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(54) **Title**: FIXED DOSE COMBINATION OF BROMONIDINE AND TIMOLOL

(57) **Abstract**: Embodiments disclosed herein are directed to fixed compositions comprising brimonidine and timolol for lowering intraocular pressure and treating glaucoma.

Fixed dose combination of brimonidine and timolol

By Inventors
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BACKGROUND OF THE INVENTION

[0001] Brimonidine and timolol are medications that have been formulated as ophthalmic solutions known to reduce intraocular pressure ("IOP") in patients with glaucoma or ocular hypertension. The medications are available as monotherapies in various countries in more than one concentration (brimonidine 0.1%, 0.15%, 0.2% and timolol 0.25% and 0.5%). These medications are known to be used concurrently for those with conditions that cannot be adequately controlled by the monotherapies. Formulating brimonidine and timolol into a fixed combination product provides advantages to patients in terms of providing an improvement in benefit-risk, and also simplifying treatment administration.

BRIEF SUMMARY OF THE INVENTION

[0002] In one embodiment, there is provided a composition for the treatment of glaucoma and elevated intraocular pressure, the composition comprising about 0.1% w/v brimonidine tartrate and about 0.68% w/v timolol maleate, the composition being configured for topical ocular administration.

[0003] In some embodiments, the composition comprises 0.1% w/v brimonidine tartrate and 0.68% w/v timolol maleate. The composition may comprise 0.1% w/v brimonidine tartrate, 0.68% w/v timolol maleate, 0.1% w/v sodium chloride, 2.15% w/v sodium phosphate dibasic heptahydrate, 0.22% w/v sodium phosphate monobasic monohydrate, and water. The composition may also comprise 0.1% w/v brimonidine

tartrate, 0.68% w/v timolol maleate, 0.6% w/v boric acid, 0.38% sodium borate decahydrate, 0.5% w/v carboxymethyl cellulose, 0.32% w/v sodium chloride, and water.

[0004] Some compositions may further comprise at least one buffer selected from the group consisting of sodium phosphate dibasic heptahydrate and sodium borate decahydrate. Preferably, the composition has a pH of about 7, or a pH of 7.0. The composition may further comprise one or both of sodium hydroxide and hydrochloric acid.

[0005] In some embodiments, administration of the composition twice daily is at least as effective as twice-daily administration of a second composition comprising a fixed dose of 0.2% w/v brimonidine tartrate and 0.5% w/v timolol maleate. In some embodiments, administration of the composition twice daily results in a lower incidence of one or more adverse events as compared to the twice-daily administration of a second composition comprising a fixed dose of 0.2% w/v brimonidine tartrate and 0.68% w/v timolol maleate. The one or more adverse events may be selected from the group consisting of allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and ocular stinging. In certain embodiments, the composition does not comprise a preservative. However, in some embodiments, the composition further comprises benzalkonium chloride. The benzalkonium chloride may be present at a concentration of about 0.001% w/v to about 0.05% w/v.

[0006] One particular embodiment is a composition for reducing intraocular pressure, the composition consisting essentially of 0.1% w/v brimonidine tartrate, 0.68% w/v timolol maleate, 0.1% w/v sodium chloride, 2.15% w/v sodium phosphate dibasic heptahydrate, 0.22% w/v sodium phosphate monobasic monohydrate, and water.

[0007] Another particular embodiments is a composition for reducing intraocular pressure, the composition consisting essentially of 0.1% w/v brimonidine tartrate, 0.68% w/v timolol maleate, 0.6% w/v boric acid, 0.38% sodium borate decahydrate, 0.5% w/v carboxymethyl cellulose, 0.32% w/v sodium chloride, and water.

[0008] In another preferred embodiment, there is provided an article of manufacture comprising packaging material and a pharmaceutical agent contained within the packaging material, wherein the packaging material comprises a label which indicates the pharmaceutical agent can be used for lowering intraocular pressure, and wherein the pharmaceutical agent is therapeutically effective for lowering intraocular pressure, the pharmaceutical agent comprising 0.1 % brimonidine tartrate and 0.68% timolol maleate.

[0009] In some embodiments, the pharmaceutical agent comprises 0.1% w/v brimonidine tartrate, 0.68% w/v timolol maleate, 0.1% w/v sodium chloride, 2.15% w/v sodium phosphate dibasic heptahydrate, 0.22% w/v sodium phosphate monobasic monohydrate, and water. In some embodiments, the pharmaceutical agent comprises 0.1% w/v brimonidine tartrate, 0.68% w/v timolol maleate, 0.6% w/v boric acid, 0.38% sodium borate decahydrate, 0.5% w/v carboxymethyl cellulose, 0.32% w/v sodium chloride, and water. The pharmaceutical agent may be provided in a unit dose preservative-free configuration. The pharmaceutical agent may be provided in a multi dose preservative-free configuration. The pharmaceutical agent may be provided in a multi dose configuration preserved with one or more preservative agents.

[0010] In yet another embodiment, there is provided a method of treating glaucoma or elevated intraocular pressure, wherein the method comprises administering an effective amount of a single composition comprising about 0.1% w/v brimonidine tartrate and about 0.68% w/v timolol maleate.

[0011] In some embodiments, the composition is administered twice daily to an eye. In some embodiments, administration of the composition twice daily results in a lower incidence of one or more adverse events as compared to the twice-daily administration of a second single composition comprising a 0.2% w/v brimonidine tartrate and 0.5% w/v timolol maleate. The one or more adverse events may be selected from the group

consisting of allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and ocular stinging.

BRIEF DESCRIPTION OF THE DRAWINGS

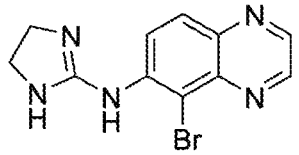
[0012] Figures 1A-C illustrate the results of an experiment measuring ocular tissue and plasma concentrations of brimonidine as a function of time.

[0013] Figures 2A-C illustrate the results of an experiment measuring ocular tissue and plasma concentrations of timolol as a function of time.

DETAILED DESCRIPTION OF THE INVENTION

[0014] Embodiments of the present invention relate to the topical ophthalmic use of brimonidine in combination with timolol for treatment of glaucoma, ocular hypertension, and reduction of intraocular pressure. Brimonidine and timolol, two drugs known to lower intraocular pressure ("IOP"), were found to demonstrate synergistic when administered in combination. Among the benefits of such fixed combinations are enhancements in therapeutic efficacy and treatment administration.

[0015] Brimonidine is an alpha adrenergic agonist represented by the following formula. The chemical name for brimonidine is 5-Bromo-6-(2-imidazolidinylideneamino) quinoxaline L-tartrate, and its structure is reproduced below.



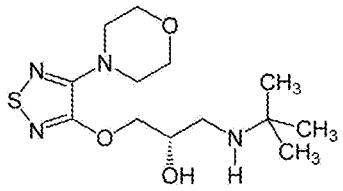
[0016] Brimonidine inhibits the activity of adenylate cyclase through the activation of a G protein-coupled receptor. This reduces cAMP and hence aqueous humor production by the iris-ciliary body. The peripheral alpha 2 agonist activity results in

vasoconstriction of blood vessels (as opposed to central alpha 2 agonist activity that decreases sympathetic tone, as can be seen by the medication clonidine). This vasoconstriction leads to the acute reduction in aqueous humor flow. An increased prostaglandin release due to alpha adrenergic stimulation from prolonged use of brimonidine increases uveoscleral outflow of aqueous humor through the trabecular meshwork, which in conjunction with brimonidine aqueous humor reduction effect helps lower IOP in treating open angle glaucoma and ocular hypertension.

[0017] Brimonidine is commercially available as a monotherapy in several concentrations (0.1%, 0.15%, 0.2% w/v brimonidine tartrate), and is sold by Allergan, Inc. as ALPHAGAN® (or AIPHAGAN® in Japan). While brimonidine is preferably administered as brimonidine tartrate, other salt forms are possible. The free base may be used as well.

[0018] Timolol is a non-selective beta-adrenergic receptor antagonist and reduces aqueous humor production through blockage of beta receptors on the ciliary epithelium. But the precise pharmacological mechanism of the ocular hypotensive action of timolol is not clearly established at this time.

[0019] The chemical name for timolol is (S)-1-(tert-butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]propan-2-ol with the chemical structure shown below.



[0020] Timolol has been commercially available in several concentrations, including 0.25% and 0.5% w/v timolol. One such brand is TIMOPTOL®. Because timolol is preferably administered using the maleate salt, the preceding concentrations may also be expressed as 0.34% and 0.68% w/v timolol maleate. Of course, timolol may be

administered in other salt forms, including the hemihydrate form. The free base may be used as well.

[0021] It should be noted that common usage frequently refers to the concentration of timolol in a composition as the free base form without a counter ion. For example, a 0.5% w/v composition of timolol would be typically understood as referring to a 0.5% w/v composition of timolol without a counter ion (i.e., in the free base form). This corresponds to an equivalent concentration of 0.68% w/v timolol maleate.

[0022] Conversely, common usage may frequently refer to the concentration of brimonidine in a composition as brimonidine tartrate without explicitly mentioning the tartrate counter ion. For example, a 0.2% w/v composition of brimonidine would typically be understood as referring to a 0.2% w/v composition of brimonidine tartrate, and not brimonidine without a counter ion. The equivalent concentration of brimonidine without a counter ion (i.e., in the free base form) would be 0.132% w/v. Similarly, a 0.1% w/v composition of brimonidine tartrate is equivalent to 0.066% w/v brimonidine free base.

[0023] In a monotherapy, 0.2%, 0.15%, or 0.1% brimonidine tartrate may be dosed three times daily, while 0.68% timolol maleate may be dosed twice daily. In certain patients, such as those where monotherapy is insufficient to adequately control intraocular pressure, these two medications may be used at the same time in a concurrent fashion. However, such treatment modalities entail some difficulties, such as having to dose one drug, wait a few minutes, and then dose the second drug. Also, since brimonidine needs to be dosed three times a day, but timolol only twice, this may entail some additional difficulties to the patient in either remembering the single brimonidine dosage or accidentally dosing with timolol. Studies have also shown that adverse events may be increased as a result of such a combined concurrent therapy.

[0024] Embodiments of the present invention are directed to a fixed dose composition comprising 0.1% w/v brimonidine tartrate and 0.68% w/v timolol maleate.

In a fixed dose composition, brimonidine and timolol are administered in a single composition (e.g., in a single bottle), rather than being administered separately. Such a fixed dose composition provides many benefits as described herein.

[0025] Certain fixed dose compositions of brimonidine and timolol, including but not limited to compositions comprising 0.1% w/v brimonidine tartrate and 0.68% w/v timolol maleate, when administered may result in less side effects compared to other drug compositions. For example, administration of the aforementioned compositions may result in less side effects as compared to the administration of a monotherapy comprising 0.2% w/v brimonidine tartrate, or 0.15% w/v brimonidine tartrate, or 0.1% w/v brimonidine tartrate. Further, administration of the aforementioned combinations may result in less side effects as compared to a fixed combination of 0.2% w/v brimonidine tartrate and 0.68% w/v timolol maleate, for example.

[0026] Examples of the reduced side effects that may be accredited to the compositions disclosed herein can include, but are not limited to, allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and stinging. The compositions disclosed herein may also reduce the incidence of other side effects such as asthenia, blepharitis, corneal erosion, depression, epiphora, eye discharge, eye dryness, eye irritation, eye pain, eyelid edema, eye lid erythema, eyelid pruritus, foreign body sensation, headache, hypertension, oral dryness, somnolence, superficial punctate keratitis, and visual disturbances.

[0027] Preferably, the compositions disclosed here are topically administered as a liquid solution, most preferably an aqueous solution. In some embodiments, a liquid emulsion is also possible. Preferably, the compositions described herein are adapted and formulated for topical administration to the eye and ocular surface.

[0028] When formulated, certain embodiments may also contain one or more viscosity enhancing agents. Viscosity enhancing agents can include viscosity enhancing polymers capable of increasing viscosity and enhancing mucoadhesion of

certain compositions. Without wishing to be bound by theory, the presence of viscosity enhancing agents may prolong the residence time of brimonidine and timolol on corneal surface of the eye, thereby providing better ocular absorption. Certain viscosity enhancing polymers include, among others, xanthan gum, sodium alginate, gellan gum, hyaluronan, pemulan, poloxamer, carbomer, polycarbophil, chitosan, gelatin, pectin, and polyvinylpyrrolidone, polyvinyl alcohol, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxylpropyl cellulose, etc. Sodium carboxymethylcellulose is used in Composition B in Table 1 as an example to increase the product viscosity.

[0029] Certain embodiments may also provide for one or more additional preservatives. Any preservatives suitable for topical ocular use and compatible with the other compounds present in the composition may be incorporated in the embodiments disclosed herein. These may include, but are not limited to, benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Purite® (stabilized chlorine dioxide), or other agents known to those skilled in the art. In a preferred embodiment, the preservative is benzalkonium chloride.

[0030] The concentration of benzalkonium chloride that may be used may be from about 0.001% w/v to about 0.05% w/v, more preferably from about 0.005% w/v to about 0.02% w/v. Suitable concentrations of thimerosal may be from about 0.001% to about 0.9% w/v. Chlorobutanol may be used from about 0.1% to about 0.5% w/v. Methylparaben may be used from about 0.1% to about 0.3% w/v. Propylparaben may be used from about 0.01% to about 0.2% w/v. Phenylethyl alcohol may be used from about 0.2% to about 0.5% w/v. Ethylenediaminetetraacetic acid (EDTA) may be used from about 0.005% to about 0.2% w/v. Sorbic acid may be used from about 0.05% to about 0.2% w/v. Purite® may be used from about 0.005% to about 0.02% w/v. Appropriate alternative concentrations may of course be used for other preservatives mentioned above.

[0031] In certain embodiments, compositions disclosed herein may be prepared as an article of manufacture comprising a pharmaceutical agent with additional packaging material. Such packaging material preferably comprises a label, which may be placed on the exterior of the packaging material, the interior, or as a separate leaflet. This label may comprise information about the composition and pharmaceutical agent contained therein, dosage information, patient safety information, regulatory information, doctor/prescribing information, and the like.

[0032] Embodiments disclosed herein may be presented, for example, in a unit dose configuration or a multidose configuration. Typically, a unit dose configuration comprises a single dose of a composition in a container. In some embodiments, this container may be in the form of a non-reusable packaging such as a capsule, LDPE plastic vials, and so forth. Preferably, a unit dose configuration comprises a composition that does not have any added preservative. A multidose configuration may be preserved or preservative-free—that is, the configuration may contain a composition that is preserved or free of preservatives— and typically permits at least two, and preferably multiple, doses to be dispensed from a container containing the multidose configuration. Containers usable in such multidose configurations may comprise typical ophthalmic dropper bottles, or other bottle types. In a multidose preservative-free configuration, to prevent from the risk of ophthalmic infections and possible spoilage of the composition remaining in the container, it is preferable to include some sort of mechanism on the container that will prevent or retard microbial growth. This may include antimicrobial coatings on the container, and container dispensing and venting configurations that prevent microbial entry into the container (e.g., filters, one-way venting, and so on).

Example 1

[0033] Shown in Table 1 are two embodiments of compositions of a fixed dose combination containing 0.1% brimonidine tartrate and 0.5% timolol free base (or 0.68% timolol maleate). These compositions are preferably buffered, isotonic, sterile, and

preservative-free ophthalmic solutions for topical administration. The container closure system used for these compositions to deliver the drugs may be unit-dose LDPE plastic vials or advanced multi-dose dropper bottles having self-preserving features to prevent contaminants from ingressing during use. Of course, preserved compositions are also possible.

Table 1. Examples of Brimonidine and Timolol Fixed Dose Combinations

No.	Ingredients	Composition A	Composition B
		% w/v	% w/v
1	brimonidine tartrate	0.1	0.1
2	timolol maleate	0.68	0.68
3	boric acid	N/A	0.6
4	sodium borate decahydrate	N/A	0.38
5	carboxymethylcellulose sodium	N/A	0.5
6	sodium chloride	0.1	0.32
7	sodium phosphate dibasic heptahydrate	2.15	N/A
8	sodium phosphate monobasic monohydrate	0.22	N/A
9	1N sodium hydroxide	Adjust to pH 7.0	Adjust to pH 7.0
10	1N hydrochloric acid		
11	purified water	QS	QS

[0034] Compared to commercially-available brimonidine and timolol monotherapy products, preservative-free embodiments of the Compositions described in Table 1 offer a better safety profile for chronic use of the products in certain patients, such as patients whose ocular surface is susceptible to damage or irritation that may be caused by certain preservatives.

[0035] Of course, it should be noted that the embodiments described above are not limited to preservative-free compositions. Any preservatives suitable for topical ocular use can be incorporated in the brimonidine/timolol combination product including, but not limited to, benzalkonium chloride and other preservatives mentioned above. For example, suitable concentrations of benzalkonium chloride may be from about 0.005% to about 0.02% w/v, for example 0.005% w/v, 0.01% w/v, or 0.02% w/v. Suitable concentrations of thimerosal may be from about 0.001% to about 0.9% w/v. Chlorobutanol may be used from about 0.1% to about 0.5% w/v. Methylparaben may be used from about 0.1% to about 0.3% w/v. Propylparaben may be used from about 0.01% to about 0.2% w/v. Phenylethyl alcohol may be used from about 0.2% to about 0.5% w/v. Ethylenediaminetetraacetic acid (EDTA) may be used from about 0.005% to about 0.2% w/v. Sorbic acid may be used from about 0.05% to about 0.2% w/v.

Example 2

[0036] A pharmacokinetic ("PK") experiment was conducted to assess ocular and systemic absorption of brimonidine and timolol in rabbits following topical dosing with the two compositions provided in Table 1.

[0037] Table 2 shows the study design for the rabbit experiment with the Table 1 compositions A and B. Rabbits were randomly assigned to groups based on body weight and received a single bilateral topical instillation of the test compositions (Composition A or B) and comparators (Aiphagan® and Timoptol®). Specifically, each group consisted of 12 female rabbits, and two animals (for a total of 4 eyes) were tested at each time point. Dosage consisted of single topical bilateral dosing with a 35 µL dose volume. Samples were collected at 15, 30, 60, 120, 240, 480 minutes post-dose time points and analyzed quantitatively to determine the tissue and plasma concentrations of brimonidine and timolol.

Table 2. Pharmacokinetics Study of 0.1% Brimonidine tartrate/0.5% Timolol Combo Composition

Group	Treatment	PK Collection Timepoints
1	Aiphagan® (0.1% brimonidine tartrate)	15, 30, 60, 120, 240, 480 minutes post dose
2	Timoptol® (0.5% timolol)	
3	Composition A	
4	Composition B	
5	Timoptol® followed by Aiphagan® [a]	15, 30, 60, 120, 240, 480 minutes post Timoptol dose
6	Aiphagan® followed by Timoptol® [a]	

[a]: 5 minute interval between dosage of the two eye drops

[0038] It was observed that timolol ocular exposure was increased when dosed with the brimonidine tartrate 0.1%/timolol 0.5% combination compositions compared to timolol 0.5% monotherapy. This finding is not obvious to those skilled in the art.

[0039] Results of the rabbit PK study are summarized in Tables 3 and 4, as well as Figures 1 and 2. Table 3 and Figure 1 show the amount of brimonidine found in the rabbit aqueous humor, iris-ciliary body, and blood plasma, though it should be noted that the results for the sequential dosing regimens are not reproduced in Figure 1. While the iris-ciliary body is the target tissue for both brimonidine and timolol due to the IOP-lowering effect of these drugs, the aqueous humor is the fluid that bathes the iris-ciliary body. Consequently, drug concentration in the aqueous humor is often highly correlated to the drug concentration in the solid tissues of the iris-ciliary body. Due to naso-lacrimal drainage, topically applied eye drops result in drug exposure in the systemic circulation and the extent of exposure is assessed by drug concentration in the blood plasma, which often correlates to systemic side effects associated with the drugs.

[0040] In the foregoing descriptions, "C_{max}" represents the peak drug concentration reached in the course of the experiment. "AUC" represents the area under the drug concentration-time curve.

[0041] Figure 1B shows that, in the iris-ciliary body, both Compositions A and B achieved higher C_{max} and AUC values for brimonidine compared to the administration of 0.1% brimonidine tartrate alone. This is a promising result because the iris-ciliary body is the target tissue for lowering IOP.

[0042] In Figures 1A and 1C, which show aqueous humor and blood plasma brimonidine concentration, respectively, both Compositions A and B resulted in lower C_{max} and AUC values compared to the administration of 0.1% brimonidine tartrate alone.

[0043] Table 3 lists the pharmacokinetic parameters obtained from the experiments illustrated in Figures 1A-C.

[0044] In Figures 2A and 2B, both Compositions A and B showed greater ocular exposure to timolol in the aqueous humor and the iris-ciliary body compared to the administration of 0.5% timolol alone. Turning to Figure 2C, blood plasma concentrations of Compositions A and B showed lower concentrations there as compared to the administration of 0.5% timolol alone. These lower plasma concentrations are preferable in order to reduce systemic exposure of timolol, which can have cardiovascular side effects.

[0045] Table 4 lists the pharmacokinetic parameters obtained from the experiments illustrated in Figures 2A-C.

Table 3. Brimonidine PK Profile

Matrix	Brimonidine (0.1%)	Composition A	Composition B	Timolol (0.5%) + Brimonidine (0.1%)[a]	Brimonidine (0.1%) + Timolol (0.5%)[a]
Brimonidine: C_{max} (ng/ml or ng/g) – (Mean ± SE)					
Aqueous Humor	818 ± 303	351 ± 175	518 ± 208	587 ± 125	468 ± 79
Iris-Ciliary Body	45.1 ± 17.9	58.8 ± 27.6	108 ± 69	68.4 ± 22.2	59.9 ± 20.7
Plasma	2.20 ± 0.04	1.49 ± 0.03	1.10 ± 0.40	1.29 ± 0.58	0.944 ± 0.076
Brimonidine: AUC (ng·hr/ml or ng·hr/g) – (Mean ± SE)					
Aqueous Humor	1000 ± 150	645 ± 138	782 ± 99	700 ± 66	646 ± 77
Iris-Ciliary Body	82.0 ± 11.4	94.1 ± 21.2	125 ± 29	87.8 ± 14.8	74.2 ± 12.5
Plasma	1.95 ± 0.07	1.53 ± 0.20	1.23 ± 0.19	1.32 ± 0.27	0.887 ± 0.142

[a]: 5 minute interval between dosage of the two eye drops

C_{max} values are comparable across groups ($p>0.05$) per one way ANOVA

Table 4. Timolol PK Profile

Matrix	Timolol (0.5%)	Composition A	Composition B	Timolol (0.5%) + Brimonidine (0.1%)[a]	Brimonidine (0.1%) + Timolol (0.5%)[a]
Timolol: C_{max} (ng/ml or ng/g) – (Mean ± SE)					
Aqueous Humor	1670 ± 90	2300 ± 1140	2890 ± 1130	2070 ± 380	3510 ± 700
Iris-Ciliary Body	1130 ± 180	3330 ± 1400	4090 ± 2140	2400 ± 380	6430 ± 1670
Plasma	21.1 ± 1.9	15.9 ± 5.2	12.4 ± 2.3	12.3 ± 0.1	16.1 ± 1.5
Timolol: AUC (ng·hr/ml or ng·hr/g) – (Mean ± SE)					
Aqueous Humor	2410 ± 160	4330 ± 910	5300 ± 630	3810 ± 260	4490 ± 550
Iris-Ciliary	1980 ± 130	6010 ± 1120	6760 ± 980	4080 ± 310	5570 ± 800

Body					
Plasma	19.6 ± 1.0	32.4 ± 2.4	23.5 ± 3.0	15.7 ± 0.3	21.4 ± 2.7

[a]: 5 minute interval between dosage of the two eye drops

C_{max} values are comparable across groups ($p>0.05$ per one way ANOVA)

[0046] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0047] The terms "a," "an," "the" and similar referents used in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of any claim. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

[0048] Groupings of alternative elements or embodiments disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any

such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

[0049] Certain embodiments are described herein, including the best mode known to the inventors for carrying out the invention. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than specifically described herein. Accordingly, the claims include all modifications and equivalents of the subject matter recited in the claims as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is contemplated unless otherwise indicated herein or otherwise clearly contradicted by context.

[0050] It is to be understood that the embodiments disclosed herein are illustrative of the principles of the claims. Other modifications that may be employed are within the scope of the claims. Thus, by way of example, but not of limitation, alternative embodiments may be utilized in accordance with the teachings herein. Accordingly, the claims are not limited to embodiments precisely as shown and described.

CLAIMS

What is claimed is:

1. A composition comprising about 0.1% w/v brimonidine tartrate and about 0.68% w/v timolol maleate.
2. The composition of claim 1, wherein the composition comprises 0.1% w/v brimonidine tartrate and 0.68% w/v timolol maleate.
3. The composition of claim 2, wherein the composition comprises 0.1% w/v brimonidine tartrate, 0.68% w/v timolol maleate, 0.1% w/v sodium chloride, 2.15% w/v sodium phosphate dibasic heptahydrate, 0.22% w/v sodium phosphate monobasic monohydrate, and water.
4. The composition of claim 2, wherein the composition comprises 0.1% w/v brimonidine tartrate, 0.68% w/v timolol maleate, 0.6% w/v boric acid, 0.38% sodium borate decahydrate, 0.5% w/v carboxymethyl cellulose, 0.32% w/v sodium chloride, and water.
5. The composition of claim 1, wherein the composition further comprises at least one buffer selected from the group consisting of sodium phosphate dibasic heptahydrate and sodium borate decahydrate.
6. The composition of any preceding claim, wherein the composition has a pH of about 7.
7. The composition of claim 6, wherein the composition has a pH of 7.0.
8. The composition of any preceding claim, wherein the composition further comprises one or both of sodium hydroxide and hydrochloric acid.
9. The composition of any preceding claim, wherein administration of the composition twice daily is at least as effective as twice-daily administration of a second composition comprising a fixed dose of 0.2% w/v brimonidine tartrate and 0.5% w/v timolol maleate.
10. The composition of any preceding claim, wherein administration of the composition twice daily results in a lower incidence of one or more adverse events as compared to the twice-daily administration of a second composition

comprising a fixed dose of 0.2% w/v brimonidine tartrate and 0.68% w/v timolol maleate.

11. The composition of claim 10, wherein the one or more adverse events are selected from the group consisting of allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and ocular stinging.
12. The composition of any preceding claim, wherein the composition does not comprise a preservative.
13. The composition of any of claims 1-11, wherein the composition further comprises benzalkonium chloride.
14. The composition of claim 13, wherein the benzalkonium chloride is present at a concentration of about 0.001% w/v to about 0.05% w/v.
15. The composition of any preceding claim, wherein the composition is configured for topical ocular administration.
16. The composition of any preceding claim, wherein the composition is for the treatment of glaucoma and elevated intraocular pressure.
17. A composition for reducing intraocular pressure, the composition consisting essentially of 0.1% w/v brimonidine tartrate, 0.68% w/v timolol maleate, 0.1% w/v sodium chloride, 2.15% w/v sodium phosphate dibasic heptahydrate, 0.22% w/v sodium phosphate monobasic monohydrate, and water.
18. A composition for reducing intraocular pressure, the composition consisting essentially of 0.1% w/v brimonidine tartrate, 0.68% w/v timolol maleate, 0.6% w/v boric acid, 0.38% sodium borate decahydrate, 0.5% w/v carboxymethyl cellulose, 0.32% w/v sodium chloride, and water.
19. An article of manufacture comprising packaging material and a pharmaceutical agent contained within the packaging material, wherein the packaging material comprises a label which indicates the pharmaceutical agent can be used for lowering intraocular pressure, and wherein the pharmaceutical agent is therapeutically effective for lowering intraocular pressure, the pharmaceutical agent comprising 0.1 % brimonidine tartrate and 0.68% timolol maleate.

20. The article of claim 19, wherein the pharmaceutical agent comprises 0.1% w/v brimonidine tartrate, 0.68% w/v timolol maleate, 0.1% w/v sodium chloride, 2.15% w/v sodium phosphate dibasic heptahydrate, 0.22% w/v sodium phosphate monobasic monohydrate, and water.
21. The article of claim 19, wherein the pharmaceutical agent comprises 0.1% w/v brimonidine tartrate, 0.68% w/v timolol maleate, 0.6% w/v boric acid, 0.38% sodium borate decahydrate, 0.5% w/v carboxymethyl cellulose, 0.32% w/v sodium chloride, and water.
22. The article of any of claims 19-21, wherein the pharmaceutical agent is provided in a unit dose preservative-free configuration.
23. The article of any of claims 19-21, wherein the pharmaceutical agent is provided in a multi dose preservative-free configuration.
24. The article of any of claims 19-21, wherein the pharmaceutical agent is provided in a multi dose configuration preserved with one or more preservative agents.
25. A method of treating glaucoma or elevated intraocular pressure, wherein the method comprises administering an effective amount of a single composition comprising about 0.1% w/v brimonidine tartrate and about 0.68% w/v timolol maleate.
26. The method of claim 25, wherein the composition is administered twice daily to an eye.
27. The method of claim 26, wherein administration of the composition twice daily results in a lower incidence of one or more adverse events as compared to the twice-daily administration of a second single composition comprising a 0.2% w/v brimonidine tartrate and 0.5% w/v timolol maleate.
28. The method of claim 27, wherein the one or more adverse events are selected from the group consisting of allergic conjunctivitis, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, ocular burning, and ocular stinging.

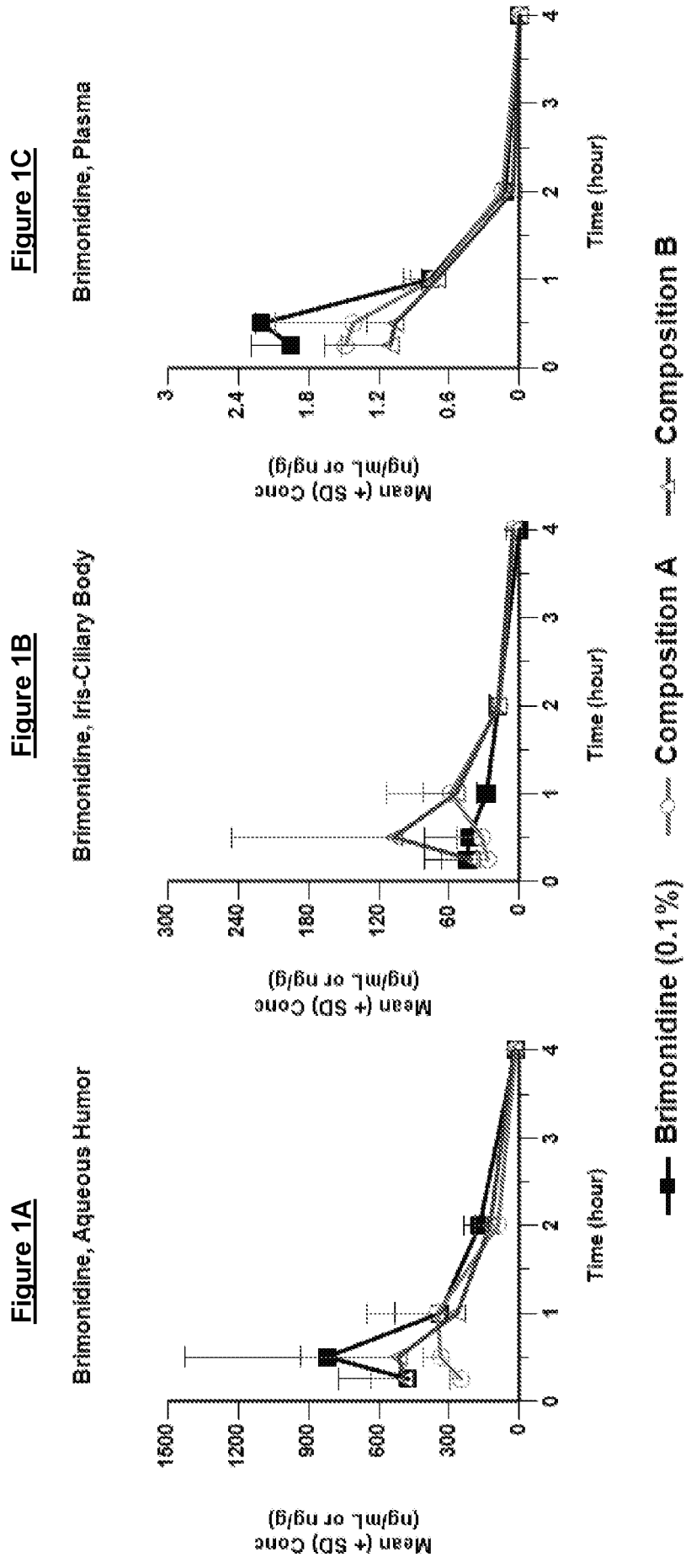

Figure 1A
Brimonidine, Aqueous Humor
Mean (+ SD) Conc (ng/mL or ng/g)
1500
1200
900
600
300
0
0
1
2
3
4
Time (hour)
Figure 1B
Brimonidine, Iris-Ciliary Body
Mean (+ SD) Conc (ng/mL or ng/g)
300
240
180
120
60
0
0
1
2
3
4
Time (hour)
Figure 1C
Brimonidine, Plasma
Mean (+ SD) Conc (ng/mL or ng/g)
3
2.4
1.8
1.2
0.6
0
0
1
2
3
4
Time (hour)
Brimonidine (0.1%)
Composition A
Composition B

Figure 2A

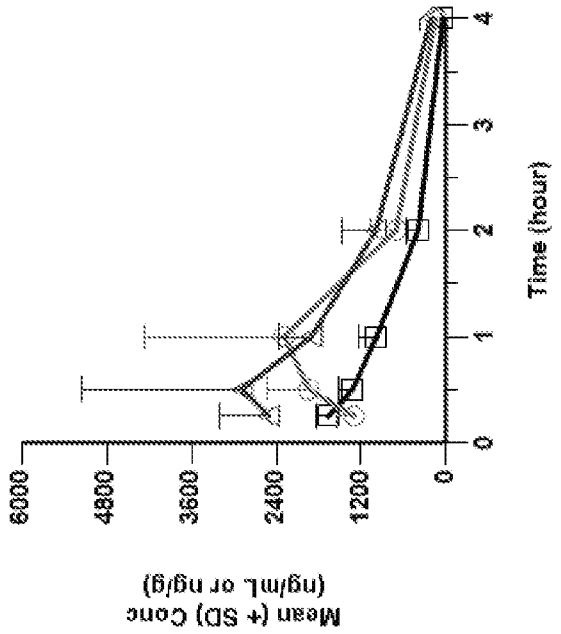


Figure 2B

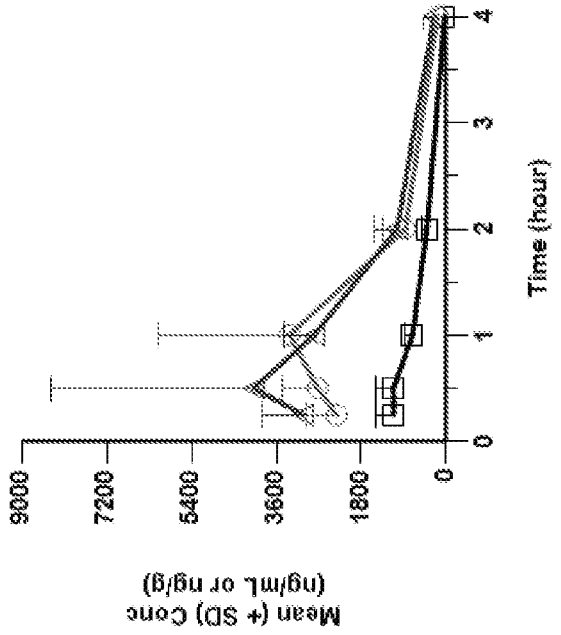
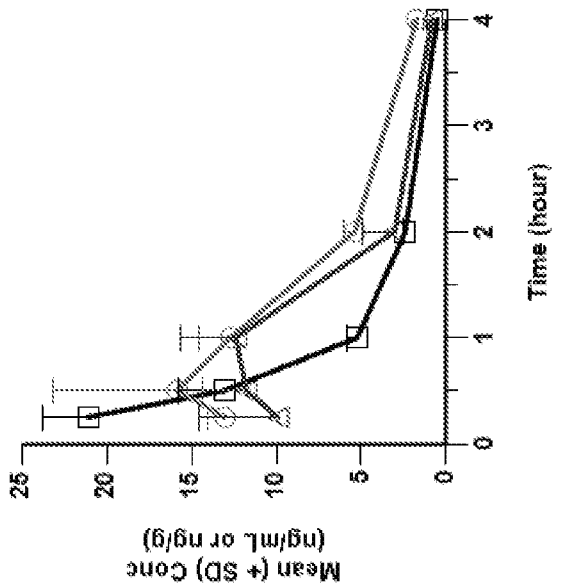


Figure 2C





INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/022874

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K47/02 A61K9/08 A61K31/498 A61K31/5377
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, CHEM ABS Data, EMBASE, 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	WO 03/088973 A1 (ALLERGAN INC [US]; CHANG CHIN-MING [US]; BECK GARY J [US]; PRATT CYNTH) 30 October 2003 (2003-10-30) examples 1-2	1-28
X	WO 2012/016000 A2 (ALLERGAN INC [US]; LIKITLERSUANG SUKHON [US]; KELLY WILLIAM F [US]; PA) 2 February 2012 (2012-02-02) claims 1-10; table 1	1-28
A	WO 2011/087790 A1 (ALLERGAN INC [US]; PUJARA CHETAN P [US]) 21 July 2011 (2011-07-21) tables 1-11	1-28

-/--

[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
1 June 2016	09/06/2016

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/022874

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SCOTT J FUDEMBERG ET AL: "Efficacy, safety, and current applications of brimonidine", EXPERT OPINION ON DRUG SAFETY, vol. 7, no. 6, 4 November 2008 (2008-11-04), pages 795-799, XP55275335, GB ISSN: 1474-0338, DOI: 10.1517/17425250802457609 page 798, paragraph 6. Expert opinion -----	1-28

1

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/022874

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(19)中华人民共和国国家知识产权局

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A61K 47/02(2006.01)
A61P 27/06(2006.01)
A61K 31/498(2006.01)

权利要求书2页 说明书8页 附图2页

(54)发明名称

溴莫尼定和噻吗洛尔的固定剂量组合

(57)摘要

本文公开的实施方案涉及用于降低眼内压和治疗青光眼的包含溴莫尼定和噻吗洛尔的固定组合物。

CN 107427460 A

1.一种组合物，其包含约0.1％w/v酒石酸溴莫尼定和约0.68％w/v马来酸噻吗洛尔。

2.如权利要求1所述的组合物，其中所述组合物包含0.1％w/v酒石酸溴莫尼定和0.68％w/v马来酸噻吗洛尔。

3.如权利要求2所述的组合物，其中所述组合物包含0.1％w/v酒石酸溴莫尼定、0.68％w/v马来酸噻吗洛尔、0.1％w/v氯化钠、2.15％w/v磷酸氢二钠七水合物、0.22％w/v磷酸二氢钠一水合物和水。

4.如权利要求2所述的组合物，其中所述组合物包含0.1％w/v酒石酸溴莫尼定、0.68％w/v马来酸噻吗洛尔、0.6％w/v硼酸、0.38％硼酸钠十水合物、0.5％w/v羧甲基纤维素、0.32％w/v氯化钠和水。

5.如权利要求1所述的组合物，其中所述组合物还包含至少一种选自由磷酸氢二钠七水合物和硼酸钠十水合物组成的组的缓冲液。

6.如任一前述权利要求所述的组合物，其中所述组合物的pH为约7。

7.如权利要求6所述的组合物，其中所述组合物的pH为7.0。

8.如任一前述权利要求所述的组合物，其中所述组合物还包含氢氧化钠和盐酸中的一种或两种。

9.如任一前述权利要求所述的组合物，其中每天两次施用所述组合物至少与每天两次施用包含固定剂量的0.2％w/v酒石酸溴莫尼定和0.5％w/v马来酸噻吗洛尔的第二组合物一样有效。

10.如任一前述权利要求所述的组合物，其中与所述每天两次施用包含固定剂量的0.2％w/v酒石酸溴莫尼定和0.68％w/v马来酸噻吗洛尔的第二组合物相比，所述每天两次施用所述组合物导致较低的一种或多种不良事件发生率。

11.如权利要求10所述的组合物，其中所述一种或多种不良事件选自由过敏性结膜炎、结膜滤泡症、结膜充血、眼睛瘙痒、眼睛灼伤和眼睛刺痛组成的组。

12.如任一前述权利要求所述的组合物，其中所述组合物不包含防腐剂。

13.如权利要求1-11中任一项所述的组合物，其中所述组合物还包含苯扎氯铵。

14.如权利要求13所述的组合物，其中所述苯扎氯铵以约0.001％w/v至约0.05％w/v的浓度存在。

15.如任一前述权利要求所述的组合物，其中所述组合物被配置用于局部眼部施用。

16.如任一前述权利要求所述的组合物，其中所述组合物用于治疗青光眼和眼内压升高。

17.一种用于降低眼内压的组合物，所述组合物基本上由0.1％w/v酒石酸溴莫尼定、0.68％w/v马来酸噻吗洛尔、0.1％w/v氯化钠、2.15％w/v磷酸氢二钠七水合物、0.22％w/v磷酸二氢钠一水合物和水组成。

18.一种用于降低眼内压的组合物，所述组合物基本上由0.1％w/v酒石酸溴莫尼定、0.68％w/v马来酸噻吗洛尔、0.6％w/v硼酸、0.38％硼酸钠十水合物、0.5％w/v羧甲基纤维素、0.32％w/v氯化钠和水组成。

19.一种制品，其包括包装材料和包含在所述包装材料中的药剂，其中所述包装材料包括指示所述药剂可用于降低眼内压的标签，并且其中所述药剂对于降低眼内压是治疗有效的，所述药剂包含0.1％酒石酸溴莫尼定和0.68％马来酸噻吗洛尔。

20.如权利要求19所述的制品，其中所述药剂包含0.1％w/v酒石酸溴莫尼定、0.68％w/v马来酸噻吗洛尔、0.1％w/v氯化钠、2.15％w/v磷酸氢二钠七水合物、0.22％w/v磷酸二氢钠一水合物和水。

21.如权利要求19所述的制品，其中所述药剂包含0.1％w/v酒石酸溴莫尼定、0.68％w/v马来酸噻吗洛尔、0.6％w/v硼酸、0.38％硼酸钠十水合物、0.5％w/v羧甲基纤维素、0.32％w/v氯化钠和水。

22.如权利要求19-21中任一项所述的制品，其中所述药剂以单位剂量不含防腐剂的配置提供。

23.如权利要求19-21中任一项所述的制品，其中所述药剂以多剂量不含防腐剂的配置提供。

24.如权利要求19-21中任一项所述的制品，其中所述药剂以用一种或多种防腐剂保存的多剂量配置来提供。

25.一种治疗青光眼或眼内压升高的方法，其中所述方法包括施用有效量的包含约0.1％w/v酒石酸溴莫尼定和约0.68％w/v马来酸噻吗洛尔的单一组合物。

26.如权利要求25所述的方法，其中每天两次施用所述组合物至眼睛。

27.如权利要求26所述的方法，其中与每天两次施用包含0.2％w/v酒石酸溴莫尼定和0.5％w/v马来酸噻吗洛尔的第二单一组合物相比，所述每天两次施用所述组合物导致较低的一种或多种不良事件发生率。

28.如权利要求27所述的方法，其中所述一种或多种不良事件选自由过敏性结膜炎、结膜滤泡症、结膜充血、眼睛瘙痒、眼睛灼伤和眼睛刺痛组成的组。

溴莫尼定和噻吗洛尔的固定剂量组合

[0001] 发明背景

[0002] 溴莫尼定和噻吗洛尔是已被配制成已知可以降低青光眼或高眼压患者眼内压(″IOP″)的眼用溶液的药物。这些药物可以一种以上浓度(溴莫尼定0.1%、0.15%、0.2%和噻吗洛尔0.25%和0.5%)在多个国家作为单一疗法使用。已知这些药物同时用于患有无法通过单一疗法充分控制的病状的患者。将溴莫尼定和噻吗洛尔配制成固定组合产品在提供效益风险改善方面为患者提供了优势,也简化了治疗施用。

[0003] 发明概述

[0004] 在一个实施方案中,提供了用于治疗青光眼和眼内压升高的组合物,所述组合物包含约0.1%w/v酒石酸溴莫尼定和约0.68%w/v马来酸噻吗洛尔,该组合物被配置用于局部眼部施用。

[0005] 在一些实施方案中,组合物包含0.1%w/v酒石酸溴莫尼定和0.68%w/v马来酸噻吗洛尔。组合物可以包含0.1%w/v酒石酸溴莫尼定、0.68%w/v马来酸噻吗洛尔、0.1%w/v氯化钠、2.15%w/v磷酸氢二钠七水合物、0.22%w/v磷酸二氢钠一水合物和水。组合物还可以包含0.1%w/v酒石酸溴莫尼定、0.68%w/v马来酸噻吗洛尔、0.6%w/v硼酸、0.38%硼酸钠十水合物、0.5%w/v羧甲基纤维素、0.32%w/v氯化钠和水。

[0006] 一些组合物还可以包含至少一种选自由磷酸氢二钠七水合物和硼酸钠十水合物组成的组的缓冲剂。优选地,组合物的pH为约7,或pH为7.0。组合物还可以包含氢氧化钠和盐酸中的一种或两种。

[0007] 在一些实施方案中,每天两次施用组合物至少与每天两次施用包含固定剂量的0.2%w/v酒石酸溴莫尼定和0.5%w/v马来酸噻吗洛尔的第二组合物一样有效。在一些实施方案中,与每天两次施用包含固定剂量的0.2%w/v酒石酸溴莫尼定和0.68%w/v马来酸噻吗洛尔的第二组合物相比,每天两次施用组合物导致一种或多种不良事件的较低发生率。一种或多种不良事件可以选自由过敏性结膜炎、结膜滤泡症(conjunctival folliculosis)、结膜充血、眼睛瘙痒、眼睛灼伤和眼睛刺痛组成的组。在某些实施方案中,组合物不包含防腐剂。然而,在一些实施方案中,组合物还包含苯扎氯铵。苯扎氯铵可以以约0.001%w/v至约0.05%w/v的浓度存在。

[0008] 一个具体实施方案是用于降低眼内压的组合物,该组合物基本上由0.1%w/v酒石酸溴莫尼定、0.68%w/v马来酸噻吗洛尔、0.1%w/v氯化钠、2.15%w/v磷酸氢二钠七水合物、0.22%w/v磷酸二氢钠一水合物和水组成。

[0009] 另一个具体实施方案是用于降低眼内压的组合物,该组合物基本上由0.1%w/v酒石酸溴莫尼定、0.68%w/v马来酸噻吗洛尔、0.6%w/v硼酸、0.38%硼酸钠十水合物、0.5%w/v羧甲基纤维素、0.32%w/v氯化钠和水组成。

[0010] 在另一个优选的实施方案中,提供了一种制品,其包括包装材料和包含在包装材料中的药剂,其中包装材料包括指示药剂可用于降低眼内压的标签,并且其中药剂对于降低眼内压是治疗有效的,该药剂包含0.1%酒石酸溴莫尼定和0.68%马来酸噻吗洛尔。

[0011] 在一些实施方案中,药剂包含0.1%w/v酒石酸溴莫尼定、0.68%w/v马来酸噻吗洛

尔、0.1％w/v氯化钠、2.15％w/v磷酸氢二钠七水合物、0.22％w/v磷酸二氢钠一水合物和水。在一些实施方案中，药剂包含0.1％w/v酒石酸溴莫尼定、0.68％w/v马来酸噻吗洛尔、0.6％w/v硼酸、0.38％硼酸钠十水合物、0.5％w/v羧甲基纤维素、0.32％w/v氯化钠和水。药剂可以以单位剂量不含防腐剂的配置提供。药剂可以以多剂量不含防腐剂的配置提供。药剂可以以用一种或多种防腐剂保存的多剂量配置来提供。

[0012] 在另一个实施方案中，提供治疗青光眼或眼内压升高的方法，其中所述方法包括施用有效量的包含约0.1％w/v酒石酸溴莫尼定和约0.68％w/v马来酸噻吗洛尔的单一组合物。

[0013] 在一些实施方案中，将组合物每天两次施用于眼睛。在一些实施方案中，与每天两次施用包含0.2％w/v酒石酸溴莫尼定和0.5％w/v马来酸噻吗洛尔的第二单一组合物相比，每天两次施用组合物导致一种或多种不良事件的较低发生率。一种或多种不良事件可以选自由过敏性结膜炎、结膜滤泡症、结膜充血、眼睛瘙痒、眼睛灼伤和眼睛刺痛组成的组。

[0014] 附图简述

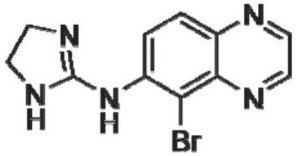
[0015] 图1A-C示出了测量随时间而变化的溴莫尼定的眼组织和血浆浓度的实验结果。

[0016] 图2A-C示出了测量随时间而变化的噻吗洛尔的眼组织和血浆浓度的实验的结果。

[0017] 发明详述

[0018] 本发明的实施方案涉及溴莫尼定与噻吗洛尔组合用于治疗青光眼、高眼压和降低眼内压的局部眼部使用。发现两种已知降低眼内压(″IOP″)的药物溴莫尼定和噻吗洛尔在联合施用时表现出协同作用。这些固定组合的益处是治疗功效和治疗施用的增强。

[0019] 溴莫尼定是由下式表示的α肾上腺素能激动剂。溴莫尼定的化学名称是5-溴-6-(2-亚咪唑烷基氨基)喹喔啉L-酒石酸盐，其结构如下再现。

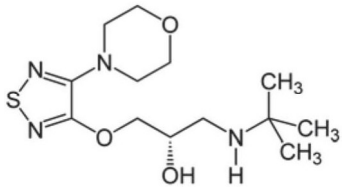
[0020] 

[0021] 溴莫尼定通过激活G蛋白偶联受体来抑制腺苷酸环化酶的活性。这减少虹膜睫状体的cAMP，从而降低房水的产生。外周α2激动剂活性导致血管收缩(与降低交感神经张力的中枢α2激动剂活性相反，正如药物可乐定(clonidine)所观察到)。这种血管收缩导致房水流动的急剧减少。由于延长使用溴莫尼定的α肾上腺素能刺激引起的前列腺素释放增加，通过小梁网增加房水的葡萄膜巩膜(uveoscleral)流出，其结合溴莫尼定房水降低作用有助于降低治疗开角型青光眼和高眼压的IOP。

[0022] 溴莫尼定作为单一疗法以几种浓度(0.1％、0.15％、0.2％w/v酒石酸溴莫尼定)可商购获得，并且由Allergan，Inc.作为ALPHAGAN®(或日本的AIPHAGAN®)出售。尽管溴莫尼定优选以酒石酸溴莫尼定的形式施用，但其它盐形式也是可能的。也可以使用游离碱。

[0023] 噻吗洛尔是非选择性β-肾上腺素能受体拮抗剂，通过阻断睫状体上皮上的β受体来减少房水产生。但是，目前尚未明确确定噻吗洛尔眼部降压作用的精确药理作用机制。

[0024] 噻吗洛尔的化学名称为(S)-1-(叔丁基氨基)-3-[(4-吗啉-4-基-1,2,5-噻二唑-3-基)氧基]丙-2-醇，化学结构如下所示。

[0025] 

[0026] 噻吗洛尔已经以几种浓度商购获得，包括0.25％和0.5％w/v噻吗洛尔。一个这样的品牌是TIMOPTOL®。因为噻吗洛尔优选使用马来酸盐进行施用，所以前述浓度也可以表示为0.34％和0.68％w/v马来酸噻吗洛尔。当然，噻吗洛尔可以以其它盐形式施用，包括半水合物形式。也可以使用游离碱。

[0027] 应该注意的是，常见的用法通常是将组合物中噻吗洛尔的浓度指定为无抗衡离子的游离碱形式。例如，0.5％w/v噻吗洛尔的组合物通常被理解为指不含抗衡离子的0.5％w/v噻吗洛尔的组合物(即呈游离碱形式)。这相当于0.68％w/v马来酸噻吗洛尔的当量浓度。

[0028] 相反，常见的用法通常可能指溴莫尼定在组合物中作为酒石酸溴莫尼定的浓度，而不明确提及酒石酸盐抗衡离子。例如，0.2％w/v溴莫尼定的组合物通常被理解为指0.2％w/v酒石酸溴莫尼定的组合物，而不是没有抗衡离子的溴莫尼定。没有抗衡离子的溴莫尼定(即呈游离碱形式)的当量浓度为0.132％w/v。类似地，0.1％w/v酒石酸溴莫尼定的组合物相当于0.066％w/v溴莫尼定游离碱。

[0029] 在单一疗法中，0.2％，0.15％或0.1％酒石酸溴莫尼定可以每天三次给药，而0.68％马来酸噻吗洛尔可以每天两次给药。在某些患者中，例如单一疗法不足以充分控制眼内压的患者，可以同时并行使用这两种药物。然而，这种治疗方式带来一些困难，例如不得不将一种药物给药，等待几分钟，然后将第二种药物给药。此外，由于溴莫尼定需要一天三次给药，而噻吗洛尔只需两次，这可能会给患者带来一些额外的困难，要么记住单次溴莫尼定剂量或偶然将噻吗洛尔给药。研究还表明，不良事件可能会由于这种组合并行疗法的结果而增加。

[0030] 本发明的实施方案涉及包含0.1％w/v酒石酸溴莫尼定和0.68％w/v马来酸噻吗洛尔的固定剂量组合物。在固定剂量组合物中，溴莫尼定和噻吗洛尔以单一组合物(例如，在单一瓶中)施用，而不是单独施用。这样的固定剂量组合物提供了如本文所述的许多益处。

[0031] 溴莫尼定和噻吗洛尔的某些固定剂量组合物，包括但不限于包含0.1％w/v酒石酸溴莫尼定和0.68％w/v马来酸噻吗洛尔的组合物，与其它药物组合物相比在施用时可能导致较少的副作用。例如，与施用包含0.2％w/v酒石酸溴莫尼定或0.15％w/v酒石酸溴莫尼定或0.1％w/v酒石酸溴莫尼定的单一疗法相比，上述组合物的施用可能导致较少的副作用。此外，与例如0.2％w/v酒石酸溴莫尼定和0.68％w/v马来酸噻吗洛尔的固定组合相比，上述组合的施用可能导致较少的副作用。

[0032] 本文公开的组合物可能被认可的减少的副作用的实例可包括但不限于过敏性结膜炎、结膜滤泡症、结膜充血、眼瘙痒、眼睛灼伤和刺痛。本文公开的组合物还可以减少其它副作用的发生率，例如虚弱、睑炎、角膜糜烂、抑郁、溢泪、眼睛分泌、眼睛干燥、眼睛刺激、眼睛疼痛、眼睑水肿、眼睑红斑、眼睑瘙痒、异物感觉、头痛、高血压、口腔干燥、嗜睡、浅表点状角膜炎和视觉障碍。

[0033] 优选地，本文公开的组合物以液体溶液，最优选水溶液局部施用。在一些实施方案中，液体乳剂也是可能的。优选地，本文所述的组合物适于和配制用于局部施用于眼睛和眼

睛表面。

[0034] 当配制时，某些实施方案还可以含有一种或多种粘度增强剂。粘度增强剂可以包括能够增加粘度并增强某些组合物的粘膜粘度的粘度增强聚合物。不希望受理论束缚，粘度增强剂的存在可延长溴莫尼定和噻吗洛尔在眼角膜表面的停留时间，从而提供更好的眼睛吸收。某些粘度增强聚合物尤其包括黄原胶、藻酸钠、结兰胶、透明质酸、pemulan、泊洛沙姆、卡波姆、聚卡波非、壳聚糖、明胶、果胶和聚乙烯吡咯烷酮、聚乙烯醇、甲基纤维素、羟丙基甲基纤维素、羟乙基纤维素、羧甲基纤维素、羟丙基纤维素等。在表1的组合物B中使用羧甲基纤维素钠作为实例来增加产品粘度。

[0035] 某些实施方案还可以提供一种或多种另外的防腐剂。适用于局部眼部使用并与组合物中存在的其它化合物相容的任何防腐剂都可以并入本文公开的实施方案中。这些可以包括但不限于苯扎氯铵、硫柳汞、氯丁醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、苯乙醇、依地酸二钠、山梨酸、Purite®(稳定的二氧化氯)或本领域技术人员已知的其它药剂。在优选的实施方案中，防腐剂是苯扎氯铵。

[0036] 可以使用的苯扎氯铵的浓度可以为约0.001％w/v至约0.05％w/v，更优选约0.005％w/v至约0.02％w/v。硫柳汞的合适浓度可以为约0.001％至约0.9％w/v。可以使用约0.1％至约0.5％w/v氯丁醇。可以使用约0.1％至约0.3％w/v对羟基苯甲酸甲酯。可以使用约0.01％至约0.2％w/v对羟基苯甲酸丙酯。可以使用约0.2％至约0.5％w/v苯乙醇。可以使用约0.005％至约0.2％w/v乙二胺四乙酸(EDTA)。可以使用约0.05％至约0.2％w/v山梨酸。可以使用约0.005％至约0.02％w/vPurite®。当然可以使用适当的替代浓度用于上述其它防腐剂。

[0037] 在某些实施方案中，本文公开的组合物可以制备成包含药剂与附加包装材料的制品。这种包装材料优选地包括标签，其可以放置在包装材料的外部、内部或作为单独的散页。该标签可以包括关于组合物和其中所含的药剂的信息、剂量信息、患者安全信息、法规信息、医生/处方信息等。

[0038] 本文公开的实施方案可以例如以单位剂量配置或多剂量配置呈现。通常，单位剂量配置包括在容器中的单一剂量的组合物。在一些实施方案中，该容器可以是不可重复使用的包装的形式，例如胶囊、LDPE塑料小瓶等。优选地，单位剂量配置包括不具有任何添加的防腐剂的组合物。多剂量配置可以是防腐的或不含防腐剂，也就是该配置可以含有防腐的或不含防腐剂的组合物，并且通常允许从含有多剂量配置的容器中分配至少两个，优选多个剂量。可用于这种多剂量配置的容器可以包括典型的眼用滴管瓶或其它瓶子类型。在多剂量不含防腐剂的配置中，为了防止眼睛感染和残留在容器中的组合物可能腐败的风险，优选在容器上包括一些预防或阻止微生物生长的机制。这可以包括容器上的抗微生物涂层，以及防止微生物进入容器的容器分配和排气配置(例如，过滤器、单向排气等)。

[0039] 实施例1

[0040] 表1所示是含有0.1％酒石酸溴莫尼定和0.5％噻吗洛尔游离碱(或0.68％马来酸噻吗洛尔)的固定剂量组合的组合物的两个实施方案。这些组合物优选是用于局部施用的缓冲、等渗、无菌且不含防腐剂的眼用溶液。用于这些组合物的递送药物的容器封闭系统可以是具有自防腐特征以防止污染物在使用过程中进入的单位剂量LDPE塑料小瓶或高级多剂量滴管瓶。当然，防腐的组合物也是可能的。

[0041] 表1.溴莫尼定和噻吗洛尔固定剂量组合的实例

编号	成分	组合物 A	组合物 B
		% w/v	% w/v
1	酒石酸溴莫尼定	0.1	0.1
2	马来酸噻吗洛尔	0.68	0.68
3	硼酸	不适用	0.6
4	硼酸钠十水合物	不适用	0.38
5	羧甲基纤维素钠	不适用	0.5
6	氯化钠	0.1	0.32
7	磷酸氢二钠七水合物	2.15	不适用
8	磷酸二氢钠一水合物	0.22	不适用
9	1N 氢氧化钠	调整至 pH 7.0	调整至 pH 7.0
10	1N 盐酸		
11	纯化水	定量	定量

[0042]

[0043] 与商购获得的溴莫尼定和噻吗洛尔单一疗法产品相比，表1中描述的组合物的不含防腐剂的实施方案为在某些患者中，例如其眼表易受可能是由某些防腐剂引起的损伤或刺激的患者中长期使用产品提供了更好的安全性。

[0044] 当然，应当注意，上述实施方案不限于不含防腐剂的组合物。适用于局部眼睛使用的任何防腐剂均可掺入溴莫尼定/噻吗洛尔组合产品中，包括但不限于以上提及的苯扎氯铵和其它防腐剂。例如，苯扎氯铵的合适浓度可以为约0.005％至约0.02％w/v，例如0.005％w/v、0.01％w/v或0.02％w/v。硫柳汞的合适浓度可以为约0.001％至约0.9％w/v。可以使用约0.1％至约0.5％w/v氯丁醇。可以使用约0.1％至约0.3％w/v对羟基苯甲酸甲酯。可以使用约0.01％至约0.2％w/v对羟基苯甲酸丙酯。可以使用约0.2％至约0.5％w/v苯乙醇。可以使用约0.005％至约0.2％w/v乙二胺四乙酸(EDTA)。可以使用约0.05％至约0.2％w/v山梨酸。

[0045] 实施例2

[0046] 进行药代动力学("PK")实验以评估局部给予在表1中提供的两种组合物后兔中溴莫尼定和噻吗洛尔的眼睛和全身吸收。

[0047] 表2显示了利用表1组合物A和B的兔实验的研究设计。基于体重将兔子随机分配到组，并接受单次双侧局部滴注试验组合物(组合物A或B)和比较剂(Aiphagan® 和Timoptol®)。具体来说，每组由12只雌兔组成，并在每个时间点测试两只动物(共4只眼)。剂量由单次局部双侧给药组成，剂量体积为35μL。在15、30、60、120、240、480分钟给药后时间点收集样品，并对其进行定量分析以确定溴莫尼定和噻吗洛尔的组织和血浆浓度。

[0048] 表2. 0.1％酒石酸溴莫尼定/0.5％噻吗洛尔二合一组合物的药代动力学研究

[0049]

组	处理	PK 收集时间点
1	Aiphagan® (0.1%酒石酸溴莫尼定)	给药后 15、30、60、120、240、480 分钟
2	Timoptol® (0.5%噻吗洛尔)	
3	组合物 A	
4	组合物 B	
5	Timoptol®，接着是 Aiphagan®[a]	Timoptol 给药后 15、30、60、120、240、480 分钟
6	Aiphagan®，接着是 Timoptol®[a]	

[0050] [a]:两滴滴眼剂剂量之间间隔5分钟

[0051] 观察到与噻吗洛尔0.5%单一疗法相比，当给予酒石酸溴莫尼定0.1%/噻吗洛尔0.5%组合组合物时，噻吗洛尔眼暴露增加。这一发现对于本领域技术人员来说是不明显的。

[0052] 兔PK研究的结果总结在表3和4以及图1和图2中。表3和图1显示了在兔房水、虹膜睫状体和血浆中发现的溴莫尼定的量，但应当注意，连续给药方案的结果在图1中不再现。尽管由于这些药物的IOP降低作用，虹膜睫状体是溴莫尼定和噻吗洛尔二者的靶组织，但房水是浸润虹膜睫状体的体液。因此，房水中的药物浓度通常与虹膜睫状体的实体组织中的药物浓度高度相关。由于鼻泪液引流，局部施加的滴眼剂导致全身循环中的药物暴露，并且通过血浆中的药物浓度来评估暴露程度，这通常与和药物相关的全身副作用相关。

[0053] 在前面的描述中，"C_{max}"表示在实验过程中达到的峰值药物浓度。"AUC"表示药物浓度-时间曲线下面积。

[0054] 图1B显示，在虹膜睫状体中，与单独施用0.1%酒石酸溴莫尼定相比，组合物A和B二者均达到较高的溴莫尼定C_{max}和AUC值。这是一个有希望的结果，因为虹膜睫状体是降低IOP的靶组织。

[0055] 在分别显示房水和血浆溴莫尼定浓度的图1A和1C中，与单独施用0.1%酒石酸溴莫尼定相比，组合物A和B二者均导致较低的C_{max}和AUC值。

[0056] 表3列出了从图1A-C所示的实验获得的药代动力学参数。

[0057] 在图2A和2B中，与单独施用0.5%噻吗洛尔相比，组合物A和B二者均显示房水和虹膜睫状体中眼睛暴露于噻吗洛尔更多。转到图2C，与单独施用0.5%噻吗洛尔相比，组合物A和B的血浆浓度显示较低的浓度。这些较低的血浆浓度是优选的，以减少可能具有心血管副作用的噻吗洛尔的全身暴露。

[0058] 表4列出了从图2A-C所示的实验获得的药代动力学参数。

[0059] 表3.溴莫尼定PK特征

[0060]

矩阵	溴莫尼定(0.1%)	组合物A	组合物B	噻吗洛尔(0.5%)+溴莫尼定(0.1%)[a]	溴莫尼定(0.1%)+噻吗洛尔(0.5%)[a]
溴莫尼定：C_{max}(ng/ml 或 ng/g)-(平均值±SE)					
房水	818±303	351±175	518±208	587±125	468±79
虹膜睫状体	45.1±17.9	58.8±27.6	108±69	68.4±22.2	59.9±20.7
血浆	2.20±0.04	1.49±0.03	1.10±0.40	1.29±0.58	0.944±0.076
溴莫尼定：AUC(ng·hr/ml 或 ng·hr/g)-(平均值±SE)					
房水	1000±150	645±138	782±99	700±66	646±77
虹膜睫状体	82.0±11.4	94.1±21.2	125±29	87.8±14.8	74.2±12.5
血浆	1.95±0.07	1.53±0.20	1.23±0.19	1.32±0.27	0.887±0.142

[0061] [a]：两滴滴眼剂剂量之间间隔5分钟

[0062] 按照单因素方差分析C_{max}值在各组间是相当的(p＞0.05)

[0063] 表4.噻吗洛尔PK特征

[0064]

矩阵	噻吗洛尔(0.5%)	组合物A	组合物B	噻吗洛尔(0.5%)+溴莫尼定(0.1%)[a]	溴莫尼定(0.1%)+噻吗洛尔(0.5%)[a]
噻吗洛尔：C_{max}(ng/ml 或 ng/g)-(平均值±SE)					
房水	1670±90	2300±1140	2890±1130	2070±380	3510±700
虹膜睫状体	1130±180	3330±1400	4090±2140	2400±380	6430±1670
血浆	21.1±1.9	15.9±5.2	12.4±2.3	12.3±0.1	16.1±1.5
噻吗洛尔：AUC(ng·hr/ml 或 ng·hr/g)-(平均值±SE)					

[0065]

房水	2410±160	4330±910	5300±630	3810±260	4490±550
虹膜睫状体	1980±130	6010±1120	6760±980	4080±310	5570±800
血浆	19.6±1.0	32.4±2.4	23.5±3.0	15.7±0.3	21.4±2.7

[0066] [a]：两滴滴眼剂剂量之间间隔5分钟

[0067] C_{max}值在各组间是相当的(按照单因素方差分析$p>0.05$)

[0068] 除非另有说明,否则在说明书和权利要求书中使用的表示成分数量、性质如分子量、反应条件等的所有数字应被理解为在所有情况下被术语“约”修饰。因此,除非有指示相反,否则在说明书和所附权利要求中阐述的数值参数是近似值,其可以根据寻求获得的期望性质而变化。至少且并不企图限制与权利要求的范围等价的教义的应用,每个数值参数应至少根据报道的有效数字的数字和通过应用通常的四舍五入技术来解释。

[0069] 在描述本发明的上下文中(尤其在以下权利要求书的上下文中)使用的术语“一个/种(a/an)”、“所述”以及类似的指代语应当解释为涵盖单数和复数,除非本文另外指明或者明显与上下文相矛盾。除非本文中另有指示或另外上下文明显矛盾,否则可以任何适当次序来执行本文中描述的所有方法。本文提供的任何和所有实例或示例性语言(例如,“如”)的使用仅旨在更好地说明本发明,并不对任何权利要求的范围构成限制。说明书中的任何语言都不应解释为指示任何未要求保护的元素是实践本发明所必需的。

[0070] 本文公开的替代元素或实施方案的分组不应被解释为限制。每个组成员可以单独地或与组中的其它成员或本文中找到的其它元素的任何组合一起被引用和要求。为了方便起见和/或可专利性,预期组中的一个或多个成员可以被包括在组中或从组中删除。当发生任何此类包含或删除时,该说明书被认为包含经修改的组,从而满足所附权利要求中使用的所有马库什组的书面描述。

[0071] 本文描述了某些实施方案,包括发明人已知的用于实施本发明的最佳模式。当然,这些描述的实施方案的变化对于本领域普通技术人员在阅读前面的描述后将变得显而易见。本发明人预期熟练技术人员会适时采用此类变化,而且本发明人预期能以除了本文具体描述的方式之外的方式来实践本发明。因此,权利要求书包括适用法律允许的权利要求中所列举的主题的所有修改和等效物。此外,除非本文另有说明或另外明确地与上下文相矛盾,否则预期其所有可能变化的上述元素的任何组合。

[0072] 应当理解,本文公开的实施方案是权利要求的原理的说明。可以采用的其它修改在权利要求的范围内。因此,作为示例而非限制,可以根据本文的教导来利用替代实施方案。因此,权利要求书不限于精确地如所示和所述的实施方案。

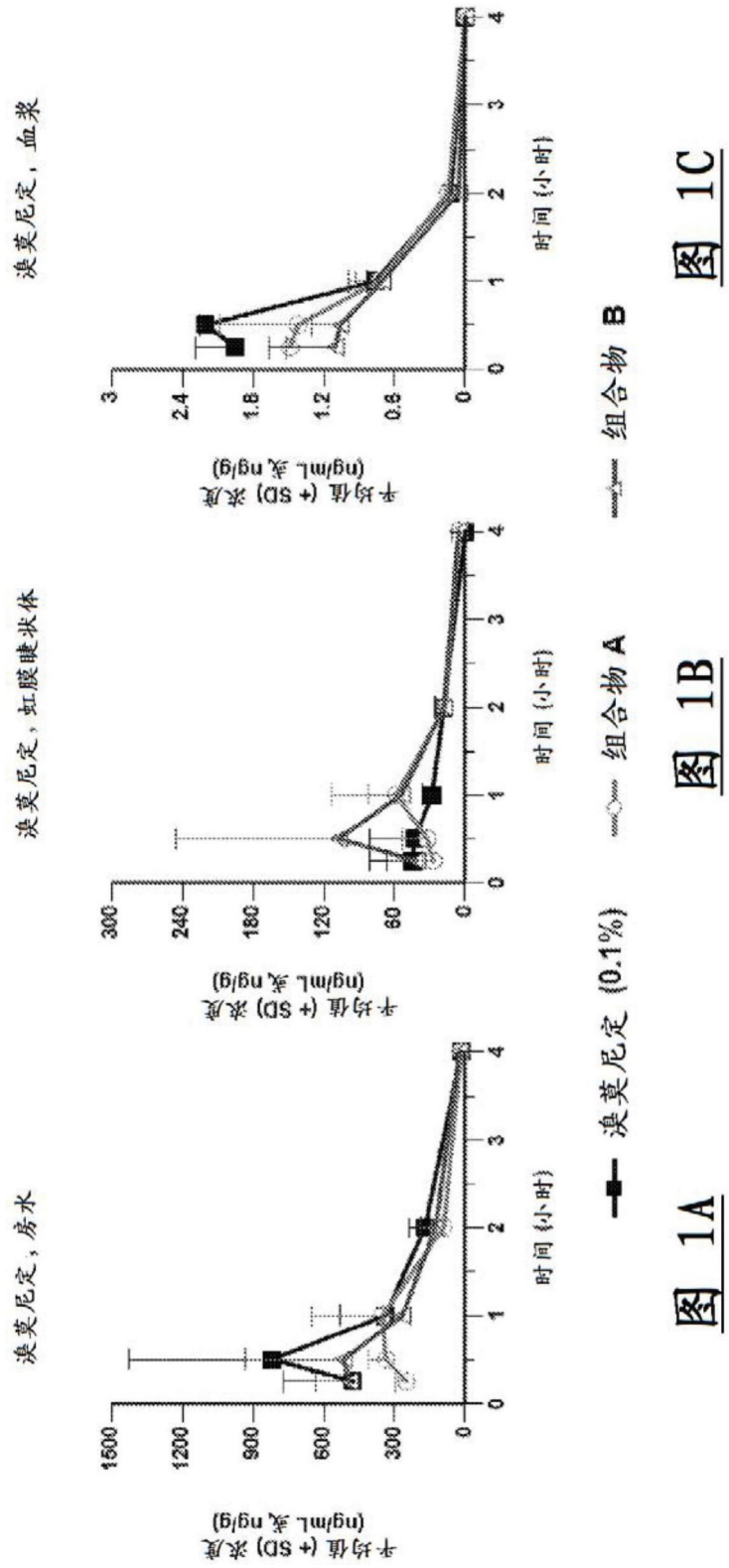

溴莫尼定，房水
溴莫尼定，虹膜睫状体
溴莫尼定，血浆
平均值 (+ SD) 浓度 (ng/mL 或 ng/g)
时间 (小时)
溴莫尼定 (0.1%)
组合物 A
组合物 B

图 1A

图 1B

图 1C

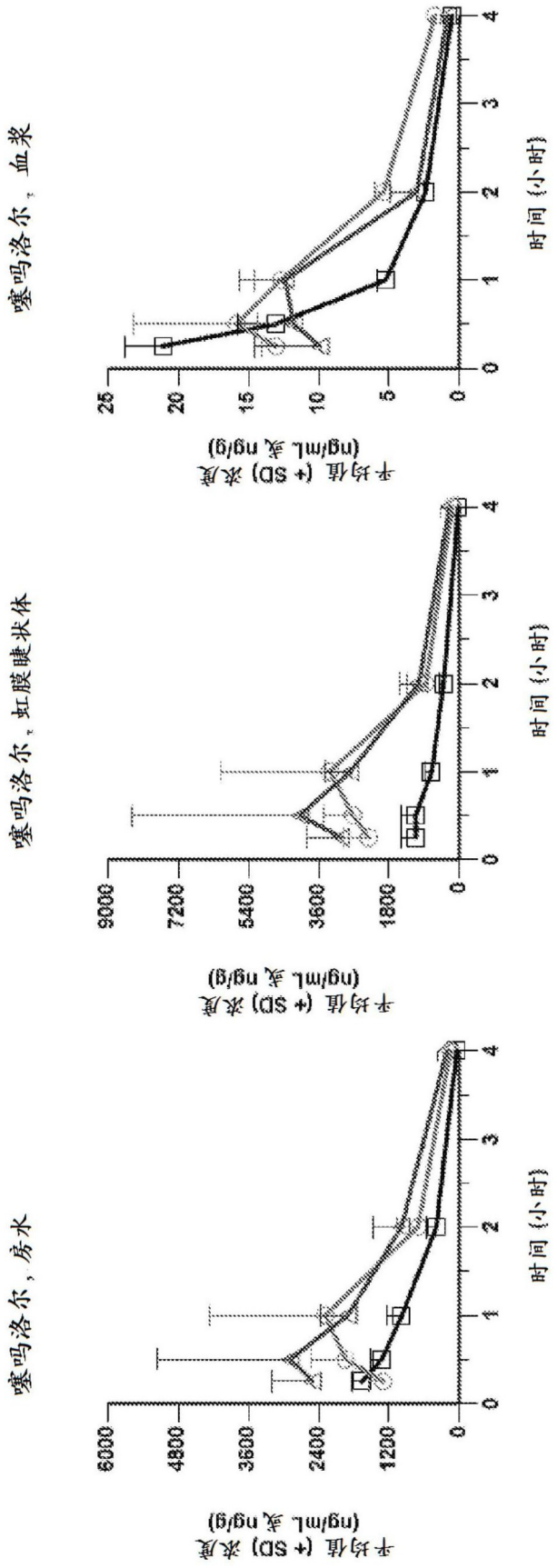

塞吗洛尔，房水
塞吗洛尔，虹膜睫状体
塞吗洛尔，血浆
平均值 (± SD) 浓度 (ng/mL 或 ng/g)
时间 (小时)
塞吗洛尔 (0.5%)
组合物 A
组合物 B

图 2A

图 2B

图 2C