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(54) Title: PHARMACEUTICAL BIODISSOLVABLE GELS FOR DRUG DELIVERY

(57) Abstract: This disclosure relates to a pharmaceutical bio-dissolvable/bioerodible aqueous gel system optionally comprising an active pharmaceutical ingredient, wherein the pharmaceutical composition makes a transition from liquid to gel near the body temperature of a mammal. These compositions may include a reversibly-gelling material, such as methylcellulose and a rheology modifier such as citrate.



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PHARMACEUTICAL BIODISSOLVABLE GELS FOR DRUG DELIVERY

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/771,529, filed
5 November 26, 2018, which is incorporated by reference herein in its entirety.

Field

This disclosure relates to a pharmaceutical biodissolvable/bioerodible gel system for
drug delivery. More particularly, the present disclosure relates to a biodissolvable aqueous gel
system for treating, modifying, and/or preventing local diseases. Properties such as
10 dissolvability, injectability, and drug release rate of the system can be controlled through
ingredients and their concentrations.

Background

One significant challenge in developing drug delivery systems is the maintenance of
15 bioavailability of the drug at intended site(s) of actions over time. Depending upon the nature
of the drug and the route of delivery, the bioavailability may be suboptimal due to, for example,
the degradation of orally delivered drugs by hepato-gastrointestinal first-pass elimination,
and/or rapid clearance of the drug from the site of application. The net results are that the dose
administered and the frequency of dosing are required to be more than necessary to achieve
20 therapeutic benefits while the undesirable adverse effects occur. Thus, it is desirable to be able
to administer drugs with an efficient temporal course of drug availability to provide steady,
prolonged, or sustained exposure of therapeutically meaningful amounts of drug while lowering
propensity to trigger adverse effects and reducing dosing frequency for improved patient
convenience and compliance.

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SUMMARY

Some embodiments include a pharmaceutical composition comprising a reverse -
thermal-gelation material, wherein the pharmaceutical composition makes a transition from
liquid to gel near the body temperature of a mammal, such as near the body temperature of a
human being.

Some embodiments include a pharmaceutical composition comprising an active pharmaceutical ingredient, wherein the pharmaceutical composition makes a transition from liquid to gel near mammalian body temperatures, and more preferably human body temperatures.

5 Some embodiments include a pharmaceutical composition comprising an active pharmaceutical ingredient, methylcellulose, and citrate.

Some embodiments include a pharmaceutical composition comprising an active pharmaceutical ingredient, methylcellulose, citrate and phosphate.

10 Some embodiments include a pharmaceutical composition comprising an active pharmaceutical ingredient, methylcellulose and phosphate.

Some embodiments include a pharmaceutical composition comprising an active pharmaceutical ingredient, methylcellulose, citrate and dimethyl sulfoxide.

Some embodiments include a pharmaceutical composition comprising an active pharmaceutical ingredient, methylcellulose, phosphate and dimethyl sulfoxide.

15 Some embodiments include a pharmaceutical composition comprising an active pharmaceutical ingredient, methylcellulose, citrate, phosphate and dimethyl sulfoxide.

Some embodiments include a method of treating a disease, comprising administering a pharmaceutical composition described herein to a mammal in need thereof.

20 Some embodiments include use of a pharmaceutical composition described herein in the manufacture of a medicament for treating a disease.

25 Some embodiments include a method of delivering an active pharmaceutical ingredient, comprising administering a pharmaceutical composition described herein to a mammal in need of the active pharmaceutical ingredient, wherein the method provides a therapeutic effect with a reduced active pharmaceutical ingredient dosing frequency. Active pharmaceutical dosing is dosing that is accompanied by action on the part of the patient or a person administering the drug. For example an injection, applying a topical composition, and swallowing an oral dosage form are examples of active pharmaceutical dosing. Thus, reducing active pharmaceutical ingredient dosing frequency involves reducing the frequency of injection, oral administration,

topical administration, etc. Some dosing is not active, such as sustained delivery of a dosage form.

Some embodiments include a method of delivering an active pharmaceutical ingredient, comprising administering a pharmaceutical composition described herein to a mammal in need of the active pharmaceutical ingredient, wherein a single administration of the active pharmaceutical ingredient provides a therapeutically effective concentration of the active pharmaceutical ingredient to the mammal for at least 5 days, at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 12 weeks, at least 4 months, at least 5 months, at least 6 months, at least 9 months, at least 12 months, or longer.

Some embodiments include a method of preparing a pharmaceutical composition having reverse thermal gelation properties, comprising: mixing a polymer agent into a slurry containing a gelation modulator and an active pharmaceutical ingredient, wherein the mixing occurs at a temperature of about 60 °C to about 80 °C; wherein the slurry is formed by a method comprising precipitating the active pharmaceutical ingredient into an aqueous liquid, and adding the gelation modulator to the slurry.

Brief Description of the Drawings

FIG. 1 shows temperature sweep Rheograms of Methylcellulose A15LV Aqueous Solutions at two different concentrations of methylcellulose.

FIG. 2 shows temperature sweep rheograms of some subject compositions having different modulators.

FIG. 3 shows temperature sweep rheograms of some subject compositions having different citrate buffer concentrations.

FIG. 4 shows temperature sweep rheograms of some subject compositions having different types of methylcellulose.

FIG. 5 shows the in vitro release of lenvatinib in several subject compositions.

FIG. 6 shows the concentration in ocular tissues after a single intravitreal injection of 1% lenvatinib in a subject composition.

FIG. 7 shows the concentration in ocular tissues after a single intravitreal injection of 1% lenvatinib in a subject composition.

FIG. 8 shows the concentration in ocular tissues after a single intravitreal injection of 1% lenvatinib in a subject composition.

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DETAILED DESCRIPTION

Locally administered pharmaceutical gels are believed to have a potential to achieve the aforementioned, desirable drug-delivery attributes. However, most approved gel products are not syringeable and/or injectable via parenteral routes, and not droppable via topical routes. Furthermore, none of the marketed ophthalmic or dermatological gel products offer reduced dosing frequency and prolonged exposure when compared with the conventional eye/skin dosage forms such as solutions, suspensions, emulsions, lotions, creams, and ointments. When prolonged release is required for parenteral, topical and local indications, people have often had more success with multi-particulate systems, devices, implants, and/or inserts rather than gels.

Reverse thermal-gelling systems, e.g. systems having an increase in flowability as temperature decreases, can be effective in modulating drug retention and release after administration. Some of the challenges to overcome include ease of administration, dosage stability, and local and systemic toxicities, so that these systems can be used therapeutically.

Generally, this disclosure relates to pharmaceutical compositions (optionally containing an active pharmaceutical ingredient) with certain rheological properties. The pharmaceutical compositions described herein may be generally referred to as “a subject composition” or “subject compositions.” Subject compositions are reversibly gelling compositions with particular properties. For example, a subject composition may make a transition from liquid to gel near the body temperature of a mammal, e.g. near the body temperature of a human, such as between about 0 °C and about 40 °C. For example, the subject composition may be a liquid at around 2-8°C, such as 7°C, and solid at a higher temperature, such as about 30-40°C, such as 37°C. While subject compositions may be used in any route of administration, the properties of subject compositions may confer advantages for parenteral and topical routes over other dosage forms (such as inserts, implants, transdermal/topical patches, etc.) currently in use for the intended purposes of the subject compositions.

A subject composition may comprise a three-dimensional network-forming, gelling material.

Subject compositions have a number of potential advantages that may overcome limitations of existing gel technologies, such as the following:

5 1) A gel composition which becomes a semi-solid at near body temperature may not be able to pass through thin needles or long catheters required for administration. Some subject compositions have proper viscosity and elasticity properties before and during administration to address this challenge.

10 2) A gel composition which becomes a semi-solid at near body temperature may not timely undergo phase transition in vivo after administration into a body, tissue, or a body cavity if the gelation kinetics is too slow or too fast. Some subject compositions have a gel-sol transition that is kinetically favorable, e.g. sufficiently rapid, so as to ensure timely gel formation for the intended indication.

15 3) When a gel is formed in-vivo, the formed gel may be weak and may not persist long enough to exert meaningful drug release effect. On the other hand, an overly durable gel may not be desirable because it may persist long after all of the drug has been released from the gel, leaving an empty gel mass in the body. Some subject compositions have proper elasticity and viscosity that allows proper formation after administration and the gel would dissolve at rates compatible and comparable to those of the drug release.

20 The viscoelastic properties of subject compositions can be modulated such that they can be administered through thin needles, catheters, and/or devices, form a gel after administration, and have a proper dissolvability to give the desired residence time required for therapeutic benefits.

25 The subject compositions allow targeted drug delivery to local tissues which may be preferred over systemic drug administration. Targeted drug delivery has been employed to maximize the local drug exposure and minimize systemic side effects. However, in order to be a successful local drug delivery, a few features may need to be achieved, such as ease of administration, adequate local tolerability and safety, delivery at an appropriate dose and volume for the target tissue, and effective disease management. It may be desirable for the

drug to be released over a suitable period of time to reduce a need for frequent administration, such as frequent injections. Increasing residence time in the target tissue can improve a local treatment method by reducing the frequency of repeated dosing. It is also desirable to improve ease of administration of the pharmaceutical composition, such as a subject composition, to improve the desirability and outcome of some local drug deliveries.

Surprisingly, many subject compositions provide a longer or modulated “residence” time of active agent in sufficient amounts to target tissues through local application as compared with conventional formulations such as injectable aqueous solutions or suspensions, and topical dosage forms. Some subject compositions can be administered to patients using conventional syringes/needles, and some can be administered using catheters or applicators.

Unless otherwise indicated, any reference to a compound such as an active pharmaceutical ingredient, or any other formulation component, includes pharmaceutically acceptable salts; acid forms; base forms; prodrugs; alternate solid forms, such as polymorphs, solvates, hydrates, tautomers, etc.; or any other chemical species that may rapidly convert to a compound described herein under conditions in which the compounds are used as described herein.

As mentioned above, some subject compositions include an active pharmaceutical ingredient in a reverse thermal gelation material, such as a reverse thermal gelation polymer, e.g. a reverse thermal gelation polymer dissolved or dispersed in water or an aqueous solution.

Any suitable polymer having reverse thermal gelation may be used in a subject composition. US 4474752, US 4478822, and CA1072413, which are incorporated by reference herein, describe examples of polymers that may provide reverse thermal gelation properties to a subject composition. “Tetronic®” polyols by BASF Wyandotte Corporation and Pluronic® poloxamer polymers may also be used to provide reverse thermal gelation properties.

In some embodiments, the subject composition comprises at least one polymer agent, Preferably, the polymer agent comprises an alkylcellulose, such as a (C₁₋₆ alkyl)cellulose, including methylcellulose, ethylcellulose, etc.

In some embodiments, the subject composition comprises (C₁₋₆ alkyl)cellulose.

In some embodiments, the subject composition comprises ethylcellulose.

In some embodiments, the subject composition comprises methylcellulose. In some embodiments, the methylcellulose has a viscosity of about 1,000-2,000 mPas, about 1,400-1,600 mPas, or about 1500 mPas.

With respect to subject compositions comprising methylcellulose (such as methylcellulose A 15LV), any suitable concentration of methylcellulose may be used, such as about 0.1-20%(w/w), about 2-10%(w/w), about 3-4%(w/w), about 4-5%(w/w), about 5-6%(w/w), about 6-7%(w/w), about 7-8%(w/w), about 8-9%(w/w), about 4-6%(w/w), about 6-8%(w/w), about 8-10%(w/w), about 4.6-4.8%(w/w), about 4.8-5%(w/w), about 5-5.2%(w/w), about 5.2-5.4%(w/w), about 5.4-5.6%(w/w), about 5.6-5.8%(w/w), about 6.6-6.8%(w/w), about 6.8-7%(w/w), 7-7.2%(w/w), about 7.2-7.4%(w/w), about 7.4-7.6%(w/w), about 7.6-7.8%(w/w), about 4.5-5.5%(w/w), about 4.8-5.2%(w/w), about 6.8-7.2%(w/w), about 6.5-7.5%(w/w), about 3-9%(w/w), or 3-12%(w/w).

With respect to subject compositions comprising methylcellulose, the degree of methoxylation of methylcellulose may be about 10-50%, about 10-15%, about 15-20%, about 20-25%, about 25-30%, about 30-35%, about 35-40%, about 40-45%, about 45-50%, about 20-22%, about 22-24%, about 24-26%, about 26-28%, about 28-30%, about 30-32%, about 32-34%, about 34-36%, about 36-38%, about 38-40%, or about 20%-35%.

Aqueous solutions of methylcellulose have reverse thermal gelation properties. However, some methylcellulose solutions have a gelation temperature that is outside of the body temperature range. Additionally, viscoelastic properties of some methylcellulose aqueous solutions are often such that they are not feasible for pharmaceutical manufacture at a large scale or administration to patients in a clinical setting.

A subject composition may contain at least one gelation modulator. A gelation modulator may modify characteristics such as gelation onset temperature, gelation kinetics, gelation temperature, elasticity profile as function of temperature, etc. The gelation modulators may be a substance such as a salt, a buffer, a solvent, a surfactant, another material, or a combination thereof. In some embodiments, several gelation modulators (such as 2, 3, 4, 5, 6, 7, 8, 9, 10, or more) could be used in one formulation in order to produce a formulation that can feasibly deliver the active pharmaceutical agent.

Examples of suitable gelation modulators may include phosphate, dihydrogen phosphate, hydrogen phosphate, tris (hydroxymethyl)aminomethane, borate, histidine, carbonate, bicarbonate, citrate, citric acid acetate, tartrate, fumarate, lactate, formate, sulfamate, oxalate, malonate, succinate, maleate, adipate, benzoate, *o*-toluate, benzene tetracarboxylate, glutamate, *e*-amino caproate, aspartate, glycinate, arginate, lysinate, taurate, ethanol, dimethyl sulfoxide, glycerin, dimethylformamide, propylene glycol, a polyethylene glycol, a vegetable oil, corn oil, olive oil, castor oil, vitamin E, a phospholipid, a polysorbate 20, a polysorbate 40, a polysorbate 60, a polysorbate 80, a mono-saccharide, a di-saccharide, dextrose, sucrose, a sugar alcohol, mannitol, sorbitol, an antioxidant, ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene, sodium bisulfate, sodium sulfite, sodium metabisulfite, EDTA, sodium carboxymethylcellulose, sodium alginate, hydroxypropylmethylcelluloses, carbomers, hyaluronic acid, a hyaluronate salt, etc., or a combination thereof. In some embodiments, the gelation modulator comprises phosphate. In some embodiments, the gelation modulator comprises dimethyl sulfoxide. In some embodiments, the gelation modulator comprises citrate.

Suitable buffers (for use as a gelation modulator, or for buffering purposes unrelated to gelation modulation) may include phosphate, dihydrogen phosphate, hydrogen phosphate, tris-(hydroxymethyl)aminomethane, borate, histidine, carbonate, bicarbonate, citrate, acetate, tartarate, fumarate, lactate, formate, sulfamate, oxalate, malonate, succinate, maleate, adipate, benzoate, *o*-toluate, benzene tetracarboxylate, glutamate, *e*-amino caproate, aspartate, glycinate, arginate, lysinate, taurate, etc., or a combination thereof. In some embodiments, the pharmaceutical composition comprises citrate, including citric acid, any salt of citric acid, or a combination thereof. In some embodiments, the pharmaceutical composition comprises phosphate, including phosphoric acid, any salt of phosphoric acid, or a combination thereof. In some embodiments, several buffers could be used in combination in a single formulation.

For those pharmaceutical compositions comprising citrate, any suitable concentration of citrate (including citric acid, a salt of citric acid, a combination of salts of citric acid, or a combination of one or more salts of citric acid and citric acid) may be used, such as 1-200 mmole/kg, about 25-200 mmole/kg, about 50-100 mmole/kg, about 100-150 mmole/kg, about 80-100 mmole/kg, about 100-120 mmole/kg, about 120-140 mmole/kg, about 96-98 mmole/kg,

about 98-100 mmole/kg, about 100-102 mmole/kg, about 102-104 mmole/kg, about 104-110 mmole/kg, about 110-112 mmole/kg, about 112-114 mmole/kg, about 114-116 mmole/kg, about 116-118 mmole/kg, about 118-120 mmole/kg, about 120-122 mmole/kg, about 97-99 mmole/kg, about 99-101 mmole/kg, about 101-103 mmole/kg, about 103-108 mmole/kg, about 108-113 mmole/kg, about 113-115 mmole/kg, about 115-117 mmole/kg, about 117-119 mmole/kg, about 90-110 mmole/kg, or about 110-130 mmole/kg.

For those pharmaceutical compositions comprising phosphate, any suitable concentration of phosphate may be used, such as 1-200 mmole/kg, about 50-100 mmole/kg, about 100-150 mmole/kg, about 80-100 mmole/kg, about 100-120 mmole/kg, about 120-140 mmole/kg, about 96-98 mmole/kg, about 98-100 mmole/kg, about 100-102 mmole/kg, about 102-104 mmole/kg, about 110-112 mmole/kg, about 112-114 mmole/kg, about 114-116 mmole/kg, about 116-118 mmole/kg, about 118-120 mmole/kg, about 120-122 mmole/kg, about 97-99 mmole/kg, about 99-101 mmole/kg, about 101-103 mmole/kg, about 113-115 mmole/kg, about 115-117 mmole/kg, about 117-119 mmole/kg, about 90-110 mmole/kg, or about 110-130 mmole/kg.

Hydrophilic solvents or hydrophobic solvents may also be used as gelation modulators or for other purposes. Suitable hydrophilic solvents include ethanol, dimethyl sulfoxide, glycerin, dimethylformamide, propylene glycol, and polyethylene glycols. Suitable hydrophobic solvents include vegetable oils (corn oil, olive oil, castor oil, etc.), vitamin E, and phospholipids.

For those pharmaceutical compositions comprising dimethyl sulfoxide, any suitable concentration of dimethyl sulfoxide may be used, such as such as about 0.1-50%(w/w), about 0.1-20%(w/w), about 0.1-10%(w/w), about 0.1-1%(w/w), about 1-10%(w/w) about 10-20%(w/w) about 20-30%(w/w) about 30-40%(w/w), about 40-50%(w/w), about 0.1-8%(w/w), about 1-2%(w/w), about 2-3%(w/w), about 3-4%(w/w), about 4-5%(w/w), about 5-6%(w/w), about 6-7%(w/w), about 4-6%(w/w), about 6-8%(w/w), about 8-9%(w/w), about 9-10%(w/w), about 10-12%(w/w), about 4.8-5%(w/w), about 5-5.2%(w/w), about 5.2-5.4%(w/w), about 4.5-5.5%(w/w), about 4.8-5.2%(w/w), about 3-9%(w/w), about 9-11%(w/w), or about 3-12%(w/w).

Other materials that may be used as gelation modulators include surfactants (such as polysorbates 20, 40, 60 and 80, and phospholipids), mono- or di- saccharides (such as dextrose,

sucrose, etc.), sugar alcohols (such as mannitol and sorbitol, etc.), antioxidants (such as Vitamin E, ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene, sodium bisulfate, sodium sulfite, sodium metabisulfite, etc.), chelating agents such as EDTA, suspending agents (such as sodium carboxymethylcellulose, sodium alginate, etc.) and viscosity enhancing agents (such as hydroxypropylmethylcelluloses, carbomers, hyaluronate, etc.).

The pharmaceutical composition may have any suitable pH, such as about 4-9, about 5-9, about 6-8, about 6-7, about 7-8, about 7-7.3, about 7.3-7.6, about 7.6-7.9, about 7.2-7.6, or about 7.4.

In some embodiments, the composition may contain less than 20%, less than 10%, less than 5%, or less than 0.5% polyethylene glycol, or may be substantially free, or completely free, of polyethylene glycol.

In some embodiments, the composition may contain less than 20%, less than 10%, less than 5%, less than 2.5% or less than 0.5% dimethyl sulfoxide, or may be substantially free, or completely free, of dimethyl sulfoxide.

In some embodiments, the composition may contain less than 20%, less than 10%, less than 5%, less than 2.5% or less than 0.5% glycerin, or may be substantially free, or completely free, of glycerin.

In some embodiments, the composition may contain less than 20%, less than 10%, less than 5%, less than 2.5% or less than 0.5% sucrose, or may be substantially free, or completely free, of sucrose.

In some embodiments, the composition may contain less than 20%, less than 10%, less than 5%, less than 2.5% or less than 0.5% polysorbate 80, or may be substantially free, or completely free, of polysorbate 80.

In some embodiments, the composition may contain less than 20%, less than 10%, less than 5%, less than 2.5% or less than 0.5% polysorbate 60, or may be substantially free, or completely free, of polysorbate 60.

In some embodiments, the composition may contain less than 20%, less than 10%, less than 5%, less than 2.5% or less than 0.5% polysorbate 40, or may be substantially free, or completely free, of polysorbate 40.

In some embodiments, the composition may contain less than 20%, less than 10%, less than 5%, less than 2.5% or less than 0.5% polysorbate 20, or may be substantially free, or completely free, of polysorbate 20. Salts, such as NaCl, KCl, Na₂SO₃, MgCl₂, FeCl₃, Na₃PO₄, etc., may also be used as gelation modulators, or for other purposes.

5 A subject composition may further contain a tonicity agent such as sodium chloride, glycerin, mannitol, dextrose, potassium chloride, etc.

A subject composition can include any desired active pharmaceutical ingredient or drug, such as but not limited to, an anti-angiogenic, an antibiotic, an antifungal, an antihistamine, an anti-inflammatory, an antineoplastic, an antiviral, a biologic, a pressure-lowering agent, a genitourinary tract agent, a hormone, or a steroid, or drug intended for dermatological,
10 gastroenteral, nasal, oncologic, ophthalmic, otic, pain-relief, respiratory, or urovaginal uses.

The subject composition may provide advantages as compared to water-insoluble drugs. To this end, subject compositions may contain dispersed solid particles of a water-insoluble drug. Solid particles can be drug itself, microspheres or microcapsules of an active pharmaceutical
15 ingredient, nanoparticles of an active pharmaceutical ingredient, or drug bound/associated to a polymer through a covalent bond or an ionic bond. Subject compositions may also, or alternatively, contain dispersed globules of a hydrophobic solvent in which a water-insoluble drug is dissolved. Some water-insoluble drugs that may benefit from use in a subject composition include steroids, NSAIDs, tyrosine kinase inhibitors, anticancer agents, antibiotics,
20 prostaglandins, immunomodulators, hormones (and their agonists and antagonists), etc.

In some embodiments, the active pharmaceutical ingredient may include a multi-kinase inhibitor, e.g. axitinib, nintedanib, pirfenidone, riociguat, sorafenib, sunitinib, lenvatinib, regorafenib, ponatinib, pazopanib, etc.

The subject composition may have rheological properties that are temperature
25 dependent. Examples of subject compositions and rheograms are shown in Examples 1-17 and FIGS. 1-4. The phase angle δ tracing as a function of temperature describes gelation kinetics, showing gelation onset temperature and the gelation speed as temperature increases. The phase shift δ is inversely related to and is used to determine the % gelation for a specific temperature. For intravitreal injection, a delayed onset with sudden, quick gelation is more

desirable than early onset with gradual gelation. The Storage Modulus (G') tracing shows the increase in solid property (elasticity) as temperature increases. The G' value at near body temperature predicts the gel strength, which is related to gel durability. The higher G' a composition is at near body temperature, the more durable the gel should be.

5 The intercept of G' tracing suggests injectability. Intercept values close to or lower than about 0.1, such as about 0.05-0.07, about 0.07-0.1, about 0.1-0.3, or about 0.3-0.5, are more favorable for applications which require a thin needle for administration. The same principle should apply to the tracing of complex viscosity as function of temperature, i.e. intercept values
10 0.3-0.5, are more favorable for applications which require a thin needles for administration.

 The slope of G' tracing as a function of temperature suggests the composition's propensity for congealing. A negative slope in cool temperature range would be more desirable for indications which require the use of a long catheter. In some embodiments, G' has a slope of about -0.001-0.003, about -0.003-0.007, about -0.007-0.01, about -0.01-0.015, or about -
15 0.012-0.02 at about 2-8 °C, about 5-15 °C, about 5-20 °C, or about 5-25 °C.

 In some embodiments, a subject composition has a first storage modulus (G') at about 37 °C and a second G' at about 5 °C, wherein the first G' is higher than the second G' , such as at least about 5-fold higher, at least about 8-fold higher, at least about 10-fold higher, at least about 20-fold higher, at least about 50-fold higher, at least about 100-fold higher, at least about
20 500-fold higher, or at least about 1000-fold higher.

 In some embodiments, a subject composition has a first complex viscosity at about 37 °C and a second complex viscosity at about 5 °C, wherein the first complex viscosity is higher than the second complex viscosity, such as at least about 1.5-fold higher, at least about 2-fold higher, at least about 5-fold higher, at least about 10-fold higher, at least about 20-fold higher, at least
25 about 50-fold higher, or at least about 100-fold higher.

 In some embodiments, a subject composition has a first loss modulus (G'') at about 37 °C and a second G'' at about 5 °C, wherein the first G'' is higher than the second G'' .

In some embodiments, a subject composition has a % gelation at about 37 °C that is at least 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99%.

In some embodiments, a subject composition has a % gelation between about 30 °C and 5 40 °C that is at least 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99%.

In some embodiments, a subject composition has a % gelation between about 2 °C and about 8 °C that is no greater than about 20%, no greater than about 10%, no greater than about 5%, no greater than about 3%, or no greater than about 1%.

10 A subject composition may be administered to a mammal in order to deliver the active pharmaceutical ingredient to the mammal, wherein the mammal is in need of said active pharmaceutical ingredient. In some embodiments, the composition may reduce active pharmaceutical ingredient dosing frequency. In some embodiments, a single administration of the active pharmaceutical ingredient provides a therapeutically effective concentration of the 15 active pharmaceutical ingredient to the mammal for at least 5 days, at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 8 weeks, at least 9 weeks, at least 10 weeks, at least 12 weeks, at least 4 months, at least 5 months, at least 6 months, at least 9 months, at least 12 months, or longer. This may be accomplished by any route of administration, including topical, intralesional injection, 20 perilesional injection, intravitreal injection, intraprostatic injection, intramuscular injection, subcutaneous injection, intradermal injections, intra-tissue injection, or by eye drop.

In some embodiments, a subject composition is obtained by mixing methylcellulose of a suitable molecular weight and viscosity with a buffer and/or a tonicity agent. Not all methylcelluloses possess the viscoelastic properties which are most desirable for 25 pharmaceutical manufacturing, or properties that are most suitable for administration to patients in clinical setting. Shown in FIG. 4 is a temperature-sweep rheogram for two types of methylcellulose (A15LV and A15C) at 5%. A15C has a higher molecular weight than A15LV. The temperature-sweep rheogram indicates that A15LV at 5% concentration is shown to have

viscoelastic properties that are feasible for formulating into parenteral preparations. Furthermore, methylcellulose A15C may be too viscoelastic to be syringeable/injectable at 5%.

Furthermore, the concentration of methylcellulose A15LV may need to be above 3% in order to have the gel-sol phase transition near the body temperature.

5 It has been discovered that some gelation modulators are more effective than the others (FIGS. 2 and 3). Citrate buffer at 116 mmole/kg is surprisingly found to be able to significantly increase gel elasticity at 37 °C. As a result, gel dissolvability in vivo is expected to be much reduced (i.e., increase gel residence time). Furthermore, Citrate buffer at 116 mmole/kg is surprisingly found to be able to change the slope of the profile from positive to negative for
10 elasticity in the temperature range of 5°C to 25°C, when compared with the elasticity profile without citrate buffer or with only 75 mmole/kg (FIG. 3). The negative slope in the temperature range of 5°C to 25°C suggests that the formulation that contains 116 mmole/kg citrate would have lower congealing risk when being administered through a needle or catheter.

For some subject compositions, the desired particle size of a poorly water-soluble drug
15 is produced/controlled/influenced through a controlled precipitation process prior to being dispersed in the aqueous solutions of methylcellulose with a desired gelation temperature, pH, and tonicity. The precipitation may be triggered through a change in pH, solvency, tonicity, or temperature. The precipitate may have a different crystalline habit from the purchased raw material, resulting in a different drug release rate. Table 3 shows four methods of incorporating
20 water insoluble drugs into subject compositions. The impact of gel strength and controlled precipitation on in-vitro drug release rate is presented in FIG. 5.

In some subject compositions, aqueous solutions of methylcellulose are formulated with proper buffers and tonicity agents so that the solutions can have a pH value and a tonicity that are suitable for the intended pharmaceutical use.

25 Subject compositions comprising an aqueous solution of methylcellulose with a desired gelation temperature, pH, and tonicity and in which one or multiple active pharmaceutical ingredients are dispersed, may be administered to patients via intravitreal, intraprostatic, intramuscular, subcutaneous, or intradermal injections to treat/prevent/manage local diseases.

A subject composition can be locally administered (through injection using needles or through applicators) to target tissues such as eyes (ocular surface, anterior and posterior segments), prostate, urinary bladder, uterus, vaginal, skin, tongue, gum, oral cavity, nose, sinus, joints, etc., and various solid tumors. When formulated with one or multiple drugs, the subject compositions can transport active agents to treat local diseases in the aforementioned target tissues. The drugs can be water soluble or water insoluble. The gel compositions can be designed over a relatively wide range of conditions so that they are a liquid at cool or room temperature and can undergo a phase transition into a semi-solid when warming up to the body temperature, making them particularly suitable.

Subject compositions provide advantages for use as droppable or injectable products because they are flowable for dropping, instillation or injection, and gel when they come into contact with the body. They also provide advantages in the controlled delivery of active pharmaceutical ingredients and/or diagnostic agents to local tissues.

Some subject compositions may be used for prevention or treatment of a disease or disorder characterized by chronic inflammation, with associated angiogenesis and fibrosis. In some embodiments, the disease or disorder includes dermal-related disorders, benign prostate hyperplasia related disorders, eye-related disorders, rosacea-related disorders, uterine fibroids and related conditions, neoplastic diseases and adhesion-related disorders. In some embodiments, the pharmaceutical bio-dissolvable/bioerodible aqueous gel system may include dispersed therein at least one active pharmaceutical ingredient, such as an active pharmaceutical ingredient designed for anti-angiogenesis, including a multi-kinase inhibitor, such as axitinib, nintedanib, pirfenidone, riociguat, sorafenib, sunitinib, lenvatinib, regorafenib, ponatinib, or pazopanib.

In some embodiments, the multi-kinase inhibitor, such as axitinib, nintedanib, pirfenidone, riociguat, sorafenib, sunitinib, lenvatinib, regorafenib, ponatinib, or pazopanib, is present in subject composition at a concentration of about 0.01-5%(wt/wt), about 0.1-1%(wt/wt), about 1-2%(wt/wt), about 2-3%(wt/wt), about 3-4%(wt/wt), about 4-5%(wt/wt), about 0.01-0.5%(wt/wt), about 0.5-1%(wt/wt), about 1-1.5%(wt/wt), about 1.5-2%(wt/wt), about 2-2.5%(wt/wt), about 2.5-3%(wt/wt), about 3-3.5%(wt/wt), about 3.5-4%(wt/wt), about

4-4.5%(wt/wt), about 4.5-5%(wt/wt), 0.01-0.1%(wt/wt), about 0.1-0.2%(wt/wt), about 0.2-0.3%(wt/wt), about 0.3-0.4%(wt/wt), about 0.4-0.5%(wt/wt), about 0.5-0.6%(wt/wt), about 0.6-0.7%(wt/wt), about 0.7-0.8%(wt/wt), about 0.8-0.9%(wt/wt), about 0.9-1%(wt/wt), about 1-1.1%(wt/wt), about 1.1-1.2%(wt/wt), about 1.2-1.3%(wt/wt), about 1.3-1.4%(wt/wt), about 1.4-1.5%(wt/wt), about 1.5-1.6%(wt/wt), about 1.6-1.7%(wt/wt), about 1.7-1.8%(wt/wt), about 1.8-1.9%(wt/wt), about 1.9-2%(wt/wt), about 2-2.2%(wt/wt), about 2.2-2.4%(wt/wt), about 2.4-2.6%(wt/wt), about 2.6-2.8%(wt/wt), about 2.8-3%(wt/wt), about 3-3.3%(wt/wt), about 3.3-3.6%(wt/wt), about 3.6-3.9%(wt/wt), about 3.9-4.3%(wt/wt), about 4.3-4.7%(wt/wt), about 4.7-5.1%(wt/wt), about 0.9-1.1%(w/w), or about 1%(wt/wt).

10 In some embodiments, the administering is by a topical formulation, intralesional injection, perilesional injection, eye drop, or by intra-tissue injection.

The term "treating" or "treatment" broadly includes any kind of treatment activity, including the diagnosis, cure, mitigation, or prevention of disease in human beings or other mammals, or any activity that otherwise affects the structure or any function of the body of human beings or other mammals.

The terms drug and active pharmaceutical ingredient may be interchangeably used.

15 Subject compositions/gel formulations that do not contain drug can be prepared as follows. This method is one example and may be successfully modified by a person skilled in the art.

20 1. Combine the prescribed amount of ingredients (buffers, salts, solvents, etc.) except methylcellulose in an appropriate amount of water according to the formulation composition. Heat the mixture to approximately 60-80°C, preferably 67-70°C with constant mixing.

25 2. Weigh accurately an appropriate amount of methylcellulose and add the powder to the hot mixture while constantly mixing. When the cellulose is well dispersed, remove the heat source, bring the batch to the target weight with water, and continue mixing until the dispersion is cooled to ambient temperature. Chill the dispersion overnight to allow full hydration of cellulose and produce the final subject composition/gel formulation without drug that exhibits appropriate/desired reverse thermal gelation properties.

3. The chilled bulk gel formulation is filled into Type 1 glass serum vials and sealed with silicone coated stoppers and aluminum crimp top. The filled and sealed vials are terminally sterilized.

Subject compositions containing a water insoluble drug may be prepared as follows. This method is one example and may be successfully modified by a person skilled in the art.

1. Preparation of a highly concentrated drug stock solution using a suitable solvent

A highly concentrated drug stock solution is prepared freshly by combining accurate amounts of the drug and a suitable solvent. After dissolving the drug in the solvent, the resulting solution may be filtered through a sterilization grade filter before use.

2. Preparation of Phase 1 drug slurry through controlled precipitation

Precipitate the drug by adding an accurate amount of the drug stock solution dropwise into a suitable and accurate amount of water according to the formulation composition while constant mixing. The resultant slurry is homogenized by a homogenizer for a suitable amount of time and at a proper speed.

3. Preparation of Final subject composition/gel formulation with drug

Accurately weigh out an appropriate amount of Phase 1 drug slurry, and combine it with appropriate amounts of solvent, buffer, salts, etc. except methylcellulose. Heat the mixture to approximately 60-80°C, preferably 67-70°C with constant mixing. Weigh accurately an appropriate amount of methylcellulose and add the powder to the hot slurry while constantly mixing. When the cellulose is well dispersed, remove the heat source, bring the batch to the target weight with water, and continue mixing until the dispersion is cooled to ambient temperature. Chill the dispersion overnight to allow full hydration of cellulose and produce the final subject composition with drug that exhibits appropriate/desired reverse-thermal-gelation properties.

4. Filling and Terminal Sterilization

The chilled bulk gel formulation with drug is filled into Type 1 glass serum vials, and sealed with silicone coated stoppers and aluminum crimp top. The filled and sealed vials are terminally sterilized.

Examples 1-20

Composition Examples 1-17 were prepared as described above with the formulas shown in Tables 1 to 6 below.

5

Table 1 Mono gelation modulator formulation systems with citrate

Ingredients	Example 1	Example 2
Methylcellulose A 15LV	5% w/w	5% w/w
Citrate buffer pH 7.4	116 mmole/kg	100 mmole/kg
Water for Injection	QS	QS

Table 2 Dual gelation modulator formulation system and triple gelation modulator formulation system.

Ingredients	Example 3*	Example 4*	Example 5	Example 6	Example 7	Example 8
Lenvatinib	1% w/w	1% w/w	1% w/w	1% w/w	1% w/w	2% w/w
DMSO	5% w/w	5% w/w	5% w/w	---	5% w/w	---
Methylcellulose A 15LV	5% w/w	5% w/w	5% w/w	5% w/w	5% w/w	5% w/w
Citrate buffer pH 7.4	100 mmole/kg	100 mmole/kg	116 mmole/kg	116 mmole/kg	116 mmole/kg	116 mmole/kg
Dibasic sodium phosphate	---	---	---	---	0.06% w/w	0.06% w/w
Water for Injection	QS	QS	QS	QS	QS	QS

- 10
- Examples 3 and 4 are identical in formulation composition but differ in the manner in which the slurry of the active pharmaceutical ingredient (API) is formed.

Table 3 Mono gelation modulator formulation systems with dimethyl sulfoxide (DMSO)

Ingredients	Example 9	Example 10	Example 11	Example 12	Example 13
Methylcellulose A15 LV	5% w/w	5% w/w	5% w/w	5% w/w	7% w/w
DMSO	0%	2.5% w/w	5% w/w	10% w/w	0% w/w
Water for injection	QS	QS	QS	QS	QS

- 15
- Examples 9, 10, 11, 12 and 13 were prepared following final bulk gel formulation process without drug described herein and then studied for gelation at 37°C. For this study, 1mL of

Examples 8, 9, 10, 11 and 12 were taken in 2mL glass vials, capped, and placed in a 37°C water bath. The vials were taken out of the water bath at 0.5h, 1h and 2h and checked for gel formation using the inverting flow test method. For this test, the vials were taken out of the water bath and then inverted for 5-6 secs. When the solution remained inverted without running/flowing, then the term “gel” is used indicating “Gel” formation, and if it flowed, indicating “Not” for no gel formation/gelation. Table 4 shows that DMSO can function as a gelation modulator for methylcellulose at all three DMSO concentrations studied (2.5%, 5% and 10%).

10 **Table 4** Inverting flow test method results of freshly prepared examples for gelation at 37°C

<u>Example</u>	<u>After 0.5h</u>	<u>After 1h</u>	<u>After 2h</u>
<u>Example 9</u>	<u>Not</u>	<u>Not</u>	<u>Not</u>
<u>Example 10</u>	<u>Not</u>	<u>Not</u>	<u>Almost</u>
<u>Example 11</u>	<u>Not</u>	<u>Gel</u>	<u>Gel</u>
<u>Example 12</u>	<u>Gel</u>	<u>Gel</u>	<u>Gel</u>
<u>Example 13</u>	<u>Not</u>	<u>Gel</u>	<u>Gel</u>

Table 5 Examples of compositions with active pharmaceutical ingredients

Ingredients	Example 14	Example 15	Example 16
Ketorolac free acid	2% w/w	-	-
Bimatoprost	-	0.5% w/w	-
Travoprost	-		0.5% w/w
DMSO	2.5% w/w	-	-
Ethanol	-	2.5% w/w	2.5% w/w
Tween 80	-	0.25% w/w	0.25% w/w
Methylcellulose A 15LV	5% w/w	5% w/w	5% w/w
Citrate buffer, pH 4.8	116 mmole/kg	116 mmole/kg	116 mmole/kg
Water for Injection	QS	QS	QS

Examples 14-16 were prepared by the method described herein. Example 14 formed a gel and was not flowable at 37°C. Examples 15 and 16 did not form a gel and were flowable at 37°C.

Table 6 Example of composition with Axitinib as active pharmaceutical ingredient

Ingredients	Example 17
Axitinib	1% w/w
DMSO	5% w/w
Methylcellulose A 15LV	5% w/w
Citrate buffer pH 7.4	116 mmole/kg
Dibasic sodium phosphate	---
Water for Injection	QS

Example 17 was prepared using a method similar to that used for Examples 3 to 8, with
 5 Axitinib as the active pharmaceutical ingredient. Example 17 formed a gel and was not flowable
 at 37°C.

Example 18

Properties of terminally sterilized Example 5 are shown in Example 18. Shown in Table 7
 10 below are physical appearance, resuspendability, flowability, injectability and assay data, and in
 vitro drug release data of terminally sterilized Example 5. FIG. 5 depicts in vitro drug release for
 several different lenvatinib formulations listed in Table 2.

Table 7 Terminally sterilized example 5

Test	Initial																		
Appearance and Resuspendability	White opaque flowable gel. Easily resuspendable by manual hand shake. Uniform gel.																		
Flowability	Chilled: flowable Room Temp: flowable 37°C: flowable																		
Injectability of Chilled Gel	27G: Injectable 31G: Injectable																		
Assay	96.7% of label claim																		
In-Vitro Drug Release (IVRT)*	<table border="1"> <thead> <tr> <th>Hours</th> <th>% cumulative release</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>0</td> </tr> <tr> <td>1</td> <td>11</td> </tr> <tr> <td>6</td> <td>16</td> </tr> <tr> <td>12</td> <td>18</td> </tr> <tr> <td>24</td> <td>23</td> </tr> <tr> <td>48</td> <td>30</td> </tr> <tr> <td>96</td> <td>36</td> </tr> <tr> <td>120</td> <td>41</td> </tr> </tbody> </table>	Hours	% cumulative release	0	0	1	11	6	16	12	18	24	23	48	30	96	36	120	41
Hours	% cumulative release																		
0	0																		
1	11																		
6	16																		
12	18																		
24	23																		
48	30																		
96	36																		
120	41																		

	144	44
	264	50
	336	53

* using USP Apparatus 2 (paddle).

Example 19

A rabbit study was carried out to evaluate the duration of residence of lenvatinib in 3 gel formulations. Rabbits in each group (Formulations listed as examples 3, 6, 4, for Groups 1, 2, 3, respectively) were administered with a 1% lenvatinib gel formulation once in each eye via intravitreal (IVT) injection at 0.5 mg eye.

In all groups, as expected the highest concentrations of lenvatinib were detected in the vitreous humor, retina, and choroid over time. Concentrations of lenvatinib steadily decreased in Groups 1 and 3 in the vitreous humor, retina, and choroid, but remained relatively steady in Group 2 over 20 weeks post the IVT dose. Concentrations of lenvatinib in the ocular tissues from Group 1 had low to no quantifiable levels of lenvatinib by Weeks 12. Group 2 had steady concentrations of lenvatinib out to Week 20 in all ocular tissues examined. Group 3 ocular tissues concentrations of lenvatinib were general steady out to Week 12 and then by Week 20 quantifiable concentrations of lenvatinib was sporadic.

Table 8 Plasma concentrations in Dutch Belted rabbits following single IVT injection of lenvatinib 1% gel

Group	Week	Concentration (ng/mL)
Group 1	2	55.3
	6	4.67
	12	<LLOQ
	20	<LLOQ
Group 2	2	11.4
	6	3.49
	12	7.53
	20	4.50
Group 3	2	32.1
	6	9.76
	12	2.48
	20	<LLOQ

LLOQ = 0.2 ng/mL

Given the rate-limiting compartment being the vitreous humor, plasma concentrations appeared to parallel those in the ocular tissues but in a much lower magnitude. Plasma lenvatinib concentrations were quantifiable up to Week 6 from Group 1, quantifiable throughout Week 20 from Group 2, and quantifiable at Week 12 but not at Week 20 for Group 3 (Table 8).

Table 9 Residence time and lenvatinib remaining in vitreous humor after single IVT injection

Formulation	1% lenvatinib (50 μ L) on Gel		
	Group 1	Group 2	Group 3
Formulation residence time	5-6 weeks	>20 weeks	11-14 weeks
	Drug Remaining in Vitreous Humor: Average Recovery (% Dose)		
Day 14 (2 weeks)	27.7%	57.9%	35.5%
Day 42 (6 weeks)	1.01%	47.1%	6.02%
Day 84 (12 weeks)	<0.01%	16.2%	0.725%
Day 140 (20 weeks)	<0.01%	7.78%	<0.01%

Table 9 shows the recoveries of the lenvatinib dose remaining in the vitreous humor after a single IVT injection with different formulations. Lenvatinib recovery in Group 1 was approximately 28% at Week 2 and then reduced to an insignificant percentage by Week 20. Lenvatinib recovery in Group 2 at week 2 was approximately 58% and reduced to approximately 8% by Week 20; the formulation administered to Group 2 has the longest residence time in the vitreous humor. In Group 3, lenvatinib recovery in vitreous humor was approximately 36% at Week 2 and reduced to an insignificant percentage by Week 20.

Fundus imaging of formulation dispersion was performed for each eye continuously on Days 0 (after dose), 3, 7, 14, 28, 42, 84, and 140. The fundus image and ocular tissue concentration results paralleled each other. Groups 1 and 3 demonstrated a faster drug release than the Group 2. The Group 2 demonstrated prolonged release of lenvatinib throughout a 20-week study duration, as demonstrated by steady lenvatinib concentrations in ocular tissues and plasma over time (FIGS. 6-8)

Example 20

A rat study was carried out to evaluate the duration of residence of lenvatinib gel after receiving a single intraprostatic injection.

5 Twelve rats in each group (Groups 1, 2, 3) were dosed with 3 different gel formulations of 1% lenvatinib (example 3, 4, and 6) and at two doses (0.2 and 2 mg). Plasma samples were collected on Study Days 3, 7, 14, 21, 28, 42, and 60 post dose. Prostrates were harvested from these rats following termination on Day 60.

10 After a single 0.2mg dose of lenvatinib, the average maximal plasma concentration of lenvatinib was 9.15, 12.0 and 5.24 ng/mL for the Group 1, 2, and 3 animals respectively. The maximal dose concentration was on Day 3. The plasma lenvatinib concentrations were detectable through Day 14, 42, and 60 post dose in Group 1, 2, and 3 respectively. The LLOQ was 0.100 ng/mL (Table 10).

15 **Table 10** Average plasma concentrations after a single intraprostatic injection of different formulations of 1% lenvatinib to rats

	Test Article	Dose Level (mg/animal)	Timepoint (day after the single intraprostatic injection on Day 1)						
			3	7	14	21	28	42	60
	Group 1	0.2	9.15	3.36	1.63	<LLOQ	<LLOQ	<LLOQ	<LLOQ
		2.0	157	73.9	43	15.6	11.5	1.72	<LLOQ
	Group 2	0.2	12	4.45	1.59	0.269	0.0858	0.0539	<LLOQ
		2.0	103	56.8	42.3	20.6	12.1	2.32	0.934
	Group 3	0.2	5.24	2.63	2.24	1.48	0.805	0.627	0.561
		2.0	24.2	11.8	12.4	7.84	5.92	5.08	5.68

LLOQ = 0.1 ng/mL

20 After delivering 2 mg of lenvatinib to rats, the maximal prostate concentration, after 60 days, of lenvatinib was in Group 3, with the highest average concentration in the ventral lobe (494,000 ng/g). The dorsolateral lobe had an average concentration of 127,000 ng/g. The 0.2 mg/animal for Group 3, ventricle lobe had an average concentration of 13,500 ng/g, the dorsolateral lobe had an average concentration of 2450 ng/g. Tissue concentrations for the

Groups 1 and 2 were essentially not detectable or very low, after 60 days, relative to the Group 3 animals. Prostate summary data is presented in Table 11.

Table 11 Average prostate concentrations of lenvatinib on day 60 after a single intraprostatic injection of different formulations of 1% lenvatinib to Sprague Dawley rats

Test Article	Dose Level (mg/animal)	VP-(ng/g)	DLP (ng/g)
Group 1	0.2	0.41	7.8
	2.0	0.505	1.37
Group 2	0.2	<LLOQ	<LLOQ
	2.0	<LLOQ	343
Group 3	0.2	13,500	2450
	2.0	49,400	127,000

LLOQ = 0.2 ng/mL or 0.8 ng/g; VP: ventral lobe of prostate, DLP: dorsolateral lobe of prostate

For each of the three formulations, there was dose dependency in the plasma concentration-time profile (Table 10). All 3 formulations demonstrated prolonged drug release from the dosing site of prostate to the plasma compartment, with C_{max} observed on Day 3. The drug release “half-life” was approximately 6, 8, and 43 days for Group 1, 2 and 3, respectively. Both Groups 1 and 2 achieved higher C_{max} than Group 3, but Group 3 maintained plasma concentration much longer than Groups 1 and 2.

Table 11 shows a controlled and sustained drug delivery system for prostate; that is in Table 11 Group 3 had the highest percentage dose remaining in the prostate on Day 60, about 2.7% and 12.7% for the 0.2 mg and 2 mg dose groups, respectively.

The following embodiments are specifically contemplated:

- Embodiment 1. A pharmaceutical composition comprising a reverse thermal gelation material, wherein the pharmaceutical composition makes a transition from liquid to gel near the body temperature of a mammal.
- 5 Embodiment 2. The pharmaceutical composition of embodiment 1, wherein the mammal is a human being.
- Embodiment 3. The pharmaceutical composition of embodiment 2, further comprising at least one active pharmaceutical ingredient,
- Embodiment 4. The pharmaceutical composition of embodiment 2 or 3, wherein the
10 pharmaceutical composition is a liquid at about 5 °C.
- Embodiment 5. The pharmaceutical composition of embodiment 1, 2, 3, or 4, wherein the pharmaceutical composition is a gel between about 35 °C and 40 °C .
- Embodiment 6. The pharmaceutical composition of embodiment 1, 2, 3, 4, or 5, further comprising methylcellulose, dimethyl sulfoxide and citrate.
- 15 Embodiment 7. A pharmaceutical composition comprising: an active pharmaceutical ingredient, methylcellulose, dimethyl sulfoxide and citrate.
- Embodiment 8. The pharmaceutical composition of embodiment 6 or 7, wherein the methylcellulose is present at a concentration of about 2% (w/w) to about 10% (w/w).
- Embodiment 9. The pharmaceutical composition of embodiment 6, 7, or 8, wherein the
20 citrate is present at a concentration of about 25 mmole/kg to about 200 mmole/kg.
- Embodiment 10. The pharmaceutical composition of embodiment 1, 2, 3, 4, 5, 6, 7, or 9, having a pH of about 5.0 to about 9.0.
- Embodiment 11. The pharmaceutical composition of embodiments 1, 2, 3, 4, 5, 6, 7, 8,
9, or 10, having a first storage modulus (G') at about 37 °C and a second G' at about 5 °C,
25 wherein the first G' is higher than the second G' .
- Embodiment 12. The pharmaceutical composition of embodiment 11, wherein the first G' is at least about tenfold higher than the second G' .
- Embodiment 13. The pharmaceutical composition of embodiments 1, 2, 3, 4, 5, 6, 7, 8,
9, 10, 11, or 12, having a first complex viscosity at about 37 °C and a second complex viscosity
30 at about 5 °C, wherein the first complex viscosity is higher than the second complex viscosity.

Embodiment 14. The pharmaceutical composition of embodiment 13, wherein the first complex viscosity is at least twofold higher than the second complex viscosity.

Embodiment 15. The pharmaceutical composition of embodiments 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 having a first loss modulus (G'') at about 37 °C and a second G'' at about 5 °C, wherein the first G'' is higher than the second G'' .

Embodiment 16. The pharmaceutical composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15, wherein the % gelation at about 37 °C is at least 70%.

Embodiment 17. The pharmaceutical composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or 16, wherein the % gelation at about 5 °C is no greater than 10%.

10 Embodiment 18. A method of treating a disease, comprising administering a pharmaceutical composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17 to a mammal in need thereof.

Embodiment 19. The method of embodiment 18, wherein the mammal is a human being.

15 Embodiment 20. Use of a pharmaceutical composition of embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 16 or 17 in the manufacture of a medicament for treating a disease.

CLAIMS

1. A pharmaceutical composition comprising a reverse thermal gelation material, wherein the pharmaceutical composition makes a transition from liquid to gel near the body temperature of a mammal.
- 5 2. The pharmaceutical composition of claim 1, wherein the mammal is a human being.
3. The pharmaceutical composition of claim 1 or 2, further comprising an active pharmaceutical ingredient.
4. The pharmaceutical composition of claim 3, wherein the active pharmaceutical ingredient is designed for anti-angiogenesis.
- 10 5. The pharmaceutical composition of claim 3, wherein the active pharmaceutical ingredient is a multi-kinase inhibitor.
6. The pharmaceutical composition of claim 3, wherein the active pharmaceutical ingredient comprises axitinib, nintedanib, pirfenidone, riociguat, sorafenib, sunitinib, lenvatinib, regorafenib, ponatinib, pazopanib, or a combination thereof.
- 15 7. The pharmaceutical composition of claim 1, 2, 3, 4, 5, or 6, wherein the pharmaceutical composition is a liquid at a temperature of about 2 °C to about 8 °C.
8. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, or 7, wherein the pharmaceutical composition is a gel at a temperature of about 30 °C to about 40 °C.
9. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7, or 8, further comprising a
20 polymer agent and a gelation modulator.
10. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, wherein the polymer agent comprises an alkylcellulose.
11. The pharmaceutical composition of claim 10, wherein the polymer agent is methylcellulose.
- 25 12. The pharmaceutical composition of claim 9, 10, or 11, wherein the gelation modulator comprises phosphate, dihydrogen phosphate, hydrogen phosphate, tris (hydroxymethyl)aminomethane, borate, histidine, carbonate, bicarbonate, citrate, citric acid acetate, tartarate, fumarate, lactate, formate, sulfamate, oxalate, malonate, succinate, maleate, adipate, benzoate, o-toluate, benzene tetracarboxylate, glutamate, e-amino
30 caproate, aspartate, glycinate, arginate, lysinate, taurate, ethanol, dimethyl sulfoxide,

glycerin, dimethylformamide, propylene glycol, a polyethylene glycol, a vegetable oil, corn oil, olive oil, castor oil, vitamin E, a phospholipid, a polysorbate 20, a polysorbate 40, a polysorbate 60, a polysorbate 80, a mono-saccharide, a di-saccharide, dextrose, sucrose, a sugar alcohol, mannitol, sorbitol, an antioxidant, ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene, sodium bisulfate, sodium sulfite, sodium metabisulfite, EDTA, sodium carboxymethylcellulose, sodium alginate, hydroxypropylmethylcelluloses, carbomers, hyaluronic acid, a hyaluronate salt, or a combination thereof.

13. The pharmaceutical composition of claim 12, wherein the gelation modulator comprises phosphate, dimethyl sulfoxide, citrate, or a combination thereof.

14. A pharmaceutical composition comprising: an active pharmaceutical ingredient, methylcellulose, dimethyl sulfoxide and citrate.

15. The pharmaceutical composition of claim 14 further comprising phosphate.

16. The pharmaceutical composition of claim 11, 14 or 15, wherein the methylcellulose is present at a concentration of about 2% (w/w) to about 10% (w/w).

17. The pharmaceutical composition of claim 16, wherein the citrate is present at a concentration of about 25 mmol/kg to about 200 mmole/kg.

18. The pharmaceutical composition of claim 17, having a pH of about 5.0 to about 9.0.

19. The pharmaceutical composition of claim 17, having a pH of about 6.0 to about 8.0.

20. A pharmaceutical composition comprising: an active pharmaceutical ingredient, methylcellulose, dimethyl sulfoxide and citrate, wherein the pharmaceutical composition has a first storage modulus (G') at about 37 °C and a second G' at about 5 °C, wherein the first G' is higher than the second G' .

21. The pharmaceutical composition of claim 20, wherein the first G' is at least about tenfold higher than the second G' .

22. The pharmaceutical composition of claim 21, having a first complex viscosity at about 37 °C and a second complex viscosity at about 5 °C, wherein the first complex viscosity is higher than the second complex viscosity.

23. The pharmaceutical composition of claim 22, wherein the first complex viscosity is at least twofold higher than the second complex viscosity.

24. The pharmaceutical composition of claim 23, having a first loss modulus (G'') at about 37°C and a second G'' at about 5 °C, wherein the first G'' is higher than the second G'' .
25. The pharmaceutical composition of claim 24, wherein the % gelation at about 37°C is at least 70%.
- 5 26. The pharmaceutical composition of claim 25, wherein the % gelation at about 5°C is no greater than 20%.
27. The pharmaceutical composition of claim 20 or 26, further comprising phosphate.
28. A method of treating a disease, comprising administering the pharmaceutical composition of claim 26 or 27 to a mammal in need thereof.
- 10 29. The method of claim 28, wherein the disease is characterized by chronic inflammation, with associated angiogenesis and fibrosis.
30. The method of claim 28, wherein the disease comprises a dermal-related disorder, a benign prostate hyperplasia related disorder, an eye-related disorder, a rosacea-related disorder, a uterine fibroid or a related condition, a neoplastic disease, or an adhesion-related disorder.
- 15 31. The method of claim 30, wherein the pharmaceutical composition is administered topically, by intralesional injection, by paralesional injection, by intravitreal injection, by intraprostatic injection, by intramuscular injection, by subcutaneous injection, by intradermal injections, by intra-tissue injection, or by eye drop.
- 20 32. The method of claim 28, 29, 30, or 31, wherein the mammal is a human being.
33. A method of delivering an active pharmaceutical ingredient, comprising administering the pharmaceutical composition of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27 to a mammal in need of the active pharmaceutical ingredient, wherein the composition provides a therapeutic effect with a reduced active pharmaceutical ingredient dosing frequency.
- 25 34. The method of claim 33, wherein the pharmaceutical composition is administered topically, by intralesional injection, by paralesional injection, by intravitreal injection, by intraprostatic injection, by intramuscular injection, by subcutaneous injection, by intradermal injections, by intra-tissue injection, or by eye drop.
- 30 35. The method of claim 33 or 34, wherein the mammal is a human being.

36. The method of claim 33, 34, or 35, wherein a single administration of the active pharmaceutical ingredient provides a therapeutically effective concentration of the active pharmaceutical ingredient to the mammal for at least 5 days.

37. The method of claim 36, wherein a single administration of the active pharmaceutical
5 ingredient provides a therapeutically effective concentration of the active pharmaceutical ingredient to the mammal for at least 6 weeks.

38. A method of preparing a pharmaceutical composition having reverse thermal gelation properties, comprising:

10 mixing a polymer agent into a slurry containing a gelation modulator and an active pharmaceutical ingredient, wherein the mixing occurs at a temperature of about 60 °C to about 80 °C;

wherein the slurry is formed by a method comprising precipitating the active pharmaceutical ingredient into an aqueous liquid, and adding the gelation modulator to the slurry.

15

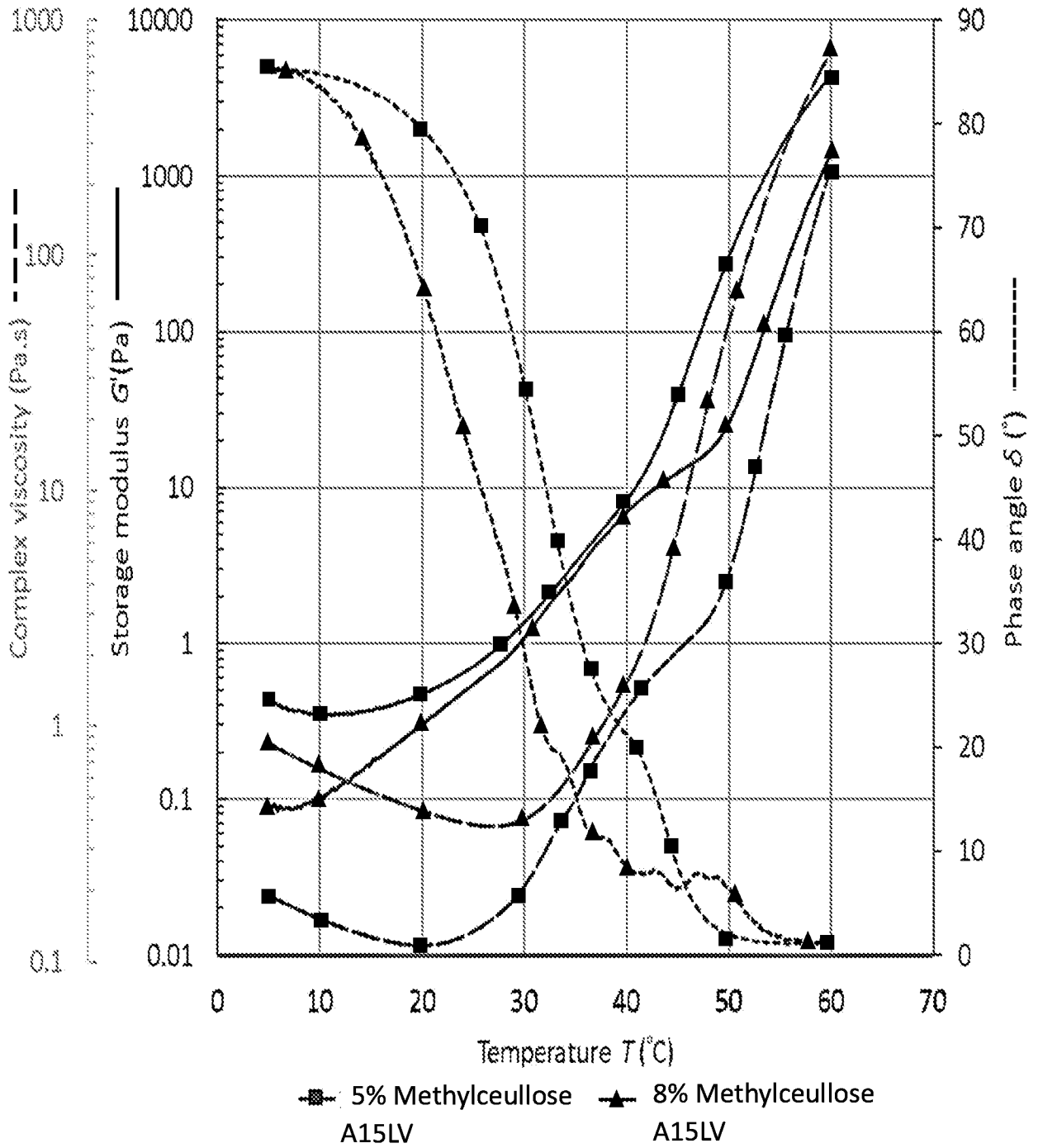


FIG. 1

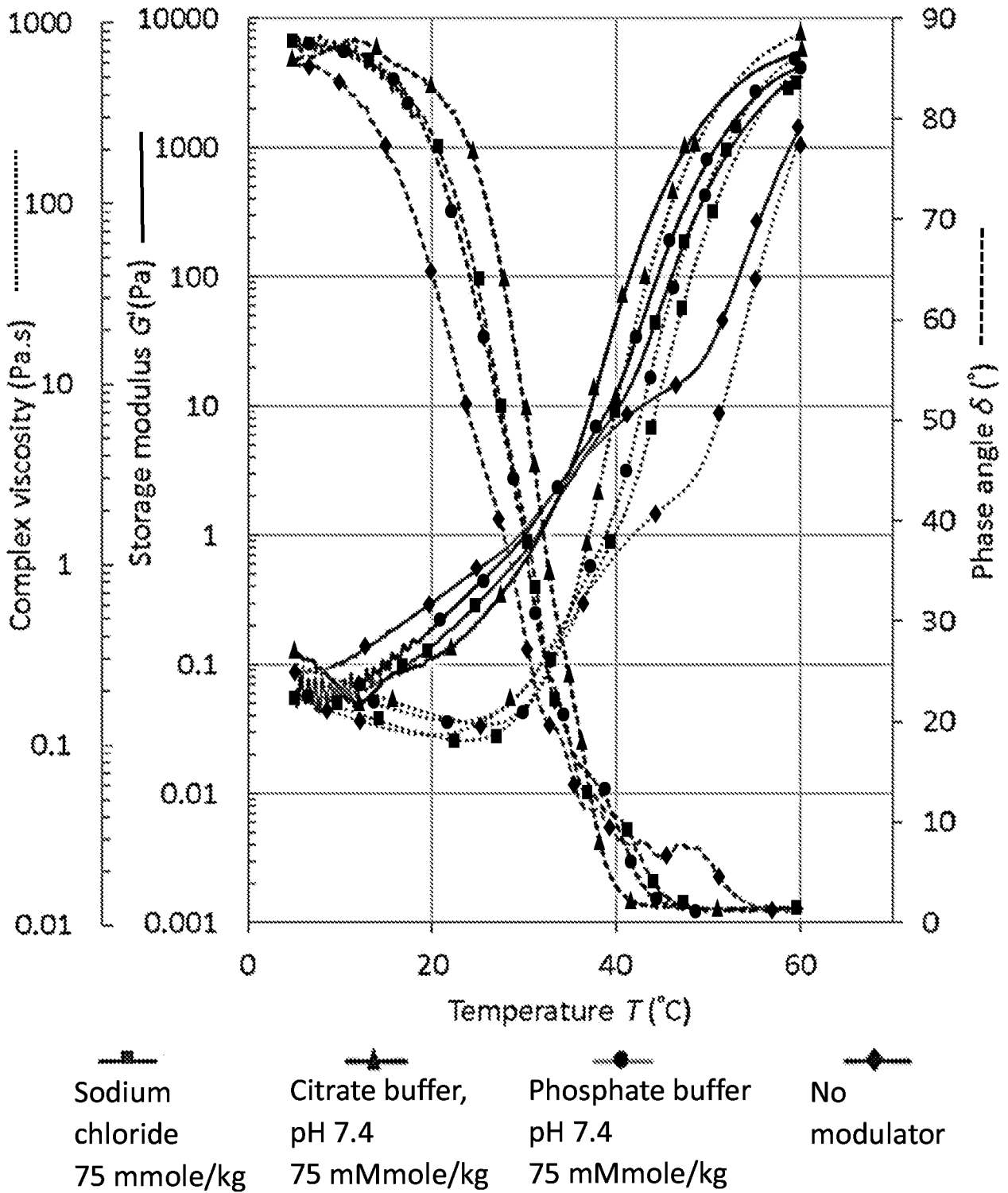


FIG. 2

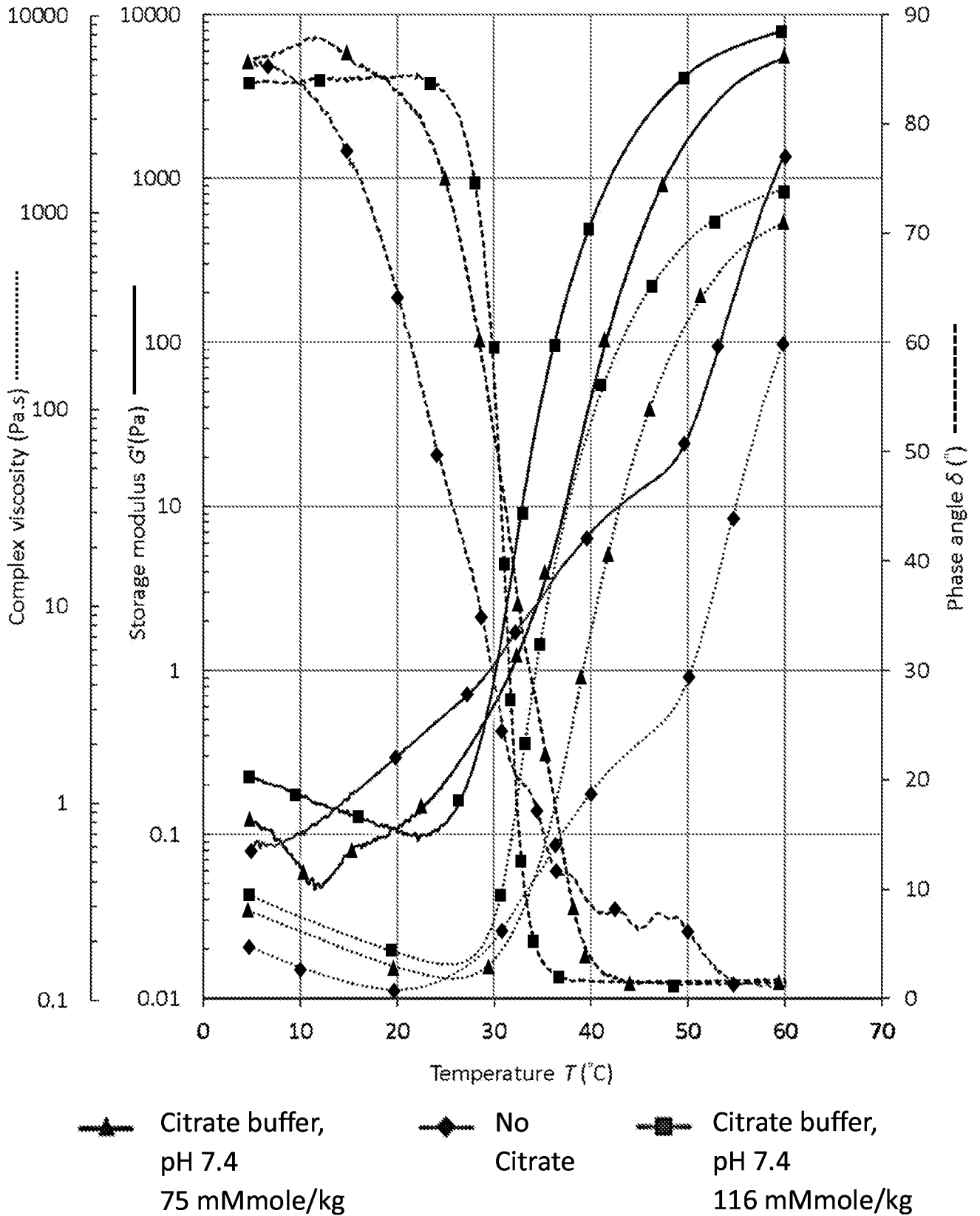


FIG. 3

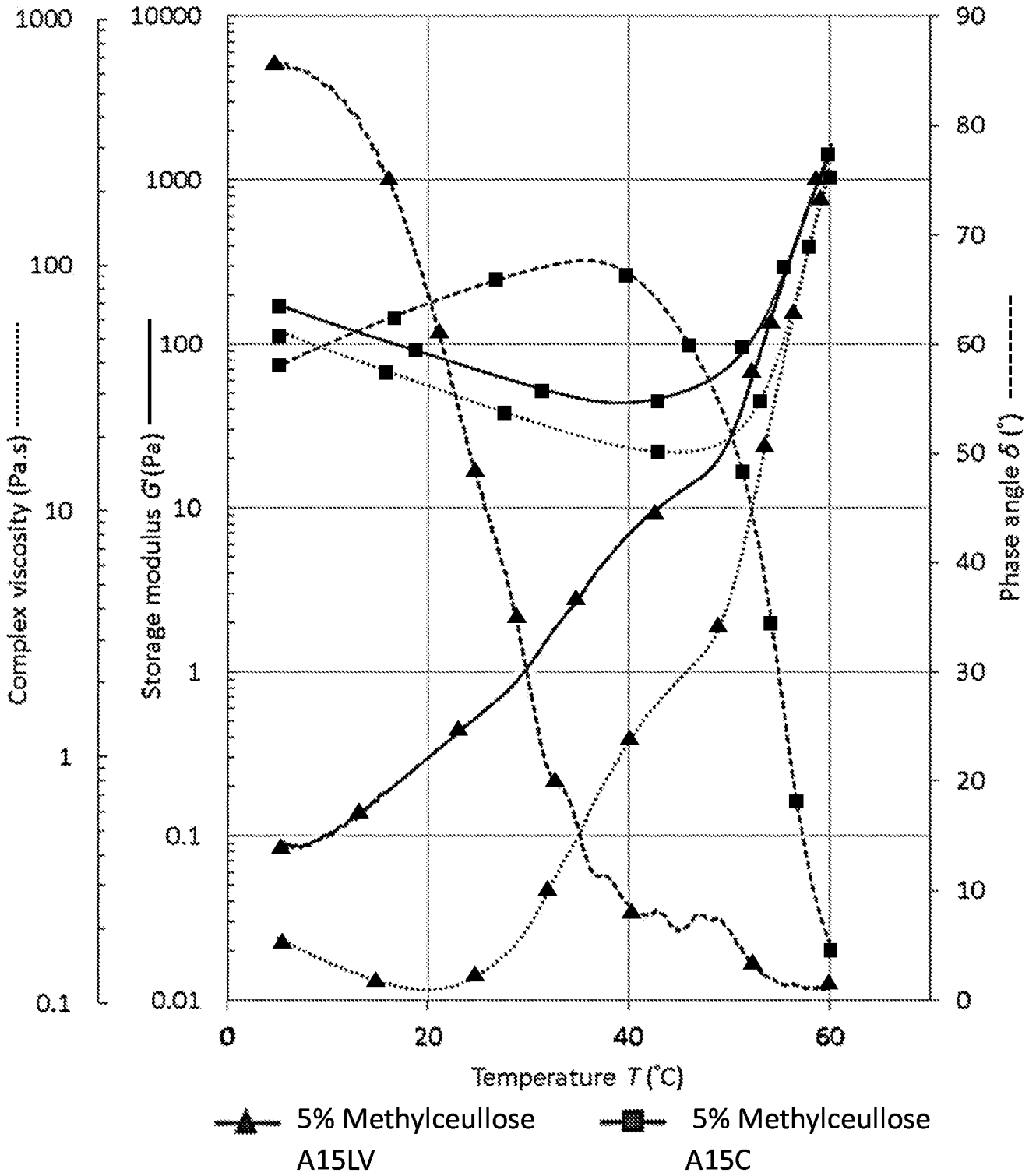


FIG. 4

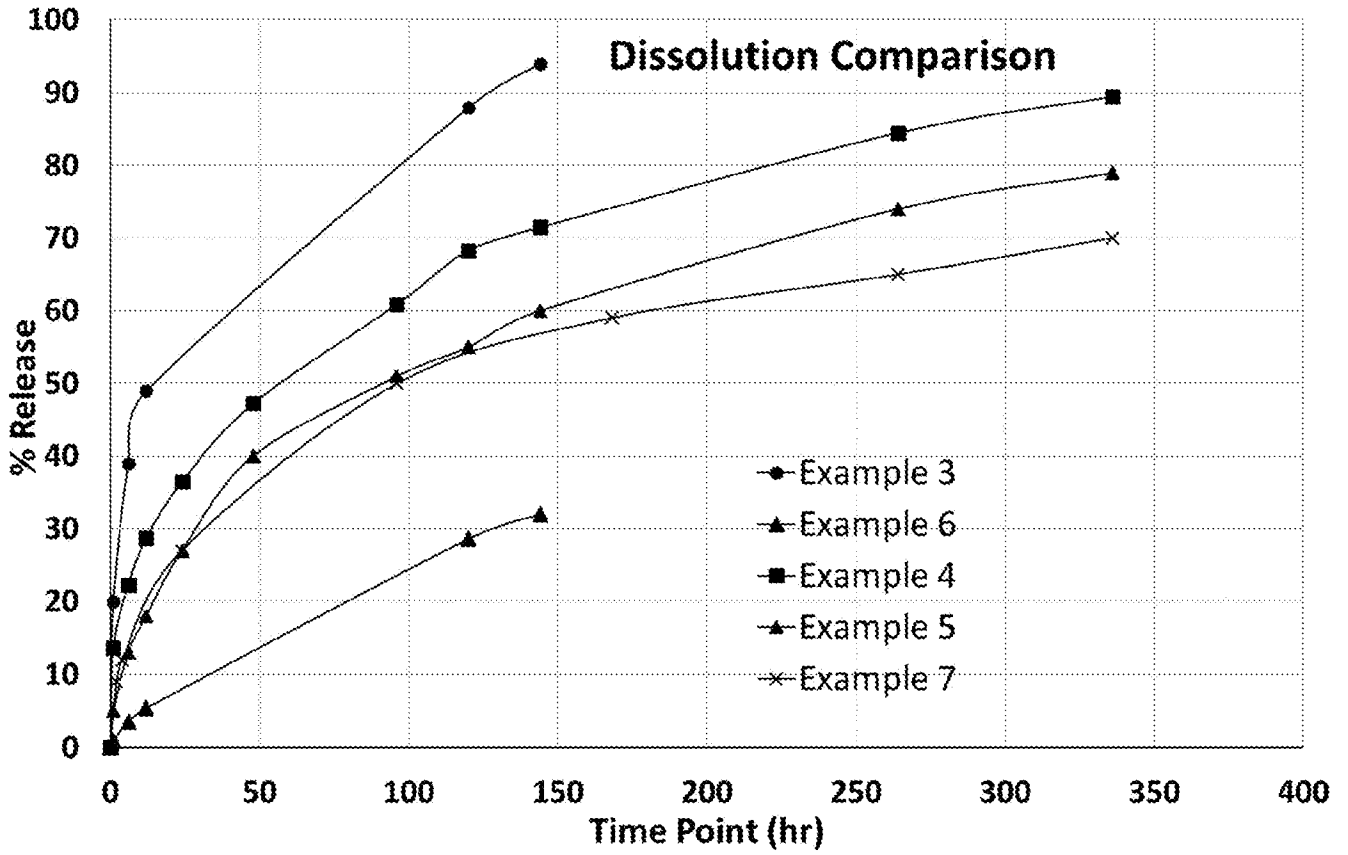


FIG. 5

Concentrations in Ocular Tissues After Single IVT Injection

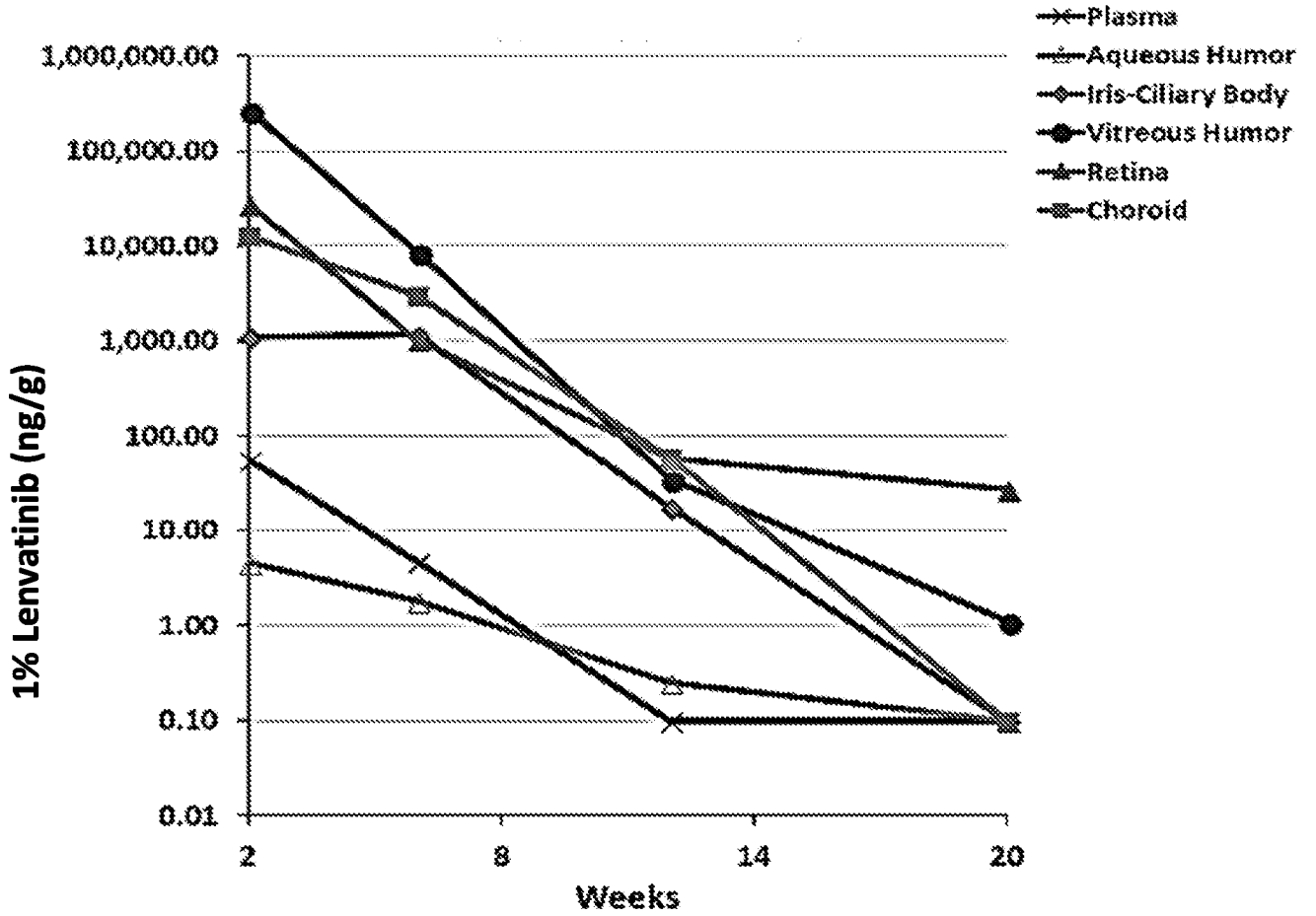


FIG. 6

Concentrations in Ocular Tissues After Single IVT Injection

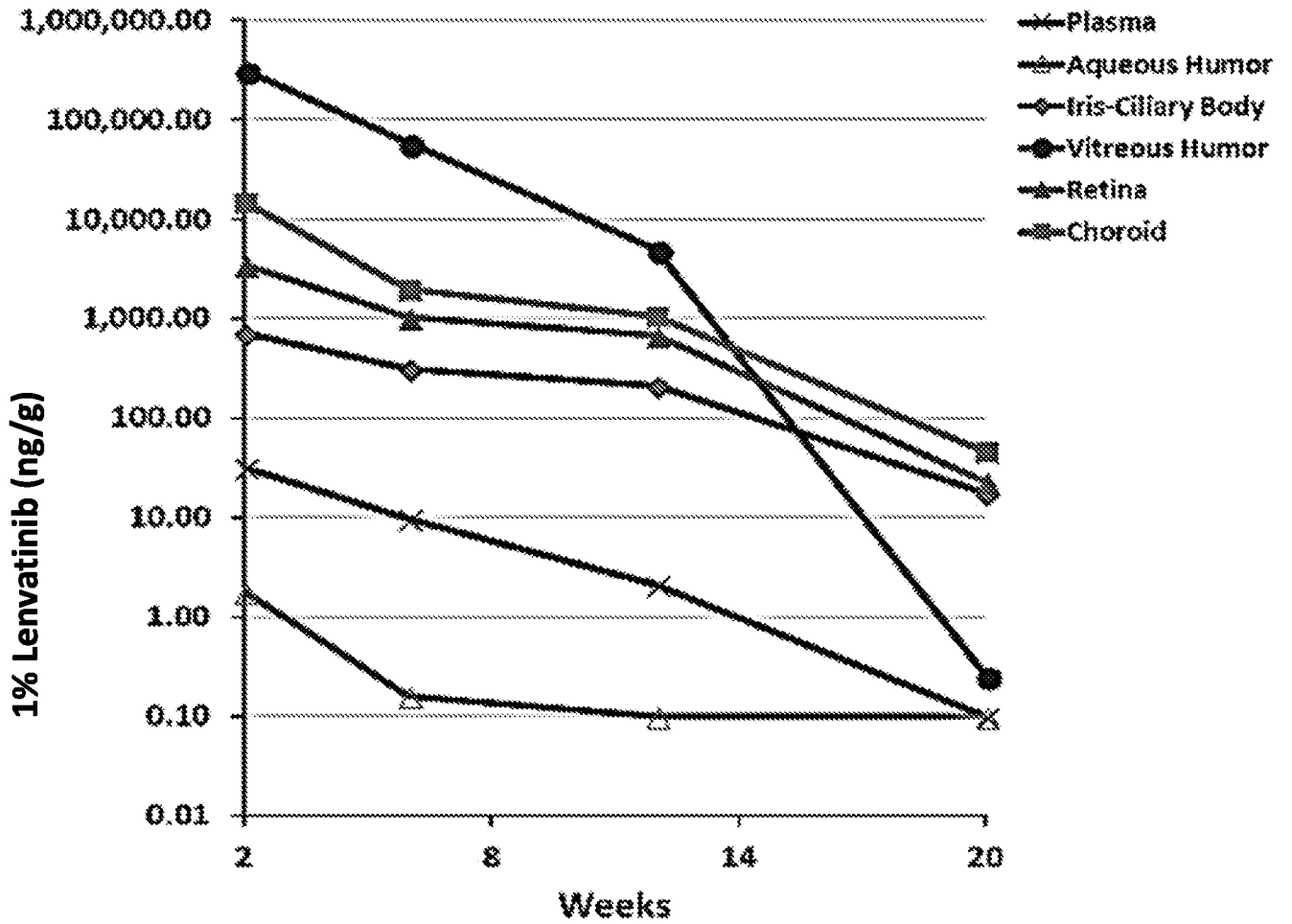


FIG. 7

Concentrations in Ocular Tissues After Single IVT Injection

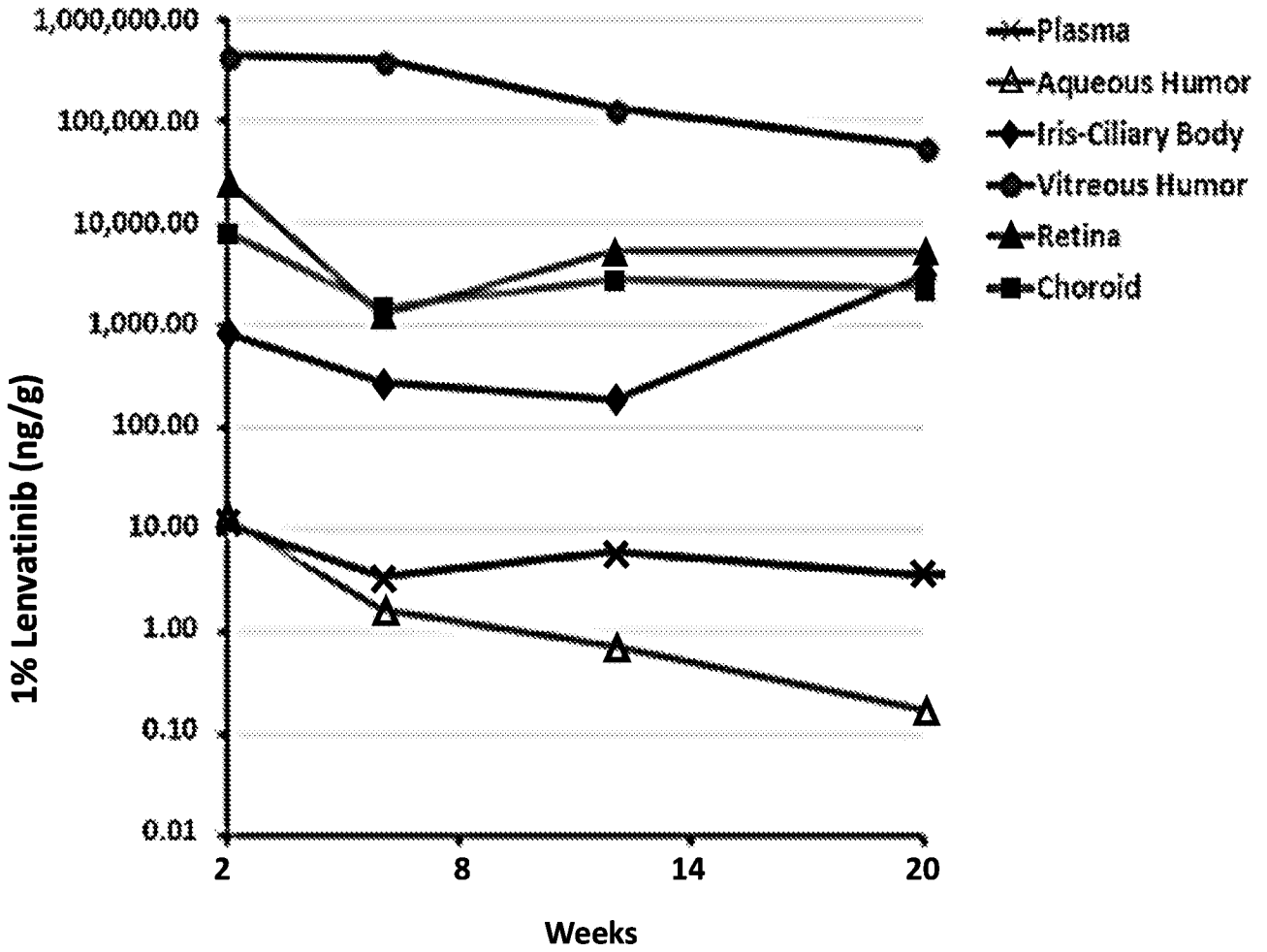


FIG. 8

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/63044

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

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

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

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

- 3. Claims Nos.: 7-13, 16-19, 28-37
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

- 1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
- 2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
- 3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

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

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/63044

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/155; A61K 31/337; A61K 31/496 (2020.01)

CPC - A61K 31/155; A61K 31/337; A61K 31/37; A61K 31/496; A61K 31/573; A61K 31/7036

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)

See Search History document

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

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----	US 5,441,732 A (Hoeg et al.) 15 August 1995 (15.08.1995) Abstract; col 3 In 50-55; col 3 In 40-45; col 4 In 20-25; col 12 In 60-65; Figure 1 and entire document	1-3,38
Y		4-6,22-26,27/26
X ----	US 2018/0228903 A1 (Children's Medical Center) 16 August 2018 (16.08.2018) Abstract, para [0012], para [0016], para [0015], para [00319], para [00204] figures 10,13 and entire document	14,15,20,21,27/20
Y		22-26,27/26
Y	WO 2018/148653 A1 (Aiviva Holding Limited) 16 August 2018 (16.08.2018) Abstract; para [0016], para [0025], para [0024]	4-6
Y	US 4,861,760 A (Mazuel et al.) 29 August 1989 (29.08.1989) Abstract; col 1 In 5 - col 3 In 40	1-6,14,15,20-27,38
Y	US 5,252,318 A (Joshi et al.) 12 October 1993 (12.10.1993) Abstract; col 2 In 65-col 5 In 10	1-6,14,15,20-27,38

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

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

"D" document cited by the applicant in the international application

"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

22 January 2020

Date of mailing of the international search report

06 FEB 2020

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