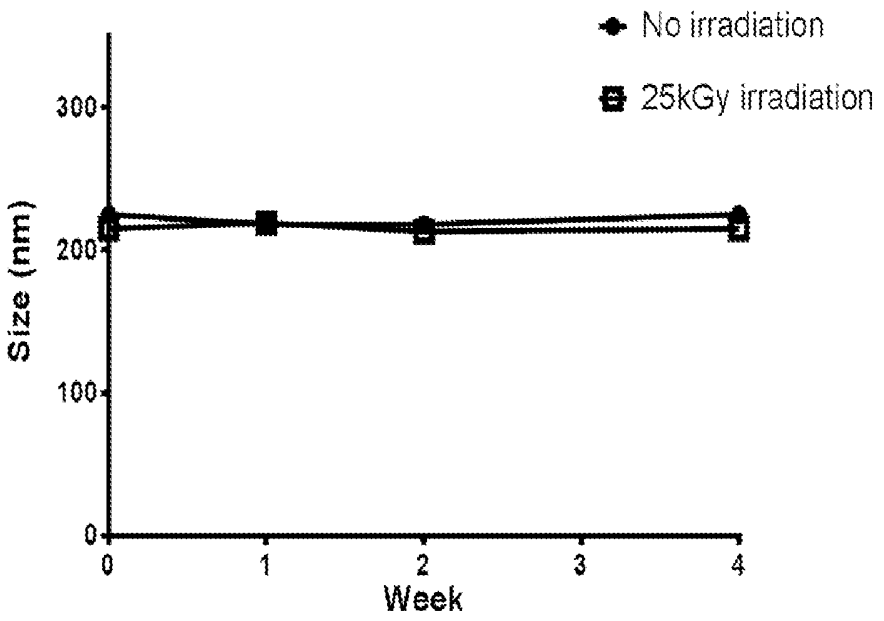


FIG. 33A

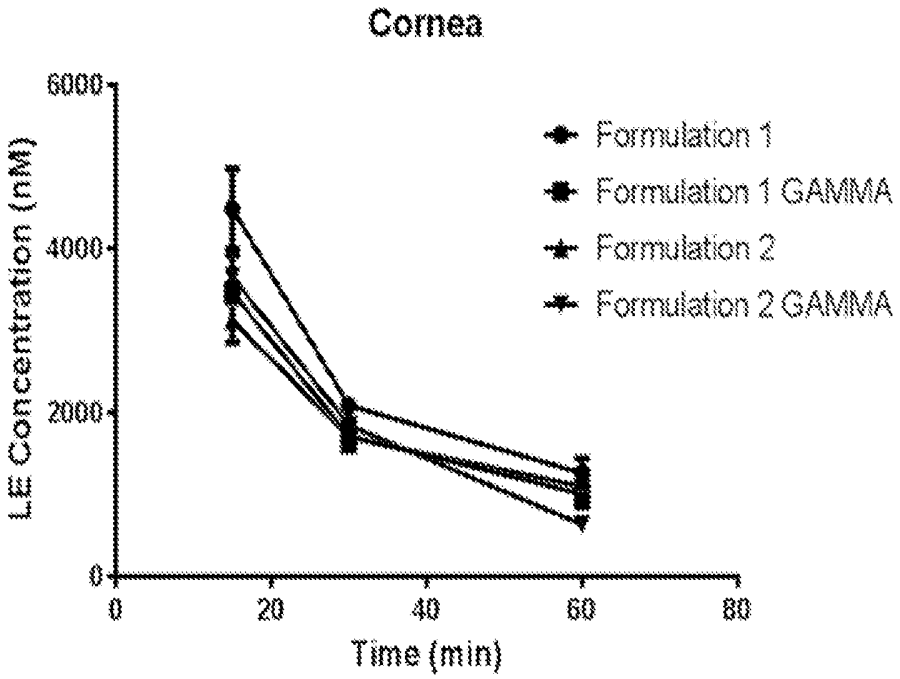


FIG. 33B

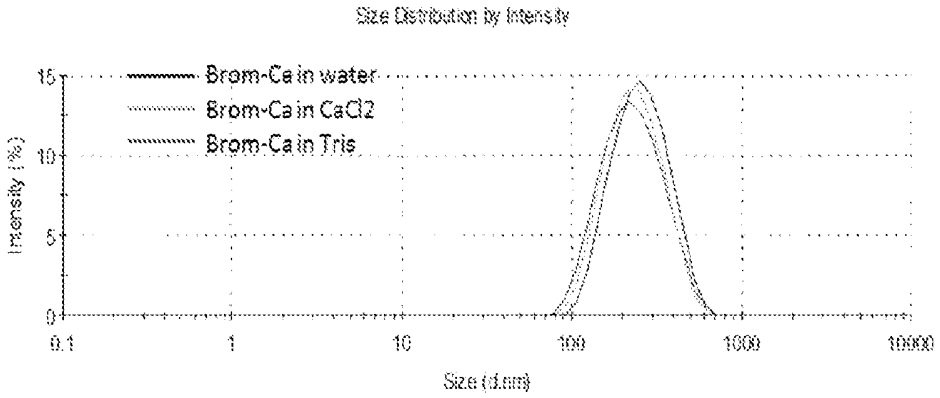

Size Distribution by Intensity
Brom-Ca in water
Brom-Ca in CaCl2
Brom-Ca in Tris
Intensity (%)
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)

FIG. 34

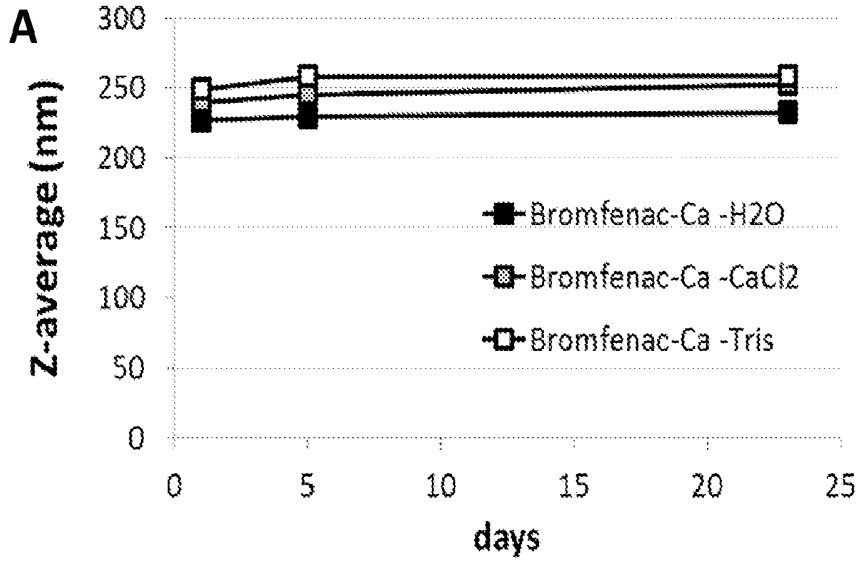


FIG. 35A

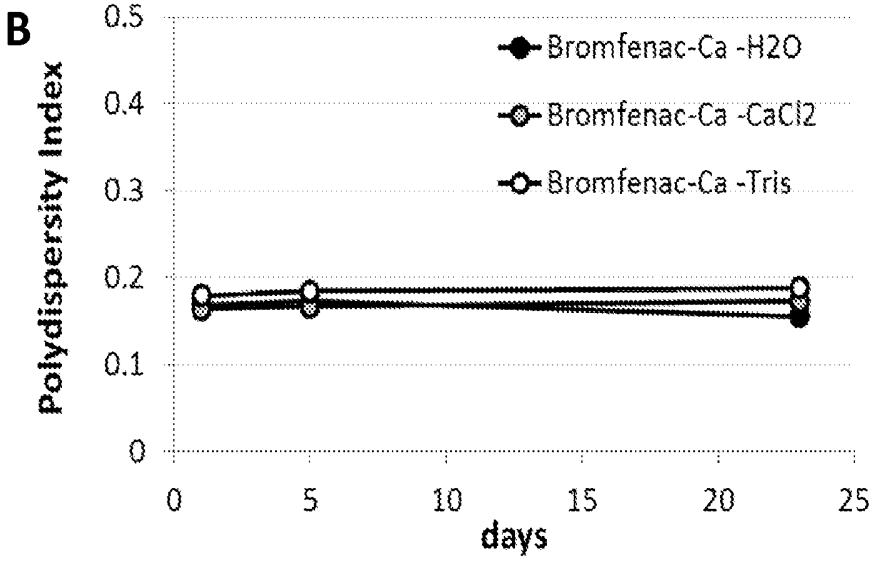


FIG. 35B

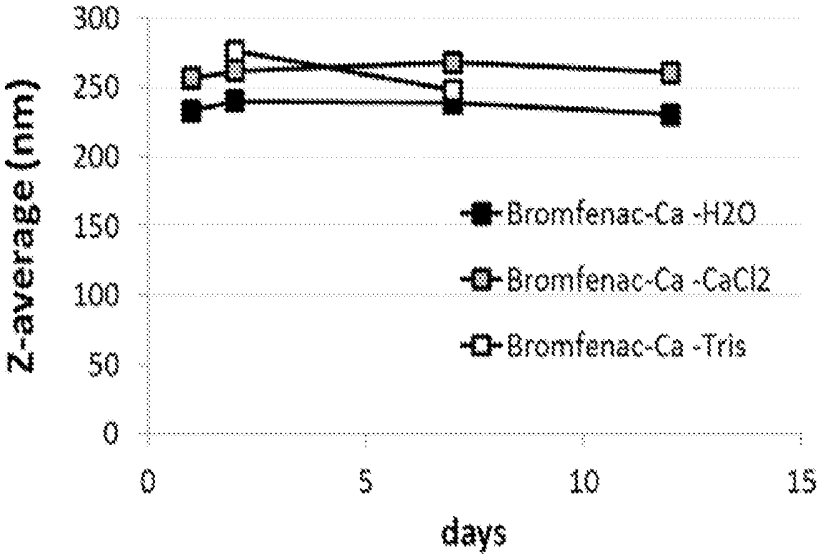


FIG. 35C

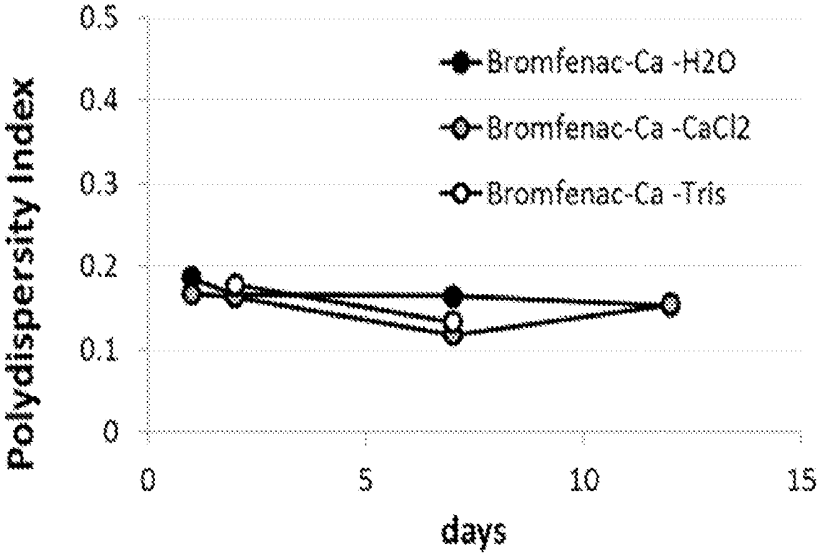


FIG. 35D

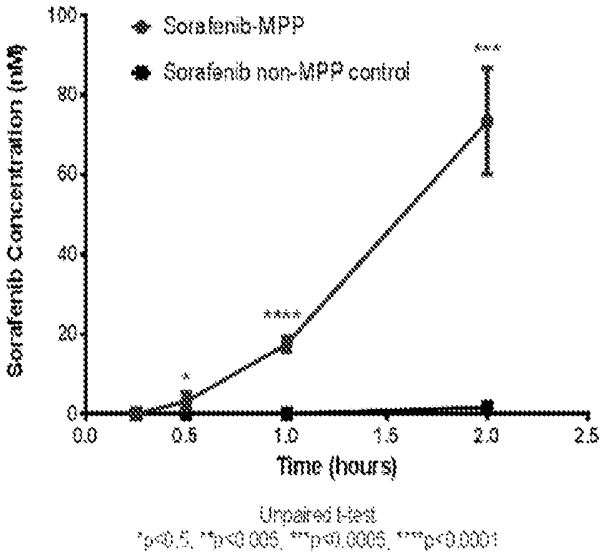


FIG. 36A

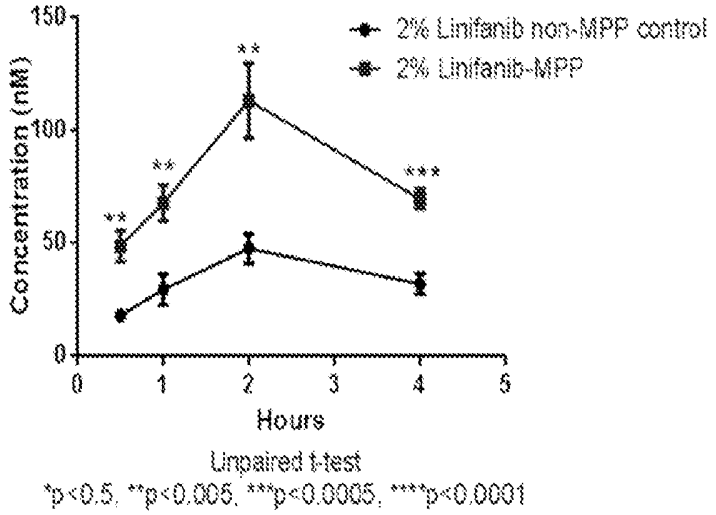


FIG. 36B

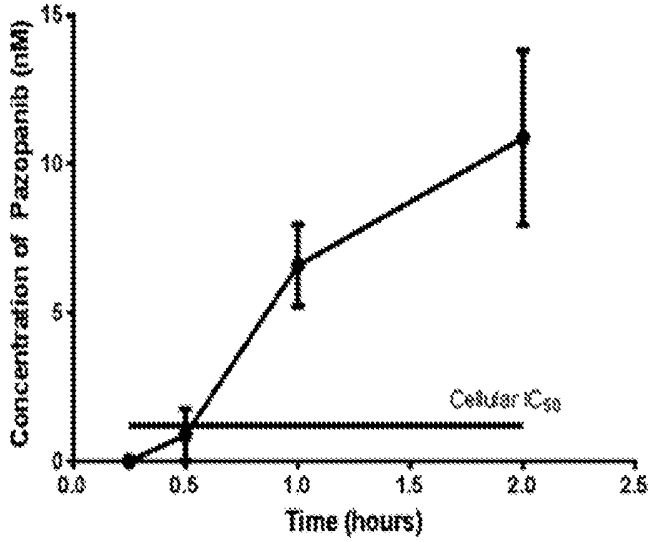


FIG. 37A

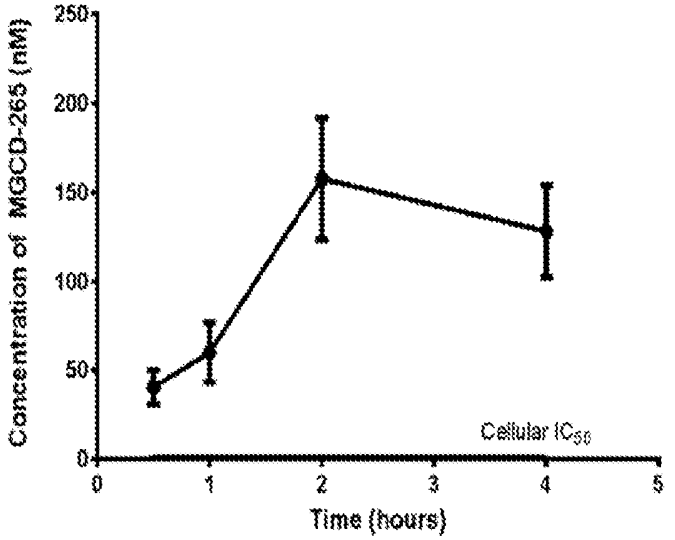


FIG. 37B

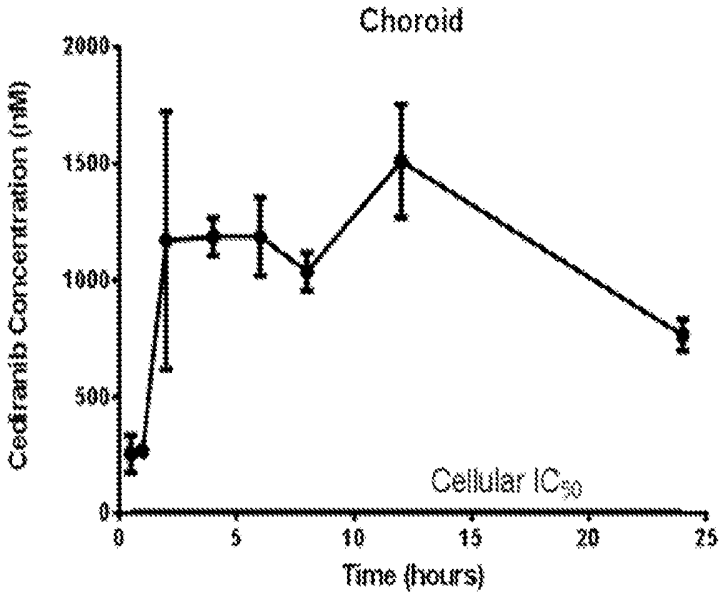


FIG. 38A

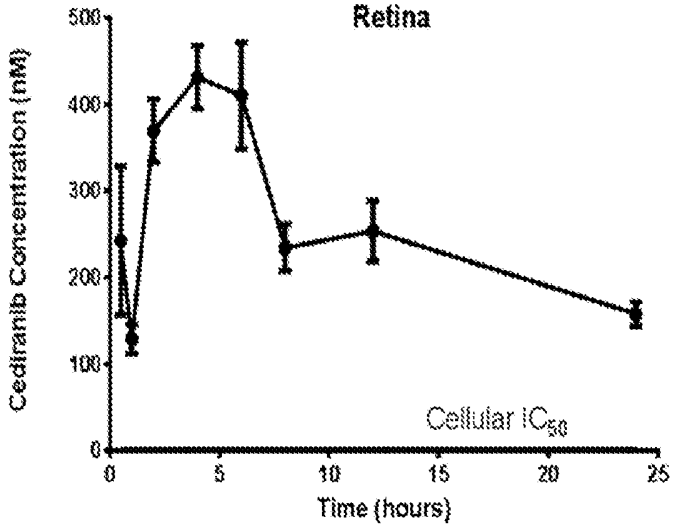


FIG. 38B

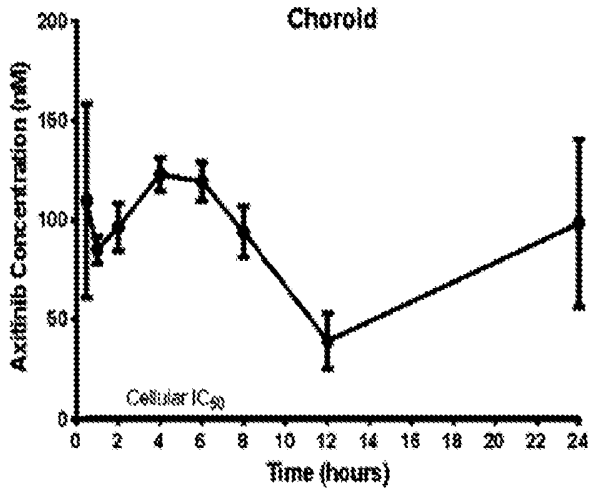


FIG. 39A

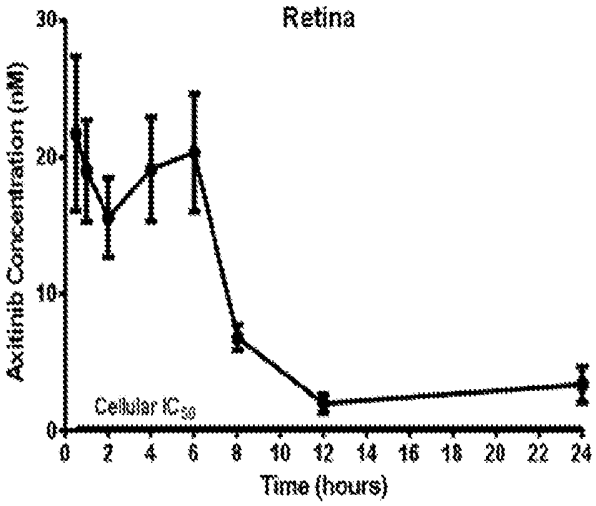


FIG. 39B

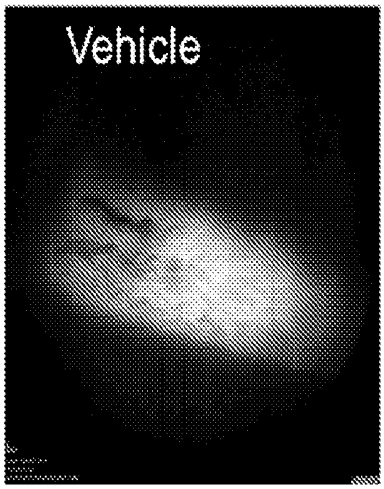


FIG. 40A

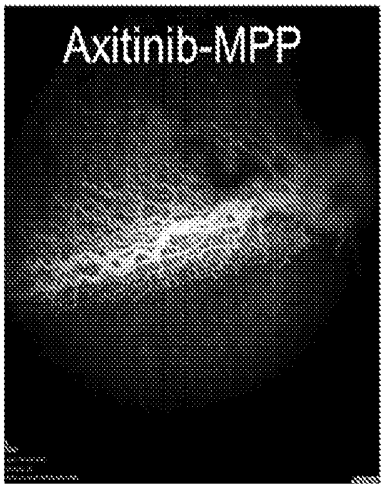


FIG. 40B

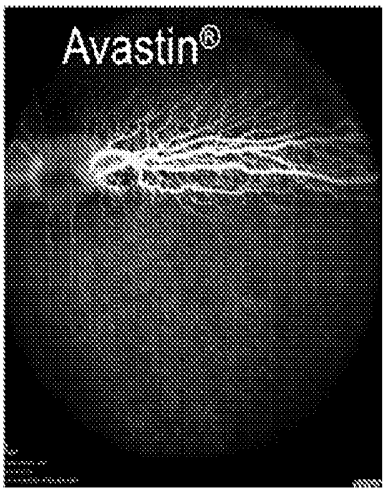


FIG. 40C

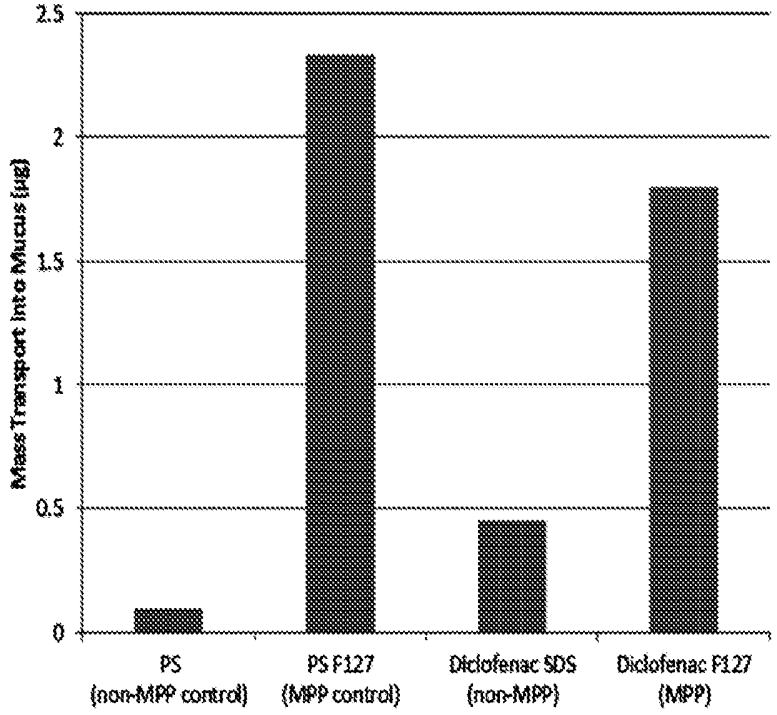

2.5
2
1.5
1
0.5
0
Mass Transport into Mucus (µg)
PS
(non-MPP control)
PS F127
(MPP control)
Diclofenac SDS
(non-MPP)
Diclofenac F127
(MPP)

FIG. 41

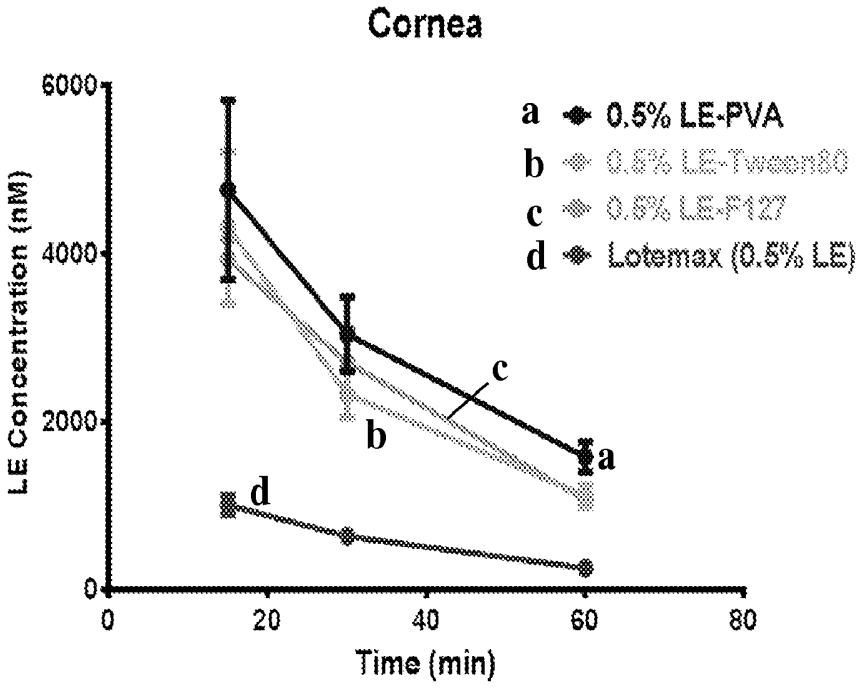

Cornea
6000
4000
2000
0
LE Concentration (nM)
0
20
40
60
80
Time (min)
a 0.5% LE-PVA
b 0.5% LE-Tween80
c 0.5% LE-F127
d Lotemax (0.5% LE)
a
b
c
d

FIG. 42

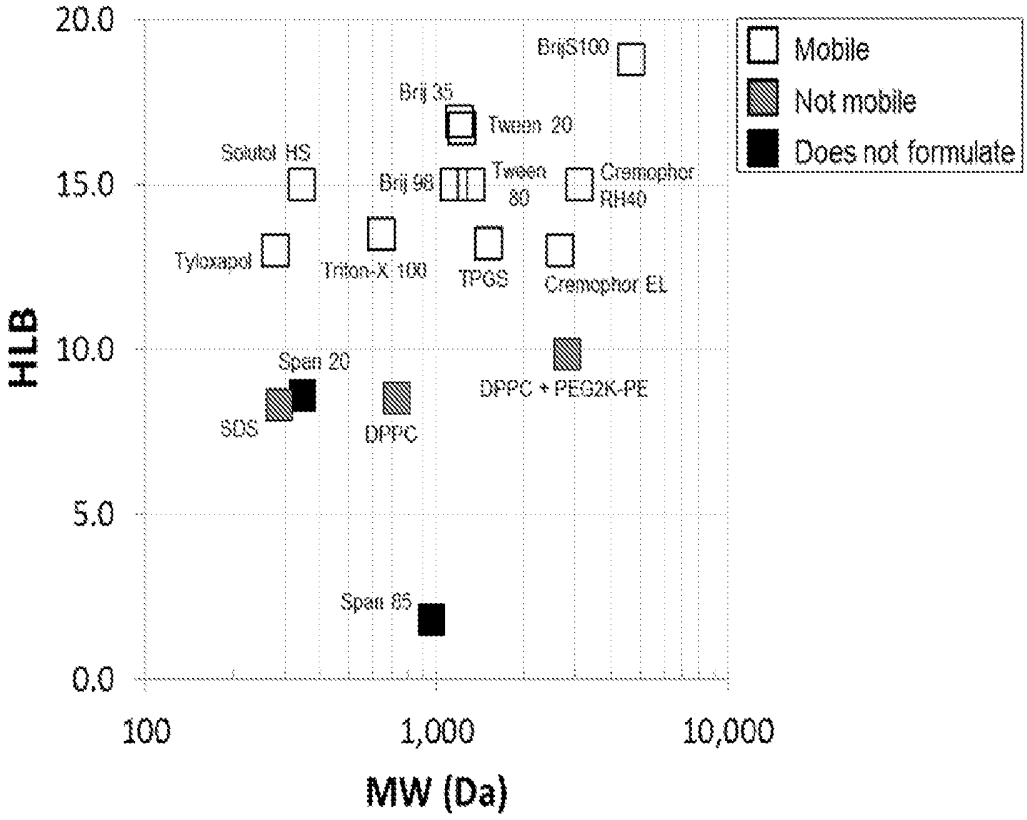

20.0
15.0
10.0
5.0
0.0
HLB
100
1,000
10,000
MW (Da)
Mobile
Not mobile
Does not formulate
BrijS100
Brij 35
Tween 20
Solutol HS
Brij 98
Tween 80
Cremophor RH40
Tyloxapol
Triton-X 100
TPGS
Cremophor EL
Span 20
DPPC + PEG2K-PE
SDS
DPPC
Span 85

FIG. 43

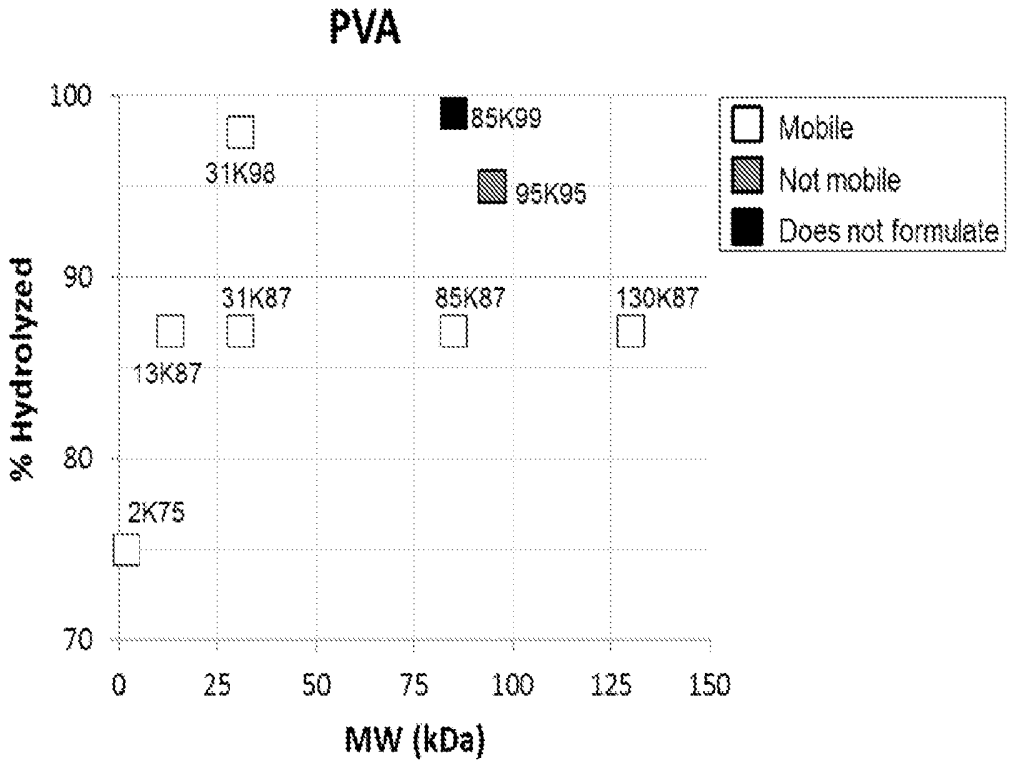

PVA
100
90
80
70
% Hydrolyzed
0
25
50
75
100
125
150
MW (kDa)
31K98
85K99
95K95
31K87
85K87
130K87
13K87
2K75
Mobile
Not mobile
Does not formulate

FIG. 44

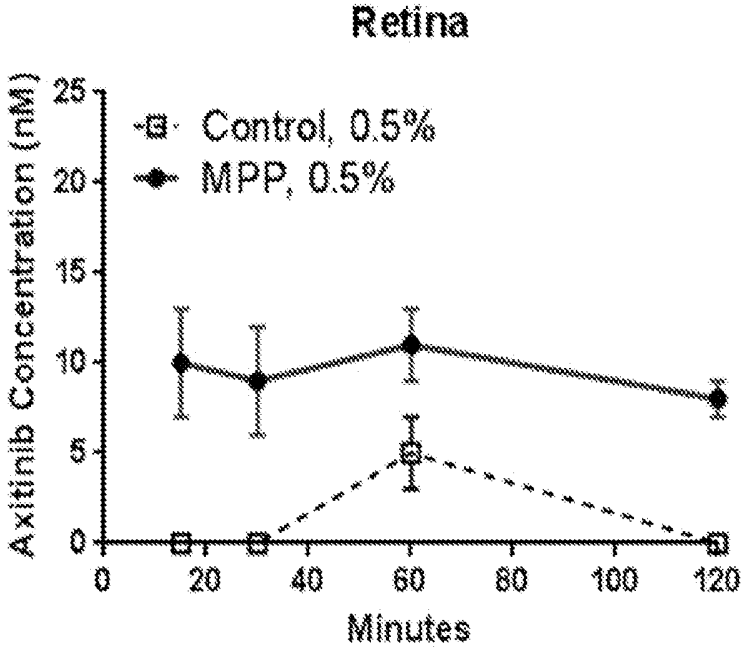

Retina
Axitinib Concentration (nM)
25
20
15
10
5
0
Control, 0.5%
MPP, 0.5%
0
20
40
60
80
100
120
Minutes

FIG. 45

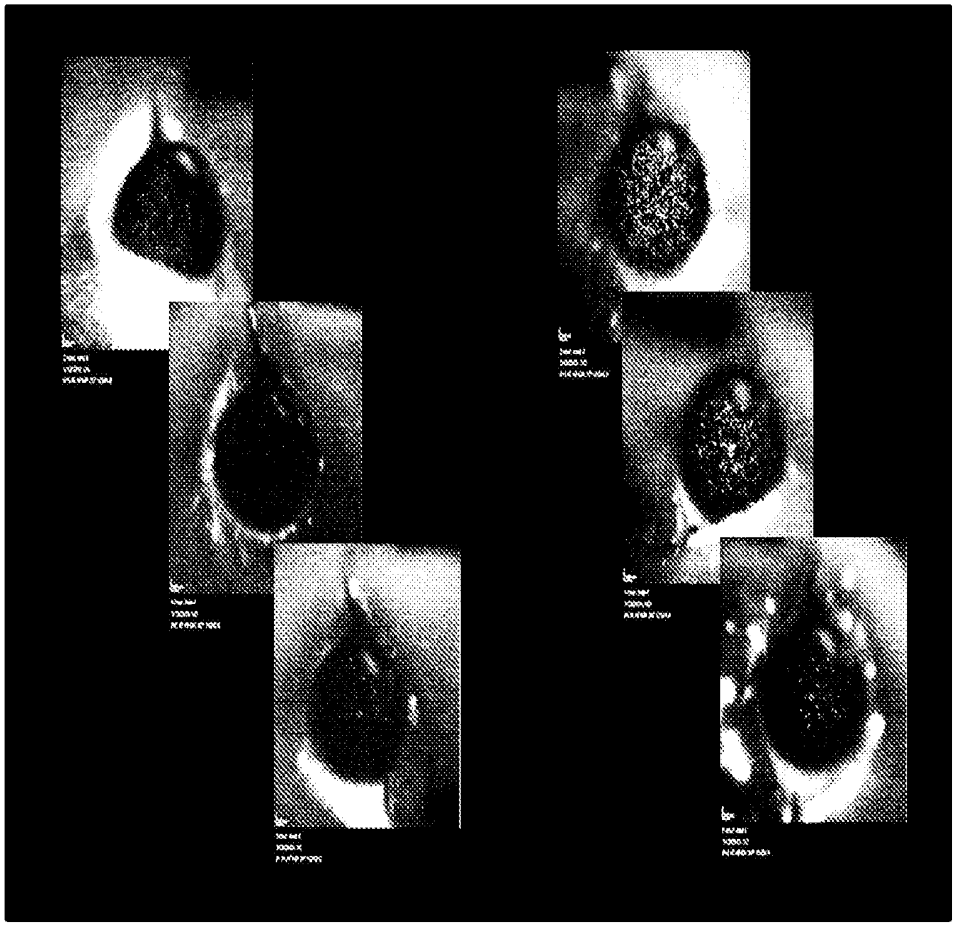


FIG. 46

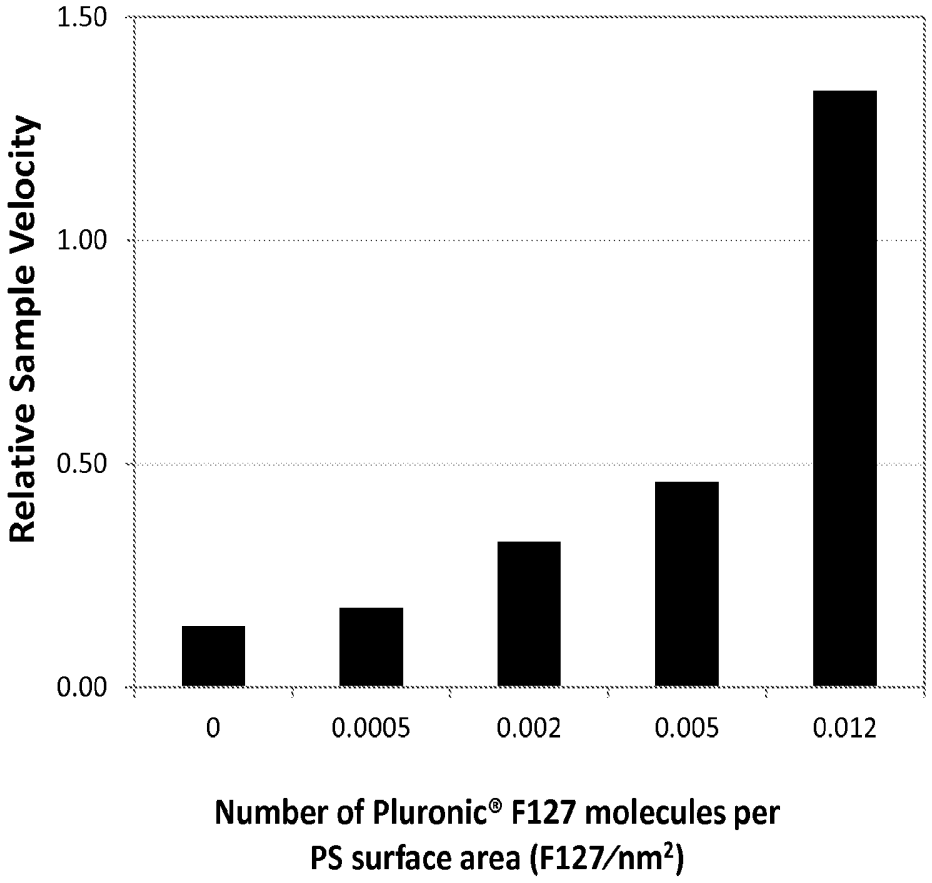

1.50
1.00
0.50
0.00
Relative Sample Velocity
0
0.0005
0.002
0.005
0.012
Number of Pluronic® F127 molecules per
PS surface area (F127/nm²)

FIG. 47

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/039540

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K47/26 A61K47/34 A61K9/10 A61K31/56
ADD.

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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, MEDLINE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/178051 A1 (PRUITT JOHN [US] ET AL) 2 August 2007 (2007-08-02) paragraph [0180] - paragraph [0182] paragraph [0197] claims 1-5	9-12,15, 52,53
X	WO 2006/094808 A2 (PHARMASOL GMBH [DE]; MOESCHWITZER JAN [DE]) 14 September 2006 (2006-09-14) page 13 page 23, line 4 - line 6 examples 1,2,7 claims 1-5	9-12,15, 52,53
X	US 2005/191359 A1 (GOLDSHTEIN RINA [IL] ET AL) 1 September 2005 (2005-09-01) claims 1-6 table 4	15

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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
10 October 2013	17/10/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sindel, Ulrike

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2011/106702 A2 (UNIV JOHNS HOPKINS [US]; MCDONNELL PETER J [US]; KHAN YASIN A [US]; LA) 1 September 2011 (2011-09-01) page 3, line 9 - line 25 examples 1-8 claims 1-60	1-4, 9-16,52, 53
Y	US 2010/222308 A1 (ZHANG JING [CN]) 2 September 2010 (2010-09-02) table 7 claims 1-18	1-4, 9-16,52, 53
Y	US 2008/194468 A1 (BODOR NICHOLAS S [US]) 14 August 2008 (2008-08-14) paragraph [0184] paragraph [0221] claims 1-30	1-4, 9-16,52, 53
Y,P	WO 2012/061703 A1 (UNIV JOHNS HOPKINS [US]; LAI SAMUEL K [US]; YANG MING [US]; WANG YING-) 10 May 2012 (2012-05-10) cited in the application paragraph [0009] paragraph [0026] paragraph [0082] paragraph [0089] - paragraph [0091] examples 1,2	1-4, 9-16,52, 53
Y	YAMAGATA TETSUO ET AL: "Improvement of the oral drug absorption of topotecan through the inhibition of intestinal xenobiotic efflux transporter, breast cancer resistance protein, by excipients", DRUG METABOLISM AND DISPOSITION, vol. 35, no. 7, July 2007 (2007-07), pages 1142-1148, XP002711274, ISSN: 0090-9556 the whole document	1-4, 9-16,52, 53
Y	US 2007/149480 A1 (GHOSH MALAY [US] ET AL) 28 June 2007 (2007-06-28) paragraph [0037] example 2 claims 1-4	5,6,14, 46,68,69
Y	US 2010/076045 A1 (CASTILLO ERNESTO J [US] ET AL) 25 March 2010 (2010-03-25) claims 1-11	5-8,14, 46,68, 69,74,78

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/039540

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2012/054923 A2 (BIND BIOSCIENCES INC [US]; DEWITT DAVID [US]; FIGUEIREDO MARIA [US]; W) 26 April 2012 (2012-04-26) paragraph [0091] - paragraph [0094] example 13 -----	7,8,74, 78

5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/039540

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

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

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

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

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

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

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

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

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

Remark on Protest

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

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

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-4, 13, 15, 16, 43, 44, 67, 77(completely); 9-12, 14, 17-42, 45, 47-66, 70-73, 75, 76, 79-91(partially)

   Pharmaceutical composition comprising coated nanoparticles with a core comprising at least 80% of loteprednol etabonate and a coating with 0.001 to 5% by weight of one or more surface altering agents selected from poloxamer, polyvinylalcohol or polysorbate

   ---

2. claims: 5, 6, 46, 68, 69(completely); 9-12, 14, 17-42, 45, 47-66, 70-73, 75, 76, 79-91(partially)

   Pharmaceutical composition comprising coated nanoparticles with a core comprising at least 80% of a receptor tyrosine kinase inhibitor and a coating with 0.001 to 5% by weight of one or more surface altering agents selected from poloxamer, polyvinylalcohol or polysorbate

   ---

3. claims: 7, 8, 74, 78(completely); 9-12, 14, 17-42, 45, 47-66, 70-73, 75, 76, 79-91(partially)

   Pharmaceutical composition comprising coated nanoparticles with a core comprising at least 80% of bromfenac calcium, diclofenac free acid or ketorolac free acid, and a coating with 0.001 to 5% by weight of one or more surface altering agents selected from poloxamer, polyvinylalcohol or polysorbate

   ---

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/039540

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2007178051 A1	02-08-2007	AU 2007210190 A1	09-08-2007
		BR PI0707314 A2	03-05-2011
		CA 2640444 A1	09-08-2007
		CN 101443018 A	27-05-2009
		EP 1976534 A1	08-10-2008
		JP 2009524665 A	02-07-2009
		KR 20080091493 A	13-10-2008
		NZ 570604 A	26-11-2010
		US 2007178051 A1	02-08-2007
		WO 2007089490 A1	09-08-2007
		ZA 200806758 A	26-08-2009
WO 2006094808 A2	14-09-2006	CA 2623112 A1	14-09-2006
		DE 102005011786 A1	14-09-2006
		EP 1868573 A2	26-12-2007
		JP 2008536812 A	11-09-2008
		US 2008279928 A1	13-11-2008
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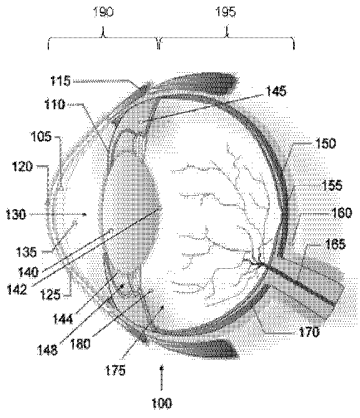
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(54)发明名称

显示提高的粘膜转移的药物纳米粒子

(57)摘要

本发明提供了有助于粒子在粘液中转移的粒子、组合物以及方法。在一些实施方案中，所述组合物和方法可以涉及对粒子，如具有低水溶解度的药剂的粒子的表面包衣进行改性。包括所述粒子的药物组合物非常适合于眼科应用，并且可以用于向眼前部和/或眼后部递送药剂。



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1. 一种适合于向眼施用的药物组合物，所述药物组合物包含：

多个包衣粒子，所述包衣粒子包含：

包含依碳酸氯替泼诺的核心粒子，其中所述依碳酸氯替泼诺占所述核心粒子的至少约80重量%；和

围绕所述核心粒子的包含一种或多种表面改变剂的包衣，

其中所述一种或多种表面改变剂包含以下中的至少一种：

a) 包含亲水性嵌段-疏水性嵌段-亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约2kDa的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约15重量%，

b) 合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约1kDa并且小于或等于约1000kDa的分子量，其中所述聚合物至少约30％水解且少于约95％水解，或

c) 聚山梨醇酯，

其中所述一种或多种表面改变剂以至少0.01个分子/平方纳米的密度存在于所述核心粒子的外表面上，

其中所述一种或多种表面改变剂以约0.001重量％至约5重量％的量存在于所述药物组合物中，

其中所述多个包衣粒子具有小于约1微米的平均最小横截面尺寸；以及

一种或多种眼科学上可接受的载体、添加剂和/或稀释剂。

2. 一种适合于向眼局部施用的药物组合物，所述药物组合物包含：

多个包衣粒子，所述包衣粒子包含：

包含依碳酸氯替泼诺的核心粒子，其中所述依碳酸氯替泼诺占所述核心粒子的至少约80重量%；以及

包含一种或多种表面改变剂的包衣，其中所述一种或多种表面改变剂包含泊洛沙姆、聚乙烯醇或聚山梨醇酯中的至少一种，

其中所述一种或多种表面改变剂以至少0.01个分子/平方纳米的密度存在于所述核心粒子的外表面上，

其中所述一种或多种表面改变剂以约0.001重量％至约5重量％的量存在于所述药物组合物中，

其中所述多个包衣粒子具有小于约1微米的平均最小横截面尺寸；以及

一种或多种眼科学上可接受的载体、添加剂和/或稀释剂。

3. 一种用于治疗患者眼的炎症、黄斑变性、黄斑水肿、葡萄膜炎、干眼症和/或其它病症的方法，所述方法包括：

向所述患者的眼施用药物组合物，所述药物组合物包含：

多个包衣粒子，所述包衣粒子包含：

包含依碳酸氯替泼诺的核心粒子，其中所述依碳酸氯替泼诺占所述核心粒子的至少约80重量%；以及

围绕所述核心粒子的包含一种或多种表面改变剂的包衣，

其中所述一种或多种表面改变剂包含以下中的至少一种：

a) 包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量%，

b) 合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30％水解且少于约 95％水解，或

c) 聚山梨醇酯，

其中所述一种或多种表面改变剂以至少 0.01 个分子 / 平方纳米的密度存在于所述核心粒子的外表面上，

其中所述一种或多种表面改变剂以约 0.001 重量％至约 5 重量％的量存在于所述药物组合物中，

其中所述多个包衣粒子具有小于约 1 微米的平均最小横截面尺寸；以及

一种或多种眼科学上可接受的载体、添加剂和 / 或稀释剂。

4. 一种用于治疗患者眼的炎症、黄斑变性、黄斑水肿、葡萄膜炎、干眼症和 / 或其它病症的方法，所述方法包括：

向所述患者的眼施用药物组合物，所述药物组合物包含：

多个包衣粒子，所述包衣粒子包含：

包含依碳酸氯替泼诺的核心粒子，其中所述依碳酸氯替泼诺占所述核心粒子的至少约 80 重量％；以及

包含一种或多种表面改变剂的包衣，其中所述一种或多种表面改变剂包含泊洛沙姆、聚乙烯醇或聚山梨醇酯中的至少一种，

其中所述一种或多种表面改变剂以至少 0.01 个分子 / 平方纳米的密度存在于所述核心粒子的外表面上，

其中所述一种或多种表面改变剂以约 0.001 重量％至约 5 重量％的量存在于所述药物组合物中，

其中所述多个包衣粒子具有小于约 1 微米的平均最小横截面尺寸；以及

一种或多种眼科学上可接受的载体、添加剂和 / 或稀释剂。

5. 一种适合于向眼施用的药物组合物，所述药物组合物包含：

多个包衣粒子，所述包衣粒子包含：

包含药剂或其盐的核心粒子，其中所述药剂或其盐占所述核心粒子的至少约 80 重量％，并且其中所述药剂或其盐包括受体酪氨酸激酶 (RTK) 抑制剂；以及

围绕所述核心粒子的包含一种或多种表面改变剂的包衣，

其中所述一种或多种表面改变剂包含以下中的至少一种：

a) 包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量％，

b) 合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30％水解且少于约 95％水解，或

c) 聚山梨醇酯，

其中所述一种或多种表面改变剂以至少 0.01 个分子 / 平方纳米的密度存在于所述核心粒子的外表面上，

其中所述一种或多种表面改变剂以约 0.001 重量％至约 5 重量％的量存在于所述药物组合物中，

其中所述多个包衣粒子具有小于约 1 微米的平均最小横截面尺寸；以及

一种或多种眼科学上可接受的载体、添加剂和 / 或稀释剂。

6. 一种用于治疗患者眼的黄斑变性、黄斑水肿和 / 或另一病症的方法，所述方法包括：

向所述患者的眼施用药物组合物，所述药物组合物包含：

多个包衣粒子，所述包衣粒子包含：

包含药剂或其盐的核心粒子，其中所述药剂或其盐占所述核心粒子的至少约 80 重量％，并且其中所述药剂或其盐包括受体酪氨酸激酶 (RTK) 抑制剂；以及

围绕所述核心粒子的包含一种或多种表面改变剂的包衣，

其中所述一种或多种表面改变剂包含以下中的至少一种：

a) 包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量％，

b) 合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30％水解且少于约 95％水解，或

c) 聚山梨醇酯，

其中所述一种或多种表面改变剂以至少 0.01 个分子 / 平方纳米的密度存在于所述核心粒子的外表面上，

其中所述一种或多种表面改变剂以约 0.001 重量％至约 5 重量％的量存在于所述药物组合物中，

其中所述多个包衣粒子具有小于约 1 微米的平均最小横截面尺寸；以及

一种或多种眼科学上可接受的载体、添加剂和 / 或稀释剂。

7. 一种适合于向眼施用的药物组合物，所述药物组合物包含：

多个包衣粒子，所述包衣粒子包含：

包含药剂或其盐的核心粒子，其中所述药剂或其盐占所述核心粒子的至少约 80 重量％，并且其中所述药剂或其盐包括溴芬酸钙、双氯芬酸游离酸、或酮咯酸游离酸；以及

围绕所述核心粒子的包含一种或多种表面改变剂的包衣，

其中所述一种或多种表面改变剂包含以下中的至少一种：

a) 包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量％，

b) 合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30％水解且少于约 95％水解，或

c) 聚山梨醇酯，

其中所述一种或多种表面改变剂以至少 0.01 个分子 / 平方纳米的密度存在于所述核心粒子的外表面上，

其中所述一种或多种表面改变剂以约 0.001 重量％至约 5 重量％的量存在于所述药物组合物中，

其中所述多个包衣粒子具有小于约 1 微米的平均最小横截面尺寸；以及

一种或多种眼科学上可接受的载体、添加剂和 / 或稀释剂。

8. 一种用于治疗患者眼的炎症、黄斑变性、黄斑水肿、葡萄膜炎、干眼症、青光眼和 / 或其它病症的方法，所述方法包括：

向所述患者的眼施用药物组合物，所述药物组合物包含：

多个包衣粒子，所述包衣粒子包含：

包含药剂或其盐的核心粒子，其中所述药剂或其盐占所述核心粒子的至少约 80 重量％，并且其中所述药剂或其盐包括溴芬酸钙、双氯芬酸游离酸、或酮咯酸游离酸；以及

围绕所述核心粒子的包含一种或多种表面改变剂的包衣，

其中所述一种或多种表面改变剂包含以下中的至少一种：

a) 包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量％，

b) 合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30％水解且少于约 95％水解，或

c) 聚山梨醇酯，

其中所述一种或多种表面改变剂以至少 0.01 个分子 / 平方纳米的密度存在于所述核心粒子的外表面上，

其中所述一种或多种表面改变剂以约 0.001 重量％至约 5 重量％的量存在于所述药物组合物中，

其中所述多个包衣粒子具有小于约 1 微米的平均最小横截面尺寸；以及

一种或多种眼科学上可接受的载体、添加剂和 / 或稀释剂。

9. 一种适合于向眼施用的药物组合物，所述药物组合物包含：

多个包衣粒子，所述包衣粒子包含：

包含药剂或其盐的核心粒子，所述药剂或其盐选自由以下组成的组：皮质类固醇、受体酪氨酸激酶 (RTK) 抑制剂、环加氧酶 (COX) 抑制剂、血管生成抑制剂、前列腺素类似物、NSAID、β 阻断剂以及碳酸酐酶抑制剂；以及

围绕所述核心粒子的包含一种或多种表面改变剂的包衣，

其中所述一种或多种表面改变剂包含以下中的至少一种：

a) 包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量％，其中所述疏水性嵌段与所述核心粒子的表面缔合，并且其中所述亲水性嵌段存在于所述包衣粒子的表面并且使得所述包衣粒子具有亲水性，

b) 合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30％水解且少于约 95％水解，或

c) 聚山梨醇酯，

其中所述一种或多种表面改变剂以至少 0.01 个分子 / 平方纳米的密度存在于所述核心粒子的外表面上，

其中所述一种或多种表面改变剂以约 0.001 重量％至约 5 重量％的量存在于所述药物组合物中；以及

一种或多种眼科学上可接受的载体、添加剂和 / 或稀释剂。

10. 一种治疗、诊断、预防或处理受试者的眼部病况的方法，所述方法包括：

向受试者的眼施用组合物，其中所述组合物包含多个包衣粒子，所述包衣粒子包含：

包含药剂或其盐的核心粒子，所述药剂或其盐选自由以下组成的组：皮质类固醇、受体酪氨酸激酶 (RTK) 抑制剂、环加氧酶 (COX) 抑制剂、血管生成抑制剂、前列腺素类似物、NSAID、β 阻断剂以及碳酸酐酶抑制剂；以及

围绕所述核心粒子的包含一种或多种表面改变剂的包衣，

其中所述一种或多种表面改变剂包含以下中的至少一种：

a) 包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量％，其中所述疏水性嵌段与所述核心粒子的表面缔合，并且其中所述亲水性嵌段存在于所述包衣粒子的表面并且使得所述包衣粒子具有亲水性，或

b) 合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30％水解且少于约 95％水解，或

c) 聚山梨醇酯；以及

向所述受试者的眼组织递送所述药剂。

11. 一种提高药剂在受试者中的眼部生物利用度的方法，所述方法包括：

向所述受试者的眼施用组合物，其中所述组合物包含多个包衣粒子，所述包衣粒子包含：

包含药剂或其盐的核心粒子，所述药剂或其盐选自由以下组成的组：皮质类固醇、受体酪氨酸激酶 (RTK) 抑制剂、环加氧酶 (COX) 抑制剂、血管生成抑制剂、前列腺素类似物、NSAID、β 阻断剂以及碳酸酐酶抑制剂；以及

围绕所述核心粒子的包含表面改变剂的包衣，

其中所述核心粒子上的所述包衣以足够的量存在以使得所述药剂在以所述组合物被施用时的所述眼部生物利用度与所述药剂在以没有所述包衣的核心粒子的形式被施用时的所述眼部生物利用度相比得以提高。

12. 一种提高药剂在受试者的组织中的浓度的方法，所述方法包括：

向所述受试者的眼施用组合物，其中所述组合物包含多个包衣粒子，所述包衣粒子包含：

包含所述药剂或其盐的核心粒子，其中所述药剂选自由以下组成的组：皮质类固醇、受

体酪氨酸激酶 (RTK) 抑制剂、环加氧酶 (COX) 抑制剂、血管生成抑制剂、前列腺素类似物、NSAID、β 阻断剂以及碳酸酐酶抑制剂 ;以及

围绕所述核心粒子的包含表面改变剂的包衣,

其中所述组织选自由视网膜、黄斑、巩膜或脉络膜组成的组 ;以及

其中所述核心粒子上的所述包衣以足够的量存在以使得所述药剂在以所述组合物被施用时在所述组织中的浓度与所述药剂在以没有所述包衣的核心粒子的形式被施用时在所述组织中的浓度相比增加了至少 10%。

13. 一种通过重复施用药物组合物来治疗受试者的眼部病况的方法,所述方法包括 :

向受试者的眼施用两剂量或更多剂量的包含依碳酸氯替泼诺的药物组合物,其中连续剂量之间的时间段是至少约 4 小时、至少约 6 小时、至少约 8 小时、至少约 12 小时、至少约 36 小时、或至少约 48 小时,

其中向眼组织递送的依碳酸氯替泼诺的量有效治疗所述受试者的眼部病况。

14. 一种通过重复施用药物组合物来治疗受试者的眼部病况的方法,所述方法包括 :

向受试者的眼施用两剂量或更多剂量的包含一种或多种药剂的药物组合物,其中连续剂量之间的时间段是至少约 4 小时、至少约 6 小时、至少约 8 小时、至少约 12 小时、至少约 36 小时、或至少约 48 小时,

其中所述一种或多种药剂选自由以下组成的组 :依碳酸氯替泼诺、索拉非尼、利尼伐尼、MGCD-265、帕唑帕尼、西地尼布、阿西替尼、溴芬酸钙、双氯芬酸游离酸、酮咯酸游离酸以及它们的组合,

其中向眼组织递送的所述药剂的量有效治疗所述受试者的眼部病况。

15. 一种适合于通过向眼施用来治疗前眼部病症的药物组合物,所述药物组合物包含 :

多个包衣粒子,所述包衣粒子包含 :

包含皮质类固醇的核心粒子 ;以及

围绕所述核心粒子的包含一种或多种表面改变剂的包衣,

其中所述一种或多种表面改变剂包含以下中的至少一种 :

a) 包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型的三嵌段共聚物,其中所述疏水性嵌段具有至少约 2kDa 的分子量,并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量%,

b) 合成聚合物,所述合成聚合物在所述聚合物的主链上具有侧羟基,所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量,其中所述聚合物至少约 30% 水解且少于约 95% 水解,或

c) 聚山梨醇酯,

其中所述多个包衣粒子具有小于约 1 微米的平均最小横截面尺寸 ;以及

其中所述核心粒子上的所述包衣以足够的量存在以使得所述皮质类固醇在向所述眼施用时在施用后 30 分钟时在所述眼的前部组成部分中的浓度与所述皮质类固醇在以没有所述包衣的核心粒子的形式被施用时在所述组织中的浓度相比增加了至少 50%,所述前部组成部分选自由角膜或房水组成的组。

16. 一种通过向眼施用来治疗前眼部病症的方法,所述方法包括 :

向受试者的眼施用组合物，其中所述组合物包含：

多个包衣粒子，所述包衣粒子包含：

包含皮质类固醇的核心粒子；以及

围绕所述核心粒子的包含一种或多种表面改变剂的包衣，

其中所述一种或多种表面改变剂包含以下中的至少一种：

a) 包含亲水性嵌段－疏水性嵌段－亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量%，

b) 合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30％水解且少于约 95％水解，或

c) 聚山梨醇酯；以及

在施用后使所述皮质类固醇在前眼部组织中的眼科学上有效的水平持续至少 12 小时，所述前眼部组织选自由睑结膜、球结膜或角膜组成的组。

17. 根据任一前述权利要求所述的组合物或方法，其中所述泊洛沙姆包括具有至少约 2kDa 的分子量的疏水性嵌段，并且其中所述泊洛沙姆包括占所述泊洛沙姆的至少约 15 重量％的亲水性嵌段。

18. 根据任一前述权利要求所述的组合物或方法，其中所述表面改变剂包含含有亲水性嵌段－疏水性嵌段－亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量％，其中所述疏水性嵌段与所述核心粒子的表面缔合，并且

其中所述亲水性嵌段存在于所述包衣粒子的表面并且使得所述包衣粒子具有亲水性。

19. 根据任一前述权利要求所述的方法，所述方法包括向所述受试者的所述眼的前部中的组织递送所述药剂。

20. 根据任一前述权利要求所述的方法，所述方法包括向所述受试者的所述眼的后部中的组织递送所述药剂。

21. 根据任一前述权利要求所述的组合物或方法，其中所述表面改变剂与所述核心粒子共价连接。

22. 根据任一前述权利要求所述的组合物或方法，其中所述表面改变剂非共价吸附到所述核心粒子。

23. 根据任一前述权利要求所述的组合物或方法，其中所述表面改变剂以如下的密度存在于所述包衣粒子的表面上：每平方纳米至少约 0.01 个、至少约 0.02 个、至少约 0.05 个、至少约 0.1 个、至少约 0.2 个、至少约 0.5 个、至少约 1 个、至少约 2 个、至少约 5 个、至少约 10 个、或至少约 20 个分子。

24. 根据任一前述权利要求所述的组合物或方法，其中所述表面改变剂包含线型聚合物，所述线型聚合物在所述聚合物的主链上具有侧羟基。

25. 根据任一前述权利要求所述的组合物或方法，其中所述三嵌段共聚物的所述亲水性嵌段占所述三嵌段共聚物的至少约 20 重量％、至少约 30 重量％、至少约 40 重量％、至少约 50 重量％、或至少约 60 重量％、和／或所述三嵌段共聚物的少于或等于约 80 重量％。

26. 根据任一前述权利要求所述的组合物或方法，其中所述三嵌段共聚物的所述疏水性嵌段部分具有至少约 3kDa、至少约 4kDa、或至少约 6kDa、和 / 或小于或等于约 20kDa、小于或等于约 10kDa、或小于或等于约 8kDa 的分子量。

27. 根据任一前述权利要求所述的组合物或方法，其中所述三嵌段共聚物是聚环氧乙烷 - 聚环氧丙烷 - 聚环氧乙烷或聚乙二醇 - 聚环氧丙烷 - 聚乙二醇。

28. 根据任一前述权利要求所述的组合物或方法，其中所述三嵌段共聚物的所述亲水性嵌段包含聚环氧乙烷或聚乙二醇或其衍生物。

29. 根据任一前述权利要求所述的组合物或方法，其中所述聚环氧乙烷或聚乙二醇嵌段具有至少约 2kDa、至少约 3kDa、或至少约 4kDa 的分子量。

30. 根据任一前述权利要求所述的组合物或方法，其中所述三嵌段共聚物的所述疏水性嵌段是聚环氧丙烷。

31. 根据任一前述权利要求所述的组合物或方法，其中所述聚环氧丙烷嵌段具有至少约 1.8kDa、至少约 2kDa、至少约 2.5kDa、至少约 3kDa、至少约 4kDa、或至少约 5kDa 的分子量。

32. 根据任一前述权利要求所述的组合物或方法，其中所述表面改变剂和 / 或聚合物具有至少约 2kDa、至少约 5kDa、至少约 10kDa、至少约 20kDa、至少约 50kDa、至少约 80kDa、至少约 100kDa、或至少约 120kDa 的分子量。

33. 根据任一前述权利要求所述的组合物或方法，其中所述聚合物具有如下的分子量：小于或等于约 200kDa、小于或等于约 180kDa、小于或等于约 150kDa、小于或等于约 130kDa、小于或等于约 100kDa、小于或等于约 80kDa、小于或等于约 50kDa、或者小于或等于约 30kDa。

34. 根据任一前述权利要求所述的组合物或方法，其中所述聚合物至少约 40％水解、至少约 50％水解、至少约 60％水解、至少约 70％水解、至少约 80％水解、或至少约 90％水解。

35. 根据任一前述权利要求所述的组合物或方法，其中所述聚合物少于或等于约 94％、少于或等于约 90％、少于或等于约 85％、或者少于或等于约 80％水解。

36. 根据任一前述权利要求所述的组合物或方法，其中所述合成聚合物是聚乙烯醇。

37. 根据任一前述权利要求所述的组合物或方法，其中所述核心粒子中的每一个均包含结晶药剂或其盐。

38. 根据任一前述权利要求所述的组合物或方法，其中所述核心粒子中的每一个均包含无定形药剂或其盐。

39. 根据任一前述权利要求所述的组合物或方法，其中所述核心粒子中的每一个均包含所述固体药剂的盐。

40. 根据任一前述权利要求所述的组合物或方法，其中所述核心粒子中的每一个均包含被封装在聚合物、脂质、蛋白质或其组合中的药剂或其盐。

41. 根据任一前述权利要求所述的组合物或方法，其中所述药剂是治疗剂或诊断剂中的至少一种。

42. 根据任一前述权利要求所述的组合物或方法，其中所述药剂是小分子、肽、拟肽、蛋白质、核酸或脂质中的至少一种。

43. 根据任一前述权利要求所述的组合物或方法，其中所述药剂或其盐是皮质类固醇。

44. 根据任一前述权利要求所述的组合物或方法，其中所述药剂或其盐是依碳酸氯替泼诺。

45. 根据任一前述权利要求所述的组合物或方法，其中所述药剂或其盐包括抗 VEGF 剂。

46. 根据任一前述权利要求所述的组合物或方法，其中所述药剂或其盐包括酪氨酸激酶抑制剂。

47. 根据任一前述权利要求所述的组合物或方法，其中所述药剂或其盐在 25℃具有小于或等于约 1mg/mL、小于或等于约 0.1mg/mL、或者小于或等于约 0.01mg/mL 的水溶解度。

48. 根据任一前述权利要求所述的组合物或方法，其中所述药剂占所述核心粒子的至少约 50 重量%、所述核心粒子的至少约 80 重量%、所述核心粒子的至少约 85 重量%、所述核心粒子的至少约 90 重量%、所述核心粒子的至少约 95 重量%、或所述核心粒子的至少约 99 重量%。

49. 根据任一前述权利要求所述的组合物或方法，其中所述核心粒子具有至少约 10nm、至少约 50nm、或至少约 100nm 并且小于或等于约 1μm 的平均尺寸。

50. 根据任一前述权利要求所述的组合物或方法，其中所述包衣粒子具有至少约 10nm、至少约 50nm 或至少约 100nm 并且小于或等于约 1μm 的平均尺寸。

51. 根据任一前述权利要求所述的组合物或方法，其中所述包衣粒子具有大于 0.5、0.6、0.7、0.8、0.9 或 1.0 的相对速度。

52. 一种药物组合物，所述药物组合物包含根据任一前述权利要求所述的组合物和一种或多种药学上可接受的载体。

53. 一种适合于向受试者的眼局部施用的药物制剂，所述药物制剂包含根据任一前述权利要求所述的组合物。

54. 根据任一前述权利要求所述的组合物或方法，其中所述核心粒子上的所述包衣以足够的量存在以使得所述药剂在以所述组合物被施用时在所述组织中的浓度与所述药剂在以没有所述包衣的核心粒子的形式被施用时在所述组织中的浓度相比增加了至少约 10%、至少约 20%、至少约 30%、至少约 40%、至少约 50%、至少约 60%、至少约 70%、至少约 80%、至少约 90%、或至少约 100%。

55. 根据任一前述权利要求所述的组合物或方法，其中所述眼部病况是后眼部病况。

56. 根据任一前述权利要求所述的组合物或方法，其中所述眼部病况是视网膜病症。

57. 根据任一前述权利要求所述的组合物或方法，其中所述眼部病况是炎症、黄斑变性、黄斑水肿、葡萄膜炎、干眼症或青光眼。

58. 根据任一前述权利要求所述的组合物或方法，其中所述受试者是人。

59. 根据任一前述权利要求所述的组合物或方法，其中所述组织是视网膜、黄斑、巩膜或脉络膜。

60. 根据任一前述权利要求所述的组合物或方法，其中所述组合物包含所述药剂的一种或多种降解物，并且其中相对于所述药剂的重量，每一种或至少一种降解物的浓度小于或等于约 2 重量%、小于或等于约 1 重量%、小于或等于约 0.8 重量%、小于或等于约 0.6 重量%、小于或等于约 0.4 重量%、小于或等于约 0.2 重量%、小于或等于约 0.15 重量%、

或者小于或等于约 0.1 重量%。

61. 根据任一前述权利要求所述的组合物或方法，其中所述组合物的多分散指数小于或等于约 0.5、小于或等于约 0.4、小于或等于约 0.3、小于或等于约 0.2、小于或等于约 0.15、小于或等于约 0.1、或者小于或等于约 0.05。

62. 根据任一前述权利要求所述的组合物，其中所述药物组合物适合于向所述眼局部施用。

63. 根据任一前述权利要求所述的组合物，其中所述药物组合物适合于直接注射到所述眼中。

64. 根据任一前述权利要求所述的方法，所述方法包括向所述眼局部施用所述药物组合物。

65. 根据任一前述权利要求所述的方法，所述方法包括通过直接注射到所述眼中来施用所述药物组合物。

66. 根据任一前述权利要求所述的方法，其中眼科学上有效的水平是 IC50 值或 IC90 值。

67. 根据任一前述权利要求所述的药物组合物或方法，其中所述药剂或其盐是皮质类固醇。

68. 根据任一前述权利要求所述的药物组合物或方法，其中所述药剂或其盐是受体酪氨酸激酶 (RTK) 抑制剂。

69. 根据任一前述权利要求所述的药物组合物或方法，其中所述 RTK 抑制剂是索拉非尼、利尼伐尼、MGCD-265、帕唑帕尼、西地尼布、阿西替尼或其组合。

70. 根据任一前述权利要求所述的药物组合物或方法，其中所述药剂或其盐是环加氧酶 (COX) 抑制剂。

71. 根据任一前述权利要求所述的药物组合物或方法，其中所述环加氧酶 (COX) 抑制剂是 COX-2 抑制剂。

72. 根据任一前述权利要求所述的药物组合物或方法，其中所述药剂或其盐是血管生成抑制剂。

73. 根据任一前述权利要求所述的药物组合物或方法，其中所述药剂或其盐是前列腺素类似物。

74. 根据任一前述权利要求所述的药物组合物或方法，其中所述药剂或其盐是 NSAID。

75. 根据任一前述权利要求所述的药物组合物或方法，其中所述药剂或其盐是 β 阻断剂。

76. 根据任一前述权利要求所述的药物组合物或方法，其中所述药剂或其盐是碳酸酐酶抑制剂。

77. 根据任一前述权利要求所述的药物组合物或方法，其中所述药剂或其盐是依碳酸氯替泼诺。

78. 根据任一前述权利要求所述的药物组合物或方法，其中所述药剂或其盐是溴芬酸钙。

79. 根据任一前述权利要求所述的药物组合物或方法，其中所述表面改变剂是包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少

约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量%。

80. 根据任一前述权利要求所述的药物组合物或方法，其中所述表面改变剂是合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30％水解且少于约 95％水解。

81. 根据任一前述权利要求所述的药物组合物或方法，其中所述表面改变剂是聚山梨醇酯。

82. 根据任一前述权利要求所述的药物组合物或方法，其中所述表面改变剂是聚乙烯醇。

83. 根据任一前述权利要求所述的药物组合物或方法，其中所述组合物具有小于或等于约 0.5、小于或等于约 0.3、或者小于或等于约 0.2 的 PDI。

84. 根据任一前述权利要求所述的药物组合物或方法，其中所述组合物具有大于或等于约 0.1 并且小于或等于约 0.5、大于或等于约 0.1 并且小于或等于约 0.3、或者大于或等于约 0.1 并且小于或等于约 0.2 的 PDI。

85. 根据任一前述权利要求所述的药物组合物或方法，其中包衣具有小于或等于约 100nm、小于或等于约 50nm、小于或等于约 30nm、或者小于或等于约 10nm 的厚度。

86. 根据任一前述权利要求所述的药物组合物或方法，其中所述组合物中存在的所述表面改变剂的总量是约 0.001 重量％至约 5 重量％、约 0.01 重量％至约 5 重量％、或者约 0.1 重量％至约 5 重量％。

87. 根据任一前述权利要求所述的药物组合物或方法，其中所述组合物包含一种或多种游离的表面改变剂；任选地，其中溶液中的一种或多种游离的表面改变剂与所述粒子的表面上的表面改变剂是相同的一种或多种表面改变剂；任选地，其中溶液中的所述一种或多种游离的表面改变剂与所述粒子的表面上的表面改变剂在所述组合物中彼此平衡。

88. 根据任一前述权利要求所述的药物组合物或方法，其中所述药剂或其盐 (A) 选自 A1、A2、A3、A4、A5、A6、A7、A8、A9、A10、A11、A12、A13、A14、A15、A16、A17、A18 或 A19；或本文所鉴定的 A1、A2、A3、A4、A5、A6、A7、A8、A9、A10、A11、A12、A13、A14、A15、A16、A17、A18 或 A19 的物质。

89. 根据任一前述权利要求所述的药物组合物或方法，其中所述表面改变剂 (B) 选自 B1、B2、B3、B4、B5、B6、B7、B8 或 B9、或者如本文所鉴定的 B1、B2、B3、B4、B5、B6、B7、B8 或 B9 的物质。

90. 根据任一前述权利要求所述的药物组合物或方法，其中所述一种或多种眼科学上可接受的载体、添加剂和 / 或稀释剂包括甘油。

91. 根据任一前述权利要求所述的药物组合物或方法，其中所述药物组合物包含所述药剂的一种或多种降解物，并且其中相对于所述药剂的重量，每一种降解物的浓度小于或等于约 1 重量％。

显示提高的粘膜转移的药物纳米粒子

技术领域

[0001] 本发明大体上涉及有助于粒子在粘液中转移的粒子、组合物以及方法。所述粒子、组合物以及方法可以用于眼科应用和/或其它应用中。

背景技术

[0002] 在包括眼、鼻、肺、胃肠道以及女性生殖道在内的各种体内进入点处存在的粘液层具有天然的粘着性，并且用以通过有效地截留病原体、过敏原以及碎片并且将它们通过粘液转换快速地去除来保护身体对抗这些病原体、过敏原以及碎片。为了通过粘液膜有效地递送治疗性粒子、诊断性粒子或成像粒子，这些粒子必须能够容易穿透粘液层以避免粘液粘着和快速的粘液清除。并入药剂的粒子（包括微粒和纳米粒子）对于眼科应用是特别有用的。然而，由于快速清除和/或其它原因，所施用的粒子往往很难以有效量被递送到眼组织中。因此，用于向眼施用（例如局部施用或直接注射）药剂的新型方法和组合物将是有益的。

发明内容

[0003] 本说明书大体上涉及有助于粒子在粘液中转移的粒子、组合物以及方法，特别是用于眼科应用和/或其它应用的粒子、组合物以及方法。

[0004] 如下文所更详细地描述，在一些实施方案中，所述组合物包含多个粒子，所述粒子包括皮质类固醇，如依碳酸氯替泼诺(loteprednol etabonate,LE)以用于治疗眼疾病或病况。所述粒子包括表面改变剂，所述表面改变剂降低粒子对粘液的粘着性和/或有助于粒子穿过生理性粘液。这些组合物优于诸如Lotemax®或Alrex®等市售制剂，因为本文所述的组合物能够更容易地穿过眼部组织的粘液层以避免粘液粘着和/或快速的粘液清除或使粘液粘着和/或快速的粘液清除减到最低程度。因此，所述组合物可以被更有效地递送到靶标组织中并且可以在其中保留更长时间。因此，本文所述的组合物可以较市售的制剂更低的剂量和/或更低的频率被施用以实现相似的或更好的暴露。此外，本文所述的组合物相对低的剂量和/或相对低频率的给药可以引起更少或严重度更低的副作用、更理想的毒性特征和/或改进的患者依从性。

[0005] 在一些实施方案中，本文所述的组合物可以包含多个粒子，所述粒子包括受体酪氨酸激酶(RTK)抑制剂，如索拉非尼(sorafenib)、利尼伐尼(linifanib)、MGCD-265、帕唑帕尼(pazopanib)、西地尼布(cediranib)以及阿西替尼(axitinib)以用于治疗眼疾病或病况。还提供了包括这些粒子的组合物，包括可以向眼局部施用的组合物。出于本文所述的原因，这些组合物可以比常规的制剂（例如这些药剂的水性悬浮液）具有某些优势。

[0006] 在某些实施方案中，本文所述的组合物可以包含多个粒子，所述粒子包括非类固醇抗炎药(NSAID)，如溴芬酸(bromfenac)的二价金属盐或三价金属盐（例如溴芬酸钙）、双氯芬酸(diclofenac)（例如双氯芬酸游离酸或其二价金属盐或三价金属盐）或酮咯酸(ketorolac)（例如酮咯酸游离酸或其二价金属盐或三价金属盐）以用于治疗眼疾病或病

况。还提供了包括这些粒子的组合物，包括可以向眼局部施用的组合物。出于本文所述的原因，这些组合物可以比常规的制剂（例如相应药剂的水溶液）具有优势。

[0007] 在一组实施方案中，提供了一种适合于向眼施用的药物组合物。所述药物组合物包含多个包衣粒子，所述包衣粒子包含：包含依碳酸氯替泼诺的核心粒子，其中所述依碳酸氯替泼诺占所述核心粒子的至少约 80 重量％；以及围绕所述核心粒子的包含一种或多种表面改变剂的包衣。所述一种或多种表面改变剂包含以下中的至少一种：a) 包含亲水性嵌段－疏水性嵌段－亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量％；b) 合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30％水解且少于约 95％水解；或 c) 聚山梨醇酯。所述一种或多种表面改变剂以至少 0.01 个分子／平方纳米的密度存在于所述核心粒子的外表面上。所述一种或多种表面改变剂以约 0.001 重量％至约 5 重量％的量存在于所述药物组合物中。所述多个包衣粒子具有小于约 1 微米的平均最小横截面尺寸。所述药物组合物还包括一种或多种眼科学上可接受的载体、添加剂和／或稀释剂。

[0008] 在另一组实施方案中，提供了一种适合于向眼局部施用的药物组合物。所述药物组合物包含多个包衣粒子，所述包衣粒子包含：包含依碳酸氯替泼诺的核心粒子，其中所述依碳酸氯替泼诺占所述核心粒子的至少约 80 重量％；以及包含一种或多种表面改变剂的包衣，其中所述一种或多种表面改变剂包含泊洛沙姆 (poloxamer)、聚乙烯醇或聚山梨醇酯中的至少一种。所述一种或多种表面改变剂以至少 0.01 个分子／平方纳米的密度存在于所述核心粒子的外表面上。所述一种或多种表面改变剂以约 0.001 重量％至约 5 重量％的量存在于所述药物组合物中。所述多个包衣粒子具有小于约 1 微米的平均最小横截面尺寸。所述药物组合物还包括一种或多种眼科学上可接受的载体、添加剂和／或稀释剂。

[0009] 在另一组实施方案中，提供了一系列方法。在一个实施方案中，提供了一种用于治疗患者眼的炎症、黄斑变性、黄斑水肿、葡萄膜炎、干眼症和／或其它病症的方法。所述方法包括向所述患者的眼施用包含多个包衣粒子的药物组合物。所述多个包衣粒子包含：包含依碳酸氯替泼诺的核心粒子，其中所述依碳酸氯替泼诺占所述核心粒子的至少约 80 重量％；以及围绕所述核心粒子的包含一种或多种表面改变剂的包衣。所述一种或多种表面改变剂包含以下中的至少一种：a) 包含亲水性嵌段－疏水性嵌段－亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量％；b) 合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30％水解且少于约 95％水解；或 c) 聚山梨醇酯。所述一种或多种表面改变剂以至少 0.01 个分子／平方纳米的密度存在于所述核心粒子的外表面上。所述一种或多种表面改变剂以约 0.001 重量％至约 5 重量％的量存在于所述药物组合物中。所述多个包衣粒子具有小于约 1 微米的平均最小横截面尺寸。所述药物组合物还包括一种或多种眼科学上可接受的载体、添加剂和／或稀释剂。

[0010] 在另一组实施方案中，提供了一种用于治疗患者眼的炎症、黄斑变性、黄斑水肿、葡萄膜炎、干眼症和／或其它病症的方法。所述方法包括向所述患者的眼施用包含多个包衣粒子的药物组合物，所述包衣粒子包含：包含依碳酸氯替泼诺的核心粒子，其中所述依碳

酸氯替泼诺占所述核心粒子的至少约 80 重量% ;以及包含一种或多种表面改变剂的包衣，其中所述一种或多种表面改变剂包含泊洛沙姆、聚乙烯醇或聚山梨醇酯中的至少一种。所述一种或多种表面改变剂以至少 0.01 个分子 / 平方纳米的密度存在于所述核心粒子的外表面上。所述一种或多种表面改变剂以约 0.001 重量%至约 5 重量%的量存在于所述药物组合物中。所述多个包衣粒子具有小于约 1 微米的平均最小横截面尺寸。所述药物组合物还包括一种或多种眼科学上可接受的载体、添加剂和 / 或稀释剂。

[0011] 在另一组实施方案中，提供了一种适合于向眼施用的药物组合物。所述药物组合物包括多个包衣粒子，所述包衣粒子包含核心粒子，所述核心粒子包含药剂或其盐。所述药剂或其盐占所述核心粒子的至少约 80 重量%，并且所述药剂或其盐包括受体酪氨酸激酶 (RTK) 抑制剂。所述多个包衣粒子还包括围绕所述核心粒子的包含一种或多种表面改变剂的包衣，其中所述一种或多种表面改变剂包含以下中的至少一种 :a) 包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量% ;b) 合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30%水解且少于约 95%水解 ;或 c) 聚山梨醇酯。所述一种或多种表面改变剂以至少 0.01 个分子 / 平方纳米的密度存在于所述核心粒子的外表面上。所述一种或多种表面改变剂以约 0.001 重量%至约 5 重量%的量存在于所述药物组合物中。所述多个包衣粒子具有小于约 1 微米的平均最小横截面尺寸。所述药物组合物还包括一种或多种眼科学上可接受的载体、添加剂和 / 或稀释剂。

[0012] 在另一组实施方案中，提供了一种用于治疗患者眼的黄斑变性、黄斑水肿和 / 或另一病症的方法。所述方法包括向所述患者的眼施用药物组合物，所述药物组合物包含多个包衣粒子，所述包衣粒子包含 :包含药剂或其盐的核心粒子，其中所述药剂或其盐占所述核心粒子的至少约 80 重量%，并且其中所述药剂或其盐包括受体酪氨酸激酶 (RTK) 抑制剂 ;以及围绕所述核心粒子的包含一种或多种表面改变剂的包衣。所述一种或多种表面改变剂包含以下中的至少一种 :

[0013] a) 包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量% ;

[0014] b) 合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30%水解且少于约 95%水解 ;或 c) 聚山梨醇酯。所述一种或多种表面改变剂以至少 0.01 个分子 / 平方纳米的密度存在于所述核心粒子的外表面上。所述一种或多种表面改变剂以约 0.001 重量%至约 5 重量%的量存在于所述药物组合物中。所述多个包衣粒子具有小于约 1 微米的平均最小横截面尺寸。所述药物组合物还包括一种或多种眼科学上可接受的载体、添加剂和 / 或稀释剂。

[0015] 在另一组实施方案中，提供了一种适合于向眼施用的药物组合物。所述药物组合物包含多个包衣粒子，所述包衣粒子包含 :包含药剂或其盐的核心粒子，其中所述药剂或其盐占所述核心粒子的至少约 80 重量%，并且其中所述药剂或其盐包括溴芬酸钙、双氯芬酸游离酸或酮咯酸游离酸 ;以及围绕所述核心粒子的包含一种或多种表面改变剂的包衣。所

述一种或多种表面改变剂包含以下中的至少一种 :a) 包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量% ;b) 合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30％水解且少于约 95％水解 ;或 c) 聚山梨醇酯。所述一种或多种表面改变剂以至少 0.01 个分子 / 平方纳米的密度存在于所述核心粒子的外表面上。所述一种或多种表面改变剂以约 0.001 重量％至约 5 重量％的量存在于所述药物组合物中。所述多个包衣粒子具有小于约 1 微米的平均最小横截面尺寸。所述药物组合物还包括一种或多种眼科学上可接受的载体、添加剂和 / 或稀释剂。

[0016] 在另一组实施方案中，提供了一种用于治疗患者眼的炎症、黄斑变性、黄斑水肿、葡萄膜炎、干眼症、青光眼和 / 或其它病症的方法。所述方法包括向所述患者的眼施用药物组合物，所述药物组合物包含多个包衣粒子，所述包衣粒子包含核心粒子，所述核心粒子包含药剂或其盐，其中所述药剂或其盐占所述核心粒子的至少约 80 重量％，并且其中所述药剂或其盐包括溴芬酸钙、双氯芬酸游离酸或酮咯酸游离酸。所述多个包衣粒子还包括围绕所述核心粒子的包含一种或多种表面改变剂的包衣，其中所述一种或多种表面改变剂包含以下中的至少一种 :a) 包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量% ;b) 合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30％水解且少于约 95％水解 ;或 c) 聚山梨醇酯。所述一种或多种表面改变剂以至少 0.01 个分子 / 平方纳米的密度存在于所述核心粒子的外表面上。所述一种或多种表面改变剂以约 0.001 重量％至约 5 重量％的量存在于所述药物组合物中。所述多个包衣粒子具有小于约 1 微米的平均最小横截面尺寸。所述药物组合物还包括一种或多种眼科学上可接受的载体、添加剂和 / 或稀释剂。

[0017] 在另一组实施方案中，提供了一种适合于向眼施用的药物组合物。所述药物组合物包含多个包衣粒子，所述包衣粒子包含包含药剂或其盐的核心粒子，所述药剂或其盐选自由以下组成的组 :皮质类固醇、受体酪氨酸激酶 (RTK) 抑制剂、环加氧酶 (COX) 抑制剂、血管生成抑制剂、前列腺素类似物、NSAID、β 阻断剂以及碳酸酐酶抑制剂。所述多个包衣粒子还包括围绕所述核心粒子的包含表面改变剂的包衣，其中所述一种或多种表面改变剂包含以下中的至少一种 :a) 包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量％，其中所述疏水性嵌段与所述核心粒子的表面缔合，并且其中所述亲水性嵌段存在于所述包衣粒子的表面并且使得所述包衣粒子具有亲水性 ;b) 合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30％水解且少于约 95％水解 ;或 c) 聚山梨醇酯。所述一种或多种表面改变剂以至少 0.01 个分子 / 平方纳米的密度存在于所述核心粒子的外表面上。所述一种或多种表面改变剂以约 0.001 重量％至约 5 重量％的量存在于所述药物组合物中。所述药物组合物还包括一种或多种眼科学上可接受的载体、添加剂和 / 或稀释剂。

[0018] 在另一组实施方案中，提供了一种治疗、诊断、预防或处理受试者的眼部病况的方法。所述方法包括向受试者的眼施用组合物，其中所述组合物包含多个包衣粒子，所述包衣粒子包含：包含药剂或其盐的核心粒子，所述药剂或其盐选自由以下组成的组：皮质类固醇、受体酪氨酸激酶（RTK）抑制剂、环加氧酶（COX）抑制剂、血管生成抑制剂、前列腺素类似物、NSAID、β 阻断剂以及碳酸酐酶抑制剂；以及围绕所述核心粒子的包含一种或多种表面改变剂的包衣。所述一种或多种表面改变剂包含以下中的至少一种：a）包含亲水性嵌段－疏水性嵌段－亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量％，其中所述疏水性嵌段与所述核心粒子的表面缔合，并且其中所述亲水性嵌段存在于所述包衣粒子的表面并且使得所述包衣粒子具有亲水性；或 b）合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30％水解且少于约 95％水解；或 c）聚山梨醇酯。所述方法包括向所述受试者的眼组织递送所述药剂。

[0019] 在另一组实施方案中，提供了一种改进药剂在受试者中的眼部生物利用度的方法。所述方法包括向所述受试者的眼施用组合物，其中所述组合物包含多个包衣粒子。所述包衣粒子包含：包含药剂或其盐的核心粒子，所述药剂或其盐选自由以下组成的组：皮质类固醇、受体酪氨酸激酶（RTK）抑制剂、环加氧酶（COX）抑制剂、血管生成抑制剂、前列腺素类似物、NSAID、β 阻断剂以及碳酸酐酶抑制剂；以及围绕所述核心粒子的包含表面改变剂的包衣。所述核心粒子上的所述包衣以足够的量存在以使得所述药剂在以所述组合物被施用时的眼部生物利用度与所述药剂在以没有所述包衣的核心粒子的形式被施用时的眼部生物利用度相比得以改进。

[0020] 在另一组实施方案中，提供了一种提高药剂在受试者的组织中的浓度的方法。所述方法包括向所述受试者的眼施用组合物，其中所述组合物包含多个包衣粒子。所述包衣粒子包含：包含所述药剂或其盐的核心粒子，其中所述药剂选自由以下组成的组：皮质类固醇、受体酪氨酸激酶（RTK）抑制剂、环加氧酶（COX）抑制剂、血管生成抑制剂、前列腺素类似物、NSAID、β 阻断剂以及碳酸酐酶抑制剂；以及围绕所述核心粒子的包含表面改变剂的包衣。所述组织选自由视网膜、黄斑、巩膜或脉络膜组成的组。所述核心粒子上的所述包衣以足够的量存在以使得所述药剂在以所述组合物被施用时在所述组织中的浓度与所述药剂在以没有所述包衣的核心粒子的形式被施用时在所述组织中的浓度相比增加了至少 10％。

[0021] 在另一组实施方案中，提供了一种通过重复施用药物组合物来治疗受试者的眼部病况的方法。所述方法包括

[0022] 向受试者的眼施用两剂量或更多剂量的包含依碳酸氯替泼诺的药物组合物，其中连续剂量之间的时间段是至少约 4 小时、至少约 6 小时、至少约 8 小时、至少约 12 小时、至少约 36 小时、或至少约 48 小时，其中向眼组织递送的依碳酸氯替泼诺的量有效治疗所述受试者的眼部病况。

[0023] 在另一组实施方案中，提供了一种通过重复施用药物组合物来治疗受试者的眼部病况的方法。所述方法包括向受试者的眼施用两剂量或更多剂量的包含一种或多种药剂的药物组合物，其中连续剂量之间的时间段是至少约 4 小时、至少约 6 小时、至少约 8 小时、至

少约 12 小时、至少约 36 小时、或至少约 48 小时。所述一种或多种药剂选自由以下组成的组 :依碳酸氯替泼诺、索拉非尼、利尼伐尼、MGCD-265、帕唑帕尼、西地尼布、阿西替尼、溴芬酸钙、双氯芬酸游离酸、酮咯酸游离酸以及它们的组合。向眼组织递送的所述药剂的量有效治疗所述受试者的眼部病况。

[0024] 在另一组实施方案中,提供了一种适合于通过向眼施用来治疗前眼部病症的药物组合物。所述药物组合物包含多个包衣粒子,所述包衣粒子包含 :包含皮质类固醇的核心粒子和围绕所述核心粒子的包含一种或多种表面改变剂的包衣。所述一种或多种表面改变剂包含以下中的至少一种 :a) 包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型的三嵌段共聚物,其中所述疏水性嵌段具有至少约 2kDa 的分子量,并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量% ;b) 合成聚合物,所述合成聚合物在所述聚合物的主链上具有侧羟基,所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量,其中所述聚合物至少约 30% 水解且少于约 95% 水解 ;或 c) 聚山梨醇酯。所述多个包衣粒子具有小于约 1 微米的平均最小横截面尺寸。所述核心粒子上的所述包衣以足够的量存在以使得所述皮质类固醇在向眼施用时在施用后 30 分钟时在所述眼的前部组成部分中的浓度与所述皮质类固醇在以没有所述包衣的核心粒子的形式被施用时在所述组织中的浓度相比增加了至少 50%,所述前部组成部分选自由角膜或房水组成的组。

[0025] 在另一组实施方案中,提供了一种通过向眼施用来治疗前眼部病症的方法。所述方法包括向受试者的眼施用组合物,其中所述组合物包含多个包衣粒子。所述多个包衣粒子包含 :包含皮质类固醇的核心粒子和围绕所述核心粒子的包含一种或多种表面改变剂的包衣。所述一种或多种表面改变剂包含以下中的至少一种 :a) 包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型的三嵌段共聚物,其中所述疏水性嵌段具有至少约 2kDa 的分子量,并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量% ;b) 合成聚合物,所述合成聚合物在所述聚合物的主链上具有侧羟基,所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量,其中所述聚合物至少约 30% 水解且少于约 95% 水解 ;或 c) 聚山梨醇酯。所述方法包括在施用后使所述皮质类固醇在前眼部组织中的眼科学上有效的水平持续至少 12 小时,所述前眼部组织选自由睑结膜、球结膜或角膜组成的组。

[0026] 根据以下对本发明的各个非限制性实施方案的详细说明,在结合附图一起考虑时,本发明的其它优势和新颖特征将变得显而易见。在本说明书和以引用方式并入的文献包括相互矛盾的和 / 或不一致的公开内容的情况下,应当以本说明书为准。如果以引用方式并入的两篇或更多篇文献包括相对于彼此相互矛盾的和 / 或不一致的公开内容,则应当以生效日期在后的文献为准。

附图说明

[0027] 将参考附图,以实施例的方式来描述本发明的非限制性实施方案,所述附图是示意性的并且并不意图按比例绘制。在附图中,所图示的每一个相同或几乎相同的元件通常由单一数字表示。为了清楚起见,并没有在每一幅图中标记出每一个元件,也没有显示本发明的每一个实施方案的每一个元件,其中图示说明对于使本领域的普通技术人员理解本发明来说不是必需的。在附图中 :

[0028] 图 1 是根据一组实施方案,具有包衣和核心的粘液穿透性粒子的示意图。

[0029] 图 2A 是显示根据一组实施方案，200nm 的羧化聚苯乙烯粒子（阴性对照）、200nm 的聚乙二醇化聚苯乙烯粒子（阳性对照）以及通过研磨制备并且被不同的表面改变剂包覆的纳米晶体粒子（样品）在人子宫颈阴道粘液 (CVM) 中的系综平均速度 $\langle V_{平均} \rangle$ 的图。

[0030] 图 2B 是显示根据一组实施方案，通过研磨制备并且被不同的表面改变剂包覆的纳米晶体粒子在 CVM 中的相对速度 $\langle V_{平均} \rangle_{相对}$ 的图。

[0031] 图 3A-3D 是显示根据一组实施方案，被不同的表面改变剂包覆的纳米晶体粒子的系综内在 CVM 中的轨迹平均速度 $V_{平均}$ 的分布的柱状图。

[0032] 图 4 是显示根据一组实施方案，相对于 PPO 嵌段的分子量和 PEO 重量含量（%）所标绘的被不同的 PEO-PPO-PEO Pluronic® 三嵌段共聚物包覆的纳米晶体粒子在 CVM 中的 $\langle V_{平均} \rangle_{相对}$ 的图。

[0033] 图 5 是显示根据一组实施方案，具有被 Pluronic® F127(MPP，粘液穿透性粒子）或十二烷基硫酸钠 (CP，常规粒子，阴性对照）包覆的不同核心物质的固体粒子穿过 CVM 的质量转移的图。

[0034] 图 6A-6C 显示根据一组实施方案，在施用商业处方依碳酸氯替泼诺、Lotemax®. 或被 Pluronic® F127 包覆的依碳酸氯替泼诺的粒子后依碳酸氯替泼诺在新西兰白兔 (New Zealand white rabbit) 的睑结膜（图 6A）、球结膜（图 6B) 以及角膜（图 6C) 中的药物水平。

[0035] 图 7A 是显示根据一组实施方案，被不同的聚乙烯醇 (PVA) 包覆的 $PSCOO^-$ 粒子在人子宫颈阴道粘液 (CVM) 中的系综平均速度 $\langle V_{平均} \rangle$ 的图。

[0036] 图 7B 是显示根据一组实施方案，被不同的 PVA 包覆的 $PSCOO^-$ 粒子在 CVM 中的相对速度 $\langle V_{平均} \rangle_{相对}$ 的图。

[0037] 图 8 是显示根据一组实施方案，根据 PVA 的分子量和水解度所标绘的与不同的 PVA 一起孵育的 $PSCOO^-$ 粒子在 CVM 中的相对速度 $\langle V_{平均} \rangle_{相对}$ 的图。每个数据点均表示使用特定的 PVA 稳定化的粒子的 $\langle V_{平均} \rangle_{相对}$。

[0038] 图 9A-9B 是显示根据一组实施方案，被不同的 PVA 包覆的 PSCOO 纳米粒子在体外在 CVM 中的总体转移的图。阴性对照是 200nm 无包衣的 PSCOO 粒子；阳性对照是 200nm 被 Pluronic® F127 包覆的 PSCOO 粒子。图 9A-9B 图示了使用两种不同的 CVM 样品所获得的数据。

[0039] 图 10A-10B 是显示根据一组实施方案，如通过在 CVM 中进行多粒子追踪所测量，通过使用不同的 PVA 乳化所制备的聚（乳酸）(PLA) 纳米粒子（样品）的系综平均速度 $\langle V_{平均} \rangle$（图 10A) 和相对样品速度 $\langle V_{平均} \rangle_{相对}$（图 10B) 的图。

[0040] 图 11 是显示根据一组实施方案，根据 PVA 的分子量和水解度所标绘的通过使用不同的 PVA 乳化所制备的 PLA 纳米粒子在 CVM 中的相对速度 $\langle V_{平均} \rangle_{相对}$ 的图。每个数据点均表示使用特定的 PVA 稳定化的粒子的 $\langle V_{平均} \rangle_{相对}$。

[0041] 图 12A-12B 是显示根据一组实施方案，如通过在 CVM 中进行多粒子追踪所测量，茫纳米粒子（样品）和对照的系综平均速度 $\langle V_{平均} \rangle$（图 12A) 和相对样品速度 $\langle V_{平均} \rangle_{相对}$（图 12B) 的图。

[0042] 图 13A-13F 是根据一组实施方案，使用不同的表面改变剂获得的茫 / 纳米晶体的代表性的 CVM 速度 ($V_{平均}$) 分布柱状图 (样品 = 茫纳米粒子，阳性对照 = 200nm 的 PS-PEG5K，阴性对照 = 200nm 的 PS-COO)。

[0043] 图 14 是根据一组实施方案，根据 PVA 的分子量和水解度所标绘的被 PVA 包覆的茫纳米晶体在 CVM 中的相对速度 $\langle V_{平均} \rangle_{相对}$ 的图。

[0044] 图 15A-15B 是显示根据一组实施方案，包括粘液层 (图 15B) 在内的眼的组成部分 (图 15A) 的示意图。

[0045] 图 15C 是显示根据一组实施方案，在局部滴注后眼部粘液层中的 MPP 和 CP 的示意图。MPP 可以容易地穿过外部粘液层向糖萼移动，而 CP 可能被固定在外粘液层中。身体天然的清除机制对外层的清除可以伴有 CP 的去除，而 MPP 保留在不太快速清除的糖萼中，从而使得在眼部表面的停留时间延长。

[0046] 图 16 是图示了根据一组实施方案，可以将局部施用的药物转运到眼后部的三条主要通路的示意图通过转移。

[0047] 图 17A-17B 是显示根据一组实施方案，在眼部 PK 研究中，在施用依碳酸氯替泼诺 (LE)MPP 制剂后 LE 在角膜中的水平高于在施用商业制剂后 LE 的水平的图。在 t = 0 时向新西兰白兔的眼局部施用相等的药物剂量。

[0048] 图 18 是显示根据一组实施方案，在滴眼剂滴注后 30 分钟 MPP (被 Pluronic® F127 包覆的依碳酸氯替泼诺纳米晶体) 在体内在眼部组织中的分布的图。向兔的每只眼中给予一次 50μL 剂量的 0.5％依碳酸氯替泼诺 MPP 制剂或商业滴剂 Lotemax®。对应当存在有人黄斑的视网膜、脉络膜以及巩膜进行采样。误差棒显示平均值的标准误差 (SEM，n = 6)。

[0049] 图 19 是显示根据一组实施方案，丙酸氟替卡松 (fluticasone propionate) 和依碳酸氯替泼诺纳米晶体的表面上 Pluronic® F127 的密度的条形图。

[0050] 图 20 是显示根据一组实施方案，相对于 PPO 嵌段的分子量和 PEO 重量含量 (％) 所标绘的通过在不同的 PEO-PPO-PEO Pluronic® 三嵌段共聚物存在下进行研磨所获得的依碳酸氯替泼诺纳米粒子的 CVM 移动性分数的图。评分准则如下 :0-0.5 分，不能移动 ;0.51-1.5 分，轻微移动 ;1.51-2.5 分，中度移动 ; 以及 2.51-3.0 分，高度移动。未能产生稳定的纳米悬浮液的样品用 * 标出并且被认为是不能移动的 (移动性分数 <0.5 分)。

[0051] 图 21 是显示以下制剂的向粘液中的质量转移数据的图 : 包含依碳酸氯替泼诺和 Pluronic® F127 的粘液穿透性粒子 (LE F127)、包含依碳酸氯替泼诺和十二烷基硫酸钠的粒子 (LE SDS)、以及市售制剂 Lotemax®。依碳酸氯替泼诺与 Pluronic® F127 的比率是 1:1(重量％)，而依碳酸氯替泼诺与 SDS 的比率是 50:1(重量％)。分别使用未处理的 200nm 羧化聚苯乙烯球粒和经 Pluronic® F127 处理的 200nm 羧化聚苯乙烯球粒作为阴性对照和阳性对照。

[0052] 图 22 显示依碳酸氯替泼诺的某些降解物的化学结构。

[0053] 图 23A-23B 是显示 LE 在体内在眼部组织中的药物代谢动力学 (PK) 的图。误差棒显示平均值的标准误差 (n = 6)。图 23A : 向兔的每只眼中给予一次 50μL 剂量的 0.5％

LE MPP 或 LE SDS。图 23B :向兔的每只眼中给予一次 50μL 剂量的 0.5% Lotemax® 或 LE SDS。Lotemax® 的数据是由在相同的设施中使用相同的技术进行的先前实验所获得的。

[0054] 图 24 是显示 LE 在体内在眼部组织中的药物代谢动力学的图。向兔的每只眼中给予一次 50μL 剂量的 0.5% Lotemax®、Lotemax® +F127、或 LE MPP。误差棒显示平均值的标准误差 (n = 6)。Lotemax® 的数据是由在相同的设施中使用相同的技术进行的先前实验所获得的。

[0055] 图 25 是显示 LE 在体内在眼部组织中的药物代谢动力学的图。向兔的每只眼中给予一次 50μL 剂量的 0.5% Lotemax® 或 0.4% LE MPP。误差棒显示平均值的标准误差 (n = 6)。

[0056] 图 26A-26R 是显示 LE 和它的两种主要代谢物 PJ-91 和 PJ-90 在体内在眼部组织 (例如结膜、角膜、房水、虹膜以及睫状体 (ICB) 和视网膜中央) 和血浆中的药物代谢动力学的图。向兔的每只眼中给予一次 50μL 剂量的 0.5% Lotemax® 或 0.4% LE MPP。误差棒显示平均值的标准误差 (n = 6)。

[0057] 图 27 是显示负载氟替卡松的各种聚乙二醇化 MPP 的体外释放曲线的图。释放条件 :37℃,含 0.5% Tween80 的 PBS。

[0058] 图 28A-28B 显示常规的纳米粒子 (图 28A) 和本文所述的 MPP(图 28B) 在人子宫颈阴道粘液中的代表性的 15 秒轨迹。MPP 避免了被截留并且能够扩散穿过粘液。

[0059] 图 29A-29B 是显示在单次局部滴注索拉非尼的 MPP(例如 MPP1 和 MPP2) 和非 MPP 对比物 (例如索拉非尼的水性悬浮液) 后在新西兰白兔的角膜 (图 29A) 和视网膜 (图 29B) 中的索拉非尼水平的图。误差棒显示平均值的标准误差 (n = 6)。

[0060] 图 30 是显示 LE 在体内在房水中的药物代谢动力学 (PK) 的图。向兔的每只眼中给予一次 35μL 剂量的 0.5% Lotemax® 凝胶或 0.4% LE MPP。误差棒显示平均值的标准误差 (n = 6)。

[0061] 图 31A 是显示 LE 在体内在新西兰白兔的房水中的药物代谢动力学的图。向兔的每只眼中给予一次 50μL 剂量的不同百分比的 LE MPP。误差棒显示平均值的标准误差 (n = 6)。

[0062] 图 31B 是显示 LE 在体内在新西兰白兔的房水中的 AUC_{0-6} 的图。向兔的每只眼中给予一次 50μL 剂量的不同百分比的 LE MPP。

[0063] 图 32 是显示 LE MPP 在离子组分 (如氯化钠) 存在下的稳定性的图。三角形 :0.45% 氯化钠。正方形 :0.9% 氯化钠。通过动态光散射 (DLS) 来监测 LE MPP。在第 -1 周时的尺寸表示在刚完成研磨之后并且在 LE MPP 在第 0 周即将被稀释至最终浓度之前 LE MPP 的粒度。图 32 指示 LE MPP 在氯化钠存在下是稳定的。

[0064] 图 33A 是显示 LE MPP 的粒子稳定性的图。通过动态光散射 (DLS) 来监测 LE MPP 的两个样品。一个样品已经曝露于 25kGy 的 γ 辐照,并且另一个样品没有曝露于 γ 辐照。

[0065] 图 33B 是显示 LE 在体内在新西兰白兔的角膜中的药物代谢动力学的图。向兔的每只眼中给予一次 50μL 剂量的包括 0.4% LE 的 LE MPP。误差棒显示平均值的标准误差

(n = 6)。

[0066] 图 34 是显示溴芬酸钙 MPP 在含有 MPP 的制剂中的示例性粒度分布的图。将溴芬酸钙在水、125mM 的 $CaCl_2$ 或 50mM 的 Tris 缓冲液中进行研磨。通过动态光散射来测量粒度。所有三种制剂均具有约 200nm 的 Z 均直径和 <0.2 的多分散指数。

[0067] 图 35A-35D 是显示包括溴芬酸钙的 MPP 在被储存在室温下时在一段较长的时间内稳定的图。图 35A :被稀释至 0.09% w/v 溴芬酸钙和 0.09% w/v Pluronic® F127(F127) 的浓度并且在室温下被储存 23 天的溴芬酸钙 (bromfenac-Ca)MPP 的 Z 均粒度。图 35B :被稀释至 0.09% w/v 溴芬酸钙和 0.09% w/v F127 的浓度并且在室温下被储存 23 天的溴芬酸钙 MPP 的多分散指数。图 35C :被稀释至 0.09% w/v 溴芬酸钙和 0.5% w/v F127 的浓度并且在室温下被储存 7 天或 12 天的溴芬酸钙 MPP 的 Z 均粒度。图 35D :被稀释至 0.09% w/v 溴芬酸钙和 0.5% w/v F127 的浓度并且在室温下被储存 7 天或 12 天的溴芬酸钙 MPP 的多分散指数。

[0068] 图 36A-36B 是显示索拉非尼和利尼伐尼在体内在新西兰白兔的视网膜中央冲压物 (center-punch) 中的药物代谢动力学的图。图 36A :向兔的每只眼中给予一次 50μL 剂量的 0.5%索拉非尼 -MPP 或 0.5%索拉非尼非 MPP 对照。误差棒显示平均值的标准误差 (n = 6)。图 36B :向兔的每只眼中给予一次 50μL 剂量的 2%利尼伐尼 -MPP 或 2%利尼伐尼非 MPP 对照。误差棒显示平均值的标准误差 (n = 6)。

[0069] 图 37A-37B 是显示帕唑帕尼和 MGCD-265 在体内在新西兰白兔的视网膜中央冲压物中的药物代谢动力学的图。图 37A :向兔的每只眼中给予一次 50μL 剂量的 0.5%帕唑帕尼 -MPP。误差棒显示平均值的标准误差 (n = 6)。还显示细胞 IC_{50} 以供参考。图 37B :向兔的每只眼中给予一次 50μL 剂量的 2% MGCD-265-MPP。误差棒显示平均值的标准误差 (n = 6)。还显示了细胞 IC_{50} 以供参考。

[0070] 图 38A-38B 是显示西地尼布在体内在 HY79b 有色兔 (pigmented rabbit) 的眼部组织中的药物代谢动力学的图。图 38A :向兔的脉络膜中给予一次 50μL 剂量的 2%西地尼布 -MPP。误差棒显示平均值的标准误差 (n = 6)。还显示了细胞 IC_{50} 以供参考。图 38B :向兔的视网膜中给予一次 50μL 剂量的 2%西地尼布 -MPP。误差棒显示平均值的标准误差 (n = 6)。还显示了细胞 IC_{50} 以供参考。

[0071] 图 39A-39B 是显示阿西替尼在体内在荷兰黑带兔 (Dutch belted rabbit) 的眼部组织中的药物代谢动力学的图。图 39A :向兔的脉络膜中给予一次 50μL 剂量的 2%阿西替尼 -MPP。误差棒显示平均值的标准误差 (n = 6)。还显示了细胞 IC_{50} 以供参考。图 39B :向兔的视网膜中给予一次 50μL 剂量的 2%阿西替尼 -MPP。误差棒显示平均值的标准误差 (n = 6)。还显示了细胞 IC_{50} 以供参考。

[0072] 图 40A-40C 是显示阿西替尼 -MPP 在兔 VEGF(血管内皮生长因子受体) 激发模型中的功效的图像。在第 1 天 - 第 6 天每 4 小时向荷兰黑带兔给予 50μL 的 5%阿西替尼 -MPP。在第 3 天,这些兔接受 VEGF 的玻璃体内注射。在第 6 天,通过荧光素血管造影术对这些兔的渗漏进行评估。在第 1 天 - 第 6 天,媒剂 (阴性对照) 组中的兔接受媒剂,每 4 小时一次。在第 1 天,Avastin® (阳性对照) 组中的兔接受一次 Avastin® 的玻璃体内注射。

[0073] 图 41 是显示含有双氯芬酸的粒子向人子宫颈阴道粘液中的总体转移的条形图。

使用不含表面改变剂的聚苯乙烯粒子 (PS) 作为非 MPP 阴性对照。使用含有处于核心中的聚苯乙烯和作为表面改变剂的 Pluronic® F127 的粒子 (PS F127) 作为 MPP 阳性对照。双氯芬酸 F127 代表含有处于核心中的双氯芬酸和作为表面改变剂的 Pluronic® F127 的粒子。双氯芬酸 SDS 代表含有处于核心中的双氯芬酸和作为表面改变剂的十二烷基硫酸钠 (SDS) 的粒子。

[0074] 图 42 是显示依碳酸氯替泼诺 (LE) 在体内在新西兰白兔的角膜中的药物代谢动力学的图。向兔的每只眼中给予一次 50 μ L 剂量的三种 LE-MPP (即 LE-F127、LE-Tween80 以及 LE-PVA) 中的每一种或 Lotemax®。PVA 具有约 2kDa 的分子量并且约 75％水解。LE 的剂量在所有情况下均为 0.5％。误差棒显示平均值的标准误差 (n = 6)。

[0075] 图 43 是显示包括某些表面改变剂包衣的依碳酸氯替泼诺 (LE) 粒子随分子量 (MW(Da)) 和疏水 - 亲水平衡 (HLB) 值而变化的粘液移动性的图。未形成处于目标范围内的粒子的样品被指示为“未配制”。

[0076] 图 44 是显示被不同的 PVA 包覆的依碳酸氯替泼诺 (LE) 粒子随 PVA 的分子量 (MW(kDa)) 和水解度 (水解％) 而变化的粘液移动性的图。未形成处于目标范围内的粒子的样品被指示为“未配制”。

[0077] 图 45 是显示阿西替尼在体内在视网膜中的 PK 的图。向兔的每只眼中给予一次 50 μ L 剂量的 0.5％阿西替尼 -MPP 或 0.5％阿西替尼非 MPP 对照。误差棒是 SEM(n = 6)。

[0078] 图 46 是显示在向朗 - 埃文斯 (Long Evans) 有色大鼠单次局部给予常规粒子 (CP) 和粘液穿透性粒子 (MPP) 后，这些粒子的眼部停留时间的差异的一组图像。

[0079] 图 47 是显示被 Pluronic® F127 包覆的聚苯乙烯粒子在粘液中的相对速度与粒子表面上 Pluronic® F127 分子的密度之间的关系的条形图。

具体实施方式

[0080] 提供了有助于粒子在粘液中转移的粒子、组合物以及方法。在一些情况下，所述粒子、组合物以及方法可以用于眼科应用和 / 或其它应用。在一些实施方案中，所述组合物和方法可以涉及对粒子，如具有低水溶解度的药剂的粒子的表面包衣进行改性。这些组合物和方法可以用于实现药剂粒子在体内有效转移穿过粘液屏障以用于广泛的应用，包括药物递送应用、成像应用以及诊断应用。在某些实施方案中，包括这些粒子的药物组合物非常适合于眼科应用，并且可以用于向眼前部、眼中部和 / 或眼后部递送药剂。

[0081] 有效转移穿过粘液屏障的粒子在本文可以被称为粘液穿透性粒子 (MPP)。这些粒子可以包括经过一种或多种表面改变剂改性的表面，与常规的粒子或非 MPP，即不包括所述一种或多种表面改变剂的粒子相比，所述一种或多种表面改变剂降低了这些粒子对粘液的粘着性，或者以其它方式增强了这些粒子穿过粘液屏障的转移。

[0082] 在一些实施方案中，所述粒子包含皮质类固醇，如依碳酸氯替泼诺以用于治疗眼疾病或病况。皮质类固醇可以例如存在于粒子的核心中。所述粒子包括表面改变剂，所述表面改变剂使所述粒子的表面改性以降低所述粒子对粘液的粘着性和 / 或促进粒子穿过生理性粘液。还提供了包括这些粒子的组合物，包括可以向眼局部施用的组合物。这些组

合物优于诸如 Lotemax® 或 Alrex® 等市售制剂，因为本文所述的组合物能够更容易地穿过眼部组织的粘液层以避免粘液粘着和 / 或快速的粘液清除或使粘液粘着和 / 或快速的粘液清除减到最低程度。因此，所述组合物可以被更有效地递送到靶标组织中并且可以在其中保留更长时间。因此，本文所述的组合物可以较市售的制剂更低的剂量和 / 或更低的频率被施用以实现相似的或更好的暴露。此外，所述组合物相对低的剂量和 / 或相对低频率的给药可以引起更少或严重度更低的副作用、更理想的毒性特征和 / 或改进的患者依从性。其它优势提供于下文中。

[0083] 在一些实施方案中，所述粒子包含一种或多种受体酪氨酸激酶抑制剂 (RTKi)，如索拉非尼、利尼伐尼、MGCD-265、帕唑帕尼、西地尼布、阿西替尼或其组合以用于治疗眼疾病或病况。所述一种或多种 RTKi 可以例如存在于粒子的核心中。还提供了包括这些粒子的组合物，包括可以向眼局部施用的组合物。出于本文所述的原因，这些组合物可以比某些常规制剂（例如相应 RTKi 的水性悬浮液）具有优势。

[0084] 在一些实施方案中，所述粒子包含非类固醇抗炎药 (NSAID)，如溴芬酸的二价金属盐（例如溴芬酸的二价金属盐，如溴芬酸钙）、双氯芬酸（例如双氯芬酸游离酸或其二价金属盐或三价金属盐，如双氯芬酸的碱土金属盐）、或酮咯酸（例如酮咯酸游离酸或其二价金属盐或三价金属盐，如酮咯酸的碱土金属盐）以用于治疗眼疾病或病况。NSAID 可以存在于例如粒子的核心中。还提供了包括这些粒子的组合物，包括可以向眼局部施用的组合物。出于本文所述的原因，这些组合物可以比某些常规制剂（例如溴芬酸钠的水溶液）具有优势。

[0085] 如下文所更详细地描述，在一些实施方案中，本文所述的粒子、组合物和 / 或制剂可以用于诊断、预防、治疗或处理处于眼后部，如处于视网膜、黄斑、脉络膜、巩膜和 / 或葡萄膜处的疾病或病况，和 / 或处于眼前部和 / 或眼中部，如处于角膜、结膜（包括睑结膜和球结膜）、虹膜以及睫状体处的疾病和病况。在一些实施方案中，所述粒子、组合物和 / 或制剂被设计成向眼局部施用。在其它实施方案中，所述粒子、组合物和 / 或制剂被设计成通过直接注射到眼中来施用。

[0086] 向眼局部地递送药物因角膜和巩膜（暴露于滴注物的组织）的有限渗透性以及眼的天然清除机制而具有挑战性：如处于常规的眼用溶液中的药物溶液通常会因引流和流泪而非常快速地从眼表面被冲走；并且如处于常规的眼用悬浮液中的药物粒子通常会被眼的快速清除的粘液层截留，并且因此也被快速地清除。因此，当前用于治疗眼前部的病况的常规眼用溶液和眼用悬浮液通常以高剂量和高频率被施用以实现并且维持功效。这种高频率高剂量的给药极大地降低了患者的依从性并且增大了局部不良作用的风险。向眼后部局部地递送药物因缺乏对局部滴注物的直接暴露并且因为与眼的这一部分有关的解剖学屏障和生理屏障而甚至更具挑战性。因此，当以常规的局部眼用溶液或眼用悬浮液的形式施用药物时，很少有（如果有的话）药物到达眼后部。因此，当前将诸如玻璃体内注射或眼周注射等有创性递送技术用于眼后部的病况。

[0087] 在一些情况下，本文所述的具有粘液穿透性的粒子、组合物和 / 或制剂可以解决这些与向眼前部（例如给药频率）和眼后部（例如足够的递送）递送有关的问题，因为所述粒子可以避免与粘液层粘着和 / 或可以更均匀地散布在眼表面上，从而避免了眼的天然清除机制并且延长了它们在眼部表面的停留时间。在一些实施方案中，所述粒子可以有效

地穿过生理性粘液以促进药物直接持续释放到下层组织中，如下文所更详细地描述。

[0088] 在一些实施方案中，本文所述的粒子具有核－壳型布置。核心可以包含任何合适的物质，如具有相对低的水溶解度的固体药剂或其盐、聚合载体、脂质和／或蛋白质。在一些实施方案中，核心还可以包含凝胶或液体。核心可以被包衣或壳包覆，所述包衣或壳包含促进粒子在粘液中的移动性的表面改变剂。如下文所更详细地描述，在一些实施方案中，表面改变剂可以包含聚合物（例如合成聚合物或天然聚合物），所述聚合物在聚合物的主链上具有侧羟基。所述聚合物的分子量和／或水解度可以经过选择以赋予所述粒子某些转移特征，如增强的穿过粘液的转移。在某些实施方案中，表面改变剂可以包含三嵌段共聚物，该三嵌段共聚物包含亲水性嵌段－疏水性嵌段－亲水性嵌段构型。所述嵌段中的每一个的分子量可以经过选择以赋予所述粒子某些转移特征，如增强的穿过粘液的转移。

[0089] 现在提供粒子的非限制性示例。如图 1 的说明性实施方案中所示，粒子 10 包括核心 16（其可以呈粒子形式，在本文中被称为核心粒子）和围绕该核心的包衣 20。在一组实施方案中，核心的实质部分由一种或多种可以产生某些有益作用和／或治疗作用的固体药剂（例如药物、治疗剂、诊断剂、成像剂）形成。核心可以是例如药剂的纳米晶体（即纳米晶体粒子）。在其它实施方案中，核心可以包括聚合载体，任选地与所封装的或以其它方式与核心缔合的一种或多种药剂。在另外的其它情况下，核心可以包括待向受试者递送的脂质、蛋白质、凝胶、液体和／或另一合适的物质。核心包括可以与一种或多种表面改变剂连接的表面 24。举例来说，在一些情况下，核心 16 由包衣 20 围绕，所述包衣 20 包括内表面 28 和外表面 32。包衣可以至少部分地由一种或多种表面改变剂 34，如聚合物（例如具有侧羟基的嵌段共聚物和／或聚合物）形成，所述一种或多种表面改变剂 34 可以与核心的表面 24 缔合。表面改变剂 34 可以通过例如以下方式与核心粒子缔合：与核心粒子共价连接、与核心粒子非共价连接、吸附到核心上、或通过离子相互作用、疏水性相互作用和／或亲水性相互作用、静电相互作用、范德华相互作用（van der Waals interaction）或其组合与核心连接。在一组实施方案中，所述表面改变剂或其部分经过选择以促进粒子转移穿过粘膜屏障（例如粘液或粘膜）。在本文所述的某些实施方案中，一种或多种表面改变剂 34 在粒子的包衣中以特定的构型进行定向。举例来说，在其中表面改变剂是三嵌段共聚物（如具有亲水性嵌段－疏水性嵌段－亲水性嵌段构型的三嵌段共聚物）的一些实施方案中，疏水性嵌段可以朝向核心表面定向，并且亲水性嵌段可以远离核心表面（例如朝向粒子的外部）定向。所述亲水性嵌段可以具有如下文所更详细地描述的促进粒子转移穿过粘膜屏障的特征。

[0090] 粒子 10 可以任选地包括一种或多种可以任选地赋予所述粒子以特异性的组分 40，如靶向部分、蛋白质、核酸以及生物活性剂。举例来说，如果存在靶向剂或靶向分子（例如蛋白质、核酸、核酸类似物、碳水化合物或小分子），那么其可以有助于将粒子引导到受试者体内的特定部位。该部位可以是例如组织、特定的细胞类型、或亚细胞区室。如果存在一种或多种组分 40，那么其可以与核心、包衣或这两者缔合；例如，它们可以与核心的表面 24、包衣的内表面 28、包衣的外表面 32 缔合和／或嵌入到包衣中。该一种或多种组分 40 可以通过共价键、吸收缔合或通过离子相互作用、疏水性相互作用和／或亲水性相互作用、静电相互作用、范德华相互作用或其组合连接。在一些实施方案中，可以使用本领域的普通技术人员已知的方法使组分与包衣粒子的一种或多种表面改变剂（例如共价）连接。

[0091] 应当了解的是，除图 1 中所示或本文所述的组分和构型以外的组分和构型可能适合于某些粒子和组合物，并且图 1 中所示的所有组分在一些实施方案中未必均存在。

[0092] 在一组实施方案中，粒子 10 在被引入到受试者体内时可以与受试者体内的一种或多种组成部分，如粘液、细胞、组织、器官、粒子、体液（例如血液）、其部分以及其组合相互作用。在一些这样的实施方案中，粒子 10 的包衣可以被设计成包括表面改变剂或其它组分，所述表面改变剂或其它组分具有允许与来自受试者的一种或多种物质发生有利的相互作用（例如转移、结合、吸附）的特性。举例来说，该包衣可以包括如下的表面改变剂或其它组分，所述表面改变剂或其它组分具有特定的亲水性、疏水性、表面电荷、官能团、结合特异性和 / 或密度以促进或减少在受试者体内的特定相互作用。一个具体的示例包括对一种或多种表面改变剂的特定的亲水性、疏水性、表面电荷、官能团、结合特异性和 / 或密度进行选择以减少粒子与受试者的粘液之间的物理相互作用和 / 或化学相互作用，以便增强粒子穿过粘液的移动性。其它示例更详细地描述于下文中。

[0093] 在一些实施方案中，一旦粒子成功地转移穿过受试者的粘膜屏障（例如粘液或粘膜），则粒子在受试者体内可以发生进一步的相互作用。在一些情况下，相互作用可以通过包衣和 / 或核心而发生，并且可以涉及例如物质（例如药剂、治疗剂、蛋白质、肽、多肽、核酸、营养物质）从受试者的一种或多种组成部分交换到粒子 10 中和 / 或从粒子 10 交换到受试者的一种或多种组成部分中。举例来说，在其中核心由药剂形成或包含药剂的一些实施方案中，来自粒子的药剂分解、释放和 / 或转移可以在受试者体内产生某些有益作用和 / 或治疗作用。因而，本文所述的粒子可以用于诊断、预防、治疗或处理某些疾病或身体病况。

[0094] 下文在本文所述的粒子适用于向受试者的粘膜屏障（例如粘液或粘膜）施用的情形下提供了使用这些粒子的具体实施例。应当了解的是，虽然本文在这种情形下以及在针对涉及物质穿过粘膜屏障转移的疾病和病况提供益处的情形下描述了许多的实施方案，但本发明不限于此并且本文所述的粒子、组合物、试剂盒以及方法可以用于预防、治疗或处理其它疾病或身体病况。

[0095] 粘液是一种粘稠的粘弹性凝胶，其在包括眼、鼻、肺、胃肠道以及女性生殖道在内的不同的体内进入点处抵御病原体、毒素以及碎片。许多合成的纳米粒子具有强粘膜粘着性并且被有效地截留在快速清除的外周粘液层中，从而极大地限制了它们在整个粘膜中的分布以及朝向下层组织的穿透性。这些被截留的粒子的停留时间受外周粘液层的转换率限制，取决于器官，所述转换率在数秒至数小时范围内。为了确保通过粘液膜有效地递送包括药剂（例如治疗剂、诊断剂和 / 或成像剂）的粒子，所述粒子必须能够容易地扩散穿过粘液屏障，从而避免粘液粘着。如下文所更详细地描述，在眼粘液中递送粒子具有特别的挑战。

[0096] 最近已经证实，使用粘液穿透性包衣对聚合纳米粒子的表面进行改性可以使得对粘液的粘着性减到最低程度并且因此允许粒子快速地穿过粘液屏障。虽然存在这些改进，但仅有少数的表面包衣已显示促进粒子的粘液穿透性。因此，对涉及用于递送药剂的粘液穿透性粒子的组合物和方法进行改进将是有益的。

[0097] 在一些实施方案中，本文所述的组合物和方法涉及不含任何聚合载体或使用最少量的聚合载体的粘液穿透性粒子。在一些实施方案中，基于聚合物的粘液穿透性粒子可能具有一种或多种固有的限制。具体来说，根据药物递送应用，这些限制可以包括以下中的一种或多种 :A) 低药物封装效率和低药物负载 :将药物封装到聚合粒子中的效率往往很低，

因为一般所用药物总量的不到10％在制造期间被封装到粒子中。此外，很少实现高于50％的药物负载。B) 使用的方便性：基于负载药物的聚合粒子的制剂一般通常需要以干粉剂的形式被储存以避免过早的药物释放，并且因此需要在使用时复原或复杂的给药装置。C) 生物相容性：在重复给药后缓慢降解的聚合物载体长期以来的积聚以及它们的毒性造成聚合药物载体的主要问题。D) 化学稳定性和物理稳定性：聚合物降解可能损害所封装的药物的稳定性。在许多封装工艺中，药物经历了从溶液相向固相的转变，所述转变在逐渐形成的固相的物理形式（即无定形对结晶对结晶多晶型物）方面并未受到良好控制。这对于包括物理稳定性和化学稳定性以及释放动力学在内的制剂性能的多个方面来说是个问题。E) 制造的复杂性：负载药物的聚合MPP的制造，特别是按比例缩放(scalability)是一个相当复杂的过程，可能涉及多个步骤和大量的毒性有机溶剂。

[0098] 在本文所述的一些实施方案中，制备粒子的组合物和方法（包括用于制备具有增强的穿过粘膜屏障的转移的粒子的某些组合物和方法）解决了上文所述的问题中的一个或多个或者全部。具体地说，在一些实施方案中，所述组合物和方法不涉及封装到聚合载体中或涉及使用最少量的聚合载体。有利地，通过避免对将药剂（例如药物、成像剂或诊断剂）封装到聚合载体中的需要或使这种需要减到最低程度，可以解决聚合MPP在药物负载、使用方便性、生物相容性、稳定性和/或制造复杂性方面的某些限制。本文所述的方法和组合物可以促进粘液穿透性粒子技术的临床研发。

[0099] 然而，应当了解的是，在其它实施方案中，可以通过封装或其它方法使药剂与聚合物载体缔合。因此，本文所提供的说明在这一方面不受限制。举例来说，虽然某些包括聚合载体的粘液穿透性粒子存在上述缺点，但在某些实施方案中，这些粒子可以是优选的。举例来说，可能优选的是，为了实现控制释放的目的和/或为了封装某些难以被配制成粒子的药剂而使用聚合物载体。因而，在本文所述的一些实施方案中，描述了包括聚合物载体的粒子。

[0100] 如下文所更详细地描述，在一些实施方案中，所述组合物和方法涉及使用有助于粒子在粘液中转移的PVA。所述组合物和方法可以涉及在特定PVA存在下通过例如乳化方法来制备粘液穿透性粒子(MPP)。在某些实施方案中，所述组合物和方法涉及通过使用特定的PVA进行非共价包覆从预制的粒子制备MPP。在其它实施方案中，所述组合物和方法涉及在特定的PVA存在下，在不存在任何聚合载体的情况下或在使用最少量的聚合载体的情况下制备MPP。然而，应当了解的是，在其它实施方案中，可以使用聚合载体。

[0101] PVA是水溶性的非离子型合成聚合物。由于它的表面活性特性，因此PVA在食品和药品工业中被广泛地用作乳液的稳定剂，并且尤其被用于使得能够通过乳化技术来封装多种多样的化合物。PVA已经获得了美国食品和药物管理局(Food and Drug Administration，FDA)的“公认安全(generally recognized as safe)”或“GRAS”认证，并且已经被用于耳部、肌内、眼内、玻璃体内、离子电渗、眼科、口服、局部以及透皮药物产品和/或药物递送系统中。

[0102] 在某些先前的研究中，许多研究已经将PVA描述为粘膜粘着性聚合物，表明或报道了在粒子配制过程中并入PVA会产生具有强粘膜粘着性的粒子。令人惊讶地，并且与认为PVA是粘膜粘着性聚合物的公认观点相反，本发明人在本发明的背景内已经发现利用特定PVA等级的组合物和方法有助于粒子在粘液中转移并且在本文所述的某些应用中不具

粘膜粘着性。具体地说，可以通过调控 PVA 的水解度和 / 或分子量来制备粘液穿透性粒子，这是先前未知的。这一发现显著地扩大了适用于制造 MPP 的技术和成分的范围。

[0103] 在本文所述的一些实施方案中，制备粒子的组合物和方法（包括用于制备具有增强的穿过粘膜屏障的转移的粒子的某些组合物和方法）解决了上文所述的问题中的一个或多个或者全部。

[0104] 应当了解的是，虽然本文中的一些说明可能涉及在包衣中使用 PVA，但在其它实施方案中，不使用 PVA 或将 PVA 结合其它聚合物一起使用。举例来说，在一些实施方案中，在本文所述的组合物和方法中可以包括 PEG、Pluronics® 和 / 或其它表面活性剂（例如聚山梨醇酯（例如 Tween 80®））（代替 PVA 或连同 PVA 一起）。在其它实施方案中，在本文所述的包衣中可以使用其它聚合物，如本文所更详细地描述的那些聚合物。

[0105] 如下文所更详细地描述，在一些实施方案中，所述组合物和方法涉及使用有助于粒子在粘液中转移的泊洛沙姆。泊洛沙姆通常是包含由两个亲水性嵌段（例如聚环氧乙烷嵌段）侧接的中心疏水性嵌段（例如聚环氧丙烷嵌段）的非离子型三嵌段共聚物。泊洛沙姆具有商品名 Pluronic®，其示例提供于下文中。

[0106] 如下文所更详细地描述，在某些实施方案中，所述组合物和方法涉及使用有助于粒子在粘液中转移的聚山梨醇酯。聚山梨醇酯通常衍生自被脂肪酸酯化的聚乙二醇化的脱水山梨糖醇（山梨糖醇的衍生物）。聚山梨醇酯的常见商标名称包括 Tween®、Alkest®、Canarcel®。聚山梨醇酯的示例包括聚氧乙烯脱水山梨糖醇单油酸酯（例如 Tween 80®）、聚氧乙烯脱水山梨糖醇单硬脂酸酯（例如 Tween 60®）、聚氧乙烯脱水山梨糖醇单棕榈酸酯（例如 Tween 40®）、以及聚氧乙烯脱水山梨糖醇单月桂酸酯（例如 Tween 20®）。

[0107] 核心粒子

[0108] 如上文参考图 1 所述，粒子 10 可以包括核心 16。该核心可以由任何合适的物质，如有机物质、无机物质、聚合物、脂质、蛋白质或其组合形成。在一组实施方案中，核心包含固体。固体可以是例如结晶或无定形固体，如结晶或无定形固体药剂（例如治疗剂、诊断剂和 / 或成像剂）或其盐。在其它实施方案中，核心可以包含凝胶或液体（例如水包油乳液或油包水乳液）。在一些实施方案中，在核心中可以存在多于一种药剂。药剂的具体示例更详细地提供于下文中。

[0109] 药剂可以任何合适的量存在于核心中，例如核心的至少约 0.01 重量%、至少约 0.1 重量%、至少约 1 重量%、至少约 5 重量%、至少约 10 重量%、至少约 20 重量%、至少约 30 重量%、至少约 40 重量%、至少约 50 重量%、至少约 60 重量%、至少约 70 重量%、至少约 80 重量%、至少约 85 重量%、至少约 90 重量%、至少约 95 重量%、或至少约 99 重量%。在一个实施方案中，核心由 100 重量%的药剂形成。在一些情况下，药剂可以如下量存在于核心中：少于或等于约 100 重量%、少于或等于约 90 重量%、少于或等于约 80 重量%、少于或等于约 70 重量%、少于或等于约 60 重量%、少于或等于约 50 重量%、少于或等于约 40 重量%、少于或等于约 30 重量%、少于或等于约 20 重量%、少于或等于约 10 重量%、少于

或等于约 5 重量%、少于或等于约 2 重量%、或者少于或等于约 1 重量%。上述范围的组合也是可能的（例如以至少约 80 重量%并且少于或等于约 100 重量%的量存在）。其它范围也是可能的。

[0110] 在其中核心粒子包含相对高的量的药剂（例如核心粒子的至少约 50 重量%）的实施方案中，与通过将药剂封装到聚合载体中所形成的粒子相比，核心粒子一般具有增加的药剂负载。这对于药物递送应用来说是一种优势，因为更高的药物负载意味着与使用含有聚合载体的粒子相比，可能需要更少数目的粒子来实现所需的作用。

[0111] 如本文所述，在其中相对高的量的聚合物或其它物质形成核心的其它实施方案中，在核心中可以存在较少量的药剂。

[0112] 所述核心可以由具有各种水溶解度（即在任选地含有一种或多种缓冲剂的水中的溶解度）和 / 或在其中固体物质被表面改变剂包覆的溶液中具有各种溶解度的固体物质形成。举例来说，所述固体物质在 25℃可以具有以下水溶解度（或在包衣溶液中的溶解度）：小于或等于约 5mg/mL、小于或等于约 2mg/mL、小于或等于约 1mg/mL、小于或等于约 0.5mg/mL、小于或等于约 0.1mg/mL、小于或等于约 0.05mg/mL、小于或等于约 0.01mg/mL、小于或等于约 1μg/mL、小于或等于约 0.1μg/mL、小于或等于约 0.01μg/mL、小于或等于约 1ng/mL、小于或等于约 0.1ng/mL、或者小于或等于约 0.01ng/mL。在一些实施方案中，固体物质可以具有以下水溶解度（或在包衣溶液中的溶解度）：至少约 1pg/mL、至少约 10pg/mL、至少约 0.1ng/mL、至少约 1ng/mL、至少约 10ng/mL、至少约 0.1μg/mL、至少约 1μg/mL、至少约 5μg/mL、至少约 0.01mg/mL、至少约 0.05mg/mL、至少约 0.1mg/mL、至少约 0.5mg/mL、至少约 1.0mg/mL、至少约 2mg/mL。上述范围的组合是可能的（例如至少约 10pg/mL 并且小于或等于约 1mg/mL 的水溶解度或在包衣溶液中的溶解度）。其它范围也是可能的。固体物质在整个 pH 值范围（例如从 pH 1 至 pH 14）内的任一点均可以具有这些范围或其它范围的水溶解度。

[0113] 在一些实施方案中，核心可以由处于由美国药典委员会 (U.S.Pharmacopeia Convention) 分类的溶解度范围中的一个范围内的物质形成：例如极易溶：>1,000mg/mL；易溶：100-1,000mg/mL；可溶：33-100mg/mL；难溶：10-33mg/mL；微溶：1-10mg/mL；极微溶：0.1-1mg/mL；以及几乎不溶：<0.1mg/mL。

[0114] 虽然核心可以是疏水的或亲水的，但在本文所述的许多实施方案中，核心基本上是疏水的。“疏水的”和“亲水的”被给予它们在本领域中普通的含义，并且如将由本领域技术人员所了解，在本文许多情况下，是相对术语。物质的相对疏水性和相对亲水性可以通过例如使用诸如接触角测角计等仪器和压紧的核心物质的粉末测量水滴在待测量的物质的平面表面上的接触角来测定。

[0115] 在一些实施方案中，物质（例如形成粒子核心的物质）具有以下接触角：至少约 20 度、至少约 30 度、至少约 40 度、至少约 50 度、至少约 60 度、至少约 70 度、至少约 80 度、至少约 90 度、至少约 100 度、至少约 110 度、至少约 120 度、或至少约 130 度。在一些实施方案中，物质具有以下接触角：小于或等于约 160 度、小于或等于约 150 度、小于或等于约 140 度、小于或等于约 130 度、小于或等于约 120 度、小于或等于约 110 度、小于或等于约 100 度、小于或等于约 90 度、小于或等于约 80 度、或者小于或等于约 70 度。上述范围的组合也是可能的（例如至少约 30 度并且小于或等于约 120 度的接触角）。其它范围也是可能的。

[0116] 可以使用多种技术来进行接触角测量；在此，提及了将被用于形成核心的起始物质的丸粒与水珠之间的静态接触角测量。用于形成核心的物质以细粉形式收到或者另外使用研钵和研杵将其研磨成细粉。为了形成在上面进行测量的表面，使用来自国际晶体实验室公司（International Crystal Labs）的7mm丸粒模组将粉末压紧。将所述物质添加到模具中并且用手施加压力以将粉末压成丸粒，未使用压丸机或高压。然后使丸粒悬空以进行测试，使得丸粒的顶部和底部（分别被定义为添加水的表面和相对的平行表面）不与任何表面接触。这通过不将丸粒从模组的衬圈中完全取出来进行。丸粒因此在侧面上触及衬圈并且在顶部或底部不发生接触。为了进行接触角测量，将水添加到丸粒的表面直到获得在30秒内具有稳定的接触角的水珠为止。通过浸没或接触用于向水珠进行添加的吸移管或注射器的尖端来向水珠中添加水。一旦获得稳定的水珠，则拍摄图像并且使用标准操作规程测量接触角。

[0117] 在其中核心包含无机物质（例如用作成像剂）的实施方案中，所述无机物质可以包括例如金属（例如Ag、Au、Pt、Fe、Cr、Co、Ni、Cu、Zn以及其它过渡金属）、半导体（例如硅、硅化合物和合金、硒化镉、硫化镉、砷化铟以及磷化铟）、或绝缘体（例如陶瓷，如氧化硅）。无机物质可以任何合适的量存在于核心中，例如至少约1重量％、至少约5重量％、至少约10重量％、至少约20重量％、至少约30重量％、至少约40重量％、至少约50重量％、至少约75重量％、至少约90重量％、或至少约99重量％。在一个实施方案中，核心由100重量％的无机物质形成。在一些情况下，无机物质可以如下量存在于核心中：少于或等于约100重量％、少于或等于约90重量％、少于或等于约80重量％、少于或等于约70重量％、少于或等于约60重量％、少于或等于约50重量％、少于或等于约40重量％、少于或等于约30重量％、少于或等于约20重量％、少于或等于约10重量％、少于或等于约5重量％、少于或等于约2重量％、或者少于或等于约1重量％。上述范围的组合也是可能的（例如以至少约1重量％并且少于或等于约20重量％的量存在）。其它范围也是可能的。

[0118] 在一些情况下，核心可以呈量子点、碳纳米管、碳纳米线或碳纳米棒的形式。在一些情况下，核心包含并非生物源性的物质或由并非生物源性的物质形成。

[0119] 在一些实施方案中，核心包括一种或多种有机物质，如合成聚合物和/或天然聚合物。合成聚合物的示例包括不可降解的聚合物（如聚甲基丙烯酸酯）和可降解的聚合物（如聚乳酸、聚乙醇酸以及其共聚物）。天然聚合物的示例包括透明质酸、壳聚糖以及胶原蛋白。可能适用于核心部分的聚合物的其它示例包括本文中适合于形成粒子上的包衣的那些聚合物，如下文所述。在一些情况下，可以使用核心中存在的一种或多种聚合物来封装或吸附一种或多种药剂。

[0120] 在某些实施方案中，核心可以包括包含脂质和/或蛋白质的药剂。其它物质也是可能的。

[0121] 如果在核心中存在聚合物，那么所述聚合物可以任何合适的量存在于核心中，例如少于或等于约100重量％、少于或等于约90重量％、少于或等于约80重量％、少于或等于约70重量％、少于或等于约60重量％、少于或等于约50重量％、少于或等于约40重量％、少于或等于约30重量％、少于或等于约20重量％、少于或等于约10重量％、少于或等于约5重量％、少于或等于约2重量％、或者少于或等于约1重量％。在一些情况下，所述聚合物可以如下量存在于核心中：至少约1重量％、至少约5重量％、至少约10重量％、至

少约 20 重量%、至少约 30 重量%、至少约 40 重量%、至少约 50 重量%、至少约 75 重量%、至少约 90 重量%、或至少约 99 重量%。上述范围的组合也是可能的（例如以至少约 1 重量%并且少于或等于约 20 重量%的量存在）。其它范围也是可能的。在一组实施方案中，所形成的核心基本上不含聚合组分。

[0122] 本文所述的粒子的核心可以包括超过一种聚合物的混合物。在一些实施方案中，核心或至少一部分核心包括第一聚合物与第二聚合物的混合物。在某些实施方案中，第一聚合物是本文所述的聚合物。在某些实施方案中，第一聚合物是相对疏水性聚合物（例如较第二聚合物具有更高的疏水性的聚合物）。在某些实施方案中，第一聚合物不是聚烷基醚。在某些实施方案中，第一聚合物是聚丙交酯 (PLA)，例如 100DL7A MW108K。在某些实施方案中，第一聚合物是聚丙交酯 - 共 - 乙交酯 (PLGA)，例如 PLGA1A MW4K。然而，在其它实施方案中，第一聚合物可以是相对亲水性聚合物（例如较第二聚合物具有更高的亲水性的聚合物）。

[0123] 在某些实施方案中，第二聚合物是本文所述的嵌段共聚物（例如二嵌段共聚物或三嵌段共聚物）。在某些实施方案中，第二聚合物是包括相对亲水性嵌段（例如聚烷基醚嵌段）和相对疏水性嵌段（例如非（聚烷基醚）嵌段）的二嵌段共聚物。在某些实施方案中，第二聚合物的聚烷基醚嵌段是 PEG（例如 PEG2K 或 PEG5K）。在某些实施方案中，第二聚合物的非（聚烷基醚）嵌段是 PLA（例如 100DL9K、100DL30 或 100DL95）。在某些实施方案中，第二聚合物的非（聚烷基醚）嵌段是 PLGA（例如 8515PLGA54K、7525PLGA15K 或 5050PLGA18K）。在某些实施方案中，第二聚合物是 100DL9K- 共 -PEG2K。在某些实施方案中，第二聚合物是 8515PLGA54K- 共 -PEG2K。

[0124] 应当了解的是，虽然描述了“第一”聚合物和“第二”聚合物，但在一些实施方案中，本文所述的粒子或核心可以仅包括一种这样的聚合物。此外，虽然提供了第一聚合物和第二聚合物的具体示例，但应当了解的是，可以使用其它聚合物，如本文所列的聚合物作为第一聚合物或第二聚合物。

[0125] 第一聚合物和第二聚合物的相对疏水性嵌段可以是相同或不同的聚合物。在一些情况下，第二聚合物的相对亲水性嵌段主要存在于包括第一聚合物和第二聚合物的核心的表面处或存在于所述核心的表面上。举例来说，第二聚合物的相对亲水性嵌段可以充当如本文所述的表面改变剂。在一些情况下，第二聚合物的相对疏水性嵌段和第一聚合物主要存在于包括第一聚合物和第二聚合物的核心的表面内部。另外的详情提供于实施例 19 中。

[0126] 第二聚合物的相对亲水性嵌段（例如聚烷基醚嵌段，如 PEG 嵌段）可以具有任何合适的分子量。在某些实施方案中，第二聚合物的相对亲水性嵌段的分子量是至少约 0.1kDa、至少约 0.2kDa、至少约 0.5kDa、至少约 1kDa、至少约 1.5kDa、至少约 2kDa、至少约 2.5kDa、至少约 3kDa、至少约 4kDa、至少约 5kDa、至少约 6kDa、至少约 8kDa、至少约 10kDa、至少约 20kDa、至少约 50kDa、至少约 100kDa、或至少约 300kDa。在某些实施方案中，第二聚合物的相对亲水性嵌段的分子量小于或等于约 300kDa、小于或等于约 100kDa、小于或等于约 50kDa、小于或等于约 20kDa、小于或等于约 10kDa、小于或等于约 8kDa、小于或等于约 6kDa、至少约 5kDa、小于或等于约 4kDa、小于或等于约 3kDa、小于或等于约 2.5kDa、小于或等于约 2kDa、小于或等于约 1.5kDa、小于或等于约 1kDa、小于或等于约 0.5kDa、小于或等于约 0.2kDa、或者小于或等于约 0.1kDa。上述范围的组合也是可能的（例如至少约 0.5kDa

并且小于或等于约 10kDa)。其它范围也是可能的。在某些实施方案中,第二聚合物的相对亲水性嵌段的分子量是约 2kDa。在某些实施方案中,第二聚合物的相对亲水性嵌段的分子量是约 5kDa。

[0127] 第二聚合物的相对疏水性嵌段(例如非(聚烷基醚)嵌段,如 PLGA 嵌段或 PLA 嵌段)可以具有任何合适的分子量。在某些实施方案中,第二聚合物的相对疏水性嵌段具有相对短的长度和/或低的分子量。在某些实施方案中,第二聚合物的相对疏水性嵌段的分子量小于或等于约 300kDa、小于或等于约 100kDa、小于或等于约 80kDa、小于或等于约 60kDa、小于或等于约 54kDa、小于或等于约 50kDa、小于或等于约 40kDa、小于或等于约 30kDa、小于或等于约 20kDa、小于或等于约 15kDa、小于或等于约 10kDa、小于或等于约 5kDa、小于或等于约 2kDa、或者小于或等于约 1kDa。在某些实施方案中,第二聚合物的 PLGA 嵌段或 PLA 嵌段的分子量是至少约 0.1kDa、至少约 0.3kDa、至少约 1kDa、至少约 2kDa、至少约 4kDa、至少约 6kDa、至少约 7kDa、至少约 8kDa、至少约 9kDa、至少约 10kDa、至少约 12kDa、至少约 15kDa、至少约 20kDa、至少约 30kDa、至少约 50kDa、或至少约 100kDa。上述范围的组合也是可能的(例如小于或等于约 20kDa 并且至少约 1kDa)。其它范围也是可能的。在某些实施方案中,第二聚合物的相对疏水性嵌段的分子量是约 9kDa。

[0128] 第二聚合物的相对亲水性嵌段(例如聚烷基醚嵌段,如 PEG 嵌段)可以任何合适的量或密度存在于本文所述的核心的表面处或存在于本文所述的核心的表面上。在某些实施方案中,第二聚合物的 PEG 嵌段以如下的密度存在于核心的表面处或存在于核心的表面上:每平方纳米核心的表面积至少约 0.001 条、至少约 0.003 条、至少约 0.03 条、至少约 0.1 条、至少约 0.15 条、至少约 0.18 条、至少约 0.2 条、至少约 0.3 条、至少约 0.5 条、至少约 1 条、至少约 3 条、至少约 30 条、或至少约 100 条 PEG 链。在某些实施方案中,第二聚合物的 PEG 嵌段以如下的密度存在于核心的表面处或存在于核心的表面上:每平方纳米核心的表面积少于或等于约 100 条、少于或等于约 30 条、少于或等于约 10 条、少于或等于约 3 条、少于或等于约 1 条、少于或等于约 0.5 条、少于或等于约 0.3 条、少于或等于约 0.2 条、少于或等于约 0.18 条、少于或等于约 0.15 条、少于或等于约 0.1 条、少于或等于约 0.03 条、少于或等于约 0.01 条、少于或等于约 0.003 条、或者少于或等于约 0.001 条 PEG 链。上述范围的组合也是可能的(例如每平方纳米核心的表面积至少约 0.03 条并且少于或等于约 1 条 PEG 链)。其它范围也是可能的。在某些实施方案中,第二聚合物的 PEG 嵌段以每平方纳米核心的表面积至少约 0.18 条 PEG 链存在于核心的表面处或存在于核心的表面上。

[0129] 第二聚合物的相对亲水性嵌段(例如聚烷基醚嵌段,如 PEG 嵌段)可以任何合适的量存在于本文所述的粒子或核心中。在某些实施方案中,第二聚合物的相对亲水性嵌段以如下量存在于核心中:所述粒子或核心的少于或等于约 90 重量%、少于或等于约 80 重量%、少于或等于约 70 重量%、少于或等于约 60 重量%、少于或等于约 50 重量%、少于或等于约 40 重量%、少于或等于约 30 重量%、少于或等于约 20 重量%、少于或等于约 10 重量%、少于或等于约 5 重量%、少于或等于约 4 重量%、少于或等于约 3 重量%、少于或等于约 2 重量%、少于或等于约 1 重量%、少于或等于约 0.5 重量%、少于或等于约 0.2 重量%、少于或等于约 0.1 重量%、少于或等于约 0.05 重量%、少于或等于约 0.02 重量%、或者少于或等于约 0.01 重量%。在某些实施方案中,第二聚合物的相对亲水性嵌段以如下量存在于核心中:所述粒子或核心的至少约 0.01 重量%、至少约 0.02 重量%、至少约 0.05 重

量%、至少约 0.1 重量%、至少约 0.2 重量%、至少约 0.5 重量%、至少约 1 重量%、至少约 2 重量%、至少约 3 重量%、至少约 4 重量%、至少约 5 重量%、至少约 10 重量%、至少约 20 重量%、至少约 30 重量%、至少约 40 重量%、至少约 50 重量%、至少约 60 重量%、至少约 70 重量%、至少约 80 重量%、或至少约 90 重量%。上述范围的组合也是可能的（例如所述粒子或核心的少于或等于约 10 重量%并且至少约 0.5 重量%）。其它范围也是可能的。在某些实施方案中，第二聚合物的相对亲水性嵌段以所述粒子或核心的少于或等于约 3 重量%存在。

[0130] 第二聚合物的相对亲水性嵌段（例如聚烷基醚嵌段，如 PEG 嵌段）和相对疏水性嵌段（例如非（聚烷基醚）嵌段，如 PLGA 嵌段或 PLA 嵌段）可以任何合适的比率存在于核心中。在某些实施方案中，第二聚合物的相对亲水性嵌段与相对疏水性嵌段的比率是至少约 1:99、至少约 10:90、至少约 20:80、至少约 30:70、至少约 40:60、至少约 50:50、至少约 60:40、至少约 70:30、至少约 80:20、至少约 90:10、或至少约 99:1w/w。在某些实施方案中，相对亲水性嵌段与相对疏水性嵌段的比率小于或等于约 99:1、小于或等于约 90:10、小于或等于约 80:20、小于或等于约 70:30、小于或等于约 60:40、小于或等于约 50:50、小于或等于约 40:60、小于或等于约 30:70、小于或等于约 20:80、小于或等于约 10:90、或者小于或等于约 1:99w/w。上述范围的组合也是可能的（例如大于约 70:30 并且小于或等于约 90:10w/w）。其它范围也是可能的。在某些实施方案中，相对亲水性嵌段与相对疏水性嵌段的比率是约 20:80w/w。

[0131] 第一聚合物（例如 PLA 或 PLGA）和第二聚合物（例如 PLA- 共 -PEG 或 PLGA- 共 -PEG）可以任何合适的比率存在于粒子或核心中。在某些实施方案中，粒子或核心中第一聚合物与第二聚合物的比率是至少约 1:99、至少约 10:90、至少约 20:80、至少约 30:70、至少约 40:60、至少约 50:50、至少约 60:40、至少约 65:35、至少约 70:30、至少约 75:25、至少约 80:20、至少约 85:15、至少约 90:10、至少约 95:5、或至少约 99:1w/w。在某些实施方案中，粒子或核心中第一聚合物与第二聚合物的比率小于或等于约 99:1、小于或等于约 95:5、小于或等于约 90:10、小于或等于约 85:15、小于或等于约 80:20、小于或等于约 75:25、小于或等于约 70:30、小于或等于约 65:35、小于或等于约 60:40、小于或等于约 50:50、小于或等于约 40:60、小于或等于约 30:70、小于或等于约 20:80、小于或等于约 10:90、或者小于或等于约 1:99w/w。上述范围的组合也是可能的（例如大于约 70:30 并且小于或等于约 90:10w/w）。其它范围也是可能的。在某些实施方案中，粒子或核心中第一聚合物与第二聚合物的比率是约 70:30w/w。在某些实施方案中，粒子或核心中第一聚合物与第二聚合物的比率是约 80:20w/w。

[0132] 本文所述的包含第一聚合物与第二聚合物的混合物的粒子或核心可以进一步包括本文所述的包衣。包衣可以处于粒子的表面处或处于粒子的表面上（例如第一聚合物和 / 或第二聚合物的表面）。在一些实施方案中，包衣包括亲水性物质。包衣可以包括本文所述的一种或多种表面改变剂，如聚合物、稳定剂和 / 或表面活性剂（例如 PVA、泊洛沙姆、聚山梨醇酯（例如 Tween 80®））。

[0133] 核心可以具有任何合适的形状和 / 或尺寸。举例来说，核心可以基本上呈球形、非球形、椭圆形、棒状、锥体形、立方体样、圆盘形、线样或不规则形状。核心可以具有例如以下的最大或最小横截面尺寸：小于或等于约 10μm、小于或等于约 5μm、小于或等于约 1μm、

小于或等于约 800nm、小于或等于约 700nm、小于或等于约 500nm、小于或等于 400nm、小于或等于 300nm、小于或等于约 200nm、小于或等于约 100nm、小于或等于约 75nm、小于或等于约 50nm、小于或等于约 40nm、小于或等于约 35nm、小于或等于约 30nm、小于或等于约 25nm、小于或等于约 20nm、小于或等于约 15nm、或者小于或等于约 5nm。在一些情况下，核心可以具有例如以下的最大或最小横截面尺寸：至少约 5nm、至少约 20nm、至少约 50nm、至少约 100nm、至少约 200nm、至少约 300nm、至少约 400nm、至少约 500nm、至少约 1μm、或至少约 5μm。上述范围的组合也是可能的（例如至少约 50nm 并且小于或等于约 500nm 的最大或最小横截面尺寸）。其它范围也是可能的。在一些实施方案中，由本文所述的方法形成的核心的尺寸具有高斯型分布 (Gaussian-type distribution)。除非另外指明，否则粒子 / 核心尺寸的测量结果在本文中指的是最小横截面尺寸。

[0134] 本领域的普通技术人员熟悉测定粒子尺寸（例如最小或最大横截面尺寸）的技术。合适的技术的示例包括 (DLS)、透射电子显微镜法、扫描电子显微镜法、电致电阻计数以及激光衍射。其它合适的技术为本领域的普通技术人员所知。虽然用于测定粒子尺寸的许多方法是已知的，但本文所述的尺寸（例如平均粒度、厚度）指的是通过动态光散射所测量的尺寸。

[0135] 形成核心粒子和包衣粒子的方法

[0136] 本文所述的核心粒子可以通过任何合适的方法形成。合适的方法可以包括例如所谓的自顶向下技术 (top-down technique)，即基于将相对大的粒子尺寸减小成较小粒子的技术（例如研磨或均质化）；或所谓的自底向上技术 (bottom-up technique)，即基于粒子从较小的粒子或单个分子增长的技术（例如沉淀或喷雾冷冻成液体）。

[0137] 在一些实施方案中，可以使用包衣包覆核心粒子。举例来说，可以在第一步骤中提供或形成核心粒子，然后可以在第二步骤中对粒子进行包覆以形成包衣粒子。在其它实施方案中，可以基本上同时（例如在单个步骤中）形成核心粒子并对其进行包覆。这些方法和其它方法的示例提供于下文中。

[0138] 在一些实施方案中，通过涉及使用配制工艺、研磨工艺和 / 或稀释工艺的方法形成本文所述的包衣粒子。在某些实施方案中，形成粒子的方法包括研磨工艺，任选地其与配制工艺和 / 或稀释工艺一起。可以使用配制工艺来形成包含核心物质、一种或多种表面改变剂以及其它组分的悬浮液或溶液，所述其它组分如溶剂、张力剂、螯合剂、盐、抗微生物剂和 / 或缓冲剂（例如柠檬酸钠和柠檬酸缓冲剂），这些物质中的每一种均如本文所述。可以使用配制容器进行配制工艺。可以将核心物质和其它组分同时或不同时添加到配制容器中。可以在容器中对核心物质和 / 或一种或多种其它组分的混合物进行搅拌和 / 或振荡或以其它方式进行搅动以促进组分悬浮和 / 或溶解。还可以单独地升高或降低含有核心物质、其它组分和 / 或混合物的流体的温度和 / 或压力以促进悬浮和 / 或溶解过程。在一些实施方案中，如本文所述在配制容器中在惰性气氛（例如氮气或氩气）下和 / 或在避光的情况下对核心物质和其它组分进行处理。随后可以对从配制容器中获得的悬浮液或溶液进行研磨工艺，之后可以进行稀释工艺。

[0139] 在涉及包含固体物质的核心的一些实施方案中，可以使用研磨工艺来减小固体物质的尺寸以形成在微米至纳米尺寸范围内的粒子。可以使用磨机或其它合适的设备来进行研磨工艺。诸如喷射研磨、冷冻研磨、球磨研磨、介质研磨、超声处理以及均质化等干磨工艺

和湿磨工艺是已知的并且可以用于本文所述的方法中。一般来说，在湿磨工艺中，在存在或不存在赋形剂的情况下对待用作核心的物质的悬浮液进行搅动以减小粒度。干磨是其中将待用作核心的物质与研磨介质在存在或不存在赋形剂的情况下混合以减小粒度的工艺。在冷冻研磨工艺中，在存在或不存在赋形剂的情况下在冷却的温度下将待用作核心的物质的悬浮液与研磨介质混合。

[0140] 在进行研磨工艺或其它合适的工艺以减小核心物质的尺寸之后，可以使用稀释工艺由悬浮液形成包衣粒子和 / 或对包衣粒子进行改性。所述包衣粒子可以包含核心物质、一种或多种表面改变剂以及其它组分，如溶剂、张力剂、螯合剂、盐、抗微生物剂以及缓冲剂（例如柠檬酸钠和柠檬酸缓冲剂）。可以使用稀释工艺以通过在添加或不添加表面改变剂和 / 或其它组分的情况下对研磨步骤期间被包覆的粒子的溶液或悬浮液进行稀释来实现目标给药浓度。在某些实施方案中，可以使用稀释工艺用第二表面改变剂将第一表面改变剂从如本文所述的粒子的表面交换下来。

[0141] 可以使用产品容器或任何其它合适的设备来进行稀释工艺。在某些实施方案中，在产品容器中对悬浮液进行稀释，即与稀释剂混合或以其它方式使用稀释剂进行处理。稀释剂可以含有如本文所述的溶剂、表面改变剂、张力剂、螯合剂、盐或抗微生物剂、或其组合。可以同时或不同时将悬浮液和稀释剂添加到产品容器中。在某些实施方案中，当由涉及研磨介质的研磨工艺获得悬浮液时，可以在将悬浮液添加到产品容器中之前将研磨介质与悬浮液分离。可以对悬浮液、稀释剂或悬浮液与稀释剂的混合物进行搅拌和 / 或振荡或以其它方式进行搅动以形成本文所述的包衣粒子。还可以单独地升高或降低悬浮液、稀释剂或混合物的温度和 / 或压力以形成包衣粒子。在一些实施方案中，在产品容器中在惰性气氛（例如氮气或氩气）下和 / 或在避光的情况下对悬浮液和稀释剂进行处理。

[0142] 在一些实施方案中，可以通过在一种或多种表面改变剂存在下对固体物质（例如药剂）进行研磨来产生本文所述的核心粒子。固体物质的小粒子可能需要一种或多种表面改变剂的存在，所述一种或多种表面改变剂在一些实施方案中可以用作稳定剂，以便使粒子的悬浮液稳定而不会在液体溶液中聚结或聚集。在一些这样的实施方案中，稳定剂可以充当表面改变剂，在粒子上形成包衣。

[0143] 如本文所述，在一些实施方案中，形成核心粒子的方法涉及选择适用于研磨并且适用于在粒子上形成包衣且使粒子具有粘液穿透性的表面改变剂。举例来说，如下文所更详细地描述，已经证实，通过在某些Pluronics®聚合物存在下对茆进行研磨所产生的模型化合物茆的200nm-500nm纳米粒子产生了可以与公认的聚乙二醇化聚合MPP相同的速率穿过生理性粘液样品的粒子。有趣的是，观测到只有一部分所测试的Pluronics®聚合物符合适用于研磨并且适用于在粒子上形成使得粒子具有粘液穿透性的包衣的准则，如下文所更详细地描述。

[0144] 在湿磨工艺中，可以在含有一种或多种表面改变剂、研磨介质、待研磨的固体（例如固体药剂）以及溶剂的分散体（例如水性分散体）中进行研磨。在溶剂中可以包括任何合适量的表面改变剂。在一些实施方案中，表面改变剂可以如下量存在于溶剂中：溶剂的至少约0.001％（重量％或％重量：体积(w:v)）、至少约0.01％、至少约0.1％、至少约0.5％、至少约1％、至少约2％、至少约3％、至少约4％、至少约5％、至少约6％、至少约7％、至少约8％、至少约10％、至少约12％、至少约15％、至少约20％、至少约40％、至少约60％、或

至少约80％。在一些情况下，表面改变剂可以约100％的量存在于溶剂中（例如在表面改变剂是溶剂的情况下）。在其它实施方案中，表面改变剂可以如下量存在于溶剂中：溶剂的少于或等于约100％、少于或等于约80％、少于或等于约60％、少于或等于约40％、少于或等于约20％、少于或等于约15％、少于或等于约12％、少于或等于约10％、少于或等于约8％、少于或等于约7％、少于或等于约6％、少于或等于约5％、少于或等于约4％、少于或等于约3％、少于或等于约2％、或者少于或等于约1％。上述范围的组合也是可能的（例如溶剂的少于或等于约5％并且至少约1％的量）。其它范围也是可能的。在某些实施方案中，表面改变剂以溶剂的约0.01％-2％的量存在于溶剂中。在某些实施方案中，表面改变剂以溶剂的约0.2％-20％的量存在于溶剂中。在某些实施方案中，表面改变剂以溶剂的约0.1％的量存在于溶剂中。在某些实施方案中，表面改变剂以溶剂的约0.4％的量存在于溶剂中。在某些实施方案中，表面改变剂以溶剂的约1％的量存在于溶剂中。在某些实施方案中，表面改变剂以溶剂的约2％的量存在于溶剂中。在某些实施方案中，表面改变剂以溶剂的约5％的量存在于溶剂中。在某些实施方案中，表面改变剂以溶剂的约10％的量存在于溶剂中。

[0145] 所选择的具体范围可能影响可以影响粒子穿透粘液的能力的因素，如粒子表面上表面改变剂包衣的稳定性、粒子上表面改变剂包衣的平均厚度、粒子上表面改变剂的定向、粒子上表面改变剂的密度、表面改变剂与药物的比率、药物浓度、所形成的粒子的尺寸、分散性以及多分散性、以及所形成的粒子的形态。

[0146] 药剂（或其盐）可以任何合适的量存在于溶剂中。在一些实施方案中，药剂（或其盐）以如下量存在：溶剂的至少约0.001％（重量％或％重量：体积(w:v)）、至少约0.01％、至少约0.1％、至少约0.5％、至少约1％、至少约2％、至少约3％、至少约4％、至少约5％、至少约6％、至少约7％、至少约8％、至少约10％、至少约12％、至少约15％、至少约20％、至少约40％、至少约60％、或至少约80％。在一些情况下，药剂（或其盐）可以如下量存在于溶剂中：溶剂的少于或等于约100％、少于或等于约90％、少于或等于约80％、少于或等于约60％、少于或等于约40％、少于或等于约20％、少于或等于约15％、少于或等于约12％、少于或等于约10％、少于或等于约8％、少于或等于约7％、少于或等于约6％、少于或等于约5％、少于或等于约4％、少于或等于约3％、少于或等于约2％、或者少于或等于约1％。上述范围的组合也是可能的（例如溶剂的少于或等于约20％并且至少约1％的量）。在一些实施方案中，药剂以上述范围存在，但以w:v计。

[0147] 溶剂中表面改变剂与药剂（或其盐）的比率也可以变化。在一些实施方案中，表面改变剂与药剂（或其盐）的比率可以是至少0.001:1（重量比、摩尔比或w:v比）、至少0.01:1、至少0.01:1、至少1:1、至少2:1、至少3:1、至少5:1、至少10:1、至少25:1、至少50:1、至少100:1、或至少500:1。在一些情况下，表面改变剂与药剂（或其盐）的比率可以小于或等于1000:1（重量比或摩尔比）、小于或等于500:1、小于或等于100:1、小于或等于75:1、小于或等于50:1、小于或等于25:1、小于或等于10:1、小于或等于5:1、小于或等于3:1、小于或等于2:1、小于或等于1:1、或者小于或等于0.1:1。上述范围的组合是可能的（例如至少5:1并且小于或等于50:1的比率）。其它范围也是可能的。

[0148] 表面改变剂的示例提供于下文中，并且可以包括例如聚合物、稳定剂以及表面活性剂。如本文所述，在一些实施方案中，表面改变剂例如在形成粒子期间可以充当稳定剂、表面活性剂和/或乳化剂。在一些实施方案中，表面改变剂可以有助于粒子在粘液中转移。

[0149] 应当了解的是，虽然在一些实施方案中，用于研磨的稳定剂在粒子表面上形成包衣，所述包衣使得粒子具有粘液穿透性，但在其它实施方案中，可以在粒子已经形成之后将所述稳定剂与一种或多种其它表面改变剂交换。举例来说，在一组方法中，可以在研磨工艺期间使用第一稳定剂 / 表面改变剂，并且所述第一稳定剂 / 表面改变剂可以包覆核心粒子的表面，然后可以将第一稳定剂 / 表面改变剂的全部或部分与第二稳定剂 / 表面改变剂交换以包覆核心粒子表面的全部或部分。在一些情况下，第二稳定剂 / 表面改变剂与第一稳定剂 / 表面改变剂相比可以使得粒子更具粘液穿透性。在一些实施方案中，可以形成具有包括多种表面改变剂的包衣的核心粒子。

[0150] 可以使用任何合适的研磨介质进行研磨。在一些实施方案中，可以使用陶瓷和 / 或聚合材料和 / 或金属。合适的材料的示例可以包括氧化锆、碳化硅、氧化硅、氮化硅、硅酸锆、氧化钇、玻璃、氧化铝 (alumina)、α 型氧化铝、氧化铝 (aluminum oxide)、聚苯乙烯、聚 (甲基丙烯酸甲酯)、钛、钢。研磨介质可以具有任何合适的尺寸。举例来说，研磨介质可以具有以下平均直径 : 至少约 0.1mm、至少约 0.2mm、至少约 0.5mm、至少约 0.8mm、至少约 1mm、至少约 2mm、或至少约 5mm。在一些情况下，研磨介质可以具有以下平均直径 : 小于或等于约 5mm、小于或等于约 2mm、小于或等于约 1mm、小于或等于约 0.8、小于或等于约 0.5mm、或者小于或等于约 0.2mm。上述范围的组合也是可能的 (例如至少约 0.5 毫米并且小于或等于约 1mm 的平均直径)。其它范围也是可能的。

[0151] 可以使用任何合适的溶剂进行研磨。溶剂的选择可以取决于诸如以下的因素 : 所研磨的固体物质 (例如药剂)、所使用的稳定剂 / 表面改变剂的具体类型 (例如可以使得粒子具有粘液穿透性的稳定剂 / 表面改变剂)、所使用的研磨材料以及其它因素。合适的溶剂可以是不使得固体物质或研磨材料基本上溶解，但使得稳定剂 / 表面改变剂溶解至合适的程度的溶剂。溶剂的非限制性示例可以包括水、缓冲溶液、其它水溶液、醇 (例如乙醇、甲醇、丁醇) 以及其混合物，所述溶剂可以任选地包括其它组分，如药物赋形剂、聚合物、药剂、盐、防腐剂、粘度调节剂、张力调节剂、掩味剂、抗氧化剂、pH 值调节剂以及其它药物赋形剂。在其它实施方案中，可以使用有机溶剂。药剂在这些溶剂或其它溶剂中可以具有任何合适的溶解度，如上文关于水溶解度或在包衣溶液中的溶解度所述的范围中的一个或多个范围内的溶解度。

[0152] 在表面改变剂存在下，可以通过对相对不溶于水的固体物质 (例如药物) 进行研磨来产生粒子 (例如纳米粒子)。某些表面改变剂除了有助于在研磨期间减小粒度之外，还可以一定方式改变所得粒子的表面，所述方式使得粒子与粘液成分的相互作用减到最低程度并且防止和 / 或减少粘液粘着，从而使得粒子具有粘液穿透性，如本文所更详细地描述。

[0153] 在其它实施方案中，可以通过乳化技术 (乳化) 形成核心粒子。一般来说，乳化技术可以涉及将待用作核心的物质溶解或分散在溶剂中 ; 然后在第二不混溶性溶剂中使这种溶液或分散体乳化，从而形成包含该物质的多个粒子。合适的乳化技术可以包括形成水包油乳液、油包水乳液、水 - 油 - 水乳液、油 - 水 - 油乳液、水包油包固体乳液以及油包水包固体乳液等，后续进行或不进行溶剂去除 (例如通过蒸发或萃取)。乳化技术是通用的并且可用于制备包含具有相对低的水溶解度的药剂以及具有相对高的水溶解度的药剂的核心粒子。

[0154] 在一些实施方案中，可以通过在一种或多种表面改变剂存在下进行乳化来产生本

文所述的核心粒子。在一些这样的实施方案中，稳定剂可以充当表面改变剂，在粒子上形成包衣（即乳化步骤和包衣步骤可以基本上同时进行）。

[0155] 在一些实施方案中，通过乳化形成核心粒子的方法涉及选择适用于乳化并且适用于在粒子上形成包衣且使得粒子具有粘液穿透性的稳定剂。举例来说，如下文所更详细地描述，已经证实，通过在某些 PVA 聚合物存在下进行乳化所产生的模型聚合物 PLA 的 200nm-500nm 纳米粒子产生了可以与公认的聚乙二醇化聚合 MPP 相同的速率穿过生理性粘液样品的粒子。有趣的是，观测到只有一部分所测试的 PVA 聚合物符合适用于乳化并且适用于在粒子上形成使得粒子具有粘液穿透性的包衣的准则，如下文所更详细地描述。

[0156] 在其它实施方案中，首先使用乳化技术形成粒子，之后使用表面改变剂包覆这些粒子。

[0157] 可以使用任何合适的溶剂和溶剂组合进行乳化。可以用作油相的溶剂的一些示例是有机溶剂，如氯仿、二氯甲烷、乙酸乙酯、乙醚、石油醚（己烷、庚烷）、以及油类，如花生油、棉籽油、红花油、芝麻油、橄榄油、玉米油、大豆油、以及硅酮油。可以用作水相的溶剂的一些示例是水和水性缓冲液。其它溶剂也是可能的。

[0158] 在其它实施方案中，可以通过沉淀技术形成核心粒子。沉淀技术（例如微量沉淀技术、纳米沉淀技术、结晶技术、控制结晶技术）可以涉及形成包含待用作核心的物质（例如药剂）和溶剂的第一溶液，其中所述物质基本上可溶于所述溶剂中。可以将该溶液添加到包含所述物质基本上不溶于其中的另一种溶剂（即反溶剂）的第二溶液中，从而形成包含所述物质的多个粒子。在一些情况下，在第一溶液和 / 或第二溶液中可以存在一种或多种表面改变剂、表面活性剂、物质和 / 或生物活性剂。可以在使核心沉淀的过程中形成包衣（例如，沉淀步骤和包衣步骤可以基本上同时进行）。在其它实施方案中，首先使用沉淀技术形成粒子，之后使用表面改变剂包覆这些粒子。

[0159] 在一些实施方案中，可以使用沉淀技术形成含有或不含药剂的聚合核心粒子。一般来说，沉淀技术涉及将待用作核心的聚合物溶解在溶剂（存在或不存在药剂）中，然后将溶液添加到可混溶的反溶剂（存在或不存在赋形剂）中以形成核心粒子。在一些实施方案中，这种技术可用于制备例如包含在水溶液中微溶 (1-10mg/L)、极微溶 (0.1-1mg/mL) 或几乎不溶 (<0.1mg/mL) 的药剂（例如具有相对低的水溶解度的药剂）的聚合核心粒子。

[0160] 可以使用任何合适的溶剂进行沉淀。在一些实施方案中，对于沉淀合适的溶剂可以包括例如丙酮、乙腈、二甲基甲酰胺、二甲亚砜、N- 甲基 -2- 吡咯烷酮、2- 吡咯烷酮、四氢呋喃。还可以使用其它有机溶剂和非有机溶剂。

[0161] 可以使用任何合适的反溶剂进行沉淀，包括本文所述的可以用于研磨的溶剂。在一组实施方案中，使用水溶液（例如水、缓冲溶液、其它水溶液、以及醇，如乙醇、甲醇、丁醇）、以及其混合物，其可以任选地包括其它组分，如药物赋形剂、聚合物以及药剂。

[0162] 用于乳化和沉淀的表面改变剂可以是聚合物、稳定剂或表面活性剂，包括本文所述的可以用于研磨的表面改变剂。

[0163] 适用于通过乳化或沉淀形成核心的全部或部分的合适聚合物的非限制性示例可以包括聚胺、聚醚、聚酰胺、聚酯、聚氨基甲酸酯、聚脲、聚碳酸酯、聚苯乙烯、聚酰亚胺、聚砜、聚氨酯、聚乙炔、聚乙烯、聚乙烯亚胺、聚异氰酸酯、聚丙烯酸酯、聚甲基丙烯酸酯、聚丙烯腈、聚芳酯、多肽、多核苷酸以及多糖。具体聚合物的非限制性示例包括聚（己内酯）

(PCL)、乙烯 - 乙酸乙烯酯聚合物 (EVA)、聚 (乳酸)(PLA)、聚 (L- 乳酸)(PLLA)、聚 (乙醇酸)(PGA)、聚 (乳酸 - 共 - 乙醇酸)(PLGA)、聚 (L- 乳酸 - 共 - 乙醇酸)(PLLGA)、聚 (D,L- 丙交酯)(PDLA)、聚 (L- 丙交酯)(PLLA)、聚 (D,L- 丙交酯 - 共 - 己内酯)、聚 (D,L- 丙交酯 - 共 - 己内酯 - 共 - 乙交酯)、聚 (D,L- 丙交酯 - 共 -PEO- 共 -D,L- 丙交酯)、聚 (D,L- 丙交酯 - 共 -PPO- 共 -D,L- 丙交酯)、聚氰基丙烯酸烷基酯、聚氨酯、聚 -L- 赖氨酸 (PLL)、甲基丙烯酸羟丙酯 (HPMA)、聚乙二醇、聚 -L- 谷氨酸、聚 (羟基酸)、聚酐、聚原酸酯、聚 (酯酰胺)、聚酰胺、聚 (酯醚)、聚碳酸酯 ;聚烯烃,如聚乙烯和聚丙烯 ;聚亚烷基二醇,如聚乙二醇 (PEG) ;聚环氧烷 (PEO) ;聚对苯二甲酸亚烷基酯,如聚 (对苯二甲酸乙二酯) ;聚乙烯醇 (PVA)、聚乙烯醚 ;聚乙烯酯,如聚 (乙酸乙烯酯) ;聚卤乙烯,如聚 (氯乙烯)(PVC) ;聚乙烯吡咯烷酮、聚硅氧烷、聚苯乙烯 (PS)、聚氨酯 ;衍生纤维素,如烷基纤维素、羟烷基纤维素、纤维素醚、纤维素酯、硝基纤维素、羟丙基纤维素、羧甲基纤维素 ;丙烯酸的聚合物,如聚 ((甲基) 丙烯酸甲酯)(PMMA)、聚 ((甲基) 丙烯酸乙酯)、聚 ((甲基) 丙烯酸丁酯)、聚 ((甲基) 丙烯酸异丁酯)、聚 ((甲基) 丙烯酸己酯)、聚 ((甲基) 丙烯酸异癸酯)、聚 ((甲基) 丙烯酸月桂酯)、聚 ((甲基) 丙烯酸苯酯)、聚 (丙烯酸甲酯)、聚 (丙烯酸异丙酯)、聚 (丙烯酸异丁酯)、聚 (丙烯酸十八酯)(在本文统称为“聚丙烯酸”)、以及其共聚物和混合物 ;聚二氧杂环己酮和它的共聚物、聚羟基烷酸酯、聚反丁烯二酸丙二酯、聚甲醛、泊洛沙姆、聚 (原酸) 酯、聚 (丁酸)、聚 (戊酸)、聚 (丙交酯 - 共 - 己内酯)、以及三亚甲基碳酸酯、聚乙烯吡咯烷酮、牛血清白蛋白、人血清白蛋白、胶原蛋白、DNA、RNA、羧甲基纤维素、壳聚糖、葡聚糖。

[0164] 适用于形成核心和 / 或表面改变剂的全部或部分的聚合物还可以包括聚乙二醇 - 维生素 E 缀合物 (在下文中,称为“PEG-VitE 缀合物”)。包括 PEG-VitE 缀合物的粒子、组合物和 / 或制剂以及制备和使用所述粒子、组合物和 / 或制剂的方法更详细地提供于国际 PCT 申请公开 WO2012/061703 中,该国际 PCT 申请公开出于所有目的以引用的方式整体并入本文中。在一些情况下,PEG-VitE 缀合物的 PEG 部分的分子量大于约 2kDa。PEG-VitE 缀合物的 PEG 部分的分子量可以经过选择以有助于如本文所述穿过粘膜屏障的粒子形成和 / 或转移。在一些实施方案中,与使用 PEG 部分具有小于约 2kDa 的分子量的 PEG-VitE 缀合物相比,使用 PEG 部分具有大于约 2kDa 的分子量的 PEG-VitE 缀合物可以允许粒子更大程度地穿过粘膜屏障。此外,在某些实施方案中,具有更高分子量的 PEG 部分可以促进药物封装。与用于药物封装的其它常用表面活性剂相比,充当表面活性剂与降低粘膜粘着性的组合能力提供了重要的益处。在一些情况下,PEG-VitE 缀合物的 PEG 部分的分子量是约 2kDa 到约 8kDa、或约 3kDa 到约 7kDa、或约 4kDa 到约 6kDa、或约 4.5kDa 到约 6.5kDa、或约 5kDa。

[0165] 在一些实施方案中,可以使用沉淀技术形成主要包含药剂的粒子 (例如纳米晶体)。一般来说,这种沉淀技术涉及将待用作核心的药剂溶解在溶剂中,然后在存在或不存在赋形剂的情况下将其添加到可混溶的反溶剂中以形成核心粒子。在一些实施方案中,这种技术可用于制备例如在水溶液中微溶 (1-10mg/L)、极微溶 (0.1-1mg/mL) 或几乎不溶 (<0.1mg/mL) 的药剂 (例如具有相对低的水溶解度的药剂) 的粒子。

[0166] 在一些实施方案中,可以使用通过盐 (或络合物) 形成而进行的沉淀来形成药剂的盐的粒子 (例如纳米晶体)。一般来说,通过盐形成而进行的沉淀包括在存在或不存在赋

形剂的情况下将待用作核心的物质溶解在溶剂中，之后添加抗衡离子或络合剂，所述抗衡离子或络合剂与药剂形成不溶性盐或络合物以形成核心粒子。这种技术可用于制备可溶于水溶液中的药剂（例如具有相对高的水溶解度的药剂）的粒子。在一些实施方案中，具有一个或多个带电荷基团或可离子化基团的药剂可以与抗衡离子（例如阳离子或阴离子）相互作用以形成盐络合物。

[0167] 可以使用多种抗衡离子形成盐络合物，包括金属（例如碱金属、碱土金属以及过渡金属）。阳离子型抗衡离子的非限制性示例包括锌、钙、铝、锌、钡以及镁。阴离子型抗衡离子的非限制性示例包括磷酸根、碳酸根以及脂肪酸。抗衡离子可以是例如单价的、二价的或三价的。其它抗衡离子是本领域已知的并且可以用于本文所述的实施方案中。其它离子型络合剂和非离子型络合剂也是可能的。

[0168] 在沉淀工艺中可以使用多种不同的酸。在一些实施方案中，合适的酸可以包括癸酸、己酸、粘酸、辛酸。在其它实施方案中，合适的酸可以包括乙酸、己二酸、L-抗坏血酸、L-天冬氨酸、癸酸（capric acid/decanoic acid）、碳酸、柠檬酸、反丁烯二酸、半乳糖二酸、D-葡庚糖酸、D-葡糖酸、D-葡糖醛酸、谷氨酸、戊二酸、甘油磷酸、乙醇酸、马尿酸、盐酸、DL-乳酸、月桂酸、顺丁烯二酸、(-)-L-苹果酸、棕榈酸、磷酸、癸二酸、硬脂酸、丁二酸、硫酸、(+)-L-酒石酸、或硫氰酸。在其它实施方案中，合适的酸可以包括海藻酸、苯磺酸、苯甲酸、(+)-樟脑酸、辛酸（caprylic acid/octanoic acid）、环拉酸、十二烷基硫酸、乙烷-1,2-二磺酸、乙烷磺酸、2-羟基-乙烷磺酸、龙胆酸、2-氧代-戊二酸、异丁酸、乳糖酸、丙二酸、甲烷磺酸、萘-1,5-二磺酸、萘-2-磺酸、1-羟基-2-萘甲酸、烟酸、油酸、乳清酸、草酸、双羟萘酸（扑酸）、丙酸、(-)-L-焦谷氨酸、或对甲苯磺酸。在另外的其它实施方案中，合适的酸可以包括2,2-二氯-乙酸、4-乙酰胺基-苯甲酸、(+)-樟脑-10-磺酸、己酸（caproic acid/hexanoic acid）、肉桂酸、甲酸、氢溴酸、DL-扁桃酸、硝酸、水杨酸、4-氨基-水杨酸、或十一碳烯酸（十一碳-10-烯酸）。还可以使用一种或多种这样的酸的混合物。

[0169] 在沉淀工艺中可以使用多种不同的碱。在一些实施方案中，合适的碱包括氨、L-精氨酸、氢氧化钙、胆碱、N-甲基-葡糖胺、赖氨酸、氢氧化镁、氢氧化钾、或氢氧化钠。在其它实施方案中，合适的碱可以包括苯乙苄胺、苄星（benzathine）、甜菜碱、丹醇（deanol）、二乙胺、2-（二乙氨基）-乙醇、哈胺（hydrabamine）、吗啉、4-(2-羟乙基)-吗啉、1-(2-羟乙基)-吡咯烷、或氨丁三醇。在其它实施方案中，合适的碱可以包括二乙醇胺（2,2'-亚氨基双（乙醇））、乙醇胺（2-氨基乙醇）、乙二胺、1H-咪唑、哌嗪、三乙醇胺（2,2',2″-次氮基三（乙醇））、或氢氧化锌。还可以使用一种或多种这样的碱的混合物。

[0170] 可以使用任何合适的溶剂来通过盐形成而进行沉淀，包括本文所述的可以用于研磨的溶剂。在一组实施方案中，使用水溶液（例如水、缓冲溶液、其它水溶液）、醇（例如乙醇、甲醇、丁醇）、以及其混合物，其可以任选包括其它组分，如药物赋形剂、聚合物以及药剂。

[0171] 在沉淀工艺中，盐可以具有比呈非盐形式的药剂低的水溶解度（或在含有盐的溶剂中的溶解度）。盐在25℃的水溶解度（或在溶剂中的溶解度）可以例如小于或等于约5mg/mL、小于或等于约2mg/mL、小于或等于约1mg/mL、小于或等于约0.5mg/mL、小于或等于约0.1mg/mL、小于或等于约0.05mg/mL、或者小于或等于约0.01mg/mL、小于或等于约1μg/

mL、小于或等于约 0.1μg/mL、小于或等于约 0.01μg/mL、小于或等于约 1ng/mL、小于或等于约 0.1ng/mL、或者小于或等于约 0.01ng/mL。在一些实施方案中，盐可以具有如下的水溶解度（或在溶剂中的溶解度）：至少约 1pg/mL、至少约 10pg/mL、至少约 0.1ng/mL、至少约 1ng/mL、至少约 10ng/mL、至少约 0.1μg/mL、至少约 1μg/mL、至少约 5μg/mL、至少约 0.01mg/mL、至少约 0.05mg/mL、至少约 0.1mg/mL、至少约 0.5mg/mL、至少约 1.0mg/mL、至少约 2mg/mL。上述范围的组合是可能的（例如至少约 0.001mg/mL 并且小于或等于约 1mg/mL 的水溶解度（或在溶剂中的溶解度））。其它范围也是可能的。盐在整个 pH 值范围（例如从 pH 1 至 pH 14）内的任一点均可以具有这些范围或其它范围的水溶解度。

[0172] 在一些实施方案中，用于沉淀的溶剂包括如本文所述的一种或多种表面改变剂，并且在粒子从溶液中沉淀出同时在所述粒子的周围可以形成一种或多种表面改变剂包衣。表面改变剂可以任何合适的浓度存在于溶剂中，如水溶液中至少约 0.001％ (w/v)、至少约 0.005％ (w/v)、至少约 0.01％ (w/v)、至少约 0.05％ (w/v)、至少约 0.1％ (w/v)、至少约 0.5％ (w/v)、至少约 1％ (w/v)、或至少约 5％ (w/v) 的浓度。在一些情况下，表面改变剂以如下浓度存在于溶剂中：小于或等于约 5％ (w/v)、小于或等于约 1％ (w/v)、小于或等于约 0.5％ (w/v)、小于或等于约 0.1％ (w/v)、小于或等于约 0.05％ (w/v)、小于或等于约 0.01％ (w/v)、或者小于或等于约 0.005％ (w/v)。上述范围的组合也是可能的（例如至少约 0.01％ (w/v) 并且小于或等于约 1％ (w/v) 的浓度）。其它范围也是可能的。

[0173] 另一种形成核心粒子的示例性方法包括冷冻干燥技术。在这种技术中，可以将药剂或其盐溶解于任选地含有表面改变剂的水溶液中。可以将抗衡离子添加至溶液中，并且可以将该溶液立即快速冷冻并且冷冻干燥。可以将干粉剂在合适的溶剂（例如水溶液，如水）中以所需的浓度复原。

[0174] 可以将抗衡离子以任何合适的范围添加至溶剂中以进行冷冻干燥。在一些情况下，抗衡离子与药剂（例如盐）的比率可以是至少 0.1:1（重量比或摩尔比）、至少 1:1、至少 2:1、至少 3:1、至少 5:1、至少 10:1、至少 25:1、至少 50:1、或至少 100:1。在一些情况下，抗衡离子与药剂（例如盐）的比率可以小于或等于 100:1（重量比或摩尔比）、小于或等于 75:1、小于或等于 50:1、小于或等于 25:1、小于或等于 10:1、小于或等于 5:1、小于或等于 3:1、小于或等于 2:1、小于或等于 1:1、或者小于或等于 0.1:1。上述范围的组合是可能的（例如至少 5:1 并且小于或等于 50:1 的比率）。其它范围也是可能的。

[0175] 如果在冷冻干燥之前在溶剂中存在表面改变剂，那么所述表面改变剂可以任何合适的浓度存在，如水溶液中至少约 0.001％ (w/v)、至少约 0.005％ (w/v)、至少约 0.01％ (w/v)、至少约 0.05％ (w/v)、至少约 0.1％ (w/v)、至少约 0.5％ (w/v)、至少约 1％ (w/v)、或至少约 5％ (w/v) 的浓度。在一些情况下，表面改变剂以如下浓度存在于溶剂中：小于或等于约 5％ (w/v)、小于或等于约 1％ (w/v)、小于或等于约 0.5％ (w/v)、小于或等于约 0.1％ (w/v)、小于或等于约 0.05％ (w/v)、小于或等于约 0.01％ (w/v)、或者小于或等于约 0.005％ (w/v)。上述范围的组合也是可能的（例如至少约 0.01％ (w/v) 并且小于或等于约 1％ (w/v) 的浓度）。其它范围也是可能的。

[0176] 溶剂中存在的表面改变剂的浓度可以高于或低于表面改变剂的临界胶束浓度 (CMC)，这取决于所使用的具体表面改变剂。在其它实施方案中，可以通过将过量的抗衡离子添加到含有药剂的溶液中来形成稳定的粒子。然后可以通过诸如离心等各种方法对沉淀

物进行洗涤。可以对所得的浆料进行超声处理。可以添加一种或多种表面改变剂以使所得粒子稳定。

[0177] 形成核心粒子的其它方法也是可能的。用于形成核心粒子的技术可以包括例如凝聚相分离；熔体分散；界面沉积；原位聚合；高分子的自组装（例如聚合电解质络合物或聚合电解质－表面活性剂络合物的形成）；喷雾干燥和喷雾冻凝；电喷雾；空气悬浮包衣；锅喷雾包衣（pan and spray coating）；冷冻干燥、空气干燥、真空干燥、流化床干燥；沉淀（例如纳米沉淀、微量沉淀）；临界流体萃取；以及平版印刷法（例如软平版印刷术、步进－闪光压印平版印刷术、干涉平版印刷术、照相平版印刷术）。

[0178] 本文所述的方法和其它方法的组合也是可能的。举例来说，在一些实施方案中，首先通过沉淀形成药剂的核心，然后通过研磨工艺将核心的尺寸进一步缩小。

[0179] 在形成药剂的粒子之后，可以任选地使所述粒子暴露于包含（第二）表面改变剂的溶液，所述（第二）表面改变剂可以与所述粒子缔合和/或包覆所述粒子。在其中药剂已经包括第一表面改变剂包衣的实施方案中，可以将第二表面改变剂的全部或部分与第二稳定剂/表面改变剂交换以包覆粒子表面的全部或部分。在一些情况下，第二表面改变剂与第一表面改变剂相比可以使得粒子更具粘液穿透性。在其它实施方案中，可以形成具有包括多种表面改变剂（例如在单层中或在多层中）的包衣的粒子。在其它实施方案中，可以形成具有多层包衣（例如每一层包衣任选地包含不同的表面改变剂）的粒子。在一些情况下，所述包衣呈单层表面改变剂的形式。其它构型也是可能的。

[0180] 在本文所述的任何方法中，可以使用表面改变剂通过将粒子在含有表面改变剂的溶液中孵育以下时间段来包覆粒子：至少约1分钟、至少约2分钟、至少约5分钟、至少约10分钟、至少约15分钟、至少约20分钟、至少约30分钟、至少约60分钟或更长时间。在一些情况下，孵育可以进行少于或等于约10小时、少于或等于约5小时、或者少于或等于约60分钟的时间段。上述范围的组合也是可能的（例如少于或等于60分钟且至少约2分钟的孵育时间段）。

[0181] 粒子包衣

[0182] 如图1中所图示的实施方案中所示，核心16可以由包含一种或多种表面改变剂的包衣20围绕。在一些实施方案中，包衣由被设置在核心表面上的一种或多种表面改变剂或其它分子形成。包衣的具体化学成分和/或组分以及一种或多种表面改变剂可以经过选择以赋予粒子某些功能，如增强的穿过粘膜屏障的转移。

[0183] 应当了解的是，围绕核心的包衣不需要完全地围绕核心，尽管这些实施方案也是可能的。举例来说，包衣可以围绕核心表面积的至少约10％、至少约30％、至少约50％、至少约60％、至少约70％、至少约80％、至少约90％、或至少约99％。在一些情况下，包衣基本上围绕核心。在其它情况下，包衣完全地围绕核心。在其它实施方案中，包衣围绕核心表面积的少于或等于约100％、少于或等于约90％、少于或等于约80％、少于或等于约70％、少于或等于约60％、或少于或等于约50％。上述范围的组合也是可能的（例如围绕核心表面积的多于80％且小于100％）。

[0184] 包衣的组分在一些情况下可以在核心的表面上均匀地分布，并且在其它情况下，不均匀地分布。举例来说，在一些情况下，包衣可以包括不包括任何物质的部分（例如孔）。如果需要的话，包衣可以被设计成允许某些分子和组分穿透和/或转移到包衣中或从包衣

中穿透出和/或转移出，但可以防止其它分子和组分穿透和/或转移到包衣中或从包衣中穿透出和/或转移出。某些分子穿透和/或转移到包衣中和/或穿过包衣的能力可以取决于例如形成包衣的表面改变剂的堆积密度以及形成包衣的组分的化学特性和物理特性。如本文所述，包衣可以包括一层物质（例如单层），或在一些实施方案中，包括多层物质。可以存在单一类型的表面改变剂，或多种类型的表面改变剂。

[0185] 粒子的包衣可以具有任何合适的厚度。举例来说，包衣可以具有以下平均厚度：至少约 1nm、至少约 5nm、至少约 10nm、至少约 30nm、至少约 50nm、至少约 100nm、至少约 200nm、至少约 500nm、至少约 1μm、或至少约 5μm。在一些情况下，包衣的平均厚度小于或等于约 5μm、小于或等于约 1μm、小于或等于约 500nm、小于或等于约 200nm、小于或等于约 100nm、小于或等于约 50nm、小于或等于约 30nm、小于或等于约 10nm、或者小于或等于约 5nm。上述范围的组合也是可能的（例如至少约 1nm 且小于或等于约 100nm 的平均厚度）。其它范围也是可能的。对于具有多层包衣的粒子，每一个包衣层均可以具有上文所述的厚度中的一种。

[0186] 在一些实施方案中，本文所述的组合物和方法可以允许核心粒子被亲水性表面改变部分所包覆而不需要使表面改变部分与核心表面共价连接。在一些这样的实施方案中，可以使用本文所述的聚合物包覆具有疏水性表面的核心，从而使得多个表面改变部分处于核心表面上而基本上不改变核心本身的特征。举例来说，可以使表面改变剂吸附到核心粒子的外表面。然而，在其它实施方案中，使表面改变剂与核心粒子共价连接。

[0187] 在其中使表面改变剂吸附到核心表面上的某些实施方案中，表面改变剂可以与溶液中表面改变剂的其它分子，任选地与其它组分（例如组合物/制剂中）平衡。在一些情况下，所吸附的表面改变剂可以本文所述的密度存在于核心的表面上。该密度可以是在表面改变剂与溶液中的其它组分平衡时的平均密度。

[0188] 可以适用于包衣中的表面改变剂包括例如聚合物、稳定剂以及表面活性剂。在某些实施方案中，本文所述的表面改变剂是聚合物。如下文所更详细地描述的适合于在包衣中用作表面改变剂的聚合物的非限制性示例包括聚乙烯醇 (PVA，例如 PVA 2K75、PVA 13K87、PVA 31K87、PVA 31K98、PVA 85K87、PVA 85K99、PVA 95K95 以及 PVA 130K87)，其中在“K”之前和之后的数字分别指示 PVA 的分子量 (kDa) 和水解度 (%)；聚乙烯吡咯烷酮（聚维酮 (Povidone)，例如 Kollidon® 17PF、Kollidon® 30 以及 Kollidon® 12PF)、烷基芳基聚醚醇（例如泰洛沙泊 (Tyloxapol)）、聚氧乙烯烷基醚（例如 Brij® 35、Brij® 98 以及 Brij® S100)、聚山梨醇酯（例如 Tween 20 和 Tween 80)、以及泊洛沙姆（如 Pluronics®（例如 Pluronic® L31、Pluronic® L35、Pluronic® L44、Pluronic® L81、Pluronic® L101、Pluronic® L121、Pluronic® P65、Pluronic® P103、Pluronic® P105、Pluronic® P123、Pluronic® F38、Pluronic® F68、Pluronic® F87、Pluronic® F108、Pluronic® F127））。上述聚合物的衍生物也是可能的。上述聚合物和本文所述的其它聚合物的组合也可以用作本发明粒子中的表面改变剂。

[0189] 本文所述的粒子的包衣和/或表面改变剂可以包含例如疏水性物质、亲水性物质

和 / 或两亲性物质或由例如疏水性物质、亲水性物质和 / 或两亲性物质形成。在一些实施方案中，包衣包括聚合物，如合成聚合物（即并非在自然界中产生的聚合物）。在其它实施方案中，所述聚合物是天然聚合物（例如蛋白质、多糖、橡胶）。在某些实施方案中，所述聚合物是表面活性聚合物。在某些实施方案中，所述聚合物是非离子型聚合物。在某些实施方案中，所述聚合物是线型合成非离子型聚合物。在某些实施方案中，所述聚合物是非离子型嵌段共聚物。在一些实施方案中，所述聚合物可以是共聚物，例如在所述共聚物中，一种重复单元是相对疏水的并且另一种重复单元是相对亲水的。该共聚物可以是例如二嵌段共聚物、三嵌段共聚物、交替共聚物、或无规共聚物。该聚合物可以带电荷或不带电荷。

[0190] 在一些实施方案中，包衣包含在聚合物的主链上具有侧羟基的合成聚合物。举例来说，在某些实施方案中，该聚合物可以包括聚乙烯醇、部分水解的聚（乙酸乙烯酯）或乙烯醇与乙酸乙烯酯的共聚物。在某些实施方案中，在聚合物的主链上具有侧羟基的合成聚合物可以包括聚乙二醇 - 聚（乙酸乙烯酯）- 聚乙烯醇共聚物、聚乙二醇 - 聚乙烯醇共聚物、聚环氧丙烷 - 聚乙烯醇共聚物、以及聚乙烯醇 - 聚（丙烯酰胺）共聚物。不希望受理论所束缚，与对照粒子相比，包括包含在聚合物的主链上具有侧羟基的合成聚合物的包衣的粒子至少部分由于在粒子表面上呈现出多个羟基而可以具有降低的粘膜粘着性。粘膜粘着性降低的一种可能的机制是羟基例如通过使粒子 / 粘液环境中的水和其它分子有序化而改变粒子的微环境。一种另外的或替代的可能性机制是羟基遮蔽了粘蛋白纤维的粘着性结构域，从而降低了粒子粘着性并且加速了粒子转移。

[0191] 此外，被在聚合物的主链上具有侧羟基的合成聚合物包覆的粒子穿透粘液的能力还可能至少部分地取决于聚合物的水解度。在一些实施方案中，聚合物的疏水性部分（例如聚合物中未水解的部分）可以允许聚合物粘着到核心表面（例如在核心表面具有疏水性的情况下），从而允许核心与聚合物之间强烈缔合。令人惊讶地，已经发现在涉及表面改变剂 PVA 的一些实施方案中，水解度过高则不允许 PVA 与核心之间充分粘着（例如在核心具有疏水性的情况下），并且因此，被这种聚合物包覆的粒子一般不表现出充分降低的粘膜粘着性。在一些实施方案中，水解度过低则不会增强粒子在粘液中的转移，这或许是因为可供用于改变粒子的微环境和 / 或遮蔽粘蛋白纤维的粘着性结构域的羟基的量较少。

[0192] 在聚合物的主链上具有侧羟基的合成聚合物可以具有任何合适的水解度（并且因此，具有不同量的羟基）。适当的水解度可以取决于另外的因素，如聚合物的分子量、核心的组成、核心的疏水性等。在一些实施方案中，合成聚合物（例如 PVA 或部分水解的聚（乙酸乙烯酯）或乙烯醇与乙酸乙烯酯的共聚物）可以至少约 30％水解、至少约 35％水解、至少约 40％水解、至少约 45％水解、至少约 50％水解、至少约 55％水解、至少约 60％水解、至少约 65％水解、至少约 70％水解、至少约 75％水解、至少约 80％水解、至少约 85％水解、至少约 87％水解、至少约 90％水解、至少约 95％水解、或至少约 98％水解。在一些实施方案中，合成聚合物可以少于或等于约 100％水解、少于或等于约 99％水解、少于或等于约 98％水解、少于或等于约 97％水解、少于或等于约 96％水解、少于或等于约 95％水解、少于或等于约 94％水解、少于或等于约 93％水解、少于或等于约 92％水解、少于或等于约 91％水解、少于或等于约 90％水解、少于或等于约 87％水解、少于或等于约 85％水解、少于或等于约 80％水解、少于或等于约 75％水解、少于或等于约 70％水解、或者少于或等于约 60％水解。上述范围的组合也是可能的（例如至少约 80％水解且少于或等于约 95％水解的聚合物）。

其它范围也是可能的。

[0193] 本文所述的合成聚合物（例如在聚合物的主链上具有侧羟基的合成聚合物）的分子量可以经过选择以降低核心的粘膜粘着性和确保聚合物与核心充分缔合。在某些实施方案中，合成聚合物的分子量是至少约 1kDa、至少约 2kDa、至少约 5kDa、至少约 8kDa、至少约 9kDa、至少约 10kDa、至少约 12kDa、至少约 15kDa、至少约 20kDa、至少约 25kDa、至少约 30kDa、至少约 40kDa、至少约 50kDa、至少约 60kDa、至少约 70kDa、至少约 80kDa、至少约 90kDa、至少约 100kDa、至少约 110kDa、至少约 120kDa、至少约 130kDa、至少约 140kDa、至少约 150kDa、至少约 200kDa、至少约 500kDa、或至少约 1000kDa。在一些实施方案中，合成聚合物的分子量小于或等于约 1000kDa、小于或等于约 500kDa、小于或等于约 200kDa、小于或等于约 180kDa、小于或等于约 150kDa、小于或等于约 130kDa、小于或等于约 120kDa、小于或等于约 100kDa、小于或等于约 85kDa、小于或等于约 70kDa、小于或等于约 65kDa、小于或等于约 60kDa、小于或等于约 50kDa、或者小于或等于约 40kDa、小于或等于约 30kDa、小于或等于约 20kDa、小于或等于约 15kDa、或者小于或等于约 10kDa。上述范围的组合也是可能的（例如至少约 10kDa 且小于或等于约 30kDa 的分子量）。上述分子量范围也可以与上述水解度范围组合以形成合适的聚合物。

[0194] 在一些实施方案中，本文所述的合成聚合物是 PVA 或包含 PVA。PVA 是具有表面活性特性的非离子型聚合物。它是通常通过聚（乙酸乙烯酯）水解而产生的合成聚合物。部分水解的 PVA 包含以下两种类型的重复单元：乙烯醇单元和其余的乙酸乙烯酯单元。乙烯醇单元是相对亲水的；乙酸乙烯酯单元是相对疏水的。在一些情况下，乙烯醇单元和乙酸乙烯酯单元的序列分布是嵌段式分布。举例来说，一系列乙烯醇单元后面可以是一系列乙酸乙烯酯单元，并且再后面又是乙烯醇单元以形成具有混合嵌段共聚物型排列的聚合物，在所述聚合物中，单元以嵌段方式分布。在某些实施方案中，重复单元形成共聚物，例如二嵌段共聚物、三嵌段共聚物、交替共聚物或无规共聚物。除 PVA 以外的聚合物也可以具有亲水性单元和疏水性单元的这些构型。

[0195] 在某些实施方案中，表面改变剂是少于或等于约 98％水解并且具有小于或等于约 75kDa 的分子量的 PVA、或少于约 95％水解的 PVA。在一些实施方案中，表面改变剂是不具有大于 95％的水解度和大于 31kDa 的分子量这两种特性的 PVA。在某些实施方案中，可以使用这些表面改变剂包覆某些药剂如皮质类固醇（例如 LE）和 / 或本文所述的其它化合物。

[0196] 在一些实施方案中，本文所述的合成聚合物的亲水性单元可以基本上存在于粒子的外表面处。举例来说，亲水性单元可以形成包衣的大部分外表面并且可以有助于使粒子在含有所述粒子的水溶液中稳定。疏水性单元可以基本上存在于包衣的内部中和 / 或存在于核心粒子的表面处，例如以促进包衣与核心的连接。

[0197] 合成聚合物的相对亲水性单元和相对疏水性单元的摩尔分数可以经过选择以分别降低核心的粘膜粘着性和确保聚合物与核心充分缔合。如本文所述，聚合物的疏水性单元的摩尔分数可以经过选择以使得聚合物与核心进行充分缔合，从而增大聚合物与核心保持粘着的可能性。合成聚合物的相对亲水性单元与相对疏水性单元的摩尔分数可以是例如至少 0.5:1、至少 1:1、至少 2:1、至少 3:1、至少 5:1、至少 7:1、至少 10:1、至少 15:1、至少 20:1、至少 25:1、至少 30:1、至少 40:1、至少 50:1、至少 75:1、或至少 100:1。在一些实施方案中，合成聚合物的相对亲水性单元与相对疏水性单元的摩尔分数可以例如小于或等

于100:1、小于或等于75:1、小于或等于50:1、小于或等于40:1、小于或等于30:1、小于或等于25:1、小于或等于20:1、小于或等于15:1、小于或等于10:1、小于或等于7:1、小于或等于5:1、小于或等于3:1、小于或等于2:1、或者小于或等于1:1。上述范围的组合也是可能的（例如至少1:1且小于或等于50:1的比率）。其它范围也是可能的。

[0198] 还可以对PVA聚合物的分子量进行调整以增强聚合物使得粒子具有粘液穿透性的有效性。具有不同的分子量和水解度的PVA聚合物的示例示于表1中。

[0199] 表1:PVA的等级。分子量(MW)和水解度值是由制造商提供的。

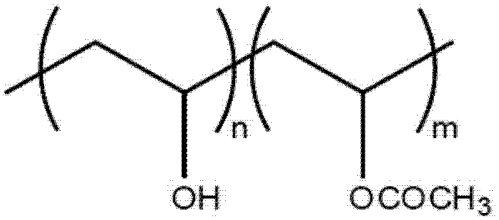
[0200]

PVA首字母缩写*	MW，kDa	水解度，%
2K75	2	75-79
9K80	9-10	80
13K87	13-23	87-89
13K98	13-23	98
31K87	31-50	87-89
31K98	31-50	98-99
57K86	57-60	86-89
85K87	85-124	87-89
85K99	85-124	99+
95K95	95	95
105K80	104	80
130K87	130	87-89

[0201] *PVA首字母缩写的解释:XXKYY,其中XX代表PVA的分子量下限(kDa)并且YY代表PVA的水解度下限(%)。

[0202] 在某些实施方案中,合成聚合物由下式表示:

[0203]



[0204] 其中n是0与22730之间(包括端值在内)的整数;并且m是0与11630之间包括端值在内的整数。在某些实施方案中,n是25与20600之间(包括端值在内)的整数。在一些实施方案中,m是5与1100之间(包括端值在内)的整数。在某些实施方案中,m是0与400之间(包括端值在内)或1与400之间(包括端值在内)的整数。应注意,n和m分别表示聚合物中乙烯醇重复单元和乙酸乙烯酯重复单元的总含量,而不是嵌段长度。

[0205] n 的值可以变化。在某些实施方案中，n 是至少 5、至少 10、至少 20、至少 30、至少 50、至少 100、至少 200、至少 300、至少 500、至少 800、至少 1000、至少 1200、至少 1500、至少 1800、至少 2000、至少 2200、至少 2400、至少 2600、至少 3000、至少 5000、至少 10000、至少 15000、至少 20000、或至少 25000。在一些情况下，n 小于或等于 30000、小于或等于 25000、小于或等于 20000、小于或等于 25000、小于或等于 20000、小于或等于 15000、小于或等于 10000、小于或等于 5000、小于或等于 3000、小于或等于 2800、小于或等于 2400、小于或等于 2000、小于或等于 1800、小于或等于 1500、小于或等于 1200、小于或等于 1000、小于或等于 800、小于或等于 500、小于或等于 300、小于或等于 200、小于或等于 100、或者小于或等于 50。上述范围的组合也是可能的（例如 n 是至少 50 且小于或等于 2000）。其它范围也是可能的。

[0206] 类似地，m 的值可以变化。举例来说，在某些实施方案中，m 是至少 5、至少 10、至少 20、至少 30、至少 50、至少 70、至少 100、至少 150、至少 200、至少 250、至少 300、至少 350、至少 400、至少 500、至少 800、至少 1000、至少 1200、至少 1500、至少 1800、至少 2000、至少 2200、至少 2400、至少 2600、至少 3000、至少 5000、至少 10000、或至少 15000。在一些情况下，m 小于或等于 15000、小于或等于 10000、小于或等于 5000、小于或等于 3000、小于或等于 2800、小于或等于 2400、小于或等于 2000、小于或等于 1800、小于或等于 1500、小于或等于 1200、小于或等于 1000、小于或等于 800、小于或等于 500、小于或等于 400、小于或等于 350、小于或等于 300、小于或等于 250、小于或等于 200、小于或等于 150、小于或等于 100、小于或等于 70、小于或等于 50、小于或等于 30、小于或等于 20、或者小于或等于 10。上述范围的组合也是可能的（例如 m 是至少 5 且小于或等于 200）。其它范围也是可能的。

[0207] 在一些实施方案中，本文所述的粒子包括包含嵌段共聚物的包衣，所述嵌段共聚物具有相对亲水性嵌段和相对疏水性嵌段。在一些情况下，亲水性嵌段可以基本上存在于粒子的外表面处。举例来说，亲水性嵌段可以形成包衣的大部分外表面并且可以有助于使粒子在含有所述粒子的水溶液中稳定。疏水性嵌段可以基本上存在于包衣的内部中和 / 或存在于核心粒子的表面处，例如以促进包衣与核心的连接。在一些情况下，所述包衣包含包括三嵌段共聚物的表面改变剂，其中该三嵌段共聚物包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型。具有亲水性嵌段 - 疏水性嵌段构型的二嵌段共聚物也是可能的。嵌段共聚物与适合用作包衣的其它聚合物的组合也是可能的。非线型嵌段构型也是可能的，如在梳型共聚物、刷型共聚物或星型共聚物中。在一些实施方案中，相对亲水性嵌段包括在聚合物的主链上具有侧羟基的合成聚合物（例如 PVA）。

[0208] 嵌段共聚物的亲水性嵌段和疏水性嵌段的分子量可以经过选择以分别降低核心的粘膜粘着性和确保嵌段共聚物与核心充分缔合。嵌段共聚物的疏水性嵌段的分子量可以经过选择以使得嵌段共聚物与核心进行充分缔合，从而增大嵌段共聚物与核心保持粘着的可能性。

[0209] 在某些实施方案中，嵌段共聚物的（一个或多个）相对疏水性嵌段或重复单元的组合分子量是至少约 0.5kDa、至少约 1kDa、至少约 2kDa、至少约 3kDa、至少约 4kDa、至少约 5kDa、至少约 6kDa、至少约 10kDa、至少约 12kDa、至少约 15kDa、至少约 20kDa、或至少约 50kDa、至少约 60kDa、至少约 70kDa、至少约 80kDa、至少约 90kDa、至少约 100kDa、至少约 110kDa、至少约 120kDa、至少约 130kDa、至少约 140kDa、至少约 150kDa、至少约 200kDa、至少

约 500kDa、或至少约 1000kDa。在一些实施方案中，(一个或多个）相对疏水性嵌段或重复单元的组合分子量小于或等于约 1000kDa、小于或等于约 500kDa、小于或等于约 200kDa、小于或等于约 150kDa、小于或等于约 140kDa、小于或等于约 130kDa、小于或等于约 120kDa、小于或等于约 110kDa、小于或等于约 100kDa、小于或等于约 90kDa、小于或等于约 80kDa、小于或等于约 50kDa、小于或等于约 20kDa、小于或等于约 15kDa、小于或等于约 13kDa、小于或等于约 12kDa、小于或等于约 10kDa、小于或等于约 8kDa、或者小于或等于约 6kDa。上述范围的组合也是可能的（例如至少约 3kDa 且小于或等于约 15kDa)。其它范围也是可能的。

[0210] 在一些实施方案中，嵌段共聚物的组合的（一个或多个）相对亲水性嵌段或重复单元占嵌段共聚物的至少约 15 重量%、至少约 20 重量%、至少约 25 重量%、至少约 30 重量%、至少约 35 重量%、至少约 40 重量%、至少约 45 重量%、至少约 50 重量%、至少约 55 重量%、至少约 60 重量%、至少约 65 重量%、或至少约 70 重量%。在一些实施方案中，嵌段共聚物的组合的（一个或多个）相对亲水性嵌段或重复单元占嵌段共聚物的少于或等于约 90 重量%、少于或等于约 80 重量%、少于或等于约 60 重量%、少于或等于约 50 重量%、或者少于或等于约 40 重量%。上述范围的组合也是可能的（例如至少约 30 重量%且少于或等于约 80 重量%）。其它范围也是可能的。

[0211] 在一些实施方案中，嵌段共聚物的（一个或多个）相对亲水性嵌段或重复单元的组合分子量可以是至少约 0.5kDa、至少约 1kDa、至少约 2kDa、至少约 3kDa、至少约 4kDa、至少约 5kDa、至少约 6kDa、至少约 10kDa、至少约 12kDa、至少约 15kDa、至少约 20kDa、或至少约 50kDa、至少约 60kDa、至少约 70kDa、至少约 80kDa、至少约 90kDa、至少约 100kDa、至少约 110kDa、至少约 120kDa、至少约 130kDa、至少约 140kDa、至少约 150kDa、至少约 200kDa、至少约 500kDa、或至少约 1000kDa。在某些实施方案中，(一个或多个）相对亲水性嵌段或重复单元的组合分子量小于或等于约 1000kDa、小于或等于约 500kDa、小于或等于约 200kDa、小于或等于约 150kDa、小于或等于约 140kDa、小于或等于约 130kDa、小于或等于约 120kDa、小于或等于约 110kDa、小于或等于约 100kDa、小于或等于约 90kDa、小于或等于约 80kDa、小于或等于约 50kDa、小于或等于约 20kDa、小于或等于约 15kDa、小于或等于约 13kDa、小于或等于约 12kDa、小于或等于约 10kDa、小于或等于约 8kDa、小于或等于约 6kDa、小于或等于约 5kDa、小于或等于约 3kDa、小于或等于约 2kDa、或者小于或等于约 1kDa。上述范围的组合也是可能的（例如至少约 0.5kDa 且小于或等于约 3kDa)。其它范围也是可能的。在其中两个亲水性嵌段侧接疏水性嵌段的实施方案中，这两个亲水性嵌段的分子量可以是基本上相同的或不同的。

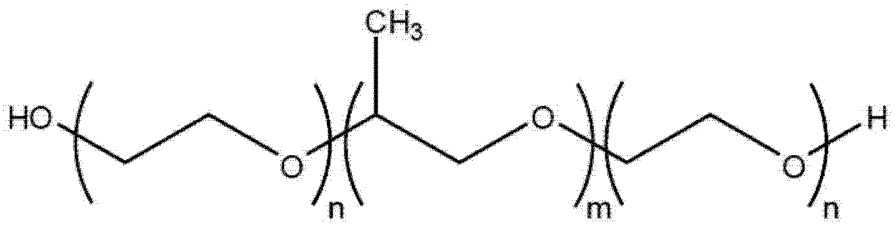
[0212] 在某些实施方案中，表面改变剂的聚合物包括聚醚部分。在某些实施方案中，该聚合物包括聚烷基醚部分。在某些实施方案中，该聚合物包括聚乙二醇尾。在某些实施方案中，该聚合物包括聚丙二醇中心部分。在某些实施方案中，该聚合物包括聚丁二醇作为中心部分。在某些实施方案中，该聚合物包括聚戊二醇作为中心部分。在某些实施方案中，该聚合物包括聚己二醇作为中心部分。在某些实施方案中，该聚合物是本文所述的聚合物中的一种的二嵌段共聚物。在某些实施方案中，该聚合物是本文所述的聚合物中的一种的三嵌段共聚物。如本文所公开，任何关于 PEG 的表述均可以被替换为聚氧化乙烯 (PEO)，并且任何关于 PEO 的表述均可以被替换为 PEG。在一些实施方案中，二嵌段共聚物或三嵌段共聚物包含在聚合物的主链上具有侧羟基的合成聚合物（例如 PVA) 作为所述嵌段中的一个或多

个（如本文所述具有不同的水解度和不同的分子量）。所述合成聚合物嵌段可以形成嵌段共聚物的中心部分或末端部分。

[0213] 在某些实施方案中，所述聚合物是聚烷基醚（例如聚乙二醇、聚丙二醇）与另一种聚合物（例如在聚合物的主链上具有侧羟基的合成聚合物（例如 PVA））的三嵌段共聚物。在某些实施方案中，所述聚合物是聚烷基醚与另一种聚烷基醚的三嵌段共聚物。在某些实施方案中，所述聚合物是聚乙二醇与另一种聚烷基醚的三嵌段共聚物。在某些实施方案中，所述聚合物是聚丙二醇与另一种聚烷基醚的三嵌段共聚物。在某些实施方案中，所述聚合物是具有至少一个聚烷基醚单元的三嵌段共聚物。在某些实施方案中，所述聚合物是两种不同的聚烷基醚的三嵌段共聚物。在某些实施方案中，所述聚合物是包括聚乙二醇单元的三嵌段共聚物。在某些实施方案中，所述聚合物是包括聚丙二醇单元的三嵌段共聚物。在某些实施方案中，所述聚合物是具有由两个更具亲水性的单元侧接的更具疏水性的单元的三嵌段共聚物。在某些实施方案中，所述亲水性单元是相同类型的聚合物。在一些实施方案中，所述亲水性单元包括在聚合物的主链上具有侧羟基的合成聚合物（例如 PVA）。在某些实施方案中，所述聚合物包括由两个更具亲水性的单元侧接的聚丙二醇单元。在某些实施方案中，所述聚合物包括两个侧接更具疏水性的单元的聚乙二醇单元。在某些实施方案中，所述聚合物是具有由两个聚乙二醇单元侧接的聚丙二醇单元的三嵌段共聚物。侧接中心嵌段的这两个嵌段的分子量可以基本上相同或不同。

[0214] 在某些实施方案中，所述聚合物具有下式：

[0215]



[0216] 其中 n 是 2 与 1140 之间（包括端值在内）的整数；并且 m 是 2 与 1730 之间（包括端值在内）的整数。在某些实施方案中，n 是 10 与 170 之间（包括端值在内）的整数。在某些实施方案中，m 是 5 与 70 之间（包括端值在内）的整数。在某些实施方案中，n 至少是 m 的 2 倍、m 的 3 倍、或 m 的 4 倍。

[0217] 在某些实施方案中，包衣包括包含（聚乙二醇）-（聚环氧丙烷）-（聚乙二醇）三嵌段共聚物（在下文中，被称作“PEG-PPO-PEG 三嵌段共聚物”）的表面改变剂，所述表面改变剂单独或与另一种聚合物组合存在于所述包衣中，所述另一种聚合物如在聚合物的主链上具有侧羟基的合成聚合物（例如 PVA）。如本文所述，在一些实施方案中，PEG 嵌段可以与 PEO 嵌段互换。PEG-PPO-PEG 三嵌段共聚物的 PEG（或 PEO）链段和 PPO 链段的分子量可以经过选择以降低粒子的粘膜粘着性，如本文所述。不希望受理论所束缚，与对照粒子相比，具有包含 PEG-PPO-PEG 三嵌段共聚物的包衣的粒子至少部分由于在粒子表面上呈现出多个 PEG（或 PEO）链段而可以具有降低的粘膜粘着性。PPO 链段可以粘着到核心表面（例如在核心表面具有疏水性的情况下），从而允许核心与三嵌段共聚物之间强烈缔合。在一些情况下，PEG-PPO-PEG 三嵌段共聚物通过非共价相互作用与核心缔合。为了进行比较，对照粒子可以是例如与所考虑的包衣粒子具有相似的尺寸的经羧酸酯改性的聚苯乙烯粒子。

[0218] 在某些实施方案中，表面改变剂包括包含泊洛沙姆的聚合物，所述泊洛沙姆具有商品名 Pluronic®。可用于本文所述的实施方案中的 Pluronic® 聚合物包括但不限于 F127、F38、F108、F68、F77、F87、F88、F98、L101、L121、L31、L35、L43、L44、L61、L62、L64、L81、L92、N3、P103、P104、P105、P123、P65、P84、以及 P85。

[0219] 某些 Pluronic® 分子的分子量的示例示于表 2 中。

[0220] 表 2：Pluronic® 分子的分子量

[0221]

Pluronic®	平均 MW	MW PPO	PEO，重	MW PEO

[0222]

			量%	
L31	1000	900	10	100
L44	2000	1200	40	800
L81	2667	2400	10	267
L101	3333	3000	10	333
P65	3600	1800	50	1800
L121	4000	3600	10	400
P103	4286	3000	30	1286
F38	4500	900	80	3600
P123	5143	3600	30	1543
P105	6000	3000	50	3000
F87	8000	2400	70	5600
F68	9000	1800	80	7200
F127	12000	3600	70	8400
P123	5750	4030	30	1730

[0223] 虽然其它范围是可能的并且可用于本文所述的某些实施方案中，但在一些实施方案中，PEG-PPO-PEG 三嵌段共聚物的疏水性嵌段具有上文所述的分子量中的一种（例如至少约 3kDa 且小于或等于约 15kDa），并且组合的亲水性嵌段具有处于上文所述的范围中的一个范围内的相对于聚合物的重量百分比（例如至少约 15 重量%、至少约 20 重量%、至少约 25 重量%、或至少约 30 重量%且小于或等于约 80 重量%）。某些符合这些准则的 Pluronic® 聚合物包括例如 F127、F108、P105 以及 P103。令人惊讶地，并且如实施例中所更详细地描述，发现这些特定的 Pluronic® 聚合物较所测试的不符合这一准则的其它 Pluronic® 聚合物来说使得某些粒子更具粘液穿透性。此外，（对于一些特定的粒子核心）并未使得粒子具有粘液穿透性的其它试剂包括某些聚合物，如聚乙烯吡咯烷酮 (PVP/Kollidon)、聚乙烯醇 - 聚乙二醇接枝共聚物 (Kollicoat IR)、羟丙基甲基纤维素 (Methocel)；Solutol HS 15、Triton X100、泰洛沙泊、cremophor RH 40；小分子，如 Span 20、Span 80、辛基葡糖苷、鲸蜡基三甲基溴化铵 (CTAB)、十二烷基硫酸钠 (SDS)。

[0224] 应当了解的是，表面改变剂使得粒子或核心具有粘液穿透性的能力可能至少部分地取决于特定的核心 / 表面改变剂组合，包括表面改变剂连接到核心的能力和 / 或核心 / 粒子表面上表面改变剂的密度。因而，在一些实施方案中，特定的表面改变剂可以增强一种类型的粒子或核心的移动性，但可以不增强另一种类型的粒子或核心的移动性。

[0225] 虽然本文的大部分说明可能涉及包含亲水性嵌段 - 疏水性嵌段 - 亲水性嵌段构型的包衣（例如 PEG-PPO-PEG 三嵌段共聚物）或包含具有侧羟基的合成聚合物的包衣，但应当了解的是，包衣不限于这些构型和物质并且其它构型和物质是可能的。

[0226] 此外，虽然本文所述的许多实施方案涉及单层包衣，但在其它实施方案中，粒子可以包括多于一层包衣（例如至少两层、三层、四层、五层或更多层包衣），并且每一层包衣均无需由粘液穿透性物质形成或无需包含粘液穿透性物质。在一些情况下，中间包衣（即核心表面与外包衣之间的包衣）可以包括促进外包衣与核心表面连接的聚合物。在许多实施方案中，粒子的外包衣包括包含促进粒子转移穿过粘液的物质的聚合物。

[0227] 因而，包衣（例如内包衣、中间包衣和 / 或外包衣）可以包括任何合适的聚合物。在一些情况下，所述聚合物可以具有生物相容性和 / 或生物可降解性。在一些情况下，聚合物质可以包含超过一种类型的聚合物（例如至少两种、三种、四种、五种或更多种聚合物）。在一些情况下，聚合物可以是如本文所述的无规共聚物或嵌段共聚物（例如二嵌段共聚物、三嵌段共聚物）。

[0228] 合适聚合物的非限制性示例可以包括聚胺、聚醚、聚酰胺、聚酯、聚氨基甲酸酯、聚脲、聚碳酸酯、聚苯乙烯、聚酰亚胺、聚砜、聚氨酯、聚乙炔、聚乙烯、聚乙烯亚胺、聚异氰酸酯、聚丙烯酸酯、聚甲基丙烯酸酯、聚丙烯腈、以及聚芳酯。具体聚合物的非限制性示例包括聚（己内酯）(PCL)、乙烯 - 乙酸乙烯酯聚合物 (EVA)、聚（乳酸）(PLA)、聚 (L- 乳酸）(PLLA)、聚（乙醇酸）(PGA)、聚（乳酸 - 共 - 乙醇酸）(PLGA)、聚 (L- 乳酸 - 共 - 乙醇酸）(PLLGA)、聚 (D,L- 丙交酯）(PDLA)、聚 (L- 丙交酯）(PLLA)、聚 (D,L- 丙交酯 - 共 - 己内酯）、聚 (D,L- 丙交酯 - 共 - 己内酯 - 共 - 乙交酯）、聚 (D,L- 丙交酯 - 共 -PEO- 共 -D,L- 丙交酯）、聚 (D,L- 丙交酯 - 共 -PPO- 共 -D,L- 丙交酯）、聚氰基丙烯酸烷基酯、聚氨酯、聚 -L- 赖氨酸 (PLL)、甲基丙烯酸羟丙酯 (HPMA)、聚乙二醇、聚 -L- 谷氨酸、聚（羟基酸）、聚酐、聚原酸酯、聚（酯酰胺）、聚酰胺、聚（酯醚）、聚碳酸酯；聚烯烃，如聚乙烯和聚丙烯；聚亚烷基二醇，如聚乙二醇 (PEG)；聚环氧烷 (PEO)；聚对苯二甲酸亚烷基酯，如聚（对苯二甲酸乙二酯）；聚乙烯醇 (PVA)、聚乙烯醚；聚乙烯酯，如聚（乙酸乙烯酯）；聚卤乙烯，如聚（氯乙烯）(PVC)；聚乙烯吡咯烷酮、聚硅氧烷、聚苯乙烯 (PS)、聚氨酯；衍生纤维素，如烷基纤维素、羟烷基纤维素、纤维素醚、纤维素酯、硝基纤维素、羟丙基纤维素、羧甲基纤维素；丙烯酸的聚合物，如聚（（甲基）丙烯酸甲酯）(PMMA)、聚（（甲基）丙烯酸乙酯）、聚（（甲基）丙烯酸丁酯）、聚（（甲基）丙烯酸异丁酯）、聚（（甲基）丙烯酸己酯）、聚（（甲基）丙烯酸异癸酯）、聚（（甲基）丙烯酸月桂酯）、聚（（甲基）丙烯酸苯酯）、聚（丙烯酸甲酯）、聚（丙烯酸异丙酯）、聚（丙烯酸异丁酯）、聚（丙烯酸十八酯）（在本文统称为“聚丙烯酸”）、以及其共聚物和混合物；聚二氧杂环己酮和它的共聚物、聚羟基烷酸酯、聚反丁烯二酸丙二酯、聚甲醛、泊洛沙姆、聚（原酸）酯、聚（丁酸）、聚（戊酸）、聚（丙交酯 - 共 - 己内酯）、以及三亚甲基碳酸酯、聚乙烯吡咯烷酮。

[0229] 聚合物的分子量可以变化。在一些实施方案中，分子量可以是至少约 0.5kDa、至少

约 1kDa、至少约 2kDa、至少约 3kDa、至少约 4kDa、至少约 5kDa、至少约 6kDa、至少约 8kDa、至少约 10kDa、至少约 12kDa、至少约 15kDa、至少约 20kDa、至少约 30kDa、至少约 40kDa、或至少约 50kDa。在一些实施方案中，所述分子量可以小于或等于约 50kDa、小于或等于约 40kDa、小于或等于约 30kDa、小于或等于约 20kDa、小于或等于约 12kDa、小于或等于约 10kDa、小于或等于约 8kDa、小于或等于约 6kDa、小于或等于约 5kDa、或者小于或等于约 4kDa。上述范围的组合是可能的（例如至少约 2kDa 且小于或等于约 15kDa 的分子量）。其它范围也是可能的。分子量可以使用诸如光散射和凝胶渗透色谱法等任何已知的技术来测定。其它方法是本领域已知的。

[0230] 在某些实施方案中，所述聚合物具有生物相容性，即所述聚合物在被插入或注射到活受试者体内时通常不会诱发不良反应；例如，它不包括显著的炎症和 / 或免疫系统例如通过 T 细胞介导的反应对聚合物产生的急性排斥。当然，应当认识到，“生物相容性”是相对术语，并且即使是对于与活组织高度相容的聚合物来说也预期会出现某种程度的免疫反应。然而，如本文所用的“生物相容性”指的是至少一部分免疫系统对物质的急性排斥，即被植入到受试者体内的非生物相容性物质激发受试者的免疫反应，所述免疫反应是足够严重的以致于由免疫系统对该物质的排斥不能被充分地控制，并且经常达到必须将该物质从受试者体内去除的程度。一种简单的测定生物相容性的测试是使聚合物在体外暴露于细胞；生物相容性聚合物是通常在中等浓度，例如在约 50 微克 /10^6个细胞的浓度不会引起显著的细胞死亡的聚合物。举例来说，生物相容性聚合物在暴露于诸如成纤维细胞或上皮细胞等细胞时，即使被这些细胞吞噬或以其它方式摄取也只可能引起少于约 20％的细胞死亡。在一些实施方案中，如果在体外将物质添加到细胞中引起了少于或等于 20％的细胞死亡，那么所述物质具有“生物相容性”，并且它们的体内施用不会诱发不想要的炎症或其它这类不良作用。

[0231] 在某些实施方案中，生物相容性聚合物可以具有生物可降解性，即该聚合物能够在生理环境内，如在体内或在被引入到细胞中时以化学方式和 / 或以生物学方式（例如通过细胞机制或通过水解）降解。举例来说，聚合物可以是在暴露于水后（例如在受试者体内）自发水解的聚合物，和 / 或聚合物可以在暴露于热后（例如在约 37℃的温度）降解。聚合物可以不同的速率进行降解，这取决于所使用的聚合物或共聚物。举例来说，聚合物的半衰期 (50％的聚合物降解成单体和 / 或其它非聚合部分的时间）可以是约数天、数周、数月、或数年，这取决于聚合物。聚合物可以例如通过酶活性或细胞机制，在一些情况下，例如通过暴露于溶菌酶（例如具有相对低的 pH 值）而被生物降解。在一些情况下，聚合物可以被分解为单体和 / 或其它非聚合部分，所述单体和 / 或其它非聚合部分可以被细胞再利用或处理而不会对细胞产生显著的毒性作用（即在将这些组分在体外添加到细胞中时杀死少于约 20％的细胞）。举例来说，聚丙交酯可以水解形成乳酸，聚乙交酯可以水解形成乙醇酸，等等。

[0232] 生物可降解聚合物的示例包括但不限于聚乙二醇 - 聚环氧丙烷 - 聚乙二醇三嵌段共聚物、聚（丙交酯）（或聚（乳酸））、聚（乙交酯）（或聚（乙醇酸））、聚（原酸酯）、聚（己内酯）、聚赖氨酸、聚（乙烯亚胺）、聚（丙烯酸）、聚（氨酯）、聚（酐）、聚（酯）、聚（三亚甲基碳酸酯）、聚（乙烯亚胺）、聚（丙烯酸）、聚（氨酯）、聚（β - 氨基酯）等、以及这些聚合物和 / 或其它聚合物的共聚物或衍生物，例如聚（丙交酯 - 共 - 乙交酯）(PLGA)。

[0233] 在某些实施方案中，聚合物可以在所需应用中可接受的时间段内进行生物降解。在某些实施方案中，如在体内疗法中，在暴露于具有 6 至 8 的 pH 值且具有 25℃至 37℃的温度的生理溶液时，这种降解在通常少于约五年、一年、六个月、三个月、一个月、十五天、五天、三天、或甚至一天或更短时间（例如 1-4 小时、4-8 小时、4-24 小时、1-24 小时）的时间段内发生。在其它实施方案中，聚合物在约一小时至数周的时间段内降解，这取决于所需的应用。

[0234] 虽然本文所述的包衣和粒子可以包括聚合物，但在一些实施方案中，本文所述的粒子包含不是聚合物（例如非聚合物）并且不是药剂的疏水性物质。举例来说，在一些实施方案中，粒子的全部或部分可以被钝化层包覆。非聚合物质的非限制性示例可以包括某些金属、蜡、以及有机物质（例如有机硅烷、全氟化或氟化有机物质）。

[0235] 在某些实施方案中，本文所述的表面改变剂是表面活性剂。表面活性剂可以吸附在相对疏水相与相对亲水相之间的界面处并且可以形成胶束。适合于在包衣中用作表面改变剂的表面活性剂的非限制性示例包括磷脂（例如 L-α-磷脂酰胆碱 (PC)、1,2-二棕榈酰基磷脂酰胆碱 (DPPC)）、DSPC、DMPC、具有各种 PEG 分子量（如本文所述的分子量）的聚乙二醇化磷脂（例如 DSPE-PEG(2000) 胺）、油酸、脱水山梨糖醇三油酸酯、脱水山梨糖醇单油酸酯、脱水山梨糖醇单月桂酸酯、聚氧乙烯脱水山梨糖醇脂肪酸酯（Tweens®）/ 聚山梨醇酯（如聚氧乙烯脱水山梨糖醇单油酸酯（例如Tween 80®）、聚氧乙烯脱水山梨糖醇单硬脂酸酯（例如 Tween 60®））、聚氧乙烯脱水山梨糖醇单棕榈酸酯（例如 Tween 40®）、聚氧乙烯脱水山梨糖醇单月桂酸酯（例如 Tween 20®））、脱水山梨糖醇脂肪酸酯（例如Span®（例如Span® 20 和Span® 85））、辛基苯酚乙氧基化物表面活性剂（例如 Triton® X-100）、离子型表面活性剂（例如 SDS）、聚氧乙烯 15 羟基硬脂酸酯（例如Solutol® HS 15）、聚乙二醇丁二酸酯（例如生育酚聚乙二醇丁二酸酯 (TPGS，例如维生素 E TPGS)）、天然卵磷脂、油基聚氧乙烯醚、硬脂基聚氧乙烯醚、月桂基聚氧乙烯醚、聚氧乙烯烷基醚、氧乙烯与氧丙烯的嵌段共聚物、聚氧乙烯硬脂酸酯、聚氧乙烯蓖麻油和它们的衍生物（例如Cremophor® EL 和Cremophor® RH 40）、维生素 -PEG 和它们的衍生物、合成卵磷脂、二乙二醇二油酸酯、油酸四氢糠酯、油酸乙酯、肉豆蔻酸异丙酯、单油酸甘油酯、单硬脂酸甘油酯、单蓖麻油酸甘油酯、鲸蜡醇、硬脂醇、聚乙二醇、鲸蜡基氯化吡啶鎓、苯扎氯铵 (benzalkonium chloride)、橄榄油、单月桂酸甘油酯、玉米油、棉籽油、以及葵花籽油。上述化合物的衍生物也是可能的。上述化合物与本文所述的其它化合物的组合也可以用作本发明粒子中的表面改变剂。

[0236] 表面改变剂（如表面活性剂）可以由亲水亲油平衡指数 (HLB) 来表征。HLB 值可以使用格里芬法 (Griffin approach) 来计算 (Griffin WC, “Classification of Surface-Active Agents by'HLB'（通过‘HLB’对表面活性剂进行分类）”, Journal of the Society of Cosmetic Chemists 1(1949):311 ;Griffin WC,“Calculation of HLB Values of Non-Ionic Surfactants（非离子型表面活性剂的 HLB 值的计算）”, Journal of the Society of Cosmetic Chemists 5(1954):249)，如等式 2 中所示：

[0237]

$$HLB = \frac{\text{分子中亲水物的重量\%}}{5} \quad \text{(等式 2)}$$

[0238] 在某些实施方案中，本文所述的表面活性剂的HLB值是至少约1、至少约2、至少约3、至少约5、小于或等于约7、至少约8、至少约9、至少约10、至少约11、至少约12、至少约13、至少约14、至少约15、至少约16、至少约17、至少约18、至少约19、或至少约20。在某些实施方案中，本文所述的表面活性剂的HLB值小于或等于约20、小于或等于约19、小于或等于约18、小于或等于约17、小于或等于约16、小于或等于约15、小于或等于约14、小于或等于约13、小于或等于约12、小于或等于约11、小于或等于约10、小于或等于约9、小于或等于约8、小于或等于约7、小于或等于约5、小于或等于约3、小于或等于约2、或者小于或等于约1。上述范围的组合也是可能的（例如至少约8且小于或等于约19的HLB值）。其它范围也是可能的。

[0239] 在某些实施方案中，本文所述的表面改变剂是稳定剂(stabilizer/stabilizing agent)。稳定剂通常是聚合物并且可能不具有独特的疏水-亲水结构域。稳定剂可以非共价方式吸附到表面和界面上。举例来说，PVA(一种水溶性的非离子型合成聚合物）在食品和药品工业中被广泛地用作稳定剂。PVA的亲水度由于PVA的化学结构和合成途径而可以通过改变它的水解度来改变。适合于在包衣中用作表面改变剂的稳定剂的其它非限制性示例包括聚乙烯吡咯烷酮（如本文所述的聚乙烯吡咯烷酮）。上述稳定剂的衍生物也是可能的。上述稳定剂与本文所述的其它稳定剂的组合可以用作本发明粒子中的表面改变剂。上述聚合物、表面活性剂以及本文所述的稳定剂的组合也可以用作表面改变剂。

[0240] 具有降低的粘膜粘着性的粒子

[0241] 如本文所述，在一些实施方案中，一种方法涉及鉴定出一种物质，如粒子，期望它的粘膜粘着性降低。需要增大的穿过粘液的扩散速率的物质可以例如具有疏水性，具有多个氢键供体或氢键受体，和/或可以带有高电荷。在一些情况下，所述物质可以包括结晶或无定形固体物质。可以用作核心的物质可以被本文所述的合适聚合物包覆，从而形成在表面上具有多个表面改变部分的粒子，以使得粘膜粘着性降低。本文中被描述为具有降低的粘膜粘着性的粒子可以替代地被表征为具有增强的穿过粘液的转移、可在粘液中移动、或具有粘液穿透性（即粘液穿透性粒子），意味着所述粒子比（阴性）对照粒子更快地转移穿过粘液。（阴性）对照粒子可以是已知具有粘膜粘着性的粒子，例如未被本文所述的包衣包覆的未改性的粒子或核心，如200nm羧化聚苯乙烯粒子。

[0242] 在某些实施方案中，本文中的方法包括例如以适用于向受试者的粘液或粘膜表面递送（例如局部递送）的制剂的形式制备经过改性的物质的药物组合物或制剂。具有表面改变部分的药物组合物可以向受试者的粘膜表面递送，例如由于粘膜粘着性降低而可以穿过受试者的粘膜屏障，和/或表现出粒子在粘膜表面延长的停留时间和/或增强的均匀分布。如本领域的普通技术人员所知，粘液是截留大部分外来粒子的具有粘弹性和粘着性的物质。被截留的粒子不能到达下层上皮和/或由粘液清除机制快速地消除。对于到达下层上皮的粒子和/或对于在粘膜组织中具有延长的停留时间的粒子，所述粒子必须快速地穿透粘液分泌物和/或避免粘液清除机制。如果粒子与粘液基本上不发生粘着，那么所述粒子可能能够在粘蛋白纤维之间的间质液中扩散并且到达下层上皮和/或不被粘液清除机

制消除。因此，使用降低粒子的粘膜粘着性的物质对粘膜粘着性物质（例如具有疏水性的药剂）进行改性可以允许向下层上皮有效地递送粒子和/或在粘膜表面处的停留时间延长。

[0243] 此外，在一些实施方案中，与更具粘膜粘着性的粒子相比，本文所述的具有降低的粘膜粘着性的粒子促进粒子在组织表面更好的分布和/或在组织表面存在的时间延长。举例来说，在一些情况下，诸如胃肠道等管腔空间（luminal space）由覆盖有粘液的表面围绕。向这一空间递送的粘膜粘着性粒子通常会通过身体的天然清除机制从所述管腔空间以及从被粘液包覆的表面去除。与粘膜粘着性粒子相比，本文所述的具有降低的粘膜粘着性的粒子可以在管腔空间中保留相对更长的一段时间。这一存在时间的延长可以防止或减少粒子的清除，和/或可以允许粒子在组织表面上更好的分布。存在时间的延长还可能影响粒子穿过管腔空间的转移，例如粒子可以分布到粘液层中并且可以到达下层上皮。

[0244] 在某些实施方案中，被本文所述的聚合物包覆的物质（例如核心）可以穿过受试者的粘液或粘膜屏障，和/或表现出延长的停留时间和/或增强粒子在粘膜表面的均匀分布，例如，与（阴性）对照粒子相比，这些物质更慢地从受试者体内被清除（例如慢了至少1倍、4倍、9倍、或甚至至少19倍）。（阴性）对照粒子可以是已知具有粘膜粘着性的粒子，例如未被本文所述的包衣包覆的未改性的粒子或核心，如200nm羧化聚苯乙烯粒子。

[0245] 在某些实施方案中，本文所述的粒子具有一定的相对速度$\langle V_{平均} \rangle_{相对}$，所述相对速度的定义如下：

[0246]

$$\langle V_{平均} \rangle_{相对} = \frac{\langle V_{平均} \rangle_{样品} - \langle V_{平均} \rangle_{阴性对照}}{\langle V_{平均} \rangle_{阳性对照} - \langle V_{平均} \rangle_{阴性对照}} \quad (等式\ 1)$$

[0247] 其中$\langle V_{平均} \rangle$是系综平均轨迹平均速度，$V_{平均}$是单个粒子在它的轨迹上平均的速度，样品是目标粒子，阴性对照是200nm羧化聚苯乙烯粒子，并且阳性对照是被2kDa-5kDa PEG稠密地聚乙二醇化的200nm聚苯乙烯粒子。

[0248] 可以使用相对速度来比较测试样品的速度与阳性对照和阴性对照这两者的速度。它因此使速度数据相对于来自不同供体的粘液样品的天然变异度归一化并且被认为是确定粒子在粘液中的移动性的严格方式。相对速度可以通过多粒子追踪技术来测量。举例来说，可以使用装备有CCD照相机的荧光显微镜在100×放大倍数下以66.7毫秒（15帧/秒）的时间分辨率对以下每一种类型的粒子在每一个样品内的若干个区域拍摄15秒影片：样品、阴性对照以及阳性对照。样品、阴性对照以及阳性对照可以是荧光粒子以对追踪进行观测。或者，可以将非荧光粒子用荧光分子、荧光标记的表面剂或荧光标记的聚合物涂覆。可以使用高级图像处理软件（例如Image Pro或MetaMorph）测量多个粒子在至少3.335秒（50帧）的时间标度内的单个轨迹。

[0249] 在一些实施方案中，本文所述的粒子在粘液中具有如下的相对速度：大于或等于约0.3、大于或等于约0.4、大于或等于约0.5、大于或等于约0.6、大于或等于约0.7、大于或等于约0.8、大于或等于约0.9、大于或等于约1.0、大于或等于约1.1、大于或等于约1.2、大于或等于约1.3、大于或等于约1.4、大于或等于约1.5、大于或等于约1.6、大于或等于约1.7、大于或等于约1.8、大于或等于约1.9、或者大于或等于约2.0。在一些实施方案中，本

文所述的粒子在粘液中具有如下的相对速度：小于或等于约 10.0、小于或等于约 8.0、小于或等于约 6.0、小于或等于约 4.0、小于或等于约 3.0、小于或等于约 2.0、小于或等于约 1.9、小于或等于约 1.8、小于或等于约 1.7、小于或等于约 1.6、小于或等于约 1.5、小于或等于约 1.4、小于或等于约 1.3、小于或等于约 1.2、小于或等于约 1.1、小于或等于约 1.0、小于或等于约 0.9、小于或等于约 0.8、或者小于或等于约 1.7。上述范围的组合是可能的（例如大于或等于约 0.5 且小于或等于约 6.0 的相对速度）。其它范围也是可能的。所述粘液可以是例如人子宫颈阴道粘液。

[0250] 在某些实施方案中，与对照粒子或相应的粒子（例如未经过改性和 / 或未被本文所述的包衣包覆的相应粒子）相比，本文所述的粒子可以更大的扩散速率扩散穿过粘液或粘膜屏障。在一些情况下，本文所述的粒子可以如下的扩散速率穿过粘液或粘膜屏障，所述扩散速率是对照粒子或相应粒子的扩散速率的至少约 10 倍、20 倍、30 倍、50 倍、100 倍、200 倍、500 倍、1000 倍、2000 倍、5000 倍、10000 倍或更多倍。在一些情况下，本文所述的粒子可以如下的扩散速率穿过粘液或粘膜屏障，所述扩散速率是对照粒子或相应粒子的扩散速率的小于或等于约 10000 倍、小于或等于约 5000 倍、小于或等于约 2000 倍、小于或等于约 1000 倍、小于或等于约 500 倍、小于或等于约 200 倍、小于或等于约 100 倍、小于或等于约 50 倍、小于或等于约 30 倍、小于或等于约 20 倍、或者小于或等于约 10 倍。上述范围的组合也是可能的（例如对照粒子或相应粒子的扩散速率的至少约 10 倍且小于或等于约 1000 倍）。其它范围也是可能的。

[0251] 出于本文所述的比较的目的，相应的粒子可以与测试粒子具有大致相同的尺寸、形状和 / 或密度，但缺少使测试粒子可在粘液中移动的包衣。在一些情况下，测量是基于约 1 秒、或约 0.5 秒、或约 2 秒、或约 5 秒、或约 10 秒的时间标度。本领域的普通技术人员将知晓用于测定几何均方位移和扩散速率的方法。

[0252] 此外，本文所述的粒子可以如下的几何均方位移穿过粘液或粘膜屏障，所述几何均方位移是相应粒子或对照粒子的几何均方位移的至少约 10 倍、20 倍、30 倍、50 倍、100 倍、200 倍、500 倍、1000 倍、2000 倍、5000 倍、10000 倍、或更多倍。在一些情况下，本文所述的粒子可以如下的几何均方位移穿过粘液或粘膜屏障，所述几何均方位移是对照粒子或相应粒子的几何均方位移的小于或等于约 10000 倍、小于或等于约 5000 倍、小于或等于约 2000 倍、小于或等于约 1000 倍、小于或等于约 500 倍、小于或等于约 200 倍、小于或等于约 100 倍、小于或等于约 50 倍、小于或等于约 30 倍、小于或等于约 20 倍、或者小于或等于约 10 倍。上述范围的组合也是可能的（例如对照粒子或相应粒子的几何均方位移的至少约 10 倍且小于或等于约 1000 倍）。其它范围也是可能的。

[0253] 在一些实施方案中，本文所述的粒子以如下的速率扩散穿过粘膜屏障，所述速率接近所述粒子可以扩散穿过水的扩散速率。在一些情况下，本文所述的粒子可以如下的扩散速率穿过粘膜屏障，所述扩散速率是所述粒子在相同条件下扩散穿过水的扩散速率的小于或等于约 1/100、小于或等于约 1/200、小于或等于约 1/300、小于或等于约 1/400、小于或等于约 1/500、小于或等于约 1/600、小于或等于约 1/700、小于或等于约 1/800、小于或等于约 1/900、小于或等于约 1/1000、小于或等于约 1/2000、小于或等于约 1/5000、小于或等于约 1/10,000。在一些情况下，本文所述的粒子可以如下的扩散速率穿过粘膜屏障，所述扩散速率是所述粒子在相同条件下扩散穿过水的扩散速率的大于或等于约 1/10,000、大于或

等于约 1/5000、大于或等于约 1/2000、大于或等于约 1/1000、大于或等于约 1/900、大于或等于约 1/800、大于或等于约 1/700、大于或等于约 1/600、大于或等于约 1/500、大于或等于约 1/400、大于或等于约 1/300、大于或等于约 1/200、或者大于或等于约 1/100。上述范围的组合也是可能的（例如所述粒子在相同条件下扩散穿过水的扩散速率的大于或等于约 1/5000 且小于 1/500）。其它范围也是可能的。所述测量可以是基于约 1 秒、或约 0.5 秒、或约 2 秒、或约 5 秒、或约 10 秒的时间标度。

[0254] 在一个具体的实施方案中，本文所述的粒子可以如下的扩散速率扩散穿过人子宫颈阴道粘液，所述扩散速率是所述粒子扩散穿过水的扩散速率的小于约 1/500。在一些情况下，测量是基于约 1 秒、或约 0.5 秒、或约 2 秒、或约 5 秒、或约 10 秒的时间标度。

[0255] 在某些实施方案中，本发明提供了以一定的绝对扩散速率行进穿过诸如人子宫颈阴道粘液等粘液的粒子。举例来说，本文所述的粒子可以如下扩散速率行进：至少约 1×10^{-4} μm/s、2×10^{-4} μm/s、5×10^{-4} μm/s、1×10^{-3} μm/s、2×10^{-3} μm/s、5×10^{-3} μm/s、1×10^{-2} μm/s、2×10^{-2} μm/s、4×10^{-2} μm/s、5×10^{-2} μm/s、6×10^{-2} μm/s、8×10^{-2} μm/s、1×10^{-1} μm/s、2×10^{-1} μm/s、5×10^{-1} μm/s、1 μm/s、或 2 μm/s。在一些情况下，所述粒子可以如下的扩散速率行进：小于或等于约 2 μm/s、小于或等于约 1 μm/s、小于或等于约 5×10^{-1} μm/s、小于或等于约 2×10^{-1} μm/s、小于或等于约 1×10^{-1} μm/s、小于或等于约 8×10^{-2} μm/s、小于或等于约 6×10^{-2} μm/s、小于或等于约 5×10^{-2} μm/s、小于或等于约 4×10^{-2} μm/s、小于或等于约 2×10^{-2} μm/s、小于或等于约 1×10^{-2} μm/s、小于或等于约 5×10^{-3} μm/s、小于或等于约 2×10^{-3} μm/s、小于或等于约 1×10^{-3} μm/s、小于或等于约 5×10^{-4} μm/s、小于或等于约 2×10^{-4} μm/s、或者小于或等于约 1×10^{-4} μm/s。上述范围的组合也是可能的（例如大于或等于约 2×10^{-4} μm/s 且小于或等于约 1×10^{-1} μm/s）。其它范围也是可能的。在一些情况下，测量是基于约 1 秒、或约 0.5 秒、或约 2 秒、或约 5 秒、或约 10 秒的时间标度。

[0256] 应当了解的是，虽然在此所述的许多移动性（例如相对速度、扩散速率）可以在人子宫颈阴道粘液中进行测量，但它们也可以在其它类型的粘液中进行测量。

[0257] 在某些实施方案中，本文所述的粒子包含给定密度的表面改变部分。表面改变部分可以是表面改变剂中例如暴露于含有粒子的溶剂的部分。举例来说，PVA 的水解的单元 / 嵌段可以是表面改变剂 PVA 的表面改变部分。在另一个实施例中，PEG 链段可以是表面改变剂 PEG-PPO-PEG 的表面改变部分。在一些情况下，表面改变部分和 / 或表面改变剂以如下的密度存在：每平方纳米至少约 0.001 个单元或分子、每平方纳米至少约 0.002 个、至少约 0.005 个、至少约 0.01 个、至少约 0.02 个、至少约 0.05 个、至少约 0.1 个、至少约 0.2 个、至少约 0.5 个、至少约 1 个、至少约 2 个、至少约 5 个、至少约 10 个、至少约 20 个、至少约 50 个、至少约 100 个单元或分子、或者每平方纳米更多个单元或分子。在一些情况下，表面改变部分和 / 或表面改变剂以如下的密度存在：每平方纳米少于或等于约 100 个单元或分子、每平方纳米少于或等于约 50 个、少于或等于约 20 个、少于或等于约 10 个、少于或等于约 5 个、少于或等于约 2 个、少于或等于约 1 个、少于或等于约 0.5 个、少于或等于约 0.2 个、少于或等于约 0.1 个、少于或等于约 0.05 个、少于或等于约 0.02 个、或者少于或等于约 0.01 个单元或分子。上述范围的组合是可能的（例如每平方纳米至少约 0.01 个且少于或等于约 1 个单元或分子的密度）。其它范围也是可能的。在一些实施方案中，上文所述的密

度值可以是在表面改变剂与溶液中的其它组分平衡时的平均密度。

[0258] 本领域的普通技术人员将知晓估算表面改变部分的平均密度的方法（参见例如 S.J.Budijono 等，Colloids and Surfaces A:Physicochem.Eng.Aspects 360(2010)105-110；以及 Joshi 等，Anal.Chim.Acta 104(1979)153-160，上述文献中的每一篇均以引用的方式并入本文）。举例来说，如本文所述，表面改变部分的平均密度可以使用 HPLC 定量和 DLS 分析来测定。首先使用 DLS 对进行表面密度测定的目标粒子的悬浮液进行尺寸测定：将小体积稀释到适当的浓度（例如约 100μg/mL），并且将 Z 均直径视为粒度的代表性测量结果。然后将剩余的悬浮液分成两个等分部分。使用 HPLC，测定第一等分部分的核心物质的总浓度和表面改变部分的总浓度。再使用 HPLC 测定第二等分部分的游离或未结合的表面改变部分的浓度。为了仅从第二等分部分中获得游离或未结合的表面改变部分，通过超速离心将粒子并且因此将任何结合的表面改变部分去除。通过用表面改变部分的总浓度减去未结合的表面改变部分的浓度，可以确定结合的表面改变部分的浓度。由于还测定了第一等分部分的核心物质的总浓度，因此可以确定核心物质与表面改变部分之间的质量比。使用表面改变部分的分子量，可以计算表面改变部分相对于核心物质的质量的数目。为了将这个数字转换成表面密度测量结果，需要计算每核心物质质量的表面积。粒子的体积近似为具有从 DLS 获得的直径的球体的体积，从而允许计算每核心物质质量的表面积。以这种方式，可以确定每表面积表面改变部分的数目。

[0259] 在某些实施方案中，本文所述的粒子包含影响所述粒子的 ζ- 电位的表面改变部分和 / 或表面改变剂。包衣粒子的 ζ 电位可以是例如至少约 -100mV、至少约 -75mV、至少约 -50mV、至少约 -40mV、至少约 -30mV、至少约 -20mV、至少约 -10mV、至少约 -5mV、至少约 5mV、至少约 10mV、至少约 20mV、至少约 30mV、至少约 40mV、至少约 50mV、至少约 75mV、或至少约 100mV。上述范围的组合是可能的（例如至少约 -50mV 且小于或等于约 50mV 的 ζ- 电位）。其它范围也是可能的。

[0260] 本文所述的包衣粒子可以具有任何合适的形状和 / 或尺寸。在一些实施方案中，包衣粒子具有与核心的形状基本上相似的形状。在一些情况下，本文所述的包衣粒子可以是纳米粒子，即粒子具有小于约 1 微米的特征尺寸，其中粒子的特征尺寸是与粒子具有相同体积的理想球体的直径。在其它实施方案中，更大的尺寸是可能的（例如约 1-10 微米）。在一些实施方案中，多个粒子还可以通过平均尺寸（例如多个粒子的平均最大横截面尺寸或平均最小横截面尺寸）来表征。多个粒子可以具有以下平均尺寸：例如小于或等于约 10μm、小于或等于约 5μm、小于或等于约 1μm、小于或等于约 800nm、小于或等于约 700nm、小于或等于约 500nm、小于或等于 400nm、小于或等于 300nm、小于或等于约 200nm、小于或等于约 100nm、小于或等于约 75nm、小于或等于约 50nm、小于或等于约 40nm、小于或等于约 35nm、小于或等于约 30nm、小于或等于约 25nm、小于或等于约 20nm、小于或等于约 15nm、或者小于或等于约 5nm。在一些情况下，多个粒子可以具有以下平均尺寸：例如至少约 5nm、至少约 20nm、至少约 50nm、至少约 100nm、至少约 200nm、至少约 300nm、至少约 400nm、至少约 500nm、至少约 1μm、或至少约 5μm。上述范围的组合也是可能的（例如至少约 50nm 且小于或等于约 500nm 的平均尺寸）。其它范围也是可能的。在一些实施方案中，由本文所述的方法形成的核心的尺寸具有高斯型分布。

[0261] 药剂

[0262] 在一些实施方案中，包衣粒子包含至少一种药剂。所述药剂可以存在于粒子的核心中和/或存在于粒子的包衣中（例如分散在整个核心和/或包衣中）。在一些情况下，药剂可以被设置在粒子的表面上（例如包衣的外表面上、包衣的内表面上、核心的表面上）。可以使用通常已知的技术（例如通过包覆、吸附、共价连接、封装、或其它方法）将药剂包含在粒子内和/或设置在粒子的一部分中。在一些情况下，药剂可以在对粒子进行包覆之前或期间存在于粒子的核心中。在一些情况下，如本文所述，药剂在形成粒子核心期间存在。

[0263] 药剂的非限制性示例包括成像剂、诊断剂、治疗剂、具有检测标记的药剂、核酸、核酸类似物、小分子、拟肽、蛋白质、肽、脂质、疫苗、病毒载体、病毒、以及表面活性剂。

[0264] 在一些实施方案中，本文所述的粒子中所含的药剂在待靶向的粘膜组织中具有治疗作用、诊断作用或成像作用。粘膜组织的非限制性示例包括口腔组织（例如包括颊膜和食道膜以及扁桃体表面）、眼部组织、胃肠组织（例如包括胃、小肠、大肠、结肠、直肠）、鼻部组织、呼吸道组织（例如包括鼻膜、咽膜、气管膜以及支气管膜）、以及生殖器组织（例如包括阴道膜、子宫颈膜以及尿道膜）。

[0265] 在本文所述的粒子中可以存在任何合适数量的药剂。举例来说，在本文所述的粒子中可以存在至少 1 种、至少 2 种、至少 3 种、至少 4 种、至少 5 种或更多种、但一般少于 10 种的药剂。

[0266] 多种具有粘膜粘着性的药物是本领域已知的并且可以用作本文所述的粒子中的药剂（参见例如 Khanvilkar K,Donovan MD,Flanagan DR,Drug transfer through mucus(药物穿过粘液的转移),Advanced Drug Delivery Reviews 48(2001)173-193；Bhat PG,Flanagan DR,Donovan MD,Drug diffusion through cystic fibrotic mucus:steady-state permeation,rheologic properties,and glycoprotein morphology(药物穿过囊性纤维化粘液的扩散：稳态的渗透、流变学特性以及糖蛋白形态),J Pharm Sci,1996 年 6 月；85(6):624-30)。药剂的另外的非限制性示例包括成像剂和诊断剂（如不透射线剂、标记的抗体、标记的核酸探针、染料，如有色染料或荧光染料等）以及佐剂（放射增敏剂、转染增强剂、趋化剂和化学吸引剂、调控细胞粘附和/或细胞运动的肽、细胞透化剂、疫苗增效剂、多药抗性和/或外排泵的抑制剂等）。

[0267] 药剂的另外的非限制性示例包括帕唑帕尼、索拉非尼、拉帕替尼 (lapatinib)、氟西奈德 (fluocinolone acetonide)、司马沙尼 (semaxanib)、阿西替尼、替沃赞尼 (tivozanib)、西地尼布、利尼伐尼、瑞戈非尼 (regorafenib)、替拉替尼 (telatinib)、瓦他拉尼 (vatalanib)、MGCD-265、OSI-930、KRN-633、比马前列素 (bimatoprost)、拉坦前列素 (latanoprost)、曲伏前列素 (travoprost)、阿洛泼林 (aloxiprin)、金诺芬 (auranofin)、阿扎丙酮 (azapropazone)、贝诺酯 (benorylate)、双氟尼酸 (diflunisal)、依托度酸 (etodolac)、芬布芬 (fenbufen)、非诺洛芬钙 (fenoprofen calcim)、氟比洛芬 (flurbiprofen)、呋塞米 (furosemide)、布洛芬 (ibuprofen)、吲哚美辛 (indomethacin)、酮洛芬 (ketoprofen)、依碳酸氯替泼诺、溴芬酸铍、溴芬酸镁、溴芬酸钙、溴芬酸锶、溴芬酸钡、溴芬酸锌、溴芬酸铜 (II)、双氯芬酸游离酸、双氯芬酸铍、双氯芬酸镁、双氯芬酸钙、双氯芬酸锶、双氯芬酸钡、双氯芬酸锌、双氯芬酸铜 (II)、酮咯酸游离酸、酮咯酸铍、酮咯酸镁、酮咯酸钙、酮咯酸锶、酮咯酸钡、酮咯酸锌、酮咯酸铜 (II)、甲氯芬那酸 (meclofenamic acid)、甲芬那酸 (mefenamic acid)、萘丁美酮 (nabumetone)、

萘普生(naproxen)、羟保泰松(oxyphenbutazone)、保泰松(phenylbutazone)、吡罗昔康(piroxicam)、舒林酸(sulindac)、阿苯达唑(albendazole)、苄芬宁羟萘酸盐(bephenium hydroxynaphthoate)、坎苯达唑(cambendazole)、二氯芬(dichlorophen)、伊维菌素(ivermectin)、甲苯咪唑(mebendazole)、奥沙尼喹(oxamniquine)、奥吩达唑(oxfendazole)、双羟萘酸奥克太尔(oxantel embonate)、吡喹酮(praziquantel)、双羟萘酸噻嘧啶(pyrantel embonate)、噻苯咪唑(thiabendazole)、盐酸胺碘酮(amiodarone HCl)、达舒平(disopyramide)、乙酸氟卡胺(flecainide acetate)、硫酸奎尼丁(quinidine sulphate)。抗细菌剂:苯明青霉素(benethamine penicillin)、西诺沙星(cinoxacin)、盐酸环丙沙星(ciprofloxacin HCl)、克拉霉素(clarithromycin)、氯苯吩嗪(clofazimine)、氯唑西林(cloxacillin)、地美环素(demeclocycline)、多西环素(doxycycline)、红霉素(erythromycin)、乙硫异烟胺(ethionamide)、亚胺培南(imipenem)、萘啶酮酸(nalidixic acid)、呋喃妥因(nitrofurantoin)、利福平(rifampicin)、螺旋霉素(spiramycin)、磺胺苯酰(sulphabenzamide)、磺胺多辛(sulphadoxine)、磺胺甲基嘧啶(sulphamerazine)、磺胺醋酰(sulphacetamide)、磺胺嘧啶(sulphadiazine)、磺胺异噁唑(sulphafurazole)、磺胺甲噁唑(sulphamethoxazole)、磺胺吡啶(sulphapyridine)、四环素(tetracycline)、甲氧苄啶(trimethoprim)、双香豆素(dicoumarol)、双嘧达莫(dipyridamole)、醋硝香豆素(nicoumalone)、苯茚二酮(phenindione)、阿莫沙平(amoxapine)、盐酸马普替林(maprotiline HCl)、盐酸米安色林(mianserin HCL)、盐酸去甲替林(nortriptyline HCl)、盐酸曲唑酮(trazodone HCL)、顺丁烯二酸曲米帕明(trimipramine maleate)、醋磺己脲(acetohexamide)、氯磺丙脲(chlorpropamide)、格列本脲(glibenclamide)、格列齐特(gliclazide)、格列吡嗪(glipizide)、妥拉磺脲(tolazamide)、甲苯磺丁脲(tolbutamide)、贝克拉胺(beclamide)、卡马西平(carbamazepine)、氯硝西泮(clonazepam)、乙苯妥英(ethotoin)、美芬妥因(methoin)、甲琥胺(methsuximide)、甲基苯巴比妥(methylphenobarbitone)、奥卡西平(oxcarbazepine)、甲乙双酮(paramethadione)、苯乙酰脲(phenacemide)、苯巴比妥(phenobarbitone)、苯妥英钠(phenytoin)、苯琥胺(phensuximide)、扑米酮(primidone)、舒噻嗪(sulthiame)、丙戊酸(valproic acid)、两性霉素(amphotericin)、硝酸布康唑(butoconazole nitrate)、克霉唑(clotrimazole)、硝酸益康唑(econazole nitrate)、氟康唑(fluconazole)、氟胞嘧啶(flucytosine)、灰黄霉素(griseofulvin)、伊曲康唑(itraconazole)、酮康唑(ketoconazole)、咪康唑(miconazole)、纳他霉素(natamycin)、制霉菌素(nystatin)、硝酸硫康唑(sulconazole nitrate)、盐酸特比萘芬(terbinafine HCl)、特康唑(terconazole)、噻康唑(tioconazole)、十一碳烯酸、别嘌呤醇(allopurinol)、丙磺舒(probenecid)、苯磺唑酮(sulphin-pyrazone)、氨氯地平(amlodipine)、贝尼地平(benidipine)、达罗地平(darodipine)、盐酸地尔硫卓(dilitazem HCl)、二氮嗪(diazoxide)、非洛地平(felodipine)、乙酸胍那苄(guanabenz acetate)、伊拉地平(isradipine)、米诺地尔(minoxidil)、盐酸尼卡地平(nicardipine HCl)、硝苯地平(nifedipine)、尼莫地平(nimodipine)、盐酸酚苄明(phenoxybenzamine HCl)、盐酸哌唑嗪(prazosin HCL)、利血平(reserpine)、盐酸特拉唑嗪(terazosin HCL)、阿莫地喹(amodiaquine)、氯喹(chloroquine)、盐酸氯丙胍(chlorproguanil

HCl)、盐酸卤泛群(halofantrine HCl)、盐酸甲氟喹(mefloquine HCl)、盐酸氯胍(proguanil HCl)、乙胺嘧啶(pyrimethamine)、硫酸奎宁(quinine sulphate)、甲磺酸二氢麦角胺(dihydroergotamine mesylate)、酒石酸麦角胺(ergotamine tartrate)、顺丁烯二酸二甲麦角新碱(methysergide maleate)、顺丁烯二酸苯噻啶(pizotifen maleate)、丁二酸舒马曲坦(sumatriptan succinate)、阿托品(atropine)、盐酸苯海索(benzhexol HCl)、比哌立登(biperiden)、盐酸普罗吩胺(ethopropazine HCl)、莨菪碱(hyoscyamine)、溴美喷酯(mepenzolate bromide)、盐酸羟苄利明(oxyphencylcimine HCl)、托吡卡胺(tropicamide)、氨鲁米特(aminoglutethimide)、安吖啶(amsacrine)、硫唑嘌呤(azathioprine)、白消安(busulphan)、苯丁酸氮芥(chlorambucil)、环孢菌素(cyclosporin)、达卡巴嗪(dacarbazine)、雌莫司汀(estramustine)、依托泊苷(etoposide)、洛莫司汀(lomustine)、美法仑(melphalan)、巯基嘌呤(mercaptopurine)、甲氨蝶呤(methotrexate)、丝裂霉素(mitomycin)、米托坦(mitotane)、米托蒽醌(mitozantrone)、盐酸甲基苄肼(procarbazine HCl)、柠檬酸他莫昔芬(tamoxifen citrate)、睾内酯(testolactone)、苄硝唑(benznidazole)、氯碘羟喹(clioquinol)、癸氧喹酯(decoquinate)、二碘羟基喹啉、二氯尼特糠酸酯(diloxanide furoate)、二硝托胺(dinitolmide)、呋喃唑酮(furzolidone)、甲硝哒唑(metronidazole)、尼莫拉唑(nimorazole)、呋喃西林(nitrofurazone)、奥硝唑(ornidazole)、替硝唑(tinidazole)、甲亢平(carbimazole)、丙硫氧嘧啶(propylthiouracil)、阿普唑仑(alprazolam)、戊巴比妥(amylobarbitone)、巴比妥(barbitone)、苯他西泮(bentazepam)、溴西泮(bromazepam)、溴哌利多(bromperidol)、溴替唑仑(brotizolam)、丁巴比妥(butobarbitone)、卡溴脲(carbromal)、氯氮卓(chlordiazepoxide)、氯美噻唑(chlormethiazole)、氯丙嗪(chlorpromazine)、氯巴占(clobazam)、氯噻西泮(clotiazepam)、氯氮平(clozapine)、地西泮(diazepam)、氟哌利多(droperidol)、炔己蚁胺(ethinamate)、氟阿尼酮(flunanisone)、氟硝西泮(flunitrazepam)、氟丙嗪(fluopromazine)、三氟噻吨癸酸酯(flupenthixol decanoate)、氟奋乃静癸酸酯(fluphenazine decanoate)、氟西泮(flurazepam)、氟哌啶醇(haloperidol)、劳拉西泮(lorazepam)、氯甲西泮(lormetazepam)、美达西泮(medazepam)、眠尔通(meprobamate)、安眠酮(methaqualone)、咪达唑仑(midazolam)、硝西泮(nitrazepam)、奥沙西泮(oxazepam)、戊巴比妥(pentobarbitone)、奋乃静(perphenazine)、匹莫齐特(pimozide)、丙氯拉嗪(prochlorperazine)、舒必利(sulpiride)、替马西泮(temazepam)、硫利达嗪(thioridazine)、三唑仑(triazolam)、佐匹克隆(zopiclone)、醋丁洛尔(acebutolol)、阿普洛尔(alprenolol)、阿替洛尔(atenolol)、拉贝洛尔(labetalol)、美托洛尔(metoprolol)、纳多洛尔(nadolol)、氧烯洛尔(oxprenolol)、品多洛尔(pindolol)、普萘洛尔(propranolol)、氨利酮(amrinone)、洋地黄毒苷(digitoxin)、地高辛(digoxin)、依诺昔酮(enoximone)、毛花苷C(lanatoside C)、甲地高辛(medigoxin)、倍氯米松(beclomethasone)、倍他米松(betamethasone)、布地奈德(budesonide)、乙酸可的松(cortisone acetate)、去氧米松(desoxymethasone)、地塞米松(dexamethasone)、乙酸氟氢可的松(fludrocortisone acetate)、氟尼缩松(flunisolide)、氟可龙(flucortolone)、丙酸氟替卡松、氢化可的松(hydrocortisone)、

甲泼尼龙(methylprednisolone)、泼尼松龙(prednisolone)、泼尼松(prednisone)、曲安西龙(triamcinolone)、乙酰唑胺(acetazolamide)、阿米洛利(amiloride)、苄氟噻嗪(bendrofluazide)、布美他尼(bumetanide)、氯噻嗪(chlorothiazide)、氯噻酮(chlorthalidone)、利尿酸(ethacrynic acid)、呋塞米(frusemide)、美托拉宗(metolazone)、螺内酯(spironolactone)、氨苯蝶啶(triamterene)、甲磺酸溴隐亭(bromocriptine mesylate)、顺丁烯二酸麦角乙脲(lysuride maleate)、比沙可啶(bisacodyl)、西咪替丁(cimetidine)、西沙必利(cisapride)、盐酸地芬诺酯(diphenoxylate HCl)、多潘立酮(domperidone)、法莫替丁(famotidine)、洛哌丁胺(loperamide)、美沙拉嗪(mesalazine)、尼扎替丁(nizatidine)、奥美拉唑(omeprazole)、盐酸昂丹司琼(ondansetron HCL)、盐酸雷尼替丁(ranitidine HCl)、柳氮磺胺吡啶(sulphasalazine)、阿伐斯汀(acrivastine)、阿司咪唑(astemizole)、桂利嗪(cinnarizine)、赛克利嗪(cyclizine)、盐酸赛庚啶(cyproheptadie HCl)、茶苯海明(dimenhydrinate)、盐酸氟桂利嗪(flunarizine HCl)、罗拉他定(loratadine)、盐酸美克洛嗪(meclozine HCl)、奥沙米特(oxatomide)、特非那丁(terfenadine)、苯扎贝特(bezafibrate)、氯贝特(clofibrate)、非诺贝特(fenofibrate)、吉非罗齐(gemfibrozil)、普罗布考(probucol)、硝酸戊酯、三硝酸甘油、二硝酸异山梨醇酯、单硝酸异山梨醇酯、季戊四醇四硝酸酯、β-胡萝卜素、维生素A、维生素B2、维生素D、维生素E、维生素K、可待因(codeine)、右丙氧芬(dextropropyoxyphene)、海洛因(diamorphine)、二氢可待因(dihydrocodeine)、美普他酚(meptazinol)、美沙酮(methadone)、吗啡(morphine)、纳布啡(nalbuphine)、喷他佐辛(pentazocine)、克罗米芬(clomiphene citrate)、丹那唑(danazol)、炔雌醇(ethinyl estradiol)、乙酸甲羟孕酮(medroxyprogesterone acetate)、美雌醇(mestranol)、甲睾酮(methyltestosterone)、炔诺酮(norethisterone)、甲基炔诺酮(norgestrel)、雌二醇(estradiol)、结合雌激素、孕酮、司坦唑醇(stanozolol)、己烯雌酚(stibestrol)、睾酮(testosterone)、替勃龙(tibolone)、安非他明(amphetamine)、右苯丙胺(dexamphetamine)、右芬氟拉明(dexfenfluramine)、芬氟拉明(fenfluramine)、以及马吲哚(mazindol)。

[0268] 在一些实施方案中,本文所述的粒子中存在的药剂可以是皮质类固醇、非类固醇抗炎药(NSAID)、受体酪氨酸激酶(RTK)抑制剂、环加氧酶(COX)抑制剂、血管生成抑制剂、糖皮质激素受体激动剂、前列腺素类似物、β-阻断剂、碳酸酐酶抑制剂、哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin,mTOR)抑制剂、钙调神经磷酸酶抑制剂、ρ激酶抑制剂、维生素、矿物质、抗组胺剂、肥大细胞稳定剂、免疫抑制剂、免疫调节剂、α-阻断剂、抗细菌剂、抗病毒剂、抗真菌剂、胆碱能激动剂、抗胆碱酯酶剂、毒蕈碱拮抗剂、拟交感神经剂、以及它们的组合。

[0269] 在某些实施方案中,本文所述的粒子中存在的药剂是皮质类固醇。在某些实施方案中,本文所述的粒子中存在的皮质类固醇选自依碳酸氯替泼诺、氢化可的松、可的松(cortisone)、替可的松(tixocortol)、泼尼松龙、甲泼尼龙、泼尼松、曲安西龙、莫米松(mometasone)、安西奈德(amcinonide)、布地奈德、地奈德(desonide)、乙酸氟轻松(fluocinonide)、氟轻松(fluocinolone)、哈西奈德(halcinonide)、倍他米松、地塞米松、氟可龙(fluocortolone)、氢化可的松、阿氯米松(aclometasone)、

泼尼卡酯(prednicarbate)、氯倍他松(clobetasone)、氯倍他索(clobetasol)、氟泼尼定(fluprednidene)、糖皮质激素、盐皮质激素、醛固酮(aldosterone)、去氧皮质酮(deoxycorticosterone)、氟氢可的松、卤贝他索(halobetasol)、二氟拉松(diflorasone)、去羟米松(desoximetasone)、氟替卡松、氟氢缩松(flurandrenolide)、阿氯米松(alclometasone)、二氟可龙(diflucortolone)、氟尼缩松、倍氯米松、二氟泼尼酯(difluprednate)、乙酸泼尼松龙、利美索龙(rimexolone)、地塞米松、氟米龙(fluorometholone)、或其组合。

[0270] 在某些实施方案中,本文所述的粒子中存在的药剂是NSAID。在某些实施方案中,本文所述的粒子中存在的NSAID选自溴芬酸、双氯芬酸、酮咯酸、氟比洛芬、奈帕芬胺(nepafenac)、舒洛芬(suprofen)、其盐(例如其碱土金属盐)、以及它们的组合。

[0271] 在某些实施方案中,本文所述的粒子中存在的药剂是受体酪氨酸激酶(RTK)抑制剂。在某些实施方案中,本文所述的粒子中存在的RTK抑制剂选自索拉非尼、利尼伐尼、MGCD-265、帕唑帕尼、西地尼布、阿西替尼、TAK-285(武田公司(Takeda))、TAK-593(武田公司)、AGN-199659(眼力健公司(Allergan))、来他替尼(lestaurtinib)、替万替尼(tivantinib)、拉帕替尼、帕尼单抗(panitumumab)、伊马替尼(imatinib)、尼罗替尼(nilotinib)、阿法替尼(afatinib)、贝伐单抗(bevacizumab)、瑞戈非尼、凡德他尼(vandetanib)、舒尼替尼(sunitinib)、以及它们的组合。

[0272] 在某些实施方案中,本文所述的粒子中存在的药剂是环加氧酶(COX)抑制剂。在某些实施方案中,本文所述的粒子中存在的COX抑制剂选自溴芬酸、塞内昔布(celecoxib)、罗非昔布(rofecoxib)、伐地考昔(valdecoxib)、帕瑞昔布(parecoxib)、罗美昔布(lumiracoxib)、依他昔布(etoricoxib)、非罗考昔(firocoxib)、舒洛芬、以及它们的组合。

[0273] 在某些实施方案中,本文所述的粒子中存在的药剂是血管生成抑制剂。在某些实施方案中,本文所述的粒子中存在的血管生成抑制剂选自索拉非尼、利尼伐尼、MGCD-265(梅特希尔基因公司(MethylGene))、帕唑帕尼、西地尼布、阿西替尼、角鲨胺(squalamine)、乳酸角鲨胺、替沃赞尼、司马沙尼、拉帕替尼、瑞戈非尼、替拉替尼、瓦他拉尼、OSI-930(安斯泰来公司(Astellas))、KRN-633(麒麟啤酒公司(Kirin Brewery))、NRP-1、血管生成素2、TSP-1、TSP-2、血管抑素、内皮抑素、血管抑制因子(vasostatin)、钙网织蛋白(calreticulin)、血小板因子-4、TIMP、CDAI、Meth-1、Meth-2、IFN-α、IFN-β、IFN-γ、CXCL10、IL-4、IL-12、IL-18、凝血酶原、抗凝血酶III片段、催乳素、VEGI、SPARC、骨桥蛋白、乳腺丝抑蛋白(maspin)、血管能抑素(canstatin)、增殖蛋白相关蛋白、休眠蛋白(restin)、TAK-285(武田公司)、TAK-593(武田公司)、AGN-199659(眼力健公司)、iSONEP(勒帕斯公司(Lpath))、MC-1101(马库克利尔公司(MacuCLEAR))、ESBA1008(爱尔康公司(Alcon))、X-82和兰尼单抗(ranibizumab)、贝伐单抗、凡德他尼、兰尼单抗、阿柏西普(aflibercept)、哌加他尼(pegaptanib)、西妥昔单抗(cetuximab)、以及它们的组合。

[0274] 在某些实施方案中,本文所述的粒子中存在的药剂是糖皮质激素受体激动剂。在某些实施方案中,本文所述的粒子中存在的糖皮质激素受体激动剂选自美普克莱(mapracorat)、利美索龙、泼尼松、地塞米松、氟米龙、甲羟松(medrysone)、以及它们的组合。

[0275] 在某些实施方案中，本文所述的粒子中存在的药剂是前列腺素类似物。在某些实施方案中，本文所述的粒子中存在的前列腺素类似物选自拉坦前列素、曲伏前列素、乌诺前列酮 (unoprostone)、比马前列素、以及它们的组合。

[0276] 在某些实施方案中，本文所述的粒子中存在的药剂是 β-阻断剂。在某些实施方案中，本文所述的粒子中存在的 β-阻断剂选自阿普洛尔、布新洛尔 (bucindolol)、卡替洛尔 (carteolol)、卡维地洛 (carvedilol)、拉贝洛尔、纳多洛尔、氧烯洛尔、喷布洛尔 (penbutolol)、品多洛尔、普萘洛尔、索他洛尔 (sotalol)、噻吗洛尔 (timolol)、顺丁烯二酸噻吗洛尔、杜仲 (eucommia bark)、醋丁洛尔、阿替洛尔、倍他索洛尔 (betaxolol)、比索洛尔 (bisoprolol)、塞利洛尔 (celiprolol)、艾司洛尔 (esmolol)、美托洛尔、奈必洛尔 (nebivolol)、丁氧胺 (butaxamine)、ICI-118,551(帝国化学工业公司 (Imperial Chemical Industries))、SR 59230A(赛诺菲研究公司 (Sanofi Recherche))、左布诺洛尔 (levobunolol)、美替洛尔 (metipranolol)、卡替洛尔、倍他索洛尔、以及它们的组合。

[0277] 在某些实施方案中，本文所述的粒子中存在的药剂是碳酸酐酶抑制剂。在某些实施方案中，本文所述的粒子中存在的碳酸酐酶抑制剂选自乙酰唑胺、布林佐胺 (brinzolamide)、多佐胺 (dorzolamide)、多佐胺和噻吗洛尔、甲醋唑胺 (methazolamide)、以及它们的组合。

[0278] 在某些实施方案中，本文所述的粒子中存在的药剂是哺乳动物雷帕霉素靶蛋白 (mTOR) 抑制剂。在某些实施方案中，本文所述的粒子中存在的 mTOR 抑制剂选自他克莫司 (tacrolimus)、西罗莫司 (sirolimus)、以及它们的组合。

[0279] 在某些实施方案中，本文所述的粒子中存在的药剂是钙调神经磷酸酶抑制剂。在某些实施方案中，本文所述的粒子中存在的钙调神经磷酸酶抑制剂选自伏孢素 (voclosporin)、环孢菌素、以及它们的组合。

[0280] 在某些实施方案中，本文所述的粒子中存在的药剂是 ρ 激酶抑制剂。在某些实施方案中，本文所述的粒子中存在的 ρ 激酶抑制剂选自SNJ-1656(千寿制药株式会社 (Senju Pharmaceuticals))、AR-2286(埃尔里制药公司 (Aerie Pharmaceuticals))、AR-13324(埃尔里制药公司)、以及它们的组合。

[0281] 在某些实施方案中，本文所述的粒子中存在的药剂是维生素。在某些实施方案中，本文所述的粒子中存在的维生素选自维生素 A、维生素 B_1、维生素 B_2(核黄素)、维生素 B_6、维生素 B_{12}、维生素 C、维生素 E、叶酸、维生素 K、以及它们的组合。

[0282] 在某些实施方案中，本文所述的粒子中存在的药剂是矿物质。在某些实施方案中，本文所述的粒子中存在的矿物质是锌。

[0283] 在某些实施方案中，本文所述的粒子中存在的药剂是抗组胺剂。在某些实施方案中，本文所述的粒子中存在的抗组胺剂选自二反丁烯二酸依美斯汀 (emedastine difumarate)、盐酸左卡巴斯汀 (levocabastine hydrochloride)、色甘酸钠 (cromolyn sodium)、以及它们的组合。

[0284] 在某些实施方案中，本文所述的粒子中存在的药剂是肥大细胞稳定剂。在某些实施方案中，本文所述的粒子中存在的肥大细胞稳定剂选自洛度沙胺氨丁三醇 (lodoxamide tromethamine)、吡嘧司特 (pemirolast)、奈多罗米 (nedocromil)、盐酸奥洛他定 (olopatadine hydrochloride)、反丁烯二酸酮替芬 (ketotifen fumarate)、氮卓斯汀

(azelastine)、依匹斯汀 (epinastine)、以及它们的组合。

[0285] 在某些实施方案中，本文所述的粒子中存在的药剂是免疫抑制剂。在某些实施方案中，本文所述的粒子中存在的免疫抑制剂选自氟尿嘧啶 (fluorouracil)、丝裂霉素、以及它们的组合。

[0286] 在某些实施方案中，本文所述的粒子中存在的药剂是免疫调节剂。在某些实施方案中，本文所述的粒子中存在的免疫调节剂是环孢素 (ciclosporin)。

[0287] 在某些实施方案中，本文所述的粒子中存在的药剂是 α－阻断剂。在某些实施方案中，本文所述的粒子中存在的 α－阻断剂是达哌唑 (dapiprazole)。

[0288] 在某些实施方案中，本文所述的粒子中存在的药剂是抗细菌剂。在某些实施方案中，本文所述的粒子中存在的抗细菌剂选自杆菌肽锌 (bacitracin zinc)、氯霉素 (chloramphenicol)、盐酸环丙沙星、红霉素、加替沙星 (gatifloxacin)、硫酸庆大霉素 (gentamicin sulfate)、左氧氟沙星 (levofloxacin)、莫西沙星 (moxifloxacin)、氧氟沙星 (ofloxacin)、磺胺乙酰钠 (sulfacetamide sodium)、多粘菌素 B(polymyxin B) 组合、硫酸妥布霉素 (tobramycin sulfate)、以及它们的组合。

[0289] 在某些实施方案中，本文所述的粒子中存在的药剂是抗病毒剂。在某些实施方案中，本文所述的粒子中存在的抗病毒剂选自三氟尿苷 (trifluridine)、阿糖腺苷 (vidarabine)、阿昔洛韦 (acyclovir)、伐昔洛韦 (valacyclovir)、泛昔洛韦 (famciclovir)、膦甲酸 (foscarnet)、更昔洛韦 (ganciclovir)、福米韦生 (fo[b1]mivirsen)、西多福韦 (cidofovir)、以及它们的组合。

[0290] 在某些实施方案中，本文所述的粒子中存在的药剂是抗真菌剂。在某些实施方案中，本文所述的粒子中存在的抗真菌剂选自两性霉素 B、纳他霉素、氟康唑、伊曲康唑、酮康唑、咪康唑、以及它们的组合。

[0291] 在某些实施方案中，本文所述的粒子中存在的药剂是胆碱能激动剂。在某些实施方案中，本文所述的粒子中存在的胆碱能激动剂选自乙酰胆碱 (acetylcholine)、卡巴胆碱 (carbachol)、毛果芸香碱 (pilocarpine)、以及它们的组合。

[0292] 在某些实施方案中，本文所述的粒子中存在的药剂是抗胆碱酯酶剂。在某些实施方案中，本文所述的粒子中存在的抗胆碱酯酶剂选自毒扁豆碱 (physostigmine)、二乙氧磷酰硫胆碱 (echothiophate)、以及它们的组合。

[0293] 在某些实施方案中，本文所述的粒子中存在的药剂是毒蕈碱拮抗剂。在某些实施方案中，本文所述的粒子中存在的毒蕈碱拮抗剂选自阿托品、东莨菪碱 (scopolamine)、后马托品 (homatropine)、环喷托酯 (cyclopentolate)、托吡卡胺、以及它们的组合。

[0294] 在某些实施方案中，本文所述的粒子中存在的药剂是拟交感神经剂。在某些实施方案中，本文所述的粒子中存在的拟交感神经剂选自地匹福林 (dipivefrin)、肾上腺素、苯福林 (phenylephrine)、安普乐定 (apraclonidine)、溴莫尼定 (brimonidine)、可卡因 (cocaine)、羟基苯丙胺 (hydroxyamphetamine)、萘甲唑啉 (naphazoline)、四氢唑啉、以及它们的组合。

[0295] 本文所述的粒子中存在的药剂还可以包括本文所述的或本领域已知的其它化合物。在某些实施方案中，本文所述的粒子中存在的药剂是微纤溶酶或 CLG561(爱尔康公司)。

[0296] 用途和药物组合物

[0297] 本文所述的粒子可以用于任何合适的应用中。在一些情况下，所述粒子是药物组合物（例如如本文所述）的一部分，例如用于通过或向粘液或粘膜表面递送药剂（例如药物、治疗剂、诊断剂、成像剂）的粒子。药物组合物可以包含本文所述的至少一种粒子和一种或多种药学上可接受的赋形剂或载体。所述组合物可以用于治疗、预防和/或诊断受试者的病况，其中所述方法包括向受试者施用所述药物组合物。要通过本文所述的制品和方法治疗的受试者或患者可以意指人或非人动物，如灵长类动物、哺乳动物、以及脊椎动物。

[0298] 涉及治疗受试者的方法可以包括预防疾病、病症或病况在可能易患所述疾病、病症和/或病况，但尚未被诊断为患病的受试者中出现；抑制所述疾病、病症或病况，例如阻碍它进展；以及减轻所述疾病、病症或病况，例如引起所述疾病、病症和/或病况消退。治疗疾病或病况包括改善具体疾病或病况的至少一个症状，即使潜在的病理生理学未受到影响（例如，通过施用镇痛剂来治疗受试者的疼痛，即使这种药剂并未对疼痛的原因进行治疗）。

[0299] 在一些实施方案中，本文所述的药物组合物向受试者的粘膜表面递送并且例如由于粘膜粘着性降低而可以穿过受试者的粘膜屏障（例如粘液），和/或可以表现出粒子在粘膜表面延长的停留时间和/或增强的均匀分布。粘膜组织的非限制性示例包括口腔组织（例如包括颊膜和食道膜以及扁桃体表面）、眼部组织、胃肠组织（例如包括胃、小肠、大肠、结肠、直肠）、鼻部组织、呼吸道组织（例如包括鼻膜、咽膜、气管膜以及支气管膜）、以及生殖器组织（例如包括阴道膜、子宫颈膜以及尿道膜）。

[0300] 本文所述的且根据本文所述的制品和方法使用的药物组合物可以包括药学上可接受的赋形剂或载体。药学上可接受的赋形剂或药学上可接受的载体可以包括任何合适类型的无毒的惰性固体、半固体或液体填充剂、稀释剂、封装材料或配制辅剂。可以用作药学上可接受的载体的物质的一些示例是糖，如乳糖、葡萄糖以及蔗糖；淀粉，如玉米淀粉和马铃薯淀粉；纤维素和它的衍生物，如羧甲基纤维素钠、乙基纤维素以及乙酸纤维素；黄蓍胶粉末；麦芽；明胶；滑石粉；赋形剂，如可可脂和栓剂蜡；油类，如花生油、棉籽油、红花油、芝麻油、橄榄油、玉米油和大豆油；二醇类，如丙二醇；酯类，如油酸乙酯和月桂酸乙酯；琼脂；洗涤剂，如 Tween 80；缓冲剂，如氢氧化镁和氢氧化铝；海藻酸；无热原的水；等渗盐水；林格氏溶液 (Ringer's solution)；乙醇；和磷酸盐缓冲溶液，以及其它无毒的相容性润滑剂，如月桂基硫酸钠和硬脂酸镁，以及根据配制人员的判断，着色剂、释放剂、包衣剂、甜味剂、调味剂和芳香剂、防腐剂以及抗氧化剂也可以存在于组合物中。如本领域的技术人员所了解，可以基于如下文所述的施用途径、所递送的药剂、药剂递送的时程等来选择赋形剂。

[0301] 含有本文所述的粒子的药物组合物可以通过本领域已知的任何途径向受试者施用。这些途径包括但不限于口服、舌下、经鼻、真皮内、皮下、肌内、经直肠、经阴道、静脉内、动脉内、脑池内、腹膜内、玻璃体内、眼周、局部（如通过粉剂、乳膏剂、软膏剂或滴剂）、经颊以及吸入施用。在一些实施方案中，本文所述的组合物可以作为注射剂（静脉内、肌内或皮下）、滴注制剂或栓剂以不经肠方式施用。如本领域的技术人员所了解，实现所需的生物作用的施用途径和有效剂量可以由所施用的药剂、靶器官、所施用的制剂、施用时程、所治疗的疾病、预期用途等来确定。

[0302] 举例来说，所述粒子可以被包括在将被配制成鼻喷雾剂的药物组合物中，以使得

穿过鼻粘液层递送所述药物组合物。作为另一个示例，所述粒子可以被包括在将被配制成吸入剂的药物组合物中，以使得穿过肺粘液层递送所述药物组合物。作为另一个示例，如果要口服施用组合物，那么可以将它配制成片剂、胶囊、颗粒剂、粉剂或糖浆。类似地，所述粒子可以被包括在将通过眼部组织、胃肠组织、鼻部组织、呼吸道组织、直肠组织、尿道组织和/或阴道组织递送的药物组合物中。

[0303] 对于通过眼部粘膜途径施用来说，主题组合物可以被配制成滴眼剂或眼用软膏。这些制剂可以通过常规手段来制备，并且如果需要的话，可以将主题组合物与任何常规的添加剂混合，所述常规的添加剂如缓冲剂或 pH 值调节剂、张力调节剂、粘度调节剂、悬浮稳定剂、防腐剂以及其它药物赋形剂。此外，在某些实施方案中，可以将本文所述的主题组合物冻干或进行另一种适当的干燥技术，如喷雾干燥。

[0304] 在一些实施方案中，可以在吸入剂或气溶胶制剂中施用的本文所述的粒子包含一种或多种可用于吸入疗法的药剂，如佐剂、诊断剂、成像剂或治疗剂。粒状药物的粒度应当允许在施用气溶胶制剂时基本上所有的药物均被吸入到肺中，并且可以例如小于约 20 微米，例如在约 1 微米至约 10 微米（例如约 1 至约 5 微米）的范围内，尽管其它范围也是可能的。可以通过常规手段，例如通过研磨或微粉化使药物的粒度减小。或者，可以通过使悬浮液雾化来向肺施用粒状药物。最终的气溶胶制剂可以含有例如相对于制剂的总重量 0.005％ -90％ w/w、0.005％ -50％、0.005％ -10％、约 0.005％ -5％ w/w、或 0.01％ -1.0％ w/w 的药物。其它范围也是可能的。

[0305] 期望的是，但绝非必要的是，本文所述的制剂不含可能引起平流层臭氧降解的组分。具体来说，在一些实施方案中，选择不含氯氟烃或并非基本上由氯氟烃组成的推进剂，所述氯氟烃如 CCl_3F、CCl_2F_2 以及 CF_3CCl_3。

[0306] 气溶胶可以包含推进剂。推进剂可以任选地含有与推进剂相比具有更高的极性和/或更高的沸点的佐剂。可以使用的极性佐剂包括（例如 C_{2-6}）脂族醇和多元醇，如乙醇、异丙醇以及丙二醇，优选乙醇。一般来说，可能仅需要少量的极性佐剂（例如 0.05％ -3.0％ w/w）来改进分散体的稳定性，使用超过 5％ w/w 的量可能倾向于使药物溶解。根据本文所述的实施方案的制剂可以含有少于 1％ w/w（例如约 0.1％ w/w）的极性佐剂。然而，本文所述的制剂可以基本上不含极性佐剂，特别是乙醇。合适的挥发性佐剂包括饱和烃，如丙烷、正丁烷、异丁烷、戊烷和异戊烷；以及烷基醚，如二甲醚。一般来说，最多 50％ w/w 的推进剂可以包含挥发性佐剂，例如最多 30％ w/w 的挥发性饱和 C_1-C_6 烃。任选地，根据本发明的气溶胶制剂可以进一步包含一种或多种表面活性剂。所述表面活性剂可以是在通过吸入施用时生理学上可接受的。在这个类别内包括诸如以下等表面活性剂：L-α-磷脂酰胆碱 (PC)、1,2-二棕榈酰基磷脂酰胆碱 (DPPC)、油酸、脱水山梨糖醇三油酸酯、脱水山梨糖醇单油酸酯、脱水山梨糖醇单月桂酸酯、聚氧乙烯脱水山梨糖醇单月桂酸酯、聚氧乙烯脱水山梨糖醇单油酸酯、天然卵磷脂、油基聚氧乙烯醚、硬脂基聚氧乙烯醚、月桂基聚氧乙烯醚、氧乙烯与氧丙烯的嵌段共聚物、合成卵磷脂、二乙二醇二油酸酯、油酸四氢糠酯、油酸乙酯、肉豆蔻酸异丙酯、单油酸甘油酯、单硬脂酸甘油酯、单蓖麻油酸甘油酯、鲸蜡醇、硬脂醇、聚乙二醇 400、鲸蜡基氯化吡啶鎓、苯扎氯铵、橄榄油、单月桂酸甘油酯、玉米油、棉籽油以及葵花籽油。

[0307] 本文所述的制剂可以通过例如借助于超声处理，在适当的容器中使粒子分散在所

选的推进剂和/或共推进剂中来制备。可以使所述粒子在共推进剂中悬浮并且填充到合适的容器中。然后将容器的阀门密封到位并且以常规的方式借助阀门通过压力填充引入推进剂。粒子因此可以悬浮或溶解在液化的推进剂中，被密封在具有计量阀的容器中并且被放入到致动器中。这些计量剂量型吸入器是本领域公知的。计量阀可以计量10μL至500μL并且优选地25μL至150μL。在某些实施方案中，可以使用干粉剂吸入器（例如旋转式吸入器(spinhaler)）来实现粒子（其仍为干粉剂）的分散。在其它实施方案中，可以使纳米球体在水性流体中悬浮并且雾化成细滴以向肺中气溶胶化。

[0308] 可以使用声波雾化器，因为它们使药剂对剪切的暴露减到最低程度，所述剪切可能引起粒子的降解。通常，通过将粒子的水性溶液或悬浮液连同常规的药学上可接受的载体和稳定剂一起配制来制备水性气溶胶。载体和稳定剂随具体组合物的要求而变，但通常包括非离子型表面活性剂(Tween、Pluronic®或聚乙二醇)、无害蛋白质（如血清白蛋白）、脱水山梨糖醇酯、油酸、卵磷脂、氨基酸（如甘氨酸）、缓冲剂、盐、糖或糖醇。气溶胶一般由等渗溶液制备。

[0309] 用于口服施用的液体剂型包括药学上可接受的乳液、微乳液、溶液、悬浮液、糖浆以及酏剂。除了活性成分（即微粒、纳米粒子、脂质体、胶束、多核苷酸/脂质复合体）之外，液体剂型还可以含有本领域中常用的惰性稀释剂，例如水或其它溶剂、增溶剂以及乳化剂，如乙醇、异丙醇、碳酸乙酯、乙酸乙酯、苯甲醇、苯甲酸苯甲酯、丙二醇、1,3-丁二醇、二甲基甲酰胺、油（特别是棉籽油、花生油、玉米油、胚芽油、橄榄油、蓖麻油以及芝麻油）、甘油、四氢糠醇、聚乙二醇以及脱水山梨糖醇的脂肪酸酯、以及其混合物。除惰性稀释剂之外，口服组合物还可以包括佐剂，如湿润剂、乳化剂和悬浮剂、甜味剂、调味剂以及芳香剂。

[0310] 可注射的制剂，例如无菌可注射水性或油性悬浮液可以根据已知技术，使用合适的分散剂或湿润剂和悬浮剂来配制。无菌可注射制剂还可以是于无毒的不经肠可接受的稀释剂或溶剂中的无菌可注射溶液、悬浮液或乳液，例如于1,3-丁二醇中的溶液。可以使用的可接受的媒剂和溶剂包含水、林格氏溶液(U.S.P.)以及等渗氯化钠溶液。另外，无菌的不挥发性油常规地被用作溶剂或悬浮介质。为此目的，可以使用任何温和的不挥发性油，包括合成的甘油单酯或甘油二酯。此外，使用脂肪酸（如油酸）来制备注射剂。在某些实施方案中，使粒子悬浮在包含1%(w/v)羧甲基纤维素钠和0.1%(v/v)Tween 80的载体流体中。

[0311] 可以例如通过借助细菌截留型过滤器过滤，或通过并入呈无菌固体组合物形式的灭菌剂来对可注射的制剂进行灭菌，可以在使用前将所述无菌固体组合物溶解或分散在无菌水或其它无菌可注射介质中。

[0312] 用于经直肠或阴道施用的组合物可以是栓剂，所述栓剂可以通过将粒子与合适的无刺激性的赋形剂或载体混合来制备，所述赋形剂或载体如可可脂、聚乙二醇或栓剂蜡，它们在环境温度是固体，但是在体温下是液体并且因此在直肠腔或阴道腔中熔融且释放粒子。

[0313] 用于口服施用的固体剂型包括胶囊、片剂、丸剂、粉剂以及颗粒剂。在这些固体剂型中，将粒子与至少一种惰性的药学上可接受的赋形剂或载体（如柠檬酸钠或磷酸二钙）和/或以下物质混合：a)填充剂或增量剂，如淀粉、乳糖、蔗糖、葡萄糖、甘露醇以及硅酸；b)粘合剂，例如羧甲基纤维素、藻酸盐、明胶、聚乙烯吡咯烷酮、蔗糖以及阿拉伯胶；c)保湿

剂，如甘油 ；d) 崩解剂，如琼脂、碳酸钙、马铃薯淀粉或木薯淀粉、海藻酸、某些硅酸盐以及碳酸钠 ；e) 溶解延迟剂 (solution retarding agent)，如石蜡 ；f) 吸收促进剂，如季铵化合物 ；g) 湿润剂，例如鲸蜡醇和单硬脂酸甘油酯 ；h) 吸收剂，如高岭土和膨润土 ；以及 i) 润滑剂，如滑石粉、硬脂酸钙、硬脂酸镁、固体聚乙二醇、月桂基硫酸钠、以及其混合物。在胶囊、片剂以及丸剂的情况下，所述剂型还可以包含缓冲剂。

[0314] 使用诸如乳糖 (lactose/milk sugar) 以及高分子量聚乙二醇等赋形剂，相似类型的固体组合物还可以被用作软填充明胶胶囊和硬填充明胶胶囊中的填充物。

[0315] 片剂、糖锭、胶囊、丸剂以及颗粒剂的固体剂型可以被制备成具有包衣和壳，如肠溶包衣和药物配制领域公知的其它包衣。它们可以任选地含有乳浊剂并且还可以具有使它们仅仅或优先地在某一部分肠道中任选地以延迟方式释放一种或多种活性成分的组成。可以使用的包埋组合物的示例包括聚合物质和蜡。

[0316] 使用诸如乳糖 (lactose/milk sugar) 以及高分子量聚乙二醇等赋形剂，相似类型的固体组合物还可以被用作软填充明胶胶囊和硬填充明胶胶囊中的填充物。

[0317] 本发明药物组合物的用于局部或透皮施用的剂型包括软膏剂、糊剂、乳膏剂、洗剂、凝胶、粉剂、溶液、喷雾剂、吸入剂、或贴剂。在无菌条件下将粒子与药学上可接受的载体以及可能需要的任何所需的防腐剂或缓冲剂混合。眼科制剂、滴耳剂以及滴眼剂也被涵盖在本发明的范围内。

[0318] 除了本文所述的粒子之外，软膏剂、糊剂、乳膏剂以及凝胶还可以含有赋形剂，如动物性脂肪和植物性脂肪、油、蜡、石蜡、淀粉、黄蓍胶、纤维素衍生物、聚乙二醇、硅酮、膨润土、硅酸、滑石粉、以及氧化锌、或其混合物。

[0319] 除了本文所述的粒子之外，粉剂和喷雾剂还可以含有赋形剂，如乳糖、滑石粉、硅酸、氢氧化铝、钙硅酸盐、以及聚酰胺粉末、或这些物质的混合物。喷雾剂可以另外含有常用的推进剂，如氯氟烃。

[0320] 透皮贴剂具有向体内提供化合物的受控递送的额外优势。这些剂型可以通过将微粒或纳米粒子溶解或分配在适当的介质中来制备。还可以使用吸收增强剂来提高化合物穿过皮肤的通量。可以通过提供速率控制膜或通过将粒子分散在聚合物基质或凝胶中来控制速率。

[0321] 本文所述的包含药剂的粒子可以向受试者施用而以如下量递送，所述量足以向受试者递送治疗有效量的所并入的作为诊断性治疗、预防性治疗或治疗性治疗的一部分的药剂。一般来说，药剂或组分的有效量指的是诱发所需生物反应所必需的量。粒子中药剂的所需浓度将取决于诸多因素，包括但不限于药物的吸收、失活和排泄率以及化合物从主题组合物中的递送速率、所需的生物学终点、待递送的药剂、靶标组织等。应当注意的是，剂量值还可以随待缓解的病况的严重度而变。应当进一步了解的是，对于任何具体的受试者，应当随时间推移根据个体需要和施用组合物或监督组合物施用的人员的专业判断对具体的给药方案进行调整。通常，将使用本领域技术人员已知的技术来确定剂量。

[0322] 待向受试者施用的任何药剂的浓度和 / 或量可以容易地由本领域的普通技术人员确定。还可利用已知的方法来测定在施用治疗性制剂之前和之后的局部组织浓度、从粒子中的扩散速率以及局部血流。

[0323] 本文所述的组合物和 / 或制剂可以具有任何合适的渗透压。在一些实施方案中，

本文所述的组合物和/或制剂可以具有以下渗透压：至少约0mOsm/L、至少约5mOsm/L、至少约25mOsm/L、至少约50mOsm/L、至少约75mOsm/L、至少约100mOsm/L、至少约150mOsm/L、至少约200mOsm/L、至少约250mOsm/L、或至少约310mOsm/L。在某些实施方案中，本文所述的组合物和/或制剂可以具有以下渗透压：小于或等于约310mOsm/L、小于或等于约250mOsm/L、小于或等于约200mOsm/L、小于或等于约150mOsm/L、小于或等于约100mOsm/L、小于或等于约75mOsm/L、小于或等于约50mOsm/L、小于或等于约25mOsm/L、或者小于或等于约5mOsm/L。上述范围的组合也是可能的（例如至少约0mOsm/L且小于或等于约50mOsm/L的渗透压）。其它范围也是可能的。组合物和/或制剂的渗透压可以通过改变例如组合物和/或制剂的溶剂中存在的盐的浓度而变化。

[0324] 在一组实施方案中，组合物和/或制剂包括包含药物的核心物质，所述药物如依碳酸氯替泼诺、索拉非尼、利尼伐尼、MGCD-265、帕唑帕尼、西地尼布、阿西替尼、溴芬酸钙、双氯芬酸（例如双氯芬酸游离酸或其二价金属盐或三价金属盐）、酮咯酸（例如酮咯酸游离酸或其二价金属盐或三价金属盐）、或本文所述的其它合适的药物。在一些实施方案中，组合物和/或制剂中存在的药物的重量与一种或多种表面改变剂（例如Pluronic® F127）的重量的比率大于或等于约1:100、大于或等于约1:30、大于或等于约1:10、大于或等于约1:3、大于或等于约1:1、大于或等于约3:1、大于或等于约10:1、大于或等于约30:1、或者大于或等于约100:1。在一些实施方案中，组合物和/或制剂中药物的重量与一种或多种表面改变剂的重量的比率小于或等于约100:1、小于或等于约30:1、小于或等于约10:1、小于或等于约3:1、小于或等于约1:1、小于或等于约1:3、小于或等于约1:10、小于或等于约1:30、或者小于或等于约1:100。上述范围的组合是可能的（例如大于或等于约1:1且小于或等于约10:1的比率）。其它范围也是可能的。在某些实施方案中，该比率是约1:1。在某些实施方案中，该比率是约2:1。在某些实施方案中，该比率是约10:1。

[0325] 在一些实施方案中，组合物和/或制剂在本文所述的形成工艺和/或稀释工艺期间可以包括上述范围的药物重量与一种或多种表面改变剂的重量的比率。在某些实施方案中，组合物和/或制剂在最终产品中可以包括上述范围的药物重量与一种或多种表面改变剂的重量的比率。

[0326] 药剂可以任何合适的量存在于组合物和/或制剂中，例如组合物和/或制剂的至少约0.01重量%、至少约0.1重量%、至少约1重量%、至少约5重量%、至少约10重量%、至少约20重量%。在一些情况下，药剂可以如下量存在于组合物和/或制剂中：少于或等于约30重量%、少于或等于约20重量%、少于或等于约10重量%、少于或等于约5重量%、少于或等于约2重量%、或者少于或等于约1重量%。上述范围的组合也是可能的（例如以至少约0.1重量%且少于或等于约10重量%的量存在）。其它范围也是可能的。在某些实施方案中，药剂是组合物和/或制剂的约0.1重量%-2重量%。在某些实施方案中，药剂是组合物和/或制剂的约2重量%-20重量%。在某些实施方案中，药剂是组合物和/或制剂的约0.2重量%。在某些实施方案中，药剂是组合物和/或制剂的约0.4重量%。在某些实施方案中，药剂是组合物和/或制剂的约1重量%。在某些实施方案中，药剂是组合物和/或制剂的约2重量%。在某些实施方案中，药剂是组合物和/或制剂的约5重量%。在某些实施方案中，药剂是组合物和/或制剂的约10重量%。

[0327] 在一组实施方案中，组合物和/或制剂包括一种或多种螯合剂。本文所用的螯合

剂指的是能够与金属离子反应以通过一个或多个键形成络合物的化合物。所述一个或多个键通常是离子键或配位键。螯合剂可以是无机化合物或有机化合物。能够催化某些化学反应（例如氧化反应）的金属离子在该金属离子与螯合剂结合而形成络合物时可能丧失它的催化活性。因此，当螯合剂与金属离子结合时，它可以显示出防腐特性。可以使用任何合适的具有防腐特性的螯合剂，如膦酸、氨基羧酸、羟基羧酸、聚胺、氨基醇、以及聚合螯合剂。螯合剂的具体示例包括但不限于乙二胺四乙酸 (EDTA)、次氮基三乙酸 (NTA)、二亚乙基三胺五乙酸 (DTPA)、N- 羟乙基乙二胺三乙酸 (HEDTA)、四硼酸盐、三乙胺二胺、以及其盐和衍生物。在某些实施方案中，螯合剂是 EDTA。在某些实施方案中，螯合剂是 EDTA 的盐。在某些实施方案中，螯合剂是 EDTA 二钠。

[0328] 螯合剂可以合适的浓度存在于包括本文所述的包衣粒子的组合物和 / 或制剂中。在某些实施方案中，螯合剂的浓度大于或等于约 0.0003 重量％、大于或等于约 0.001 重量％、大于或等于约 0.003 重量％、大于或等于约 0.01 重量％、大于或等于约 0.03 重量％、大于或等于约 0.05 重量％、大于或等于约 0.1 重量％、大于或等于约 0.3 重量％、大于或等于约 1 重量％、或者大于或等于约 3 重量％。在某些实施方案中，螯合剂的浓度小于或等于约 3 重量％、小于或等于约 1 重量％、小于或等于约 0.3 重量％、小于或等于约 0.1 重量％、小于或等于约 0.05 重量％、小于或等于约 0.03 重量％、小于或等于约 0.01 重量％、小于或等于约 0.003 重量％、小于或等于约 0.001 重量％、或者小于或等于约 0.0003 重量％。上述范围的组合是可能的（例如大于或等于约 0.01 重量％且小于或等于约 0.3 重量％的浓度）。其它范围也是可能的。在某些实施方案中，螯合剂的浓度是约 0.001 重量％ -0.1 重量％。在某些实施方案中，螯合剂的浓度是约 0.005 重量％。在某些实施方案中，螯合剂的浓度是约 0.01 重量％。在某些实施方案中，螯合剂的浓度是约 0.05 重量％。在某些实施方案中，螯合剂的浓度是约 0.1 重量％。

[0329] 在一些实施方案中，螯合剂在本文所述的形成工艺和 / 或稀释工艺期间可以上述范围中的一个或多个范围存在于组合物和 / 或制剂中。在某些实施方案中，螯合剂在最终产品中可以上述范围中的一个或多个范围存在于组合物和 / 或制剂中。

[0330] 在一些实施方案中，在包括本文所述的包衣粒子的组合物和 / 或制剂中可以包括抗微生物剂。本文所用的抗微生物剂指的是有效抑制、预防或抵抗诸如细菌、微生物、真菌、病毒、芽孢、酵母、霉菌以及一般与感染相关的其它微生物等微生物的生物活性剂。抗微生物剂的示例包括头孢菌素 (cephaloporin)、克林霉素 (clindamycin)、氯霉素、碳青霉烯 (carbapenem)、米诺环素 (minocycline)、利福平 (rifampin)、青霉素 (penicillin)、单酰胺菌素 (monobactam)、喹诺酮、四环素、大环内酯 (macrolide)、磺胺类抗生素、甲氧苄啶、夫西地酸 (fusidic acid)、氨基糖苷、两性霉素 B、唑类、氟胞嘧啶、西洛芬净 (cilofungin)、杀细菌性硝基呋喃化合物、金属银或含有约 2.5 重量％铜的银合金的纳米粒子、柠檬酸银、乙酸银、苯甲酸银、巯氧吡啶铋 (bismuth pyrithione)、巯氧吡啶锌、过碳酸锌、过硼酸锌、铋盐、对羟基苯甲酸酯（例如苯甲酸甲酯、苯甲酸乙酯、苯甲酸丙酯、苯甲酸丁酯以及苯甲酸辛酯）、柠檬酸、苯扎氯铵 (BAC)、利福霉素 (rifamycin) 以及过碳酸钠。

[0331] 抗微生物剂可以合适的浓度存在于包括本文所述的包衣粒子的组合物和 / 或制剂中。在某些实施方案中，抗微生物剂的浓度可以大于或等于约 0.0003 重量％、大于或等于约 0.001 重量％、大于或等于约 0.003 重量％、大于或等于约 0.01 重量％、大于或等于约

0.03 重量%、大于或等于约 0.1 重量%、大于或等于约 0.3 重量%、大于或等于约 1 重量%、或者大于或等于约 3 重量%。在某些实施方案中，抗微生物剂的浓度可以小于或等于约 3 重量%、小于或等于约 1 重量%、小于或等于约 0.3 重量%、小于或等于约 0.1 重量%、小于或等于约 0.03 重量%、小于或等于约 0.01 重量%、小于或等于约 0.003 重量%、小于或等于约 0.001 重量%、或者小于或等于约 0.0003 重量%。上述范围的组合是可能的（例如大于或等于约 0.001 重量%且小于或等于约 0.1 重量%的浓度）。其它范围也是可能的。在某些实施方案中，抗微生物剂的浓度是约 0.001 重量% -0.05 重量%。在某些实施方案中，抗微生物剂的浓度是约 0.002 重量%。在某些实施方案中，抗微生物剂的浓度是约 0.005 重量%。在某些实施方案中，抗微生物剂的浓度是约 0.01 重量%。在某些实施方案中，抗微生物剂的浓度是约 0.02 重量%。在某些实施方案中，抗微生物剂的浓度是约 0.05 重量%。

[0332] 在一些实施方案中，抗微生物剂在本文所述的形成工艺和 / 或稀释工艺期间可以上述范围中的一个或多个范围存在于组合物和 / 或制剂中。在某些实施方案中，抗微生物剂在最终产品中可以上述范围中的一个或多个范围存在于组合物和 / 或制剂中。

[0333] 在一些实施方案中，在包括本文所述的包衣粒子的组合物和 / 或制剂中可以包括张力剂。本文所用的张力剂指的是可以用于将制剂的组合物调节到所需的渗透压范围的化合物或物质。在某些实施方案中，所需的渗透压范围是与血液相容的等渗范围。在某些实施方案中，所需的渗透压范围是低渗范围。在某些实施方案中，所需的渗透压范围是高渗范围。张力剂的示例包括甘油、乳糖、甘露醇、右旋糖、氯化钠、硫酸钠、山梨糖醇、盐水 - 柠檬酸钠 (SSC) 等。在某些实施方案中，可以使用一种或多种张力剂的组合。在某些实施方案中，张力剂是甘油。在某些实施方案中，张力剂是氯化钠。

[0334] 张力剂（如本文所述的张力剂）可以合适的浓度存在于包括本文所述的包衣粒子的组合物和 / 或制剂中。在某些实施方案中，张力剂的浓度大于或等于约 0.003 重量%、大于或等于约 0.01 重量%、大于或等于约 0.03 重量%、大于或等于约 0.1 重量%、大于或等于约 0.3 重量%、大于或等于约 1 重量%、大于或等于约 3 重量%、大于或等于约 10 重量%、大于或等于约 20 重量%、或者大于或等于约 30 重量%。在某些实施方案中，张力剂的浓度小于或等于约 30 重量%、小于或等于约 10 重量%、小于或等于约 3 重量%、小于或等于约 1 重量%、小于或等于约 0.3 重量%、小于或等于约 0.1 重量%、小于或等于约 0.03 重量%、小于或等于约 0.01 重量%、或者小于或等于约 0.003 重量%。上述范围的组合是可能的（例如大于或等于约 0.1 重量%且小于或等于约 10 重量%的浓度）。其它范围也是可能的。在某些实施方案中，张力剂的浓度是约 0.1% -1%。在某些实施方案中，张力剂的浓度是约 0.5% -3%。在某些实施方案中，张力剂的浓度是约 0.25 重量%。在某些实施方案中，张力剂的浓度是约 0.45 重量%。在某些实施方案中，张力剂的浓度是约 0.9 重量%。在某些实施方案中，张力剂的浓度是约 1.2 重量%。在某些实施方案中，张力剂的浓度是约 2.4 重量%。在某些实施方案中，张力剂的浓度是约 5 重量%。

[0335] 在一些实施方案中，张力剂在本文所述的形成工艺和 / 或稀释工艺期间可以上述范围中的一个或多个范围存在于组合物和 / 或制剂中。在某些实施方案中，张力剂在最终产品中可以上述范围中的一个或多个范围存在于组合物和 / 或制剂中。

[0336] 在一些实施方案中，本文所述的组合物和 / 或制剂可以具有以下渗透压 :至少约 0mOsm/L、至少约 5mOsm/L、至少约 25mOsm/L、至少约 50mOsm/L、至少约 75mOsm/L、至少约

100mOsm/L、至少约 150mOsm/L、至少约 200mOsm/L、至少约 250mOsm/L、至少约 310mOsm/L、或者至少约 450mOsm/L。在某些实施方案中，本文所述的组合物和 / 或制剂可以具有以下渗透压 ：小于或等于约 450mOsm/L、小于或等于约 310mOsm/L、小于或等于约 250mOsm/L、小于或等于约 200mOsm/L、小于或等于约 150mOsm/L、小于或等于约 100mOsm/L、小于或等于约 75mOsm/L、小于或等于约 50mOsm/L、小于或等于约 25mOsm/L、或者小于或等于约 5mOsm/L。上述范围的组合也是可能的（例如至少约 0mOsm/L 且小于或等于约 50mOsm/L 的渗透压）。其它范围也是可能的。

[0337] 在本领域中应当了解的是，包含粒子的制剂的离子强度可能影响粒子的多分散性。多分散性是制剂中粒度的异质性的量度。粒度的异质性可能是由于单个粒度的差异和 / 或在制剂中存在聚集。如果粒子具有基本上相同的尺寸、形状和 / 或质量，那么包含所述粒子的制剂被认为是基本上均质的或“单分散的”。包含具有不同尺寸、形状和 / 或质量的粒子的制剂被认为是异质的或“多分散的”。

[0338] 包含粒子的制剂的离子强度还可能影响粒子的胶体稳定性。举例来说，制剂的相对高的离子强度可能引起制剂的粒子凝结并且因此可能使制剂不稳定。在一些实施方案中，通过粒子间排斥力使包含粒子的制剂稳定。举例来说，粒子可以带电荷或带静电荷。两个带电荷的粒子可以彼此排斥，从而防止碰撞和聚集。当粒子间排斥力变弱或变成引力时，粒子可能开始聚集。举例来说，当制剂的离子强度增加到一定水平时，粒子的电荷（例如负电荷）可能被制剂中存在的带相反电荷的离子（例如溶液中的 Na^+ 离子）中和。因此，所述粒子可能发生碰撞并且彼此粘合而形成具有更大尺寸的聚集体（例如簇集体或絮凝物）。所形成的粒子聚集体的尺寸也可能不同，并且因此，制剂的多分散性也可能增加。举例来说，当制剂的离子强度增加到超过一定水平时，包含具有相似尺寸的粒子的制剂可能变成包含具有不同尺寸的粒子的制剂（例如归因于聚集）。在聚集的过程中，聚集体的尺寸可能增长并且最终沉降到容器的底部，并且所述制剂被认为是胶体不稳定的。一旦制剂中的粒子形成聚集体，就通常难以使这些聚集体瓦解成单个粒子。

[0339] 本文所述的某些制剂显示出意想不到的特性，尤其是在制剂中一种或多种离子张力剂（例如盐，如 NaCl）以一定浓度的存在实际上降低了或维持了制剂中存在的粒子的聚集度和 / 或不显著增加聚集。参见例如实施例 14。在某些实施方案中，在将一种或多种离子张力剂添加到制剂中时，制剂的多分散性降低、相对恒定、或不发生显著量的变化。

[0340] 举例来说，在一些实施方案中，在增添的离子强度存在下和 / 或当组合物和 / 或制剂的增添的离子强度保持相对恒定或增加（例如在形成工艺和 / 或稀释工艺期间）时，组合物和 / 或制剂的多分散性相对恒定。在某些实施方案中，当离子强度增加至少 50％时，多分散性增加小于或等于约 200％、小于或等于约 150％、小于或等于约 100％、小于或等于约 75％、小于或等于约 50％、小于或等于约 30％、小于或等于约 20％、小于或等于约 10％、小于或等于约 3％、或者小于或等于约 1％。在某些实施方案中，当离子强度增加至少 50％时，多分散性增加大于或等于约 1％、大于或等于约 3％、大于或等于约 10％、大于或等于约 30％、或者大于或等于约 100％。上述范围的组合是可能的（例如多分散性增加小于或等于 50％且大于或等于 1％）。其它范围也是可能的。

[0341] 可以通过多种手段，如将一种或多种离子张力剂（例如盐，如 NaCl）添加到制剂中来控制（例如增加）本文所述的制剂的离子强度。在某些实施方案中，本文所述的制剂的

离子强度大于或等于约 0.0005M、大于或等于约 0.001M、大于或等于约 0.003M、大于或等于约 0.01M、大于或等于约 0.03M、大于或等于约 0.1M、大于或等于约 0.3M、大于或等于约 1M、大于或等于约 3M、或者大于或等于约 10M。在某些实施方案中，本文所述的制剂的离子强度小于或等于约 10M、小于或等于约 3M、小于或等于约 1M、小于或等于约 0.3M、小于或等于约 0.1M、小于或等于约 0.03M、小于或等于约 0.01M、小于或等于约 0.003M、小于或等于约 0.001M、或者小于或等于约 0.0005M。上述范围的组合是可能的（例如大于或等于约 0.01M 且小于或等于约 1M 的离子强度）。其它范围也是可能的。在某些实施方案中，本文所述的制剂的离子强度是约 0.1M。在某些实施方案中，本文所述的制剂的离子强度是约 0.15M。在某些实施方案中，本文所述的制剂的离子强度是约 0.3M。

[0342] 在某些实施方案中，在将一种或多种离子张力剂添加到制剂中时，制剂的多分散性不发生变化。在某些实施方案中，在将一种或多种离子张力剂添加到制剂中时，多分散性不显著增加。在某些实施方案中，在将一种或多种离子张力剂添加到制剂中时，多分散性增加到本文所述的水平。

[0343] 本文所述的制剂的多分散性可以通过多分散指数 (PDI) 来测量。PDI 被用于描述粒度分布的宽度并且经常通过对由动态光散射 (DLS) 测量的强度自相关函数进行累积量分析来计算。这些参数的计算在标准 ISO 13321:1996E 和 ISO22412:2008 中加以定义。PDI 是无量纲的，并且当通过 DLS 测量时按比例缩放，使得小于 0.05 的值指示高度单分散的样品，而大于 0.7 的值指示非常宽的尺寸分布。在某些实施方案中，本文所述的制剂和 / 或组合物的 PDI 小于或等于约 1、小于或等于约 0.9、小于或等于约 0.8、小于或等于约 0.7、小于或等于约 0.6、小于或等于约 0.5、小于或等于约 0.4、小于或等于约 0.3、小于或等于约 0.2、小于或等于约 0.15、小于或等于约 0.1、小于或等于约 0.05、小于或等于约 0.01、或者小于或等于约 0.005。在某些实施方案中，本文所述的制剂和 / 或组合物的 PDI 大于或等于约 0.005、大于或等于约 0.01、大于或等于约 0.05、大于或等于约 0.1、大于或等于约 0.15、大于或等于约 0.2、大于或等于约 0.3、大于或等于约 0.4、大于或等于约 0.5、大于或等于约 0.6、大于或等于约 0.7、大于或等于约 0.8、大于或等于约 0.9、或者大于或等于约 1。上述范围的组合是可能的（例如大于或等于约 0.1 且小于或等于约 0.5 的 PDI）。其它范围也是可能的。在某些实施方案中，制剂的 PDI 是约 0.1。在某些实施方案中，制剂的 PDI 是约 0.15。在某些实施方案中，制剂的 PDI 是约 0.2。

[0344] 在某些实施方案中，本文所述的组合物和 / 或制剂可以具有高度分散性并且不倾向于形成聚集体。即使当粒子确实形成聚集体时，聚集体也可以在不对组合物和 / 或制剂进行剧烈搅动的情况下容易地被分解成单个粒子。

[0345] 一般来说，期望在向受试者施用之前或之时制剂是无菌的。无菌的制剂基本上不含病原性微生物，如细菌、微生物、真菌、病毒、芽孢、酵母、霉菌以及一般与感染相关的其它微生物。在一些实施方案中，可以对包括本文所述的包衣粒子的组合物和 / 或制剂进行无菌工艺和 / 或其它灭菌工艺。无菌工艺通常涉及通过诸如热、γ 辐照、环氧乙烷或过滤等处理对制剂的组分、最终制剂和 / 或药物产品的容器闭合件进行灭菌，然后在无菌环境中组合。在一些情况下，无菌工艺是优选的。在其它实施方案中，最终灭菌是优选的。

[0346] 其它灭菌方法的示例包括辐射灭菌（例如 γ 辐射、电子辐射或 x 射线辐射）、热灭菌、无菌过滤、以及环氧乙烷灭菌。术语“辐射”与“辐照”在本文可互换使用。不同于其它

灭菌方法，辐射灭菌具有高穿透能力和即时作用的优势，且在一些情况下不需要控制温度、压力、真空或湿度。在某些实施方案中，用于对本文所述的包衣粒子进行灭菌的辐射是 γ 辐射。可以足以杀死包衣粒子中或包衣粒子上大部分的或基本上全部的微生物的量施加 γ 辐射。本文所述的包衣粒子的温度和辐射率在整个 γ 辐射期间可以是相对恒定的。γ 辐照可以在任何合适的温度（例如环境温度、约 40℃、约 30℃至约 50℃）进行。除非另外指明，否则本文所述的 γ 辐照的测量指的是在约 40℃进行的测量。

[0347] 在其中使用灭菌工艺的实施方案中，可能期望所述工艺：(1) 不显著改变本文所述的包衣粒子的粒度；(2) 不显著改变本文所述的包衣粒子的活性成分（如药物）的完整性；以及 (3) 在所述工艺期间或之后不产生不可接受浓度的杂质。在某些实施方案中，在所述工艺期间或之后产生的杂质是本文所述的包衣粒子的活性成分的降解物。举例来说，当活性成分是依碳酸氯替泼诺 (LE) 时，LE 的降解物可以包括 11β,17α- 二羟基 -3- 氧代雄甾 -1,4- 二烯 -17- 甲酸 (PJ-90)、17α-[（乙氧羰基）氧基]-11β- 羟基 -3- 氧代雄甾 -1,4- 二烯 -17β- 甲酸 (PJ-91)、17α-[（乙氧羰基）氧基]-11β- 羟基 -3- 氧代雄甾 -4- 烯 -17- 甲酸氯甲酯 (tetradeca) 和 / 或 17α-[（乙氧羰基）氧基]-3,11- 二氧代雄甾 -1,4- 二烯 -17- 甲酸氯甲酯 (11-keto)，如图 22 中所示。

[0348] 在某些实施方案中，用于对本文所述的组合物和 / 或制剂进行灭菌的工艺引起一种或多种降解物以如下量存在于制剂中：少于或等于约 10 重量%（相对于未降解药物的重量）、少于或等于约 3 重量%、少于或等于约 2 重量%、少于或等于约 1.5 重量%、少于或等于约 1 重量%、少于或等于约 0.9 重量%、少于或等于约 0.8 重量%、少于或等于约 0.7 重量%、少于或等于约 0.6 重量%、少于或等于约 0.5 重量%、少于或等于约 0.4 重量%、少于或等于约 0.3 重量%、少于或等于约 0.2 重量%、少于或等于约 0.15 重量%、少于或等于约 0.1 重量%、少于或等于约 0.03 重量%、少于或等于约 0.01 重量%、少于或等于约 0.003 重量%、或者少于或等于约 0.001 重量%。在一些实施方案中，所述工艺在制剂中产生以下量的降解物：大于或等于约 0.001 重量%、大于或等于约 0.003 重量%、大于或等于约 0.01 重量%、大于或等于约 0.03 重量%、大于或等于约 0.1 重量%、大于或等于约 0.3 重量%、大于或等于约 1 重量%、大于或等于约 3 重量%、或者大于或等于约 10 重量%。上述范围的组合也是可能的（例如少于或等于约 1 重量%且大于或等于约 0.01 重量%）。其它范围也是可能的。

[0349] 在一些实施方案中，经受 γ 辐照的组合物和 / 或制剂包括具有处于上述范围中的一个或多个范围的浓度的降解物。在一组实施方案中，药物是依碳酸氯替泼诺并且降解物是 PJ-90、PJ-91、tetradeca 和 / 或 11-keto。在某些实施方案中，所述降解物中的一种或多种或每一种以上述范围中的一个或多个范围（例如少于或等于约 1 重量%、少于或等于约 0.9 重量%、少于或等于约 0.8 重量%、少于或等于约 0.7 重量%、少于或等于约 0.6 重量%、少于或等于约 0.5 重量%、少于或等于约 0.4 重量%、少于或等于约 0.3 重量%、少于或等于约 0.2 重量%、或者少于或等于约 0.1 重量%）存在于组合物和 / 或制剂中。其它范围也是可能的。

[0350] 在一些实施方案中，在组合物和 / 或制剂中包括一种或多种添加剂以有助于实现相对低量的一种或多种降解物。举例来说，如实施例 13 中所述，与不包括甘油的依碳酸氯替泼诺制剂相比，依碳酸氯替泼诺制剂中甘油的存在使得在使用 γ 辐照对制剂进行灭菌

之后，降解物 tetradeca 的量相对较低。

[0351] 当在灭菌工艺中使用 γ 辐照时，所使用的 γ 辐射的累积量可以变化。在某些实施方案中，γ 辐射的累积量大于或等于约 0.1kGy、大于或等于约 0.3kGy、大于或等于约 1kGy、大于或等于约 3kGy、大于或等于约 10kGy、大于或等于约 30kGy、大于或等于约 100kGy、或者大于或等于约 300kGy。在某些实施方案中，γ 辐射的累积量小于或等于约 0.1kGy、小于或等于约 0.3kGy、小于或等于约 1kGy、小于或等于约 3kGy、小于或等于约 10kGy、小于或等于约 30kGy、小于或等于约 100kGy、或者小于或等于约 300kGy。上述范围的组合是可能的（例如大于或等于约 1kGy 且小于或等于约 30kGy）。其它范围也是可能的。在某些实施方案中，利用多次剂量的辐射来实现所需的累积辐射剂量。

[0352] 本文所述的组合物和 / 或制剂可以具有任何合适的 pH 值。除非另有规定，否则术语“pH 值”指的是在环境温度（例如约 20℃、约 23℃或约 25℃）测量的 pH 值。组合物和 / 或制剂具有例如酸性 pH 值、中性 pH 值、或碱性 pH 值，并且可以取决于例如要将组合物和 / 或制剂递送到体内何处。在某些实施方案中，组合物和 / 或制剂具有生理 pH 值。在某些实施方案中，组合物和 / 或制剂的 pH 值是至少约 1、至少约 2、至少约 3、至少约 4、至少约 5、至少约 6、至少约 6.2、至少约 6.4、至少约 6.6、至少约 6.8、至少约 7、至少约 7.2、至少约 7.4、至少约 7.6、至少约 7.8、至少约 8、至少约 8.2、至少约 8.4、至少约 8.6、至少约 8.8、至少约 9、至少约 10、至少约 11、或者至少约 12。在某些实施方案中，组合物和 / 或制剂的 pH 值小于或等于约 12、小于或等于约 11、小于或等于约 10、小于或等于约 9、小于或等于约 8.8、小于或等于约 8.6、小于或等于约 8.4、小于或等于约 8.2、小于或等于约 8、小于或等于约 7.8、小于或等于约 7.6、小于或等于约 7.4、小于或等于约 7.2、小于或等于约 7、小于或等于约 6.8、小于或等于约 6.6、小于或等于约 6.4、小于或等于约 6.2、小于或等于约 6、小于或等于约 5、小于或等于约 4、小于或等于约 3、小于或等于约 2、或者小于或等于约 1。上述范围的组合是可能的（例如至少约 5 且小于或等于约 8.2 的 pH 值）。其它范围也是可能的。在某些实施方案中，本文所述的组合物和 / 或制剂的 pH 值是至少约 5 并且小于或等于约 8。

[0353] 用于治疗眼部病况的方法、组合物以及制剂

[0354] 哺乳动物的眼是包含外覆盖物的复杂器官，所述外覆盖物包括巩膜（眼外部坚韧的白色部分）和角膜（覆盖瞳孔和虹膜的透明外部）。眼的示例性示意图示于图 15A 中。如图 15A 中在中间横截面上以图示方式所示，从前部到后部，眼 100 包括以下特征，所述特征包括而不限于：角膜 105、虹膜 110（可以响应于环境光而打开和闭合的帘样特征）、结膜 115（由稀薄的复层柱状上皮构成，覆盖巩膜，并且衬于眼睑的内侧）、泪膜 120（其可以包括油层、水层以及粘液层，其中一个或多个粘液层具有多种功能，如用作泪膜的锚定部以及帮助它粘附到眼上）、角膜上皮 125（覆盖角膜前面的多个细胞层，充当保护角膜的屏障、阻止泪液中的流体自由流动、以及防止细菌进入）、前房 130（填充有被称作房水 135 的水样透明流体并且由前面的角膜和虹膜界定的中空特征）、晶状体 140（连同角膜一起有助于使光折射从而在视网膜上聚焦的透明双凸面结构）、睫状体 145（由睫状肌和睫状突构成的圆周组织）、睫状小带 146（连接睫状体与晶状体的纤维束环）、后房 148（前面由虹膜并且后面由睫状小带和睫状体界定的狭窄空间并且也容纳房水）、视网膜 150、黄斑 155、巩膜 160、视神经 165（也被称为颅神经，从视网膜向脑传递视觉信息）、脉络膜 170、以及玻璃体房 175（填充有被称作玻璃体液 180 的粘性流体）。玻璃体房占据了眼内部容积的约 2/3，而前房和后

房占据了眼内部容积的约 1/3。

[0355] 如图 15B 中以图示方式所示，在眼中，在球结膜 116（覆盖眼球，在巩膜上方，与下层巩膜紧密结合，并且随着眼球运动而运动）、睑结膜 117（衬于眼睑内）、结膜穹窿 118（在球结膜与睑结膜之间形成接合部并且允许眼睑和眼球自由运动的疏松且具柔性的组织）以及角膜处存在多个粘液层。这些粘液层形成与局部施用的药物接触的完整表面。因此，局部施用的药物通常必须穿过这些粘液层以到达各种下层眼组织。

[0356] 如图 15A 中以图示方式所示，以大括弧 190 描绘的眼前部或者眼前节或前段一般包括位于晶状体囊 144（具有弹性并且使晶状体保持在恒定张力下的透明膜样结构）的后壁 142 或睫状肌前面的组织或流体。眼前部包括例如结膜、角膜、虹膜、泪膜、前房、后房、晶状体和晶状体囊以及使前眼部区域或部位血管化、维持或受神经支配的血管、淋巴管和神经。

[0357] 如图 15A 中以图示方式所示，以大括弧 195 描绘的眼后部或者眼后节或后段一般包括位于晶状体囊的后壁或睫状肌后面的组织或流体。眼后部包括例如脉络膜、巩膜（位于经过晶状体囊后壁的平面后方的位置上）、玻璃体液、玻璃体房、视网膜、黄斑、视神经、以及使后眼部区域或部位血管化或受神经支配的血管和神经。

[0358] 如下文所更详细地描述，在一些实施方案中，本文所述的粒子、组合物和 / 或制剂可以用于诊断、预防、治疗或处理处于眼后部，如处于视网膜、黄斑、脉络膜、巩膜和 / 或葡萄膜处的疾病或病况。

[0359] 视网膜是眼中分 10 层的精密神经组织膜，其与视神经相连续，接收外部对象的图像并且将视觉冲动通过视神经传递到脑中。视网膜是柔软的和半透明的并且含有视紫红质。它由外色素层和分九层的视网膜感觉层 (retina proper) 组成。这九层从最内层开始是内界膜、视层 (stratum opticum)、神经节细胞层、内丛状层、内核层、外丛状层、外核层、外界膜、以及视杆视锥层。视网膜的外表面与脉络膜接触；内表面与玻璃体接触。视网膜在前部较薄，它在前部几乎一直延伸到睫状体，并且除了在后表面正中央处的薄弱点（在此处聚焦是最好的）以外，视网膜在后部较厚。光感受器在前部终止于睫状体处的锯齿状锯齿缘，但视网膜的膜延伸超过睫状突和虹膜的后部。如果视网膜暴露于直射的阳光，那么它会变得混浊和不透明。

[0360] 黄斑或黄斑部 (macula lutea) 是接近人眼视网膜中央的椭圆形的高度色素沉着的黄色斑点。它具有约 5mm 的直径并且在组织学上常常被定义为具有两层或更多层神经节细胞。靠近它中央的是中心凹，所述中心凹是眼中含有最大浓度的视锥细胞并且产生中心高分辨率视力的小凹陷。黄斑还含有旁中心凹 (parafovea) 和中心凹周 (perifovea)。由于黄斑的颜色是黄色的，因此它吸收了进入眼中的过量蓝光和紫外光，并且充当了视网膜的这一区域的天然遮阳物 (sunblock)（类似于太阳眼镜）。这种黄色源于它的叶黄素和玉米黄质的含量，所述叶黄素和玉米黄质是来源于饮食的黄色叶黄素类胡萝卜素。在黄斑处以玉米黄质为主，而在视网膜中的其它区域以叶黄素为主。有一些证据表明这些类胡萝卜素保护色素沉着的区域避免某些类型的黄斑变性。黄斑的结构是特化用于高敏度的视力。在黄斑内是含有高密度的视锥（具有高敏度的光感受器）的中心凹和中心小凹。

[0361] 脉络膜也被称为脉络膜 (choroidea) 或脉络层 (choroid coat)，是眼的血管层，它含有结缔组织并且位于视网膜与巩膜之间。人脉络膜在眼的远后端处是最厚的 (0.2mm)，

而在边远区域，它逐渐变窄到 0.1mm。脉络膜为视网膜的外层提供氧和营养。脉络膜连同睫状体和虹膜一起形成葡萄膜。

[0362] 巩膜指的是覆盖眼球后六分之五的坚韧的无弹性的不透明膜。它维持了眼球的大小和形态并且与使眼球运动的肌肉连接。在后部，它被视神经穿过并且与透明的角膜一起构成了覆盖眼球的三层膜的最外层。

[0363] 葡萄膜指的是眼的处于巩膜下方的纤维膜，它包括虹膜、睫状体以及脉络膜。

[0364] 眼科疗法可以通过向眼外表面局部地施用诸如滴眼剂等组合物来进行。滴眼剂施用由于它的方便性、无创性、局限的作用以及相对的患者舒适度而是迄今为止向眼递送药物的最理想途径。然而，以溶液（例如眼用溶液）形式向眼局部施用的药物可能因引流和流泪而从眼表面被快速地清除。以粒子（例如眼用悬浮液）形式向眼局部施用的药物通常会被眼中的粘液层或泪膜截留。眼的天然清除机制将被截留在所述层中的物质去除，并且因此，被截留在这一层中的药物也被快速地清除。因此，通过局部施用途径在眼中，特别是在眼后部中，如后巩膜、葡萄膜（位于眼的中间血管层中，由虹膜、睫状体以及脉络膜构成）、玻璃体、脉络膜、视网膜以及视神经乳头 (ONH)，或甚至角膜的内部部分中实现所需的药物水平往往是困难的。

[0365] 举例来说，角膜和结膜天然地由 3-40μm 的粘液层覆盖。如图 15C 中以图示方式所示，外层包含分泌的粘蛋白 310（通过粘蛋白转换和眨眼快速地清除），所述粘蛋白的主要作用是从眼的水层 305 中截留和消除过敏原、病原体以及碎片（包括药物粒子）。内层（厚度最多 500nm）由拴系到上皮 315（糖萼）上的粘蛋白形成，所述粘蛋白保护下层组织免受磨损应力损伤并且不太快速地被清除。不希望受理论所束缚，认为常规的粒子 (CP ；即非 MPP) 被截留在外部粘液层中并且容易从眼部表面被清除。因此，常规的粒子可能在这些粒子中所含的药物可以被转移到眼的其它部分（例如通过扩散或其它机制）之前被清除。相反，本文所述的粒子（例如 MPP）可以避免与分泌的粘蛋白粘着，并且因此可以穿透外周粘液层并且到达缓慢清除的糖萼，从而延长了粒子的停留时间并且使药物释放持续（图 15C）。这表明本文所述的粒子可以远比被截留在外部粘液中的 CP 有效地向下层组织（角膜、结膜等）递送药物。此外，本文所述的制剂可以在整个眼表面上产生粒子和 / 或药剂的均匀覆盖，其中没有本文所述的包衣的常规制剂由于它们被固定在粘液中而可能不会如此均匀地散布。因此，本文所述的制剂可以通过更均匀的覆盖来增强功效。这进而连同更高的浓度一起可以增强穿过粘液的穿透性。

[0366] 此外，使用本文所述的粒子进行局部施用可以解决与其它向眼的递送方式（如注射方法以及使用局部凝胶或插入物）相关的一些挑战。注射方法可以有效地向眼后部递送药物，但这些方法是有创性的并且可能不是理想的。可能有助于向眼递送药物的其它递送方法，如局部凝胶和 / 或各种插入物从患者舒适度的观点来看也不太理想。

[0367] 存在其它与向眼局部施用有关的挑战。眼对药剂的吸收受到确保眼正常发挥功能的一些保护性机制和其它伴随的因素严重限制，所述因素是例如 ：滴注溶液的引流 ；流泪和泪液转换 ；代谢 ；泪液蒸发 ；无成效的 (non-productive) 吸收 / 吸附 ；有限的角膜区域和不良的角膜渗透性 ；以及由泪液蛋白结合。因此，能够在眼表面实现并且维持高浓度的药剂的滴眼剂达延长的持续时间将是理想的。

[0368] 举例来说，当眼中流体的体积超过 7 微升至 10 微升的正常泪液体积时，所施用

的剂量通过鼻泪管系统被引流到鼻咽和胃肠道中。因此，滴注的剂量（一至两滴，对应于50-100微升）中未通过从眼睑裂中溢出而被消除的部分可能被快速地引流，并且剂量与吸收表面（角膜和巩膜）的接触时间可能缩短到例如最长两分钟。

[0369] 流泪和生理性泪液转换（例如在人类中在正常情况下每分钟16％）可以甚至因滴注轻度刺激性溶液而受到刺激并增多。最终的结果是所施用的药物被稀释以及药剂的损失加速。

[0370] 局部施用的负载药物的微粒和纳米粒子具有延长眼部停留时间和增强药物的局部生物利用度而不会引起与其它持续释放制剂（如凝胶、软膏剂以及插入物）有关的不适的潜能。然而，对于这些粒子来说主要的屏障是眼部表面处（例如睑结膜、球结膜以及角膜处；图15B）的粘液层。这种粘液的天然作用是清除碎片和过敏原，有效地截留并且快速地从眼部表面去除包括负载药物的纳米粒子在内的几乎所有外来粒子。为了延长药物在眼部表面处的停留时间以及将药物递送到更接近下层组织的部位，药物载体/粒子可能需要避免与快速清除的粘液粘着。因此，能够避免与粘液粘着或具有降低的与粘液的粘着性的药物载体/粒子将是理想的。

[0371] 对于向眼中递送有效量的药剂，可以使用高剂量和/或高频率的给药。然而，高剂量的药剂增大了局部副作用和全身副作用的风险。此外，高频率的施用是不合需要的，因为它给患者带来不便，往往造成较差的依从性。因此，通过使用适当的制剂（如本文所述的制剂）改进药剂的粘液穿透性由于可以在不需要使用高剂量和/或高频率给药的情况下实现药剂在眼中的有效浓度而变得有利。

[0372] 此外，不希望受理论所束缚，认为局部施用的药剂可以通过以下三条主要通路中的一条或多条转移到眼后部：1)跨玻璃体跨角膜扩散，继而进入到玻璃体中并且随后分布到眼部组织中（图16，通路205）；2)葡萄膜-巩膜途径，即跨角膜扩散，穿过前房，并且通过房水朝向后部组织引流到葡萄膜-巩膜组织（图16，通路210）；以及3)眼周途径，即渗透穿过结膜以进入到眼球筋膜(tenon)的眼周液中，在巩膜周围扩散，继而穿过巩膜、脉络膜以及视网膜扩散（图16，通路215)(Uday B.Kompella和Henry F.Edelhauser；Drug Product Development for the Back of the Eye(《用于眼后部的药物产品研发》)，第1版；斯普林格出版社(Springer)；2011年）。由于解剖学上的膜屏障（即角膜、结膜以及巩膜）和泪管引流，因此在局部药物施用之后在眼后部获得治疗性药物浓度可能相当具有挑战性。由于与眼后部有关的解剖学屏障和生理屏障，因此到达眼的这一部分是甚至更具挑战性的任务。由于这些屏障不能使用无创性方法来改变，因此在将提高眼部生物利用度并且解决向眼局部施用的其它挑战的眼用组合物和制剂方面的改进将是有益的。

[0373] 可以根据以下事实推断研发这类制剂的紧迫性：视力障碍和失明的主要原因是与眼后段有关的病况。这些病况可以包括而不限于年龄相关眼部变性疾病，如年龄相关黄斑变性(AMD)、增生性玻璃体视网膜病(PVR)、视网膜眼部病况、视网膜损伤、黄斑水肿（例如黄斑囊样水肿(CME)或糖尿病性黄斑水肿(DME))、以及眼内炎。青光眼往往被认为是影响房水流动（并且因此影响眼内压(IOP)）的前房病况，但它也具有后段组成部分。事实上，某些形式的青光眼的特征并不在于高IOP，而主要仅在于视网膜变性。

[0374] 在某些实施方案中，这些病况和其它病况可以使用本文所述的粘液穿透性粒子、组合物以及制剂来治疗、诊断、预防或处理。举例来说，可以利用含有粘液穿透性粒子的滴

眼剂的局部施用在不对患者进行有创性程序（如玻璃体内注射）的情况下向眼后部有效地递送抗 AMD 药物并且治疗 AMD。或者，举例来说，可以利用含有负载抗炎药（例如皮质类固醇或 NSIAD）的粘液穿透性粒子的滴眼剂的局部施用以降低的给药频率来治疗眼部炎症。

[0375] 本文所述的粒子、组合物以及方法至少部分地由于粒子的粘液穿透特性而可以解决本文所述的与向眼前部和 / 或眼后部递送药剂有关的挑战。不希望受理论所束缚，认为本文所述的具有粘液穿透特性的粒子能够避免与包覆眼的粘液粘着并且有效地穿过所述粘液。由于这些粒子穿过了眼组织（例如睑结膜、球结膜、角膜或泪膜）的粘液层，因此它们避免了被身体的天然清除机制快速地清除并且实现了在眼前部延长的停留时间。然后在粒子和 / 或药剂例如通过图 16 中所述的机制之一朝向眼后部转移时，所述粒子可以溶解和 / 或可以释放药剂。相反，不具粘液穿透性的粒子或药物可能与粘液粘着，并且可能被身体的天然清除机制快速地清除，使得在施用之后不久在眼前部剩余不足量的粒子或药物。因此，相对低量的粒子或药物可供用于向眼后部转移（例如通过扩散或其它机制）。举例来说，如实施例 3 和实施例 8 中所更详细地描述，将包括不能有效地穿透粘液的药剂依碳酸氯替泼诺 (LE) 的粒子的市售眼用悬浮液 Lotemax® 与具有 Pluronic® F127 包衣的 LE 粒子进行比较。这种药物通常用于治疗眼前部组织的炎症。令人惊讶地，当药剂 LE 的粒子被使得它们具有粘液穿透性的 Pluronic® F127、Tween 80® 或某些 PVA 的包衣包覆时，不仅如实施例 3 和实施例 34 中所述，向眼前部（例如角膜、虹膜 / 睫状体、房水）的眼部表面的递送得到显著增强，而且如实施例 8 中所述，向眼中部和眼后部（例如视网膜、脉络膜以及巩膜）的递送也得到增强。这些结果是出乎意料的，特别是因为 LE 先前并未显示在作为滴眼剂局部给药时穿透到眼后部。此外，传统观念认为被 Pluronic® F127 包覆的 LE 粒子将会因流泪而从眼部表面快速地被冲走，因为许多人先前已经报道纳米级药物粒子高度可溶于含有它们的溶液中，并且因此，预计表现得更像不能持续释放的常规溶液。应当了解的是，虽然本文中的大部分说明涉及对眼后部或眼后段的组织进行治疗、诊断、预防或处理，但本文所述的方法、组合物以及制剂不限于此，并且眼的其它部分可以得益于本文所述的方法、组合物以及制剂。

[0376] 此外，在实施例 21 和 29-33 中描述了包括 RTK 抑制剂（例如索拉非尼、利尼伐尼、MGCD-265、帕唑帕尼、西地尼布以及阿西替尼）的粒子和组合物，所述粒子和组合物表现出 RTK 抑制剂在眼后部增强的暴露。

[0377] 现在更详细地描述眼中可以通过本文所述的方法、组合物以及制剂靶向或治疗的部分。

[0378] 在一些实施方案中，本文所述的方法、粒子、组合物和 / 或制剂可以用于靶向和 / 或治疗受试者的结膜。结膜指的是衬于眼睑的内表面和巩膜的前部的粘膜。睑结膜衬于眼睑的内表面并且是厚的、不透明的并且富含血管的。球结膜是松散连接的、稀薄的并且透明的，覆盖巩膜或眼的前三分之一。

[0379] 在某些实施方案中，本文所述的方法、粒子、组合物和 / 或制剂可以用于靶向和 / 或治疗受试者的角膜的全部或部分。角膜指的是眼的凸形透明前部，占眼球的最外层膜的六分之一。它允许光穿过它到达晶状体。角膜是具有以下五层的纤维结构 ：前角膜上皮，与结膜的上皮相连续 ；前界层（前弹力膜 (Bowman's membrane)）；固有基质 (substantial

propria)；后界层（后弹力膜 (Descemet's membrane)）；以及前房的内皮（皮肤角质层）。它是致密的、厚度均一的并且无血管的，并且它像穹窿一样突出在巩膜以外，所述巩膜形成眼的最外层膜的其余六分之五。角膜曲度在不同的个体之间以及在同一个人处于不同的年龄阶段时有所不同；年轻时的曲度比年老时的曲度更明显。

[0380] 在一些实施方案中，本文所述的方法、粒子、组合物和/或制剂可以用于靶向和/或治疗受试者的眼后部或眼后段内的部分，如视网膜、脉络膜和/或巩膜。从眼内侧开始并朝向眼后部，处于眼后部的三个主要层是视网膜，它含有神经；脉络膜，它含有血液供给；以及巩膜，它是眼白。

[0381] 在一些实施方案中，本文所述的方法、粒子、组合物和/或制剂可以用于治疗、诊断、预防或处理眼部病况，即影响或累及眼或眼的一个或多个部分或区域的疾病、病痛或病况。从广义上讲，眼包括眼球和构成眼球的组织和流体、眼周肌肉（如斜肌和直肌）以及眼球内或靠近眼球的视神经部分。

[0382] 在一些实施方案中，本文所述的方法、粒子、组合物和/或制剂可以用于治疗、诊断、预防或处理受试者眼前部的眼部病况。一般来说，如本文所述，眼前部（或者前节或前段）眼部病况是影响或累及眼前部的组织或流体的疾病、病痛或病况。眼前部的眼部病况包括例如以下的疾病、病痛或病况：手术后炎症；葡萄膜炎；感染；无晶状体；假晶状体；散光；眼睑痉挛；白内障；结膜疾病；结膜炎；角膜疾病；角膜溃疡；干眼综合征；眼睑疾病；泪器疾病；泪管阻塞；近视；老花眼；瞳孔病症；角膜新血管生成；屈光异常以及斜视。在一些实施方案中，青光眼可以被认为是眼前部的眼部病况，因为青光眼治疗的临床目标可以是降低眼前房中房水的高压（即降低眼内压）。

[0383] 在一些实施方案中，本文所述的方法、粒子、组合物和/或制剂可以用于治疗、诊断、预防或处理受试者眼后部的眼部病况。一般来说，如本文所述，眼后部或后眼部病况是主要影响或累及眼后部的组织或流体的疾病、病痛或病况。后眼部病况可以包括诸如以下的疾病、病痛或病况：眼内黑色素瘤；急性黄斑视神经网膜病；白塞氏病 (Behcet's disease)；脉络膜新血管生成；葡萄膜炎；糖尿病性葡萄膜炎；组织胞浆菌病；感染，如真菌或病毒引起的感染；黄斑变性，如急性黄斑变性、非渗出性年龄相关的黄斑变性以及渗出性年龄相关的黄斑变性；水肿，如黄斑水肿（例如黄斑囊样水肿 (CME) 和糖尿病性黄斑水肿 (DME)）；多灶性脉络膜炎；影响后眼部部位或位置的眼部创伤；眼部肿瘤；视网膜病症，如视网膜中央静脉阻塞、糖尿病性视网膜病（包括增生性糖尿病性视网膜病）、增生性玻璃体视网膜病 (PVR)、视网膜动脉阻塞性疾病、视网膜脱离、葡萄膜炎视网膜病；交感性眼炎；伏格特-小柳-原田 (Vogt Koyanagi-Harada, VKH) 综合征；葡萄膜扩散 (uveal diffusion)；由眼部激光治疗所引起或受眼部激光治疗影响的后眼部病况；由下列因素引起或受下列因素影响的后眼部病况：光动力学疗法、光凝术、放射性视网膜病、视网膜前膜病症、视网膜分支静脉阻塞、前部缺血性视神经病、非视网膜病糖尿病性视网膜功能障碍、色素性视网膜炎、视网膜母细胞瘤以及青光眼。在一些实施方案中，青光眼可以被认为是一种后眼部病况，因为治疗目标是防止因视网膜细胞或视神经细胞受损或丧失而导致的视力丧失或降低所述视力丧失的出现率（即神经保护作用）。

[0384] 在一些实施方案中，本文所述的方法、粒子、组合物和/或制剂可以用于治疗、诊断、预防或处理受试者的干眼症。干眼症是泪液不足以润滑和滋养眼的一种病况。泪液对

于维持眼的前表面健康和提供清晰的视野来说是必要的。患有干眼症的人不产生足够的泪液或者泪液的质量较差。干眼症是一种常见的并且往往是慢性的问题，特别是在年龄较大的成年人中。

[0385] 随着眼睑的每一次眨动，泪液散布于被称作角膜的眼的前表面上。泪液提供了润滑作用，降低了眼感染的风险，将眼中的异物冲走，并且保持眼表面光滑和清洁。眼中过量的泪液流入处于眼睑的内眼角中的小引流管中，所述引流管在鼻后部引流。泪液是由眼睑中和眼睑周围的若干腺体（例如泪腺）产生的。泪液的产生伴随年龄、各种医学病况或因某些药物的副作用而倾向于减少。诸如风和干燥气候等环境条件也可以通过增加泪液蒸发而影响泪液的体积。当正常的泪液产生量减少或泪液从眼中过快地蒸发时，可以产生干眼症的症状。

[0386] 最常见形式的干眼症归因于泪液的水层的量不足。这种病况被称作干燥性角结膜炎 (KCS)，也被称为干眼综合征。

[0387] 对于干眼症的治疗旨在恢复或维持眼中泪液的正常量以便使干燥和相关的不适减到最低程度并且维持眼健康。这些目标可以通过不同的途径来实现，如提高泪腺的泪液产生、调节结膜的粘蛋白产生以及抑制眼组织的炎症。举例来说，Restasis® (0.05％环孢菌素）是降低结膜和泪腺中 T 细胞的活性的免疫抑制剂。在研发新的干眼症治疗中的挑战包括鉴定潜在的疾病和原因、观测到结果的时间长度 (3-6 个月）、以及治疗仅可以在干眼症人群中的 10％ -15％中起作用的事实。药物递送也可能是一种挑战。尽管在干眼症的治疗中所靶向的眼组织处于眼前部，但仍可能有一部分局部施用的药剂被结膜、泪膜以及角膜中的粘液固定。在一些实施方案中，本文所述的粒子、制剂以及组合物可以通过有助于药剂有效地递送到适当的组织、促进粒子在眼表面上更均匀的和 / 或广泛的覆盖、和 / 或避免粒子 / 药剂被清除或使粒子 / 药剂的清除减到最低程度来解决这些问题。

[0388] 在一些实施方案中，本文所述的方法、粒子、组合物和 / 或制剂可以用于治疗、诊断、预防或处理受试者眼中的炎症。炎症与多种眼部病症有关。炎症也可能由包括白内障手术在内的许多眼科手术程序引起。常常使用皮质类固醇作为眼部抗炎剂，然而，它们通常需要高频率的给药。

[0389] 为了防止手术后炎症，可以预防性地给予类固醇或 NSAID（非类固醇抗炎药）。当前对手术后炎症的治疗包括类固醇（例如 Lotemax® (0.5％依碳酸氯替泼诺）、Durezol® (0.05％二氟泼尼酯）、Pred Mild® (0.12％乙酸泼尼松龙）、以及 Omnipred® (1％乙酸泼尼松龙））和 NSAID（例如Bromday® (0.09％溴芬酸）、Nevanac® (0.1％奈帕芬胺）、Acular LS® (0.4％酮咯酸氨丁三醇）、Acuvail® (0.45％酮咯酸氨丁三醇））、Toradol® （酮咯酸氨丁三醇）、Sprix® （酮咯酸氨丁三醇）、Voltaren® (0.1％双氯芬酸）、Aclonac® （双氯芬酸）、以及 Cataflam® （双氯芬酸）。对于治疗手术后炎症来说最大的挑战之一是依从性，因为滴眼剂从眼表面被快速清除，因此大部分当前市售的类固醇或 NSAID 滴眼剂必须每天施用多次以实现并且维持治疗作用。在一些实施方案中，本文所述的粒子、组合物和 / 或制剂可以包括这些类固醇药剂中的一种或多种。举例来说，如实

施例中所更详细地描述，与相等剂量的不包括合适的聚合包衣的商业制剂相比，包括本文所述的某些聚合包衣的依碳酸氯替泼诺（Lotemax® 的成分）的粒子在新西兰白兔的各种眼部组织中产生显著更高的药物水平。这一数据表明所述包衣粒子与商业制剂相比可以每天施用更少的次数来实现并且维持治疗作用。

[0390] 多种局部 NSAID 制剂（例如 Bromday®（0.09％溴芬酸））是可在市场上获得的。表 17 提供了有关这些制剂、它们对应的商品名、活性药物成分（API）、给药浓度以及给药频率的列表。这些制剂中的大多数（即 Bromday®、Flurbiprofen®、Acular® 以及 Voltaren®）是以活性成分完全被溶解的溶液形式提供的。

[0391] 已经发现，溴芬酸容易通过内酰胺的形成而在溶液中降解，特别是在低于中性 pH 值的情况下（表 18）。表 18 中的数据显示当降低含有溴芬酸钠的水溶液的 pH 值（例如从 pH 7.8 降低到 pH 5.8）时，观测到更多的溴芬酸降解物。

[0392] 为了增强溴芬酸的局部递送，这进而可以转换成较低的剂量以改进安全性或增强对眼中部和眼后部的病况的治疗，可能期望将溴芬酸配制成包含溴芬酸核心的 MPP 的悬浮液。此外，将溴芬酸配制成 MPP 的悬浮液可以允许溴芬酸在制剂中的浓度增加而基本上不增加降解物的浓度（例如与溴芬酸的水溶液相比）。然而，由于溴芬酸钠相对高的水溶解度而难以将它配制成固体粒子或结晶粒子。在一些实施方案中，例如由于溴芬酸游离酸（溴芬酸 FA）在水性 Pluronic® F127 存在下显著降解（表 19），因此溴芬酸 FA 也可能难以被研发成贮存稳定性 MPP 悬浮液制剂。

[0393] 表 17. 当前可获得的以局部递送的 NSAID 为特色的产品。

[0394]

商品名	制造商	API	API 的浓度 (% w/v)	治疗频率(每天滴数)	剂型
Bromday®	博士伦公司 (Bausch & Lomb)	溴芬酸钠	0.09	1	溶液
Ocufen®	眼力健公司	氟比洛芬	0.03	4	溶液

[0395]

Acular®、Acular LS®、Acuvail®	眼力健公司	酮咯酸氨丁三醇	0.4-0.5	2-4	溶液
Voltaren®	诺华公司 (Novartis)	双氯芬酸钠	0.1	4	溶液
Nevanac®	爱尔康公司	奈帕芬胺	0.1	3	悬浮液

[0396] 所列的产品被开处方用于在手术后施用，不同的是Ocufen®，它在手术之前 2 小时内施用。

[0397] 表 18. 溴芬酸钠在不同的 pH 值下的化学降解。*

[0398]

pH 值	峰面积%
5.8	3.16
6.8	0.05
7.8	0

[0399] *以在将 0.02%溴芬酸钠的水溶液在室温储存 5 天后溴芬酸的内酰胺降解物的色谱峰面积%来测定溴芬酸钠的化学稳定性。

[0400] 表 19. 溴芬酸游离酸在Pluronic® F127 存在下在未缓冲的水性悬浮液中的化学降解。*

[0401]

Pluronic® F127 的浓度 (% w/v)	**溴芬酸 FA 的浓度 (% w/v)**	**峰面积%**
0.50	0.5	12.0 (第 14 天)
5	5	10.2 (第 5 天)

[0402] *以在将溴芬酸游离酸的水性悬浮液在室温储存 5 天或 14 天后溴芬酸的内酰胺降解物的色谱峰面积%来测定溴芬酸游离酸的化学稳定性。

[0403] 如本文所述，期望研发在对于向眼局部施用合适的 pH 值下稳定的包含 NSAID（例如溴芬酸、双氯芬酸、酮咯酸或其盐）的组合物。在一些实施方案中，这类组合物包括溴芬酸、双氯芬酸、酮咯酸或其盐的固体粒子或结晶粒子，所述粒子可以有效地穿透粘液。所述粒子可以包括本文所述的一种或多种可以降低粒子的粘膜粘着性的表面改变剂（例如泊洛沙姆、聚山梨醇酯（例如 Tween 80®）、PVA）。

[0404] 在一些实施方案中，本文所述的粒子、组合物和 / 或制剂包括溴芬酸的二价金属盐，如溴芬酸的二价金属盐。举例来说，溴芬酸的二价金属盐可以是相对不溶于水的并且可以包括例如溴芬酸铍、溴芬酸镁、溴芬酸钙、溴芬酸锶、溴芬酸钡、溴芬酸锌、或溴芬酸铜 (II)。在一些实施方案中，包括溴芬酸的二价金属盐的粒子可以具有本文所述的范围的水溶解度（例如至少约 0.001mg/mL 且小于或等于约 1mg/mL）。

[0405] 在某些实施方案中，本文所述的粒子、组合物和 / 或制剂包括双氯芬酸 FA。在某些实施方案中，本文所述的粒子、组合物和 / 或制剂包括双氯芬酸的金属盐，如双氯芬酸的碱土金属盐。在某些实施方案中，本文所述的粒子、组合物和 / 或制剂包括酮咯酸 FA。在某些

实施方案中，本文所述的粒子、组合物和 / 或制剂包括酮咯酸的金属盐，如酮咯酸的碱土金属盐。这些化合物的三价金属盐也是可能的。

[0406] 本文所述的溴芬酸的二价金属盐（例如溴芬酸钙）与溴芬酸钠和 / 或溴芬酸的其它单价盐相比具有更小的水溶性和更大的疏水性。举例来说，溴芬酸钙在 25℃的水溶解度是约 0.15mg/mL。与更具水溶性和亲水性的溴芬酸钠相比，溴芬酸的二价金属盐可能更适合于使用本文所述的方法（例如研磨和 / 或沉淀）加工成 MPP。溴芬酸的二价金属盐主要以固体（例如结晶）形式存在于 MPP 中，因此可能不太易于降解并且在化学上更稳定。此外，包括溴芬酸的二价金属盐的 MPP 的组合物和 / 或制剂中溴芬酸的二价金属盐的相对高的浓度不受溴芬酸的二价金属盐的水溶解度和 / 或降解物的形成所限制。因此，与溶解在溶液中的游离酸形式相比，本文所述的包含溴芬酸的二价金属盐的粒子、组合物和 / 或制剂可以允许组合物或制剂中的溴芬酸的浓度更高。在一些实施方案中，这些粒子、组合物和 / 或制剂允许在向眼施用后溴芬酸在眼部组织中的浓度更高。

[0407] 出于本文关于溴芬酸钙和溴芬酸的游离酸形式所论述的类似原因，具有更小的水溶性和亲水性的双氯芬酸 FA 和其金属盐（例如二价金属盐或三价金属盐）与双氯芬酸钠和 / 或双氯芬酸的其它单价盐相比可能更适合于被加工成具有粘液穿透性的粒子、组合物和 / 或制剂。类似地，较酮咯酸氨丁三醇和 / 或酮咯酸的其它单价盐具有更小的水溶性和亲水性的酮咯酸 FA 和其金属盐（例如二价金属盐或三价金属盐）可以形成为粘液穿透性粒子、组合物和 / 或制剂。此外，由于双氯芬酸 FA 或酮咯酸 FA 或者其二价金属盐或三价金属盐可以不受它们的水溶解度限制，因此这些化合物可以分别与双氯芬酸钠或酮咯酸氨丁三醇的水性制剂相比更高的浓度存在于本文所述的粒子、组合物和 / 或制剂中。

[0408] 在某些实施方案中，本文所述的药剂（例如 NSAID，如溴芬酸的二价金属盐（例如溴芬酸钙）、双氯芬酸 FA、双氯芬酸的金属盐（例如二价金属盐或三价金属盐）、酮咯酸 FA 或酮咯酸的金属盐（例如二价金属盐或三价金属盐）；受体酪氨酸激酶 (RTK) 抑制剂，如索拉非尼、利尼伐尼、MGCD-265、帕唑帕尼、西地尼布、以及阿西替尼；或皮质类固醇，如 LE) 以如下量存在于本文所述的组合物和 / 或制剂中：至少约 0.001％ w/v、至少约 0.003％ w/v、至少约 0.01％ w/v、至少约 0.02％ w/v、至少约 0.05％ w/v、至少约 0.1％ w/v、至少约 0.2％ w/v、至少约 0.3％ w/v、至少约 0.4％ w/v、至少约 0.5％ w/v、至少约 0.6％ w/v、至少约 0.8％ w/v、至少约 1％ w/v、至少约 1.5％ w/v、至少约 2％ w/v、至少约 3％ w/v、至少约 4％ w/v、至少约 5％ w/v、至少约 6％ w/v、至少约 8％ w/v、至少约 10％ w/v、至少约 20％ w/v、至少约 30％ w/v、至少约 40％ w/v、或者至少约 50％ w/v。在某些实施方案中，药剂以如下量存在于本文所述的组合物和 / 或制剂中：少于或等于约 50％ w/v、少于或等于约 40％ w/v、少于或等于约 30％ w/v、少于或等于约 20％ w/v、少于或等于约 10％ w/v、少于或等于约 8％ w/v、少于或等于约 6％ w/v、少于或等于约 5％ w/v、少于或等于约 4％ w/v、少于或等于约 3％ w/v、少于或等于约 2％ w/v、少于或等于约 1.5％ w/v、少于或等于约 1％ w/v、少于或等于约 0.8％ w/v、少于或等于约 0.6％ w/v、少于或等于约 0.5％ w/v、少于或等于约 0.4％ w/v、少于或等于约 0.3％ w/v、少于或等于约 0.2％ w/v、少于或等于约 0.1％ w/v、少于或等于约 0.05％ w/v、少于或等于约 0.02％ w/v、少于或等于约 0.01％ w/v、少于或等于约 0.003％ w/v、或者少于或等于约 0.001％ w/v。上述范围的组合也是可能的（例如至少约 0.5％ w/v 且少于或等于 5％ w/v）。其它范围也是可能的。

[0409] 在某些实施方案中，溴芬酸的二价金属盐（例如溴芬酸钙）以约 0.09％ w/v 或更大量存在于本文所述的组合物和/或制剂中。在某些实施方案中，溴芬酸的二价金属盐（例如溴芬酸钙）以约 0.5％ w/v 或更大量存在于本文所述的组合物和/或制剂中。在某些实施方案中，双氯芬酸 FA 或酮咯酸 FA 或者其金属盐（例如二价金属盐或三价金属盐）以约 0.5％ w/v 或更大量存在于本文所述的组合物和/或制剂中。

[0410] 在一些实施方案中，包括溴芬酸的二价金属盐或本文所述的其它药剂的 MPP 的组合物和/或制剂可以具有对眼不具刺激性的 pH 值，如弱碱性 pH 值（例如 pH 8）、生理 pH 值（即约 pH 7.4）、基本上中性的 pH 值（例如约 pH 7）、弱酸性 pH 值（例如约 pH 5-6）、或其范围（例如约 pH 5-7 或 pH 6-7）。在这些 pH 值下，MPP、组合物和/或制剂可以具化学稳定性和胶体稳定性，并且与某些市售制剂相比，可以在眼部组织中实现治疗和/或预防有效的药物水平达更长的持续时间。本文所述的益处可以进一步使得与某些市售制剂相比所需的剂量更低，以使得这种治疗的安全性改进和/或局部递送增强以治疗眼中部和眼后部的病况。

[0411] 在一些实施方案中，本文所述的方法、粒子、组合物和/或制剂可以用于治疗、诊断、预防或处理受试者的青光眼。青光眼是其中视神经以特征模式受损的眼疾病。这可以永久地损伤患眼的视力并且如果不予治疗，则导致失明。它通常与眼（房水）中流体压力升高有关。术语高眼压用于 IOP 持续升高而没有任何相关的视神经损伤的人。相反，术语正常眼压性青光眼或低眼压性青光眼用于存在视神经损伤以及相关的视野缺失，但具有正常或低的 IOP 的那些人。

[0412] 神经损伤涉及视网膜神经节细胞以特征模式丧失。存在许多不同亚型的青光眼，但它们都可以被认为是一种类型的视神经病。眼内压升高（例如高于 21mmHg 或 2.8kPa）是对于青光眼来说最重要的并且唯一可缓和的风险因素。然而，一些人可能多年来一直具有高眼压但从未产生损伤，而其他人可以在相对低的眼压下产生神经损伤。未经过治疗的青光眼可以导致视神经的永久性损伤和随之而来的视野缺失，随时间推移可以发展成失明。

[0413] 当前对青光眼的治疗可以包括使用增加房水流出的前列腺素类似物（例如 Xalatan® (0.005％拉坦前列素）、Lumigan® (0.03％和 0.01％的比马前列素）、以及 Travatan Z® (0.004％曲伏前列素））；减少房水产生的 β-阻断剂（例如 Timoptic® (0.5％和 0.25％的噻吗洛尔））；减少房水产生并且增加流出的 α 激动剂（例如 Alphagan® (0.1％和 0.15％的酒石酸溴莫尼定））；减少房水产生的碳酸酐酶抑制剂（例如 Trusopt® (2％多佐胺））；以及增加常规流出的胆碱能药物（缩瞳剂）（例如 Isopto® (1％、2％以及 4％的毛果芸香碱））。在一些实施方案中，本文所述的粒子、制剂以及组合物可以通过促进药剂有效地递送到适当的组织以及避免药剂被清除或使药剂的清除减到最低程度来解决上文所述的问题。举例来说，本文所述的粒子、组合物和/或制剂可以包括这些或其它前列腺素类似物、β-阻断剂、α 激动剂、碳酸酐酶抑制剂以及胆碱能药物中的一种或多种，并且可以包括本文所述的包衣以促进粒子穿过粘液并且允许有效地递送药剂。

[0414] 在一些实施方案中，本文所述的方法、粒子、组合物和/或制剂可以用于治疗、诊断、预防或处理受试者的葡萄膜炎。葡萄膜炎是葡萄膜的炎症，葡萄膜是眼夹在视网膜与眼

白（巩膜）之间的血管层。葡萄膜朝向眼前部延伸并且由虹膜、脉络膜层以及睫状体组成。最常见类型的葡萄膜炎是被称作虹膜炎的虹膜炎症（前葡萄膜炎）。葡萄膜炎还可能出现在眼后段（例如脉络膜处）。葡萄膜的炎症可以复发并且如果不予治疗，则可以导致诸如失明等严重的问题（占全世界失明的 10％）。早期诊断和治疗对于预防葡萄膜炎的并发症是重要的。

[0415] 当前对葡萄膜炎的治疗包括滴眼剂（例如 TobraDex®（0.1％地塞米松 /0.3％妥布霉素）和 Zylet®（0.5％依碳酸氯替泼诺 /0.3％妥布霉素））；于透明质酸钠中的“凝胶悬浮液”的玻璃体内注射剂（例如 Trivaris®（8％曲安奈德（triamcinolone acetonide））；于羧甲基纤维素和 Tween 80 中的“水性悬浮液”的玻璃体内注射剂（例如 Triesence®（4％曲安奈德））；以及植入物（例如 Retisert®（0.59mg 氟西奈德）和 Ozurdex®（0.7mg 地塞米松））。还使用口服类固醇和 NSAID。在研发新的葡萄膜炎治疗中的挑战包括针对后葡萄膜炎的无创性递送、由于葡萄膜的高度血管形成所致的清除、长期类固醇使用的副作用，如 IOP 升高和白内障。在一些实施方案中，本文所述的粒子、组合物和 / 或制剂可以包括可以向受试者局部施用的这些药物中的一种或多种。

[0416] 在一些实施方案中，本文所述的方法、粒子、组合物和 / 或制剂可以用于治疗、诊断、预防或处理受试者的年龄相关的黄斑变性 (AMD)。AMD 是通常侵害年龄较大的成年人并且由于损伤视网膜而导致视野中心（黄斑）的视力丧失的医学病况。它以“干性”和“湿性”形式出现。它是年龄较大的成年人 (>50 岁）失明和视力障碍的主要原因。黄斑变性可以使得很难或不可能辨别或识别人脸，尽管保留了足够的周边视力以允许进行其它日常生活活动。黄斑是视网膜的中央区域，它提供了最精细的中心视力。在干性（非渗出性）形式中，被称作玻璃膜疣的细胞碎片积聚在视网膜与脉络膜之间，并且视网膜可以变得脱离。在更为严重的湿性（渗出性）形式中，血管从视网膜后面的脉络膜生长，并且视网膜也可以变得脱离。可以用激光凝固术以及用阻止并且有时逆转血管生长的药物对它进行治疗。尽管侵害较年轻个体的一些黄斑营养不良有时被称为黄斑变性，但该术语一般指年龄相关的黄斑变性 (AMD 或 ARMD)。

[0417] 年龄相关的黄斑变性开始于黄斑中视网膜色素上皮与下层脉络膜之间的特征性黄色沉积物（玻璃膜疣）。大多数出现这些早期变化（被称为年龄相关的黄斑病）的人具有良好的视力。带有玻璃膜疣的人可以继续发展成晚期 AMD。当玻璃膜疣大且数目众多并且与黄斑下方色素细胞层的紊乱有关时，该风险是相当高的。最近的研究表明大且柔软的玻璃膜疣与胆固醇沉积物升高有关并且可能对降胆固醇剂有反应。

[0418] 潜在的对 AMD 的治疗包括使用诸如以下的药剂：维替泊芬 (verteporfin)（例如 Chlorin®、Visudyne®）、沙利度胺 (thalidomide)（例如 Ambiodry®、Synovir®、Thalomid®）、他拉泊芬钠 (talaporfin sodium)（例如 Aptocine®、Laserphyrin®、Litx®）、兰尼单抗（例如 Lucentis®）、哌加他尼八钠（例如 Macugen®、Macuverse®）、异丙基乌诺前列酮（例如 Ocuseva®、Rescula®）、干扰素

β（例如Feron®）、氟西奈德（例如Envision TD®、Retisert®）、依维莫司（everolimus）（例如Afinitor®、Certican®、Votubia®、Zortress®）、艾库组单抗（eculizumab）（例如Solaris®、Soliris®）、地塞米松（例如Osurdex®、Ozurdex®、Posurdex®、Surodex®）、卡那单抗（canakinumab）（例如Ilaris®）、溴芬酸（Bromday®）眼用药物（例如Bronac®、Bronuck®、Xibrom®、Yellox®、溴莫尼定（例如Alphagan®、Bromoxidine®、Enidin®）、乙酸阿奈可他（anecortave acetate）（例如Retaane®、Edex®、Prostavasin®、Rigidur®、Vasoprost®、Viridal®）、阿柏西普眼用溶液（例如Eyelea®、Eylea®、VEGF-Trap-Eye®）、奥克纤溶酶（ocriplasmin）（例如Iluvien®、Medidur®、Medidur FA®）、西罗莫司（例如Perceiva®）、NT-501、KH-902、康普瑞汀磷酸二钠氨丁三醇（fosbretabulin tromethamine）（例如Zybrestat®）、AL-8309、阿根尼森（aganirsen）（例如Norvess®）、伏洛昔单抗（volociximab）（例如Opthotec®）、曲安西龙（例如爱康生物科技有限公司（Icon Bioscience））、TRC-105、布利沙福（Burixafor）（例如TG-0054）、TB-403（例如R-7334）、角鲨胺（例如Evizon®）、SB-623、S-646240、RTP-801i-14（例如PF-4523655）、RG-7417（例如FCFD-4514S）、AL-78898A（例如POT-4）、PG-11047（例如CGC-11047）、盐酸帕唑帕尼、索匹珠单抗（sonepcizumab）（例如Asonep®、Sphingomab®）、帕利泊芬（padeliporfin）（例如Stakel®）、OT-551、奥特组单抗（ontecizumab）、NOX-A12、hCNS-SC、Neu-2000、NAFB001、MA09-hRPE、LFG-316、iCo-007（例如ISIS-13650）、hI-con1、GSK-933776A、GS-6624（例如AB-0024）、ESBA-1008、艾普他伦（epitalon）、E-10030（例如ARC-127）、达特西普（dalantercept）、MP-0112、CNTO-2476、CERE-120、AAV-NTN、CCX-168、溴莫尼定-DDS、贝伐尼布钠（bevasiranib sodium）（例如Cand5）、柏替木单抗（bertilimumab）、AVA-101、ALG-1001、AL-39324、AGN-150998、ACU-4429、A6（例如Paralit®）、TT-30、sFLT-01基因疗法、RetinoStat®、PRS-050（例如Angiocal®）、PF-4382923、帕洛米德-529（Palomid-529）、MC-1101、GW-824575、Dz13（例如TRC-093）、D93、CDX-1135（例如TP10）、ATL-1103、ARC-1905、XV-615、湿性AMD抗体（例如普西维达公司（pSivida））、VEGF/rGel、VAR-10200、VAL-566-620-MULTI、TKI、TK-001、STP-601、干性AMD干细胞疗法（例如艾赛特公司（EyeCyte））、OpRegen、SMT-D004、SAR-397769、RTU-007、RST-001、RGNX-004、RFE-007-CAI、视网膜变性程序（例如奥法晋公司（Orphagen））、视网膜细胞（例如ISCO公司）、ReN003、PRM-167、ProDex、光敏开关（Photoswitch）（例如光敏开关生物科学公司（Photoswitch Biosciences））、帕金森氏病疗法（Parkinson's therapy）、OMS-721、OC-10X、NV.AT.08、NT-503、NAFB002、NADPH氧化酶抑制剂（例如阿利美拉科学公

司(Alimera Sciences))、MC-2002、枸杞抗血管生成蛋白多糖(lycium anti-angiogenic proteoglycan)、IXSVEGF、整合素抑制剂、GW-771806、GBS-007、Eos-013、EC-400、干性AMD疗法(例如神经元系统公司(Neuron Systems))、CGEN-25017、CERE-140、AP-202、AMD疗法(例如瓦伦斯医药公司(Valens Therapeutics))、AMD疗法(例如阿玛纳医药公司(Amarna Therapeutics))、AMD RNAi疗法(例如RXi公司)、ALK-001、AMD疗法(例如阿西昂特公司(Aciont))、AC-301、4-IPP、锌-单半胱氨酸络合物(例如阿德纳公司(Adeona))、瓦他拉尼、TG-100-344、普啉司他(prinomastat)、PMX-53、新伐司他(Neovastat)、美加明(mecamylamine)、JSM-6427、JPE-1375、CereCRIB、BA-285、ATX-S10、AG-13958、维替泊芬/αvβ3缀合物、VEGF/rGel、VEGF-皂草素、VEGF-R2拮抗剂(例如阿洛斯托公司(Allostera))、VEGF抑制剂(例如参天公司(Santen))、VEGF拮抗剂(例如方舟公司(Ark))、Vangiolux®、三苯甲烷(例如阿利美拉))、TG-100-801、TG-100-572、TA-106、T2-TrpRS、SU-0879、干细胞疗法(例如辉瑞公司(Pfizer)和UCL公司)、SOD模拟物(例如伊诺泰克公司(Inotek))、SHEF-1、罗他泊芬(rostaporfin)(例如Photrex®、Purlytin®、SnET2)、RNA干扰(例如艾德拉公司(Idera)和默克公司(Merck))、rhCFHp(例如奥普塞隆公司(Optherion))、视网膜-NPY、视网膜色素变性疗法(例如米梅托根公司(Mimetogen))、AMD基因疗法(例如诺华公司)、视网膜基因疗法(例如健赞公司(Genzyme))、AMD基因疗法(例如哥白尼公司(Copernicus))、视网膜营养不良疗法(例如佛维亚公司(Fovea)和健赞公司)、拉莫特公司(_Ramot)计划第K-734B号、PRS-055、猪RPE细胞(例如金维克公司(GenVec))、PMI-002、PLG-101(例如BiCentis®)、PJ-34、PI3K缀合物(例如西马弗瑞公司(Semafore))、PhotoPoint、Pharmaprojects第6526号、哌加他尼钠(例如SurModics®)、PEDF ZFP TF、PEDF基因疗法(例如金维克公司)、PDS-1.0、PAN-90806、Opt-21、OPK-HVB-010、OPK-HVB-004、眼科药物(例如塞尔乐沃公司(Cell NetwoRx))、眼用化合物(例如阿斯利康公司(AstraZenca)和爱尔康公司)、OcuXan、NTC-200、NT-502、NOVA-21012、Neurosolve®、神经保护剂(例如BDSI公司)、MEDI-548、MCT-355、McEye®、LentiVue®、LYN-002、LX-213、特沙弗林镥(lutetium texaphyrin)(例如Antrin®)、LG-339抑制剂(例如莱斯康公司(Lexicon))、KDR激酶抑制剂(例如默克公司)、ISV-616、INDUS-815C、ICAM-1适体(例如埃特科公司(Eyetech))、刺猬蛋白拮抗剂(hedgehog antagonist)(例如奥普萨莫公司(Opthalmo))、GTx-822、GS-102、颗粒酶B/VEGF®、基因疗法(例如埃格特公司(EyeGate))、GCS-100模拟程序、FOV-RD-27、成纤维细胞生长因子(例如拉莫特公司)、芬维A胺(fenretinide)、F-200(例如Eos-200-F)、Panzem SR®、ETX-6991、ETX-6201、EG-3306、Dz-13、双硫仑(disulfiram)(例如ORA-102)、双氯芬酸(例如奥普莫法马公司(Ophthalmopharma))、ACU-02、CLT-010、CLT-009、CLT-008、CLT-007、CLT-006、CLT-005、CLT-004、CLT-003(例如Chirovis®)、CLT-001、Cethrin®(例如BA-210)、塞内昔布、CD91拮抗剂(例如奥普莫法马公司)、CB-42、BNC-4、卵

黄状黄斑病蛋白 (bestrophin)、巴马司他 (batimastat)、BA-1049、AVT-2、AVT-1、atu012、Ape1 程序 (例如 ApeX-2)、抗 VEGF 抗体 (例如格瑞锋公司 (Gryphon))、AMD ZFP(例如吐尔根公司 (ToolGen))、AMD 疗法 (例如奥普塞隆公司)、AMD 疗法 (例如伊赛尔克斯公司 (ItherX))、干性 AMD 疗法 (例如奥普科公司 (Opko))、AMD 疗法 (例如 CSL 公司)、AMD 疗法 (例如药典公司 (Pharmacopeia) 和眼力健公司)、AMD 治疗性蛋白质 (例如伊赛尔克斯公司)、AMD RNAi 疗法 (例如生物分子治疗法公司 (BioMolecular Therapeutics))、AM-1101、ALN-VEG01、AK-1003、AGN-211745、ACU-XSP-001(例 如 Excellair®)、ACU-HTR-028、ACU-HHY-011、ACT-MD(例如新神经公司 (NewNeural))、ABCA4 调节剂 (例如阿克替夫帕斯公司 (Active Pass))、A36(例如埃恩顿公司 (Angstrom))、267268(例如 SB-267268)、贝伐单抗 (例如 Avastin®)、阿柏西普 (例如 Eylea®)、131-I-TM-601、凡德他尼 (例如 Caprelsa®、Zactima®、Zictifa®)、苹果酸舒尼替尼 (例如 Sutene®、Sutent®、索拉非尼 (例如 Nexavar®)、帕唑帕尼 (例如 Armala®、Patorma®、Votrient®)、阿西替尼 (例如 Inlyta®)、替沃赞尼、XL-647、RAF-265、派格他尼 (pegdinetanib)(例如 Angiocept®、帕唑帕尼、MGCD-265、艾芦库单抗 (icrucumab)、佛瑞替尼 (foretinib)、ENMD-2076、BMS-690514、瑞戈非尼、雷莫芦单抗 (ramucirumab)、普替德辛 (plitidepsin)(例如 Aplidin®)、奥兰替尼 (orantinib)、尼达尼布 (nintedanib)(例如 Vargatef®)、莫特塞尼 (motesanib)、米哚妥林 (midostaurin)、利尼伐尼、替拉替尼、兰伐替尼 (lenvatinib)、艾莫泰德 (elpamotide)、多韦替尼 (dovitinib)、西地尼布 (例如 Recentin®)、JI-101、卡博替尼 (cabozantinib)、布立尼布 (brivanib)、阿帕替尼 (apatinib)、Angiozyme®、X-82、SSR-106462、瑞贝替尼 (rebastinib)、PF-337210、IMC-3C5、CYC116、AL-3818、VEGFR2 抑制剂 (例如 AB 科学公司 (AB Science))、VEGF/rGel(例如克雷顿生物技术公司 (Clayton Biotechnologies))、TLK-60596、TLK-60404、R84 抗体 (例如游隼公司 (Peregrine))、MG-516、FLT4 激酶抑制剂 (例如萨罗姆公司 (Sareum))、flt-4 激酶抑制剂 (萨罗姆公司)、DCC-2618、CH-330331、XL-999、XL-820、瓦他拉尼、SU-14813、司马沙尼、KRN-633、CEP-7055、CEP-5214、ZK-CDK、ZK-261991、YM-359445、YM-231146、VEGFR2 激酶抑制剂 (例如武田公司)、VEGFR-2 激酶抑制剂 (例如韩美公司 (Hanmi))、VEGFR-2 拮抗剂 (例如安斐曼科斯公司 (Affymax))、VEGF/rGel(例如德亚公司 (Targa))、VEGF-TK 抑制剂 (例如阿斯利康公司)、酪氨酸激酶抑制剂 (例如雅培公司 (Abbott))、酪氨酸激酶抑制剂 (例如雅培公司)、Tie-2 激酶抑制剂 (例如 GSK 公司)、SU-0879、SP-5.2、索拉非尼珠粒 (例如 Nexavar® 珠粒)、SAR-131675、Ro-4383596、R-1530、Pharmaprojects 第 6059 号、OSI-930、OSI-817、OSI-632、MED-A300、L-000021649、KM-2550、激酶抑制剂 (例如梅特希尔基因公司)、激酶抑制剂 (例如安进公司 (Amgen))、Ki-8751、KDR 激酶抑制剂 (例如细胞技术公司 (Celltech))、KDR 激酶抑制剂 (例如默克公司)、KDR 激酶抑制剂 (例如安进公司)、KDR 抑制剂 (例如雅培公司)、KDR 抑制剂 (例如 LGLS)、JNJ-17029259、IMC-1C11、Flt 3/4 抗癌剂 (例如哨兵公司

(Sentinel))、EG-3306、DP-2514、DCC-2157、CDP-791、CB-173、c-kit 抑制剂（例如迪赛孚尔公司 (Deciphera))、BIW-8556、抗癌剂（例如博莱科公司 (Bracco) 和戴克斯公司 (Dyax))、抗 Flt-1 单克隆抗体（例如英克隆公司 (ImClone))、AGN-211745、AEE-788、以及 AB-434。

[0419] 激光疗法也可用于湿性 AMD。小分子抗 VEGF 疗法正在研究当中，但当前均未获得批准。在研发新的 AMD 治疗中的挑战包括鉴定治疗、向黄斑的递送、副作用以及患者对玻璃体内注射的依从性。

[0420] 除了本文所述的其它身体病况之外，在一些实施方案中，本文所述的方法、粒子、组合物和 / 或制剂还可以用于治疗、诊断、预防或处理受试者的黄斑水肿（例如黄斑囊样水肿 (CME) 或（糖尿病性黄斑水肿 (DME))。CME 是侵害眼的视网膜中央或黄斑的病症。当这种病况存在时，在黄斑中出现多个囊肿样（囊样）流体区域并且引起视网膜肿胀或水肿。CME 可能伴有多种疾病，如视网膜静脉阻塞、葡萄膜炎和 / 或糖尿病。CME 通常在白内障手术后出现。

[0421] 当前对 CME 的治疗包括施用 NSAID（如溴芬酸（例如 Bromday®））。NSAID 可以与皮质类固醇一起局部或玻璃体内共同施用。通常通过玻璃体内注射皮质类固醇对 CME 的严重且持续的病例进行治疗，所述玻璃体内注射是有创性的并且昂贵的程序。

[0422] 当患有糖尿病的患者的视网膜中的血管开始渗漏到黄斑中时出现 DME，所述黄斑是眼产生精细的中心视力的部分。这些漏出物导致黄斑变厚和肿胀，从而进行性地扭曲敏锐的视力。虽然肿胀可能不导致失明，但影响可以致使中心视力严重丧失。

[0423] 当前对 DME 的治疗包括不便的且有创的 Lucentis®（兰尼单抗）注射剂。另一种对 DME 的治疗是激光光凝术。激光光凝术是其中使用激光烧灼渗漏的血管或施加灼烧模式以减少水肿的视网膜程序。这种程序有不合意的副作用，包括周边视力和夜间视力部分丧失。

[0424] 由于上文所述的缺点，因此需要用于治疗和 / 或预防黄斑水肿（例如 CME 或 DME) 的经改进的制剂。本文所述的包括 NSAID（例如溴芬酸钙）的粒子、组合物和 / 或制剂在适合于向眼局部施用的 pH 值下是稳定的并且可以解决上文针对当前用于黄斑水肿的治疗方法所述的问题。（参见例如实施例 27-28)。

[0425] 本文所述的粒子、组合物和 / 或制剂可以通过多种途径递送到眼中，所述途径包括而不限于以任何可接受的形式（例如片剂、液体、胶囊、粉剂等）口服施用；以任何可接受的形式（例如贴剂、滴眼剂、乳膏剂、凝胶、雾化、泪点塞 (punctal plug)、药物洗脱隐形眼镜、离子电渗以及软膏剂）局部施用；通过任何可接受的形式（例如静脉内、腹膜内、肌内、皮下、肠胃外以及硬膜外）的注射；以及通过植入或使用贮器 (reservoir)（例如皮下泵、鞘内泵、栓剂、生物可降解递送系统、非生物可降解递送系统以及其它植入的延长释放或缓慢释放装置或制剂）。

[0426] 部分地由于通过注射向眼中施用粒子、组合物和 / 或制剂是有创性的（引起患者不适并且还可以导致甚至比所治疗的疾病更为严重的并发症）并且口服给药往往导致粒子、组合物和 / 或制剂在眼中的分布较低，因此在一些实施方案中，局部递送可能是优选的。局部递送的关键益处包括无创性特征、减少了全身暴露的局限作用、相对的患者舒适度以及易于施用。

[0427] 依从性是源于多种因素的问题，所述因素从患者难以记得滴用滴剂到在身体上施用滴剂有困难到令人不快的副作用。其它问题包括药物的快速清除和全身暴露。

[0428] 如本文所述，在一些实施方案中，粒子、组合物和 / 或制剂可以向受试者的眼局部施用，并且药剂可以被递送到眼后部（例如视网膜、脉络膜、玻璃体以及视神经）。粒子、组合物和 / 或制剂可以用于治疗、诊断、预防或处理诸如年龄相关的黄斑变性、糖尿病性视网膜病、视网膜静脉阻塞、视网膜动脉阻塞、黄斑水肿、手术后炎症、葡萄膜炎、视网膜炎、增生性玻璃体视网膜病以及青光眼等病症。

[0429] 在某些实施方案中，本文所述的粒子、组合物以及方法可用于使眼成像。在某些实施方案中，本文所述的粒子、组合物以及方法可用于诊断眼部病况。

[0430] 在一些实施方案中，本文所述的药物组合物的眼部递送包括向眼部表面、向泪腺或泪管引流系统、向眼睑、向眼前段、向眼后段和 / 或向眼周空间递送。在某些实施方案中，本文所述的药物组合物可以向角膜、虹膜 / 睫状体、房水、玻璃体液、视网膜、脉络膜和 / 或巩膜递送。与递送并非在本文被鉴定为具有粘液穿透性的粒子的治疗作用相比，递送本文所述的药物组合物的治疗作用可以有所改进。

[0431] 在一些实施方案中，通过本文所述的粒子、组合物和 / 或方法递送到眼中的药剂可以是皮质类固醇。在某些实施方案中，所述药剂是依碳酸氯替泼诺。在某些实施方案中，所述药剂包括以下中的一种或多种：氢化可的松、可的松、替可的松、泼尼松龙、甲泼尼龙、泼尼松、曲安西龙、莫米松、安西奈德、布地奈德、地奈德、乙酸氟轻松、氟轻松、哈西奈德、倍他米松、地塞米松、氟可龙、氢化可的松、阿氯米松、泼尼卡酯、氯倍他松、氯倍他索、氟泼尼定、糖皮质激素、盐皮质激素、醛固酮、去氧皮质酮、氟氢可的松、卤贝他索、二氟拉松、去羟米松、氟替卡松、氟氢缩松、阿氯米松、二氟可龙、氟尼缩松、以及倍氯米松。

[0432] 在某些实施方案中，本文所述的粒子、组合物以及方法可用于将皮质类固醇（如上文所述的一种）递送到眼中用以治疗眼的炎症。在某些实施方案中，所述粒子、组合物以及方法可用于将皮质类固醇递送到眼中用以治疗黄斑变性、黄斑水肿、其它视网膜病症、或本文所述的其它病况。

[0433] 在一些实施方案中，通过本文所述的粒子、组合物以及方法递送到眼中的药剂可以是非类固醇抗炎药 (NSAID)。在某些实施方案中，所述药剂是溴芬酸的二价金属盐（例如溴芬酸钙）。在某些实施方案中，所述药剂是双氯芬酸（例如双氯芬酸游离酸或其二价金属盐或三价金属盐）。在某些实施方案中，所述药剂是酮咯酸（例如酮咯酸游离酸或其二价金属盐或三价金属盐）。在某些实施方案中，所述药剂是水杨酸盐（例如阿斯匹林 (aspirin)（乙酰水杨酸）、双氟尼酸或双水杨酯 (salsalate)）。在某些实施方案中，所述药剂是丙酸衍生物（例如布洛芬、萘普生、非诺洛芬、酮洛芬、右酮洛芬 (dexketoprofen)、氟比洛芬、奥沙普秦 (oxaprozin) 以及洛索洛芬 (loxoprofen)）。在某些实施方案中，所述药剂是乙酸衍生物（例如吲哚美辛、舒林酸、依托度酸、酮咯酸、双氯芬酸以及萘丁美酮）。在某些实施方案中，所述药剂是烯醇酸（昔康 (oxicam)）衍生物（例如吡罗昔康、美洛昔康 (meloxicam)、替诺昔康 (tenoxicam)、屈昔康 (droxicam)、氯诺昔康 (lornoxicam) 以及伊索昔康 (isoxicam)）。在某些实施方案中，所述药剂是芬那酸 (fenamic acid) 衍生物（芬那酸盐）（例如甲芬那酸、甲氯芬那酸、氟芬那酸 (flufenamic acid) 以及托芬那酸 (tolfenamic acid)）。在某些实施方案中，所述药剂是环加氧酶 (cox) 抑制剂，如 cox-1 抑

制剂或 cox-2 抑制剂（例如溴芬酸钙）。在某些实施方案中，所述药剂是选择性 cox-2 抑制剂（昔布类 (coxib)）（例如塞内昔布、罗非昔布、伐地考昔、帕瑞昔布、罗美昔布、依他昔布以及非罗考昔）。在某些实施方案中，所述药剂是磺酰苯胺（例如尼美舒利 (nimesulide)）。在某些实施方案中，所述药剂是利克飞龙 (licofelone)。

[0434] 在某些实施方案中，本文所述的粒子、组合物以及方法可用于将 NSAID（如上文所述的一种）递送到眼中用以治疗眼的炎症或本文所述的其它病况。在一些实施方案中，通过本文所述的粒子、组合物以及方法递送到眼中的药剂可以是血管生成抑制剂。在某些实施方案中，所述药剂是内源性血管生成抑制剂（例如 VEGFR-1（例如帕唑帕尼（Votrient®）、西地尼布（Recentin®）、替沃赞尼 (AV-951)、阿西替尼（Inlyta®）、司马沙尼）、HER2（拉帕替尼（Tykerb®、Tyverb®）、利尼伐尼 (ABT-869)、MGCD-265 以及 KRN-633)、VEGFR-2（例如瑞戈非尼 (BAY 73-4506)、替拉替尼 (BAY 57-9352)、瓦他拉尼 (PTK787、PTK/ZK)、MGCD-265、OSI-930 以及 KRN-633)、NRP-1、血管生成素 2、TSP-1、TSP-2、血管抑素、内皮抑素、血管抑制因子、钙网织蛋白、血小板因子 -4、TIMP、CDAI、Meth-1、Meth-2、IFN-α、IFN-β、IFN-γ、CXCL10、IL-4、IL-12、IL-18、凝血酶原（三环域 -2(kringle domain-2)）、抗凝血酶 III 片段、催乳素、VEGI、SPARC、骨桥蛋白、乳腺丝抑蛋白、血管能抑素、增殖蛋白相关蛋白、索拉非尼（Nexavar®））以及休眠蛋白）。在某些实施方案中，所述药剂是外源性血管生成抑制剂（例如贝伐单抗、伊曲康唑、羧胺三唑 (carboxyamidotriazole)、TNP-470、CM101、IFN-α、IL-12、血小板因子 -4、苏拉明 (suramin)、SU5416、血小板反应蛋白、VEGFR 拮抗剂、血管生成抑制性类固醇 + 肝素、源自于软骨的血管生成抑制因子、基质金属蛋白酶抑制剂、血管抑素、内皮抑素、2- 甲氧基雌二醇、替可加兰 (tecogalan)、四硫钼酸盐、沙利度胺、血小板反应蛋白、催乳素、$\alpha_v\beta_3$抑制剂、利诺胺 (linomide) 以及他喹莫德 (tasquinimod))。

[0435] 在某些实施方案中，本文所述的粒子、组合物以及方法可用于将血管生成抑制剂（如上文所述的那些）递送到眼中用以治疗黄斑变性、其它视网膜病症或本文所述的其它病况。在一些实施方案中，通过本文所述的粒子、组合物以及方法递送到眼中的药剂可以是前列腺素类似物。在某些实施方案中，所述药剂是拉坦前列素、曲伏前列素、乌诺前列酮或比马前列素。

[0436] 在一些实施方案中，本文所述的粒子、组合物和 / 或制剂中的药剂是 RTK 抑制剂。在某些实施方案中，所述药剂是索拉非尼。举例来说，如实施例 21、25 以及 29 中所更详细地描述，与相等剂量的不包括合适的表面改变剂的索拉非尼粒子相比，施用包括本文所述的某些表面改变剂的索拉非尼粒子使得兔的各种眼部组织（例如眼后部的组织）中索拉非尼的水平显著更高。

[0437] 在某些实施方案中，本文所述的粒子、组合物和 / 或制剂中的药剂是利尼伐尼。举例来说，如实施例 29 中所更详细地描述，施用含有利尼伐尼的 MPP 增强了利尼伐尼在兔的眼后部的暴露。

[0438] 在某些实施方案中，本文所述的粒子、组合物和 / 或制剂中的药剂是 MGCD-265。举例来说，如实施例 30 中所更详细地描述，施用含有 MGCD-265 的 MPP 在兔的眼后部产生了治

疗相关水平的 MGCD-265。

[0439] 在某些实施方案中，本文所述的粒子、组合物和 / 或制剂中的药剂是帕唑帕尼。举例来说，如实施例 30 中所更详细地描述，施用含有帕唑帕尼的 MPP 在兔的眼后部产生了治疗相关水平的帕唑帕尼。

[0440] 在某些实施方案中，本文所述的粒子、组合物和 / 或制剂中的药剂是西地尼布。举例来说，如实施例 31 中所更详细地描述，单次局部施用西地尼布 -MPP 在兔的眼后部产生治疗相关的西地尼布水平达 24 小时。

[0441] 在某些实施方案中，本文所述的粒子、组合物和 / 或制剂中的药剂是阿西替尼。举例来说，如实施例 32 和 33 中所更详细地描述，单次局部施用阿西替尼 -MPP 在兔的眼后部产生治疗相关的阿西替尼水平达 24 小时，并且阿西替尼 -MPP 减少了兔 VEGF（血管内皮生长因子受体）激发模型中的血管渗漏。

[0442] 上文和本文所述的结果表明与某些市售制剂（如必须被注射到眼中的那些）相比，本文所述的粒子、组合物和 / 或制剂可以被局部施用以在治疗 AMD、其它视网膜病症或本文所述的其它病况方面实现并且维持治疗作用。

[0443] 在某些实施方案中，本文所述的粒子、组合物以及方法可用于将前列腺素类似物（如上文所述的一种）递送到眼中用以治疗青光眼或本文所述的其它病况。

[0444] 在一些实施方案中，通过本文所述的粒子、组合物以及方法递送到眼中的药剂可以是 β 阻断剂。在某些实施方案中，所述药剂是非选择性 β 阻断剂（例如阿普洛尔、布新洛尔、卡替洛尔、卡维地洛、拉贝洛尔、纳多洛尔、氧烯洛尔、喷布洛尔、品多洛尔、普萘洛尔、索他洛尔、噻吗洛尔以及杜仲）。在某些实施方案中，所述药剂是 β_1选择性阻断剂（例如醋丁洛尔、阿替洛尔、倍他索洛尔、比索洛尔、塞利洛尔、艾司洛尔、美托洛尔以及奈必洛尔）。在某些实施方案中，所述药剂是 β_2选择性阻断剂（例如丁氧胺和 ICI-118,551）。在某些实施方案中，所述药剂是 β_3选择性阻断剂（例如 SR 59230A）。

[0445] 在某些实施方案中，本文所述的粒子、组合物以及方法可用于将 β 阻断剂（如上文所述的一种）递送到眼中用以治疗青光眼或本文所述的其它病况。

[0446] 在某些实施方案中，通过本发明的粒子、组合物以及方法递送到眼中的药剂可以是碳酸酐酶抑制剂。在某些实施方案中，所述药剂是乙酰唑胺、布林佐胺、多佐胺、多佐胺和噻吗洛尔、或甲醋唑胺。

[0447] 在某些实施方案中，本文所述的粒子、组合物以及方法可用于将碳酸酐酶抑制剂（如上文所述的那些）递送到眼中用以治疗青光眼或本文所述的其它病况。如本文所述，在一些实施方案中，与某些现有的粒子、组合物和 / 或制剂相比，本文所述的粒子、组合物和 / 或制剂可以改进或增加向受试者的眼局部施用的药剂的眼部生物利用度，所述眼部生物利用度被定义为在施用后在目标眼部组织中的药物浓度相对于时间的曲线下面积 (AUC)。在一些实施方案中，药剂的眼部生物利用度可能至少部分地由于包含所述药剂的核心粒子上使得所述粒子具有粘液穿透性的包衣而与和所考虑的包衣粒子具有相似尺寸，但不包括所述包衣的药剂粒子相比有所增加。

[0448] 在一些实施方案中，本文所述的粒子、组合物和 / 或制剂使药剂的眼部生物利用度增加了至少约 10％、至少约 20％、至少约 30％、至少约 40％、至少约 50％、至少约 60％、至少约 70％、至少约 80％、至少约 90％、至少约 100％、至少约 150％、至少约 200％、至少约

5 倍、至少约 10 倍、至少约 20 倍、至少约 50 倍、至少约 100 倍、至少约 500 倍、或至少约 1000 倍。在某些实施方案中，本文所述的粒子、组合物和 / 或制剂使药剂的眼部生物利用度增加少于或等于约 1000 倍、少于或等于约 500 倍、少于或等于约 100 倍、少于或等于约 50 倍、少于或等于约 20 倍、少于或等于约 10 倍、少于或等于约 5 倍、增加少于或等于约 200％、少于或等于约 150％、少于或等于约 100％、少于或等于约 90％、少于或等于约 80％、少于或等于约 70％、少于或等于约 60％、少于或等于约 50％、少于或等于约 40％、少于或等于约 30％、少于或等于约 20％、或者少于或等于约 10％。上述范围的组合也是可能的（例如增加至少约 10％且少于或等于约 10 倍）。其它范围也是可能的。在一些情况下，眼前部的组织和 / 或流体处药剂的 AUC 增加。在其它情况下，眼后部的组织和 / 或流体处药剂的 AUC 增加。

[0449] 一般来说，眼部生物利用度的增加可以通过获得测试组合物与对照组合物之间在目标眼部组织中（例如在房水中）测量的 AUC 的差值，并且用所述差值除以对照组合物的生物利用度来计算。测试组合物可以包括包含药剂的粒子，并且所述粒子可以被表征为具有粘液穿透性（例如在粘液中具有大于约 0.5 的相对速度或本文所述的另一其它相对速度）。对照组合物可以包括包含与测试组合物中存在的药剂相同的药剂的粒子，所述粒子与测试组合物的粒子具有基本上相似的尺寸，但不具粘液穿透性（例如在粘液中具有小于或等于约 0.5 的相对速度或本文所述的另一其它相对速度）。

[0450] 药剂的眼部生物利用度可以在适当的动物模型中（例如在新西兰白兔模型中）测量。在施用后随时间的变化来测量在适当的眼部组织或流体中药剂的浓度以及在适当时它的一种或多种代谢物的浓度。

[0451] 其它测量药剂的眼部生物利用度的方法是可能的。

[0452] 如本文所述，在一些实施方案中，当使用本文所述的粒子、组合物和 / 或制剂递送药剂（例如通过向眼局部施用）时，与使用含有相同的药剂的某些现有粒子、组合物和 / 或制剂递送药剂时相比（或与递送与所考虑的包衣粒子相同（例如具有相似的尺寸）但不包括包衣的药剂相比），药剂在眼部组织和 / 或流体中的浓度可以增加。在某些实施方案中，施用一定剂量的粒子、组合物和 / 或制剂，之后测量眼的组织和 / 或流体中药剂的浓度。为了进行比较，所施用剂量的本文所述的粒子、组合物和 / 或制剂中所包括的药剂的量可以与所施用剂量的现有粒子、组合物和 / 或制剂中所包括的药剂的量相似或基本上相等。在某些实施方案中，在施用一定剂量的本文所述的粒子、组合物和 / 或制剂或现有的粒子、组合物和 / 或制剂后一定的时间（“给药后时间”）测量药剂在眼的组织和 / 或流体中的浓度。在某些实施方案中，对浓度进行测量的时间是给药后约 1 分钟、约 10 分钟、约 30 分钟、约 1 小时、约 2 小时、约 3 小时、约 4 小时、约 5 小时、约 6 小时、约 7 小时、约 8 小时、约 9 小时、约 10 小时、约 11 小时、约 12 小时、约 18 小时、约 24 小时、约 36 小时、或约 48 小时。

[0453] 在一些实施方案中，组织和 / 或流体中药剂的浓度可能至少部分地由于包含所述药剂的核心粒子上使得所述粒子具有粘液穿透性的包衣而和与所考虑的包衣粒子具有相同的药剂（例如具有相似的尺寸）但不包括所述包衣的粒子相比有所增加。在一些实施方案中，本文所述的粒子、组合物和 / 或制剂使组织和 / 或流体中药剂的浓度增加了至少约 10％、至少约 20％、至少约 30％、至少约 40％、至少约 50％、至少约 60％、至少约 70％、至少约 80％、至少约 90％、至少约 100％、至少约 200％、至少约 300％、至少约 400％、至少约 500％、或至少约 10 倍、至少约 20 倍、至少约 50 倍、至少约 100 倍、至少约 1000 倍、至少约 10^4

倍、至少约 10^5 倍、或至少约 10^6 倍。在一些情况下，本文所述的粒子、组合物和 / 或制剂使组织和 / 或流体中药剂的浓度增加了少于或等于约 10^6 倍、少于或等于约 10^5 倍、少于或等于约 10^4 倍、1000 倍、少于或等于约 100 倍、少于或等于约 10 倍、少于或等于约 500％、少于或等于约 400％、少于或等于约 300％、少于或等于约 200％、少于或等于约 100％、少于或等于约 90％、少于或等于约 80％、少于或等于约 70％、少于或等于约 60％、少于或等于约 50％、少于或等于约 40％、少于或等于约 30％、少于或等于约 20％、或者少于或等于约 10％。上述范围的组合也是可能的（例如增加了大于或等于约 10％且少于或等于约 90％）。其它范围也是可能的。在一些情况下，在眼前部的组织和 / 或流体处药剂的浓度增加。在其它情况下，在眼后部的组织和 / 或流体处药剂的浓度增加。

[0454] 可以使用适当的动物模型在体内随时间的变化来测量适当的眼部流体或组织中药剂的眼部浓度以及在适当时它的一种或多种代谢物的眼部浓度。一种测定药剂的眼部浓度的方法涉及对眼进行解剖以分离目标组织（例如在与受试者相当的动物模型中）。然后通过 HPLC 或 LC/MS 分析测定目标组织中药剂的浓度。

[0455] 在某些实施方案中，施用本文所述的粒子与获得用于测量浓度或 AUC 的样品之间的时间段少于约 1 小时、少于或等于约 2 小时、少于或等于约 3 小时、少于或等于约 4 小时、少于或等于约 6 小时、少于或等于约 12 小时、少于或等于约 36 小时、或者少于或等于约 48 小时。在某些实施方案中，所述时间段是至少约 1 小时、至少约 2 小时、至少约 3 小时、至少约 4 小时、至少约 6 小时、至少约 8 小时、至少约 12 小时、至少约 36 小时、或至少约 48 小时。上述范围的组合也是可能的（例如连续剂量之间多于或等于约 3 小时且少于或等于约 12 小时的时间段）。其它范围也是可能的。

[0456] 其它测量药剂在受试者或动物模型的眼中的浓度的方法也是可能的。在一些实施方案中，可以直接或间接（例如从受试者的眼中获取诸如玻璃体液等流体样品）测量受试者的眼中药剂的浓度。

[0457] 一般来说，眼部部位中药剂浓度的增加可以通过获得测试组合物与对照组合物之间所测量的浓度的差值，并且用所述差值除以对照组合物的浓度来计算。测试组合物可以包括包含药剂的粒子，并且所述粒子可以被表征为具有粘液穿透性（例如具有大于约 0.5 的相对速度或本文所述的另一其它相对速度）。对照组合物可以包括包含与测试组合物中存在的药剂相同的药剂的粒子，所述粒子与测试组合物的粒子具有基本上相似的尺寸，但不具粘液穿透性（例如具有小于约 0.5 的相对速度或本文所述的另一其它相对速度）。

[0458] 如本文所述，在一些实施方案中，本文所述的粒子、组合物和 / 或制剂或其组分以足够的量存在以与在不存在本文所述的粒子、组合物以及制剂或其组分的情况下向眼部组织施用的药剂相比，提高药剂在眼部组织中的生物利用度和 / 或浓度。

[0459] 所述眼部组织可以是本文所述的眼部组织，如前眼部组织（例如睑结膜、球结膜或角膜）。所述药剂可以是如本文所述的任何合适的药剂，如皮质类固醇（例如依碳酸氯替泼诺）、RTK 抑制剂（例如索拉非尼、利尼伐尼、MGCD-265、帕唑帕尼、西地尼布以及阿西替尼）、NSAID（例如溴芬酸钙）、或 cox 抑制剂（例如溴芬酸钙）。在某些实施方案中，制剂的包含药剂的核心粒子以足够的量存在以提高药剂在眼部组织中的生物利用度和 / 或浓度。在某些实施方案中，制剂的包含药剂的核心粒子上的包衣以足够的量存在以提高药剂在眼部组织中的生物利用度和 / 或浓度。在某些实施方案中，制剂的包含药剂的核心粒子上的

包衣以足够的量存在以在向眼部组织施用所述制剂后以下的一段时间之后提高药剂在眼部组织中的浓度：至少 10 分钟、至少 20 分钟、至少 30 分钟、至少 1 小时、至少 2 小时、至少 3 小时、至少 4 小时、至少 6 小时、至少 9 小时、至少 12 小时、至少 18 小时、或至少 24 小时。在某些实施方案中，制剂的包含药剂的核心粒子上的包衣以足够的量存在以在向眼部组织施用所述制剂后以下的一段时间之后提高药剂在眼部组织中的浓度：少于或等于 24 小时、少于或等于 18 小时、少于或等于 12 小时、少于或等于 9 小时、少于或等于 6 小时、少于或等于 4 小时、少于或等于 3 小时、少于或等于 2 小时、少于或等于 1 小时、少于或等于 30 分钟、少于或等于 20 分钟、或者少于或等于 10 分钟。上述范围的组合也是可能的（例如在至少 10 分钟且少于或等于 2 小时后药剂的浓度增加）。其它范围也是可能的。在某些实施方案中，制剂的包含药剂的核心粒子上的包衣以足够的量存在以在向眼部组织施用所述制剂后约 30 分钟之后提高药剂在眼部组织中的浓度。

[0460] 如本文所述，在一些实施方案中，本文所述的粒子、组合物和 / 或制剂可以各种剂量形式向受试者的眼局部施用。举例来说，本文所述的粒子、组合物和 / 或制剂可以单一单位剂量的形式施用或以多次单一单位剂量的形式重复施用。单位剂量是包含预定量的药剂的本文所述的粒子、组合物和 / 或制剂的个别量。在一些实施方案中，在使用本文所述的具有粘液穿透性包衣的粒子的情况下，与不具有这种包衣的粒子相比，需要更少的给药次数（例如给药次数的 1/2、1/3 或 1/4）。

[0461] 实现治疗有效量或预防有效量所需的本文所述的粒子、组合物和 / 或制剂的确切量将在受试者之间有所不同，这取决于例如受试者的物种、年龄以及一般状况、副作用或病症的严重度、具体化合物的特征、施用方式等。本文所述的粒子、组合物和 / 或制剂可以利用重复施用来递送，其中在连续的剂量之间存在一段时间。重复施用可能是有利的，因为它可以允许使眼暴露于治疗有效量或预防有效量的药剂足够长的一段时间以使得眼部病况得到治疗、预防或处理。在某些实施方案中，连续剂量之间的时间段少于或等于约 1 小时、少于或等于约 2 小时、少于或等于约 3 小时、少于或等于约 4 小时、少于或等于约 6 小时、少于或等于约 12 小时、少于或等于约 36 小时、或者少于或等于约 48 小时。在某些实施方案中，连续剂量之间的时间段是至少约 1 小时、至少约 2 小时、至少约 3 小时、至少约 4 小时、至少约 6 小时、至少约 12 小时、至少约 36 小时、或至少约 48 小时。上述范围的组合也是可能的（例如连续剂量之间多于或等于约 3 小时且少于或等于约 12 小时的时间段）。其它范围也是可能的。

[0462] 向眼部组织递送本文所述的粒子、组合物和 / 或制剂可以在施用（例如局部施用或通过直接注射来施用）后在眼部组织中产生眼科学上有效的药物水平达延长的时间段。药物的眼科学上有效的水平指的是足以诱发眼部组织的所需生物反应，即治疗眼部疾病的量。如本领域技术人员所应了解，药物的眼科学上有效的水平可以根据诸如以下的因素而变化：所需的生物学终点、药物的药物代谢动力学、所治疗的眼部疾病、施用方式、以及受试者的年龄和健康状况。在某些实施方案中，药物的眼科学上有效的水平是药物单独或与其它疗法组合在治疗眼部病况方面提供治疗益处的量。药物的眼科学上有效的水平可以涵盖改进整体疗法、减少或避免眼部病况的症状或原因、或增强另一种治疗剂的治疗功效的水平。

[0463] 在一些实施方案中，眼科学上有效的药物水平可以至少部分地通过药剂在施用后

在眼部组织中的最大浓度（C_{max}）来计量。在一些情况下，与相似剂量的市售粒子、组合物以及制剂相比，向眼部组织递送如本文所述的包含药剂的粒子、组合物和/或制剂可以使得在施用后所述药剂在眼部组织中的 C_{max} 更高。在某些实施方案中，从施用本文所述的粒子、组合物和/或制剂获得的 C_{max} 比通过施用市售的粒子、组合物和/或制剂获得的 C_{max} 高至少约 3%、至少约 10%、至少约 30%、至少约 100%、至少约 200%、至少约 300%、至少约 400%、至少约 500%、至少约 1000%、或至少约 3000%。在某些实施方案中，从施用本文所述的粒子、组合物和/或制剂获得的 C_{max} 比通过施用市售的粒子、组合物和/或制剂获得的 C_{max} 高少于或等于约 3000%、少于或等于约 1000%、少于或等于约 500%、少于或等于约 400%、少于或等于约 300%、少于或等于约 200%、少于或等于约 100%、少于或等于约 30%、少于或等于约 10%、或者少于或等于约 3%。上述范围的组合也是可能的（例如至少约 30%且少于或等于约 500%的 C_{max} 增加）。其它范围也是可能的。

[0464] 在一些实施方案中，眼科学上有效的药物水平是至少部分地通过如本领域所知的药物的最低有效浓度（例如 IC_{50} 或 IC_{90}）来计量的。

[0465] 在其中眼科学上有效的药物水平（或 C_{max}、IC_{50} 或 IC_{90}）在眼部组织中存在达施用后的长的时间段的某些实施方案中，施用后的长时间段可以在数小时至数天的范围内。在某些实施方案中，施用后的长时间段是至少 1 小时、至少 2 小时、至少 4 小时、至少 6 小时、至少 9 小时、至少 12 小时、至少 1 天、至少 2 天、至少 3 天、至少 4 天、至少 5 天、至少 6 天、或至少 1 周。在某些实施方案中，施用后的长时间段少于或等于 1 周、少于或等于 6 天、少于或等于 5 天、少于或等于 4 天、少于或等于 3 天、少于或等于 2 天、少于或等于 1 天、少于或等于 12 小时、少于或等于 9 小时、少于或等于 6 小时、少于或等于 4 小时、少于或等于 2 小时、少于或等于 1 小时。上述范围的组合也是可能的（例如至少约 4 小时且少于或等于约 1 周的长时间段）。其它范围也是可能的。

[0466] 在某些实施方案中，本文所述的粒子、组合物和/或制剂可以处在足以向受试者的眼递送有效量的药剂以获得所需的治疗作用或预防作用的剂量水平。在某些实施方案中，向适当的眼组织递送的药剂的有效量是每克组织重量至少约 10^{-3}ng、每克组织重量至少约 10^{-2}ng、每克组织重量至少约 10^{-1}ng、每克组织重量至少约 1ng、每克组织重量至少约 10^{1}ng、每克组织重量至少约 10^{2}ng、每克组织重量至少约 10^{3}ng、每克组织重量至少约 10^{4}ng、每克组织重量至少约 10^{5}ng、或每克组织重量至少约 10^{6}ng。在某些实施方案中，向眼递送的药剂的有效量是每克组织重量小于或等于约 10^{6}ng、每克组织重量小于或等于约 10^{5}ng、每克组织重量小于或等于约 10^{4}ng、每克组织重量小于或等于约 10^{3}ng、每克组织重量小于或等于约 10^{2}ng、每克组织重量小于或等于约 10^{1}ng、每克组织重量小于或等于约 1ng、每克组织重量小于或等于约 10^{-1}ng、每克组织重量小于或等于约 10^{-2}ng、或者每克组织重量小于或等于约 10^{-3}ng。上述范围的组合也是可能的（例如每克组织重量至少约 10^{-2}ng 且每克组织重量小于或等于约 10^{3}ng 的药剂的有效量）。其它范围也是可能的。在某些实施方案中，本文所述的粒子、组合物和/或制剂可以处在足以向受试者的眼后部递送有效量的药剂以获得所需的治疗作用或预防作用的剂量水平。

[0467] 应当了解的是，如本文所述的剂量范围提供了有关将所提供的粒子、组合物和/或制剂向成年人施用的指导。待向例如儿童或青少年施用的量可以由执业医师或本领域技术人员确定并且可以低于向成年人施用的量或与向成年人施用的量相同。

[0468] 本文所述的粒子、组合物和/或制剂可以通过任何方法，例如通过滴剂、粉剂、软膏剂或乳膏剂局部施用。其它局部施用途径或形式也是可能的。

[0469] 在某些实施方案中，本文所述的组合物和/或制剂被包装成即用型贮存稳定性悬浮液。滴眼剂制剂是传统上的液体制剂（溶液或悬浮液），所述液体制剂可以被包装在滴瓶（其分配标准滴体积的液体）中或一次性使用（individual use）的滴管（通常用于无防腐剂的滴剂；使用一次即被丢弃）中。这些制剂是即用型的并且可以自行施用。在一些情况下，应当在使用之前振荡瓶子以确保制剂的均质性，但可能不需要其它准备。这可能是最简单并且最方便的眼部递送方法。可以与传统的滴眼剂制剂相同的方式对本文所述的组合物和/或制剂进行包装。它们可以悬浮液的形式储存并且可以保持允许粒子避免与粘液粘着的特征。

[0470] 所述药剂可以是本文所述的那些药剂中的一种。在某些实施方案中，药剂是NSAID、RTK抑制剂、cox抑制剂、皮质类固醇、血管生成抑制剂、前列腺素类似物、β阻断剂或碳酸酐酶抑制剂。在某些实施方案中，药剂是依碳酸氯替泼诺。在某些实施方案中，剂是索拉非尼。在某些实施方案中，药剂是利尼伐尼。在某些实施方案中，药剂是MGCD-265。在某些实施方案中，药剂是帕唑帕尼。在某些实施方案中，药剂是西地尼布。在某些实施方案中，药剂是阿西替尼。在某些实施方案中，药剂是溴芬酸的二价金属盐（例如溴芬酸钙）。在某些实施方案中，药剂是溴芬酸铍、溴芬酸镁、溴芬酸锶或溴芬酸钡、溴芬酸锌、或溴芬酸铜(II)。其它药剂也是可能的。

[0471] 在一组实施方案中，提供了适合于向眼施用的药物组合物。所述药物组合物包含多个包衣粒子，所述包衣粒子包含：核心粒子，所述核心粒子包含A)药剂或其盐或由A)药剂或其盐形成，其中A)所述药剂或其盐占所述核心粒子的至少约80重量%；以及围绕所述核心粒子的包衣，所述包衣包含一种或多种B)表面改变剂或由一种或多种B)表面改变剂形成。所述一种或多种表面改变剂以C)至少0.01个分子/平方纳米的密度存在于所述核心粒子的外表面上。所述一种或多种表面改变剂以约0.001重量%至约5重量%的量存在于所述药物组合物中。所述多个包衣粒子具有小于约1微米的平均最小横截面尺寸。所述药物组合物还包括一种或多种眼科学上可接受的载体、添加剂和/或稀释剂。还提供了对眼使用和施用这些药物组合物的方法。

[0472] 在一些实施方案中，A)药剂或其盐可以选自：A1)皮质类固醇、A2)糖皮质激素受体激动剂(SEGRA)、A3)RTK抑制剂、A4)NSAID、A5)mTOR抑制剂、A6)钙调神经磷酸酶抑制剂、A7)类前列腺素(prostanoid)、A8)ρ激酶抑制剂、A9)核黄素、A10)Cox-2抑制剂、A11)血管生成抑制剂、A12)前列腺素类似物、A13)β阻断剂、A14)碳酸酐酶抑制剂、A15)抗组胺剂、A16)肥大细胞稳定剂、A17)免疫抑制剂、A18)α-阻断剂、A19)抗生素；以及它们的组合。

[0473] 在一些实施方案中，B)表面改变剂可以选自：B1)包含亲水性嵌段-疏水性嵌段-亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约2kDa的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约15重量%（例如某些泊洛沙姆）；B2)合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约1kDa并且小于或等于约1000kDa的分子量，其中所述聚合物至少约30%水解且少于约95%水解（例如聚乙烯醇、部分水解的聚（乙酸乙烯酯）或乙烯醇与乙酸乙烯酯的共聚物）；B3)

聚山梨醇酯；B4）辛基苯酚乙氧基化物表面活性剂；B5）聚氧乙烯羟基硬脂酸酯；B6）聚氧乙烯蓖麻油衍生物；B7）烷基芳基聚醚醇；B8）聚乙二醇丁二酸酯；B9）聚氧乙烯烷基醚；以及它们的组合。

[0474] 在某些实施方案中，A1）皮质类固醇可以选自：A1a）依碳酸氯替泼诺、A1b）地塞米松、A1c）曲安西龙、A1d）乙酸氟轻松、A1e）泼尼松龙、A1f）氟米龙、A1g）二氟泼尼酯、A1h）氟替卡松、以及它们的组合。

[0475] 在某些实施方案中，A2）糖皮质激素受体激动剂可以选自：A2a）美普克莱、A2b）利美索龙、以及它们的组合。

[0476] 在某些实施方案中，A3）RTK 抑制剂可以选自：A3a）索拉非尼、A3b）利尼伐尼、A3c）MGCD-265（梅特希尔基因公司）、A3d）帕唑帕尼、A3e）西地尼布、A3f）阿西替尼、以及它们的组合。

[0477] 在某些实施方案中，A4）NSAID 可以选自：A4a）奈帕芬胺、A4b）溴芬酸（例如溴芬酸钙）、A4c）双氯芬酸（例如双氯芬酸游离酸）、A4d）酮咯酸（例如酮咯酸游离酸）、以及它们的组合。

[0478] 在某些实施方案中，A5）mTOR 抑制剂可以选自：A5a）他克莫司、A5b）西罗莫司、以及它们的组合。

[0479] 在某些实施方案中，A6）钙调神经磷酸酶抑制剂可以选自：A6a）环孢菌素、A6b）伏孢素、以及它们的组合。

[0480] 在某些实施方案中，A7）类前列腺素可以选自：A7a）拉坦前列素、A7b）比马前列素、A7c）曲伏前列素、以及它们的组合。

[0481] 在某些实施方案中，A8）ρ 激酶抑制剂可以选自：A8a）SNJ-1656、A8b）AR-12286、A8c）AR-13324、以及它们的组合。

[0482] 在某些实施方案中，A10）Cox-2 抑制剂可以选自：A10a）塞内昔布、A10b）伐地考昔、以及它们的组合。

[0483] 在某些实施方案中，B1）包含亲水性嵌段-疏水性嵌段-亲水性嵌段构型的三嵌段共聚物，其中所述疏水性嵌段具有至少约 2kDa 的分子量，并且所述亲水性嵌段占所述三嵌段共聚物的至少约 15 重量%，所述三嵌段共聚物可以选自：B1a）泊洛沙姆、B1b）Pluronic F127、B1c）Pluronic P123、B1d）Pluronic P103、B1e）Pluronic P105、B1f）Pluronic F108、以及它们的组合。

[0484] 在某些实施方案中，B2）合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基，所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa 的分子量，其中所述聚合物至少约 30％水解且少于约 95％水解，所述合成聚合物可以选自：B2a）聚乙烯醇、B2b）PVA 13K87、B2c）PVA 31K98、B2d）PVA31K87、B2e）PVA 9K80、B2f）PVA 2K75、B2g）PVA 57K87、B2h）PVA85K87、B2i）PVA105K80、B2j）PVA130K87、以及它们的组合。

[0485] 在某些实施方案中，B3）聚山梨醇酯可以选自：B3a）Tween 20、B3b）Tween80、以及它们的组合。

[0486] 在某些实施方案中，B4）辛基苯酚乙氧基化物表面活性剂可以是：B4a）Triton X100。

[0487] 在某些实施方案中，B5）聚氧乙烯羟基硬脂酸酯可以是：B5a）Solutol HS15。

[0488] 在某些实施方案中，B6）聚氧乙烯蓖麻油衍生物可以选自：B6a)Cremophor EL、B6b)Cremophor RH 40、以及它们的组合。

[0489] 在某些实施方案中，B7）烷基芳基聚醚醇可以是：B7a）泰洛沙泊。

[0490] 在某些实施方案中，B8）聚乙二醇丁二酸酯可以是：B8a）维生素 E-TPGS。

[0491] 在某些实施方案中，B9）聚氧乙烯烷基醚可以选自：B9a)Brij 35、B9b)Brij98、B9c)Brij S100、以及它们的组合。

[0492] 在某些实施方案中，C）所述核心粒子的外表面上存在的一种或多种表面改变剂的密度可以选自：C1）至少 0.01 个分子 / 平方纳米的密度、C2）至少 0.05 个分子 / 平方纳米的密度、C3）至少 0.1 个分子 / 平方纳米的密度、C4）至少 0.15 个分子 / 平方纳米的密度、或 C5）至少 0.2 个分子 / 平方纳米的密度。

[0493] 应当了解的是，在本文所述的组合物和 / 或制剂中可以存在本文公开的以下的任何组合：A）药剂或其盐（例如 A1-A19 以及其在本文中所鉴定的物质）、B）表面改变剂（例如 B1-B9 以及其在本文中所鉴定的物质）和 / 或 C）所述核心粒子的外表面上存在的一种或多种表面改变剂的密度（例如 C1-C5）。此外，这些组合可以结合本文所述的参数一起存在，所述参数如表面改变剂的重量％的具体范围或值、包衣粒子的平均尺寸或最小横截面尺寸、pH 值、包衣厚度、PDI、载体和稀释剂的类型等。

[0494] 在一些实施方案中，药物组合物中 A）药剂或其盐与 B）表面改变剂的组合可以选自：A1、B1（即 A1 与 B1）；A1、B2；A1、B3；A1、B4；A1、B5；A1、B6；A1、B7；A1、B8；A1、B9；A2、B1；A2、B2；A2、B3；A2、B4；A2、B5；A2、B6；A2、B7；A2、B8；A2、B9；A3、B1；A3、B2；A3、B3；A3、B4；A3、B5；A3、B6；A3、B7；A3、B8；A3、B9；A4、B1；A4、B2；A4、B3；A4、B4；A4、B5；A4、B6；A4、B7；A4、B8；A4、B9；A5、B1；A5、B2；A5、B3；A5、B4；A5、B5；A5、B6；A5、B7；A5、B8；A5、B9；A6、B1；A6、B2；A6、B3；A6、B4；A6、B5；A6、B6；A6、B7；A6、B8；A6、B9；A7、B1；A7、B2；A7、B3；A7、B4；A7、B5；A7、B6；A7、B7；A7、B8；A7、B9；A8、B1；A8、B2；A8、B3；A8、B4；A8、B5；A8、B6；A8、B7；A8、B8；A8、B9；A9、B1；A9、B2；A9、B3；A9、B4；A9、B5；A9、B6；A9、B7；A9、B8；A9、B9；A10、B1；A10、B2；A10、B3；A10、B4；A10、B5；A10、B6；A10、B7；A10、B8；A10、B9；A11、B1；A11、B2；A11、B3；A11、B4；A11、B5；A11、B6；A11、B7；A11、B8；A11、B9；A12、B1；A12、B2；A12、B3；A12、B4；A12、B5；A12、B6；A12、B7；A12、B8；A12、B9；A13、B1；A13、B2；A13、B3；A13、B4；A13、B5；A13、B6；A13、B7；A13、B8；A13、B9；A14、B1；A14、B2；A14、B3；A14、B4；A14、B5；A14、B6；A14、B7；A14、B8；A14、B9；A15、B1；A15、B2；A15、B3；A15、B4；A15、B5；A15、B6；A15、B7；A15、B8；A15、B9；A16、B1；A16、B2；A16、B3；A16、B4；A16、B5；A16、B6；A16、B7；A16、B8；A16、B9；A17、B1；A17、B2；A17、B3；A17、B4；A17、B5；A17、B6；A17、B7；A17、B8；A17、B9；A18、B1；A18、B2；A18、B3；A18、B4；A18、B5；A18、B6；A18、B7；A18、B8；A18、B9；A19、B1；A19、B2；A19、B3；A19、B4；A19、B5；A19、B6；A19、B7；A19、B8；A19、B9；以及它们的组合。

[0495] 在一些实施方案中，药物组合物中 A）药剂或其盐与 B）表面改变剂的组合可以选自：A1、B1a；A1、B1b；A1、B1c；A1、B1d；A1、B1e；A1、B1f；A1、B2a；A1、B2b；A1、B2c；A1、B2d；A1、B2e；A1、B2f；A1、B2g；A1、B2h；A1、B2i；A1、B2j；A1、B3a；A1、B3b；A1、B4a；A1、B5a；A1、B6a；A1、B6b；A1、B7a；A1、B8a；A1、B9a；A1、B9b；A1、B9c；A2、B1a；A2、B1b；A2、B1c；A2、B1d；A2、B1e；A2、B1f；A2、B2a；A2、B2b；A2、B2c；A2、B2d；A2、B2e；A2、B2f；A2、B2g；A2、B2h；A2、B2i；A2、B2j；A2、B3a；A2、B3b；A2、B4a；A2、B5a；A2、B6a；A2、B6b；A2、B7a；A2、B8a；A2、B9a；

A2、B9b ;A2、B9c ;A3、B1a ;A3、B1b ;A3、B1c ;A3、B1d ;A3、B1e ;A3、B1f ;A3、B2a ;A3、B2b ;A3、B2c ;A3、B2d ;A3、B2e ;A3、B2f ;A3、B2g ;A3、B2h ;A3、B2i ;A3、B2j ;A3、B3a ;A3、B3b ;A3、B4a ;A3、B5a ;A3、B6a ;A3、B6b ;A3、B7a ;A3、B8a ;A3、B9a ;A3、B9b ;A3、B9c ;A4、B1a ;A4、B1b ;A4、B1c ;A4、B1d ;A4、B1e ;A4、B1f ;A4、B2a ;A4、B2b ;A4、B2c ;A4、B2d ;A4、B2e ;A4、B2f ;A4、B2g ;A4、B2h ;A4、B2i ;A4、B2j ;A4、B3a ;A4、B3b ;A4、B4a ;A4、B5a ;A4、B6a ;A4、B6b ;A4、B7a ;A4、B8a ;A4、B9a ;A4、B9b ;A4、B9c ;A5、B1a ;A5、B1b ;A5、B1c ;A5、B1d ;A5、B1e ;A5、B1f ;A5、B2a ;A5、B2b ;A5、B2c ;A5、B2d ;A5、B2e ;A5、B2f ;A5、B2g ;A5、B2h ;A5、B2i ;A5、B2j ;A5、B3a ;A5、B3b ;A5、B4a ;A5、B5a ;A5、B6a ;A5、B6b ;A5、B7a ;A5、B8a ;A5、B9a ;A5、B9b ;A5、B9c ;A6、B1a ;A6、B1b ;A6、B1c ;A6、B1d ;A6、B1e ;A6、B1f ;A6、B2a ;A6、B2b ;A6、B2c ;A6、B2d ;A6、B2e ;A6、B2f ;A6、B2g ;A6、B2h ;A6、B2i ;A6、B2j ;A6、B3a ;A6、B3b ;A6、B4a ;A6、B5a ;A6、B6a ;A6、B6b ;A6、B7a ;A6、B8a ;A6、B9a ;A6、B9b ;A6、B9c ;A7、B1a ;A7、B1b ;A7、B1c ;A7、B1d ;A7、B1e ;A7、B1f ;A7、B2a ;A7、B2b ;A7、B2c ;A7、B2d ;A7、B2e ;A7、B2f ;A7、B2g ;A7、B2h ;A7、B2i ;A7、B2j ;A7、B3a ;A7、B3b ;A7、B4a ;A7、B5a ;A7、B6a ;A7、B6b ;A7、B7a ;A7、B8a ;A7、B9a ;A7、B9b ;A7、B9c ;A8、B1a ;A8、B1b ;A8、B1c ;A8、B1d ;A8、B1e ;A8、B1f ;A8、B2a ;A8、B2b ;A8、B2c ;A8、B2d ;A8、B2e ;A8、B2f ;A8、B2g ;A8、B2h ;A8、B2i ;A8、B2j ;A8、B3a ;A8、B3b ;A8、B4a ;A8、B5a ;A8、B6a ;A8、B6b ;A8、B7a ;A8、B8a ;A8、B9a ;A8、B9b ;A8、B9c ;A9、B1a ;A9、B1b ;A9、B1c ;A9、B1d ;A9、B1e ;A9、B1f ;A9、B2a ;A9、B2b ;A9、B2c ;A9、B2d ;A9、B2e ;A9、B2f ;A9、B2g ;A9、B2h ;A9、B2i ;A9、B2j ;A9、B3a ;A9、B3b ;A9、B4a ;A9、B5a ;A9、B6a ;A9、B6b ;A9、B7a ;A9、B8a ;A9、B9a ;A9、B9b ;A9、B9c ;A10、B1a ;A10、B1b ;A10、B1c ;A10、B1d ;A10、B1e ;A10、B1f ;A10、B2a ;A10、B2b ;A10、B2c ;A10、B2d ;A10、B2e ;A10、B2f ;A10、B2g ;A10、B2h ;A10、B2i ;A10、B2j ;A10、B3a ;A10、B3b ;A10、B4a ;A10、B5a ;A10、B6a ;A10、B6b ;A10、B7a ;A10、B8a ;A10、B9a ;A10、B9b ;A10、B9c ;A11、B1a ;A11、B1b ;A11、B1c ;A11、B1d ;A11、B1e ;A11、B1f ;A11、B2a ;A11、B2b ;A11、B2c ;A11、B2d ;A11、B2e ;A11、B2f ;A11、B2g ;A11、B2h ;A11、B2i ;A11、B2j ;A11、B3a ;A11、B3b ;A11、B4a ;A11、B5a ;A11、B6a ;A11、B6b ;A11、B7a ;A11、B8a ;A11、B9a ;A11、B9b ;A11、B9c ;A12、B1a ;A12、B1b ;A12、B1c ;A12、B1d ;A12、B1e ;A12、B1f ;A12、B2a ;A12、B2b ;A12、B2c ;A12、B2d ;A12、B2e ;A12、B2f ;A12、B2g ;A12、B2h ;A12、B2i ;A12、B2j ;A12、B3a ;A12、B3b ;A12、B4a ;A12、B5a ;A12、B6a ;A12、B6b ;A12、B7a ;A12、B8a ;A12、B9a ;A12、B9b ;A12、B9c ;A13、B1a ;A13、B1b ;A13、B1c ;A13、B1d ;A13、B1e ;A13、B1f ;A13、B2a ;A13、B2b ;A13、B2c ;A13、B2d ;A13、B2e ;A13、B2f ;A13、B2g ;A13、B2h ;A13、B2i ;A13、B2j ;A13、B3a ;A13、B3b ;A13、B4a ;A13、B5a ;A13、B6a ;A13、B6b ;A13、B7a ;A13、B8a ;A13、B9a ;A13、B9b ;A13、B9c ;A14、B1a ;A14、B1b ;A14、B1c ;A14、B1d ;A14、B1e ;A14、B1f ;A14、B2a ;A14、B2b ;A14、B2c ;A14、B2d ;A14、B2e ;A14、B2f ;A14、B2g ;A14、B2h ;A14、B2i ;A14、B2j ;A14、B3a ;A14、B3b ;A14、B4a ;A14、B5a ;A14、B6a ;A14、B6b ;A14、B7a ;A14、B8a ;A14、B9a ;A14、B9b ;A14、B9c ;A15、B1a ;A15、B1b ;A15、B1c ;A15、B1d ;A15、B1e ;A15、B1f ;A15、B2a ;A15、B2b ;A15、B2c ;A15、B2d ;A15、B2e ;A15、B2f ;A15、B2g ;A15、B2h ;A15、B2i ;A15、B2j ;A15、B3a ;A15、B3b ;A15、B4a ;A15、B5a ;A15、B6a ;A15、B6b ;A15、B7a ;A15、B8a ;A15、B9a ;A15、B9b ;A15、B9c ;A16、B1a ;A16、B1b ;A16、B1c ;A16、B1d ;A16、B1e ;A16、B1f ;A16、B2a ;A16、B2b ;A16、B2c ;A16、B2d ;A16、B2e ;A16、B2f ;A16、B2g ;A16、B2h ;A16、B2i ;A16、B2j ;A16、B3a ;A16、B3b ;A16、B4a ;A16、B5a ;A16、B6a ;A16、B6b ;A16、B7a ;A16、B8a ;A16、B9a ;A16、

B9b ;A16、B9c ;A17、B1a ;A17、B1b ;A17、B1c ;A17、B1d ;A17、B1e ;A17、B1f ;A17、B2a ;A17、B2b ;A17、B2c ;A17、B2d ;A17、B2e ;A17、B2f ;A17、B2g ;A17、B2h ;A17、B2i ;A17、B2j ;A17、B3a ;A17、B3b ;A17、B4a ;A17、B5a ;A17、B6a ;A17、B6b ;A17、B7a ;A17、B8a ;A17、B9a ;A17、B9b ;A17、B9c ;A18、B1a ;A18、B1b ;A18、B1c ;A18、B1d ;A18、B1e ;A18、B1f ;A18、B2a ;A18、B2b ;A18、B2c ;A18、B2d ;A18、B2e ;A18、B2f ;A18、B2g ;A18、B2h ;A18、B2i ;A18、B2j ;A18、B3a ;A18、B3b ;A18、B4a ;A18、B5a ;A18、B6a ;A18、B6b ;A18、B7a ;A18、B8a ;A18、B9a ;A18、B9b ;A18、B9c ;A19、B1a ;A19、B1b ;A19、B1c ;A19、B1d ;A19、B1e ;A19、B1f ;A19、B2a ;A19、B2b ;A19、B2c ;A19、B2d ;A19、B2e ;A19、B2f ;A19、B2g ;A19、B2h ;A19、B2i ;A19、B2j ;A19、B3a ;A19、B3b ;A19、B4a ;A19、B5a ;A19、B6a ;A19、B6b ;A19、B7a ;A19、B8a ;A19、B9a ;A19、B9b ;A19、B9c ;以及它们的组合。

[0496] 在一些实施方案中，药物组合物中 A) 药剂或其盐与 B) 表面改变剂的组合可以选自 :A1a、B1 ;A1b、B1 ;A1c、B1 ;A1d、B1 ;A1e、B1 ;A1f、B1、A1g、B1 ;A1h、B1 ;A2a、B1 ;A2b、B1 ;A3a、B1 ;A3b、B1 ;A3c、B1 ;A3d、B1 ;A3e、B1、A3f、B1 ;A4a、B1 ;A4b、B1 ;A4c、B1 ;A4d、B1 ;A5a、B1 ;A5b、B1 ;A6a、B1 ;A6b、B1 ;A7a、B1 ;A7b、B1 ;A7c、B1 ;A8a、B1 ;A8b、B1 ;A8c、B1 ;A10a、B1 ;A10b、B1 ;A1a、B2 ;A1b、B2 ;A1c、B2 ;A1d、B2 ;A1e、B2 ;A1f、B2、A1g、B2 ;A1h、B2 ;A2a、B2 ;A2b、B2 ;A3a、B2 ;A3b、B2 ;A3c、B2 ;A3d、B2 ;A3e、B2、A3f、B2 ;A4a、B2 ;A4b、B2 ;A4c、B2 ;A4d、B2 ;A5a、B2 ;A5b、B2 ;A6a、B2 ;A6b、B2 ;A7a、B2 ;A7b、B2 ;A7c、B2 ;A8a、B2 ;A8b、B2 ;A8c、B2 ;A10a、B2 ;A10b、B2 ;A1a、B3 ;A1b、B3 ;A1c、B3 ;A1d、B3 ;A1e、B3 ;A1f、B3、A1g、B3 ;A1h、B3 ;A2a、B3 ;A2b、B3 ;A3a、B3 ;A3b、B3 ;A3c、B3 ;A3d、B3 ;A3e、B3、A3f、B3 ;A4a、B3 ;A4b、B3 ;A4c、B3 ;A4d、B3 ;A5a、B3 ;A5b、B3 ;A6a、B3 ;A6b、B3 ;A7a、B3 ;A7b、B3 ;A7c、B3 ;A8a、B3 ;A8b、B3 ;A8c、B3 ;A10a、B3 ;A10b、B3 ;A1a、B4 ;A1b、B4 ;A1c、B4 ;A1d、B4 ;A1e、B4 ;A1f、B4、A1g、B4 ;A1h、B4 ;A2a、B4 ;A2b、B4 ;A3a、B4 ;A3b、B4 ;A3c、B4 ;A3d、B4 ;A3e、B4、A3f、B4 ;A4a、B4 ;A4b、B4 ;A4c、B4 ;A4d、B4 ;A5a、B4 ;A5b、B4 ;A6a、B4 ;A6b、B4 ;A7a、B4 ;A7b、B4 ;A7c、B4 ;A8a、B4 ;A8b、B4 ;A8c、B4 ;A10a、B4 ;A10b、B4 ;A1a、B5 ;A1b、B5 ;A1c、B5 ;A1d、B5 ;A1e、B5 ;A1f、B5、A1g、B5 ;A1h、B5 ;A2a、B5 ;A2b、B5 ;A3a、B5 ;A3b、B5 ;A3c、B5 ;A3d、B5 ;A3e、B5、A3f、B5 ;A4a、B5 ;A4b、B5 ;A4c、B5 ;A4d、B5 ;A5a、B5 ;A5b、B5 ;A6a、B5 ;A6b、B5 ;A7a、B5 ;A7b、B5 ;A7c、B5 ;A8a、B5 ;A8b、B5 ;A8c、B5 ;A10a、B5 ;A10b、B5 ;A1a、B6 ;A1b、B6 ;A1c、B6 ;A1d、B6 ;A1e、B6 ;A1f、B6、A1g、B6 ;A1h、B6 ;A2a、B6 ;A2b、B6 ;A3a、B6 ;A3b、B6 ;A3c、B6 ;A3d、B6 ;A3e、B6、A3f、B6 ;A4a、B6 ;A4b、B6 ;A4c、B6 ;A4d、B6 ;A5a、B6 ;A5b、B6 ;A6a、B6 ;A6b、B6 ;A7a、B6 ;A7b、B6 ;A7c、B6 ;A8a、B6 ;A8b、B6 ;A8c、B6 ;A10a、B6 ;A10b、B6 ;A1a、B7 ;A1b、B7 ;A1c、B7 ;A1d、B7 ;A1e、B7 ;A1f、B7、A1g、B7 ;A1h、B7 ;A2a、B7 ;A2b、B7 ;A3a、B7 ;A3b、B7 ;A3c、B7 ;A3d、B7 ;A3e、B7、A3f、B7 ;A4a、B7 ;A4b、B7 ;A4c、B7 ;A4d、B7 ;A5a、B7 ;A5b、B7 ;A6a、B7 ;A6b、B7 ;A7a、B7 ;A7b、B7 ;A7c、B7 ;A8a、B7 ;A8b、B7 ;A8c、B7 ;A10a、B7 ;A10b、B7 ;A1a、B8 ;A1b、B8 ;A1c、B8 ;A1d、B8 ;A1e、B8 ;A1f、B8、A1g、B8 ;A1h、B8 ;A2a、B8 ;A2b、B8 ;A3a、B8 ;A3b、B8 ;A3c、B8 ;A3d、B8 ;A3e、B8、A3f、B8 ;A4a、B8 ;A4b、B8 ;A4c、B8 ;A4d、B8 ;A5a、B8 ;A5b、B8 ;A6a、B8 ;A6b、B8 ;A7a、B8 ;A7b、B8 ;A7c、B8 ;A8a、B8 ;A8b、B8 ;A8c、B8 ;A10a、B8 ;A10b、B8 ;A1a、B9 ;A1b、B9 ;A1c、B9 ;A1d、B9 ;A1e、B9 ;A1f、B9、A1g、B9 ;A1h、B9 ;A2a、B9 ;A2b、B9 ;A3a、B9 ;A3b、B9 ;A3c、B9 ;A3d、B9 ;A3e、B9、A3f、B9 ;A4a、B9 ;A4b、B9 ;A4c、B9 ;A4d、B9 ;A5a、B9 ;A5b、B9 ;A6a、B9 ;A6b、B9 ;A7a、B9 ;A7b、B9 ;A7c、B9 ;A8a、B9 ;A8b、B9 ;A8c、B9 ;A10a、B9 ;A10b、B9 ;以及它们

的组合。

[0497] 在一些实施方案中，药物组合物中 A) 药剂或其盐与 B) 表面改变剂的组合可以选自：A1a、B1a；A1a、B1b；A1a、B1c；A1a、B1d；A1a、B1e；A1a、B1f；A1a、B2a；A1a、B2b；A1a、B2c；A1a、B2d；A1a、B2e；A1a、B2f；A1a、B2g；A1a、B2h；A1a、B2i；A1a、B2j；A1a、B3a；A1a、B3b；A1a、B4a；A1a、B5a；A1a、B6a；A1a、B6b；A1a、B7a；A1a、B8a；A1a、B9a；A1a、B9b；A1a、B9c；A1b、B1a；A1b、B1b；A1b、B1c；A1b、B1d；A1b、B1e；A1b、B1f；A1b、B2a；A1b、B2b；A1b、B2c；A1b、B2d；A1b、B2e；A1b、B2f；A1b、B2g；A1b、B2h；A1b、B2i；A1b、B2j；A1b、B3a；A1b、B3b；A1b、B4a；A1b、B5a；A1b、B6a；A1b、B6b；A1b、B7a；A1b、B8a；A1b、B9a；A1b、B9b；A1b、B9c；A1c、B1a；A1c、B1b；A1c、B1c；A1c、B1d；A1c、B1e；A1c、B1f；A1c、B2a；A1c、B2b；A1c、B2c；A1c、B2d；A1c、B2e；A1c、B2f；A1c、B2g；A1c、B2h；A1c、B2i；A1c、B2j；A1c、B3a；A1c、B3b；A1c、B4a；A1c、B5a；A1c、B6a；A1c、B6b；A1c、B7a；A1c、B8a；A1c、B9a；A1c、B9b；A1c、B9c；A1d、B1a；A1d、B1b；A1d、B1c；A1d、B1d；A1d、B1e；A1d、B1f；A1d、B2a；A1d、B2b；A1d、B2c；A1d、B2d；A1d、B2e；A1d、B2f；A1d、B2g；A1d、B2h；A1d、B2i；A1d、B2j；A1d、B3a；A1d、B3b；A1d、B4a；A1d、B5a；A1d、B6a；A1d、B6b；A1d、B7a；A1d、B8a；A1d、B9a；A1d、B9b；A1d、B9c；A1e、B1a；A1e、B1b；A1e、B1c；A1e、B1d；A1e、B1e；A1e、B1f；A1e、B2a；A1e、B2b；A1e、B2c；A1e、B2d；A1e、B2e；A1e、B2f；A1e、B2g；A1e、B2h；A1e、B2i；A1e、B2j；A1e、B3a；A1e、B3b；A1e、B4a；A1e、B5a；A1e、B6a；A1e、B6b；A1e、B7a；A1e、B8a；A1e、B9a；A1e、B9b；A1e、B9c；A1f、B1a；A1f、B1b；A1f、B1c；A1f、B1d；A1f、B1e；A1f、B1f；A1f、B2a；A1f、B2b；A1f、B2c；A1f、B2d；A1f、B2e；A1f、B2f；A1f、B2g；A1f、B2h；A1f、B2i；A1f、B2j；A1f、B3a；A1f、B3b；A1f、B4a；A1f、B5a；A1f、B6a；A1f、B6b；A1f、B7a；A1f、B8a；A1f、B9a；A1f、B9b；A1f、B9c；A1g、B1a；A1g、B1b；A1g、B1c；A1g、B1d；A1g、B1e；A1g、B1f；A1g、B2a；A1g、B2b；A1g、B2c；A1g、B2d；A1g、B2e；A1g、B2f；A1g、B2g；A1g、B2h；A1g、B2i；A1g、B2j；A1g、B3a；A1g、B3b；A1g、B4a；A1g、B5a；A1g、B6a；A1g、B6b；A1g、B7a；A1g、B8a；A1g、B9a；A1g、B9b；A1g、B9c；A1h、B1a；A1h、B1b；A1h、B1c；A1h、B1d；A1h、B1e；A1h、B1f；A1h、B2a；A1h、B2b；A1h、B2c；A1h、B2d；A1h、B2e；A1h、B2f；A1h、B2g；A1h、B2h；A1h、B2i；A1h、B2j；A1h、B3a；A1h、B3b；A1h、B4a；A1h、B5a；A1h、B6a；A1h、B6b；A1h、B7a；A1h、B8a；A1h、B9a；A1h、B9b；A1h、B9c；A2a、B1a；A2a、B1b；A2a、B1c；A2a、B1d；A2a、B1e；A2a、B1f；A2a、B2a；A2a、B2b；A2a、B2c；A2a、B2d；A2a、B2e；A2a、B2f；A2a、B2g；A2a、B2h；A2a、B2i；A2a、B2j；A2a、B3a；A2a、B3b；A2a、B4a；A2a、B5a；A2a、B6a；A2a、B6b；A2a、B7a；A2a、B8a；A2a、B9a；A2a、B9b；A2a、B9c；A2b、B1a；A2b、B1b；A2b、B1c；A2b、B1d；A2b、B1e；A2b、B1f；A2b、B2a；A2b、B2b；A2b、B2c；A2b、B2d；A2b、B2e；A2b、B2f；A2b、B2g；A2b、B2h；A2b、B2i；A2b、B2j；A2b、B3a；A2b、B3b；A2b、B4a；A2b、B5a；A2b、B6a；A2b、B6b；A2b、B7a；A2b、B8a；A2b、B9a；A2b、B9b；A2b、B9c；A3a、B1a；A3a、B1b；A3a、B1c；A3a、B1d；A3a、B1e；A3a、B1f；A3a、B2a；A3a、B2b；A3a、B2c；A3a、B2d；A3a、B2e；A3a、B2f；A3a、B2g；A3a、B2h；A3a、B2i；A3a、B2j；A3a、B3a；A3a、B3b；A3a、B4a；A3a、B5a；A3a、B6a；A3a、B6b；A3a、B7a；A3a、B8a；A3a、B9a；A3a、B9b；A3a、B9c；A3b、B1a；A3b、B1b；A3b、B1c；A3b、B1d；A3b、B1e；A3b、B1f；A3b、B2a；A3b、B2b；A3b、B2c；A3b、B2d；A3b、B2e；A3b、B2f；A3b、B2g；A3b、B2h；A3b、B2i；A3b、B2j；A3b、B3a；A3b、B3b；A3b、B4a；A3b、B5a；A3b、B6a；A3b、B6b；A3b、B7a；A3b、B8a；A3b、B9a；A3b、B9b；A3b、B9c；A3c、B1a；A3c、B1b；A3c、B1c；A3c、B1d；A3c、B1e；A3c、B1f；A3c、B2a；A3c、B2b；A3c、B2c；

A3c、B2d ;A3c、B2e ;A3c、B2f ;A3c、B2g ;A3c、B2h ;A3c、B2i ;A3c、B2j ;A3c、B3a ;A3c、B3b ;
A3c、B4a ;A3c、B5a ;A3c、B6a ;A3c、B6b ;A3c、B7a ;A3c、B8a ;A3c、B9a ;A3c、B9b ;A3c、B9c ;
A3d、B1a ;A3d、B1b ;A3d、B1c ;A3d、B1d ;A3d、B1e ;A3d、B1f ;A3d、B2a ;A3d、B2b ;A3d、B2c ;
A3d、B2d ;A3d、B2e ;A3d、B2f ;A3d、B2g ;A3d、B2h ;A3d、B2i ;A3d、B2j ;A3d、B3a ;A3d、B3b ;
A3d、B4a ;A3d、B5a ;A3d、B6a ;A3d、B6b ;A3d、B7a ;A3d、B8a ;A3d、B9a ;A3d、B9b ;A3d、B9c ;
A3e、B1a ;A3e、B1b ;A3e、B1c ;A3e、B1d ;A3e、B1e ;A3e、B1f ;A3e、B2a ;A3e、B2b ;A3e、B2c ;
A3e、B2d ;A3e、B2e ;A3e、B2f ;A3e、B2g ;A3e、B2h ;A3e、B2i ;A3e、B2j ;A3e、B3a ;A3e、B3b ;
A3e、B4a ;A3e、B5a ;A3e、B6a ;A3e、B6b ;A3e、B7a ;A3e、B8a ;A3e、B9a ;A3e、B9b ;A3e、B9c ;
A3f、B1a ;A3f、B1b ;A3f、B1c ;A3f、B1d ;A3f、B1e ;A3f、B1f ;A3f、B2a ;A3f、B2b ;A3f、B2c ;
A3f、B2d ;A3f、B2e ;A3f、B2f ;A3f、B2g ;A3f、B2h ;A3f、B2i ;A3f、B2j ;A3f、B3a ;A3f、B3b ;
A3f、B4a ;A3f、B5a ;A3f、B6a ;A3f、B6b ;A3f、B7a ;A3f、B8a ;A3f、B9a ;A3f、B9b ;A3f、B9c ;
A4a、B1a ;A4a、B1b ;A4a、B1c ;A4a、B1d ;A4a、B1e ;A4a、B1f ;A4a、B2a ;A4a、B2b ;A4a、B2c ;
A4a、B2d ;A4a、B2e ;A4a、B2f ;A4a、B2g ;A4a、B2h ;A4a、B2i ;A4a、B2j ;A4a、B3a ;A4a、B3b ;
A4a、B4a ;A4a、B5a ;A4a、B6a ;A4a、B6b ;A4a、B7a ;A4a、B8a ;A4a、B9a ;A4a、B9b ;A4a、B9c ;
A4b、B1a ;A4b、B1b ;A4b、B1c ;A4b、B1d ;A4b、B1e ;A4b、B1f ;A4b、B2a ;A4b、B2b ;A4b、B2c ;
A4b、B2d ;A4b、B2e ;A4b、B2f ;A4b、B2g ;A4b、B2h ;A4b、B2i ;A4b、B2j ;A4b、B3a ;A4b、B3b ;
A4b、B4a ;A4b、B5a ;A4b、B6a ;A4b、B6b ;A4b、B7a ;A4b、B8a ;A4b、B9a ;A4b、B9b ;A4b、B9c ;
A4c、B1a ;A4c、B1b ;A4c、B1c ;A4c、B1d ;A4c、B1e ;A4c、B1f ;A4c、B2a ;A4c、B2b ;A4c、B2c ;
A4c、B2d ;A4c、B2e ;A4c、B2f ;A4c、B2g ;A4c、B2h ;A4c、B2i ;A4c、B2j ;A4c、B3a ;A4c、B3b ;
A4c、B4a ;A4c、B5a ;A4c、B6a ;A4c、B6b ;A4c、B7a ;A4c、B8a ;A4c、B9a ;A4c、B9b ;A4c、B9c ;
A4d、B1a ;A4d、B1b ;A4d、B1c ;A4d、B1d ;A4d、B1e ;A4d、B1f ;A4d、B2a ;A4d、B2b ;A4d、B2c ;
A4d、B2d ;A4d、B2e ;A4d、B2f ;A4d、B2g ;A4d、B2h ;A4d、B2i ;A4d、B2j ;A4d、B3a ;A4d、B3b ;
A4d、B4a ;A4d、B5a ;A4d、B6a ;A4d、B6b ;A4d、B7a ;A4d、B8a ;A4d、B9a ;A4d、B9b ;A4d、B9c ;
A5a、B1a ;A5a、B1b ;A5a、B1c ;A5a、B1d ;A5a、B1e ;A5a、B1f ;A5a、B2a ;A5a、B2b ;A5a、B2c ;
A5a、B2d ;A5a、B2e ;A5a、B2f ;A5a、B2g ;A5a、B2h ;A5a、B2i ;A5a、B2j ;A5a、B3a ;A5a、B3b ;
A5a、B4a ;A5a、B5a ;A5a、B6a ;A5a、B6b ;A5a、B7a ;A5a、B8a ;A5a、B9a ;A5a、B9b ;A5a、B9c ;
A5b、B1a ;A5b、B1b ;A5b、B1c ;A5b、B1d ;A5b、B1e ;A5b、B1f ;A5b、B2a ;A5b、B2b ;A5b、B2c ;
A5b、B2d ;A5b、B2e ;A5b、B2f ;A5b、B2g ;A5b、B2h ;A5b、B2i ;A5b、B2j ;A5b、B3a ;A5b、B3b ;
A5b、B4a ;A5b、B5a ;A5b、B6a ;A5b、B6b ;A5b、B7a ;A5b、B8a ;A5b、B9a ;A5b、B9b ;A5b、B9c ;
A6a、B1a ;A6a、B1b ;A6a、B1c ;A6a、B1d ;A6a、B1e ;A6a、B1f ;A6a、B2a ;A6a、B2b ;A6a、B2c ;
A6a、B2d ;A6a、B2e ;A6a、B2f ;A6a、B2g ;A6a、B2h ;A6a、B2i ;A6a、B2j ;A6a、B3a ;A6a、B3b ;
A6a、B4a ;A6a、B5a ;A6a、B6a ;A6a、B6b ;A6a、B7a ;A6a、B8a ;A6a、B9a ;A6a、B9b ;A6a、B9c ;
A6b、B1a ;A6b、B1b ;A6b、B1c ;A6b、B1d ;A6b、B1e ;A6b、B1f ;A6b、B2a ;A6b、B2b ;A6b、B2c ;
A6b、B2d ;A6b、B2e ;A6b、B2f ;A6b、B2g ;A6b、B2h ;A6b、B2i ;A6b、B2j ;A6b、B3a ;A6b、B3b ;
A6b、B4a ;A6b、B5a ;A6b、B6a ;A6b、B6b ;A6b、B7a ;A6b、B8a ;A6b、B9a ;A6b、B9b ;A6b、B9c ;
A7a、B1a ;A7a、B1b ;A7a、B1c ;A7a、B1d ;A7a、B1e ;A7a、B1f ;A7a、B2a ;A7a、B2b ;A7a、B2c ;
A7a、B2d ;A7a、B2e ;A7a、B2f ;A7a、B2g ;A7a、B2h ;A7a、B2i ;A7a、B2j ;A7a、B3a ;A7a、B3b ;
A7a、B4a ;A7a、B5a ;A7a、B6a ;A7a、B6b ;A7a、B7a ;A7a、B8a ;A7a、B9a ;A7a、B9b ;A7a、B9c ;
A7b、B1a ;A7b、B1b ;A7b、B1c ;A7b、B1d ;A7b、B1e ;A7b、B1f ;A7b、B2a ;A7b、B2b ;A7b、B2c ;

A7b、B2d ;A7b、B2e ;A7b、B2f ;A7b、B2g ;A7b、B2h ;A7b、B2i ;A7b、B2j ;A7b、B3a ;A7b、B3b ;A7b、B4a ;A7b、B5a ;A7b、B6a ;A7b、B6b ;A7b、B7a ;A7b、B8a ;A7b、B9a ;A7b、B9b ;A7b、B9c ;A7c、B1a ;A7c、B1b ;A7c、B1c ;A7c、B1d ;A7c、B1e ;A7c、B1f ;A7c、B2a ;A7c、B2b ;A7c、B2c ;A7c、B2d ;A7c、B2e ;A7c、B2f ;A7c、B2g ;A7c、B2h ;A7c、B2i ;A7c、B2j ;A7c、B3a ;A7c、B3b ;A7c、B4a ;A7c、B5a ;A7c、B6a ;A7c、B6b ;A7c、B7a ;A7c、B8a ;A7c、B9a ;A7c、B9b ;A7c、B9c ;A8a、B1a ;A8a、B1b ;A8a、B1c ;A8a、B1d ;A8a、B1e ;A8a、B1f ;A8a、B2a ;A8a、B2b ;A8a、B2c ;A8a、B2d ;A8a、B2e ;A8a、B2f ;A8a、B2g ;A8a、B2h ;A8a、B2i ;A8a、B2j ;A8a、B3a ;A8a、B3b ;A8a、B4a ;A8a、B5a ;A8a、B6a ;A8a、B6b ;A8a、B7a ;A8a、B8a ;A8a、B9a ;A8a、B9b ;A8a、B9c ;A8b、B1a ;A8b、B1b ;A8b、B1c ;A8b、B1d ;A8b、B1e ;A8b、B1f ;A8b、B2a ;A8b、B2b ;A8b、B2c ;A8b、B2d ;A8b、B2e ;A8b、B2f ;A8b、B2g ;A8b、B2h ;A8b、B2i ;A8b、B2j ;A8b、B3a ;A8b、B3b ;A8b、B4a ;A8b、B5a ;A8b、B6a ;A8b、B6b ;A8b、B7a ;A8b、B8a ;A8b、B9a ;A8b、B9b ;A8b、B9c ;A8c、B1a ;A8c、B1b ;A8c、B1c ;A8c、B1d ;A8c、B1e ;A8c、B1f ;A8c、B2a ;A8c、B2b ;A8c、B2c ;A8c、B2d ;A8c、B2e ;A8c、B2f ;A8c、B2g ;A8c、B2h ;A8c、B2i ;A8c、B2j ;A8c、B3a ;A8c、B3b ;A8c、B4a ;A8c、B5a ;A8c、B6a ;A8c、B6b ;A8c、B7a ;A8c、B8a ;A8c、B9a ;A8c、B9b ;A8c、B9c ;A10a、B1a ;A10a、B1b ;A10a、B1c ;A10a、B1d ;A10a、B1e ;A10a、B1f ;A10a、B2a ;A10a、B2b ;A10a、B2c ;A10a、B2d ;A10a、B2e ;A10a、B2f ;A10a、B2g ;A10a、B2h ;A10a、B2i ;A10a、B2j ;A10a、B3a ;A10a、B3b ;A10a、B4a ;A10a、B5a ;A10a、B6a ;A10a、B6b ;A10a、B7a ;A10a、B8a ;A10a、B9a ;A10a、B9b ;A10a、B9c ;A10b、B1a ;A10b、B1b ;A10b、B1c ;A10b、B1d ;A10b、B1e ;A10b、B1f ;A10b、B2a ;A10b、B2b ;A10b、B2c ;A10b、B2d ;A10b、B2e ;A10b、B2f ;A10b、B2g ;A10b、B2h ;A10b、B2i ;A10b、B2j ;A10b、B3a ;A10b、B3b ;A10b、B4a ;A10b、B5a ;A10b、B6a ;A10b、B6b ;A10b、B7a ;A10b、B8a ;A10b、B9a ;A10b、B9b ;A10b、B9c ;以及它们的组合。

[0498] 在一些实施方案中，药物组合物中 A) 药剂或其盐、B) 表面改变剂、以及 C) 所述核心粒子的外表面上存在的一种或多种表面改变剂的密度的组合可以选自 :A1、B1、C1 ;A1、B1、C2 ;A1、B1、C3 ;A1、B1、C4 ;A1、B1、C5 ;A1、B2、C1 ;A1、B2、C2 ;A1、B2、C3 ;A1、B2、C4 ;A1、B2、C5 ;A1、B3、C1 ;A1、B3、C2 ;A1、B3、C3 ;A1、B3、C4 ;A1、B3、C5 ;A1、B4、C1 ;A1、B4、C2 ;A1、B4、C3 ;A1、B4、C4 ;A1、B4、C5 ;A1、B5、C1 ;A1、B5、C2 ;A1、B5、C3 ;A1、B5、C4 ;A1、B5、C5 ;A1、B6、C1 ;A1、B6、C2 ;A1、B6、C3 ;A1、B6、C4 ;A1、B6、C5 ;A1、B7、C1 ;A1、B7、C2 ;A1、B7、C3 ;A1、B7、C4 ;A1、B7、C5 ;A1、B8、C1 ;A1、B8、C2 ;A1、B8、C3 ;A1、B8、C4 ;A1、B8、C5 ;A1、B9、C1 ;A1、B9、C2 ;A1、B9、C3 ;A1、B9、C4 ;A1、B9、C5 ;A2、B1、C1 ;A2、B1、C2 ;A2、B1、C3 ;A2、B1、C4 ;A2、B1、C5 ;A2、B2、C1 ;A2、B2、C2 ;A2、B2、C3 ;A2、B2、C4 ;A2、B2、C5 ;A2、B3、C1 ;A2、B3、C2 ;A2、B3、C3 ;A2、B3、C4 ;A2、B3、C5 ;A2、B4、C1 ;A2、B4、C2 ;A2、B4、C3 ;A2、B4、C4 ;A2、B4、C5 ;A2、B5、C1 ;A2、B5、C2 ;A2、B5、C3 ;A2、B5、C4 ;A2、B5、C5 ;A2、B6、C1 ;A2、B6、C2 ;A2、B6、C3 ;A2、B6、C4 ;A2、B6、C5 ;A2、B7、C1 ;A2、B7、C2 ;A2、B7、C3 ;A2、B7、C4 ;A2、B7、C5 ;A2、B8、C1 ;A2、B8、C2 ;A2、B8、C3 ;A2、B8、C4 ;A2、B8、C5 ;A2、B9、C1 ;A2、B9、C2 ;A2、B9、C3 ;A2、B9、C4 ;A2、B9、C5 ;A3、B1、C1 ;A3、B1、C2 ;A3、B1、C3 ;A3、B1、C4 ;A3、B1、C5 ;A3、B2、C1 ;A3、B2、C2 ;A3、B2、C3 ;A3、B2、C4 ;A3、B2、C5 ;A3、B3、C1 ;A3、B3、C2 ;A3、B3、C3 ;A3、B3、C4 ;A3、B3、C5 ;A3、B4、C1 ;A3、B4、C2 ;A3、B4、C3 ;A3、B4、C4 ;A3、B4、C5 ;A3、B5、C1 ;A3、B5、C2 ;A3、B5、C3 ;A3、B5、C4 ;A3、B5、C5 ;A3、B6、C1 ;A3、B6、C2 ;A3、B6、C3 ;A3、B6、C4 ;A3、B6、C5 ;A3、B7、C1 ;A3、B7、C2 ;A3、B7、C3 ;A3、B7、C4 ;A3、B7、C5 ;A3、B8、C1 ;A3、B8、C2 ;A3、B8、C3 ;A3、B8、C4 ;A3、

B8、C5 ;A3、B9、C1 ;A3、B9、C2 ;A3、B9、C3 ;A3、B9、C4 ;A3、B9、C5 ;A4、B1、C1 ;A4、B1、C2 ;A4、B1、C3 ;A4、B1、C4 ;A4、B1、C5 ;A4、B2、C1 ;A4、B2、C2 ;A4、B2、C3 ;A4、B2、C4 ;A4、B2、C5 ;A4、B3、C1 ;A4、B3、C2 ;A4、B3、C3 ;A4、B3、C4 ;A4、B3、C5 ;A4、B4、C1 ;A4、B4、C2 ;A4、B4、C3 ;A4、B4、C4 ;A4、B4、C5 ;A4、B5、C1 ;A4、B5、C2 ;A4、B5、C3 ;A4、B5、C4 ;A4、B5、C5 ;A4、B6、C1 ;A4、B6、C2 ;A4、B6、C3 ;A4、B6、C4 ;A4、B6、C5 ;A4、B7、C1 ;A4、B7、C2 ;A4、B7、C3 ;A4、B7、C4 ;A4、B7、C5 ;A4、B8、C1 ;A4、B8、C2 ;A4、B8、C3 ;A4、B8、C4 ;A4、B8、C5 ;A4、B9、C1 ;A4、B9、C2 ;A4、B9、C3 ;A4、B9、C4 ;A4、B9、C5 ;A5、B1、C1 ;A5、B1、C2 ;A5、B1、C3 ;A5、B1、C4 ;A5、B1、C5 ;A5、B2、C1 ;A5、B2、C2 ;A5、B2、C3 ;A5、B2、C4 ;A5、B2、C5 ;A5、B3、C1 ;A5、B3、C2 ;A5、B3、C3 ;A5、B3、C4 ;A5、B3、C5 ;A5、B4、C1 ;A5、B4、C2 ;A5、B4、C3 ;A5、B4、C4 ;A5、B4、C5 ;A5、B5、C1 ;A5、B5、C2 ;A5、B5、C3 ;A5、B5、C4 ;A5、B5、C5 ;A5、B6、C1 ;A5、B6、C2 ;A5、B6、C3 ;A5、B6、C4 ;A5、B6、C5 ;A5、B7、C1 ;A5、B7、C2 ;A5、B7、C3 ;A5、B7、C4 ;A5、B7、C5 ;A5、B8、C1 ;A5、B8、C2 ;A5、B8、C3 ;A5、B8、C4 ;A5、B8、C5 ;A5、B9、C1 ;A5、B9、C2 ;A5、B9、C3 ;A5、B9、C4 ;A5、B9、C5 ;A6、B1、C1 ;A6、B1、C2 ;A6、B1、C3 ;A6、B1、C4 ;A6、B1、C5 ;A6、B2、C1 ;A6、B2、C2 ;A6、B2、C3 ;A6、B2、C4 ;A6、B2、C5 ;A6、B3、C1 ;A6、B3、C2 ;A6、B3、C3 ;A6、B3、C4 ;A6、B3、C5 ;A6、B4、C1 ;A6、B4、C2 ;A6、B4、C3 ;A6、B4、C4 ;A6、B4、C5 ;A6、B5、C1 ;A6、B5、C2 ;A6、B5、C3 ;A6、B5、C4 ;A6、B5、C5 ;A6、B6、C1 ;A6、B6、C2 ;A6、B6、C3 ;A6、B6、C4 ;A6、B6、C5 ;A6、B7、C1 ;A6、B7、C2 ;A6、B7、C3 ;A6、B7、C4 ;A6、B7、C5 ;A6、B8、C1 ;A6、B8、C2 ;A6、B8、C3 ;A6、B8、C4 ;A6、B8、C5 ;A6、B9、C1 ;A6、B9、C2 ;A6、B9、C3 ;A6、B9、C4 ;A6、B9、C5 ;A7、B1、C1 ;A7、B1、C2 ;A7、B1、C3 ;A7、B1、C4 ;A7、B1、C5 ;A7、B2、C1 ;A7、B2、C2 ;A7、B2、C3 ;A7、B2、C4 ;A7、B2、C5 ;A7、B3、C1 ;A7、B3、C2 ;A7、B3、C3 ;A7、B3、C4 ;A7、B3、C5 ;A7、B4、C1 ;A7、B4、C2 ;A7、B4、C3 ;A7、B4、C4 ;A7、B4、C5 ;A7、B5、C1 ;A7、B5、C2 ;A7、B5、C3 ;A7、B5、C4 ;A7、B5、C5 ;A7、B6、C1 ;A7、B6、C2 ;A7、B6、C3 ;A7、B6、C4 ;A7、B6、C5 ;A7、B7、C1 ;A7、B7、C2 ;A7、B7、C3 ;A7、B7、C4 ;A7、B7、C5 ;A7、B8、C1 ;A7、B8、C2 ;A7、B8、C3 ;A7、B8、C4 ;A7、B8、C5 ;A7、B9、C1 ;A7、B9、C2 ;A7、B9、C3 ;A7、B9、C4 ;A7、B9、C5 ;A8、B1、C1 ;A8、B1、C2 ;A8、B1、C3 ;A8、B1、C4 ;A8、B1、C5 ;A8、B2、C1 ;A8、B2、C2 ;A8、B2、C3 ;A8、B2、C4 ;A8、B2、C5 ;A8、B3、C1 ;A8、B3、C2 ;A8、B3、C3 ;A8、B3、C4 ;A8、B3、C5 ;A8、B4、C1 ;A8、B4、C2 ;A8、B4、C3 ;A8、B4、C4 ;A8、B4、C5 ;A8、B5、C1 ;A8、B5、C2 ;A8、B5、C3 ;A8、B5、C4 ;A8、B5、C5 ;A8、B6、C1 ;A8、B6、C2 ;A8、B6、C3 ;A8、B6、C4 ;A8、B6、C5 ;A8、B7、C1 ;A8、B7、C2 ;A8、B7、C3 ;A8、B7、C4 ;A8、B7、C5 ;A8、B8、C1 ;A8、B8、C2 ;A8、B8、C3 ;A8、B8、C4 ;A8、B8、C5 ;A8、B9、C1 ;A8、B9、C2 ;A8、B9、C3 ;A8、B9、C4 ;A8、B9、C5 ;A9、B1、C1 ;A9、B1、C2 ;A9、B1、C3 ;A9、B1、C4 ;A9、B1、C5 ;A9、B2、C1 ;A9、B2、C2 ;A9、B2、C3 ;A9、B2、C4 ;A9、B2、C5 ;A9、B3、C1 ;A9、B3、C2 ;A9、B3、C3 ;A9、B3、C4 ;A9、B3、C5 ;A9、B4、C1 ;A9、B4、C2 ;A9、B4、C3 ;A9、B4、C4 ;A9、B4、C5 ;A9、B5、C1 ;A9、B5、C2 ;A9、B5、C3 ;A9、B5、C4 ;A9、B5、C5 ;A9、B6、C1 ;A9、B6、C2 ;A9、B6、C3 ;A9、B6、C4 ;A9、B6、C5 ;A9、B7、C1 ;A9、B7、C2 ;A9、B7、C3 ;A9、B7、C4 ;A9、B7、C5 ;A9、B8、C1 ;A9、B8、C2 ;A9、B8、C3 ;A9、B8、C4 ;A9、B8、C5 ;A9、B9、C1 ;A9、B9、C2 ;A9、B9、C3 ;A9、B9、C4 ;A9、B9、C5 ;A10、B1、C1 ;A10、B1、C2 ;A10、B1、C3 ;A10、B1、C4 ;A10、B1、C5 ;A10、B2、C1 ;A10、B2、C2 ;A10、B2、C3 ;A10、B2、C4 ;A10、B2、C5 ;A10、B3、C1 ;A10、B3、C2 ;A10、B3、C3 ;A10、B3、C4 ;A10、B3、C5 ;A10、B4、C1 ;A10、B4、C2 ;A10、B4、C3 ;A10、B4、C4 ;A10、B4、C5 ;A10、B5、C1 ;A10、B5、C2 ;A10、B5、C3 ;A10、B5、C4 ;A10、B5、C5 ;A10、B6、C1 ;A10、B6、C2 ;A10、B6、C3 ;A10、B6、C4 ;A10、B6、C5 ;A10、B7、C1 ;A10、B7、C2 ;A10、B7、C3 ;A10、

B7、C4 ;A10、B7、C5 ;A10、B8、C1 ;A10、B8、C2 ;A10、B8、C3 ;A10、B8、C4 ;A10、B8、C5 ;A10、B9、C1 ;A10、B9、C2 ;A10、B9、C3 ;A10、B9、C4 ;A10、B9、C5 ;A11、B1、C1 ;A11、B1、C2 ;A11、B1、C3 ;A11、B1、C4 ;A11、B1、C5 ;A11、B2、C1 ;A11、B2、C2 ;A11、B2、C3 ;A11、B2、C4 ;A11、B2、C5 ;A11、B3、C1 ;A11、B3、C2 ;A11、B3、C3 ;A11、B3、C4 ;A11、B3、C5 ;A11、B4、C1 ;A11、B4、C2 ;A11、B4、C3 ;A11、B4、C4 ;A11、B4、C5 ;A11、B5、C1 ;A11、B5、C2 ;A11、B5、C3 ;A11、B5、C4 ;A11、B5、C5 ;A11、B6、C1 ;A11、B6、C2 ;A11、B6、C3 ;A11、B6、C4 ;A11、B6、C5 ;A11、B7、C1 ;A11、B7、C2 ;A11、B7、C3 ;A11、B7、C4 ;A11、B7、C5 ;A11、B8、C1 ;A11、B8、C2 ;A11、B8、C3 ;A11、B8、C4 ;A11、B8、C5 ;A11、B9、C1 ;A11、B9、C2 ;A11、B9、C3 ;A11、B9、C4 ;A11、B9、C5 ;A12、B1、C1 ;A12、B1、C2 ;A12、B1、C3 ;A12、B1、C4 ;A12、B1、C5 ;A12、B2、C1 ;A12、B2、C2 ;A12、B2、C3 ;A12、B2、C4 ;A12、B2、C5 ;A12、B3、C1 ;A12、B3、C2 ;A12、B3、C3 ;A12、B3、C4 ;A12、B3、C5 ;A12、B4、C1 ;A12、B4、C2 ;A12、B4、C3 ;A12、B4、C4 ;A12、B4、C5 ;A12、B5、C1 ;A12、B5、C2 ;A12、B5、C3 ;A12、B5、C4 ;A12、B5、C5 ;A12、B6、C1 ;A12、B6、C2 ;A12、B6、C3 ;A12、B6、C4 ;A12、B6、C5 ;A12、B7、C1 ;A12、B7、C2 ;A12、B7、C3 ;A12、B7、C4 ;A12、B7、C5 ;A12、B8、C1 ;A12、B8、C2 ;A12、B8、C3 ;A12、B8、C4 ;A12、B8、C5 ;A12、B9、C1 ;A12、B9、C2 ;A12、B9、C3 ;A12、B9、C4 ;A12、B9、C5 ;A13、B1、C1 ;A13、B1、C2 ;A13、B1、C3 ;A13、B1、C4 ;A13、B1、C5 ;A13、B2、C1 ;A13、B2、C2 ;A13、B2、C3 ;A13、B2、C4 ;A13、B2、C5 ;A13、B3、C1 ;A13、B3、C2 ;A13、B3、C3 ;A13、B3、C4 ;A13、B3、C5 ;A13、B4、C1 ;A13、B4、C2 ;A13、B4、C3 ;A13、B4、C4 ;A13、B4、C5 ;A13、B5、C1 ;A13、B5、C2 ;A13、B5、C3 ;A13、B5、C4 ;A13、B5、C5 ;A13、B6、C1 ;A13、B6、C2 ;A13、B6、C3 ;A13、B6、C4 ;A13、B6、C5 ;A13、B7、C1 ;A13、B7、C2 ;A13、B7、C3 ;A13、B7、C4 ;A13、B7、C5 ;A13、B8、C1 ;A13、B8、C2 ;A13、B8、C3 ;A13、B8、C4 ;A13、B8、C5 ;A13、B9、C1 ;A13、B9、C2 ;A13、B9、C3 ;A13、B9、C4 ;A13、B9、C5 ;A14、B1、C1 ;A14、B1、C2 ;A14、B1、C3 ;A14、B1、C4 ;A14、B1、C5 ;A14、B2、C1 ;A14、B2、C2 ;A14、B2、C3 ;A14、B2、C4 ;A14、B2、C5 ;A14、B3、C1 ;A14、B3、C2 ;A14、B3、C3 ;A14、B3、C4 ;A14、B3、C5 ;A14、B4、C1 ;A14、B4、C2 ;A14、B4、C3 ;A14、B4、C4 ;A14、B4、C5 ;A14、B5、C1 ;A14、B5、C2 ;A14、B5、C3 ;A14、B5、C4 ;A14、B5、C5 ;A14、B6、C1 ;A14、B6、C2 ;A14、B6、C3 ;A14、B6、C4 ;A14、B6、C5 ;A14、B7、C1 ;A14、B7、C2 ;A14、B7、C3 ;A14、B7、C4 ;A14、B7、C5 ;A14、B8、C1 ;A14、B8、C2 ;A14、B8、C3 ;A14、B8、C4 ;A14、B8、C5 ;A14、B9、C1 ;A14、B9、C2 ;A14、B9、C3 ;A14、B9、C4 ;A14、B9、C5 ;A15、B1、C1 ;A15、B1、C2 ;A15、B1、C3 ;A15、B1、C4 ;A15、B1、C5 ;A15、B2、C1 ;A15、B2、C2 ;A15、B2、C3 ;A15、B2、C4 ;A15、B2、C5 ;A15、B3、C1 ;A15、B3、C2 ;A15、B3、C3 ;A15、B3、C4 ;A15、B3、C5 ;A15、B4、C1 ;A15、B4、C2 ;A15、B4、C3 ;A15、B4、C4 ;A15、B4、C5 ;A15、B5、C1 ;A15、B5、C2 ;A15、B5、C3 ;A15、B5、C4 ;A15、B5、C5 ;A15、B6、C1 ;A15、B6、C2 ;A15、B6、C3 ;A15、B6、C4 ;A15、B6、C5 ;A15、B7、C1 ;A15、B7、C2 ;A15、B7、C3 ;A15、B7、C4 ;A15、B7、C5 ;A15、B8、C1 ;A15、B8、C2 ;A15、B8、C3 ;A15、B8、C4 ;A15、B8、C5 ;A15、B9、C1 ;A15、B9、C2 ;A15、B9、C3 ;A15、B9、C4 ;A15、B9、C5 ;A16、B1、C1 ;A16、B1、C2 ;A16、B1、C3 ;A16、B1、C4 ;A16、B1、C5 ;A16、B2、C1 ;A16、B2、C2 ;A16、B2、C3 ;A16、B2、C4 ;A16、B2、C5 ;A16、B3、C1 ;A16、B3、C2 ;A16、B3、C3 ;A16、B3、C4 ;A16、B3、C5 ;A16、B4、C1 ;A16、B4、C2 ;A16、B4、C3 ;A16、B4、C4 ;A16、B4、C5 ;A16、B5、C1 ;A16、B5、C2 ;A16、B5、C3 ;A16、B5、C4 ;A16、B5、C5 ;A16、B6、C1 ;A16、B6、C2 ;A16、B6、C3 ;A16、B6、C4 ;A16、B6、C5 ;A16、B7、C1 ;A16、B7、C2 ;A16、B7、C3 ;A16、B7、C4 ;A16、B7、C5 ;A16、B8、C1 ;A16、B8、C2 ;A16、B8、C3 ;A16、B8、C4 ;A16、B8、C5 ;A16、B9、C1 ;A16、B9、C2 ;A16、B9、C3 ;A16、B9、C4 ;A16、B9、C5 ;A17、B1、C1 ;A17、B1、C2 ;A17、B1、C3 ;A17、B1、C4 ;A17、

B1、C5 ;A17、B2、C1 ;A17、B2、C2 ;A17、B2、C3 ;A17、B2、C4 ;A17、B2、C5 ;A17、B3、C1 ;A17、B3、C2 ;A17、B3、C3 ;A17、B3、C4 ;A17、B3、C5 ;A17、B4、C1 ;A17、B4、C2 ;A17、B4、C3 ;A17、B4、C4 ;A17、B4、C5 ;A17、B5、C1 ;A17、B5、C2 ;A17、B5、C3 ;A17、B5、C4 ;A17、B5、C5 ;A17、B6、C1 ;A17、B6、C2 ;A17、B6、C3 ;A17、B6、C4 ;A17、B6、C5 ;A17、B7、C1 ;A17、B7、C2 ;A17、B7、C3 ;A17、B7、C4 ;A17、B7、C5 ;A17、B8、C1 ;A17、B8、C2 ;A17、B8、C3 ;A17、B8、C4 ;A17、B8、C5 ;A17、B9、C1 ;A17、B9、C2 ;A17、B9、C3 ;A17、B9、C4 ;A17、B9、C5 ;A18、B1、C1 ;A18、B1、C2 ;A18、B1、C3 ;A18、B1、C4 ;A18、B1、C5 ;A18、B2、C1 ;A18、B2、C2 ;A18、B2、C3 ;A18、B2、C4 ;A18、B2、C5 ;A18、B3、C1 ;A18、B3、C2 ;A18、B3、C3 ;A18、B3、C4 ;A18、B3、C5 ;A18、B4、C1 ;A18、B4、C2 ;A18、B4、C3 ;A18、B4、C4 ;A18、B4、C5 ;A18、B5、C1 ;A18、B5、C2 ;A18、B5、C3 ;A18、B5、C4 ;A18、B5、C5 ;A18、B6、C1 ;A18、B6、C2 ;A18、B6、C3 ;A18、B6、C4 ;A18、B6、C5 ;A18、B7、C1 ;A18、B7、C2 ;A18、B7、C3 ;A18、B7、C4 ;A18、B7、C5 ;A18、B8、C1 ;A18、B8、C2 ;A18、B8、C3 ;A18、B8、C4 ;A18、B8、C5 ;A18、B9、C1 ;A18、B9、C2 ;A18、B9、C3 ;A18、B9、C4 ;A18、B9、C5 ;A19、B1、C1 ;A19、B1、C2 ;A19、B1、C3 ;A19、B1、C4 ;A19、B1、C5 ;A19、B2、C1 ;A19、B2、C2 ;A19、B2、C3 ;A19、B2、C4 ;A19、B2、C5 ;A19、B3、C1 ;A19、B3、C2 ;A19、B3、C3 ;A19、B3、C4 ;A19、B3、C5 ;A19、B4、C1 ;A19、B4、C2 ;A19、B4、C3 ;A19、B4、C4 ;A19、B4、C5 ;A19、B5、C1 ;A19、B5、C2 ;A19、B5、C3 ;A19、B5、C4 ;A19、B5、C5 ;A19、B6、C1 ;A19、B6、C2 ;A19、B6、C3 ;A19、B6、C4 ;A19、B6、C5 ;A19、B7、C1 ;A19、B7、C2 ;A19、B7、C3 ;A19、B7、C4 ;A19、B7、C5 ;A19、B8、C1 ;A19、B8、C2 ;A19、B8、C3 ;A19、B8、C4 ;A19、B8、C5 ;A19、B9、C1 ;A19、B9、C2 ;A19、B9、C3 ;A19、B9、C4 ;A19、B9、C5 ;以及它们的组合。

[0499] 在包含多个具有特征 A)(例如 A1-A19 以及其中所鉴定的物质)、以及 B)(例如 B1-B9 以及其中所鉴定的物质)和 C)(例如 C1-C5)的合适组合的包衣粒子的上述药物组合物中,在一些实施方案中,所述包衣粒子包括包含固体药剂或其盐或由固体药剂或其盐形成的核心粒子,其中所述药剂或盐在 25℃在整个 pH 值范围内的任一点具有小于或等于约 1mg/mL 的水溶解度(例如在 25℃小于或等于约 0.1mg/mL),其中所述药剂或其盐占所述核心粒子的至少约 80 重量%(例如至少约 90 重量%、至少约 95 重量%、至少约 99 重量%)。表面改变剂可以吸附到核心粒子的表面。包衣粒子在粘液中可以具有大于 0.5 的相对速度。包衣粒子可以具有至少约 20nm 且小于或等于约 1μm(例如小于或等于约 500nm)的平均尺寸。包衣的厚度可以例如小于或等于约 50nm(例如小于或等于约 30nm、小于或等于约 10nm)。所述药物组合物可以包括一种或多种药学上可接受的载体、添加剂和/或稀释剂。任选地,所述一种或多种眼科学上可接受的载体、添加剂和/或稀释剂包括甘油。在一些实施方案中,多个包衣粒子处于含有组合物中的一种或多种游离表面改变剂(例如未与粒子连接的表面改变剂)的溶液(例如水溶液)中。溶液中的一种或多种游离表面改变剂和粒子表面上的表面改变剂 B) 可以是相同的一种或多种表面改变剂并且可以在组合物中彼此平衡。组合物中存在的表面改变剂的总量可以是例如约 0.001 重量%至约 5 重量%(例如约 0.01 重量%至约 5 重量%、或约 0.1 重量%至约 5 重量%)。在一些实施方案中,组合物的 PDI 小于或等于约 0.5(例如小于或等于约 0.3、或小于或等于约 0.2),并且任选地大于或等于约 0.1。在一些实施方案中,所述药物组合物包含药剂的一种或多种降解物,并且组合物中每一种降解物的浓度均小于或等于约 1 重量%(相对于药剂的重量)。还提供了向患者或受试者(例如向眼、粘液或粘膜)使用和/或递送这些组合物的方法。

[0500] 在涉及上述药物组合物的一组具体的实施方案中，表面改变剂 B) 是或包含三嵌段共聚物，所述三嵌段共聚物包含亲水性嵌段－疏水性嵌段－亲水性嵌段构型，其中所述疏水性嵌段具有至少约 3kDa 的分子量，所述亲水性嵌段占所述三嵌段共聚物的至少约 30 重量%，其中所述亲水性嵌段包含或是具有至少约 2kDa 的分子量的聚环氧乙烷，其中所述疏水性嵌段与核心粒子的表面（例如通过吸附）缔合，并且其中所述亲水性嵌段存在于包衣粒子的表面并且使得所述包衣粒子具有亲水性。

[0501] 在上文所述的某些实施方案中，其中 B) 表面改变剂是泊洛沙姆，所述泊洛沙姆选自 Pluronic® P123、Pluronic® P103、Pluronic® P105、Pluronic® F127 以及它们的组合。在一些实施方案中，所述泊洛沙姆不是 Pluronic® F68 或 Pluronic® F108。

[0502] 在涉及上述药物组合物的另一组具体的实施方案中，表面改变剂 B) 是或包含合成聚合物，所述合成聚合物在所述聚合物的主链上具有侧羟基。所述聚合物具有至少约 1kDa 并且小于或等于约 1000kDa（例如小于或等于约 200kDa）的分子量，并且可以至少约 30％水解（例如至少约 70％水解）且少于或等于约 98％水解（例如少于约 95％水解）。所述合成聚合物可以是例如聚乙烯醇、部分水解的聚（乙酸乙烯酯）或乙烯醇与乙酸乙烯酯的共聚物。（在某些实施方案中，所述聚合物是少于或等于约 98％水解并且具有小于或等于约 75kDa 的分子量的 PVA、或少于约 95％水解的 PVA。）所述表面改变剂可以吸附到核心粒子的表面。

[0503] 在上文所述的某些实施方案中，其中 B) 表面改变剂是 PVA，所述 PVA 选自 PVA 13K87、PVA 31K98、PVA 31K87、PVA 9K80、PVA 2K75、PVA 57K87、PVA 85K87、PVA105K80、PVA130K87 以及它们的组合。

[0504] 如本文所述，上文所述的这些药物组合物可以包括任何合适的药剂 A) 和表面改变剂的密度 C)。

[0505] 在考虑以下实施例后将进一步了解本发明的这些方面和其它方面，所述实施例旨在阐明本发明的某些具体的实施方案，而非旨在限制本发明如由权利要求书所限定的范围。

[0506] 实施例

[0507] 实施例 1

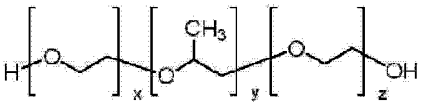
[0508] 下文描述了使非聚合固体粒子形成为粘液穿透性粒子的方法的非限制性实施例。芘（一种疏水性的天然发出荧光的化合物）被用作核心粒子并且通过在不同的表面改变剂存在下进行研磨工艺来制备。表面改变剂围绕核心粒子形成包衣。对不同的表面改变剂进行评价以确定包衣粒子穿透粘液的有效性。

[0509] 将芘在水性分散体中在不同的表面改变剂存在下进行研磨以确定某些表面改变剂是否可以：1) 有助于将粒度减小到数百纳米，以及 2) 以物理方式（非共价方式）使所产生的纳米粒子的表面由粘膜惰性 (mucoinert) 包衣所包覆，所述粘膜惰性包衣将使粒子与粘液成分的相互作用减到最低程度并且防止粘液粘着。在这些实验中，所述表面改变剂充当围绕核心粒子的包衣，并且测试所得粒子在粘液中的移动性，尽管在其它实施方案中，可以使所述表面改变剂与能够增强粒子在粘液中的移动性的其它表面改变剂交换。所测试的表面改变剂包括表 2 中所列的多种聚合物、低聚物以及小分子，包括药学上相关的赋形

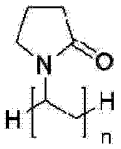
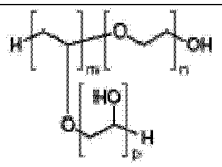
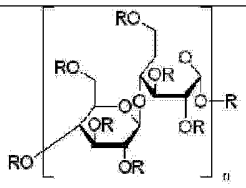
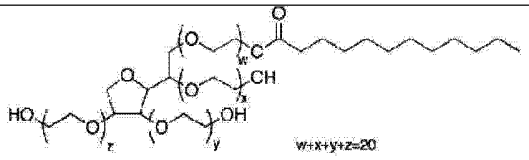
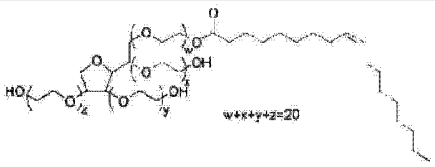
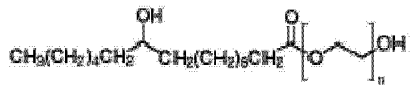
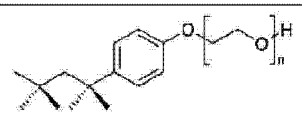
剂，如聚环氧乙烷－聚环氧丙烷－聚环氧乙烷嵌段共聚物（Pluronics®）、聚乙烯吡咯烷酮(Kollidon)、以及羟丙基甲基纤维素(Methocel)等。

[0510] 表2：使用茫作为模型化合物所测试的表面改变剂。

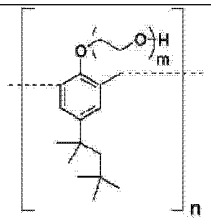
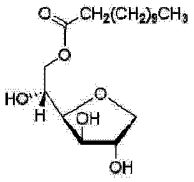
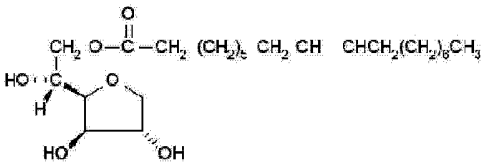
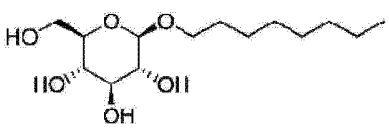
[0511]

聚合表面改变剂			
稳定剂	首字母缩写或商品名	等级或分子量	化学结构
聚环氧乙烷-聚环氧丙烷-聚环氧乙烷	Pluronic®	F127、F108、F68、F87、F38、P123、P105、P103、P65、	

[0512]

嵌段共聚物		L121、L101、L81、L44、L31	
聚乙烯吡咯烷酮	PVP	Kollidon 17(9K)、Kollidon 25(26K)、Kollindon 30(43K)	
PVA-聚乙二醇接枝共聚物		Kollicoat IR	
羟丙基甲基纤维素	HPMC	Methocel E50、Methocel K100	
低聚表面改变剂			
Tween 20			
Tween 80			
Solutol HS 15			
Triton X100			

[0513]

泰洛沙泊	
Cremophor RH 40	
小分子表面改变剂	
Span 20	
Span 80	
辛基葡糖苷	
鲸蜡基三甲基溴化铵(CTAB)	
十二烷基硫酸钠(SDS)	

[0514] 使用研磨介质对含有茋和上列的表面改变剂中的一种的水性分散体进行研磨直到粒度减小到低于 500nm 为止。表 3 列出了通过在不同的表面改变剂存在下进行研磨所获得的茋粒子的粒度特征。粒度是通过动态光散射来测量的。当使用 Pluronics® L101、L81、L44、L31、Span 20、Span 80 或辛基葡糖苷作为表面改变剂时，未能获得稳定的纳米悬浮液。因此，由于这些表面改变剂不能有效地帮助减小粒度，所以将它们排除在进一步的研究之外。

[0515] 表 3：在通过对茋与不同的表面改变剂进行研磨所获得的纳米悬浮液中通过 DLS

所测量的粒度。

[0516]

稳定剂	N-均直径(nm)
Pluronic® F127	239
Pluronic® F108	267
Pluronic® P105	303
Pluronic® P103	319
Pluronic® P123	348
Pluronic® L121	418
Pluronic® F68	353
Pluronic® P65	329
Pluronic® F87	342
Pluronic® F38	298
Pluronic® L101	不可测量*
Pluronic® L81	不可测量*
Pluronic® L44	不可测量*
Pluronic® L31	不可测量*
PVA 13K	314
PVA 31K	220
PVA 85K	236
Kollicoat IR	192
Kollidon 17 (PVP 9K)	163
Kollidon 25 (PVP 26K)	210
Kollindon 30 (PVP 43K)	185
Methocel E50	160
Methocel K100	216
Tween 20	381
Tween 80	322

[0517]

Solutol HS	378
Triton X100	305
泰洛沙泊	234
Cremophor RH40	373
SDS	377
CTAB	354
Span 20	不可测量*
Span 80	不可测量*
辛基葡糖苷	不可测量*

[0518] *与Pluronics® L101、L81、L44、L31、Span 20、Span 80、辛基葡糖苷进行研磨未能有效地减小茫的粒度并且未能产生稳定的纳米悬浮液。

[0519] 使用荧光显微镜法和多粒子追踪软件对来自所产生的纳米悬浮液的茫纳米粒子在人子宫颈阴道粘液(CVM)中的移动性和分布进行了表征。在典型的实验中,将≤0.5μL的纳米悬浮液(如果必要的话,稀释到约1%的表面活性剂浓度)连同对照一起添加到20μl的新鲜CVM中。使用常规的纳米粒子(来自英杰公司(Invitrogen)的200nm发出黄绿色荧光的经羧酸酯改性的聚苯乙烯微球体)作为阴性对照以确认CVM样品的屏障特性。使用被5kDa PEG共价包覆的红色荧光聚苯乙烯纳米粒子作为具有公认的MPP行为的阳性对照。使用装备有CCD照相机的荧光显微镜,在100× 放大倍数下以66.7毫秒(15帧/秒)的时间分辨率对以下每一种类型的粒子在每一个样品内的若干个区域拍摄15秒影片:样品(茫)、阴性对照以及阳性对照(茫的天然蓝色荧光允许独立于对照对茫纳米粒子进行观测)。随后使用高级图像处理软件,在至少3.335秒(50帧)的时间标度内测量多个粒子的单个轨迹。所得的转移数据在此处以轨迹平均速度$V_{平均}$和系综平均速度$\langle V_{平均}\rangle$的形式呈现,所述轨迹平均速度$V_{平均}$即单个粒子在它的轨迹上平均的速度,所述系综平均速度$\langle V_{平均}\rangle$即在粒子的系综上平均的$V_{平均}$。为了使得能够容易地在不同的样品之间进行比较以及使速度数据相对于CVM样品的可穿透性的天然变异度归一化,根据等式1中所示的公式来确定相对样品速度$\langle V_{平均}\rangle_{相对}$。

[0520] 在对所产生的茫纳米粒子的移动性进行定量之前,通过显微镜法在低放大倍数(10×、40×)下对它们在粘液样品中的空间分布进行评估。发现茫/Methocel纳米悬浮液在CVM中未实现均匀的分布并且强烈地聚集成比粘液筛目尺寸大得多的区域(数据未显示)。这种聚集指示粘膜粘着性行为并且有效地阻止粘液穿透。因此,认为不需要对粒子移动性进行进一步定量分析。类似于阳性对照,所有其它所测试的茫/稳定剂系统均在CVM中实现了相当均匀的分布。多粒子追踪确认在所有所测试的样品中,阴性对照高度受限,而阳性对照具有高度的移动性,如通过阳性对照的$\langle V_{平均}\rangle$显著大于阴性对照的$\langle V_{平均}\rangle$所证实(表4)。

[0521] 表4:茫/稳定剂纳米粒子(样品)和对照在CVM中的系综平均速度$\langle V_{平均}\rangle$(μm/s)和相对样品速度$\langle V_{平均}\rangle_{相对}$。

[0522]

稳定剂	阴性对照		阳性对照		样品		样品(相对)	
	<V 平均>	SD	<V 平均>	SD	<V 平均>	SD	<V 平均>相对	SD
Pluronic F127	0.58	0.18	5.97	0.54	6.25	0.72	1.05	0.18
Pluronic F108	0.43	0.64	5.04	1.88	4.99	1.47	0.99	0.55
Pluronic P105	0.56	0.52	4.38	1.36	4.47	2.11	1.02	0.69
Pluronic P103	0.58	0.77	4.5	2.01	4.24	1.95	0.93	0.74
Pluronic P123	0.56	0.44	4.56	1.44	3.99	1.66	0.86	0.54
Pluronic L121	0.42	0.3	4.27	2.04	0.81	0.51	0.10	0.16
Pluronic F68	0.56	0.52	4.38	1.36	0.81	0.7	0.07	0.23
Pluronic P65	0.26	0.25	4.52	2.15	0.53	0.56	0.06	0.15
Pluronic F87	0.95	1.6	5.06	1.34	0.74	0.78	-0.05	-0.43
Pluronic F38	0.26	0.1	5.73	0.84	0.54	0.29	0.05	0.06
Kollicoat IR	0.62	0.62	5.39	0.55	0.92	0.81	0.06	0.22
Kollidon 17	1.69	1.8	5.43	0.98	0.82	0.59	-0.23	-0.52
Kollidon 25	0.41	0.34	5.04	0.64	1.29	1.09	0.19	0.25
Kollindon 30	0.4	0.2	4.28	0.57	0.35	0.11	-0.01	0.06
Methocel E50**								
Methocel K100**								
Tween 20	0.77	0.93	5.35	1.76	1.58	2.02	0.18	0.49
Tween 80	0.46	0.34	3.35	1.89	0.94	0.5	0.17	0.24
Solutol HS	0.42	0.13	3.49	0.5	0.8	0.6	0.12	0.20
Triton X100	0.26	0.13	4.06	1.11	0.61	0.19	0.09	0.07
泰洛沙泊	0.5	0.5	3.94	0.58	0.42	0.23	-0.02	-0.16
Cremophor RH40	0.48	0.21	3.2	0.97	0.49	0.24	0.00	0.12
SDS	0.3	0.12	5.99	0.84	0.34	0.15	0.01	0.03
CTAB	0.39	0.09	4.75	1.79	0.32	0.31	-0.02	-0.07

[0523] * 未产生稳定的纳米悬浮液，因此不具粘液穿透性（未测量在 CVM 中的速度）

[0524] ** 在 CVM 中聚集，因此不具粘液穿透性（未测量在 CVM 中的速度）

[0525] 发现在某些（但重要的是，并非全部）表面改变剂存在下获得的纳米粒子以与阳性对照相同的速率或几乎相同的速度迁移穿过 CVM。具体来说，使用 Pluronics® F127、F108、P123、P105 以及 P103 稳定化的茫纳米粒子表现出超过阴性对照的 $\langle V_{平均} \rangle$ 约一个数量级并且与阳性对照的 $\langle V_{平均} \rangle$ 在实验误差范围内没有差别的 $\langle V_{平均} \rangle$，如表 4 和图 2A 中所示。对于这些样品，$\langle V_{平均} \rangle_{相对}$ 值超过 0.5，如图 2B 中所示。

[0526] 另一方面，使用其它表面改变剂获得的茫纳米粒子大部分或完全被固定，如由不大于 0.4 以及对于大部分表面改变剂来说不大于 0.1 的相应 $\langle V_{平均} \rangle_{相对}$ 值所证实（表 4 和图 2B）。此外，图 3A-3D 是显示粒子的系综内 $V_{平均}$ 的分布的柱状图。这些柱状图阐明与使用 Pluronic® 87 和 Kollidon 25 稳定化的样品（被选为代表性的粘膜粘着性样品）的粘膜粘着性行为相反，使用 Pluronic® F127 和 Pluronic® F108 稳定化的样品具有粘膜扩散性行为（对于使用 Pluronic® P123、P105 以及 P103 稳定化的样品获得了相似的柱状图，但未在此显示）。

[0527] 为了对使茫纳米晶体具有粘液穿透性的Pluronics®的特征进行鉴定，相对于所使用的Pluronics®的PPO嵌段的分子量和PEO重量含量（%）来标绘茫/Pluronic®纳米晶体的$\langle V_{平均} \rangle_{相对}$（图4）。得出的结论是，至少那些具有至少3kDa的PPO嵌段和至少约30重量%的PEO含量的Pluronics®使纳米晶体具有粘液穿透性。不希望受任何理论所束缚，认为如果疏水性PPO嵌段的分子量是足够的（例如在一些实施方案中，是至少约3kDa），那么所述嵌段可以提供与核心粒子表面的有效缔合；而如果Pluronic®的PEO含量是足够的（例如在一些实施方案中，是至少30重量%），那么所述亲水性PEO嵌段存在于包衣粒子的表面并且可以保护所述包衣粒子免于与粘蛋白纤维发生粘着性相互作用。如本文所述，在一些实施方案中，表面改变剂的PEO含量可以被选为大于或等于约10重量%（例如至少约15重量%、或至少约20重量%），因为10重量%的PEO部分使粒子具有粘膜粘着性。

[0528] 实施例2

[0529] 这个实施例描述了使用不同的非聚合固体粒子形成粘液穿透性粒子。

[0530] 将实施例1中所述的技术应用于其它非聚合固体粒子以显示所述方法的通用性。使用F127作为表面改变剂来包覆多种被用作核心粒子的活性药物。选择十二烷基硫酸钠(SDS)作为阴性对照以便将每一种药物与相同化合物的具有相似尺寸的纳米粒子比较。使用研磨介质对含有药剂和Pluronic® F127或SDS的水性分散体进行研磨直到粒度减小到低于300nm为止。表5列出了使用这种方法研磨的所选出的代表性药物的粒度。

[0531] 表5：在SDS和F127存在下研磨的所选出的代表性药物的粒度。

[0532]

药物	稳定剂	Z 均直径 (nm)	PDI
丙酸氟替卡松	F127	203	0.114
	SDS	202	0.193
呋塞米	F127	217	0.119
	SDS	200	0.146
伊曲康唑	F127	155	0.158
	SDS	168	0.163
泼尼松龙	F127	273	0.090
	SDS	245	0.120
依碳酸氯替泼诺	F127	241	0.123
	SDS	241	0.130
布地奈德	F127	173	0.112
	SDS	194	0.135
吲哚美辛	F127	225	0.123
	SDS	216	0.154

[0533] 为了测量药物纳米粒子穿透粘液的能力，研发了一种新的测定法，所述测定法测量纳米粒子向粘液样品中的质量转移。大部分的药物并非天然发出荧光并且因此难以使用粒子追踪显微镜技术来测量。新研发的总体转移测定法不需要所分析的粒子发出荧光或经过染料标记。在这种方法中，在毛细管中采集 20μL 的 CVM 并且使用粘土将一端密封。然后将毛细管的开口端浸入到粒子的 20μL 水性悬浮液中，所述水性悬浮液含 0.5％ w/v 的药物。在所需的时间，通常 18 小时之后，将毛细管从悬浮液中取出并且将外部擦干净。将容纳粘液样品的毛细管放入到超速离心管中。将提取介质添加到该管中并且孵育 1 小时，同时进行混合，以将粘液从毛细管中取出并且从粘液中提取药物。然后使样品旋转以去除粘蛋白和其它不溶性组分。然后可以使用 HPLC 对所提取的样品中药物的量进行定量。这些实验的结果与显微镜法的那些结果有良好的一致性，显示粘液穿透性粒子与常规的粒子之间在转移方面存在明显的差别。所选出的代表性药物的转移结果示于图 5 中。这些结果确证了使用芘获得的显微镜法 / 粒子追踪研究结果并且证实了可扩展用于常见的活性药物化合物；使用 F127 包覆非聚合固体纳米粒子增强了粘液穿透性。

[0534] 在实施例 1-2、4-6 以及 10 中，子宫颈阴道粘液 (CVM) 样品是从年龄在 18 岁或更大的健康女性志愿者获得的。通过如由产品资料所述将 Softcup® 月经采集杯插入到阴道内达 30 秒至 2 分钟来采集 CVM。然后在取出后，通过在 50mL 离心管中以约 30×G 至约 120×G 进行平缓离心从 Softcup® 中收集 CVM。在实施例 1 中，使用未稀释的并且新鲜的 CVM（在冷藏条件下储存不长于 7 天）。使用阴性对照 (200nm 羧化聚苯乙烯粒子）和阳性对照（经 PEG 5K 改性的 200nm 聚苯乙烯粒子）对实施例 1 中所使用的所有 CVM 样品的屏障和转移进

行验证。在实施例 2 中，将 CVM 冻干和复原。在实施例 2 中，将粘液在 -50℃冷冻，然后冻干至干燥。然后将样品储存在 -50℃。在使用之前，通过使用研钵和研杵将固体磨成细粉、之后添加水达到等于原始体积至原始体积的 2 倍的最终体积来将粘液复原。然后将复原的粘液在 4℃孵育 12 小时并且如实施例 2 中所述进行使用。使用阴性对照（200nm 羧化聚苯乙烯粒子）和阳性对照（被 F127 包覆的 200nm 聚苯乙烯粒子）对实施例 2 中所使用的所有 CVM 样品的屏障和转移进行验证。

[0535] 实施例 3

[0536] 这个实施例描述了使用包含药物依碳酸氯替泼诺 (LE) 的核心形成粘液穿透性粒子。

[0537] 为了证实在递送非聚合固体粒子方面的增强的粘液穿透性值，将依碳酸氯替泼诺的 MPP 制剂 (LE MPP；通过实施例 2 中所述的方法制备的被 Pluronic® F127 包覆的 LE 粒子）与当前市售的制剂 Lotemax® 比较。Lotemax® 是被批准用于治疗表面眼部炎症的类固醇滴眼剂。常规的粒子，如 Lotemax® 中的那些粒子被眼中周边的快速清除的粘液层广泛地截留，并且因此也被快速地清除。LE MPP 能够避免与粘液粘着，并且有效地穿过粘液以促进药物直接持续释放到下层组织。增强药物在靶标部位的暴露将允许降低总剂量，从而提高患者的依从性和安全性。在体内，与相等剂量的 Lotemax® 相比，向新西兰白兔单次局部滴注 LE MPP 在睑结膜、球结膜以及角膜中产生显著更高的药物水平（图 6A-6C）。在 2 小时之时，来自 MPP 的 LE 水平是来自 Lotemax® 的 LE 水平的 6 倍、3 倍以及 8 倍（分别是睑结膜、球结膜以及角膜）。值得注意的是，在 2 小时之时来自 MPP 的 LE 水平是在 30 分钟时来自 Lotemax® 的 LE 水平的约 2 倍。这些结果证实与商业制剂相比，使用 MPP 技术可实现增强的暴露。

[0538] 实施例 4

[0539] 下文描述了通过某些聚乙烯醇聚合物 (PVA) 的物理吸附从预制的聚合粒子形成粘液穿透性粒子的方法的非限制性实施例。使用羧化聚苯乙烯纳米粒子 (PSCOO) 作为具有公认的强粘膜粘着性行为的预制粒子 / 核心粒子。PVA 充当围绕核心粒子形成包衣的表面改变剂。对具有不同的分子量 (MW) 和水解度的 PVA 进行评价以确定包衣粒子穿透粘液的有效性。

[0540] 将 PSCOO 粒子在水溶液中在不同的 PVA 聚合物存在下孵育以确定某些 PVA 是否可以以物理方式（非共价方式）使核心粒子由粘膜惰性包衣所包覆，所述粘膜惰性包衣将使粒子与粘液成分的相互作用减到最低程度并且使得粒子在粘液中快速穿透。在这些实验中，PVA 充当围绕核心粒子的包衣，并且测试所得粒子在粘液中的移动性，尽管在其它实施方案中，可以使 PVA 与可以增强粒子在粘液中的移动性的其它表面改变剂交换。所测试的 PVA 的平均分子量在 2kDa 至 130kDa 的范围内并且平均水解度在 75％至 99+％的范围内。所测试的 PVA 列于上文所示的表 1 中。

[0541] 粒子改性工艺如下：从英杰公司购得 200nm 经羧化改性的红色荧光聚苯乙烯纳米粒子 (PSCOO)。将 PSCOO 粒子 (0.4 重量％ -0.5 重量％）在室温在 PVA 水溶液 (0.4 重量％ -0.5 重量％）中孵育至少 1 小时。

[0542] 使用荧光显微镜法和多粒子追踪软件对改性的纳米粒子在人子宫颈阴道粘液(CVM)中的移动性和分布进行表征。在典型的实验中,将≤ 0.5μL 的经过孵育的纳米悬浮液(使用 0.5 重量%的相应 PVA 的水溶液稀释约 10 倍)连同对照一起添加到 20μl 的新鲜 CVM 中。使用常规的纳米粒子(来自英杰公司的 200nm 发出蓝色荧光的经羧酸酯改性的聚苯乙烯微球体)作为阴性对照以确认 CVM 样品的屏障特性。使用被 2kDa PEG 共价包覆的黄绿色荧光聚苯乙烯纳米粒子作为具有公认的 MPP 行为的阳性对照。使用装备有 CCD 照相机的荧光显微镜,在 100× 放大倍数下以 66.7 毫秒(15 帧/秒)的时间分辨率对以下每一种类型的粒子在每一个样品内的若干个区域拍摄 15 秒影片:样品(通过德克萨斯红(Texas Red)滤光片组观测)、阴性对照(通过 DAPI 滤光片组观测)、以及阳性对照(通过 FITC 滤光片组观测)。随后使用高级图像处理软件,在至少 3.335 秒(50 帧)的时间标度内测量多个粒子的单个轨迹。所得的转移数据在此处以轨迹平均速度 $V_{平均}$ 和系综平均速度 $\langle V_{平均} \rangle$ 的形式呈现,所述轨迹平均速度 $V_{平均}$ 即单个粒子在它的轨迹上平均的速度,所述系综平均速度 $\langle V_{平均} \rangle$ 即在粒子的系综上平均的 $V_{平均}$。为了使得能够容易地在不同的样品之间进行比较以及使速度数据相对于 CVM 样品的可穿透性的天然变异度归一化,然后根据等式 1 中所示的公式将系综平均(绝对)速度转换成相对样品速度 $\langle V_{平均} \rangle_{相对}$。多粒子追踪确认在所有所测试的 CVM 样品中,阴性对照受限,而阳性对照是可移动的,如由阳性对照与阴性对照的 $\langle V_{平均} \rangle$ 的差异所证实(表 6)。

[0543] 表 6:与不同的 PVA 一起孵育的纳米粒子(样品)和对照在 CVM 中的转移:系综平均速度 $\langle V_{平均} \rangle$(μm/s)和相对样品速度 $\langle V_{平均} \rangle_{相对}$。

[0544]

稳定剂	阴性对照		阳性对照		样品		样品(相对)	
	$\langle V_{平均} \rangle$	SD	$\langle V_{平均} \rangle$	SD	$\langle V_{平均} \rangle$	SD	$\langle V_{平均} \rangle_{相对}$	SD
PVA2K75	1.39	0.33	3.3	0.68	3.44	0.7	1.07	0.59
PVA9K80	0.4	0.08	5.13	1.16	4.88	1.74	0.95	0.44
PVA13K87	0.56	0.61	5.23	1.24	4.92	1.77	0.93	0.49
PVA31K87	0.53	0.63	4.48	1.38	3.69	1.94	0.80	0.60
PVA57K86	0.5	0.25	5.74	1.11	4.76	0.91	0.81	0.25
PVA85K87	0.29	0.28	4.25	0.97	4.01	0.71	0.94	0.31
PVA105K80	0.98	0.52	5.44	0.86	4.93	0.66	0.89	0.27
PVA130K87	1.41	0.56	3.75	0.82	3.57	0.6	0.92	0.53
PVA95K95	0.51	0.36	3.19	0.68	0.45	0.19	-0.02	-0.15
PVA13K98	0.43	0.17	3.42	1.65	0.5	0.76	0.02	0.26
PVA31K98	0.41	0.23	6.03	1.19	0.26	0.14	-0.03	-0.05
PVA85K99	0.28	0.1	4.7	0.82	0.53	0.77	0.06	0.18

[0545] 发现在某些(但有趣的是,并非全部)PVA 存在下孵育的纳米粒子以与阳性对照相同的速率或几乎相同的速度转移穿过 CVM。具体来说,使用 PVA2K75、PVA9K80、PVA13K87、PVA31K87、PVA57K86、PVA85K87、PVA105K80 以及 PVA130K87 稳定化的粒子表现出显著超过阴性对照的 $\langle V_{平均} \rangle$ 并且与阳性对照的 $\langle V_{平均} \rangle$ 在实验误差范围内没有差别的 $\langle V_{平均} \rangle$。结果示于表 6 和图 7A 中。对于这些样品,$\langle V_{平均} \rangle_{相对}$ 值超过 0.5,如图 7B 中所示。

[0546] 另一方面,与 PVA95K95、PVA13K98、PVA31K98 以及 PVA85K99 一起孵育的纳米粒子

大部分或完全被固定，如由不大于 0.1 的相应 $\langle V_{平均} \rangle_{相对}$ 值所证实（表 6 和图 7B）。

[0547] 为了对使粒子具有粘液穿透性的 PVA 的特征进行鉴定，相对于所使用的 PVA 的 MW 和水解度来标绘通过与不同的 PVA 一起孵育所制备的纳米粒子的 $\langle V_{平均} \rangle_{相对}$（图 8）。得出的结论是，至少那些具有小于 95％的水解度的 PVA 使纳米晶体具有粘液穿透性。不希望受任何理论所束缚，认为如果 PVA 中不水解（乙酸乙烯酯）单元的含量是足够的（例如在一些实施方案中，是大于 5％），那么 PVA 的这些链段可以提供与核心粒子表面有效的疏水缔合；而包衣粒子的表面存在的 PVA 的亲水性（乙烯醇）单元使所述包衣粒子具有亲水性并且可以保护所述包衣粒子免于与粘液发生粘着性相互作用。

[0548] 为了进一步确认特定的 PVA 等级通过物理吸附使粘膜粘着性粒子转化成粘液穿透性粒子的能力，使用总体转移测定法对与不同的 PVA 一起孵育的 PSCOO 纳米粒子进行测试。在这种方法中，在毛细管中采集 20μL 的 CVM 并且使用粘土将一端密封。然后将毛细管的开口端浸入到粒子的 20μL 水性悬浮液中，所述水性悬浮液含 0.5％ w/v 的药物。在所需的时间，通常 18 小时之后，将毛细管从悬浮液中取出并且将外部擦干净。将容纳粘液样品的毛细管放入到超速离心管中。将提取介质添加到该管中并且孵育 1 小时，同时进行混合，以将粘液从毛细管中取出并且从粘液中提取药物。然后使样品旋转以去除粘蛋白和其它不溶性组分。然后可以使用 HPLC 对所提取的样品中药物的量进行定量。这些实验的结果与显微镜法的那些结果有良好的一致性，证实阳性对照（粘液穿透性粒子）与阴性对照（常规的粒子）之间在转移方面存在明显的差别。与不同的 PVA 一起孵育的 PSCOO 纳米粒子的总体转移的结果示于图 9 中。这些结果确证了使用与不同的 PVA 一起孵育的 PSCOO 纳米粒子获得的显微镜法 / 粒子追踪研究结果并且证实了将纳米粒子与部分水解的 PVA 一起孵育增强了粘液穿透性。

[0549] 实施例 5

[0550] 下文描述了通过在某些聚乙烯醇聚合物 (PVA) 存在下进行乳化工艺来形成粘液穿透性粒子的方法的非限制性实施例。使用聚丙交酯 (PLA) 作为通过水包油乳化工艺形成核心粒子的物质，所述聚丙交酯是一种生物可降解的药学上相关的聚合物。PVA 充当乳液表面改变剂和围绕所产生的核心粒子形成包衣的表面改变剂。对具有不同的分子量 (MW) 和水解度的 PVA 进行评价以确定所形成的粒子穿透粘液的有效性。

[0551] 在水溶液中在不同的 PVA 存在下使 PLA 的二氯甲烷溶液乳化以确定某些 PVA 是否可以以物理方式（非共价方式）使所产生的纳米粒子的表面由将使得粒子在粘液中快速穿透所包覆。在这些实验中，PVA 充当围绕乳化的有机相的液滴形成稳定化包衣的表面活性剂，所述乳化的有机相的液滴在凝固后形成核心粒子。测试所得粒子在粘液中的移动性，尽管在其它实施方案中，可以使 PVA 与可以增强粒子在粘液中的移动性的其它表面改变剂交换。所测试的 PVA 的平均分子量在 2kDa 至 130kDa 的范围内并且平均水解度在 75％至 99+％的范围内。所测试的 PVA 列于上文所示的表 1 中。

[0552] 乳化 - 溶剂蒸发工艺如下：在约 4mL 的 PVA 水溶液 (0.5 重量％ -2 重量％）中，通过超声处理使约 0.5mL 的 20-40mg/ml PLA（聚丙交酯，等级 100DL7A，购自苏尔迪克斯公司 (Surmodics)）的二氯甲烷溶液乳化以获得具有 <500nm 的目标数均粒度的稳定的乳液。立即在减压下在室温下对所获得的乳液进行充分的旋转蒸发以去除有机溶剂。通过 1 微米的玻璃纤维过滤器对所获得的悬浮液进行过滤以去除任何凝聚物。表 7 列出了使用不同的

PVA 通过这种乳化程序所获得的纳米悬浮液的粒度特征。在所有情况下，将荧光有机染料尼罗红 (Nile Red) 添加到乳化的有机相中以对所得的粒子进行荧光标记。

[0553] 表 7 ：在使用不同的 PVA 通过乳化工艺所获得的纳米悬浮液中通过 DLS 所测量的粒度。

[0554]

PVA 等级	Z 均直径 (nm)	N 均直径 (nm)
PVA2K75	186	156
PVA10K80	208	173
PVA13K98	245	205
PVA31K87	266	214
PVA31K98	245	228
PVA85K87	356	301
PVA85K99	446	277
PVA95K95	354	301
PVA105K80	361	300
PVA130K87	293	243

[0555] 使用荧光显微镜法和多粒子追踪软件对所产生的纳米粒子在人子宫颈阴道粘液 (CVM) 中的移动性和分布进行表征。在典型的实验中，将≤ 0.5μL 的纳米悬浮液（如果必要的话，稀释到约 0.5％的 PVA 浓度）连同对照一起添加到 20μl 的新鲜 CVM 中。使用常规的纳米粒子（来自英杰公司的 200nm 发出蓝色荧光的经羧酸酯改性的聚苯乙烯微球体）作为阴性对照以确认 CVM 样品的屏障特性。使用被 2kDa PEG 共价包覆的黄绿色荧光聚苯乙烯纳米粒子作为具有公认的 MPP 行为的阳性对照。使用装备有 CCD 照相机的荧光显微镜，在 100× 放大倍数下以 66.7 毫秒 (15 帧 / 秒）的时间分辨率对以下每一种类型的粒子在每一个样品内的若干个区域拍摄 15 秒影片 ：样品（由于封装的尼罗红而通过德克萨斯红滤光片组观测）、阴性对照（通过 DAPI 滤光片组观测）、以及阳性对照（通过 FITC 滤光片组观测）。随后使用高级图像处理软件，在至少 3.335 秒 (50 帧）的时间标度内测量多个粒子的单个轨迹。所得的转移数据在此处以轨迹平均速度 $V_{平均}$ 和系综平均速度 $\langle V_{平均} \rangle$ 的形式呈现，所述轨迹平均速度 $V_{平均}$ 即单个粒子在它的轨迹上平均的速度，所述系综平均速度 $\langle V_{平均} \rangle$ 即在粒子的系综上平均的 $V_{平均}$。为了使得能够容易地在不同的样品之间进行比较以及使速度数据相对于 CVM 样品的可穿透性的天然变异度归一化，然后根据等式 1 中所示的公式将系综平均（绝对）速度转换成相对样品速度 $\langle V_{平均} \rangle_{相对}$。多粒子追踪确认在所有所测试的 CVM 样品中，阴性对照受限，而阳性对照是可移动的，如由阳性对照与阴性对照的 $\langle V_{平均} \rangle$ 的差异所证实（表 8）。

[0556] 表 8 ：使用不同的 PVA 通过乳化工艺获得的 PLA 纳米粒子（样品）和对照在 CVM 中的转移 ：系综平均速度 $\langle V_{平均} \rangle$（μm/s) 和相对样品速度 $\langle V_{平均} \rangle_{相对}$。

[0557]

稳定剂	阴性对照		阳性对照		样品		样品(相对)	
	$<V_{平均}>$	SD	$<V_{平均}>$	SD	$<V_{平均}>$	SD	$<V_{平均}>_{相对}$	SD
PVA2K75	0.95	0.64	5.5	0.92	5.51	1.2	1.00	0.39
PVA9K80	0.72	0.47	5.61	0.79	4.6	1.5	0.79	0.35
PVA31K87	0.63	0.60	4.94	1.50	3.36	1.84	0.63	0.51
PVA85K87	0.57	0.4	4.49	1.21	2.9	1.56	0.59	0.45
PVA105K80	0.69	0.56	4.85	1.54	3.55	1.26	0.69	0.43
PVA130K87	0.95	0.54	4.98	1.25	3.46	1.23	0.62	0.39
PVA95K95	1.39	1.28	5.72	1.57	1.63	1.5	0.06	0.46
PVA13K98	1.02	0.49	5.09	0.99	2.61	1.54	0.39	0.41
PVA31K98	1.09	0.6	5.09	0.9	2.6	1.13	0.38	0.34
PVA85K99	0.47	0.33	5.04	2.2	0.81	0.77	0.07	0.19

[0558] 发现在某些（但有趣的是，并非全部）PVA 存在下所制备的纳米粒子以与阳性对照相同的速率或几乎相同的速度转移穿过 CVM。具体来说，使用 PVA2K75、PVA9K80、PVA13K87、PVA31K87、PVA85K87、PVA105K80 以及 PVA130K87 稳定化的粒子表现出显著超过阴性对照的 $<V_{平均}>$ 并且与阳性对照的 $<V_{平均}>$ 在实验误差范围内没有差别的 $<V_{平均}>$，如表 8 和图 10A 中所示。对于这些样品，$<V_{平均}>_{相对}$ 值超过 0.5，如图 10B 中所示。

[0559] 另一方面，使用 PVA95K95、PVA13K98、PVA31K98 以及 PVA85K99 获得的芘纳米粒子大部分或完全被固定，如由不大于 0.4 的相应 $<V_{平均}>_{相对}$ 值所证实（表 8 和图 10B）。为了对使粒子具有粘液穿透性的 PVA 的特征进行鉴定，相对于所使用的 PVA 的 MW 和水解度来标绘使用不同的 PVA 所制备的纳米粒子的 $<V_{平均}>_{相对}$（表 6 和图 7B）。得出的结论是，至少那些具有小于 95％的水解度的 PVA 使纳米晶体具有粘液穿透性。不希望受任何理论所束缚，认为如果 PVA 中不水解（乙酸乙烯酯）单元的含量是足够的（例如在一些实施方案中，是大于 5％），那么 PVA 的这些链段可以提供与核心粒子表面有效的疏水缔合；而包衣粒子的表面存在的 PVA 的亲水性（乙烯醇）单元使所述包衣粒子具有亲水性并且可以保护所述包衣粒子免于与粘液发生粘着性相互作用。

[0560] 实施例 6

[0561] 下文描述了通过在某些聚乙烯醇聚合物 (PVA) 存在下进行研磨来形成粘液穿透性非聚合固体粒子的方法的非限制性实施例。使用芘（一种模型疏水性化合物）作为通过研磨加以处理的核心粒子。PVA 充当促进核心粒子的粒度减小的研磨助剂和围绕核心粒子形成包衣的表面改变剂。对具有不同的分子量 (MW) 和水解度的 PVA 进行评价以确定研磨过的粒子穿透粘液的有效性。

[0562] 将芘在水性分散体中在不同的 PVA 存在下进行研磨以确定具有一定的 MW 和水解度的 PVA 是否可以：1) 有助于将粒度减小到数百纳米，以及 2) 以物理方式（非共价方式）使所产生的纳米粒子的表面由粘膜惰性包衣所包覆，所述粘膜惰性包衣将使粒子与粘液成分的相互作用减到最低程度并且防止粘液粘着。在这些实验中，PVA 充当围绕核心粒子的

包衣，并且测试所得粒子在粘液中的移动性。所测试的PVA的平均分子量在2kDa至130kDa的范围内并且平均水解度在75%至99+%的范围内。所测试的PVA列于上文所示的表1中。以类似方式对表中所列的多种其它聚合物、低聚物以及小分子进行测试，包括药学上相关的赋形剂，如聚乙烯吡咯烷酮(Kollidon)、羟丙基甲基纤维素(Methocel)、Tween、Span等。

[0563] 表9：使用茏作为模型化合物所测试的其它表面改变剂。

[0564]

化学品家族	等级
聚乙烯吡咯烷酮(PVP)	Kollidon 17 Kollidon 25 Kollindon 30
PVA-聚乙二醇接枝共聚物	Kollicoat IR
羟丙基甲基纤维素(HPMC)	Methocel E50 Methocel K100
非离子型聚氧乙烯表面活性剂	Solutol HS 15 Span 20 Span 80 Triton X100 Tween 20 Tween 80 泰洛沙泊
非离子型小分子表面活性剂	辛基葡糖苷
离子型小分子表面活性剂	鲸蜡基三甲基溴化铵(CTAB) 十二烷基硫酸钠(SDS)

[0565] 将含有茏和上列的表面改变剂中的一种的水性分散体与研磨介质一起搅拌直到粒度减小到低于500nm(如通过动态光散射所测量)为止。表10列出了通过在不同的表面改变剂存在下进行研磨所获得的茏粒子的粒度特征。当使用Span20、Span 80或辛基葡糖苷作为表面改变剂时，未能获得稳定的纳米悬浮液。因此，由于这些表面改变剂不能有效地帮助减小粒度，所以将它们排除在进一步的研究之外。

[0566] 表10：在通过对茏与不同的表面改变剂进行研磨所获得的纳米悬浮液中通过DLS所测量的粒度。

[0567]

稳定剂	Z 均直径(nm)	N 均直径(nm)
PVA2K75	340	301
PVA9K80	380	337
PVA13K87	375	326
PVA13K98	396	314
PVA31K87	430	373
PVA31K98	344	220
PVA85K87	543	434
PVA85K99	381	236
PVA95K95	534	392
PVA130K87	496	450
Kollidon 17	237	163
Kollidon 25	307	210
Kollindon 30	255	185
Kollicoat IR	364	192
Methocel E50	244	160
Methocel K100	375	216
Tween 20	567	381
Tween 80	553	322
Solutol HS	576	378
Triton X100	410	305
泰洛沙泊	334	234
Cremophor RH40	404	373
Span 20	不可测量*	
Span 80	不可测量*	
辛基葡糖苷	不可测量*	
SDS	603	377
CTAB	432	354

[0568] *与 Span 20、Span 80、辛基葡糖苷进行研磨未能有效地减小花的粒度并且未能产生稳定的纳米悬浮液。

[0569] 使用荧光显微镜法和多粒子追踪软件对所产生的花纳米粒子在人子宫颈阴道粘液(CVM)中的移动性和分布进行表征。在典型的实验中,将≤0.5μL的纳米悬浮液(如果必要的话,稀释到约1%的表面活性剂浓度)连同对照一起添加到20μl的新鲜CVM中。使用常规的纳米粒子(来自英杰公司的200nm发出黄绿色荧光的经羧酸酯改性的聚苯乙烯微

球体）作为阴性对照以确认 CVM 样品的屏障特性。使用被 5kDa PEG 共价包覆的红色荧光聚苯乙烯纳米粒子作为具有公认的 MPP 行为的阳性对照。使用装备有 CCD 照相机的荧光显微镜，在 100× 放大倍数下以 66.7 毫秒（15 帧 / 秒）的时间分辨率对以下每一种类型的粒子在每一个样品内的若干个区域拍摄 15 秒影片：样品（芘）、阴性对照以及阳性对照（芘的天然蓝色荧光允许独立于对照对芘纳米粒子进行观测）。随后使用高级图像处理软件，在至少 3.335 秒（50 帧）的时间标度内测量多个粒子的单个轨迹。所得的转移数据在此处以轨迹平均速度 $V_{平均}$ 和系综平均速度 $\langle V_{平均} \rangle$ 的形式呈现，所述轨迹平均速度 $V_{平均}$ 即单个粒子在它的轨迹上平均的速度，所述系综平均速度 $\langle V_{平均} \rangle$ 即在粒子的系综上平均的 $V_{平均}$。为了能够容易地在不同的样品之间进行比较以及使速度数据相对于 CVM 样品的可穿透性的天然变异度归一化，然后根据等式 1 中所示的公式将系综平均（绝对）速度转换成相对样品速度 $\langle V_{平均} \rangle_{相对}$。

[0570] 在对芘粒子的移动性进行定量之前，对它们在粘液样品中的空间分布进行目视评估。发现芘 /Methocel 纳米悬浮液在 CVM 中未实现均匀的分布并且强烈地聚集成比粘液筛目尺寸大得多的区域（数据未显示）。这种聚集指示粘膜粘着性行为并且有效地阻止粘液穿透。因此，认为不需要对粒子移动性进行进一步定量分析。类似于阳性对照，所有其它所测试的芘 / 稳定剂系统均在 CVM 中实现了相当均匀的分布。多粒子追踪确认在所有所测试的 CVM 样品中，阴性对照受限，而阳性对照是可移动的，如由阳性对照与阴性对照的 $\langle V_{平均} \rangle$ 的差异所证实（表）。

[0571] 表 11：使用不同的表面改变剂所获得的芘纳米粒子（样品）和对照在 CVM 中的转移：系综平均速度 $\langle V_{平均} \rangle$（μm/s）和相对样品速度 $\langle V_{平均} \rangle_{相对}$。

[0572]

稳定剂	阴性对照		阳性对照		样品		样品(相对)	
	$\langle V_{平均} \rangle$	SD	$\langle V_{平均} \rangle$	SD	$\langle V_{平均} \rangle$	SD	$\langle V_{平均} \rangle_{相对}$	SD
PVA2K75	0.4	0.24	5.73	0.73	4.73	1.08	0.81	0.24
PVA9K80	0.36	0.20	6.00	0.70	6.19	1.13	1.03	0.24
PVA13K87	1.01	1.21	5.09	0.98	4.54	1.03	0.87	0.51

[0573]

PVA31K87	1.28	1.14	4.88	0.6	4.57	1.123	0.91	0.55
PVA85K87	1.05	0.9	4.1	0.57	3.3	0.98	0.74	0.51
PVA130K87	0.51	0.82	5.29	0.73	4.12	1.49	0.76	0.40
PVA95K95	0.4	0.27	4.53	1.03	0.67	0.6	0.07	0.16
PVA13K98	0.61	0.42	2.13	0.99	1.29	0.57	0.45	0.56
PVA31K98	0.68	0.87	5.77	1.24	2.69	2.02	0.39	0.45
PVA85K99	0.43	0.23	5.42	0.97	2.23	1.60	0.36	0.33
Kollicoat IR	0.62	0.62	5.39	0.55	0.92	0.81	0.06	0.22
Kollidon 17	1.69	1.8	5.43	0.98	0.82	0.59	-0.23	-0.52
Kollidon 25	0.41	0.34	5.04	0.64	1.29	1.09	0.19	0.25
Kollindon 30	0.4	0.2	4.28	0.57	0.35	0.11	-0.01	0.06
Methocel E50*								
Methocel K100*								
Tween 20	0.77	0.93	5.35	1.76	1.58	2.02	0.18	0.49
Tween 80	0.46	0.34	3.35	1.89	0.94	0.5	0.17	0.24
Solutol HS	0.42	0.13	3.49	0.5	0.8	0.6	0.12	0.20
Triton X100	0.26	0.13	4.06	1.11	0.61	0.19	0.09	0.07
泰洛沙泊	0.5	0.5	3.94	0.58	0.42	0.23	-0.02	-0.16
Cremophor RH40	0.48	0.21	3.2	0.97	0.49	0.24	0.00	0.12
SDS	0.3	0.12	5.99	0.84	0.34	0.15	0.01	0.03
CTAB	0.39	0.09	4.75	1.79	0.32	0.31	-0.02	-0.07

[0574] *在 CVM 中聚集，因此不具粘液穿透性（未测量在 CVM 中的速度）

[0575] 发现在某些（但有趣的是，并非全部）PVA 存在下所获得的纳米粒子以与阳性对照相同的速率或几乎相同的速度转移穿过 CVM。具体来说，使用 PVA2K75、PVA9K80、PVA13K87、PVA31K87、PVA85K87 以及 PVA130K87 稳定化的芘纳米粒子表现出显著超过阴性对照的 $\langle V_{平均} \rangle$ 并且与阳性对照的 $\langle V_{平均} \rangle$ 在实验误差范围内没有差别的 $\langle V_{平均} \rangle$，如表 11 和图 12A 中所示。对于这些样品，$\langle V_{平均} \rangle_{相对}$ 值超过 0.5，如图 12B 中所示。

[0576] 另一方面，使用包括 PVA95K95、PVA13K98、PVA31K98 以及 PVA85K99 在内的其它表面改变剂获得的芘纳米粒子大部分或完全被固定，如由不大于 0.5 以及对于大部分的表面改变剂来说不大于 0.4 的相应 $\langle V_{平均} \rangle_{相对}$ 值所证实（表 11 和图 12B）。此外，图 13A-13F 是显示粒子的系综内 $V_{平均}$ 的分布的柱状图。这些柱状图阐明与使用 PVA31K98、PVA85K99、Kollidon 25 以及 Kollicoat IR 稳定化的样品（被选为代表性的粘膜粘着性样品）的粘膜粘着性行为相反，使用 PVA2K75 和 PVA9K80 稳定化的样品具有粘膜扩散性行为（对于使用 PVA13K87、PVA31K87、PVA85K87 以及 PVA130K87 稳定化的样品获得了相似的柱状图，但未在此显示）。

[0577] 为了对使芘纳米晶体具有粘液穿透性的 PVA 的特征进行鉴定，相对于所使用的 PVA 的 MW 和水解度来标绘使用不同的 PVA 稳定化的芘纳米晶体的 $\langle V_{平均} \rangle_{相对}$（图 14）。得出的结论是，至少那些具有小于 95％的水解度的 PVA 使纳米晶体具有粘液穿透性。不希望受任何理论所束缚，认为如果 PVA 中不水解（乙酸乙烯酯）链段的含量是足够的（例如在一些实施方案中，是大于 5％），那么 PVA 的这些链段可以提供与核心粒子表面有效的疏水缔合；而包衣粒子的表面存在的 PVA 的亲水性（乙烯醇）链段使所述包衣粒子具有亲水性并且可以保护所述包衣粒子免于与粘液发生粘着性相互作用。

[0578] 实施例 7

[0579] 这个实施例显示来自包含封装药剂的聚合核心的粘液穿透性粒子和包含不具有任何聚合载体的药物核心的粘液穿透性粒子的药剂的经改进眼部递送。

[0580] 为了证实在向眼递送药剂方面的增强的粘液穿透性值，在单次相等剂量的Lotemax®（当前市售的依碳酸氯替泼诺(LE)的眼用悬浮液，依碳酸氯替泼诺是被指示用于治疗眼部炎症的软类固醇）、MPP1（包含封装LE的聚合核心的粘液穿透性粒子）以及MPP2（包含LE核心的粘液穿透性粒子）之后测量新西兰白兔的角膜中依碳酸氯替泼诺的浓度。MPP1粒子是通过使依碳酸氯替泼诺与聚（丙交酯）(100DL2A，来自苏尔迪克斯公司）一起从丙酮溶液中纳米沉淀到水溶液中来制备的。MPP2粒子是通过实施例2中所述的方法制备的。MPP1粒子和MPP2粒子这两者均被Pluronic® F127所包覆。如图17A和图17B中所示，与具有与MPP制剂的粒子浓度相同的粒子浓度的商业滴剂相比，MPP1制剂和MPP2制剂在角膜中产生了更高的药物水平。不希望受任何理论所束缚，认为常规的粒子，如Lotemax®中的那些粒子被眼中周边的快速清除的粘液层广泛地截留，并且因此被快速地清除；而MPP粒子能够避免与粘液粘着，并且因此，实现了在眼部表面延长的停留时间并且促进药物直接持续释放到下层组织。

[0581] 实施例8

[0582] 这个实施例显示来自被Pluronic® F127包覆的粘液穿透性粒子的药剂向包括视网膜、脉络膜以及巩膜在内的眼后部的经改进递送，对于常规粒子并未观测到这种情形。与常规的粒子相比，被Pluronic® F127包覆的粒子向角膜和虹膜的递送也有所改进。

[0583] 为了证实在递送非聚合固体粒子方面的增强的粘液穿透性值，将依碳酸氯替泼诺的MPP制剂(LE MPP；通过实施例2中所述的方法制备的被Pluronic® F 127包覆的LE粒子）与当前市售的制剂Lotemax®比较。Lotemax®是被批准用于治疗眼部炎症的类固醇滴眼剂。常规的粒子，如Lotemax®中的那些粒子被眼中周边的快速清除的粘液层广泛地截留，并且因此被快速地清除。LE MPP能够避免与粘液粘着，并且有效地穿过粘液以促进药物直接持续释放到下层组织。不仅如实施例3中所述向眼部表面的递送得到增强，而且向眼中部和眼后部的递送也得到增强。在体内，与相等剂量的Lotemax®相比，向新西兰白兔单次局部滴注LE MPP在角膜、虹膜/睫状体、房水、视网膜、脉络膜以及巩膜中产生了显著更高的药物水平（图18）。当前商业滴眼剂被用于治疗前眼部病症，但并不有效治疗后眼部病症，因为药物并未到达眼后部。在此，使用8mm冲压物对应当定位有人黄斑的视网膜、脉络膜以及巩膜进行采样。在眼后部，Lotemax®的LE水平低于检测极限，而LE MPP向视网膜、脉络膜以及巩膜递送可检测水平的LE。这些结果证实了非聚合固体MPP途径优于常规途径的效用。

[0584] 实施例9

[0585] 这个实施例描述了对包含药剂的纳米晶体核心的粒子的表面上Pluronic® F127的密度的测量。

[0586] 使用研磨介质对含有药剂和Pluronic® F127的水性分散体进行研磨直到粒度减

小到低于300nm为止。将来自研磨过的悬浮液的小体积稀释到适当的浓度（例如约100μg/mL）并且将Z均直径视作粒度的代表性测量结果。然后将剩余的悬浮液分成两个等分部分。使用HPLC，测定第一等分部分的药物（在此是依碳酸氯替泼诺或丙酸氟替卡松）的总浓度和表面改变部分（在此是Pluronic® F127）的总浓度。再使用HPLC测定第二等分部分的游离或未结合的表面改变部分的浓度。为了仅从第二等分部分中获得游离或未结合的表面改变部分，通过超速离心将粒子并且因此将任何结合的表面改变部分去除。通过用表面改变部分的总浓度减去未结合的表面改变部分的浓度，确定结合的表面改变部分的浓度。由于还测定了第一等分部分的药物的总浓度，因此可以确定核心物质与表面改变部分之间的质量比。使用表面改变部分的分子量，可以计算表面改变部分相对于核心物质的质量的数目。为了将这个数字转换成表面密度测量结果，需要计算每核心物质质量的表面积。粒子的体积近似为具有从DLS获得的直径的球体的体积，从而允许计算每核心物质质量的表面积。以这种方式，确定每表面积表面改变部分的数目。图19显示针对依碳酸氯替泼诺和丙酸氟替卡松进行表面部分密度测定的结果。

[0587] 实施例10

[0588] 下文描述了使用包含药物依碳酸氯替泼诺(LE)的核心通过在不同的Pluronic®表面改变剂存在下进行研磨来形成粘液穿透性粒子的方法的非限制性实施例。

[0589] 使用研磨介质并且在稳定剂存在下对呈水性悬浮液形式的LE进行研磨。对作为表面改变剂的不同等级的Pluronic（列于表12中）进行测试以确定某些Pluronic等级是否可以：1）有助于将LE的粒度减小到亚微米范围，以及2）以物理方式（非共价方式）使所产生的LE纳米粒子的表面由粘膜惰性包衣所包覆，所述粘膜惰性包衣将使粒子与粘液成分的相互作用减到最低程度并且防止粘液粘着。在这些实验中，Pluronic充当围绕核心粒子的包衣，并且测试所得粒子在粘液中的移动性，尽管在其它实施方案中，可以使所述表面改变剂与可以增强粒子在粘液中的移动性的其它表面改变剂交换。

[0590] 进行研磨工艺直到LE粒子较小并且多分散性较低（即如通过动态光散射所测量，Z均粒子直径低于500nm并且多分散指数<0.20）为止。表12列出了通过在不同的Pluronic®存在下进行研磨所获得的LE粒子的粒度特征。粒度是通过动态光散射来测量的。在Pluronic® L31、L35、L44或L81存在下对LE进行研磨未能产生稳定的纳米悬浮液。因此，由于这些Pluronic不能有效地帮助减小粒度，所以将它们排除在进一步的研究之外。

[0591] 使用允许使荧光和非荧光的纳米级对象可视化的CytoViva®高分辨率照明系统通过暗视野显微镜法对来自所产生的纳米悬浮液的LE纳米粒子在新鲜的未稀释的人子宫颈阴道粘液(CVM)中的移动性进行表征。在典型的实验中，将0.5μL纳米悬浮液添加到预先沉积到显微镜载片上的20μL孔中的20μL未稀释的CVM中。使用CCD照相机，在100×放大倍数下以66.7毫秒（15帧/秒）的时间分辨率自每一个样品内的若干个随机选择的区域拍摄15秒影片。在单盲实验中由独立的观测人员按照移动性递增的顺序在0至3分的量表上对影片中粒子的移动性进行评分。评分准则如下：0-0.5分，不能移动；0.51-1.5分，轻微移动；1.51-2.5分，中度移动；以及2.51-3.0分，高度移动。

[0592] 随Pluronic®聚合物的PPO组分的分子量(MW PPO)和PEO组分的重量百分比(%PEO)的变化,将每一种LE/Pluronic样品的平均移动性分数绘制于图20中。发现在Pluronic® F87、F108以及F127存在下研磨的LE产生了在CVM中高度移动的粒子(移动性分数>2.51分)。这对应于具有MW PPO≥2.3kDa和%PEO≥70%的物理特性的Pluronic®聚合物。在Pluronic® P103、P105以及P123中研磨的LE纳米晶体具有中度移动性(移动性分数为1.51-2.50分)。这种Pluronic®类别的相应物理特性是MW PPO≥3.3kDa和30%≤%PEO≤70%。Pluronic® L121、P65、F38以及F68产生了不能移动的LE纳米晶体(移动性分数<0.50分)。这组Pluronic®聚合物组成了具有MW PPO≤1.9kDa和%PEO≤10%的那些聚合物。物理特性也落入先前提及的MW PPO和%PEO类别中的Pluronic® L31、L35、L44或L81未能产生小且单分散的粒子并且在该分析中被认为是不能移动的(移动性分数<0.50分)。

[0593] 不希望受任何理论所束缚,认为如果疏水性PPO嵌段的分子量是足够的(例如在一些实施方案中,是至少约2.3kDa),那么所述嵌段可以提供与核心LE粒子表面的有效缔合;而如果Pluronic®的PEO含量是足够的(例如在一些实施方案中,是至少30重量%),那么所述亲水性PEO嵌段存在于包衣LE粒子的表面并且可以保护包衣LE粒子免于与粘蛋白纤维发生粘着性相互作用。如本文所述,在一些实施方案中,表面改变剂的PEO含量可以被选为大于或等于约10重量%(例如至少约15重量%、或至少约20重量%),因为10重量%的PEO部分使粒子具有粘膜粘着性。

[0594] 有趣的是,提供高度移动性(移动性分数>2.51分)所需的PPO嵌段的分子量在LE被用作核心时是至少约2.3kDa,相比之下,在芘被用作核心时,是至少约3kDa。这个数据表明表面改变剂(例如PPO嵌段的分子量)可以根据待包覆的核心而变化以对粒子的移动性进行调控。

[0595] 表12:在通过对LE与不同的Pluronic®表面改变剂进行研磨所获得的纳米悬浮液中通过动态光散射(DLS)所测量的粒度。

[0596]

Pluronic®等级	Z 均直径(nm)	多分散指数
L31*	不可测量*	不可测量*
L35*	不可测量*	不可测量*
L44*	不可测量*	不可测量*
L81*	不可测量*	不可测量*
L101*	不可测量*	不可测量*
L121	343	0.18
P65	224	0.06
P103	251	0.08
P105	356	0.19
P123	281	0.12
F38	233	0.10
F68	404	0.13
F87	316	0.07
F108	294	0.12
F127	404	0.13

[0597] *表示未能有效地减小 LE 的粒度并且未能产生稳定的纳米悬浮液的样品。对于这些样品，Z 均直径大于至少 1μm 并且不可使用 DLS 测量。

[0598] 实施例 11

[0599] 下文描述了在其它组分存在下使用包含药物依碳酸氯替泼诺 (LE) 的核心形成粘液穿透性粒子 (MPP) 的方法的非限制性实施例，所述其它组分如 Pluronic®、甘油、氯化钠 (NaCl)、乙二胺四乙酸二钠 (Na_2EDTA) 以及苯扎氯铵 (BAC)。

[0600] 所述形成依碳酸氯替泼诺粘液穿透性粒子 (LE MPP) 的方法涉及两个连续的步骤：研磨和稀释。在研磨步骤中，在研磨介质存在下对含有约 2% -20% 依碳酸氯替泼诺（粗晶体或微粉化的晶体）、约 0.2% -20% Pluronic® F127、约 0.5% -3% 甘油、约 0.1% -1% 氯化钠以及约 0.001% -0.1% EDTA 的粗水性悬浮液进行研磨以产生尺寸在 200nm-300nm 范围的依碳酸氯替泼诺粒子的纳米悬浮液。

[0601] 在随后的稀释步骤中，在产品容器中将与研磨介质分离的所获得的纳米结晶悬浮液与含有约 0.5% -3% 甘油、约 0.1% -1% 氯化钠、约 0.001% -0.1% EDTA 以及约 0.001% -0.05% BAC 的研磨后稀释剂混合。这种方法产生了包括约 0.1% -2% 依碳酸氯替泼诺、约 0.01% -2% Pluronic® F127、约 0.5% -3% 甘油、约 0.1% -1% 氯化钠、约 0.001% -0.1% EDTA 以及约 0.001% -0.05% BAC 的组合物。

[0602] 实施例 12

[0603] 下文描述了 Pluronic® F127 对制剂的粘液穿透特性的作用的非限制性实施例。

[0604] 使用与实施例 10 中所述的方法类似的方法形成制剂。图 21 显示以下制剂的向粘液中的质量转移数据 :包含依碳酸氯替泼诺和 Pluronic® F127 的粒子 (LE F127)、包含依碳酸氯替泼诺和十二烷基硫酸钠但不包含 Pluronic® F127 的粒子 (LE SDS)、以及市售制剂 Lotemax®。依碳酸氯替泼诺与 Pluronic® F127 的比率是 1:1(重量%),并且依碳酸氯替泼诺与 SDS 的比率是 50:1(重量%)。根据实施例 2 中所述的程序测量质量转移。图 21 中所示的结果指示 LE F127 的粘液穿透特性是 LE SDS 的约 20 倍并且是 Lotemax® 的约 40 倍。认为包括依碳酸氯替泼诺核心和 F127 包衣的药物的眼用制剂可以增强药物的眼部暴露。

[0605] 实施例 13

[0606] 这个非限制性实施例显示可以对依碳酸氯替泼诺 (LE)MPP 进行 γ 辐照以进行最终灭菌而不会不利地影响 LE MPP 的粒子稳定性、化学稳定性以及药物代谢动力学,并且甘油给予 LE MPP 以针对 γ 辐照的化学保护。

[0607] 对制剂进行 γ 辐照可以引起化学降解和自由基的产生并且是一个问题,特别是在水性制剂中。LE 是被设计成通过两个酯键的水解或酶促裂解而代谢成 PJ-91 和 PJ-90 的软类固醇。当 LE 暴露于 γ 辐照时,形成 17α-[(乙氧羰基) 氧基]-11β- 羟基 -3- 氧代雄甾 -4- 烯 -17- 甲酸氯甲酯 (tetradeca) 和 17α-[(乙氧羰基) 氧基]-3,11- 二氧代雄甾 -1,4- 二烯 -17- 甲酸氯甲酯 (11-keto)。当对 LE 进行 γ 辐照时,出现少量的 11-keto,而 tetradeca 的量快速增加到高于 1%。

[0608] 使用与实施例 10-11 中所述的方法类似的方法形成包含 LE 和不同浓度的甘油的制剂。表 13 显示在制剂暴露于 γ 辐射后 LE 的某些降解物的浓度。在以 25kGy 的剂量使用钴 60 γ 辐照源的情况下,在进行 γ 辐照后立即测量降解物的浓度 (“经过 γ 辐照 (最初)”) 以及在进行 γ 辐照后 4 周测量降解物的浓度 (“经过 γ 辐照 (4 周后)”)。在不含甘油的 LE MPP 中,在对 LE MPP 进行 γ 辐照后,tetradeca 的量增加到 18 倍。相反,在 γ 辐照后,在含有 1.2%或 2.4%甘油的 LE MPP 中形成很少的 tetradeca。令人惊讶地,在所有情况下,PJ-91 和 PJ-90 的水平均降低。虽然在 γ 辐照后观测到 11-keto,但 11-keto 的水平不超过 0.2%。结果显示当制剂中存在甘油时,在 γ 辐射后,产生少得多的 tetradeca。使用不同浓度的甘油 (例如 1.2 重量%和 2.4 重量%),并且所得的制剂在暴露于 γ 辐射后产生相似水平的 tetradeca。这些结果是出人意料的并且表明常用作张力剂的甘油可以在 γ 辐射期间给予制剂以化学保护。

[0609] 表 13 :在 LE 制剂暴露于 25kGy 的 γ 辐射后 LE 的浓度和 LE 的某些降解物的浓度。*

[0610]

制剂组成	γ辐射的时间	浓度 (重量%)				
		PJ-90	PJ-91	LE	Tetradeca	11-keto
LE、F127、NaCl、EDTA、BAC	未经过辐照	0.48	0.97	97.22	0.08	0.04
	经过γ辐照(最初)	0.07	0.45	96.51	1.45	0.13
	经过γ辐照(4周后)	0.07	0.46	96.55	1.49	0.16
LE、F127、2.4%甘油、EDTA、BAC	未经过辐照	0.48	0.87	97.21	0.08	0.05
	经过γ辐照(最初)	0.31	0.70	97.28	0.10	0.15
	经过γ辐照(4周后)	0.36	0.81	97.24	0.11	0.16
LE、F127、1.2%甘油、NaCl、EDTA、BAC	未经过辐照	0.38	0.78	97.93	0.06	0.09
	经过γ辐照(最初)	0.29	0.48	98.04	0.09	0.16
	经过γ辐照(2周后)	0.28	0.50	97.80	0.15	0.20

[0611] *这个实施例中所用的LE MPP是实验室规模的批次并且可能纯度低于本文所述的其它实施例中所使用的批次。

[0612] 除了粒子制剂的化学稳定性之外，制剂的物理稳定性也极为重要。如图33A中所示，含有氯化钠和甘油的LE MPP制剂显示在暴露于25kGy的γ辐照后一个月内粒度没有变化。

[0613] 还研究了γ辐照对LE MPP的药物代谢动力学(PK)的影响以探究LE MPP的性能是否不受γ辐照的影响。在体内，向新西兰白兔单次局部滴注已经过25kGy的γ辐照的LE MPP(制剂1γ、制剂2γ)在兔的角膜中产生了与未暴露于γ辐照的LE MPP(制剂1、制剂2；图33B)的LE水平相同的LE水平。在图33B中，制剂1(和制剂1γ)包括比制剂2(和制剂2γ)高的水平的Pluronic® F127。这些结果证实可以通过γ辐照对LE MPP进行最终灭菌而不会对LE MPP的粒子稳定性、API(活性药物成分)化学稳定性或PK造成不利影响。

[0614] 实施例14

[0615] 这个非限制性实施例显示NaCl有益于在使用水稀释制剂期间本文所述的LE MPP制剂的稳定性。

[0616] 使用与实施例10-11中所述的方法类似的方法形成包含LE和一种或多种张力剂(例如NaCl、泰洛沙泊、甘油以及SSC(柠檬酸钠和约1％NaCl的水溶液))的制剂。图14显示在使用水将制剂稀释10倍之前和之后通过动态光散射(DLS)所测量的LE制剂的粒度和多分散指数(PDI)。在其中制剂不包括NaCl的条目1、4以及5中，在使用水稀释制剂后，粒度(通过直径所测量)增大到约2-3倍，这很可能归因于粒子聚集。在条目4和5中，PDI也增大到约2-3倍。相反，在其中制剂包括NaCl的条目2、3、6以及7中，在使用水稀释制剂后，粒度保持相对恒定。在条目2、3以及7中，PDI也未显著增大。这些结果是出人意料的，因为将NaCl(张力剂)添加到粒子制剂中会提高制剂的离子强度，并且一般已知会通过引起粒子聚集而使粒子制剂不稳定。在此观测到相反的作用。

[0617] 表14：在使用水稀释10倍之前和之后通过动态光散射(DLS)所测量的LE制剂的粒度和多分散指数(PDI)。

[0618]

条目	制剂组成	稀释前		稀释后	
		直径 (nm)	PDI	直径 (nm)	PDI
1	1%-5% LE、1%-5% F127	208	0.148	395	0.156
2	1%-5% LE、1%-5% F127、0.9% NaCl、0.05% EDTA、0.01% BAC	188	0.102	187	0.122
3	1%-5% LE、1%-5% F127、0.9% NaCl、0.1%泰洛沙泊、0.05% EDTA、0.01% BAC	190	0.128	193	0.139
4	1%-5% LE、1%-5% F127、2.4%甘油、0.05% EDTA、0.01% BAC	197	0.133	514	0.409
5	1%-5% LE、1%-5% F127、2.4%甘油、0.1%泰洛沙泊、0.05% EDTA、0.01% BAC	191	0.116	389	0.337
6	1%-5% LE、1%-5% F127、SSC、0.05% EDTA、0.01% BAC	212	0.096	244	0.176
7	1%-5% LE、1%-5% F127、SSC、0.1%泰洛沙泊、0.05% EDTA、0.01% BAC	212	0.100	246	0.095

[0619] 实施例 15

[0620] 这个非限制性实施例显示当向眼局部施用时，与具有相似尺寸的非 MPP 相比，LE MPP 使得暴露增强。

[0621] 将 LE MPP 与 LE SDS 粒子（具有相似尺寸的非 MPP）比较（表 15）。使用与实施例 10-11 中所述的方法类似的方法产生 LE SDS 粒子，不同的是使用十二烷基硫酸钠 (SDS) 包覆粒子。常规的粒子，如 SDS 中所包覆的那些粒子被眼中周边的快速清除的粘液层广泛地截留并且被快速地清除。LE MPP 能够避免与粘液粘着，并且有效地穿过粘液以促进药物直接持续释放到下层组织。在体内，与相等剂量的 LE SDS 相比，向新西兰白兔单次局部滴注 LE MPP 使 LE 在角膜中的浓度的 AUC 增大到 4.4 倍，尽管 LE MPP 和 LE SDS 这两者是具有相似尺寸的纳米粒子（图 23A）。此外，虽然 LE SDS 与Lotemax®（一种可商购的微粒）的粒度不同，但从接受 LE SDS 给药的兔获得的 LE 的浓度在统计学上等同于从接受Lotemax®给药的兔获得的 LE 的浓度（图 23B）。这些结果证实 MPP 能够增强使用 MPP 配制的药物在眼中的暴露并不仅仅是因为 MPP 的小的粒度。

[0622] 表 15：通过动态光散射 (DLS) 所测量的 LE SDS 和 LE MPP 的粒度和多分散指数 (PDI)。

[0623]

样品	直径 (nm)	PDI
LE SDS	240	0.143
LE MPP	241	0.096

[0624] 实施例 16

[0625] 这个非限制性实施例显示当向眼局部施用时，与被 Pluronic® F127 包覆的 Lotemax® 相比，LE MPP 使得暴露增强。

[0626] 将 LE MPP 与 Lotemax®+F127 比较，Lotemax®+F127 是通过将 F127(0.5 重量％）添加到 Lotemax® 中所形成的制剂。在体内，与相等剂量的 Lotemax® 或 Lotemax®+F127 相比，向新西兰白兔单次局部滴注 LE MPP 在角膜中产生显著更高的 LE 暴露（图 24)。LE MPP 与 Lotemax® 和 Lotemax®+F127 相比使 LE 在角膜中的浓度的 AUC 分别增大到 4.4 倍和 2.3 倍。虽然与单独的 Lotemax® 相比，Lotemax®+F127 的确使 LE 在角膜中的浓度的 AUC 增大到 2 倍，但这些结果证实 MPP 能够增强使用 MPP 配制的药物在眼中的暴露并不仅仅是因为该制剂中存在 Pluronic® F127。

[0627] 实施例 17

[0628] 这个非限制性实施例显示包括 LE MPP 的制剂与 Lotemax® 相比增强 LE 在眼前房中的暴露。

[0629] 为了证实来自 LE MPP 的增强的 LE 暴露不仅平移到眼表面，而且在眼球内穿过，将由 LE MPP 和 Lotemax® 制剂获得的在房水中的 LE 水平进行比较。在体内，与一定剂量的 Lotemax® 相比，虽然事实上 Lotemax® 的剂量大了 20％，但向新西兰白兔单次局部滴注 LE MPP 在房水中产生显著更高的 LE 水平（图 25)。与 Lotemax®（含有 0.5％的 LE) 相比，LE MPP（含有 0.4％的 LE) 使 AUC_{0-3} 小时增大到 3 倍。这些结果证实可使用 MPP 技术实现的增强的暴露并不局限于眼表面，而是延伸到前房中。此外，与 Lotemax® 相比，使用 LE MPP 制剂可以使 LE 的剂量降低 20％并且仍然可以实现增强的暴露。

[0630] 实施例 18

[0631] 这个非限制性实施例证实与 Lotemax® 相比，包括含有少了 20％的 LE 的 LE MPP 的制剂显示在兔眼和血浆中改进的暴露。

[0632] 为了证实 LE MPP 可以在低于诸如 Lotemax® 等当前市售制剂的剂量下维持增强的暴露，以比 Lotemax® 低 20％的剂量给予 LE MPP。测定来自 LE MPP 和 Lotemax® 的 LE 以及它的两种主要代谢物 PJ-91 和 PJ-90 的水平。在体内，与一定剂量的含有 0.5 重量％

LE 的Lotemax®相比，虽然事实上Lotemax®的剂量比 LE MPP 的剂量大 20％，但向新西兰白兔单次局部滴注含有 0.4 重量％ LE 的 LE MPP 在所测试的所有组织 / 流体（例如结膜、角膜、房水、虹膜和睫状体（ICB）、视网膜中央以及血浆）中产生显著更高水平的 LE（图 26A-26R）。药物代谢动力学参数列于表 16 中。这些结果证实与Lotemax®相比，使用 LE MPP 制剂可以使 LE 的剂量降低 20％并且仍然实现增强的暴露。

[0633] 表 16：体内眼部组织中依碳酸氯替泼诺（LE）的药物代谢动力学参数。向兔的每一只眼中给予一次 50μL 剂量的 0.5％Lotemax®或 0.4％ LE MPP。

[0634]

		血浆	房水	结膜	角膜	虹膜和睫状体(ICB)	视网膜(中央冲压物)
Lotemax®	T_{max} (h)	0.25	0.50	0.083	0.083	0.50	0.50
	C_{max} (nM)	0.704	14.0	2430	1330	105	4.47
	$t_{1/2消除}$ (h)	1.88	2.31	4.26	3.75	3.04	9.18
	$AUC_{0-最后}$ (nM·h)	1.62	30.0	3450	2420	194	14.8
	AUC_{0-inf} (nM·h)	1.69	30.5	4070	2710	200	22.4
LE MPP	T_{max} (h)	0.50	0.50	0.083	0.083	0.25	0.50
	C_{max} (nM)	2.55	43.7	6280	4850	293	14.5
	$t_{1/2消除}$ (h)	1.71	1.57	1.92	1.89	1.49	1.55
	$AUC_{0-最后}$ (nM·h)	4.55	66.0	3450	3570	442	31.5
	AUC_{0-inf} (nM·h)	4.71	66.4	3490	3610	445	31.9

[0635] 实施例 19

[0636] 这个非限制性实施例证实含有聚乙二醇化共聚物和非聚乙二醇化形成核心的聚合物的负载氟替卡松的 MPP 的氟替卡松释放曲线。

[0637] 根据与本文所述的方法（例如实施例 21 中所述的方法）类似的方法，通过使氟替卡松与作为主要聚合物的 PLA7A（苏尔迪克斯公司，100DLA7A，MW ＝ 108KDa）和作为次要聚合物的聚乙二醇化共聚物（例如 100DL9K-PEG2K 或 8515PLGA54K-PEG2K）共同沉淀来制备负载氟替卡松的 MPP。所测试的聚合组分的比率是 10/90、20/80 以及 30/70（其中 PLA7A

在所有情况下均为主要组分）。对不同的聚乙二醇化共聚物进行测试以探究嵌段组成（即PEG 嵌段的 MW 相比于疏水性嵌段的 MW）对所得粒子的特性的影响。具体来说，对所得粒子穿透粘液、控制药物释放、以及在整个配制工艺过程中维持胶体稳定性的能力进行评估。

[0638] 发现虽然许多组合物产生令人满意的药物释放和粘液穿透性，但它们当中的大多数未能实现良好的胶体稳定性（参见图 27）。胶体稳定性尤为重要，因为当前的配制工艺涉及通过离心和重悬对 MPP 进行分离和纯化。许多组合物部分地由于不能使在离心步骤之后获得的产物重悬而表现出不良的胶体稳定性。产生具有良好的胶体稳定性以及对药物释放良好的控制（例如，如在这个实施例中在体外在 24 小时内连续释放）的 MPP 的组合物似乎在粒子中相对低的总 PEG 含量（例如总聚合物含量的小于约 3 重量％）下具有相对高的 PEG 在粒子上的表面覆盖度（例如每平方纳米至少约 0.18 条 PEG 链）。换句话说，与 PLA7A 与具有相对长的疏水性嵌段的 PEG- 共聚物（例如 8515PLGA54K-PEG2K）的类似组合相比，PLA7A 与具有相对短的疏水性嵌段的 PEG- 共聚物（例如 100DL9K-PEG2K）的组合产生更具胶体稳定性的 MPP（参见图 27）。

[0639] 实施例 20

[0640] 这个非限制性实施例证实包含索拉非尼的 MPP 避免了被截留在人子宫颈阴道粘液中并且能够扩散穿过粘液。

[0641] 可以根据本文所述的方法（例如实施例 21 和 29 中所述的方法）制备包含索拉非尼的 MPP。通过如实施例 2 和实施例 10 中所分别描述的总体转移法和 / 或显微镜法对常规的纳米粒子和本文所述的 MPP 在人子宫颈阴道粘液中的移动性进行表征。结果示于图 28A-28B 中。常规的纳米粒子被截留在人子宫颈阴道粘液中，而本文所述的 MPP 避免了被截留并且能够扩散穿过粘液。

[0642] 实施例 21

[0643] 这个非限制性实施例证实局部递送被配制成 MPP 的索拉非尼（一种小分子受体酪氨酸激酶 (RTK) 抑制剂）极大地改进了眼的视网膜和脉络膜中索拉非尼的水平。这个实施例还显示眼前段组织中索拉非尼的水平取决于 MPP 的释放速率并且可以降低而不显著影响索拉非尼在眼后部的水平。

[0644] 通过以下研磨程序制备具有相对快速的药物释放的负载索拉非尼的 MPP(MPP1)：将含有药物和 Pluronic F127(F127) 的水性分散体与作为研磨介质的氧化锆珠粒一起搅拌，直到如通过动态光散射所测量，粒度减小到低于 300nm 为止。这种方法使用由 FDA 批准用于眼用产品的赋形剂并且产生 MPP 的稳定的水性纳米悬浮液。

[0645] 通过将索拉非尼封装到饰有本文所述的包衣的生物可降解的聚合纳米粒子中来制备具有相对缓慢的药物释放动力学的负载索拉非尼的 MPP(MPP2)。举例来说，在搅拌下将在四氢呋喃中含有索拉非尼游离碱 (LC Labs 公司）、PLA（聚丙交酯，100DL7A，苏尔迪克斯公司）以及 PLA-PEG（聚乙二醇 - 共 - 聚丙交酯，100DL-mPEG2K，苏尔迪克斯公司）的溶液以受控的速率添加到过量的 Pluronic® F127 水溶液中。在室温下对所产生的粒子进行搅拌以使挥发物蒸发并且使未被封装的索拉非尼结晶出来。通过借助具有合适尺寸的玻璃纤维过滤器过滤去除未被封装的索拉非尼的晶体。将纳米粒子通过离心从滤液中分离并且使用水性 Pluronic® F127 洗涤一次。使纳米粒子的最终产物在 Pluronic® F127 中重悬。

[0646] 通过 HPLC 确认 MPP 制剂中的索拉非尼浓度。使用 Zetasizer Nano ZS90(马尔文仪器公司 (Malvern Instruments)) 通过动态光散射来测量 MPP 的尺寸。在 37℃在 50mM 磷酸盐缓冲液 (pH 7.4) 中在 0.5% Tween 80 存在下对体外药物释放进行评价以确保漏槽条件 (sink condition),如远低于饱和溶解度的实验条件。

[0647] 在合同研究组织 (contract research organization) 处在新西兰白兔 (NZW) 中评价在单次局部施用 MPP 或非 MPP 比较物后索拉非尼的药物代谢动力学。使用索拉非尼的水性悬浮液作为非 MPP 比较物。每只动物的两只眼均接受含有 5mg/mL 索拉非尼的 50μL 局部滴注物 (n = 6)。在各个时间点采集眼部组织,包括角膜以及眼后部的脉络膜和视网膜的 8mm 冲压物。所述冲压物用于对处于眼后部的应当存在人黄斑的区域进行靶定,因为这一区域是 AMD 疗法的靶标。通过 LC/MS 测定索拉非尼的水平。

[0648] 如上文所述配制的 MPP1 和 MPP2 形成稳定的纳米悬浮液,Z 均直径分别是 187nm(PDI = 0.172) 和 222nm(PDI = 0.058)。由于 MPP1 基本上是纯药物索拉非尼的悬浮液,因此药物释放主要由药物溶解来驱动,这是相对快速的。在 MPP2 的情况下,药物索拉非尼被封装在 PLA 聚合物中,并且药物负载是 20%。使 MPP2 的聚合物组成 (包括 PLA 的分子量、PLA 与 PLA-PEG 的比率、以及 PLA-PEG 的组成) 系统地发生改变以实现与 MPP1 有显著区别的释放速率。MPP2 制剂显示在体外在约 24 小时内连续的药物释放。

[0649] 在角膜中,与比较物相比,单次剂量的快速释放的 MPP1 制剂产生了高达 18 倍的索拉非尼水平,并且维持了与比较物相比至少 6 倍的增高达至少 6 小时。相比之下,缓慢释放的 MPP2 制剂仅产生了与比较物相比在 6 小时的过程中稳定持续的约 2 倍的增高。然而,在后段组织 (例如视网膜和脉络膜) 中,MPP1 和 MPP2 这两者产生同样高的索拉非尼水平,远胜过比较物 (图 29A-29B)。事实上,由 MPP 制剂在视网膜中产生的索拉非尼的水平接近或超过所报道的索拉非尼针对 VEGFR-2(37ng/g) 和 PDGFR-β (14ng/g) 的细胞 IC_{50} 值,所述索拉非尼是具有相对低效力的第一代 RTK 抑制剂。此外,这两种 MPP 制剂均被良好地耐受,如由德莱兹评分 (Draize scoring) 所评估。

[0650] 这些结果不仅证实了以下概念验证 :本文所述的 MPP 和其组合物可以通过局部施用极大地增强药剂向眼后部的递送,而且还表明了局部递送被配制成 MPP 的小分子 RTK 抑制剂可以具有治疗广泛的眼部疾病 (如 AMD) 的潜能。

[0651] 实施例 22

[0652] 这个非限制性实施例证实与 Lotemax® 凝胶相比,包括 LE MPP 的制剂改进了 LE 在兔眼的房水中的暴露。

[0653] 为了证实不仅与市售的悬浮液制剂相比,而且还与市售的凝胶制剂相比,LE MPP 可以以较低的剂量维持增强的 LE 暴露,当使用 LE MPP(以 0.4% LE 给药) 和 Lotemax® 凝胶 (以 0.5% LE 给药) 时测定 LE 的水平。凝胶制剂和软膏剂制剂被普遍地用于试图通过递送于粘性基质中的 LE 来提高眼中的暴露。凝胶制剂和软膏剂制剂往往会使视力模糊并且与液体滴眼剂相比不太舒适并且更难配置。

[0654] 为了产生 LE MPP,根据本文所述的方法使用研磨程序。举例来说,使用研磨介质对含有 LE 和 Pluronic® F127(F127) 的水性分散体进行研磨直到如通过动态光散射所测量,粒度减小到低于约 300nm 为止。基于先前所述的表征方法在人子宫颈阴道粘液中对粘液移

动性进行表征。

[0655] 在体内，与一定剂量的Lotemax®凝胶相比，虽然事实上Lotemax®凝胶的剂量高了20％并且处于粘性基质中，但向新西兰白兔单次局部滴注LE MPP(KPI-121)在房水中产生更高的LE水平（图30）。LE MPP的AUC_{0-3}是Lotemax®凝胶的AUC_{0-3}的1.5倍。LE MPP的C_{max}是Lotemax®凝胶的C_{max}的2.4倍。这些结果指示本文所述的MPP胜过Lotemax®凝胶中所用的粘性基质，并且与Lotemax®凝胶相比，使用LE MPP制剂可以使LE的剂量降低20％并且仍然可以实现相似或增强的暴露。

[0656] 实施例23

[0657] 这个非限制性实施例证实LE MPP在新西兰白兔的房水中显示出剂量依赖性暴露。

[0658] 为了证实来自LE MPP制剂的LE的暴露具有剂量依赖性，进行剂量范围研究(dose ranging study)。为了产生LE MPP，根据本文所述的方法使用研磨工艺。举例来说，使用研磨介质对含有药物和Pluronic® F127(F127)的水性分散体进行研磨直到如通过动态光散射所测量，粒度减小到低于约300nm为止。基于先前所述的表征方法在人子宫颈阴道粘液中对粘液移动性进行表征。进行稀释，得到包括0.4％、0.5％、0.6％或1％ LE的LE MPP悬浮液。在体内，向新西兰白兔单次局部滴注LE MPP在兔的房水中产生对所给予的剂量具有依赖性的LE水平（图31A-31B）。这些结果证实LE MPP表现出剂量依赖性药物代谢动力学(PK)。

[0659] 实施例24

[0660] 这个非限制性实施例证实LE MPP可以在一种或多种诸如氯化钠等离子组分存在下稳定地配制。

[0661] 为了证实LE MPP可以使用诸如离子盐等离子组分来配制，并且可以在这种制剂中保持物理稳定，将氯化钠（一种对于人具有公知的安全性特征的张力剂）引入到LE MPP中。本领域通常已知的是，不应当将离子组分添加到粒子悬浮液中，因为离子组分倾向于使粒子悬浮液不稳定。令人惊讶地，LE MPP的情况并非如此。

[0662] 已知的是，为了实现具有约300mOsm/kg的渗透压的制剂，制剂中氯化钠的浓度通常是约0.9％。1.2％甘油与0.45％氯化钠的组合一般也产生等渗溶液并且对该组合进行测试以对不同水平的氯化钠进行比较。

[0663] 为了产生纳米粒子，根据本文所述的方法使用研磨工艺。举例来说，使用研磨介质对含有LE和Pluronic® F127(F127)的水性分散体进行研磨直到如通过动态光散射所测量，粒度减小到低于约300nm为止。通过使用动态光散射(DLS)监测制剂中粒子的尺寸来测试所得的等渗制剂的物理稳定性。发现含有两种不同浓度的氯化钠的制剂中的粒子在尺寸方面非常稳定，如图32中所示。在图32中，以三角形标记所描绘的数据比以圆形标记所描绘的数据具有更高的NaCl在制剂中的百分比。这些结果证实LE MPP可以在诸如氯化钠等离子组分存在下被配制成稳定的组合物。

[0664] 实施例25

[0665] 这个非限制性实施例证实含有Pluronic® F127和双氯芬酸或酮咯酸的粒子可以

具有粘液穿透性。

[0666] 为了证实包含含有 NSAID 的核心并且包含表面改变剂（例如 Pluronic® F127）的粒子可以具有粘液穿透性，对两种 NSAID，即双氯芬酸和酮咯酸进行研究。

[0667] 为了形成含有双氯芬酸或酮咯酸的粒子，根据本文所述的方法使用研磨程序。在一组实验中，使用研磨介质对含有 Pluronic® F127 以及酮咯酸游离酸和双氯芬酸游离酸中的一种的水性分散体进行研磨直到如通过动态光散射所测量，粒度减小到低于约 300nm 为止。为了产生具有相似尺寸的非 MPP 比较物，使用相似的研磨程序，不同的是使用 SDS 而不是 Pluronic® F127 作为表面改变剂。基于先前所述的显微镜法在人子宫颈阴道粘液中对所产生的粒子的粘液移动性进行表征。在双氯芬酸的情况下，此外还通过先前所述的总体转移法对粘液移动性进行表征。结果示于图 41 中。数据证实含有 Pluronic® F127 以及酮咯酸和双氯芬酸中的一种的粒子具有粘液穿透性，而含有 SDS 以及酮咯酸和双氯芬酸中的一种的粒子不具粘液穿透性。

[0668] 实施例 26

[0669] 这个非限制性实施例证实一种形成包括溴芬酸钙的 MPP 以及其组合物和 / 或制剂的方法。

[0670] 使用与实施例 2 中所述的方法类似的方法来制备包括作为核心的溴芬酸钙和作为粘膜惰性表面改变剂的 Pluronic® F127(F127) 的 MPP 以及包括这些 MPP 的组合物和 / 或制剂。在一组实验中，使用氧化锆珠粒作为研磨介质在含有溴芬酸钙和 Pluronic® F127 的水性分散体中对溴芬酸钙进行纳米研磨，直到如通过动态光散射所测量，粒度减小到低于 300nm 为止。如果需要的话，可以将所得的经过纳米研磨的悬浮液稀释到更低的浓度。在一些实验中，在水、125mM 的 $CaCl_2$ 或 50mM 的 Tris 缓冲液中对溴芬酸钙进行研磨，得到三种制剂。通过动态光散射来测量这三种制剂中所获得的 MPP 的粒度，并且将结果示于图 34 中。所有三种制剂均具有约 200nm 的 Z 均直径和 <0.2 的多分散指数。这些数据证实溴芬酸钙 MPP 的尺寸小且均一，并且因此适合于眼部施用。

[0671] 实施例 27

[0672] 这个非限制性实施例证实包括溴芬酸钙的 MPP 以及其组合物和 / 或制剂当被储存在室温下时稳定。

[0673] 可以根据实施例 26 中的方法来制备包括溴芬酸钙的 MPP 以及其组合物和 / 或制剂。将 MPP、组合物和 / 或制剂在室温储存数天，并且通过动态光散射来测定 MPP 的 Z 均粒度和多分散指数。结果示于图 35A-35D 中。这些数据证实溴芬酸钙 MPP 当被储存在室温下时在延长的时间段内维持良好的粒度稳定性。

[0674] 通过荧光显微镜法和高分辨率暗视野显微镜法确认溴芬酸钙 MPP 在人子宫颈阴道粘液中增强的粘液移动性（数据未显示）。

[0675] 实施例 28

[0676] 这个非限制性实施例证实含有溴芬酸钙 MPP 的组合物和 / 或制剂中的赋形剂可以改进溴芬酸钙 MPP 的化学稳定性。

[0677] 为了改进 MPP 中溴芬酸钙的化学稳定性，对用于研磨步骤和最终制剂的具有以下

作用的不同赋形剂组合物进行探究：(1) 降低溴芬酸的溶解度或 (2) 维持溴芬酸保持最稳定时所处的 pH 值范围。表 20 显示溴芬酸钙 MPP 在两种缓冲液 (125mM $CaCl_2$ 和 50mM Tris) 中以及为了比较，在未缓冲的水中的 pH 值和溶解度。与在水中的化学稳定性相比，溴芬酸钙 MPP 在降低药物溶解度的 125mM $CaCl_2$ 中以及在将溶液的 pH 值维持在约 8 的 50mM Tris 中的化学稳定性显著增强。

[0678] 表 20：在室温在不同的赋形剂组合物存在下含有 0.09％ w/v 溴芬酸的溴芬酸钙 MPP 悬浮液的 pH 值、溶解度以及化学稳定性。*

[0679]

制剂：溴芬酸钙悬浮液(0.09% w/v 的溴芬酸)				
媒剂		制剂特性		
缓冲液	Pluronic®F127 的浓度 (% w/v)	pH 值	溶解度 (mg/mL)	峰面积%*
无(水)	0.5	6.87	0.21	0.13 (第 7 天)
	0.09	6.75	0.20	0.09 (第 23 天)
125 mM $CaCl_2$	0.5	6.48	0.03	0 (第 7 天)
	0.09	6.60	0.07	0 (第 23 天)
50 mM Tris 缓冲液	0.5	8.03	0.25	0(第 7 天)
	0.09	7.98	0.27	0 (第 23 天)

[0680] *以溴芬酸的内酰胺降解物的色谱峰面积％来测定溴芬酸钙的化学稳定性。

[0681] 实施例 29

[0682] 这个非限制性实施例证实含有索拉非尼或利尼伐尼的 MPP 增强索拉非尼或利尼伐尼在兔的眼后部的暴露。

[0683] 为了证实增强的粘液穿透性不仅可用于眼前部，而且也可以在眼后部产生增强的暴露，将索拉非尼和利尼伐尼这两种受体酪氨酸激酶抑制剂配制成 MPP。作用于血管内皮生长因子受体 (VEGFR) 的小分子 RTK 抑制剂具有作为用于年龄相关的黄斑变性 (AMD) 的疗法的潜能。如果局部递送 RTK 抑制剂可以在眼后部提供足够水平的 RTK 抑制剂，则可以避免当前疗法所用的重复玻璃体内注射。向眼后部递送 RTK 抑制剂还将有益于侵害后段组织的许多其它疾病。

[0684] 为了产生含有 RTK 抑制剂（例如索拉非尼和利尼伐尼）的 MPP，使用与用于依碳酸氯替泼诺的研磨程序类似的研磨程序：使用研磨介质对含有 RTK 抑制剂和 F127 或十二烷基硫酸钠 (SDS) 的水性分散体进行研磨直到如通过动态光散射所测量，粒度减小到低于约 300nm 为止。基于先前所述的表征方法在人子宫颈阴道粘液中对粘液移动性进行表征。索拉非尼和利尼伐尼在与 F127 进行研磨时被加工成 MPP 并且在与 SDS 进行研磨时被加工成非 MPP。

[0685] 在体内，向新西兰白兔单次局部滴注 50μL 的 0.5％索拉非尼 -MPP 在兔的视网膜中产生的索拉非尼水平在 2 小时之时是由非 MPP 对照产生的索拉非尼水平的 45 倍并且是细胞 IC_{50}的 96 倍（图 36A）。从应当存在人黄斑的视网膜获取 8mm 直径的中央冲压物以测量索拉非尼在 AMD 疗法所应靶向的眼后部的水平。索拉非尼 -MPP 以统计显著量优于索拉非尼非 MPP。

[0686] 在体内，向新西兰白兔单次局部滴注 50μL 的 2％利尼伐尼 -MPP 在视网膜中央冲压物中产生的利尼伐尼水平在所研究的整个 4 小时内是由非 MPP 对照产生的利尼伐尼水平的约 2 倍并且在 4 小时之时是细胞 IC_{50}的 777 倍（图 36B）。再一次，MPP 与非 MPP 之间的差异具有统计显著性。

[0687] 这些结果证实增强的粘液穿透性可以使得能够实现药物在眼后部的更高暴露。这种技术的应用可以用于改进药物在眼的任何组织（无论是在眼部表面还是在眼后部）中的暴露。

[0688] 实施例 30

[0689] 这个非限制性实施例证实含有 MGCD-265 或帕唑帕尼的 MPP 在兔的眼后部产生治疗相关水平的 MGCD-265 或帕唑帕尼。

[0690] 为了证实 MPP 技术可广泛地应用于向眼后部以治疗相关（例如治疗有效）水平递送小分子 RTK 抑制剂，对以下另外的两种化合物进行研究：MGCD-265 和帕唑帕尼。

[0691] 为了产生 MPP，使用与用于依碳酸氯替泼诺的研磨程序类似的研磨程序：使用研磨介质对含有 MGCD-265 或帕唑帕尼和 F127 的水性分散体进行研磨直到如通过动态光散射所测量，粒度减小到低于约 300nm 为止。基于先前所述的表征方法在人子宫颈阴道粘液中对粘液移动性进行表征。当与 F127 进行研磨时，MGCD-265 和帕唑帕尼这两者均被加工成 MPP。

[0692] 在体内，向新西兰白兔单次局部滴注 50μL 的 0.5％帕唑帕尼 -MPP 在视网膜中央冲压物中产生的帕唑帕尼水平在 4 小时之时是细胞 IC_{50}的 9 倍（图 37A）。

[0693] 在体内，向新西兰白兔单次局部滴注 50μL 的 2％ MGCD-265-MPP 在视网膜中产生的 MGCD-265 水平在 30 分钟时是细胞 IC_{50}的 37 倍并且在 4 小时之时是细胞 IC_{50}的 116 倍（图 37B）。

[0694] 这些结果连同实施例 29 一起证实多种 RTK 抑制剂可以被配制成 MPP，并且使用局部施用在眼后部实现的 RTK 抑制剂的水平与 RTK 抑制剂的活性浓度（细胞 IC_{50}）有关。

[0695] 实施例 31

[0696] 这个非限制性实施例证实单次局部施用西地尼布 -MPP 在兔的眼后部产生治疗相关的药物水平达 24 小时。

[0697] 为了证实含有药物的 MPP 将治疗相关的药物水平在兔的眼后部维持 24 小时的时间段的潜能，将西地尼布（一种 RTK 抑制剂）配制成 MPP。如果局部递送药物可以在眼后部提供治疗相关水平的药物，那么可以避免当前 AMD 疗法中所用的重复玻璃体内注射。理想情况下，这种局部疗法将在眼后部维持药物水平以使得给药频率较低。

[0698] 为了产生 MPP，使用与用于依碳酸氯替泼诺的研磨程序类似的研磨程序：使用研磨介质对含有西地尼布和 Pluronic® F127 的水性分散体进行研磨直到如通过动态光散射所测量，粒度减小到低于约 300nm 为止。基于先前所述的表征方法在人子宫颈阴道粘液中

对粘液移动性进行表征。当与 F127 进行研磨时，西地尼布被加工成 MPP。

[0699] 在体内，向 HY79b 有色兔单次局部滴注 50μL 的 2％西地尼布 -MPP 在兔的脉络膜中产生的西地尼布水平在 24 小时之时是细胞 IC_{50}的 4,800 倍（图 38A）并且在兔的视网膜中产生的西地尼布水平在 24 小时之时是细胞 IC_{50}的 1,000 倍（图 38B）。这些结果证实可使用 MPP 技术在眼后部实现的暴露可以处在治疗相关范围内，并且相关的药物暴露可以被维持较长的一段时间（例如至少 24 小时）。

[0700] 实施例 32

[0701] 这个非限制性实施例证实单次局部施用阿西替尼 -MPP 在荷兰黑带兔的眼后部产生治疗相关的阿西替尼水平达 24 小时。

[0702] 为了证实 MPP 将治疗相关的药物水平在兔的眼后部维持 24 小时的时间段的潜能，将阿西替尼（一种 RTK 抑制剂）配制成 MPP。如果局部递送药物可以在眼后部提供治疗相关水平的药物，那么可以避免当前 AMD 疗法所用的重复玻璃体内注射。理想情况下，这种局部疗法将在眼后部维持药物水平以使得给药频率较低。

[0703] 为了产生纳米粒子，使用与用于依碳酸氯替泼诺的研磨程序类似的研磨程序：使用研磨介质对含有阿西替尼和 F127 的水性分散体进行研磨直到如通过动态光散射所测量，粒度减小到低于约 300nm 为止。基于先前所述的表征方法在人子宫颈阴道粘液中对粘液移动性进行表征。当与 F127 进行研磨时，阿西替尼被加工成 MPP。

[0704] 在体内，向荷兰黑带兔单次局部滴注 50μL 的 2％阿西替尼 -MPP 在兔的脉络膜中产生治疗相关的药物水平，所述水平在 24 小时之时是细胞 IC_{50}的 1,100 倍（图 39A），并且在兔的视网膜中产生的水平在 24 小时之时是细胞 IC_{50}的 37 倍（图 39B）。这些结果证实可使用 MPP 技术在眼后部实现的暴露可以处在治疗相关范围内，并且相关的药物暴露可以被维持较长的一段时间（例如至少 24 小时）。

[0705] 实施例 33

[0706] 这个非限制性实施例证实阿西替尼 -MPP 减少了兔 VEGF（血管内皮生长因子受体）激发模型中的血管渗漏。

[0707] 为了证实 MPP 技术在治疗眼后部的眼疾病方面的治疗潜能，在急性 VEGF 激发模型中对阿西替尼 -MPP 进行研究。在这种模型中，向荷兰黑带兔给予 VEGF 的玻璃体内注射以刺激血管生长。使用荧光素血管造影术来确定兔产生异常的血管和渗漏的程度。在使用媒剂、阿西替尼 -MPP 或 Avastin® 治疗后来自荧光素血管造影术的代表性图像示于图 40A-40C 中。接受媒剂给药的兔显示出大量的血管生长、迂曲以及渗漏。接受 Avastin® 治疗的兔没有显示出视网膜的血管结构变化，所述 Avastin® 在标示外（off-label）常被用于治疗人的 AMD 并且与阿西替尼具有不同的作用机制。接受阿西替尼 -MPP 治疗的兔显示出某种程度的血管生长，但渗漏显著少于媒剂组。这些结果证实可使用 MPP 技术在眼后部实现的暴露足以显著地减少急性激发模型中的血管渗漏，并且具有作为 AMD 和其它眼后部疾病的有效疗法的潜能。

[0708] 实施例 34

[0709] 这个非限制性实施例证实与 Lotemax® 相比，含有 Pluronic® F127、Tween 80®

或 PVA 作为表面改变剂的 LE MPP 在兔中显示出改进的 LE 暴露。

[0710] 为了证实 LE MPP 增强 LE 的暴露的能力不限于在 LE MPP 中包括 F127 作为表面改变剂，对以下另外的两种表面改变剂进行研究：Tween 80®和聚乙烯醇 (PVA)。Tween 80® 是经 FDA 批准的表面改变剂，它由形成头部基团的聚乙二醇化的脱水山梨糖醇和烷基尾组成。Tween 80®与多种其它表面改变剂（例如 F127 和 PVA）的不同之处尤其在于它是低聚的并且因此具有显著更低的分子量。PVA 是经 FDA 批准的聚合物，它是通过例如使聚乙酸乙烯酯部分水解，从而产生聚乙酸乙烯酯与聚乙烯醇的无规共聚物而产生的。PVA 与多种其它表面改变剂（例如 F127 和 Tween 80®）的不同之处尤其在于它不含 PEG。在实施例 4-6 中，显示某些 PVA 使得能够穿透粘液，而其它 PVA 则不会。这种差异性粘液穿透行为可以通过 PVA 的分子量和水解度来控制。基于来自这些实施例的结果，选择具有约 2kDa 的分子量并且约 75％水解的 PVA 对 LE MPP 的粘液穿透特性进行研究。

[0711] 为了形成 LE MPP，如本文所述使用研磨程序。在一组实验中，使用研磨介质对含有 LE 和选自 F127、Tween 80®以及 PVA(2kDa，75％水解）的一种表面改变剂的水性分散体进行研磨直到如通过动态光散射所测量，粒度减小到低于约 300nm 为止。基于先前所述的表征方法在人子宫颈阴道粘液中对粘液移动性进行表征。所有三种 LE MPP（即 LE-F127、LE-Tween80 以及 LE-PVA）均显示出粘液穿透特性（图 42）。

[0712] 在体内，向新西兰白兔单次局部滴注这三种 LE MPP 中的每一种在兔的角膜中产生的 LE 水平均显著高于由以类似方式施予的 Lotemax®给药所产生的 LE 水平（图 42）。这些结果证实含有药物的 MPP、组合物和 / 或制剂基于粒子的粘液穿透特性增强了药物的暴露。

[0713] 实施例 35

[0714] 以下非限制性实施例描述了在产生包含依碳酸氯替泼诺 (LE) 作为核心物质的粘液穿透性粒子方面对不同的表面改变剂进行的评估。

[0715] 在这个实施例中，使用研磨介质在不同的表面活性剂或稳定剂存在下对呈水性悬浮液形式的 LE（一种相对疏水性药剂）进行研磨。所测试的表面活性剂和稳定剂的包括分子量 (MW)、HLB 值（对于表面活性剂）以及水解度（对于 PVA）在内的特征列于表 21 中。进行研磨工艺直到 LE 粒子小且均一，即如通过动态光散射 (DLS) 所测量，Z 均直径 (D) ≤ 500nm 并且多分散指数 (PDI)<0.20。如通过 DLS 所测量的 LE 纳米粒子的所得粒度和多分散指数也列于表 21 中。

[0716] 并非所有的表面改变剂均能够在研磨期间有效地帮助减小粒度并且产生 LE 的稳定的纳米悬浮液。当使用 Span® 20、Span® 80、Kollidon® 12PF、Kollidon® 17PF 作为表面改变剂时，未能获得 LE 的稳定纳米悬浮液。

[0717] 表 21：所测试的表面改变剂的特征（分子量 (MW)、HLB 值（对于表面活性剂）、水解度（对于 PVA））、以及通过对依碳酸氯替泼诺 (LE) 与表面改变剂进行研磨所获得的纳米悬浮液由 DLS 所测量的粒度 (D 和 PDI)。

[0718]

表面改变剂		MW (Da)	HLB	D (nm)	PDI
表面活性剂	Brij® 35	1200	16.9[1]	332	0.155
	Brij® 98	1150	15[+]	324	0.148
	Brij® S100	4670	18.8[+]	404	0.103
	Cremophor® EL	2650	13[1]	200	0.099
	Cremophor® RH 40	3,090	15[1]	301	0.102
	维生素 E-TPGS	1513	13[+]	252	0.151
	Triton® X-100	647	13.5[+]	203	0.126
	SDS	288	8.3[#]	266	0.073
	Tween® 20	1228	16.7[1]	228	0.119
	Tween® 80	1310	15[1]	206	0.129
	Span® 20	346	8.6[1]	>1000	>0.2
	Span® 85	957	1.8[1]	>1000	NM
	Solutol® HS 15	345	15[+]	284	0.131
	DPPC	734	8.5[#]	248	0.148
	DPPC+PEG2K-PE	734(DPPC) 2804(PEG2K-DSPE)	9.85[#]	188	0.092
	泰洛沙泊	280	13[2]	271	0.087
稳定剂	Kollidon® 12PF	2500	NA	>1000	>0.2
	Kollidon® 17PF	9000	NA	>1000	>0.2
	Kollidon® 30	50000	NA	211	0.104
	PVA	**MW (kDa)**	**水解%**	**D (nm)**	**PDI**
	PVA 2K75	2	75-79	172	0.105
	PVA 13K87	13-23	87-89	333	0.112
	PVA 31K87	31-50	87-89	253	0.085
	PVA 31K98	31-50	98-99	281	0.105

[0719]

[0720]

	PVA 85K87	85-124	87-89	323	0.136
	PVA 85K99	85-124	≥99	>500	>0.2
	PVA 95K95	95	95	366	0.136
	PVA 130K87	130	87-89	388	0.131

[0721] NA 表示不适用 ;NM 表示不可测量。

[0722] +表示如从供应商获得的 HLB 值。

[0723] # 表示如等式 2 中所示使用格里芬法计算的 HLB 值。

[0724] [1]Handbook of Pharmaceutical Excipients(《药物赋形剂手册》), 第 4 版 , Rowe, Sheskey 以及 Weller, 英国医药出版社 (Pharmaceutical Press), 2003 年。

[0725] [2]Pharmaceutical Suspensions(《药物悬浮液》), Kulshreshtha, Singh, Wall, 斯普林格出版社 , 2010 年。

[0726] 通过高分辨率暗视野显微镜法在复原的子宫颈阴道粘液 (CVM)(如实施例 2 中所述) 中对来自所产生的纳米悬浮液的 LE 纳米粒子的粘液穿透能力进行表征。在典型的样品制备中,将 20μL 再水化的 CVM 和 0.5μL 具有 5% w/v LE 的纳米粒子浓度的纳米悬浮液沉积到显微镜载片上。在于 DPPC 或 DPPC+2PEG-PE 中被研磨的 LE 的情况下,使用 1μL 具有 1% w/v LE 的浓度的纳米悬浮液。在暗视野显微镜下在高放大倍数 (100×) 下以 15 秒的时间长度和 66.7 毫秒 (15 帧 / 秒) 的时间分辨率对粘液样品内的随机区域拍摄视频。通过对所录制的视频中粒子的移动度 (即总体粒子的速度和看似可移动的粒子的量) 与公认的阳性对照 (在Pluronic® F127 中研磨的 LE 纳米粒子,“可移动的”或“具有粘液穿透性”) 和阴性对照 (在 SDS 中研磨的 LE 纳米粒子,“不能移动的”或“不具粘液穿透性”) 进行比较来目视确定视频中 LE 纳米粒子的移动性,并且分别分类为“可移动的”和“不能移动的”。

[0727] 结果表明以下表面改变剂使 LE 纳米粒子具有粘液穿透性 :Brij® 35、Brij® 98、Brij® S 100、Cremophor® EL、Cremophor® RH 40、TPGS、Triton® X-100、Tween® 20、Tween® 80、Solutol® HS、泰洛沙泊、PVA 2K75、PVA 13K87、PVA 31K87、PVA 31K98、PVA 85K87 以及 PVA 130K87。

[0728] 为了对使 LE 纳米晶体具有粘液穿透性的表面活性剂的特征进行鉴定,相对于所使用的表面活性剂的 MW 和 HLB 值来标绘通过与不同的表面活性剂进行研磨所获得的 LE 纳米粒子的移动性 (图 43)。不希望受任何理论所束缚,结果表明具有 HLB>10 的表面活性剂可以产生可在 CVM 中移动的 LE 纳米晶体,而具有低于 10 的 HLB 的表面活性剂要么产生不能在 CVM 中移动的纳米晶体 (例如 SDS、DPPC、DPPC+PEG2K-PE),要么不能够形成稳定的纳米晶体悬浮液 (例如Span® 20 和Span® 85)。

[0729] 为了对使 LE 纳米晶体具有粘液穿透性的 PVA 的特征进行鉴定,相对于所使用的 PVA 的 MW 和水解度来标绘通过与不同的 PVA 进行研磨所获得的 LE 纳米粒子的移动性 (图 44)。观测到同时具有水解度 >95% 和分子量 >31kDa 这两种特性的那些 PVA 未能产生稳定

的纳米晶体或具有粘液穿透性的纳米晶体。不希望受任何理论所束缚，认为如果 PVA 中未水解的链段（乙酸乙烯酯）的含量是足够的（例如在一些实施方案中，等于或大于 2%），那么 PVA 的这些链段可以提供与核心粒子表面有效的疏水缔合；而包衣粒子的表面存在的 PVA 的亲水性链段（乙烯醇）使所述包衣粒子具有亲水性并且可以保护所述包衣粒子免于与粘液发生粘着性相互作用。

[0730] 实施例 36

[0731] 为了证实增强的粘液穿透性不仅可用于眼前部，而且也可以在眼后部产生增强的暴露，将阿西替尼（一种受体酪氨酸激酶抑制剂 (RTKi)）配制成 MPP。作用于血管内皮生长因子受体 (VEGFR) 的小分子 RTKi 具有作为用于年龄相关的黄斑变性 (AMD) 的疗法的潜能。如果局部递送可以在眼后部提供足够水平的药物，则可以避免当前疗法所用的重复玻璃体内注射。向眼后部的递送还将有益于侵害后段组织的许多其它疾病。

[0732] 为了产生纳米粒子，使用与用于依碳酸氯替泼诺的研磨程序类似的研磨程序：使用研磨介质对含有药物和 Pluronic F127(F127) 或十二烷基硫酸钠 (SDS) 的水性分散体进行研磨直到如通过动态光散射所测量，粒度减小到低于 300nm 为止。基于先前所述的表征方法在人子宫颈阴道粘液中对粘液移动性进行表征。阿西替尼在与 F127 进行研磨时被表征为具有粘液穿透性（即产生 MPP），而在与 SDS 进行研磨时被表征为不具粘液穿透性。

[0733] 在体内，向新西兰白兔单次局部滴注 50μL 的 0.5%阿西替尼 -MPP 在视网膜中产生治疗相关的药物水平，所述药物水平是细胞 IC_{50} 的 100 倍（图 45）。这些结果证实可使用 MPP 技术在眼后部实现增强的暴露并且所述增强的暴露达到治疗相关范围。

[0734] 实施例 37

[0735] 这个非限制性实施例显示阐明在向朗 - 埃文斯有色大鼠单次局部给予常规的粒子 (CP) 和粘液穿透性粒子 (MPP) 之后这两种粒子的眼部停留时间的差异的体内成像数据。

[0736] CP（发出近红外荧光 (780nm/820nm) 的羧化聚苯乙烯粒子，直径为 200nm）购自佛斯佛瑞克斯 (Phosphorex) 公司，并且未进一步改性（除了使用去离子水稀释到 0.9% w/w 的粒子浓度之外）即使用。通过将上述 CP 与 Pluronic® F127 组合以产生 0.9% w/w 的粒子浓度和 0.9% w/w 的 Pluronic® F127 浓度从上述 CP 制备 MPP。在体内成像研究中，向朗 - 埃文斯有色大鼠 (n = 8) 的左眼中给予 5μl 剂量的 CP 并且以相等的粒子浓度向右眼中给予 MPP。在给药后的 2 小时、4 小时以及 6 小时之时 (n = 2/ 时间点)，使用海德堡 (Heidelberg) 照相机以提供均匀的图像放大的固定灵敏度获取图像。

[0737] 在接受 MPP 的眼中观测到更均匀的分布和更大程度的角膜染色（图 46），从而确认 MPP 使得在眼部表面的停留时间更长。在结膜染色方面的差异也是显而易见的，尽管差异没那么大（数据未显示）。

[0738] 实施例 38

[0739] 这个非限制性实施例显示被 Pluronic® F127 包覆的聚苯乙烯 (PS) 粒子在粘液中的相对速度与粒子表面上 Pluronic® F127 的密度之间的关系。

[0740] 在一组实验中，使羧化 PS 纳米粒子 (200nm，0.5% w/v) 的水性分散体在室温在不同浓度的 Pluronic® F127 存在下平衡至少 24 小时。如下对所获得的 PS/Pluronic® F127

纳米粒子的表面上Pluronic® F127分子的密度进行定量。对PS/ Pluronic® F127混合物进行超速离心以使粒子完全沉降。因此，与PS结合的Pluronic® F127连同这些粒子一起沉降；未与PS结合的Pluronic® F127保留在上清液中。通过凝胶渗透色谱法(GPC)测量所获得的上清液中Pluronic® F127的浓度($C_{F127(游离)}$)。在这个实验中，使用装配有G1362A折射率检测器的Agilent 1100HPLC系统和分析用Agilent PLgel 5μm混合C柱。如下计算结合的Pluronic® F127的浓度($C_{F127(结合)}$)：

[0741] $C_{F127(结合)} = C_{F127} - C_{F127(游离)}$

[0742] 其中C_{F127}是混合物中存在的Pluronic® F127的总浓度。然后如下计算每PS的表面积Pluronic® F127分子的数目(F127/nm²)：

[0743]

$$F127/nm^2 = \frac{N_A \times C_{F127(结合)}}{SA \times C_{PS}}$$

[0744] 其中N_A是阿伏伽德罗数(Avogadro number)，$C_{F127(结合)}$是结合的Pluronic® F127的摩尔浓度(摩尔/升)，SA是根据制造商(英杰公司)的说明书计算的PS粒子的比表面积(nm^2/g)，并且C_{PS}是混合物中PS的质量浓度(g/L)。在计算中使用由制造商(巴斯夫公司(BASF))说明的Pluronic® F127的数均分子量。

[0745] 如实施例1和4-6中所述使用荧光显微镜法和多粒子追踪软件以在人子宫颈阴道粘液中的相对速度来测量PS/Pluronic® F127粒子穿透粘液的能力。具体来说，样品是目标粒子，阴性对照是不具有聚合物包衣的200nm发出荧光的经羧酸酯改性的聚苯乙烯粒子，并且阳性对照是具有2kDa或5kDa PEG的致密包衣的200nm发出荧光的聚苯乙烯粒子(其具有公认的减少的粘膜粘着行为)。将样品、阴性对照以及阳性对照彼此通过它们的荧光色彩区分开。在典型的实验中，将≤0.5μL的粒子悬浮液连同阳性对照和阴性对照一起添加到20μL新鲜的子宫颈阴道粘液中。使用装备有CCD照相机的荧光显微镜，在100×放大倍数下以66.7毫秒(15帧/秒)的时间分辨率对以下每一种类型的粒子在每一个样品内的若干个区域拍摄15秒(s)影片：样品、阴性对照以及阳性对照。随后使用高级图像处理软件，在至少3.335秒(50帧)的时间标度内测量多个粒子的单个轨迹。

[0746] 图47中所示的结果指示当粒子表面上Pluronic® F127分子的密度增加时，被Pluronic® F127包覆的PS粒子在粘液中的相对速度增大。

[0747] 其它实施方案

[0748] 虽然已经在本文描述并且阐明了本发明的若干个实施方案，但本领域的普通技术人员将容易地预想到用于执行本文所描述的功能和/或获得本文所描述的结果和/或一种或多种优势的多种其它手段和/或结构，并且这些变化和/或修改中的每一个均被认为在本发明的范围内。更一般地说，本领域技术人员将容易了解的是，本文所描述的所有参数、尺寸、材料以及配置都意在为示例性的，并且实际的参数、尺寸、材料和/或配置将取决

于使用本发明的教导的一个或多个具体的应用。本领域技术人员仅使用常规的实验就将认识到或能够确定本文所描述的本发明的具体实施方案的多个等同方案。因此，应当了解的是，上述实施方案是仅以举例的方式来呈现的，并且在所附权利要求书和其等同方案的范围内，本发明可以按除所具体描述和要求的方案以外的方案来实施。本发明涉及本文所描述的每一种单独的特征、系统、制品、材料、试剂盒和/或方法。此外，如果这些特征、系统、制品、材料、试剂盒和/或方法并非相互不一致，那么两种或更多种所述特征、系统、制品、材料、试剂盒和/或方法的任何组合都被包括在本发明的范围内。

[0749] 除非清楚地作出相反的指示，否则如本文在说明书和权利要求书中所用的不定冠词“一(a/an)”应当被理解为意指“至少一”。

[0750] 如本文在说明书和权利要求书中所用的短语“和/或”应当被理解为意指以这种方式联在一起的要素中的“任何一个或两个”，即这些要素在一些情况下结合存在而在其它情况下分开存在。除非清楚地作出相反的指示，否则除由“和/或”子句所明确地标识的要素外的其它要素可以任选地存在，无论是与所明确地标识的那些要素相关还是不相关。因此，作为非限制性示例，提到的“A和/或B”在结合开放式语言(如“包含”)使用时可以在一个实施方案中指A而没有B(任选地包括除B以外的要素)；在另一个实施方案中指B而没有A(任选地包括除A以外的要素)；在又一个实施方案中指A和B这两者(任选地包括其它要素)；等等。

[0751] 如本文在说明书和权利要求书中所用的“或”应当被理解为与如上文所定义的“和/或”具有相同的含义。举例来说，当分开列表中的项目时，“或”或者“和/或”应当被解释为包括性的，即不仅包括多个要素或要素列表中的至少一个，而且也包括其中多于一个，以及任选地另外的未列出的项目。仅清楚地作出相反指示的术语(如“……中的仅一个”或“……中的确切一个”，或者在被用于权利要求书中时，“由……组成”)将指的是包括多个要素或要素列表中的确切一个要素。一般来说，如本文所用的术语“或”当后面有排他性的术语(如“任何一个”、“……中的一个”、“……中的仅一个”或“……中的确切一个”)时，应当仅被解释为指示排他性的替代物(即“一个或另一个而非两者”)。“基本上由……组成”在被用于权利要求书中时应当具有它如在专利法领域中所用的普通含义。

[0752] 如本文在说明书和权利要求书中参考一个或多个要素的列表所用的短语“至少一个”应当被理解为意指选自该要素列表中的任何一个或多个要素中的至少一个要素，但未必包括该要素列表内明确列出的每一个要素中的至少一个，并且不排除该要素列表中要素的任何组合。这一定义还允许，除短语“至少一个”所指的要素列表内明确标识的要素以外的要素可以任选地存在，无论与所明确标识的那些要素相关还是不相关。因此，作为非限制性示例，“A和B中的至少一个”(或等同地，“A或B中的至少一个”，或者等同地，“A和/或B中的至少一个”)可以在一个实施方案中指至少一个A(任选地包括多于一个A)，而不存在B(并且任选地包括除B以外的要素)；在另一个实施方案中，指至少一个B(任选地包括多于一个B)，而不存在A(并且任选地包括除A以外的要素)；在又一个实施方案中，指至少一个A(任选地包括多于一个A)，以及至少一个B(任选地包括多于一个B)(并且任选地包括其它要素)；等等。

[0753] 在权利要求书中以及在上述说明书中，所有过渡性短语，如“包含”、“包括”、“带有”、“具有”、“含有”、“涉及”、“拥有”等均应当被理解为开放性的，即意指包括但不限于。只

有过渡性短语“由……组成”和“基本上由……组成”分别应当是封闭式或半封闭式的过渡性短语，如United States Patent Office Manual of Patent Examining Procedures(《美国专利局专利审查程序手册》)的第2111.03节中所述。

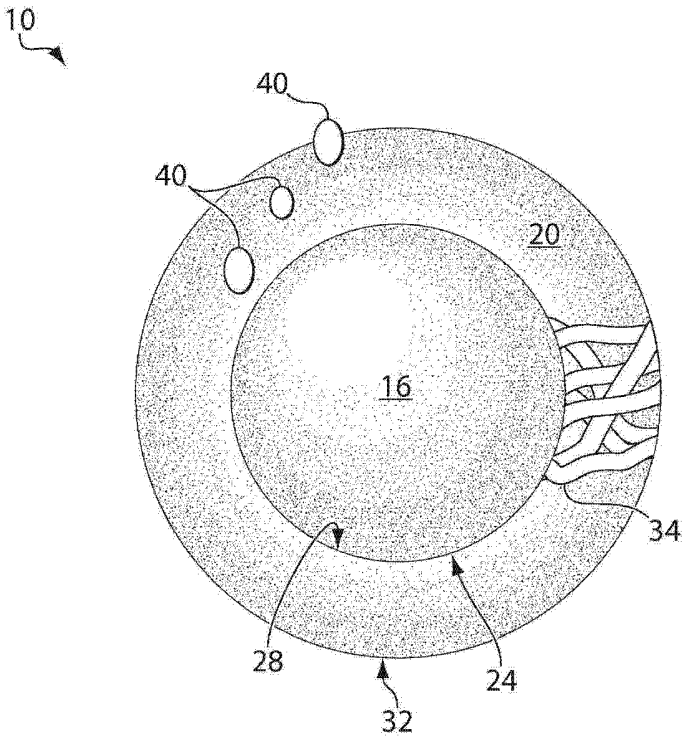

10
40
40
20
16
34
28
24
32

图 1

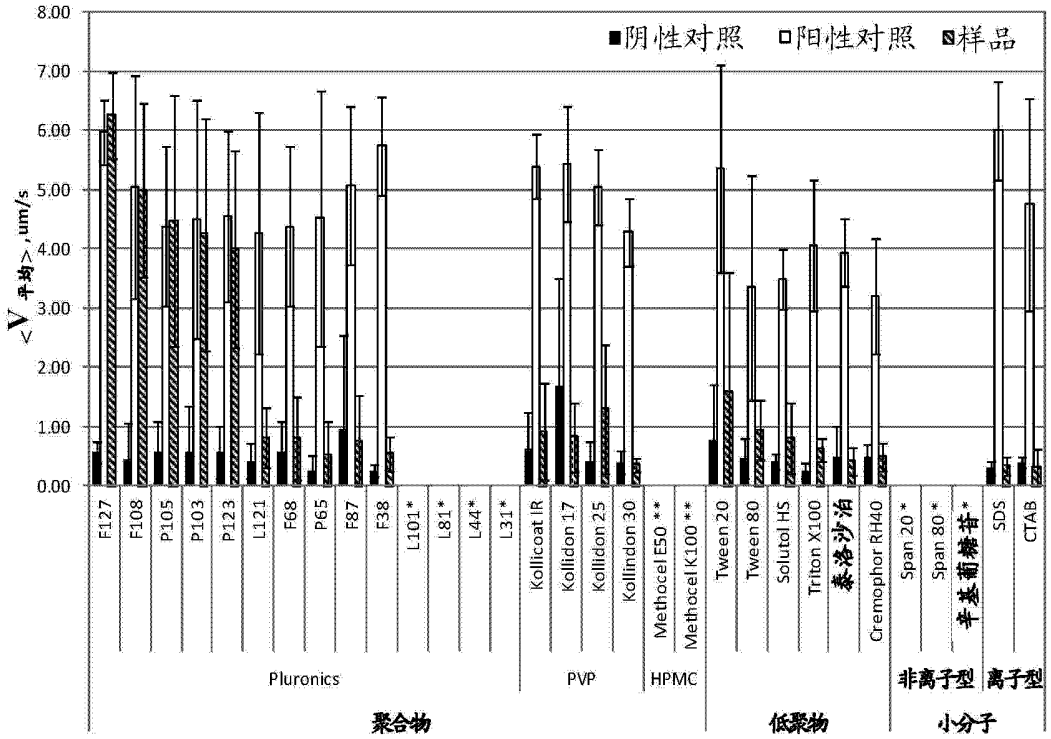

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7.00
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3.00
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1.00
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阴性对照
阳性对照
样品
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F108
P105
P103
P123
L121
F68
P65
F87
F38
L101*
L81*
L44*
L31*
Kollicoat IR
Kollidon 17
Kollidon 25
Kollindon 30
Methocel E50 **
Methocel K100 **
Tween 20
Tween 80
Solutol HS
Triton X100
泰洛沙泊
Cremophor RH40
Span 20 *
Span 80 *
辛基酚聚醚*
SDS
CTAB
Pluronics
PVP
HPMC
非离子型
离子型
聚合物
低聚物
小分子

图 2A

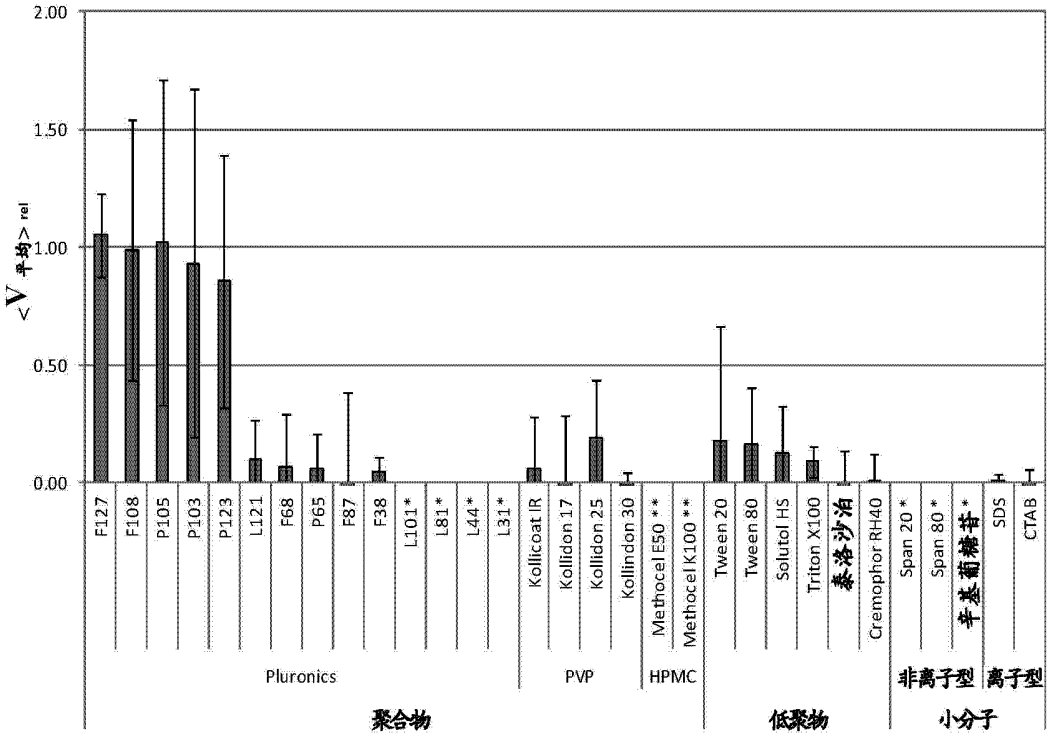
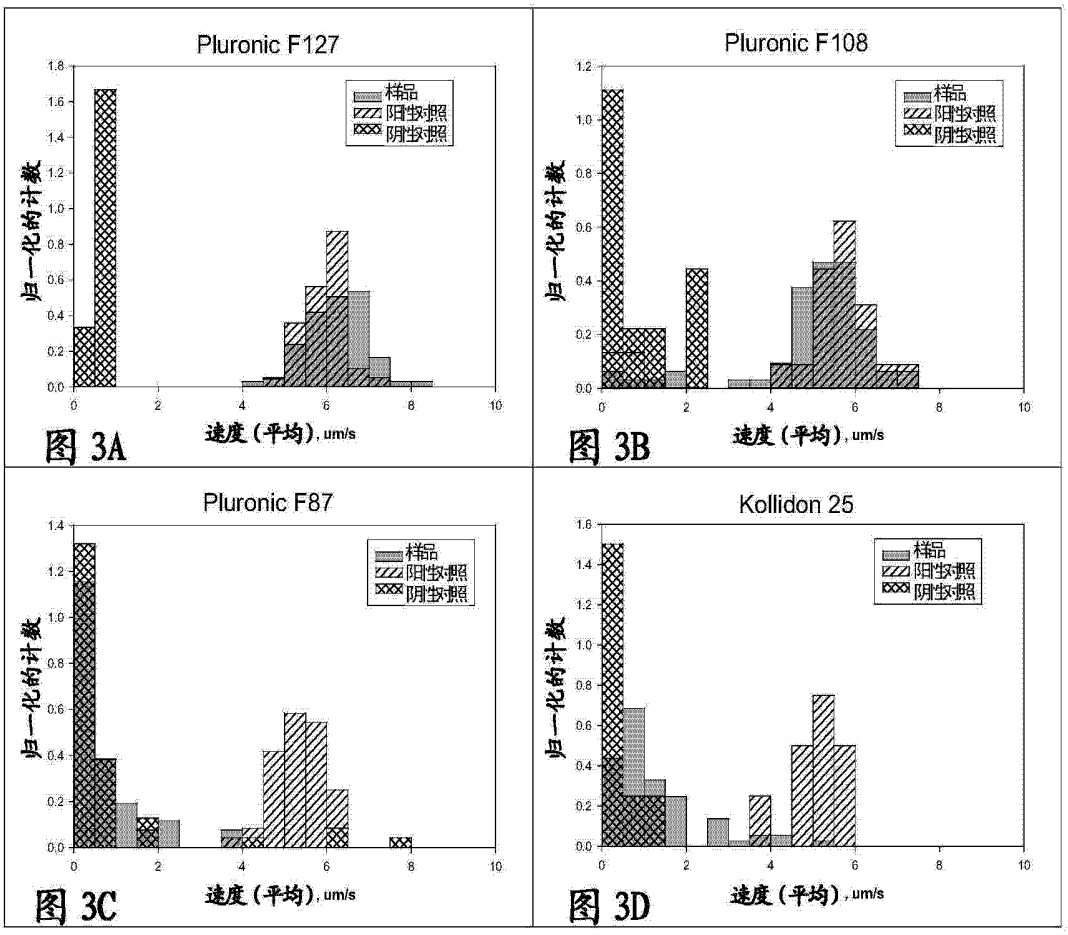

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L101*
L81*
L44*
L31*
Kollicoat IR
Kollidon 17
Kollidon 25
Kollindon 30
Methocel E50 **
Methocel K100 **
Tween 20
Tween 80
Solutol HS
Triton X100
泰洛沙泊
Cremophor RH40
Span 20 *
Span 80 *
辛基葡糖苷 *
SDS
CTAB
Pluronics
PVP
HPMC
聚合物
低聚物
非离子型
小分子
离子型

图 2B


Pluronic F127
样品
阳性对照
阴性对照
归一化的计数
速度(平均), um/s
图 3A
Pluronic F108
样品
阳性对照
阴性对照
归一化的计数
速度(平均), um/s
图 3B
Pluronic F87
样品
阳性对照
阴性对照
归一化的计数
速度(平均), um/s
图 3C
Kollidon 25
样品
阳性对照
阴性对照
归一化的计数
速度(平均), um/s
图 3D

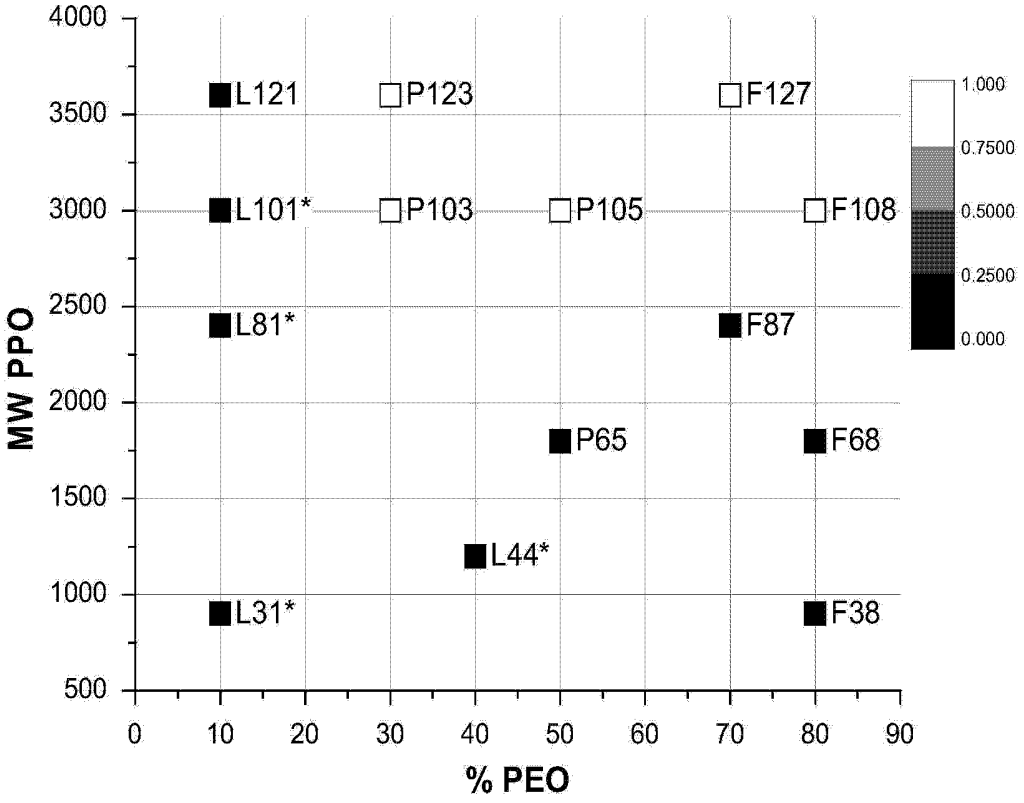

4000
3500
3000
2500
2000
1500
1000
500
MW PPO
0
10
20
30
40
50
60
70
80
90
% PEO
L121
P123
F127
L101*
P103
P105
F108
L81*
F87
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F68
L44*
L31*
F38
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0.000

图 4

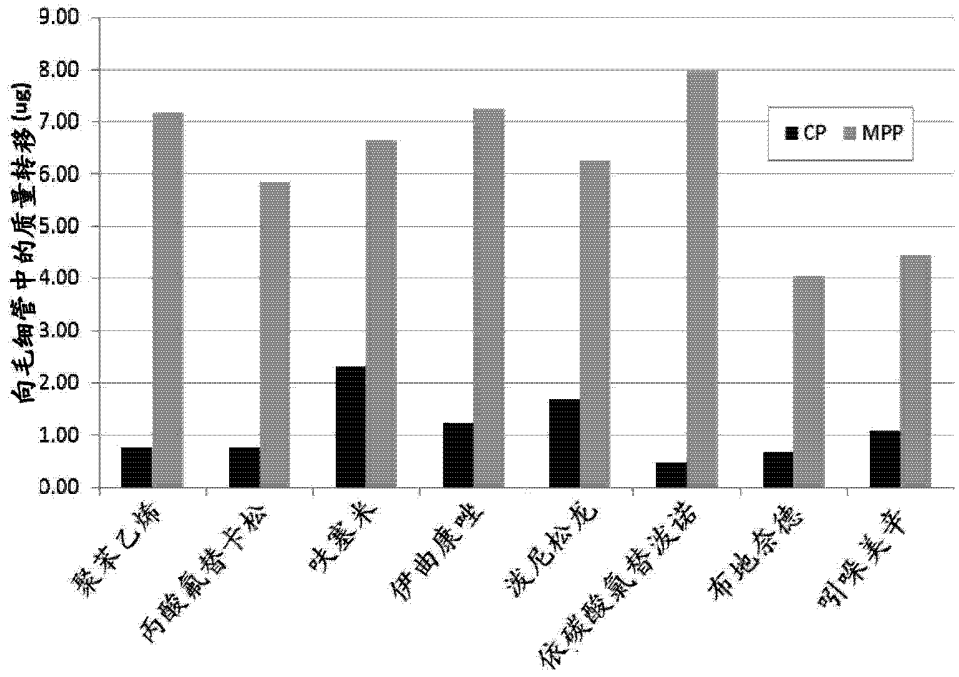

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CP
MPP
聚苯乙烯
丙酸氟替卡松
呋塞米
伊曲康唑
泼尼松龙
依碳酸氯替泼诺
布地奈德
吲哚美辛

图 5

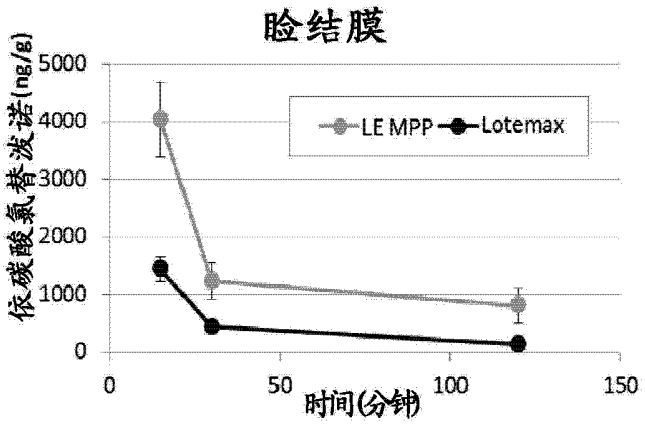

睑结膜
依碳酸氯替波诺(ng/g)
5000
4000
3000
2000
1000
0
0
50
100
150
时间(分钟)
LE MPP
Lotemax

图 6A

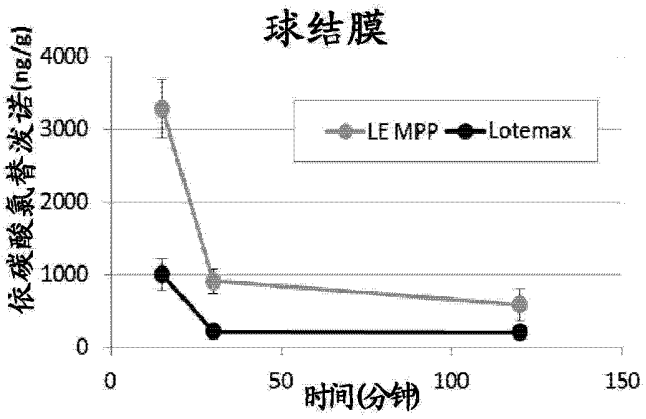

球结膜
依碳酸氯替波诺(ng/g)
4000
3000
2000
1000
0
0
50
100
150
时间(分钟)
LE MPP
Lotemax

图 6B

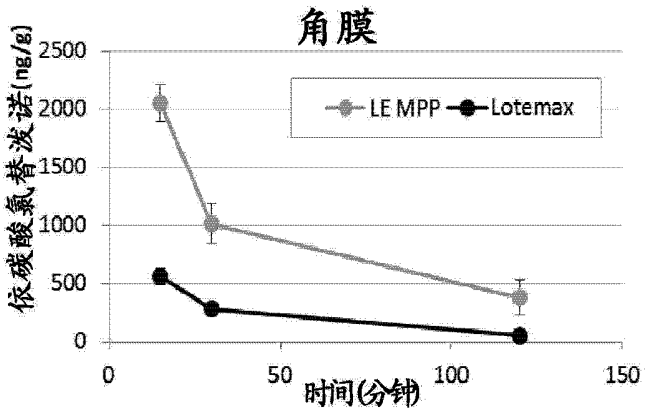

角膜
依碳酸氯替波诺(ng/g)
2500
2000
1500
1000
500
0
0
50
100
150
时间(分钟)
LE MPP
Lotemax

图 6C

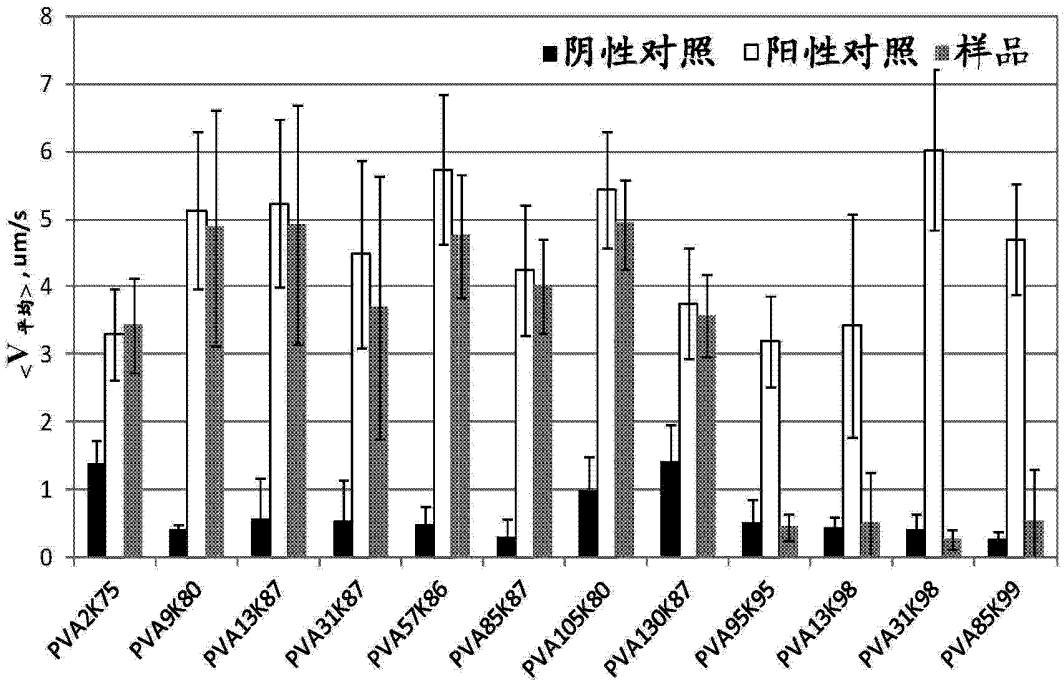

阴性对照
阳性对照
样品
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PVA31K87
PVA57K86
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PVA85K99

图 7A

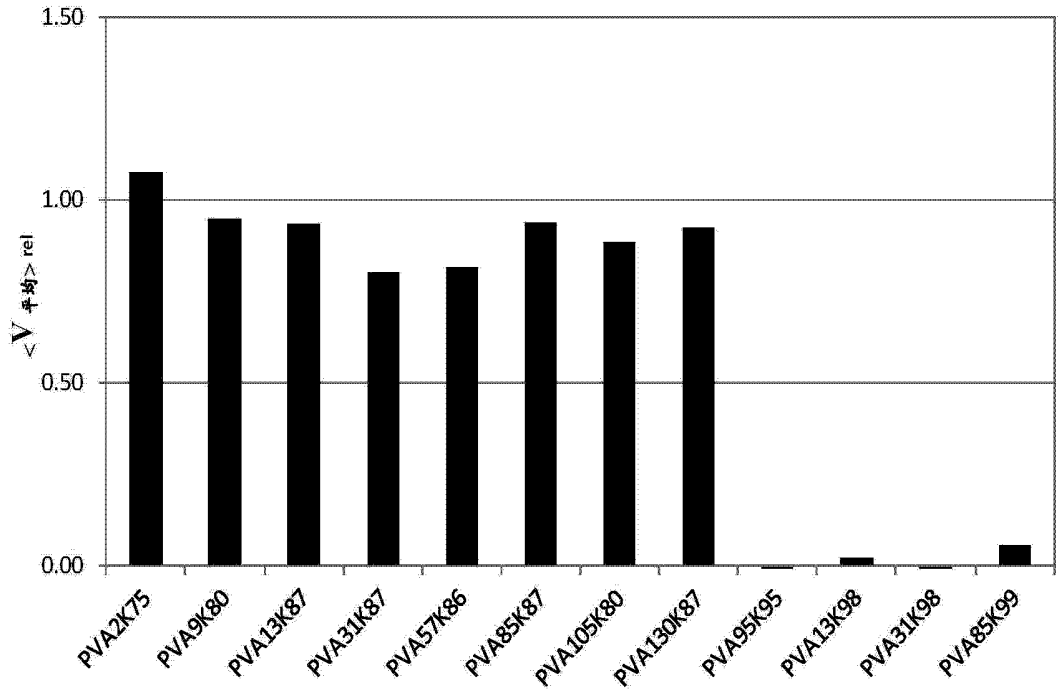

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PVA95K95
PVA13K98
PVA31K98
PVA85K99

图 7B

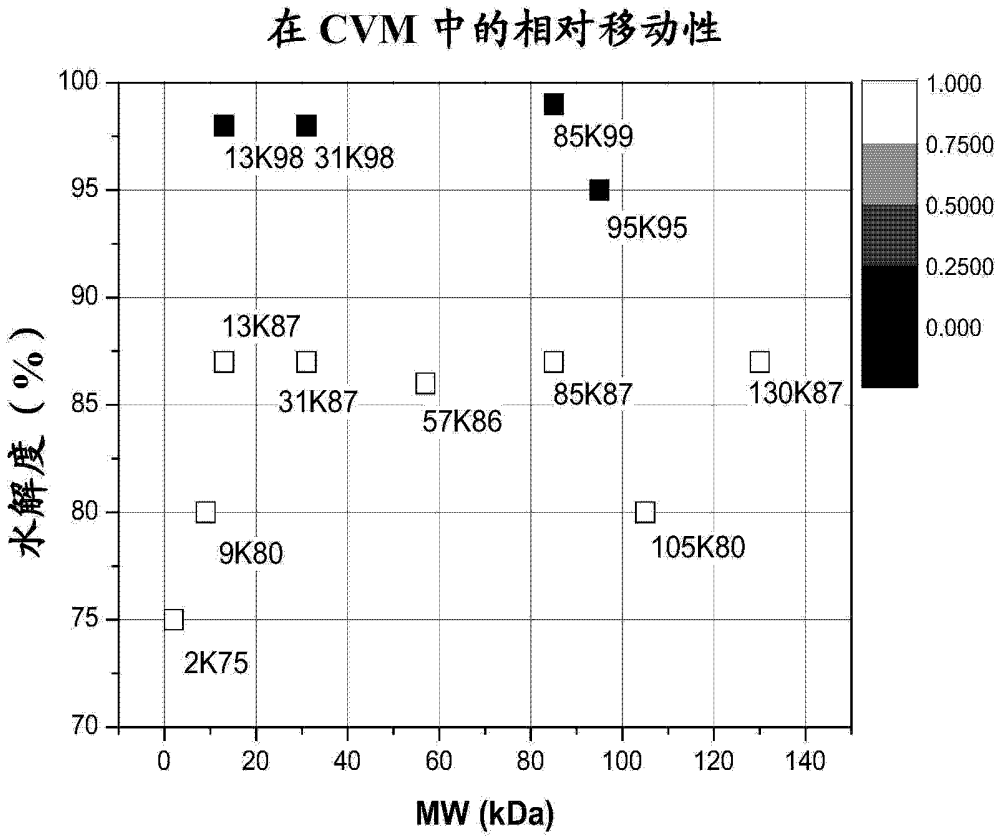

在 CVM 中的相对移动性
水解度（%）
MW (kDa)
13K98
31K98
85K99
95K95
13K87
31K87
57K86
85K87
130K87
9K80
105K80
2K75
1.000
0.7500
0.5000
0.2500
0.000

图 8

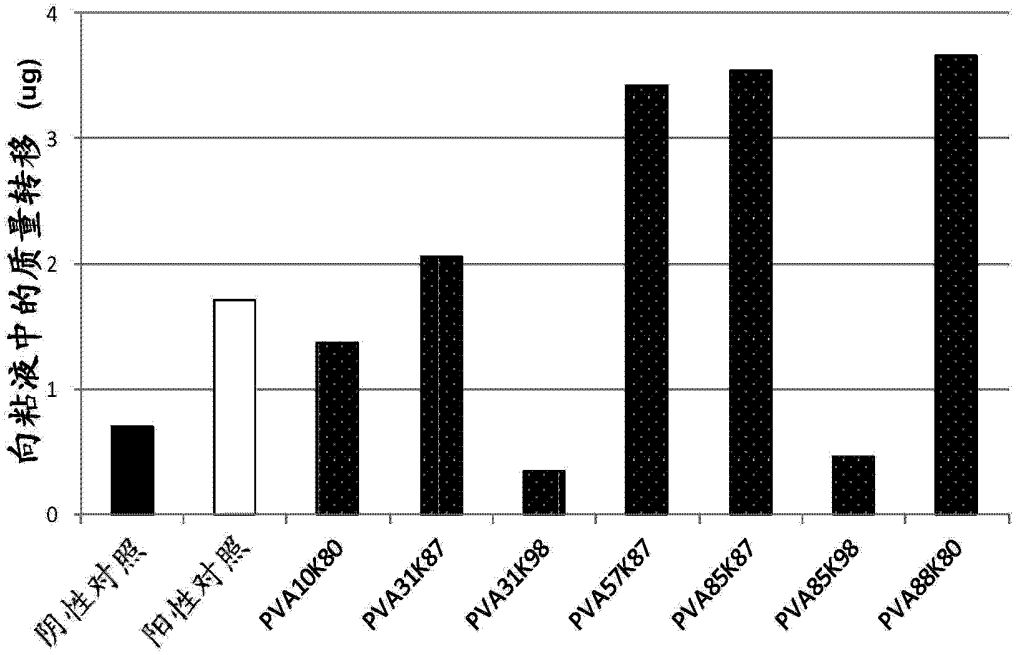

向粘液中的质量转移 (ug)
阴性对照
阳性对照
PVA10K80
PVA31K87
PVA31K98
PVA57K87
PVA85K87
PVA85K98
PVA88K80

图 9A

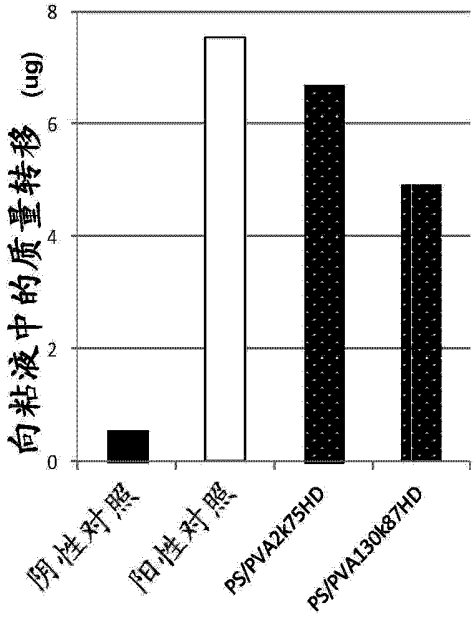

向粘液中的质量转移 (ug)
8
6
4
2
0
阴性对照
阳性对照
PS/PVA2K75HD
PS/PVA130k87HD

图 9B

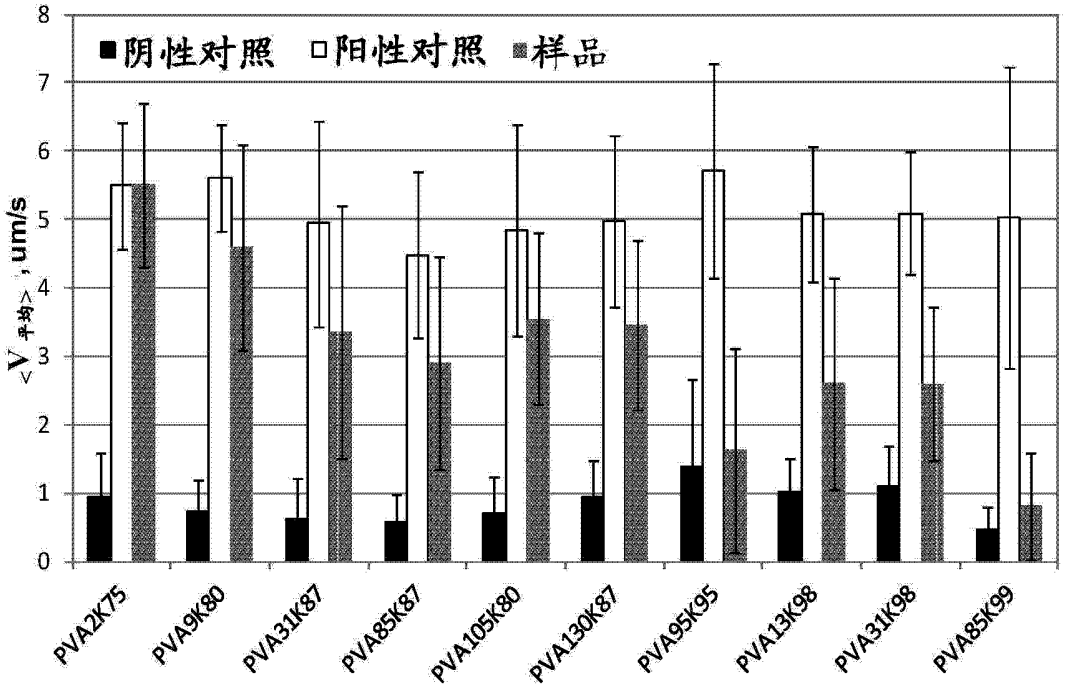

■阴性对照 □阳性对照 ■样品
<V平均>, um/s
8
7
6
5
4
3
2
1
0
PVA2K75
PVA9K80
PVA31K87
PVA85K87
PVA105K80
PVA130K87
PVA95K95
PVA13K98
PVA31K98
PVA85K99

图 10A

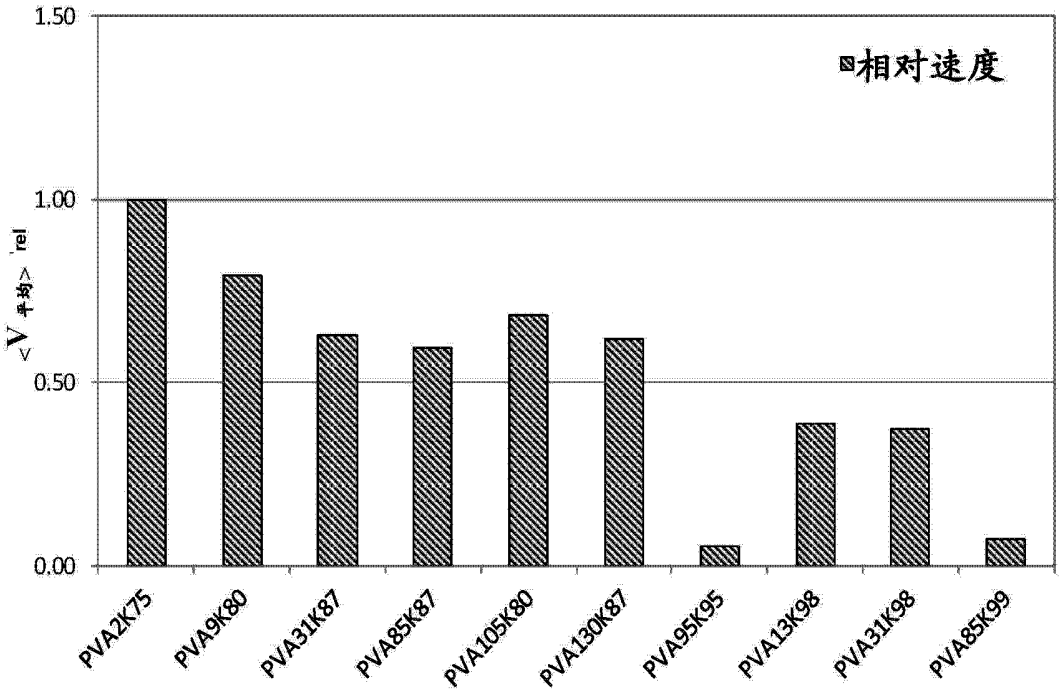

1.50
1.00
0.50
0.00
相对速度
PVA2K75
PVA9K80
PVA31K87
PVA85K87
PVA105K80
PVA130K87
PVA95K95
PVA13K98
PVA31K98
PVA85K99

图 10B

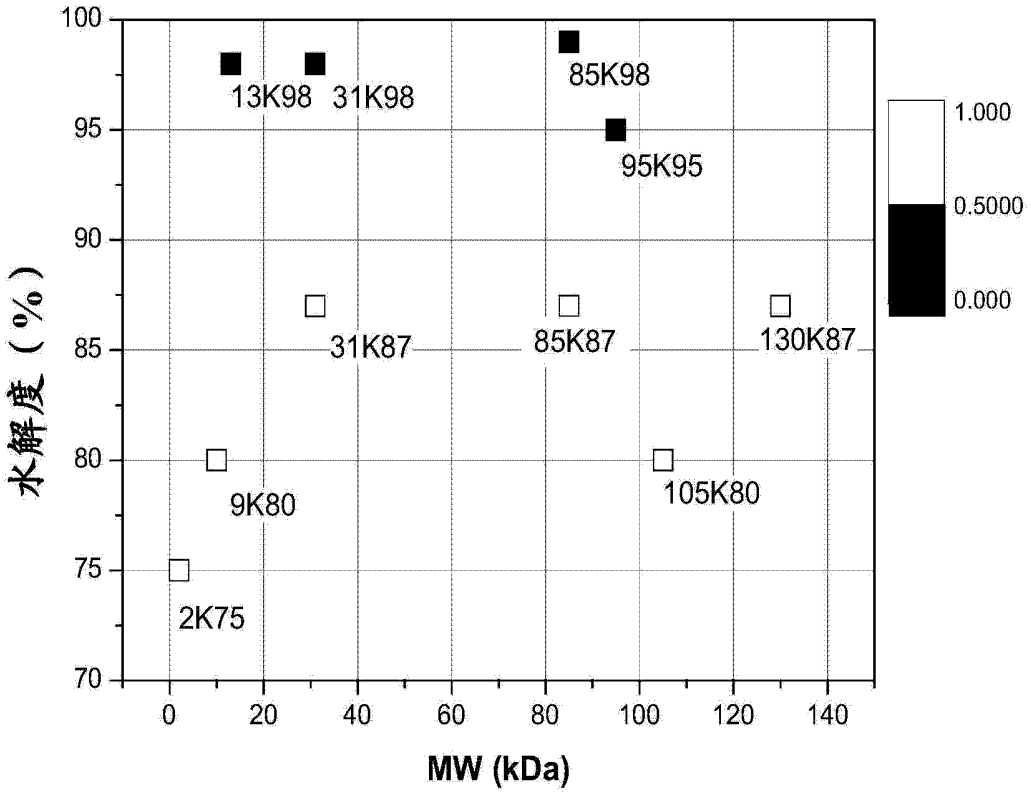

100
95
90
85
80
75
70
0
20
40
60
80
100
120
140
水解度（%）
MW (kDa)
13K98
31K98
85K98
95K95
31K87
85K87
130K87
9K80
105K80
2K75
1.000
0.5000
0.000

图 11

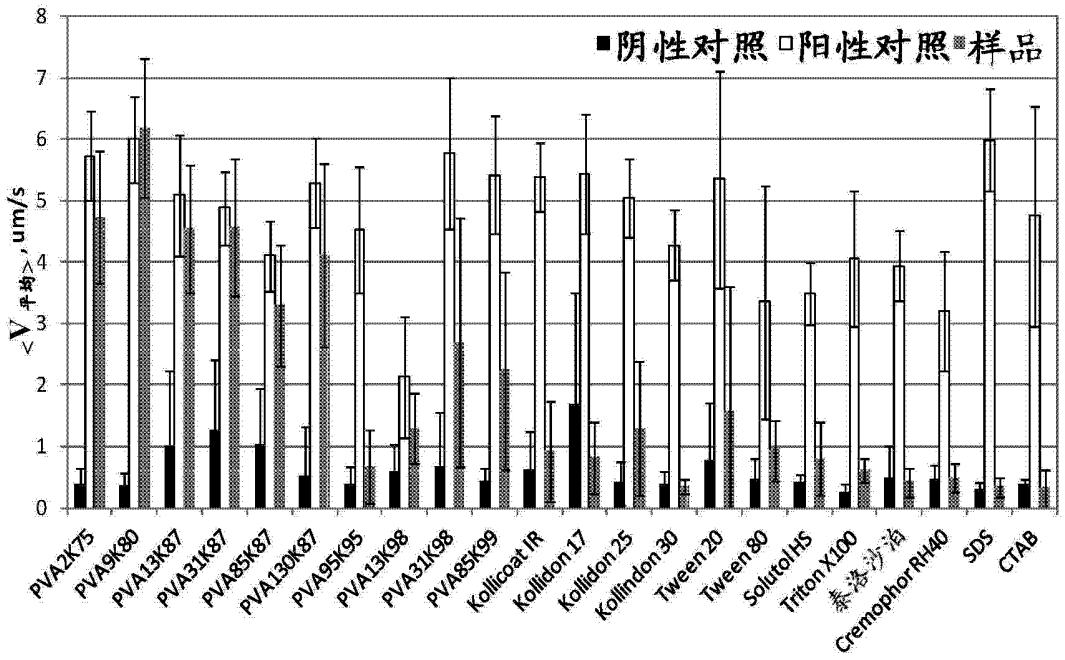

■阴性对照 □阳性对照 ▪样品
<V平均>, um/s
0
1
2
3
4
5
6
7
8
PVA2K75
PVA9K80
PVA13K87
PVA31K87
PVA85K87
PVA130K87
PVA95K95
PVA13K98
PVA31K98
PVA85K99
Kollicoat IR
Kollidon 17
Kollidon 25
Kollindon 30
Tween 20
Tween 80
Solutol HS
Triton X100
泰洛沙泊
Cremophor RH40
SDS
CTAB

图 12A

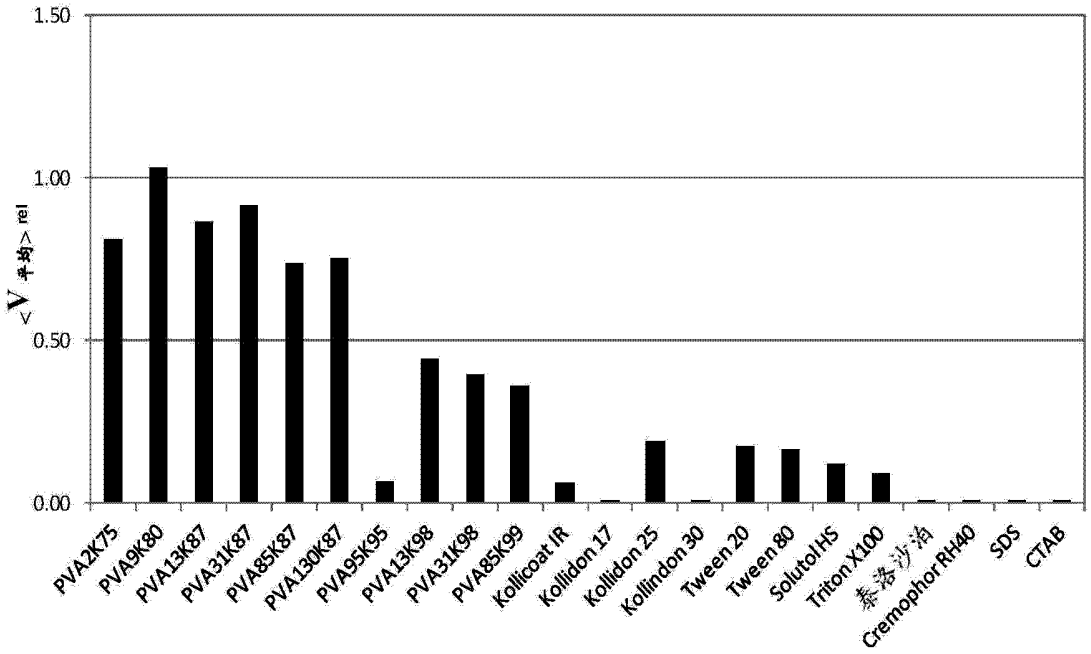
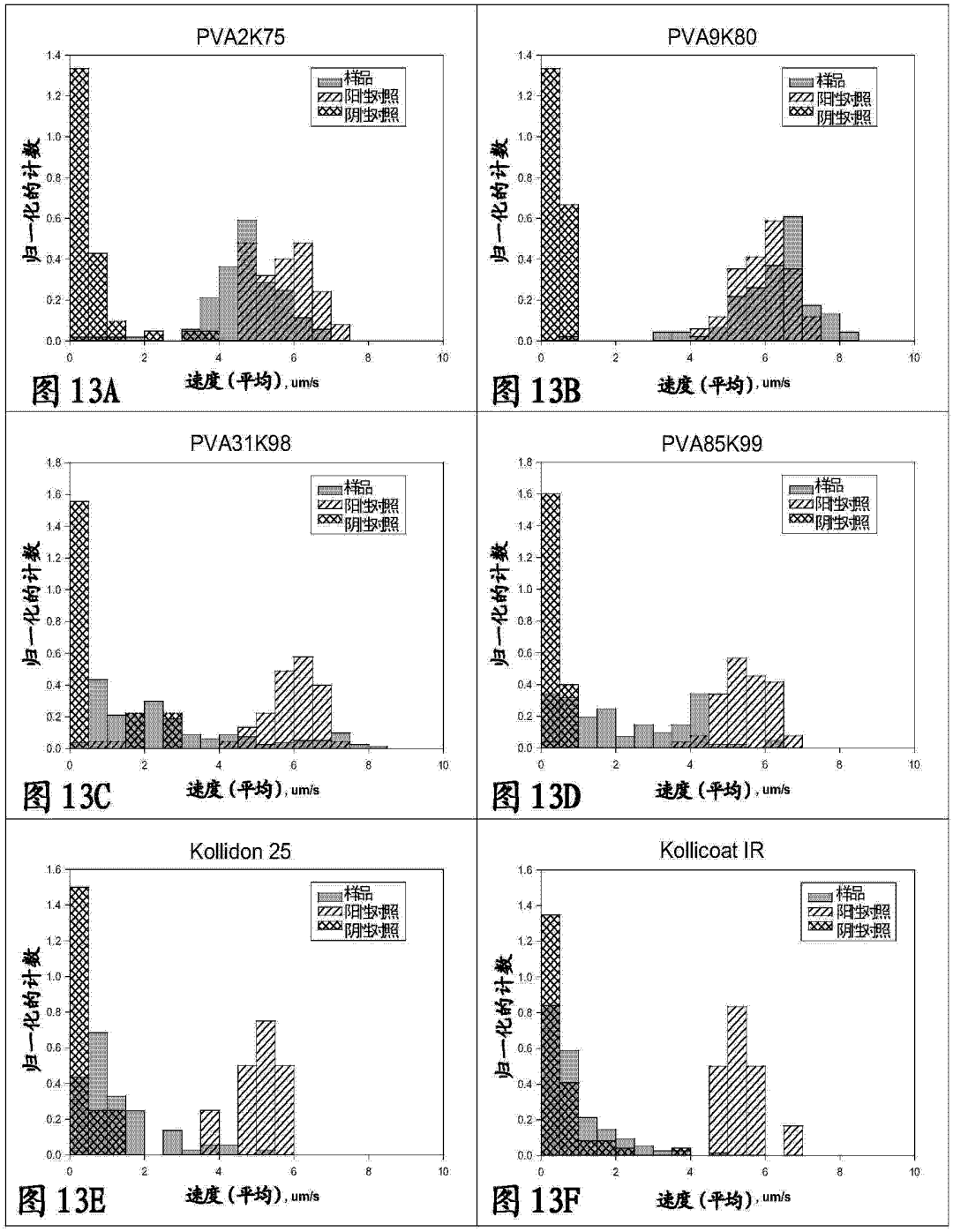

<V平均> rel
0.00
0.50
1.00
1.50
PVA2K75
PVA9K80
PVA13K87
PVA31K87
PVA85K87
PVA130K87
PVA95K95
PVA13K98
PVA31K98
PVA85K99
Kollicoat IR
Kollidon 17
Kollidon 25
Kollindon 30
Tween 20
Tween 80
Solutol HS
Triton X100
泰洛沙泊
Cremophor RH40
SDS
CTAB

图 12B


PVA2K75
样品
阳性对照
阴性对照
归一化的计数
速度(平均), um/s
图 13A
PVA9K80
样品
阳性对照
阴性对照
归一化的计数
速度(平均), um/s
图 13B
PVA31K98
样品
阳性对照
阴性对照
归一化的计数
速度(平均), um/s
图 13C
PVA85K99
样品
阳性对照
阴性对照
归一化的计数
速度(平均), um/s
图 13D
Kollidon 25
样品
阳性对照
阴性对照
归一化的计数
速度(平均), um/s
图 13E
Kollicoat IR
样品
阳性对照
阴性对照
归一化的计数
速度(平均), um/s
图 13F

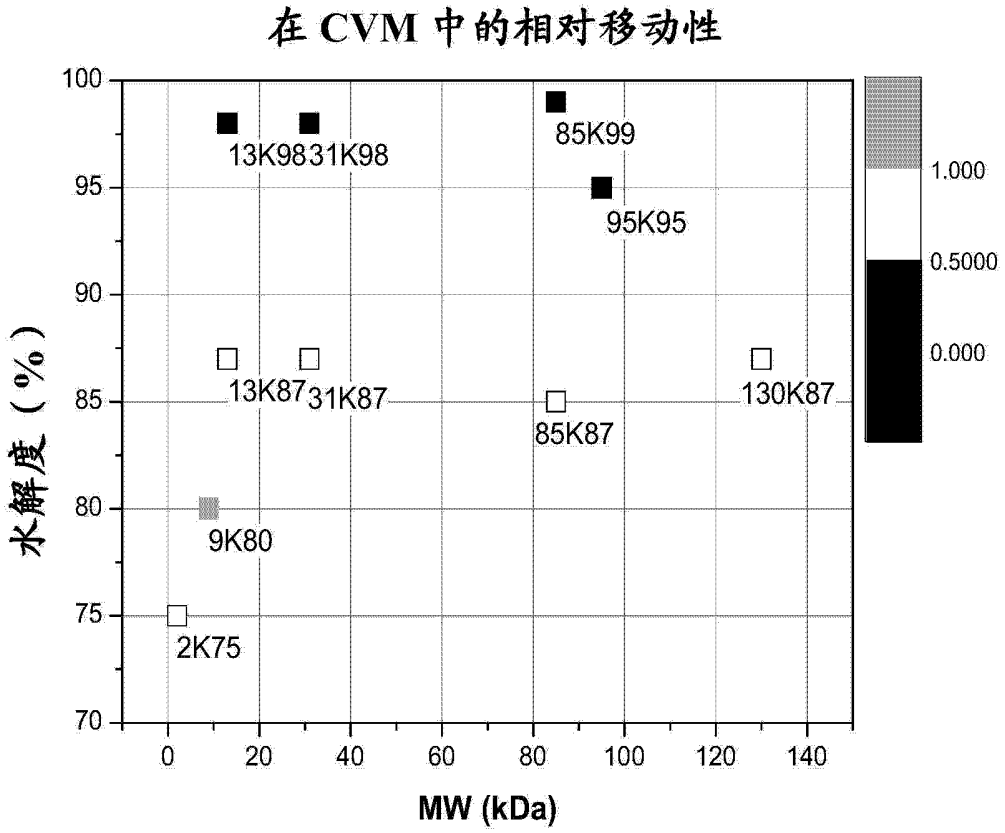

在 CVM 中的相对移动性
水解度（%）
MW (kDa)
13K98
31K98
85K99
95K95
13K87
31K87
85K87
130K87
9K80
2K75
1.000
0.5000
0.000
100
95
90
85
80
75
70
0
20
40
60
80
100
120
140

图 14

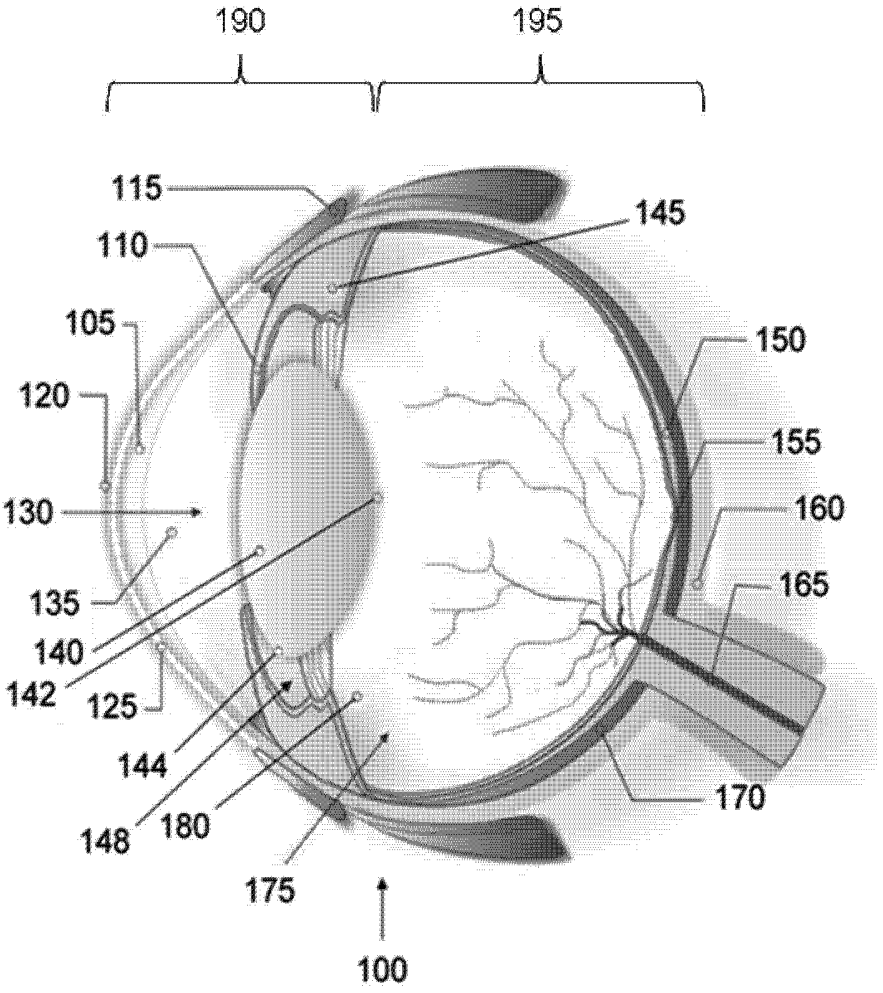

190
195
115
110
105
120
130
135
140
142
125
144
148
180
175
100
145
150
155
160
165
170

图 15A

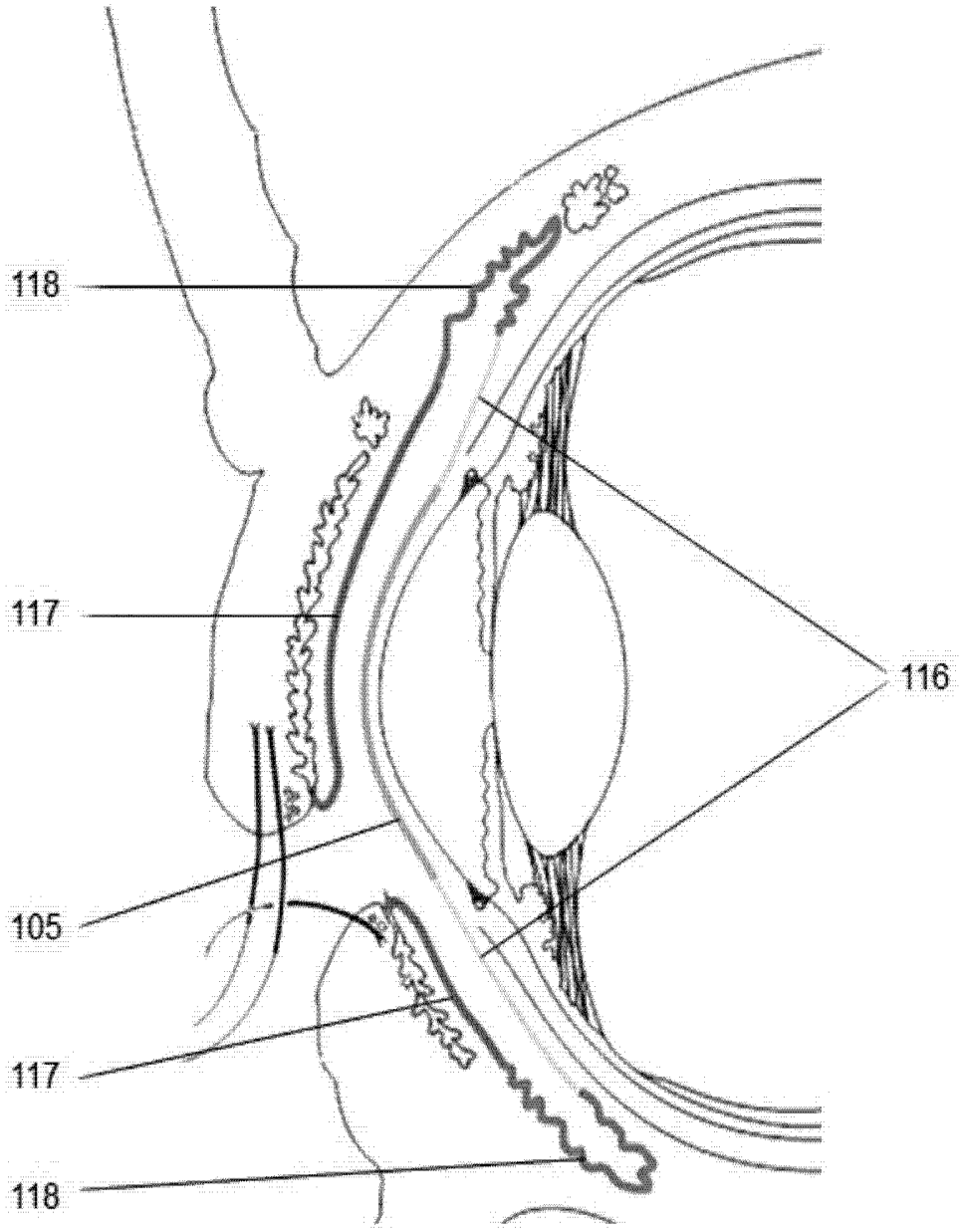


图 15B

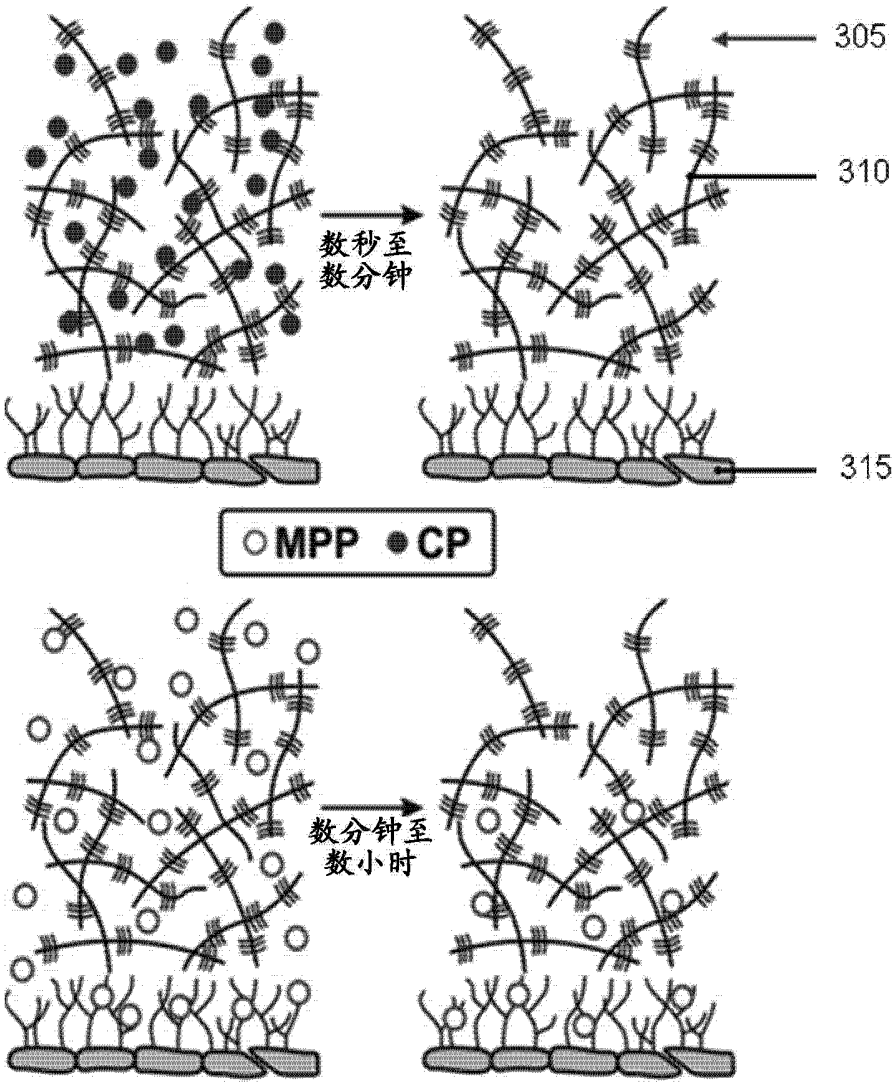


图 15C

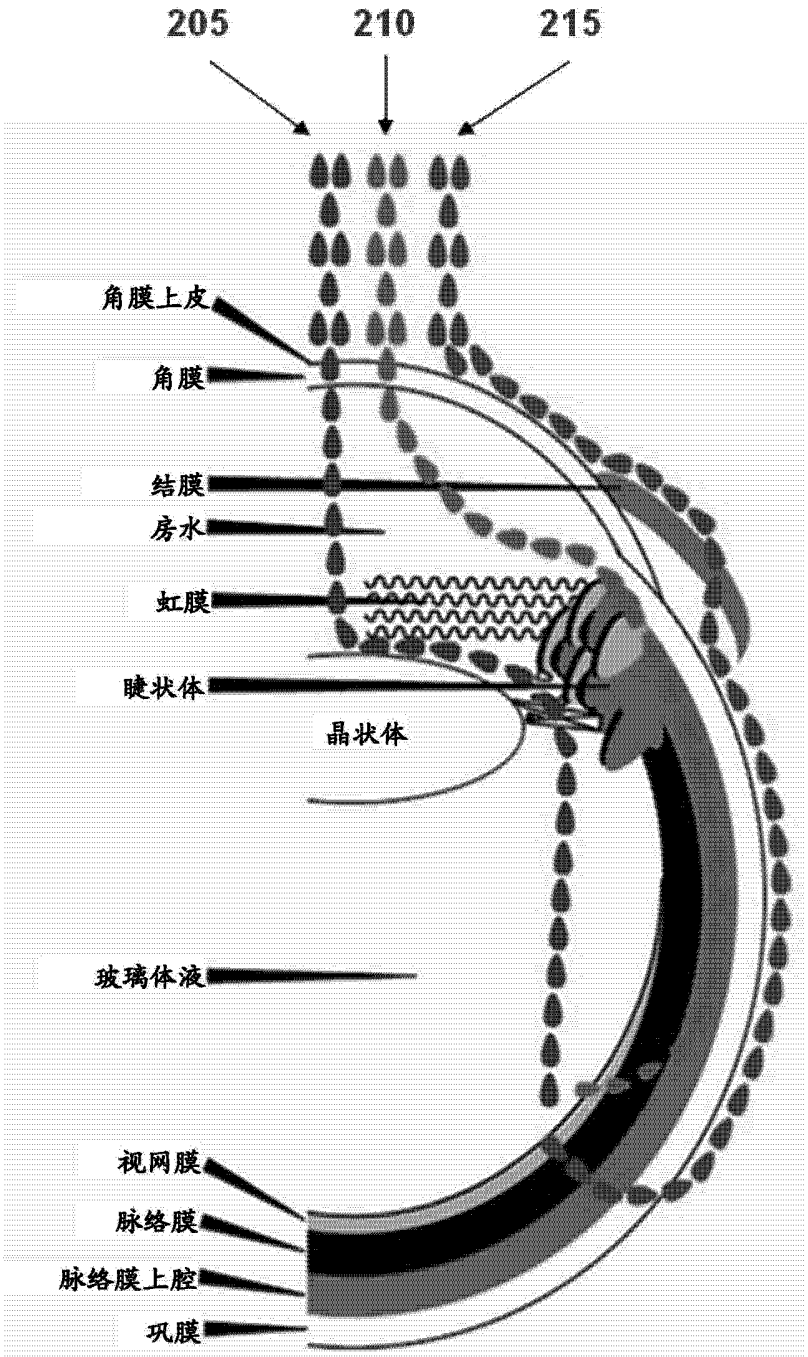


图 16

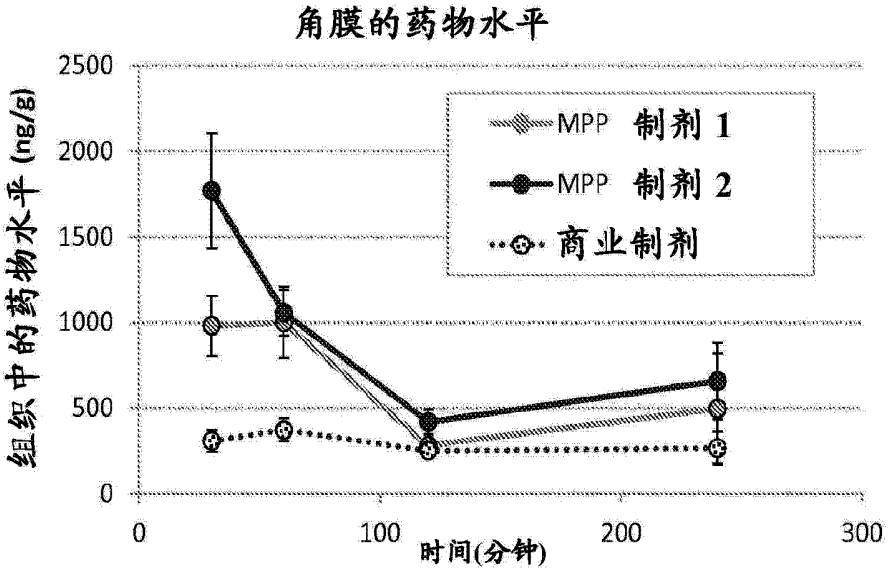

角膜的药物水平
组织中的药物水平 (ng/g)
2500
2000
1500
1000
500
0
0
100
200
300
时间(分钟)
MPP 制剂 1
MPP 制剂 2
商业制剂

图 17A

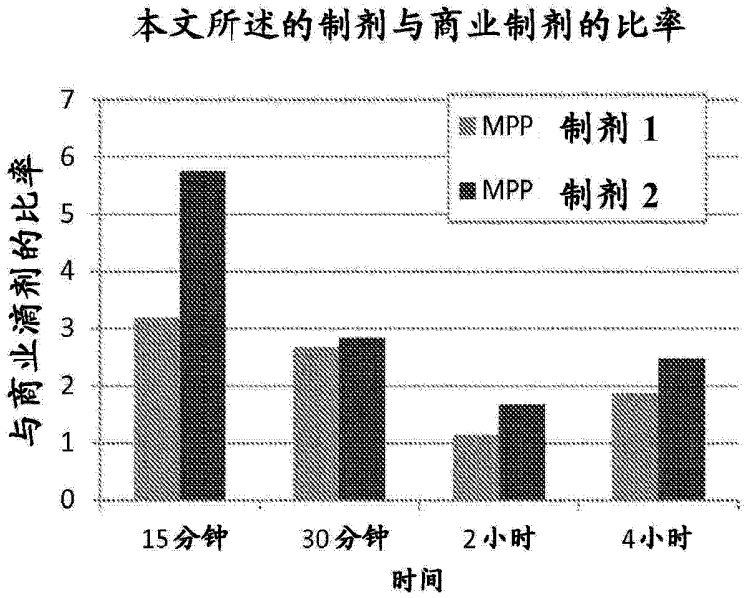

本文所述的制剂与商业制剂的比率
与商业滴剂的比率
7
6
5
4
3
2
1
0
15分钟
30分钟
2小时
4小时
时间
MPP 制剂 1
MPP 制剂 2

图 17B

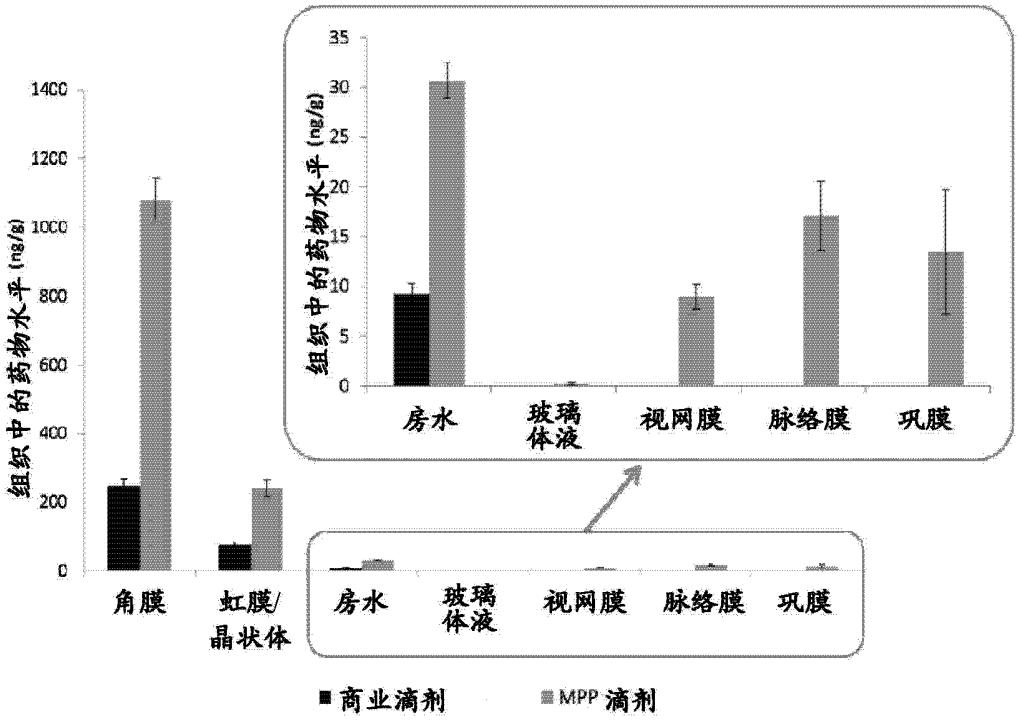

组织中的药物水平 (ng/g)
1400
1200
1000
800
600
400
200
0
角膜
虹膜/晶状体
房水
玻璃体液
视网膜
脉络膜
巩膜
35
30
25
20
15
10
5
0
房水
玻璃体液
视网膜
脉络膜
巩膜
商业滴剂
MPP 滴剂

图 18

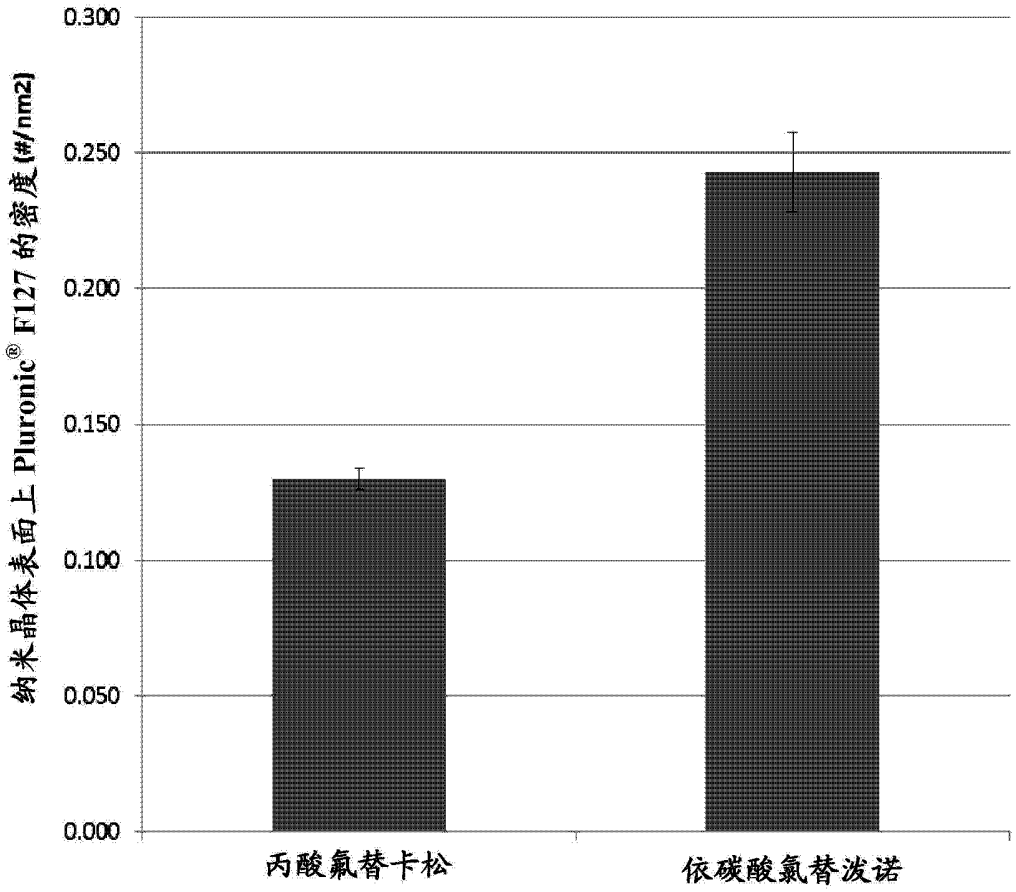

0.300
0.250
0.200
0.150
0.100
0.050
0.000
纳米晶体表面上 Pluronic® F127 的密度(#/nm2)
丙酸氟替卡松
依碳酸氯替泼诺

图 19

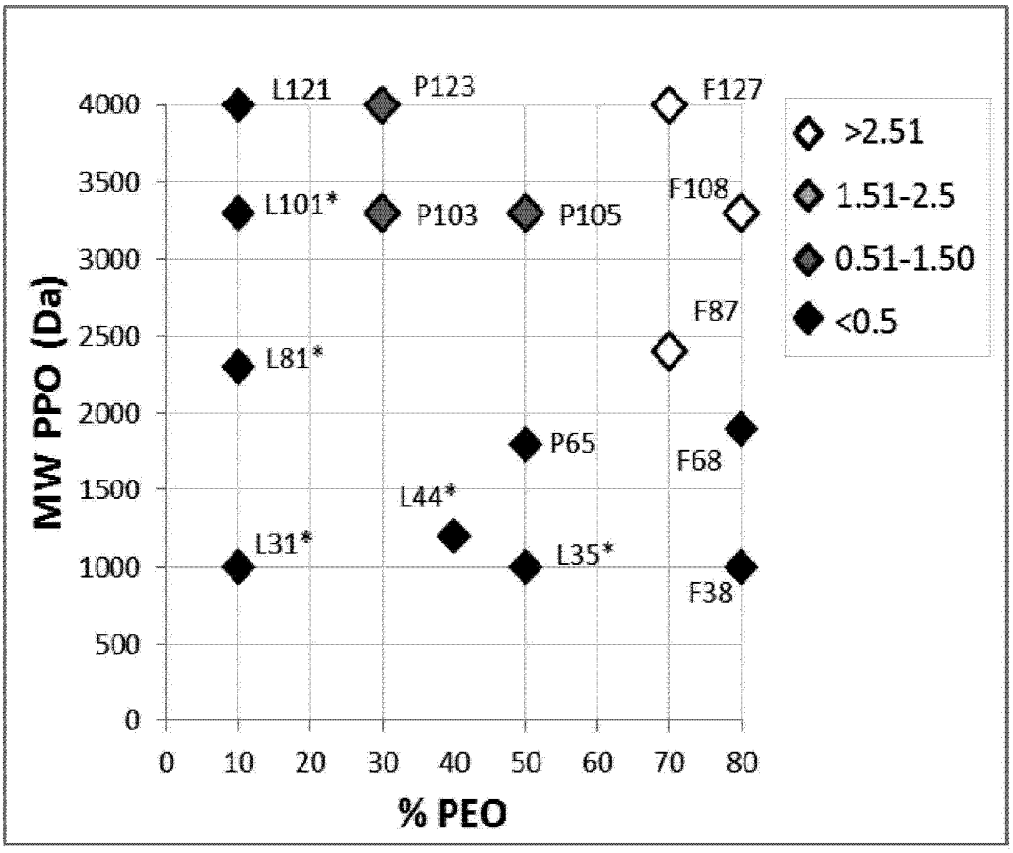

MW PPO (Da)
% PEO
0
500
1000
1500
2000
2500
3000
3500
4000
0
10
20
30
40
50
60
70
80
L121
P123
F127
L101*
P103
P105
F108
F87
L81*
P65
F68
L44*
L31*
L35*
F38
>2.51
1.51-2.5
0.51-1.50
<0.5

图 20

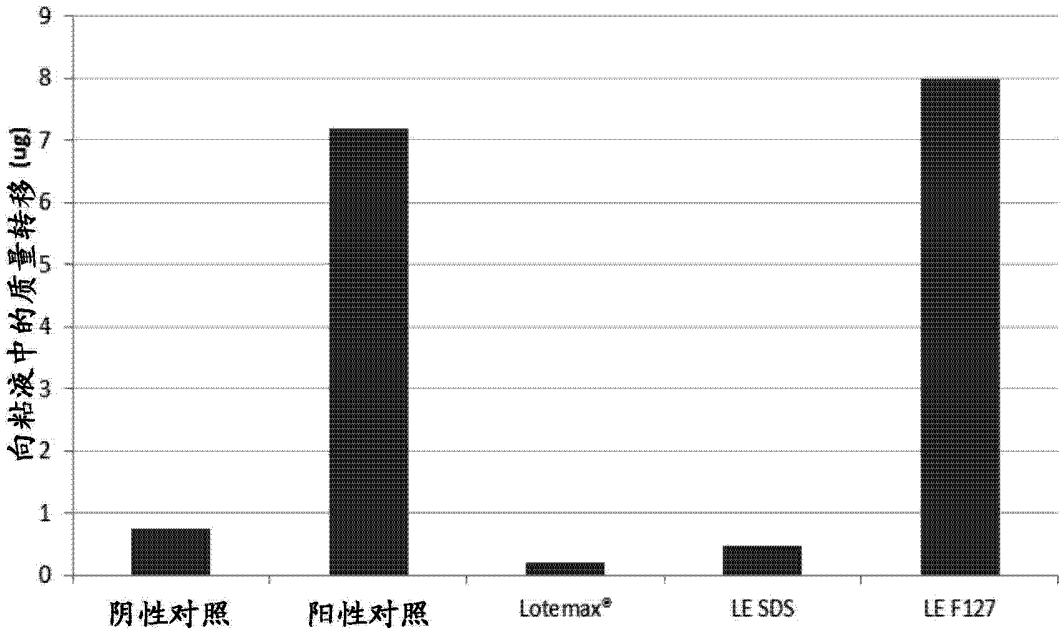
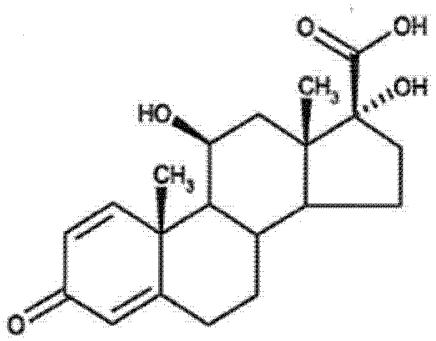
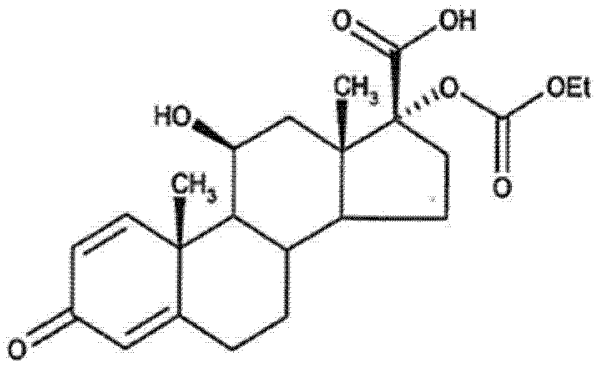

向粘液中的质量转移 (ug)
0
1
2
3
4
5
6
7
8
9
阴性对照
阳性对照
Lotemax®
LE SDS
LE F127

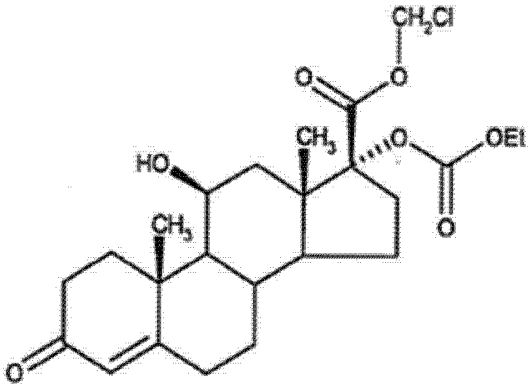
图 21



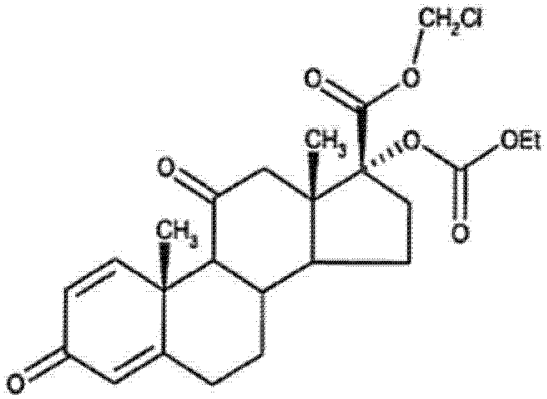
PJ90



PJ91



17α-[(乙氧羰基)氧基]-11β-羟基-3-氧代雄甾-4-烯-17-甲酸氯甲酯（tetradeca）



17α-[(乙氧羰基)氧基]-3,11-二氧代雄甾-1,4-二烯-17-甲酸氯甲酯(11-keto)

图 22

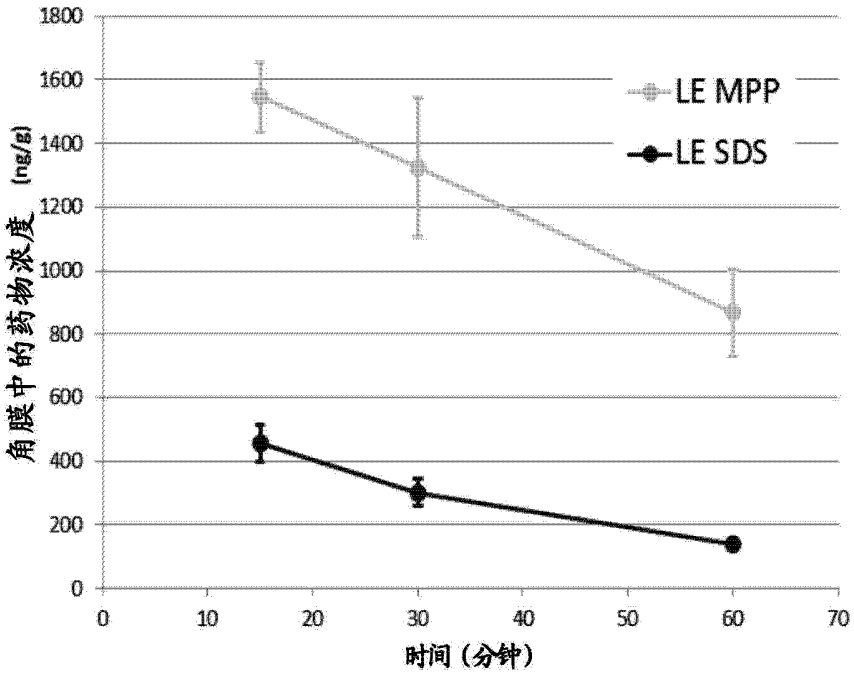

1800
1600
1400
1200
1000
800
600
400
200
0
角膜中的药物浓度 (ng/g)
LE MPP
LE SDS
0
10
20
30
40
50
60
70
时间（分钟）

图 23A

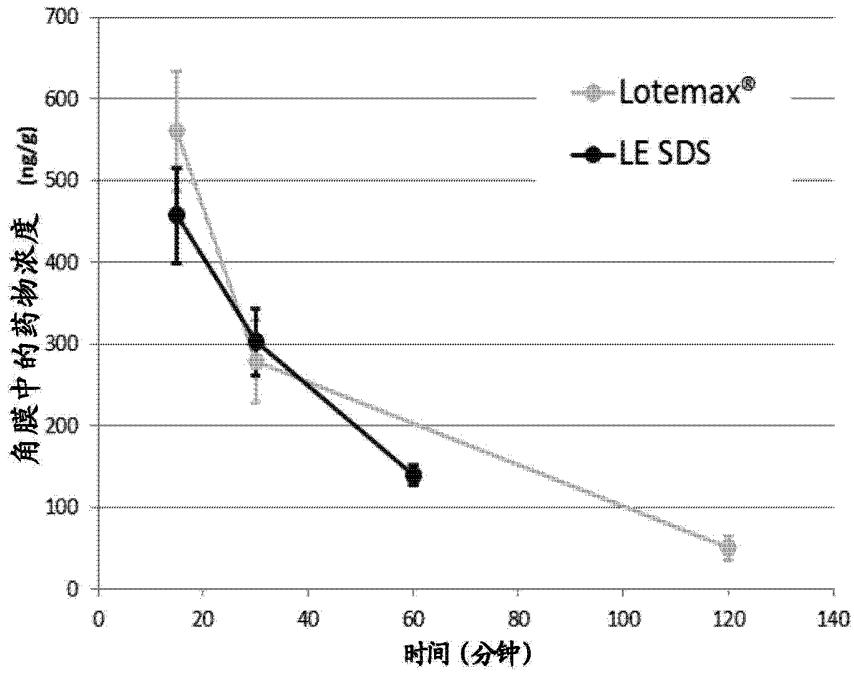

700
600
500
400
300
200
100
0
角膜中的药物浓度 (ng/g)
Lotemax®
LE SDS
0
20
40
60
80
100
120
140
时间（分钟）

图 23B

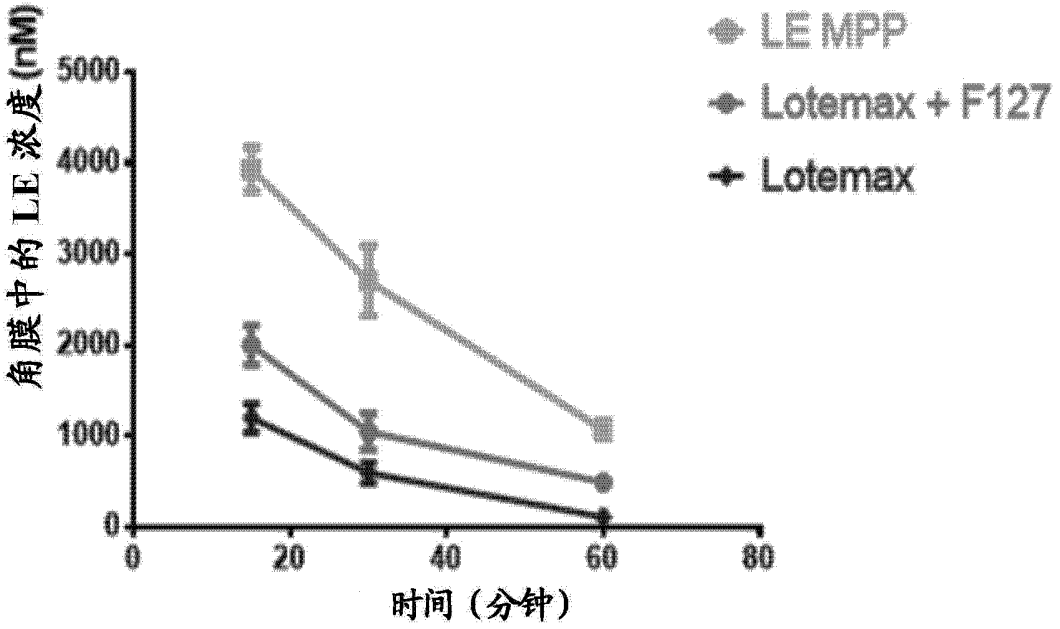

LE MPP
Lotemax + F127
Lotemax
角膜中的 LE 浓度 (nM)
5000
4000
3000
2000
1000
0
0
20
40
60
80
时间（分钟）

图 24

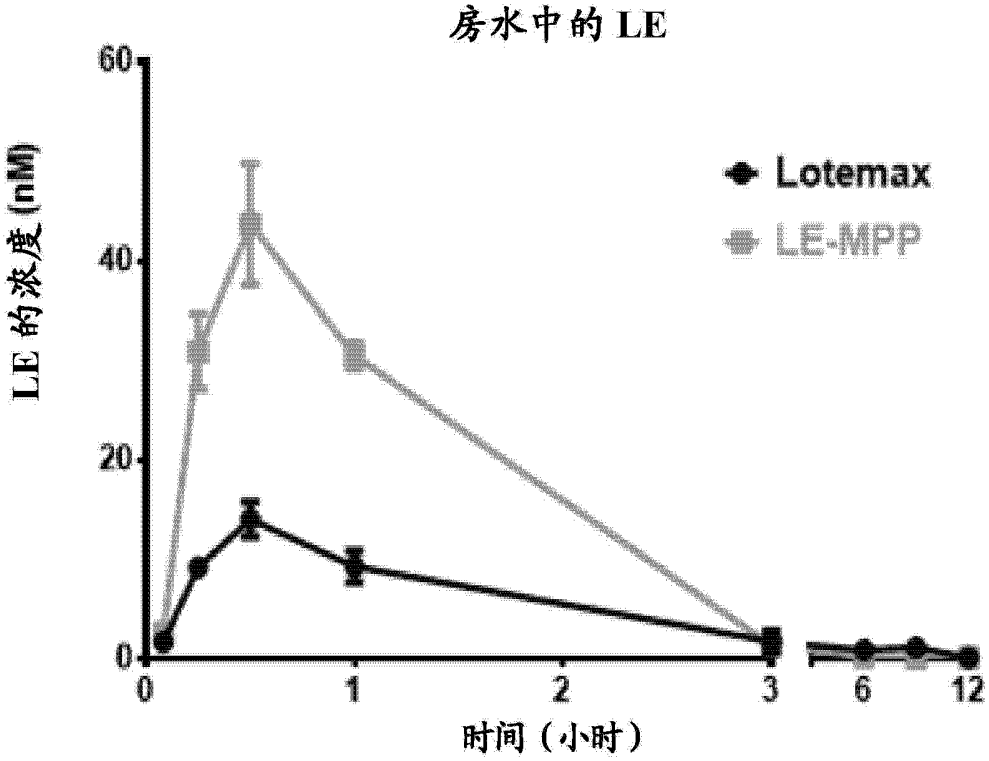

房水中的 LE
Lotemax
LE-MPP
LE 的浓度 (nM)
60
40
20
0
0
1
2
3
6
12
时间（小时）

图 25

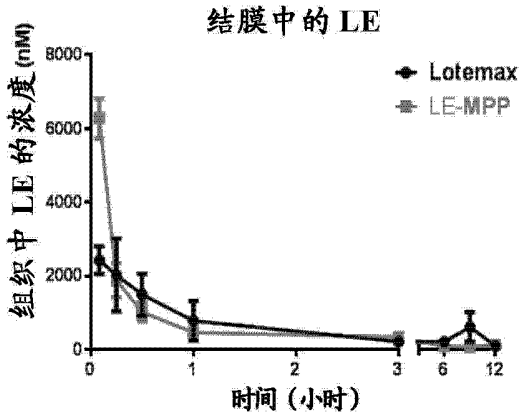


图 26A

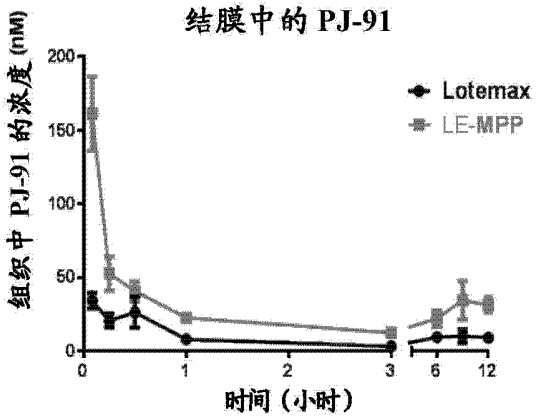


图 26B

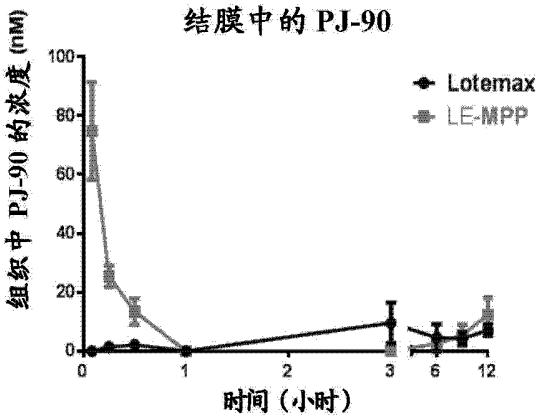


图 26C

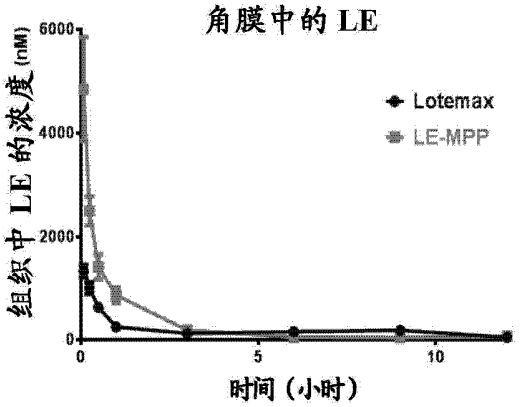


图 26D

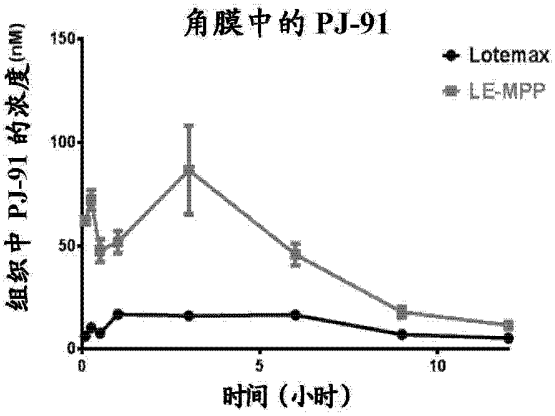


图 26E

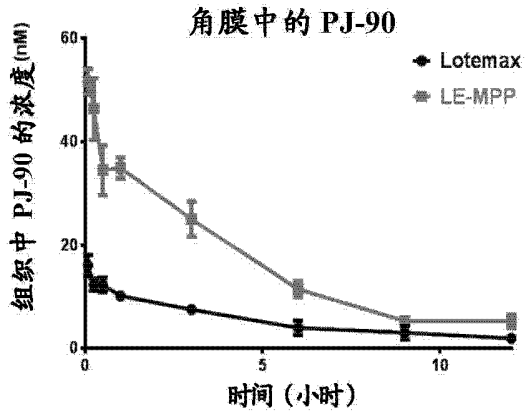


图 26F

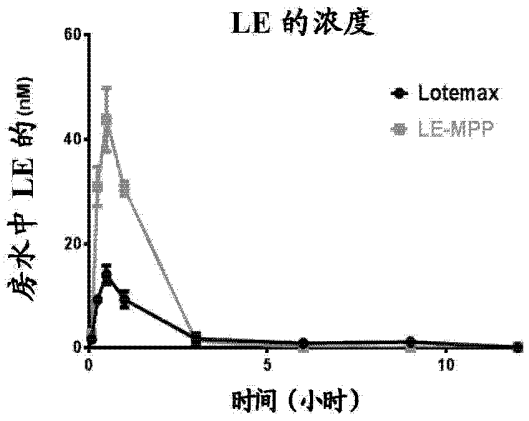


图 26G

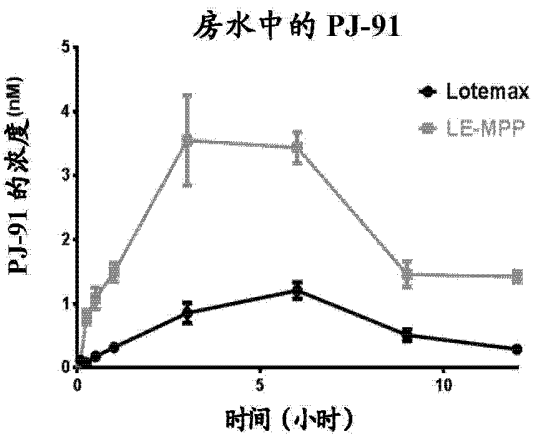


图 26H

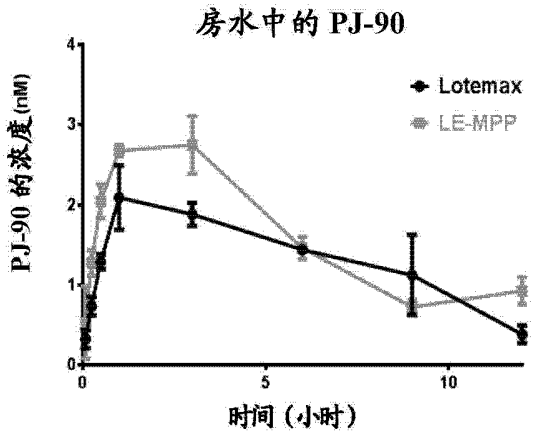


图 26I

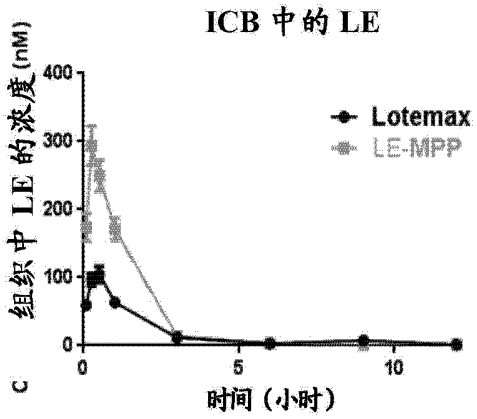


图 26J

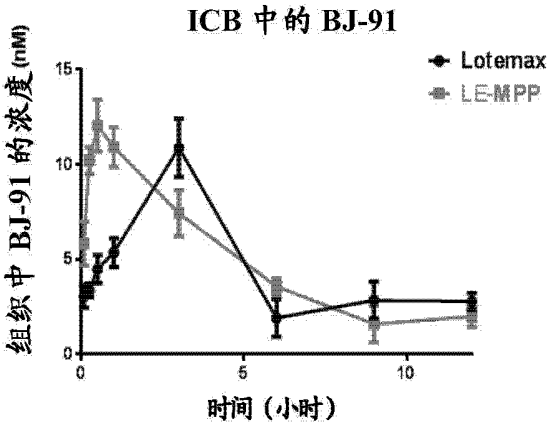


图 26K

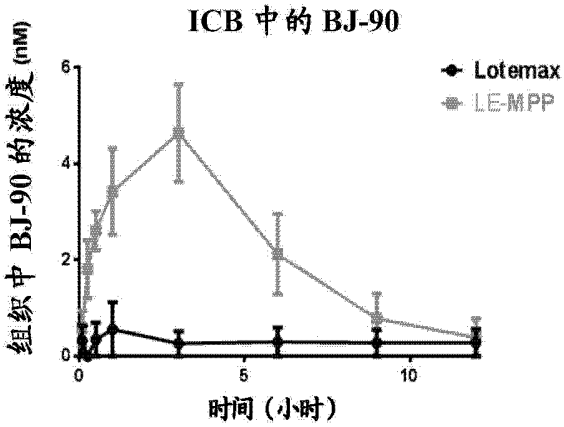


图 26L

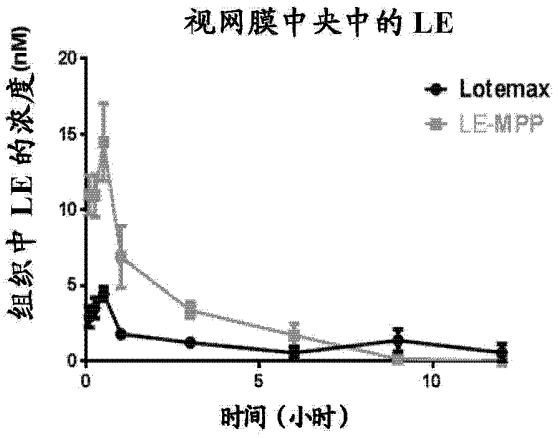


图 26M

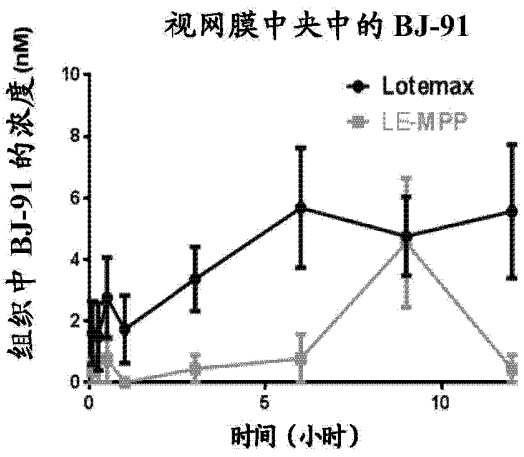


图 26N

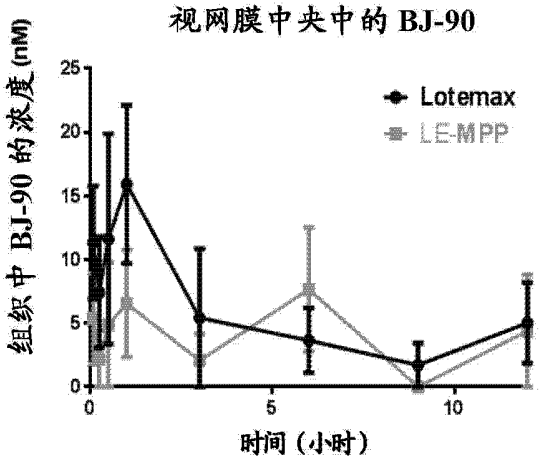


图 26O

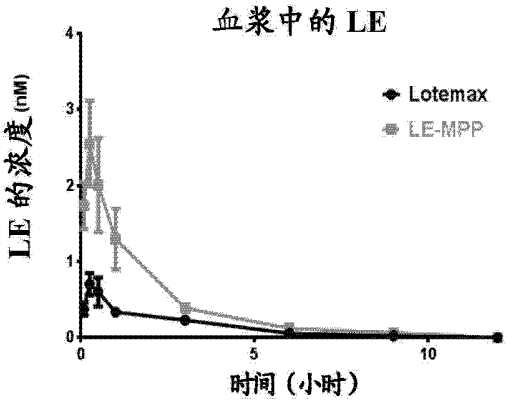


图 26P

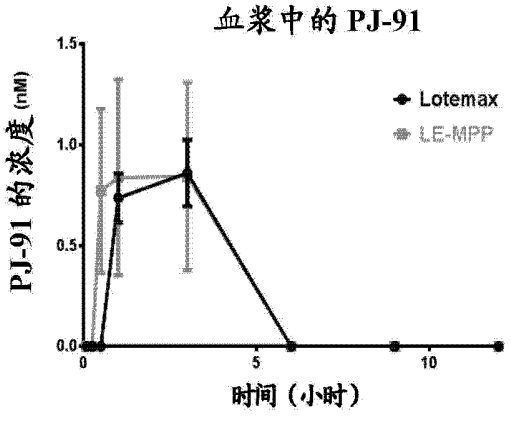


图 26Q

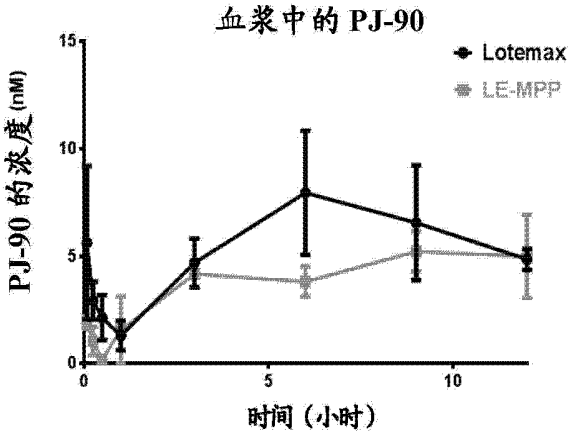


图 26R

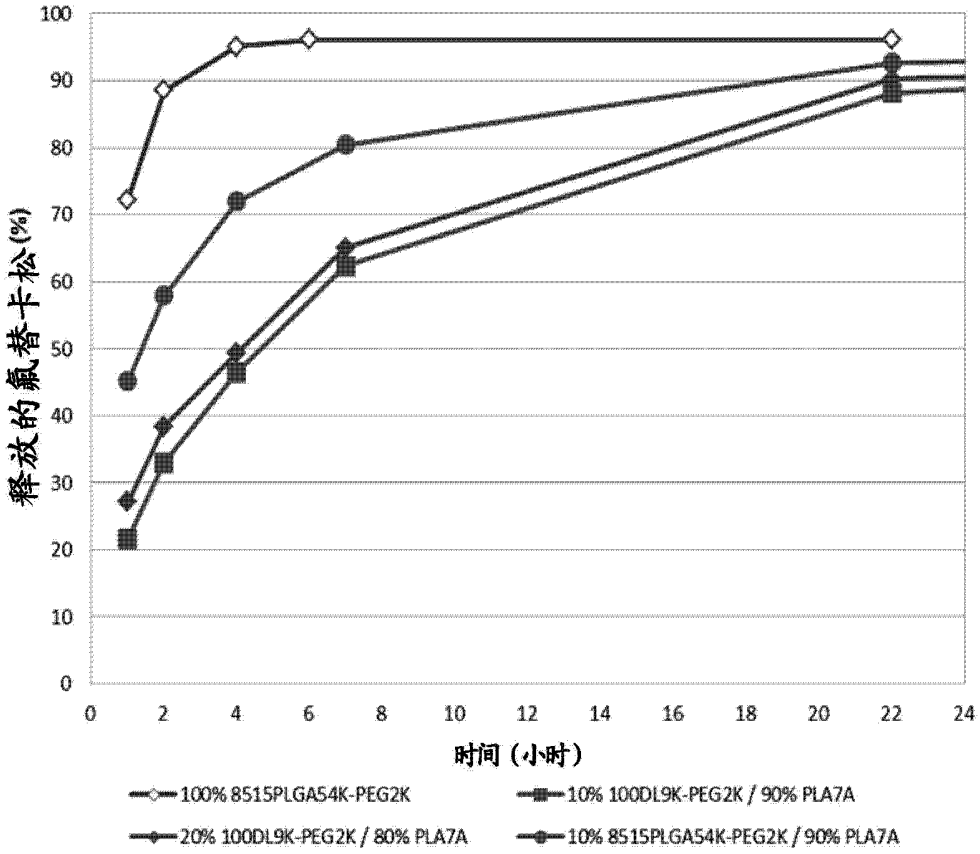


图 27

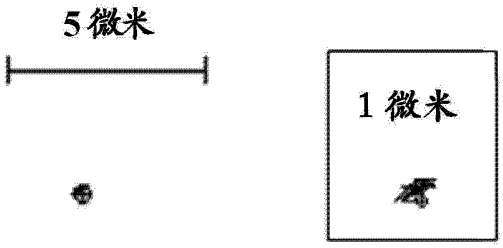


图 28A



图 28B

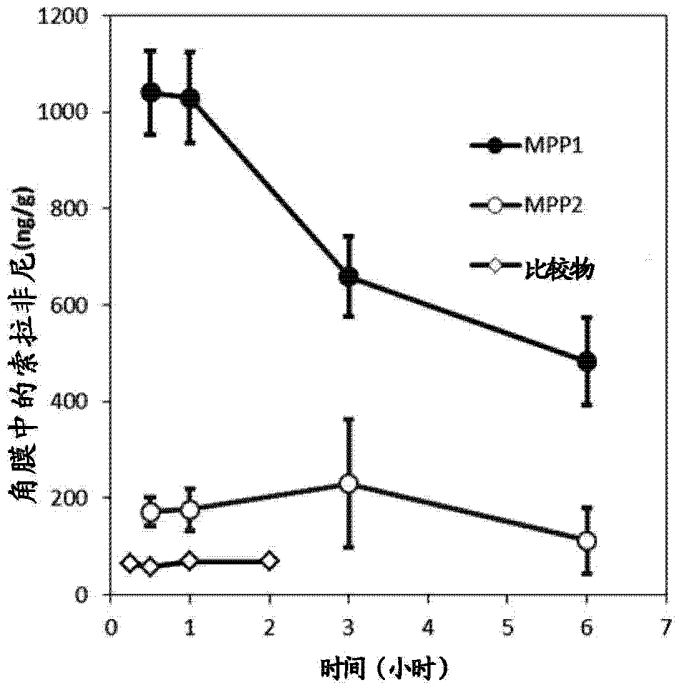

1200
1000
800
600
400
200
0
角膜中的索拉非尼(ng/g)
0
1
2
3
4
5
6
7
时间（小时）
MPP1
MPP2
比较物

图 29A

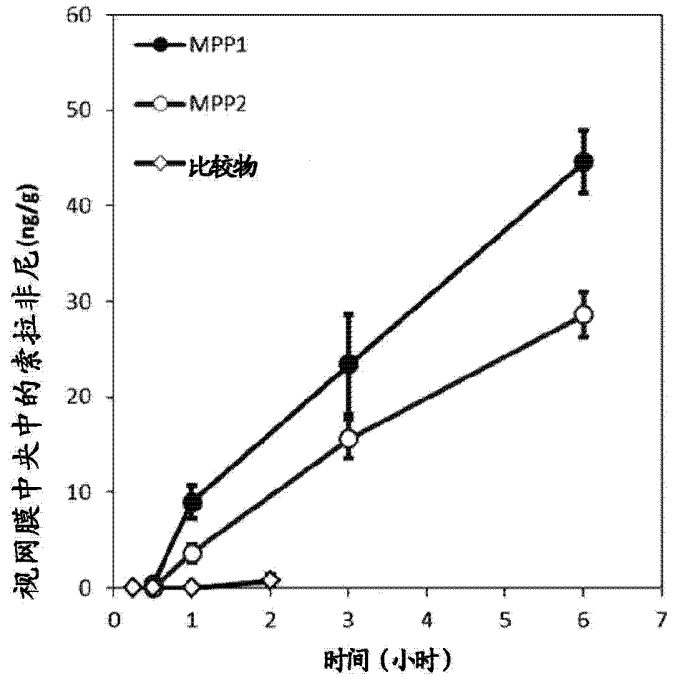

60
50
40
30
20
10
0
视网膜中央中的索拉非尼(ng/g)
0
1
2
3
4
5
6
7
时间（小时）
MPP1
MPP2
比较物

图 29B

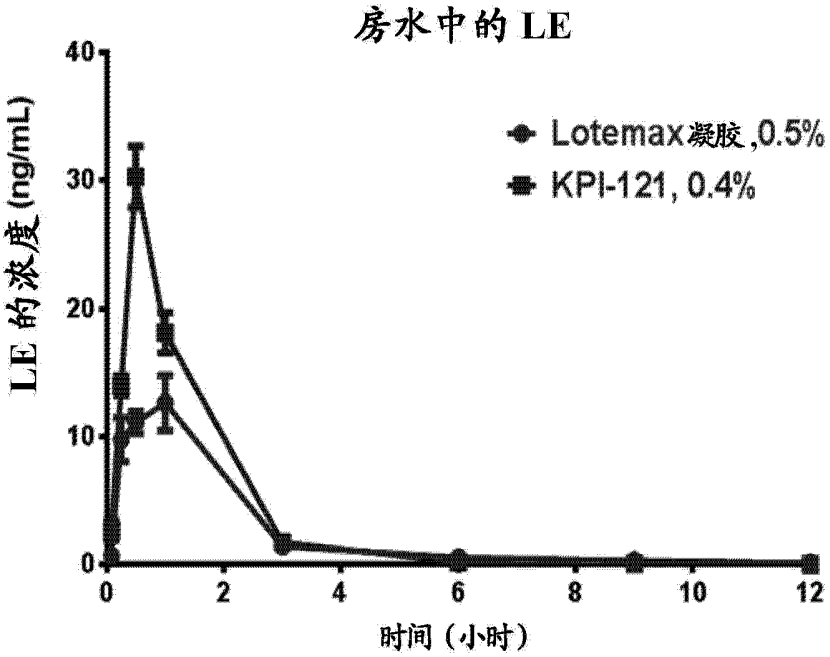

房水中的 LE
LE 的浓度 (ng/mL)
40
30
20
10
0
0
2
4
6
8
10
12
时间（小时）
Lotemax凝胶,0.5%
KPI-121, 0.4%

图 30

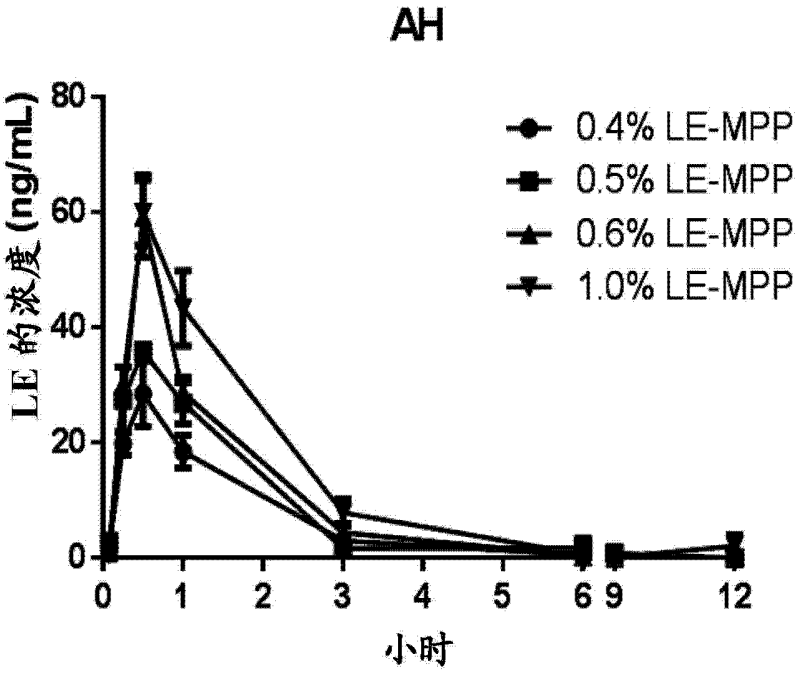

AH
LE 的浓度 (ng/mL)
80
60
40
20
0
0
1
2
3
4
5
6
9
12
小时
0.4% LE-MPP
0.5% LE-MPP
0.6% LE-MPP
1.0% LE-MPP

图 31A

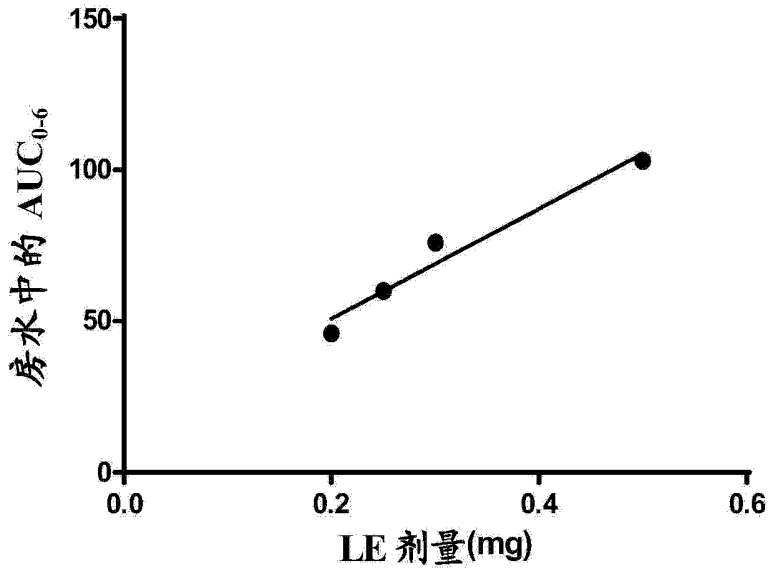

150
100
50
0
房水中的 AUC0-6
0.0
0.2
0.4
0.6
LE 剂量(mg)

图 31B

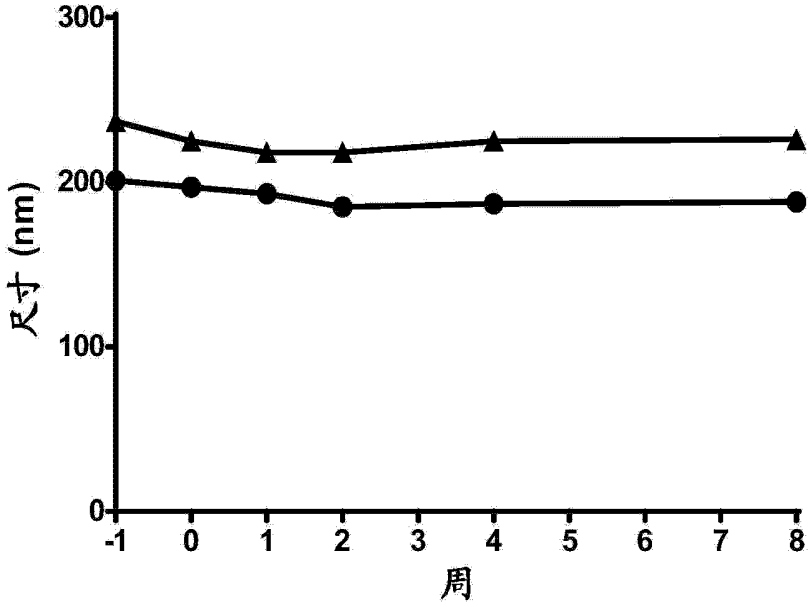

300
200
100
0
尺寸 (nm)
-1
0
1
2
3
4
5
6
7
8
周

图 32

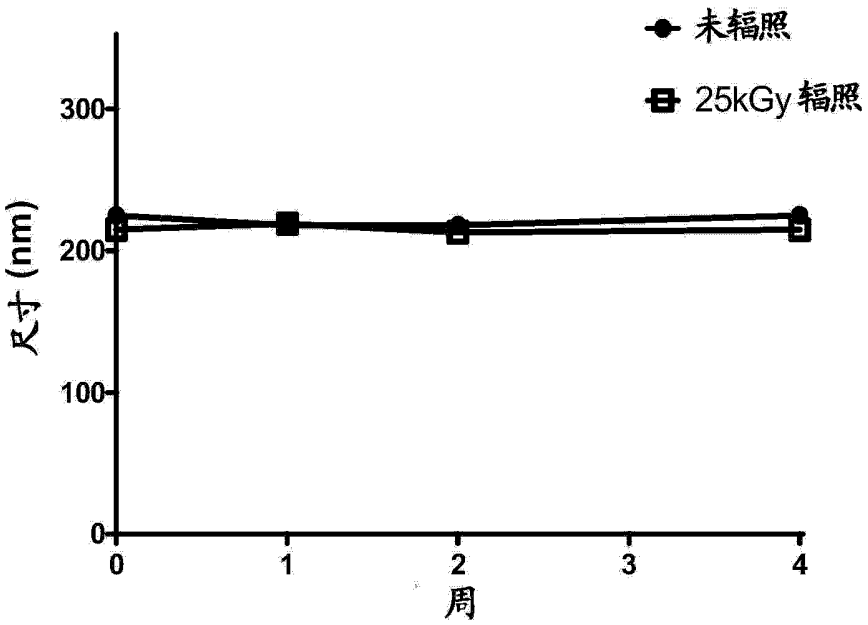

未辐照
25kGy 辐照
尺寸 (nm)
300
200
100
0
0
1
2
3
4
周

图 33A

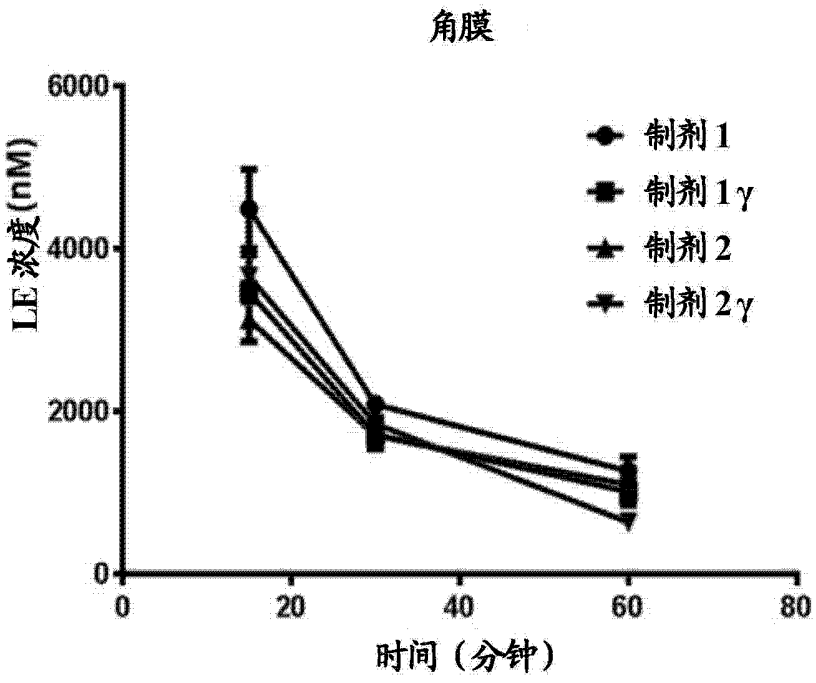

角膜
LE 浓度(nM)
6000
4000
2000
0
0
20
40
60
80
时间（分钟）
制剂 1
制剂 1γ
制剂 2
制剂 2γ

图 33B

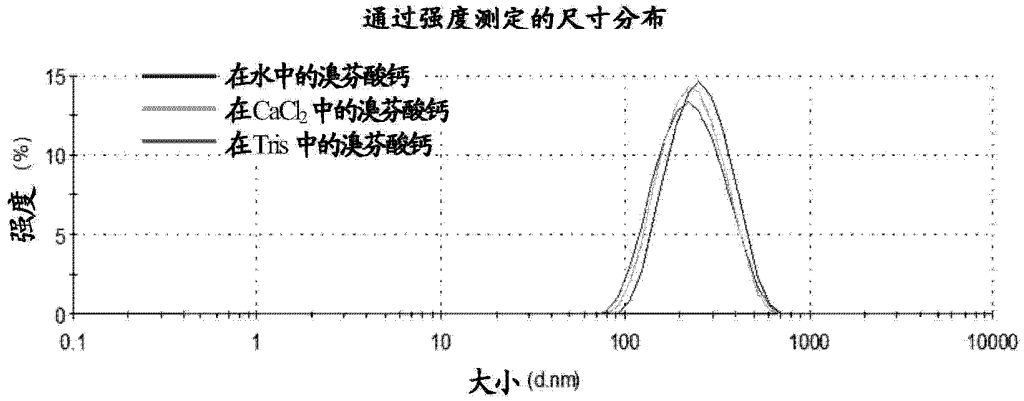

通过强度测定的尺寸分布
在水中的溴芬酸钙
在CaCl2中的溴芬酸钙
在Tris中的溴芬酸钙
强度（%）
15
10
5
0
0.1
1
10
100
1000
10000
大小 (d.nm)

图 34

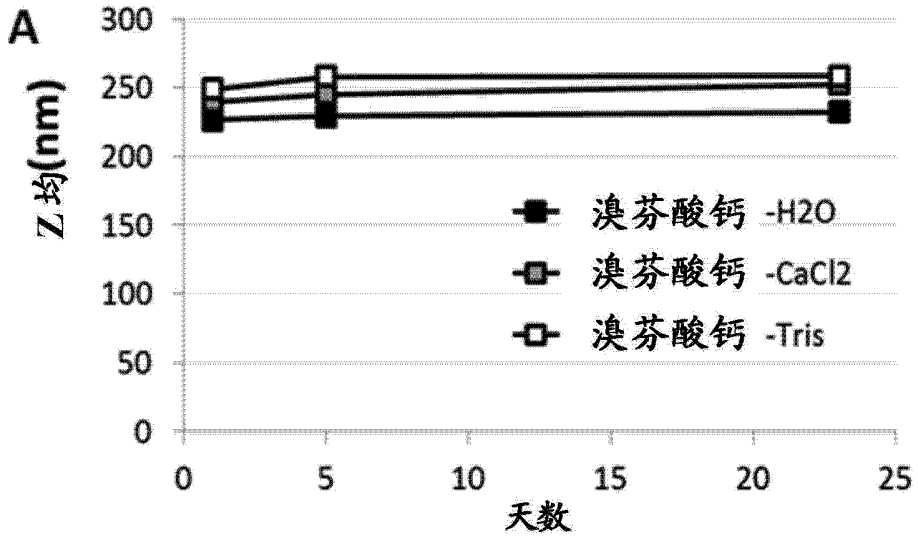

A
Z均(nm)
300
250
200
150
100
50
0
0
5
10
15
20
25
天数
溴芬酸钙 -H2O
溴芬酸钙 -CaCl2
溴芬酸钙 -Tris

图 35A

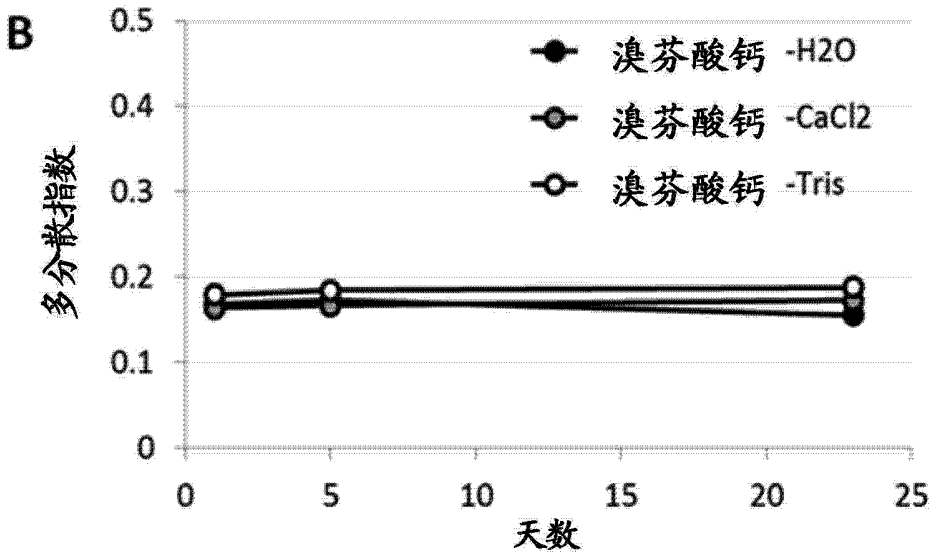

B
0.5
0.4
0.3
0.2
0.1
0
多分散指数
0
5
10
15
20
25
天数
溴芬酸钙 -H2O
溴芬酸钙 -CaCl2
溴芬酸钙 -Tris

图 35B

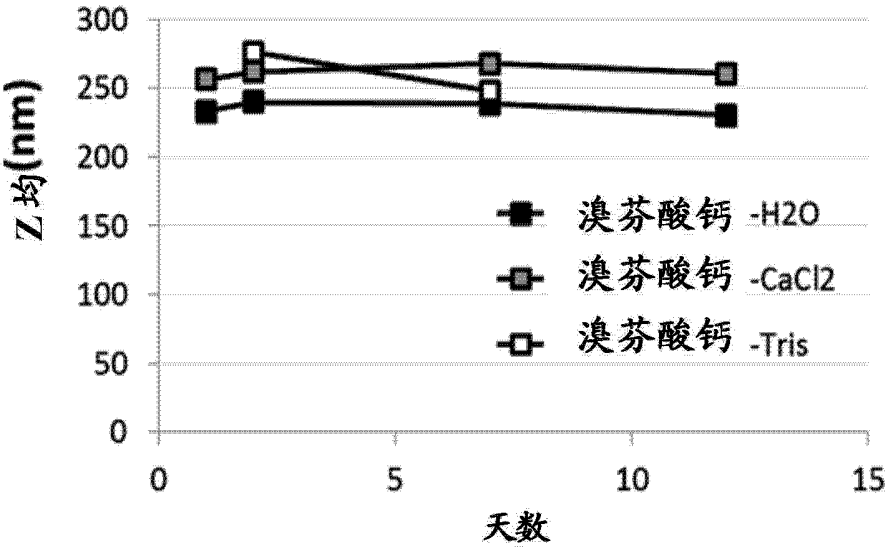

300
250
200
150
100
50
0
Z 均(nm)
0
5
10
15
天数
溴芬酸钙 -H2O
溴芬酸钙 -CaCl2
溴芬酸钙 -Tris

图 35C

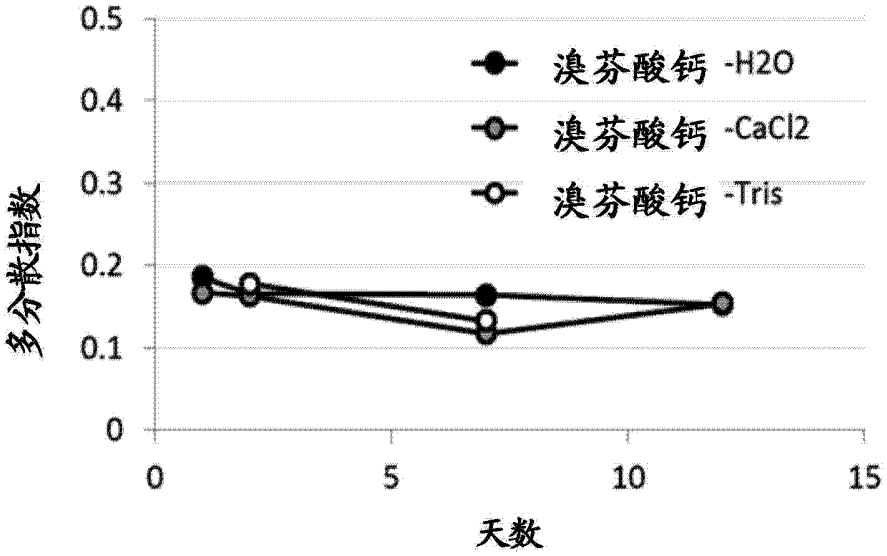

0.5
0.4
0.3
0.2
0.1
0
多分散指数
0
5
10
15
天数
溴芬酸钙 -H2O
溴芬酸钙 -CaCl2
溴芬酸钙 -Tris

图 35D

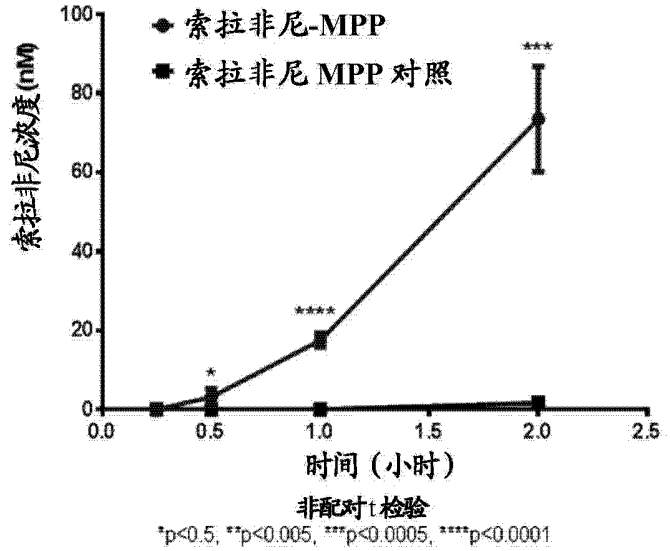

索拉非尼-MPP
索拉非尼 MPP 对照
索拉非尼浓度(nM)
100
80
60
40
20
0
0.0
0.5
1.0
1.5
2.0
2.5
时间（小时）
*
****
***
非配对t检验
*p<0.5, **p<0.005, ***p<0.0005, ****p<0.0001

图 36A

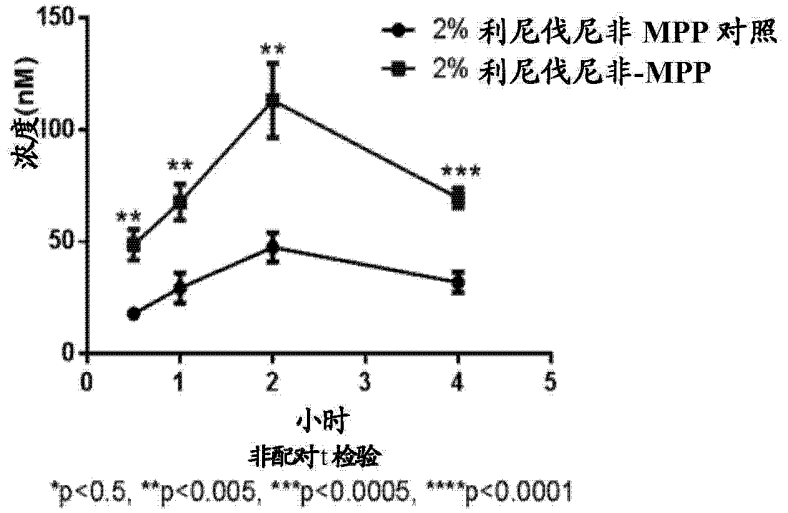

2% 利尼伐尼非 MPP 对照
2% 利尼伐尼非-MPP
浓度(nM)
150
100
50
0
0
1
2
3
4
5
小时
**
**
**
***
非配对t检验
*p<0.5, **p<0.005, ***p<0.0005, ****p<0.0001

图 36B

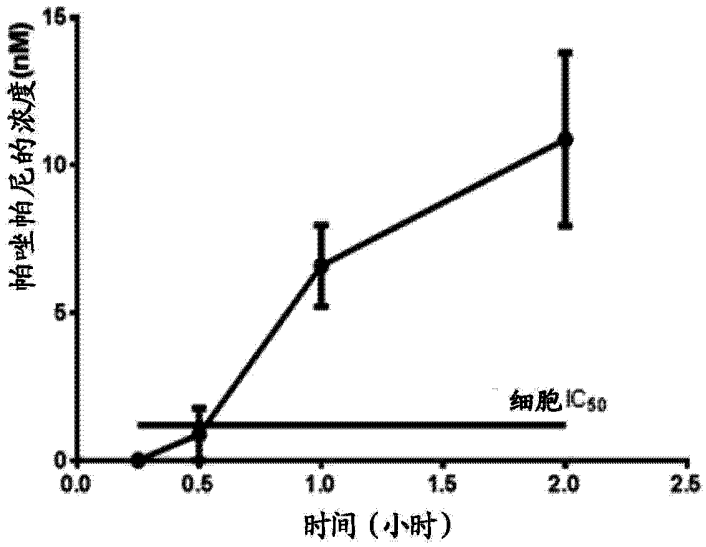

帕唑帕尼的浓度(nM)
15
10
5
0
0.0
0.5
1.0
1.5
2.0
2.5
细胞IC50
时间（小时）

图 37A

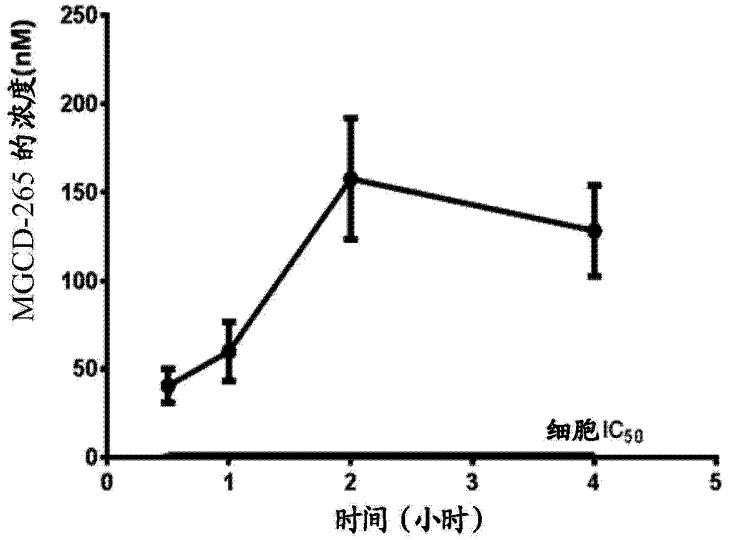

MGCD-265 的浓度(nM)
250
200
150
100
50
0
细胞 IC_{50}
0
1
2
3
4
5
时间（小时）

图 37B

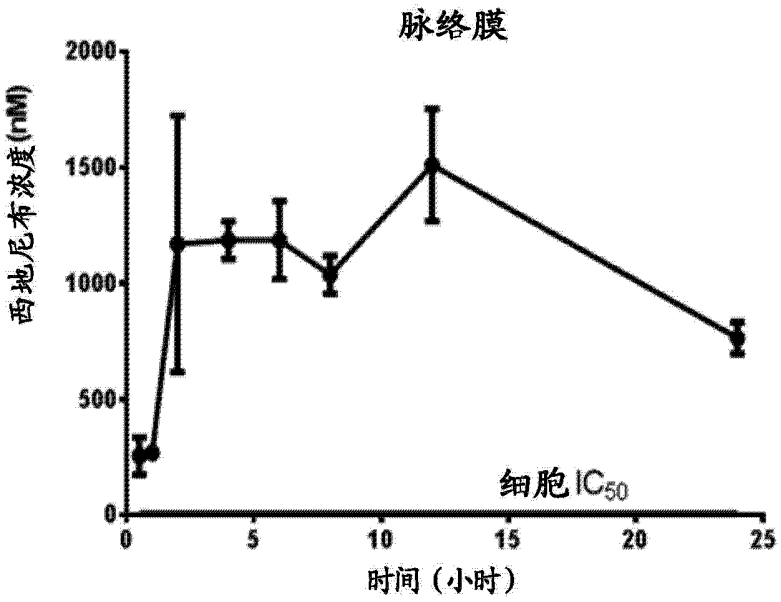

脉络膜
西地尼布浓度(nM)
2000
1500
1000
500
0
细胞 IC_{50}
0
5
10
15
20
25
时间（小时）

图 38A

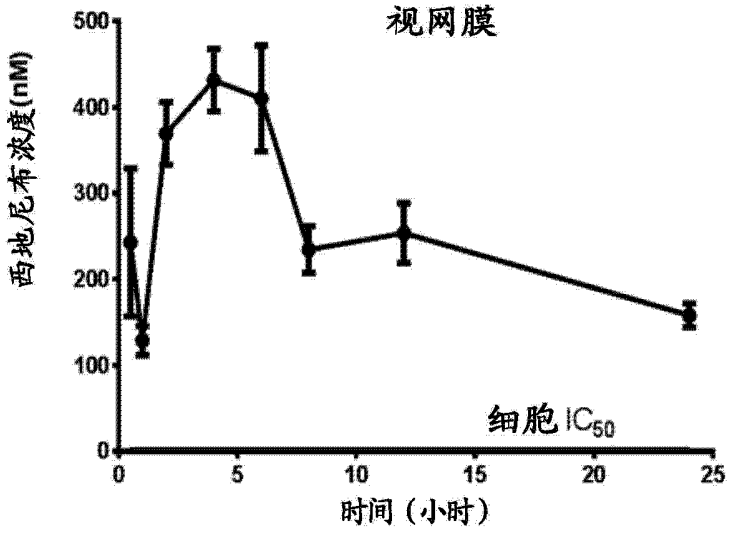

视网膜
西地尼布浓度(nM)
500
400
300
200
100
0
细胞 IC50
0
5
10
15
20
25
时间（小时）

图 38B

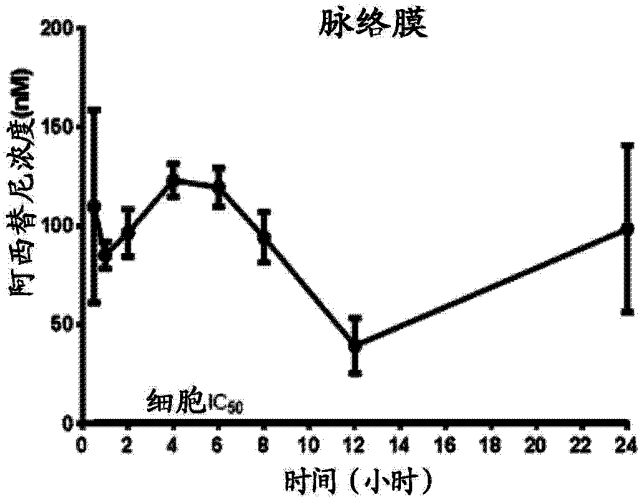

脉络膜
阿西替尼浓度(nM)
200
150
100
50
0
细胞IC50
0
2
4
6
8
10
12
14
16
18
20
22
24
时间（小时）

图 39A

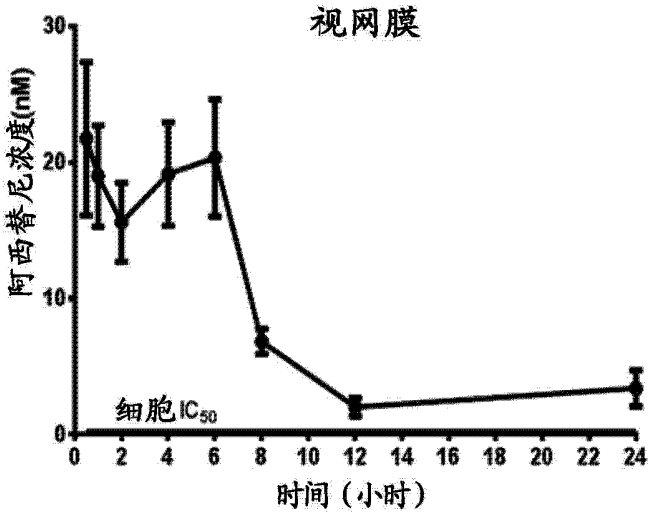


图 39B

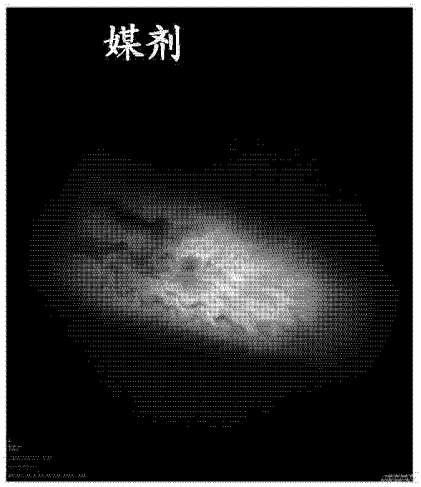


图 40A

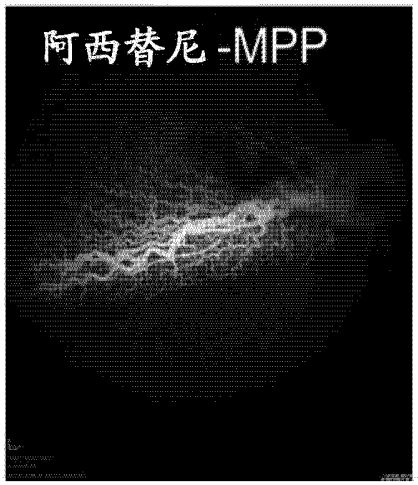


图 40B

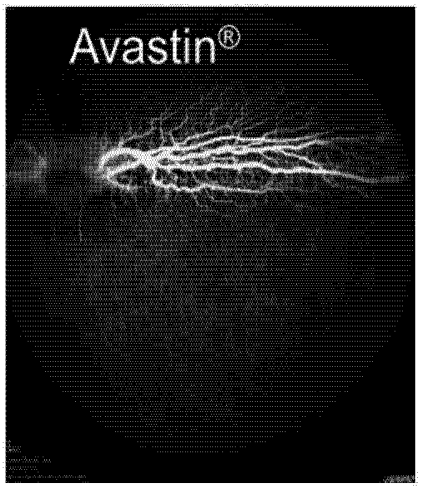


图 40C

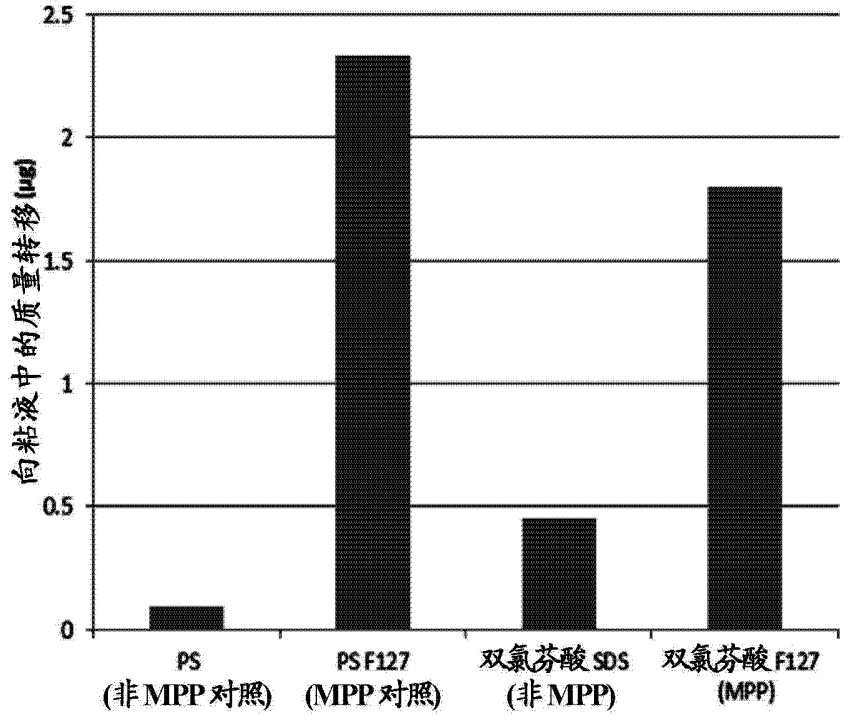

向粘液中的质量转移(ug)
2.5
2
1.5
1
0.5
0
PS
(非 MPP 对照)
PS F127
(MPP 对照)
双氯芬酸 SDS
(非 MPP)
双氯芬酸 F127
(MPP)

图 41

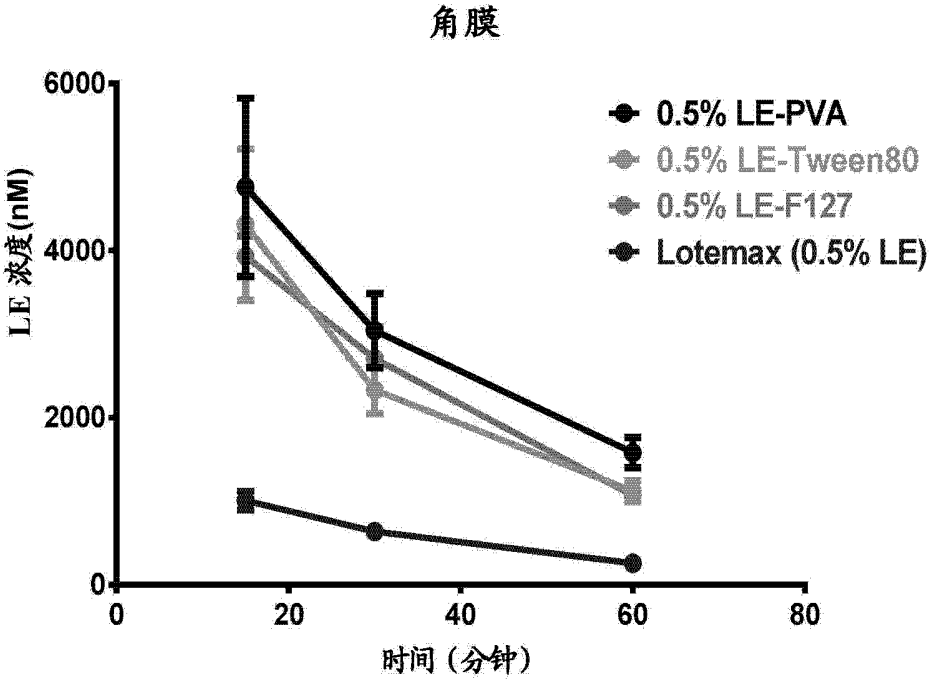

角膜
LE 浓度(nM)
6000
4000
2000
0
0
20
40
60
80
时间（分钟）
0.5% LE-PVA
0.5% LE-Tween80
0.5% LE-F127
Lotemax (0.5% LE)

图 42

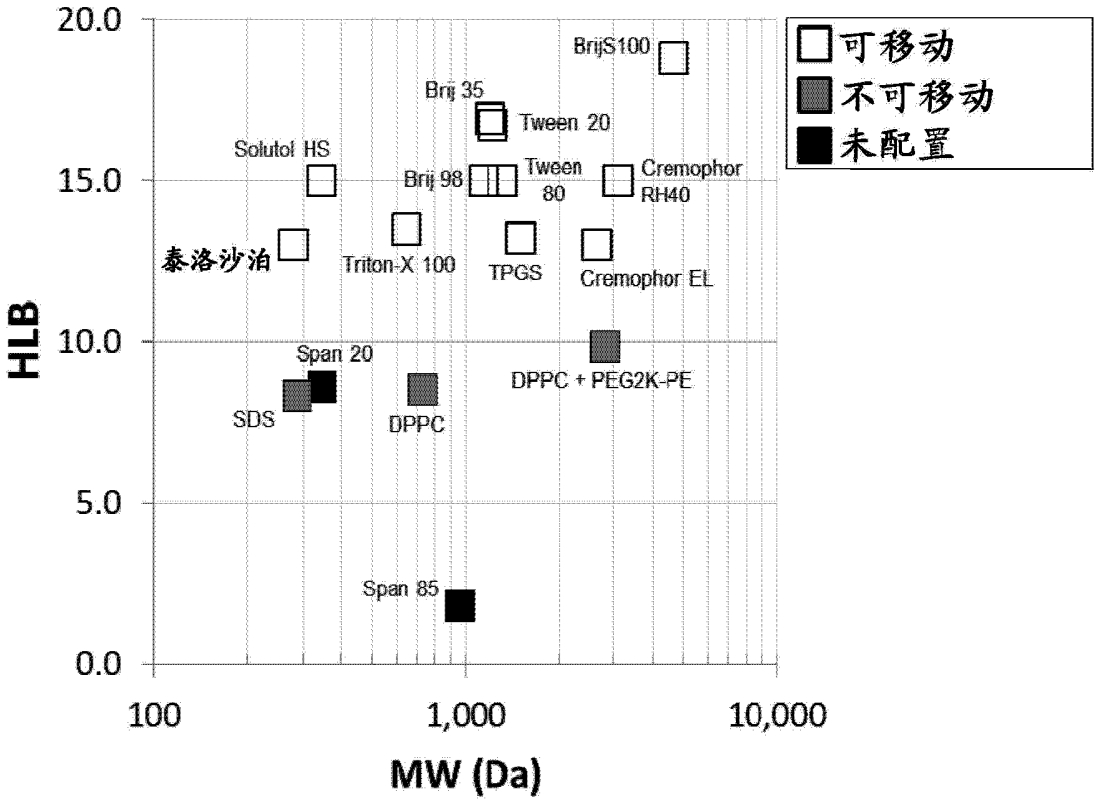

20.0
15.0
10.0
5.0
0.0
HLB
100
1,000
10,000
MW (Da)
可移动
不可移动
未配置
BrijS100
Brij 35
Tween 20
Solutol HS
Brij 98
Tween 80
Cremophor RH40
泰洛沙泊
Triton-X 100
TPGS
Cremophor EL
Span 20
DPPC + PEG2K-PE
SDS
DPPC
Span 85

图 43

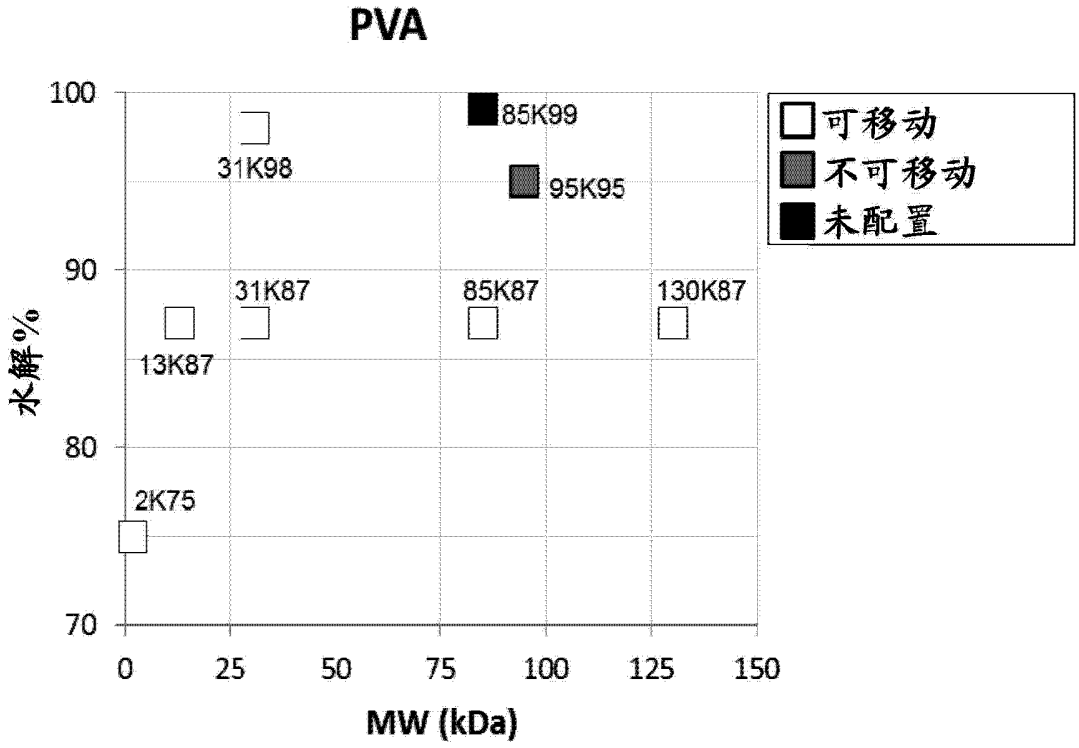

PVA
100
90
80
70
水解%
0
25
50
75
100
125
150
MW (kDa)
可移动
不可移动
未配置
85K99
31K98
95K95
31K87
85K87
130K87
13K87
2K75

图 44

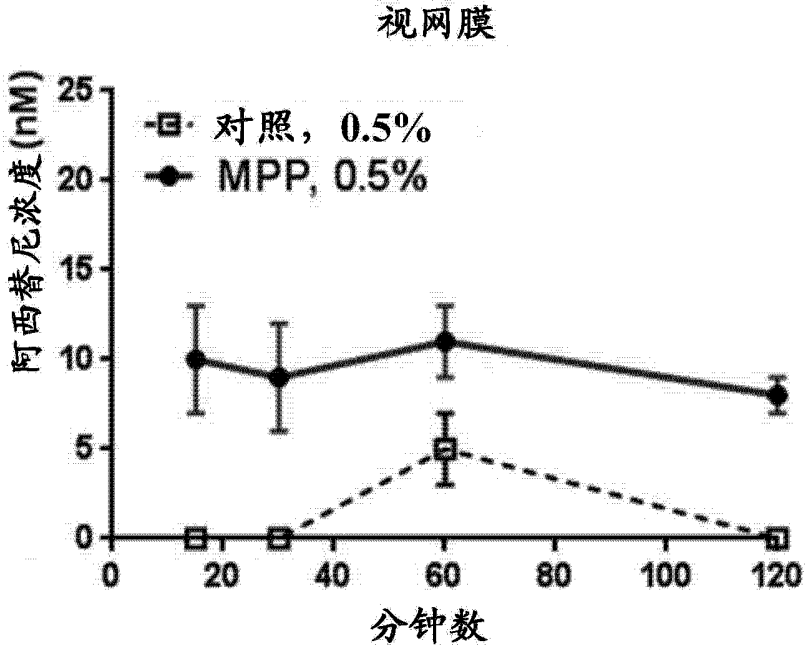


图 45

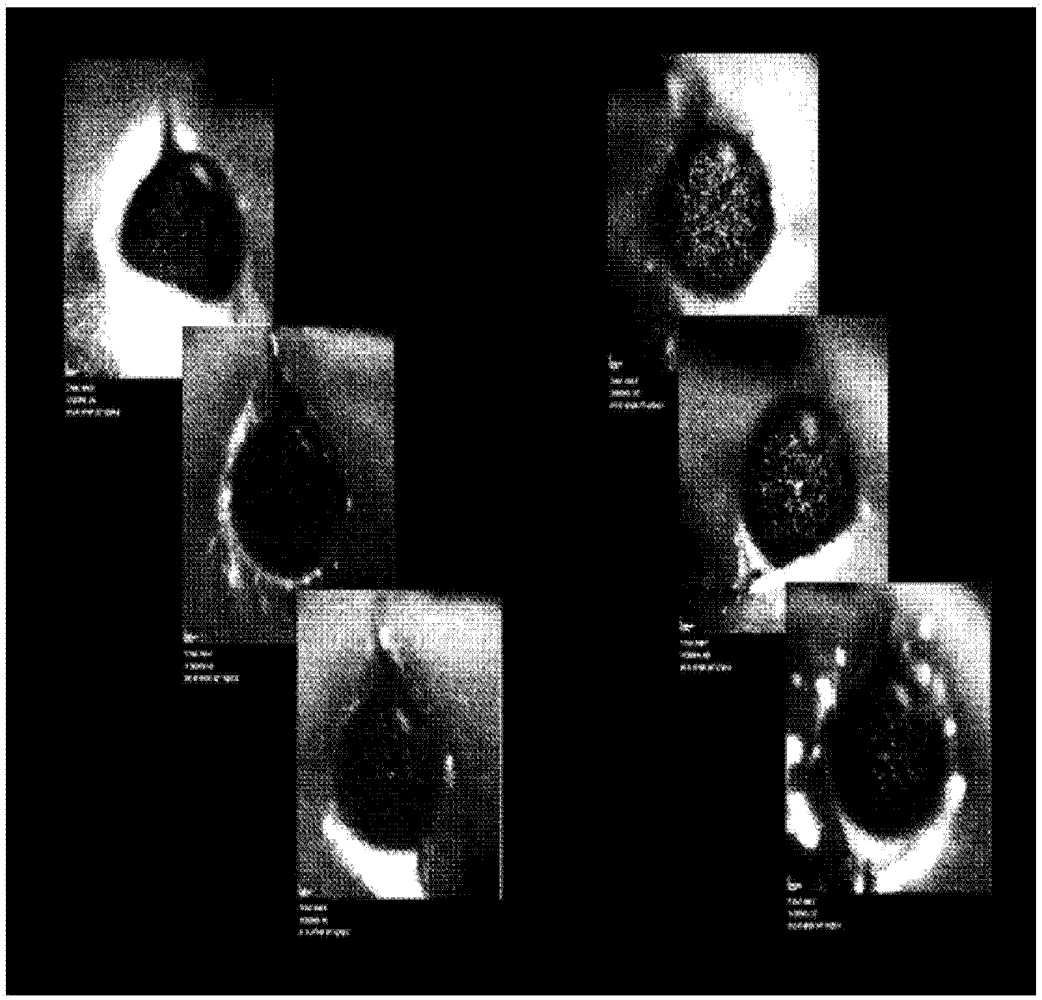


图 46

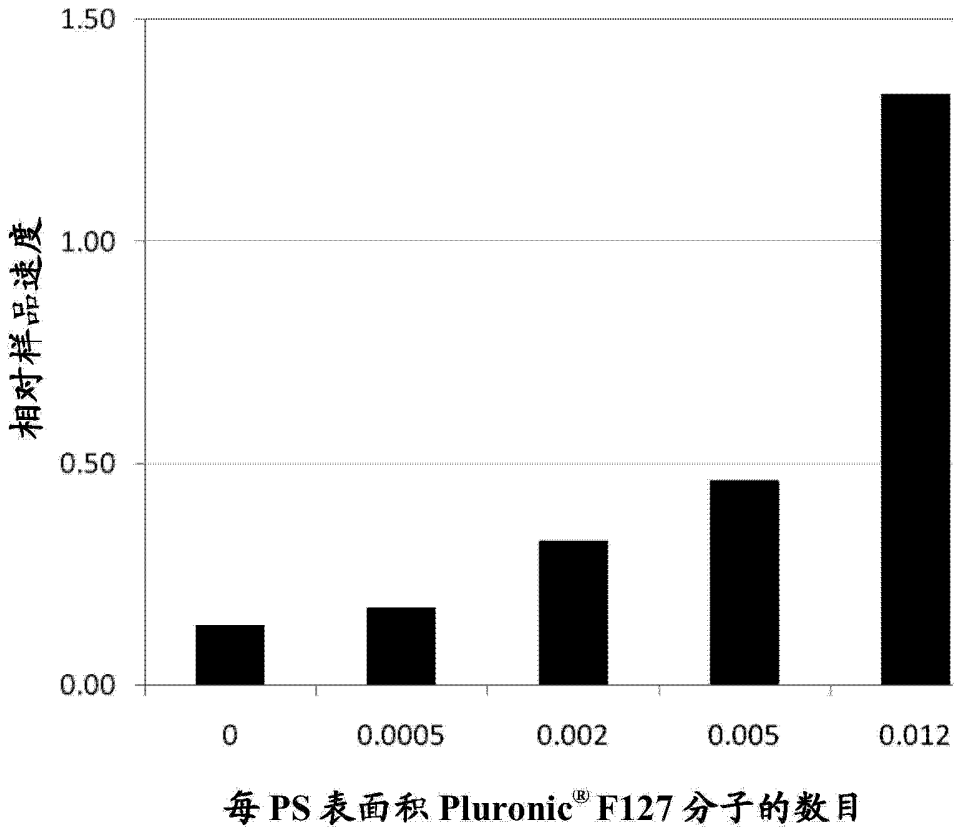

1.50
1.00
0.50
0.00
相对样品速度
0
0.0005
0.002
0.005
0.012
每 PS 表面积 Pluronic® F127 分子的数目

图 47