

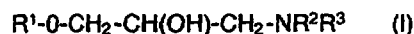
Description

This invention relates to ophthalmic formulations useful in controlling and lowering intraocular pressure (IOP) in the treatment of glaucoma. The formulations of the present invention are characterized as long lasting (sustained release) and are initially and continually comfortable to the eye. Specifically, the invention relates to formulations of the above characteristics which comprise, inter alia, a basic active and cationic exchange resin (finely divided) dispersed in an aqueous solution or gel of an acidic, mucomimetic polymer. Such resulting aqueous gel or pourable liquid formulations are characterized by controlled cationic-anionic interactions, which appear to be responsible for the resulting comfort and sustained release properties.

J. Pharm.Sci., vol.60, N°9, sept. 1971, p.1343-1345, discloses that neomycin sulphate can be incorporated into a polymer gel, without compromising the latter's stability, if it is firstly absorbed onto a specified cation exchange resin and the resultant neomycin sulphate-resinate is then admixed with the polymer gel. It would appear, that the gels discussed therein, are intended for topical skin application.

The term "basic active" means the active ingredient or ingredients in the disclosed formulations which have the desired effect on intraocular pressure and which bear, or are capable of bearing, a positive charge during formulation of the final product or as formulated in the final product form. Thus, the term basic, or cationic, active is descriptive for purposes of the disclosure and claims.

Such basic actives include all presently known beta blockers which demonstrate the requisite cationic charge and IOP effect. Typically, such beta blockers are represented by the following generic structure, which structure also represents the beta blocker basic actives of the present disclosure:



wherein: R¹ is a substituted or unsubstituted cyclic or aliphatic moiety; cyclic moieties include mono- and polycyclic structures which may contain one or more heteroatoms selected from C, N, and O; R² and R³ are independently selected from H and substituted and unsubstituted alkyl. Beta blockers of Structure (I), above, are discussed in detail in the following references:

Annual Reports in Medicinal Chemistry 14, 81-87 (1979); J. Med. Chem. 1983, 26,1570-1576; ibid., 1984, 27, 503-509; ibid., 1983, 26, 7-11; ibid., 1983, 26, 1561-1569; ibid., 1983 1109-1112; ibid., 1983, 26, 950-957; ibid., 1983, 26, 649-657; and ibid., 1983, 26, 352-357. Representative of such basic actives are: betaxolol, timolol, befunolol, labetalol, propranolol, bupranolol, metaprolol, bunolol, esmalol, pindolol, carteolol, hepunolol, metipranolol, celiprolol, azotinolol (S-596), diacetolol, acebutolol, salbutamol, atenolol, isoxaprolol, and the like.

The definition of basic active also includes the following classes of drugs which are used in treatment of ocular hypertension and glaucoma: pilocarpine; epinephrine; proepinephrine; norepinephrine; pronorepinephrine; clonidine; and clonidine derivatives, for example, p-aminoclonidine and p-acetoamidoclonidine.

Thus, in summary, the basic active component of the present invention is defined by its intraocular pressure lowering effect or static control thereof, and by its cationic nature in an aqueous medium in the pH range of from 3.0 to 8.5. The following patent publications further representatively demonstrate the basic actives of the present invention:

U.S. Patents Nos. 4,252,984; 3,309,406; 3,619,370; 3,655,663; 3,657,237; 4,012,444; 3,663,607; 3,836,671; 3,857,952; 3,202,660; and 2,774,789.

The ophthalmic formulations of the present invention can be in the form of: anhydrous salts; pourable, aqueous dispersions; and aqueous gels. The formulations comprise, in addition to conventional ingredients which provide, for example, bacteriostatic and formulatory balance functions, a critical polyanionic polymer, a cation exchange resin and the basic active of choice. Such anhydrous salt forms are incorporated into ointments or solid ocular inserts which form colloidal gels *in situ* on administration to the eye. The pourable liquid and gel embodiments are applied topically to the eye. It should be noted that such liquid and gel embodiments can be obtained from the anhydrous form on formulation with water.

The formulations of the present invention demonstrate sustained release of the basic active and are comfortable on topical administration to the eye. It should be noted, in a general sense, that a stinging sensation results when the basic actives, identified above, are administered neat. Thus, achieving both comfort and sustained release is an unexpected result and permits administration of a class of compounds that otherwise might not be considered.

Polyanionic Polymer Component

The high molecular weight, polyanionic polymers useful in the present invention have a molecular weight of from 50,000 to 6 million. The polymers are characterized as having carboxylic acid functional groups, and preferably contain from 2 to 7 carbon atoms per functional group. The gels which form during the preparation of the ophthalmic polymer dispersion have a viscosity of from 1,000 to 300,000 cps. In addition to the basic active-polymer (anionic-cationic) interactions, mentioned above, the high molecular weight polymers used in the compositions of the present invention thicken the compositions to provide a gel, and provide a special type of rheology, i.e., plastic viscosity, which is translatable to the sustained release and comfort of the final compositions. Such compositions range in pH from 3.0 to 8.5.

The pourable liquid embodiments (administered as drops to the eye) of the present invention have a viscosity of from 1 to 20,000 cps. The pH requirements are the same as recited above for the gel final products, i.e., pH 3.0-8.5.

The third pharmaceutical form of the present invention, the anhydrous salt form, is derived from a salt of the polycarboxylic acid polymer and the basic active. (The presence of the cationic ion exchange resin also contributes to salt formation; the nature of the ion exchange resin, in all embodiments of the present invention, is defined below.) Such salts can be formulated, or reconstituted, to aqueous gels and pourable dispersions, as described above, on addition of water; or can be formulated as ocular inserts according to known technology and shapes; or they can be combined with an oleaginous vehicle to form an ophthalmic ointment. All such final ophthalmic pharmaceutical forms are fully described below.

The term "plastic viscosity", above, is indicative of a material that does not perceptibly flow until a certain force or stress value is exceeded; this force or stress is referred to as the yield value. While not wishing to be bound by any theory, it is believed that the increased duration of activity of the compositions of the present invention is related, in part, to the yield value. The compositions of the present invention exhibit a unique response to shear stress. When the yield value is exceeded, the gel structure is altered temporarily, allowing the gel to flow. In the eye, this mechanism is partially attributable to the blinking eyelid. When the stress is removed (eyelid at rest), the structure of the gel is partially re-established. Other factors which explain the duration of the formulations of the present invention are related to ionic interactions, and a release mechanism which is explained by a dynamic equilibrium involving normal tear production and the displacement of basic active cations by cations present in tears. This mechanism is mentioned again, below.

Suitable polymers useful in the present invention are carboxyl vinyl polymers. Preferred polymers of this class include the so called Carbomers, available under the trade name Carbopol from the B.F. Goodrich Company; and ethylene maleic anhydride polymeric material, available under the trade name EMA from the Monsanto Company. The known and readily available polymers Carbopol 934 and 940 are specifically preferred. The polymers are used in the aqueous gel compositions at a level up to about 8% by weight; pourable liquid compositions comprise 0.05% to 2.0% by weight polymer.

Basic Active

The preferred basic actives of the present invention are those disclosed above. The most preferred basic actives are betaxolol and timolol. The basic active, in the gel and pourable liquid embodiments, is present at a level of from 0.01 to 4.0 wt. %; the most preferred range is from 0.10 to 1.0 wt. %.

Ion Exchange Resin

The cationic resin component of the formulations of the present invention provides an additional means of sustained release of the basic active, and appears to be necessary for initial and prolonged comfort. Such resins are characterized as either strongly acidic such as those having sulfonic acid functionality, or weakly acidic cation exchangers such as those having carboxylic acid functionality. The resin must be incorporated as a finely divided powder, that is, 95% of the resulting spheroidal particles must have a diameter less than 20.0 μm . The release of the basic active held by the cation exchange resin and the anionic polymer is achieved when ions naturally present in the tear fluid, principally sodium and potassium, compete with the bound basic active for sites on the polymer vehicle and the ion exchange resin. Thus released, the basic active is presented to the eye surface for transport to the receptor sites.

Any pharmaceutical grade cationic ion exchange resin is suitable for the formulation, and they can be used either in the hydrogen form or in the sodium form. Such resins are readily available, for example, from Rohm & Haas under the "Amberlite" tradename and from Dow Chemical Co. under the "Dowex"

tradename.

The ion exchange resin component is preferably present in the formulations of the present invention at a level of from 0.05% to 10.0% by weight. The average particle size diameter of the resin preferably ranges from 1 to 20 μm .

The particle size of the resin is important, both with respect to mode of action and comfort. Typically the average particle size of the commercially available form of the ion exchange material of choice is 40 to 150 μm . Such particles are preferably reduced to a particle size range of 1.0 to 25 μm by ball milling, according to known techniques.

10 Other Ingredients

Antimicrobial Preservative:

Ophthalmic products are typically packaged in multidose form. Preservatives are thus required to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Onamer M, or other agents known to those skilled in the art. Typically such preservatives are employed at a level of from 0.001% to 1.0% by weight.

20 Tonicity Agents:

The tonicity, or osmolality, of the product can be adjusted to either hypotonicity, isotonicity or hypertonicity relative to normal tears by use of conventional materials known to the art. Such tonicity agents, however, are limited to nonionic compounds and typically, when employed, range from 0.0% to 10% weight percent in the final product. Nonionic agents representatively include: mannitol, dextrose, glycerine and propyleneglycol; their presence in the final product form, however, is optional.

Formulation

The compositions are formulated in three basic states: 1.) gels; 2.) pourable liquids; and 3.) anhydrous salts:

1.) Gels

The cationic exchange resin component is dispersed in water. The basic active component is then added with stirring. The polyanionic polymer component is then added. The resulting product has a viscosity ranging from 1000 to 300,000 cps depending on the anionic polymer concentration. The resulting pH is 3.0 to 8.5, which may be adjusted, if necessary, with HCl or NaOH.

2.) Pourable Liquids

The cationic exchange resin component is dispersed in 10 to 50 vol. percent of total water taken in formulation, and then basic active is dispersed and/or dissolved with stirring. The polyanionic polymer, as an aqueous dispersion, is added until the desired pH of the product is obtained. The pH of the product can be adjusted to the desired value by varying basic active/polymer/resin ratio. If desired, final pH of product can be adjusted with addition of either NaOH or HCl. The preferred pH range for ophthalmic formulations is from 3.0 to 8.5. The final product is a dispersion, which may require high energy mixing to break any agglomeration to achieve uniformity. Other formulation ingredients are then added with mixing. The resulting product has a viscosity ranging from 1.0 to 20,000 cps depending on the anionic polymer concentration.

3.) Anhydrous Salts

The basic active, the ion exchange resin, and the polyanionic polymer are combined in water, and following mixing, are lyophilized to a powder. Fillers like mannitol and other materials may be added to facilitate the freeze/drying processing according to techniques well known to those skilled in the art. The anhydrous salts produced in this manner can then be formulated or reconstituted to aqueous gels and liquids, or can be formulated and shaped as ocular insets. The lyophilized powder can also be combined with a nonaqueous vehicle to form an ophthalmic ointment.

Such anhydrous salt embodiments of the present invention can also be prepared by extracting the initial aqueous dispersion with an organic solvent such as ethanol, chloroform, benzene, or the like, and evaporating the organic solvent to produce the desired salt complex. The resulting product is substantially equivalent to the above-described lyophilized product.

Utility

The Ophthalmic formulations of the present invention are administered to the eyes as gels, pourable liquids (eye drops), and in the form of ointments and ocular inserts; the latter classifications are formulated form anhydrous salts. All such compositions are formulated to control the release of the basic active upon administration to the eye and thereby provide a sustained release effect. Typically such administration is necessary once or twice per day. The precise dosage regimen is left to the routine discretion of the clinician.

The following examples illustrate, but do not limit the compositional or method of treatment aspects of the present invention.

Example 1

Preparation of Betaxolol Free Base from Betaxolol Hydrochloride:

Betaxolol Hydrochloride is disclosed in U.S. Patent 4,252,984, and is commercially available.

Betaxolol Hydrochloride (0.88 moles) is dissolved in water and the solution is chilled in an ice-bath. To this solution is added a solution of sodium hydroxide (0.97 moles) in water portionwise to make the mixture basic while it is stirred vigorously. At this point the pH of the mixture is approximately 9.6. The resulting white solid is collected by filtration and washed with a large volume of water.

After press/drying in the filter funnel, the semi-dry solid is resuspended in a large volume of water and stirred for 1-2 hours. The white solid is collected by filtration and washed with a large volume of water to afford salt-free Betaxolol free base, which is dried in vacuo.

	Product Composition		
	A (wt%)	B (wt%)	C (wt%)
Betaxolol	0.50	0.25	1.0
CARBOPOL-934 P (Carbomer)	0.25	0.15	0.35
Sodium Poly(Styrene-Divinyl Benzene) Sulfonate	0.25	0.125	0.50
Benzalkonium Chloride	0.01	0.01	0.01
Mannitol	5.0	5.0	5.0
Water	To Make 100%		

Procedure

Finely divided Amberlite IRP-69 resin, a sodium poly(styrene-divinyl benzene) sulfonate, and the betaxolol are mixed in 50% of the total water volume component to form a uniform dispersion. The Carbopol-934P is added slowly as an aqueous dispersion. The mixture is homogenized at high speed. The other ingredients are added as aqueous solutions. The final volume is made on addition of water. The resultant products, A, B and C, are white uniform suspensions.

Example 2

	Product Composition		
	A (wt%)	B (wt%)	C (wt%)
Betaxolol Base	0.50	0.25	1.0
Poly(Styrene-DivinyI Benzene)Sulfonic acid	0.25	0.125	0.5
Carbopol-934P	0.20	0.1	0.35
Benzalkonium Chloride	0.01	0.01	0.01
Mannitol	5.0	5.0	5.0
Water	To Make 100%		

Procedure

The solutions A,B and C of Example 2 are prepared following the procedure of Example 1. The resulting products are white to off-white uniform suspensions with pH between 5.5 to 6.5.

Following the procedure of Examples 1 and 2, substantially equivalent results are obtained when the betaxolol component is replaced by an equivalent amount of timolol, or by any of the previously identified beta blockers and other basic actives, respectively.

Claims

1. A sustained release ophthalmic pharmaceutical composition for controlling and lowering intraocular pressure, comprising a basic active which is effective to lower intraocular pressure, an anionic mucomimetic polymer, and a cation exchange resin.
2. A composition as claimed in claim 1 wherein the composition is an aqueous dispersion.
3. A sustained release ophthalmic pharmaceutical composition for controlling and lowering intraocular pressure as claimed in claim 1, comprising an aqueous dispersion of the basic active, an anionic mucomimetic polymer, and a finely divided cation exchange resin.
4. A composition as claimed in any of claims 1-3 wherein the basic active is betaxolol.
5. A composition as claimed in any of claims 1-3 wherein the basic active is timolol.
6. A composition as claimed in any of claims 1-3 wherein the basic active is selected from pilocarpine, epinephrine, proepinephrine, norepinephrine, pronorepinephrine, clonidine, p-aminoclonidine, p-acetoamidoclonidine, or a beta-blocker selected from betaxolol, timolol, acebutolol, alprenolol, atenolol, bevantolol, bucomolol, bupranolol, butidine, bunitolol, bunolol, butocrolol, butamine, carazolol, carteolol, exaprolol, indenolol, iprocrolol, labetolol, mepindolol, metipranolol, metaprolol, moprolol, nadolol, nifenalol, oxprenolol, pamatolol, paragolol, penbutolol, pindolol, practolol, procinolol, pronethalol, propranolol, sotalol, tazolol, tiprenolol, tolamolol, toliprolol, befunolol, esmalol, hepunolol, celiprolol, azotinolol, diacetalol, acebutolol, salbutanol, and isoxaprolol.
7. A composition according to claim 1 which is a sustained release ophthalmic pharmaceutical composition in the form of an aqueous gel, a pourable aqueous dispersion, or anhydrous salt, for controlling and lowering intraocular pressure comprising:

a therapeutically effective amount of a beta blocker of the formula:



wherein R¹ is a substituted or unsubstituted cyclic or aliphatic moiety, and R² and R³ are independently selected for H and substituted and unsubstituted alkyl;

an amount of an anionic mucomimetic polymer having carboxylic acid functional groups which



Example 2

	Product Composition		
	A (wt%)	B (wt%)	C (wt%)
Betaxolol Base	0.50	0.25	1.0
Poly(Styrene-Divinyl Benzene)Sulfonic acid	0.25	0.125	0.5
Carbopol-934P	0.20	0.1	0.35
Benzalkonium Chloride	0.01	0.01	0.01
Mannitol	5.0	5.0	5.0
Water	To Make 100%		

Procedure

The solutions A,B and C of Example 2 are prepared following the procedure of Example 1. The resulting products are white to off-white uniform suspensions with pH between 5.5 to 6.5.

Following the procedure of Examples 1 and 2, substantially equivalent results are obtained when the betaxolol component is replaced by an equivalent amount of timolol, or by any of the previously identified beta blockers and other basic actives, respectively.

Claims

1. A sustained release ophthalmic pharmaceutical composition for controlling and lowering intraocular pressure, comprising a basic active which is effective to lower intraocular pressure, an anionic mucomimetic polymer, and a cation exchange resin.
2. A composition as claimed in claim 1 wherein the composition is an aqueous dispersion.
3. A sustained release ophthalmic pharmaceutical composition for controlling and lowering intraocular pressure as claimed in claim 1, comprising an aqueous dispersion of the basic active, an anionic mucomimetic polymer, and a finely divided cation exchange resin.
4. A composition as claimed in any of claims 1-3 wherein the basic active is betaxolol.
5. A composition as claimed in any of claims 1-3 wherein the basic active is timolol.
6. A composition as claimed in any of claims 1-3 wherein the basic active is selected from pilocarpine, epinephrine, proepinephrine, norepinephrine, pronorepinephrine, clonidine, p-aminoclonidine, p-acetoamidoclonidine, or a beta-blocker selected from betaxolol, timolol, acebutolol, alprenolol, atenolol, bevantolol, bucomolol, bupranolol, butidine, bunitolol, bunolol, butocrolol, butamine, carazolol, carteolol, exaprolol, indenolol, iprocrolol, labetolol, mepindolol, metipranolol, metaprolol, moprolol, nadolol, nifenalol, oxprenolol, pamatolol, paragolol, penbutolol, pindolol, practolol, procinolol, pronethalol, propranolol, sotalol, tazolol, tiprenolol, tolamolol, toliprolol, befunolol, esmalol, hepunolol, celiprolol, azotinolol, diacetolol, acebutolol, salbutanol, and isoxaprolol.
7. A composition according to claim 1 which is a sustained release ophthalmic pharmaceutical composition in the form of an aqueous gel, a pourable aqueous dispersion, or anhydrous salt, for controlling and lowering intraocular pressure comprising:

a therapeutically effective amount of a beta blocker of the formula:



wherein R^1 is a substituted or unsubstituted cyclic or aliphatic moiety, and R^2 and R^3 are independently selected for H and substituted and unsubstituted alkyl;

an amount of an anionic mucomimetic polymer having carboxylic acid functional groups which

comprise from 2 to 7 carbon atoms per function group and a molecular weight from 50,000 to 6 million such that the composition in the form of an aqueous gel or pourable aqueous dispersion has a viscosity of 1 to 20,000 cps.; and a particulate cation exchange resin at a concentration of from 0.05% to 10.0% by weight, the composition having a pH of from about 3.0 to 8.5.

8. A composition as claimed in claim 7 wherein the particulate cation exchange resin is in the form of a finely divided powder, said powder consisting of spherical particles.
9. A composition as claimed in claim 7 or claim 8 wherein the cation exchange resin is sodium poly-(styrene divinylbenzene) sulfonic acid and the beta blocker is betaxolol.
10. A composition as claimed in any of claims 7-9 wherein the beta blocker is present at a concentration of about 0.25 wt.%, the anionic mucomimetic polymer is present at a concentration of about 0.20 wt.%, and the cation exchange resin is present at a concentration of about 0.25 wt.%.
11. A composition as claimed in any of the preceding claims, wherein the cation exchange resin consists of particles ranging in size from 1.0 to 25 μm .
12. A composition as claimed in any of claims 1-10 for use in the manufacture of a medicament for controlling and lowering intraocular pressure.

Patentansprüche

1. Ophthalmologische pharmazeutische Zusammensetzung mit verzögerter Wirkstofffreisetzung zur Kontrolle und Senkung des intraokularen Druckes, umfassend einen basischen Wirkstoff, der zur Senkung des intraokularen Druckes wirksam ist, ein anionisches mucomimetisches Polymer und ein Kationenaustauscherharz.
2. Zusammensetzung nach Anspruch 1, worin die Zusammensetzung eine wäßrige Dispersion ist.
3. Ophthalmologische pharmazeutische Zusammensetzung mit verzögerter Wirkstofffreisetzung zur Kontrolle und Senkung des intraokularen Druckes nach Anspruch 1, umfassend eine wäßrige Dispersion des basischen Wirkstoffs, ein anionisches mucomimetisches Polymer und ein feinteiliges Kationenaustauscherharz.
4. Zusammensetzung nach irgendeinem der Ansprüche 1-3, worin der basische Wirkstoff Betaxolol ist.
5. Zusammensetzung nach irgendeinem der Ansprüche 1-3, worin der basische Wirkstoff Timolol ist.
6. Zusammensetzung nach irgendeinem der Ansprüche 1-3, worin der basische Wirkstoff ausgewählt ist unter Pilocarpin, Epinephrin, Proepinephrin, Norepinephrin, Pronorepinephrin, Clonidin, p-Aminoclonidin, p-Acetoainidoclonidin oder einem Beta-Blocker, ausgewählt unter Betaxolol, Timolol, Acebutolol, Alprenolol, Atenolol, Bevantolol, Bucamolol, Bupranolol, Butidrin, Bunitolol, Bunolol, Butocrolol, Butamin, Carazolol, Carteolol, Exaprolol, Indenolol, Iprocrolol, Labetolol, Mepindolol, Metipranolol, Metaprolol, Moprolol, Nadolol, Nifenalol, Oxprenolol, Pamatolol, Paragolol, Penbutolol, Pindolol, Practolol, Procinolol, Pronethalol, Propranolol, Sotalol, Tazolol, Tiprenolol, Tolamolol, Toliprolol, Befunolol, Esmalol, Hepunolol, Celiprolol, Azotinolol, Diacetalol, Acebutolol, Salbutanol und Isoxaprolol.
7. Zusammensetzung nach Anspruch 1, welche eine ophthalmologische pharmazeutische Zusammensetzung mit verzögerter Wirkstofffreisetzung in Form eines wäßrigen Gels, einer gießfähigen wäßrigen Dispersion oder eines wasserfreien Salzes zur Kontrolle und Senkung des intraokularen Druckes ist, umfassend:

eine therapeutisch wirksame Menge eines Beta-Blockers der Formel:



worin R^1 eine substituierte oder unsubstituierte cyclische oder aliphatische Gruppe ist und R^2 und R^3 unabhängig ausgewählt sind aus H und substituiertem oder unsubstituiertem Alkyl;



5 une Menge eines anionischen mucomimetischen Polymers mit funktionellen Carbonsäure-Gruppen, welche 2 bis 7 Kohlenstoffatome pro funktionelle Gruppe umfassen, und einem Molekulargewicht von 50.000 bis 6 Millionen, so daß die Zusammensetzung in Form eines wäßrigen Gels oder einer gießfähigen wäßrigen Dispersion eine Viskosität von 1 bis 20.000 cP hat; und ein teilchenförmiges Kationenaustauscherharz in einer Konzentration von 0,05 bis 10,0 Gewichtsprozent, wobei die Zusammensetzung einen pH von etwa 3,0 bis 8,5 hat.

8. Zusammensetzung nach Anspruch 7, worin das teilchenförmige Kationenaustauscherharz in Form eines feinteiligen Pulvers vorliegt, welches aus kugelförmigen Teilchen besteht.

9. Zusammensetzung nach Anspruch 7 oder Anspruch 8, worin das Kationenaustauscherharz Natrium-poly(styroldivinylbenzol)-sulfonsäure ist und der Beta-Blocker Betaxolol ist.

10. Zusammensetzung nach irgendeinem der Ansprüche 7-9, worin der Beta-Blocker in einer Konzentration von etwa 0,25 Gewichtsprozent vorhanden ist, das anionische mucomimetische Polymer in einer Konzentration von etwa 0,20 Gewichtsprozent vorhanden ist und das Kationenaustauscherharz in einer Konzentration von etwa 0,25 Gewichtsprozent vorhanden ist.

11. Zusammensetzung nach irgendeinem der vorangehenden Ansprüche, worin das Kationenaustauscherharz aus Teilchen mit einer Größe im Bereich von 1,0 bis 25 µm besteht.

12. Zusammensetzung nach irgendeinem der Ansprüche 1-10 zur Verwendung bei der Herstellung eines Medikaments zur Kontrolle und Senkung des intraokularen Druckes.

25 Revendications

1. Une composition pharmaceutique ophtalmique à libération prolongée pour contrôler et abaisser la pression intra-oculaire, comprenant un actif basique qui est efficace pour abaisser la pression intra-oculaire, un polymère mucomimétique anionique et une résine échangeuse de cations.

2. Une composition selon la revendication 1, dans laquelle la composition est une dispersion aqueuse.

3. Une composition pharmaceutique ophtalmique à libération prolongée pour contrôler et abaisser la pression intra-oculaire selon la revendication 1, comprenant une dispersion aqueuse de l'actif basique, un polymère mucomimétique anionique et une résine échangeuse de cations finement divisée.

4. Une composition selon l'une quelconque des revendications 1 à 3, dans laquelle l'actif basique est le bétaxolol.

5. Une composition selon l'une quelconque des revendications 1 à 3, dans laquelle l'actif basique est le timolol.

6. Une composition selon l'une quelconque des revendications 1 à 3, dans laquelle l'actif basique est choisi parmi la pilocarpine, l'épinéphrine, la proépinéphrine, la norépinéphrine, la pronorépinéphrine, la clonidine, la p-aminoclonidine, la p-acétoamidoclonidine, ou un bêta-bloquant choisi parmi le bétaxolol, le timolol, l'acébutolol, l'alprénolol, l'aténolol; le bévantalol, le bucomolol, le buprénolol, la butidine, le bunitolol, le bunolol, le butocrolol, la butamine, le carazolol, le cartéolol, l'exaprolol, l'indénolol, l'iprocrolol, le labétolol, le mépindolol, le métipranolol, le métaprolol, le moprolol, le nadolol, le nifénalol, l'oxprénolol, le pamatolol, le paragolol, le penbutolol, le pindolol, le practolol, le procinolol, le pronéthanol, le propanolol, le sotalol, le tazolol, le tiprénolol, le tolamolol, le toliprolol, le béfonolol, l'esmalol, l'hépunolol, le céliprolol, l'azotinolol, le diacétalol, l'acébutolol, le salbutanol et l'isoxaprolol.

7. Une composition selon la revendication 1 qui est une composition pharmaceutique ophtalmique à libération prolongée sous la forme d'un gel aqueux, d'une dispersion aqueuse pouvant être versée ou d'un sel anhydre, pour contrôler et abaisser la pression intra-oculaire comprenant :
une quantité thérapeutiquement efficace d'un bêta-bloquant de formule :



dans laquelle R¹ est un motif aliphatique ou cyclique substitué ou non, et R² et R³ sont indépendamment choisis parmi H et un alkyle substitué ou non;

une quantité d'un polymère mucomimétique anionique possédant des groupes fonctionnels acide carboxylique qui comprennent de 2 à 7 atomes de carbone par groupe fonctionnel et un poids moléculaire de 50 000 à 6 millions, de façon que la composition possède une viscosité de 1 à 20 000 cps sous la forme d'un gel aqueux ou d'une dispersion aqueuse versable; et une résine particulière échangeuse de cations à une concentration de 0,05 % à 10,0 % en poids, la composition possédant un pH d'environ 3,0 à environ 8,5.

8. Une composition selon la revendication 7, dans laquelle la résine particulière échangeuse de cations est sous la forme d'une poudre finement divisée, ladite poudre consistant en des particules sphériques.
9. Une composition selon la revendication 7 ou 8, dans laquelle la résine échangeuse de cations est l'acide poly(styrène-divinyle-benzène) sulfonique et le bêta-bloquant est le bêtaxolol.
10. Une composition selon l'une quelconque des revendications 7 à 9, dans laquelle le bêta-bloquant est présent à une concentration d'environ 0,25 % en poids, le polymère mucomimétique anionique est présent à une concentration d'environ 0,20 % en poids, et la résine échangeuse de cations est présente à une concentration d'environ 0,25 % en poids.
11. Une composition selon l'une quelconque des revendications précédentes, dans laquelle la résine échangeuse de cations consiste en des particules variant en taille de 1.0 à 25 µm.
12. Une composition selon l'une quelconque des revendications 1 à 10, pour utilisation dans la fabrication d'un médicament pour contrôler et abaisser la pression intra-oculaire.

