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(54) Title: PHARMACEUTICAL COMPOSITIONS

(57) Abstract: The invention is directed to an ophthalmic composition adapted for topical once-a-day administration to the eye comprising an ophthalmic drug, in particular to an ophthalmic composition comprising an ophthalmic drug and at least one polymer selected from one or more of i) a polyoxyethylene-polyoxypropylene co-polymer or block co-polymer, and ii) a cross-linked acrylic acid polymer.

Pharmaceutical Compositions

This invention relates to pharmaceutical, in particular ophthalmic compositions, e.g. gels, and a method for treating ocular disorders/diseases by once-a-day administration of said compositions.

Ophthalmic compositions have often to be applied several, typically two to four times a day, like, for instance, ophthalmic compositions comprising ketotifen which are known, e.g. from WO 01/07049, and commercially available, e.g. under the trade names Zaditen® or Zaditor®. Such repeated administration is not optimal in practice, e.g. for optimal treatment the patient has to have the medicament always available and is disturbed several times a day by the need of administering the composition. Therefore such multiple administration of a drug, in particular of an ophthalmic composition, leads generally to the problem of overdosing and/or underdosing. Overdosing, however, may typically generate ocular irritation, whereas underdosing may typically lead to re-occurrence of the symptoms.

There is thus a need for a so-called once-a-day administration of ophthalmic drugs. It has now been found that ophthalmic compositions can be formulated for once-a-day administration. Said compositions provide a therapeutic effect of the drug they comprise, for instance of an ophthalmic drug like ketotifen, at the eye over about 24 hours. Such compositions are surprisingly well tolerated, and produce a highly reliable and reproducible clinical result in a patient treated therewith.

Therefore, in one aspect the present invention provides an ophthalmic composition being adapted for topical once-a-day administration of ophthalmic drug (hereinafter compositions of the present invention).

Suitable ophthalmic drugs include anti-inflammatory drugs such as indomethacin, diclofenac, tenoxicam, piroxicam, hydrocortisone, medrysone, prednisolone, methylprednisolone, betamethasone, triamcinolone acetonide, dexamethasone, fluorometholone; drugs against allergy such as ketotifen, antazoline, cromoglycate; drugs for treatment of glaucoma such as timolol, betaxolol, carteolol, befunolol, levobunolol, pilocarpine, unoprostone, latanoprost, valsartan; miotics such as pilocarpine, aceclidine, carbachol, acetycholine; mydriatics such as tropicamide, atropine, phenylephrine, cyclopentolate, scopolamine, homatropine, napha-

zoline; antibiotics such as lomefloxacine, pefloxacine, gentamicine, sulfacetamide, sulfadicramide, sulfadiazine, neomycine, framycitine, polymixine B, kanamycine, tobramycine, amikacine, tetracycline, oxytetracycline, bacitracine, chloramphenicol, doxycicline, minocycline, erythromycine, rifamycine, streptomycine; antiviral drugs such as idoxuridine, 5-iodo-2'-deoxycytidine, vidarabine, trifluridine, acyclovir, foscarnet, interferon; anaesthetics such as tetracaine, oxybuprocaine, lidocaine; antimycotics such as amphotericine B, nystatine, fluorocytosine, griseofulvine; antiseptics such as chlorhexidine, picloxidine; and trophic agents such as ascorbic acid, retinol. Preferably the ophthalmic drug is selected from diclofenac, prednisolone, ketotifen, timolol, valsartan, griseofulvine, ascorbic acid and retinol, or is, very particularly, ketotifen.

Suitable ophthalmic drugs may be e.g. in their free base or acid form, or in form of a pharmaceutically acceptable salt thereof and may be used in combination of two or more than two.

The concentration of ophthalmic drug is preferably from about 0.005 – 5%, preferably 0.01 – 2%, even more preferably from 0.01 – 1%, e.g. 0.01 to 0.2%, e.g. 0.01 to 0.1% and in particular from 0.01 to 0.05, preferably 0.02 – 0.04%, in each case by weight based on the total weight of the composition.

A drug is preferably in solution. If desired, however, the compositions of the present invention may be in the form of a suspension, e.g. containing particles of an ophthalmic drug, in particular ketotifen, e.g. with a mean particle diameter of 200 to 25000 nm.

The compositions of the present invention may comprise pharmaceutically acceptable excipients, which are suitable for ophthalmic compositions. The excipients of the compositions of the present invention and the compositions themselves should, in general, not detrimentally affect the lacrimal system nor the ocular tear film.

Information on the properties, specifications and characteristics are described e.g in standard texts such as Fiedler, H.P.; 1996; Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete; Editio Cantor Verlag Aulendorf (Germany), and Kibbe, A.H.; 2000; Handbook of Pharmaceutical Excipients, a joint publication of Pharmaceutical Press,

London (UK), and American Pharmaceutical Association, Washington (US) as well as manufacturers' brochures, the contents of which are incorporated herein by reference.

The compositions of the present invention may typically comprise (1.) biocompatible polymers (thickeners). Such a polymer may be a thermo-reversible polymer e.g. one which increases the viscosity of the composition on increasing temperature. Additionally such polymers may exhibit muco-adhesive properties.

A wide variety of polymers may be chosen but we have found the following are particularly preferred.

1.1 polyoxyethylene-polyoxypropylene copolymers and preferably block co-polymers. Preferably the polyoxypropylene polymer number is from about 10 to about 60. Preferably the polyoxyethylene polymer number is from about 10 to about 150. Examples include such as those known and commercially available under the trade names Lutrol® and Poloxamer® (Fiedler, loc. cit., p. 1200, 1203; Handbook of Pharmaceutical Excipients, loc. cit., page 386) and in particular Poloxamer® 407 and Lutrol® F127, having a melting point of about 52 to 57°C.

1.2 acrylic acid homo- and co-polymers, which preferably are cross-linked; preferably carboxypolymethylene. Preferred molecular weights are between about 500,000, preferably from 1,000,000 to about 10,000,000 Daltons. Preferably, the acid groups comprise between 56 and 68% by weight of the total polymer.
Preferably it is crosslinked with a polyol, e.g.

1.2.1 with divinyl glycol, such as those known and commercially available under the trade name Noveon® from BFGoodrich, and in particular Noveon® AA-1, or

1.2.2 with allylsucrose or allypentaerythritol, such as those known and commercially available under the trade name Carbopol® from BFGoodrich. Examples include those known and commercially available under the trade name Carbopol® and in particular Carbopol® 980; 981 and 984.

The exact amounts of polymer/thickener components may vary within wide limits, e.g. to produce a composition of the present invention within the viscosity indicated above. For example the amount may be from e.g. 0.1 to 20%, e.g. 0.1 to 16, preferably 1 to 10%, by weight of the total composition.

Preferably the present invention provides ophthalmic compositions comprising an ophthalmic drug like e.g. ketotifen and at least one polymer such as i) a polyoxyethylene-polyoxypropylene co-polymer or block co-polymer, and ii) a cross-linked acrylic acid polymer, e.g. as hereinabove described, e.g. adapted for topical once-a-day administration to the eye.

Preferably both polymer/thickener components component i) and ii) are present e.g. in a weight ratio of i):ii) of e.g. 1:200 to 1:5, e.g. 1:50 to 1:20.

The compositions of the present invention may further comprise (2.) a tonicity enhancing agent. Suitable tonicity enhancing agents are, e.g.

2.1 ionic compounds, such as alkali metal or alkaline earth metal halides, such as $CaCl_2$, KBr, KCl, LiCl, NaI, NaBr or NaCl, or boric acid, and/or

2.2 non-ionic compounds such as urea, glycerol, sorbitol, mannitol, propylene glycol, or dextrose.

Conveniently, sufficient tonicity enhancing agent is added to impart to the ready-for-use ophthalmic composition an osmolality of approximately from 50 to 1000 mOsmol, preferred from 100 to 400 mOsmol, more preferred from 200 to 400 mOsmol and even more preferred from 280 to 350 mOsmol.

For the adjustment of the pH, preferably to a physiological pH, addition of (3.) a pharmaceutically acceptable buffer system. Examples of buffer substances are acetate, ascorbate, borate, hydrogen carbonate/carbonate, citrate, gluconate, lactate, phosphate, propionate and tromethamine (tris-(hydroxymethyl)-aminomethane, TRIS) buffers. Trometh-amine buffer is preferred. The buffer substance added is typically of an amount to ensure and maintain a physiologically tolerable pH range. The pH range is generally in the range of from 4 to 9, preferably from 4.5 to 8.5 and more preferably from 5.0 to 8.2.

The compositions of the present invention may further comprise (4.) a preservative, e.g. on storage or to inhibit microbial growth after opening a closed container holding such a composition and exposing such a composition to the air. A preservative may typically be selected from e.g.

4.1 a quaternary ammonium compound such as e.g. benzalkonium chloride (N-benzyl-N-(C_8-C_{18}-alkyl)-N,N-dimethylammonium chloride), benzoxonium chloride, cetrimide (hexadecyl-trimethylammonium bromide) or the like.

4.2 alkyl-mercury salts of thiosalicylic acid, such as e.g. thiomersal, phenylmercuric nitrate, phenylmercuric acetate or phenylmercuric borate,

4.3 parabens, such as e.g. methylparaben or propylparaben,

4.4 alcohols, such as e.g. chlorobutanol, benzyl alcohol or phenyl ethanol,

4.5 biguanide derivatives, such as e.g. chlorohexidine or polyhexamethylene biguanide,

4.6 sodium perborate,

4.7 imidazolidinyl urea as known and commercially available under the trade name Germal®II,

4.8 sorbic acid,

4.9 stabilized oxychloro complexes such as known and commercially available under the trade name Purite®,

4.10 polyglycol-polyamine condensation resins, such as known and commercially available e.g. under the trade name Polyquart® from Henkel KGaA, and

4.11 a mixture of any components 4.1 to 4.10.

Preferred preservatives are quaternary ammonium compounds, in particular benzalkonium chloride and cetrimide. Where appropriate, a sufficient amount of preservative is added to the ophthalmic composition to ensure protection against secondary contaminations during use caused by bacteria and fungi, e.g. the preferred preservatives are present in an amount of about 0.001-0.02%.

A pharmaceutical composition may additionally require the presence of (5.) a solubilizer, in particular if the active or the inactive ingredients tends to form a suspension or an emulsion. A solubilizer suitable for an above concerned composition is e.g.

5.1 octylphenoxy-poly(ethylenoxy)-ethanol (tyloxapol) known and commercially available under the trade name Triton®, e.g. Triton ® WR 1339, (Fiedler, loc. cit., p 1609),

5.2 polyethylene glycol glyceryl fatty acid ester. The fatty acid ester may include mono and/or di and/or tri fatty acid ester. The fatty acid constituent may include both saturated and unsaturated fatty acids having a chain length of from e.g. C_8-C_{20}. The polyethylene glycols may have e.g. from 5 to 40 [CH_2-CH_2-O] units, e.g. 5 or 30 units. Particularly suitable is polyethylene glycol (15) glyceryl monostearate or polyethylene

glycol (15) glyceryl monooleate which is commercially available, e.g. under the trade name TGMS®-15 or TGMO®-15, respectively, e.g. from Nikko Chemicals Co., Ltd. Further suitable is polyethylene glycol (30) glyceryl monooleate which is commercially available, e.g. under the trade name Tagat® O, e.g. from Goldschmidt (H. Fiedler, loc cit, vol. 2, p. 1502-1503). Further suitable are polyethylene glycol glyceryl C_8-C_{10} fatty acid ester with from 5 to 10 [CH_2-CH_2-O] units, e.g. 7 units, e.g. Cetiol® HE, or Labrasol®

5.3 polyoxyethylene C_{8-20} fatty acid esters, e.g. polyoxyethylene stearic acid esters of the type known and commercially available under the trade name Myrj® (Fiedler, loc. cit., 2, p. 1042) or Brij® (Fiedler, loc. cit., p. 259; Handbook of Pharmaceutical Excipients, loc. cit., p. 367). An especially preferred product of this class is Myrj® 52 having a D^{25} of about 1.1, a melting point of about 40 to 44°C, an HLB value of about 16.9, an acid value of about 0 to 1 and a saponification value of about 25 to 35,

5.4 glycerol ethers (Fiedler, loc. cit., p.701),

5.5 cyclodextrins, e.g. α-, β- or γ-cyclodextrin, e.g. alkylated, hydroxyalkylated, carboxy-alkylated or alkyloxycarbonyl-alkylated derivatives, or mono- or diglycosyl-α-, β- or γ-cyclodextrin, mono- or dimaltosyl-α-, β- or γ- cyclodextrin or panosyl-cyclodextrin, e.g. such as known and commercially available under the trade name Cavamax® or Cavasol® from Wacker Chemie. An especially preferred product of this class is hydroxypropyl-χ-cyclodextrin, e.g. as known and commercially available under the trade name Cavasol® W7 HP or Cavasol® W8 HP. A mixture of cyclodextrins may also be used.

5.6 polyoxyethylene-sorbitan- C_{8-20} fatty acid esters (polysorbates) e.g. produced by co-polymerising ethylene oxide with fatty acid esters of a sorbitol and its anhydrides of e.g. mono- and tri- lauryl, palmityl, stearyl and oleyl esters e.g. of the type known and commercially available under the trade name Tween® (Fiedler, loc.cit., p.1615) including the products Tween®

20 [polyoxyethylene(20)sorbitanmonolaurate],

21 [polyoxyethylene(4)sorbitanmonolaurate],

40 [polyoxyethylene(20)sorbitanmonopalmitate],

60 [polyoxyethylene(20)sorbitanmonostearate],

65 [polyoxyethylene(20)sorbitantristearate],

80 [polyoxyethylene(20)sorbitanmonooleate],

81 [polyoxyethylene(5)sorbitanmonooleate],

85 [polyoxyethylene(20)sorbitantrioleate].

Especially preferred products of this class are Tween®20 and Tween®80.

5.7 reaction products of natural or hydrogenated vegetable oils and ethylene glycol, i.e. polyoxyethylene glycolated natural or hydrogenated vegetable oils, for example polyoxyethylene glycolated natural or hydrogenated castor oils. Such products may be obtained in known manner, e.g. by reaction of a natural or hydrogenated castor oil or fractions thereof with ethylene oxide, e.g. in a molar ratio of from about 1:35 to about 1:60, with optional removal of free polyethylene glycol components from the product, e.g. in accordance with the methods disclosed in German Auslegeschriften 1,182,388 and 1,518,819. Especially suitable are the various tensides available under the trade name Cremophor®. Particularly suitable are the products Cremophor®RH 40 having a saponification no. ca. 50-60, an acid no.=<1, an iodine no.=<1, a water content (Fischer)=<2%, an n_D^{60} =ca.1,453-1,457 and an HLB=ca. 14-16; Cremophor®RH 60 having a saponification no.=ca. 40-50, an acid no. =<1, an iodine no.=<1, a water content (Fischer)=ca. 4.5-5.5%, an n_D^{25}=ca.1.453-1,457 and an HLB=ca.15-17; and Cremophor®EL having a molecular weight (by steam osmometry)=ca. 1630, a saponification no.=ca. 65-70, an acid no.=ca. 2, an iodine no.=ca. 28-32 and an n_D^{25} =ca.1.471 (c.f. Fiedler loc. cit. p. 326-327). Also suitable for use in this category are the various tensides available under the trade name Nikkol®, e.g. Nikkol®HCO-60. Said product Nikkol®HCO-60 is a reaction product of hydrogenated castor oil and ethylene oxide exhibiting the following characteristics: acid no.=ca. 0.3; saponification no.=ca. 47.4; hydroxy value=ca. 42.5. pH (5%)=ca. 4.6; Color APHA=ca. 40; m.p.=ca. 36.0°C.; Freezing point=ca. 32.4°C.; H_2O content (%, KF)=ca. 0.03, and/or

5.8 mixtures of the components 5.1 to 5.7.

Especially preferred solubilizers are Cremophor®EL, Cremophor®RH 40, octylphenoxypoly(ethylenoxy)ethanol (tyloxapol) and cyclodextrins. The concentration used depends especially on the concentration of the active ingredient. The amount added is typically sufficient to solubilize the active ingredient. For example, the concentration of the solubilizer is from 0.1 to 5000 times the concentration of the active ingredient, preferably 0.5 to 1000, e.g. 1 to 500.

Further excipients may be comprised in the compositions of the present invention, which may in particular function as a combined stabilizer/solubilizer. Such a combined additional

stabilizer/solubilizer is for example a cyclodextrin or a mixture of cyclodextrins. A preferred cyclodextrin is in particular selected from the group of α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, dimethyl-β-cyclodextrin, randomly methylated β-cyclodextrin and dimethyl-γ-cyclodextrin. The amount is generally in the range of from approximately 0.01 to approximately 90% by weight, more preferably in the range of from 0.1 - 20% by weight.

The ophthalmic compositions may comprise further pharmaceutically acceptable excipients, such as (6.) emulsifiers, (7.) wetting agents or (8.) fillers, such as, e.g. the polyethylene glycols (Fiedler, loc. cit., p. 2108, Handbook of Pharmaceutical Excipients, loc. cit., p 392) such as PEG 200, 300, 400 and 600, or Carbowax® 1000, 1500, 4000, 6000 and 10000.

Other excipients that may be used if desired are listed below but they are not intended to limit in any way the scope of the possible excipients. They are especially (9.) complexing agents, such as disodium-ethylenediamine tetraacetate, ethylenediamine tetraacetic acid (EDTA), (10.) antioxidants, such as ascorbic acid, acetylcysteine, cysteine, sodium hydrogen sulfite, butylated hydroxyanisole, butylated hydroxytoluene or alpha-tocopherol acetate; (11.) stabilizers, such thiourea, thiosorbitol, sodium dioctyl sulfosuccinate or monothioglycerol; or (12.) other excipients, such as, for example, lauric acid sorbitol ester, triethanol amine oleate or palmitic acid ester. Preferred exipients are complexing agents, such as disodium-EDTA. The amount and type of excipient added is in accordance with the particular requirements and is generally in the range of from about 0.0001 to about 90% by weight.

In another embodiment, the present invention provides for compositions further comprising (13.) an ophthalmic carrier. Such carriers are typically adapted for topical administration, and are for example

13.1 water,

13.2 mixtures of water and water-miscible solvents, such as C_1- to C_7-alkanols,

13.3 vegetable oils or mineral oils comprising from 0.5 to 5% by weight hydroxyethyl-cellulose, ethyl oleate, carboxymethyl-cellulose, polyvinyl-pyrrolidone,

13.4 water-soluble polymers for ophthalmic uses, such as, for example, cellulose derivatives, such as methylcellulose, alkali metal salts of carboxy-methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, methylhydroxypropyl-cellulose and hydroxypropylcellulose,

13.5 acrylates or methacrylates, such as salts of polyacrylic acid or ethyl acrylate, polyacrylamides,

13.6 natural products, such as gelatin, alginates, pectins, tragacanth, karaya gum, gellan gum such as Gelrite®, xanthan gum, carrageenin, agar and acacia,

13.7 starch derivatives, such as starch acetate and hydroxypropyl starch,

13.8 synthetic products, such as polyvinyl alcohol, polyvinylpyrrolidone, polyvinyl methyl ether, polyethylene oxide, or

13.9 mixtures of those polymers.

Preferred carriers are water, cellulose derivatives, such as methylcellulose, alkali metal salts of carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, methylhydroxypropylcellulose and hydroxypropylcellulose, or mixtures thereof. The concentration of the carrier is, for example, from 1 to 100 000 times the concentration of the active ingredient.

It will be appreciated that although the excipients have been described above by reference to a particular function any particular excipient may have alternative or multiple functions, e.g. cyclodextrin or a mixture of cyclodextrins may act as e.g. stabilizer, complexing agent and/or solubilizer.

Applicants have found that compositions of the present invention with moderate viscosity, e.g. from 500 to 2000, e.g. about 1000 to 2000 mPa s at 20-25°C are particularly comfortable to apply. Upon instillation into the eye, the viscosity of the compositions of the present invention generally decreases, due to dilution with tear liquid. Nevertheless, and particularly surprising, the compositions of the present invention still have a good or even excellent retention after instillation into the eye.

If desired, the excipients of the compositions of the present invention and the amounts thereof may be chosen such, that the viscosity of the compositions increases from storage temperatures, e.g. 20°C, to the temperatures at the surface of the eyes, e.g. 32-34°C, so that the compositions are of relatively low viscosity when in the container, for instance a drop bottle, and have a viscosity in the range indicated above on the eye. This can e. g. be achieved by incorporation of thermo-reversible polymers.

The compositions of the present invention are stable, as indicated by conventional tests, e.g. under stressed conditions, such as 15h at 80°C or 1 month at 40°C. The compositions of the present invention are stable over 2, even 3, years showing less than 5 % degradation of the ketotifen at 20 to 30°C.

An expressly preferred embodiment of the compositions according to the instant invention comprises ketotifen or a pharmaceutically acceptable salt thereof as the ophthalmic drug, in particular, ketotifen hydrogen fumarate, preferably in a concentration from 0.005 to 0.2%, even more preferably from 0.01 – 0.1%, e.g. 0.01 to 0.05%, e.g. 0.01 to 0.04% and in particular from 0.02 – 0.04%, even more preferably about 0.025%, by weight based on the total weight of the composition.

Said compositions preferably comprise at least one polymer selected from polyoxyethylene-polyoxypropylene co-polymers or block co-polymers, cross-linked acrylic acid polymers and mixtures thereof.

A specific type of the aforementioned compositions furthermore comprises benzalkonium chloride as preservative, and a solubilizer, in particular selected from a reaction product of natural or hydrogenated oils and ethylene glycol and octylphenoxy-poly(ethylenoxy)ethanol.

The ophthalmic compositions of the present invention may be prepared in conventional manner e.g. by mixing the ketotifen and appropriate excipients.

The compositions of the present invention are preferably clear, preferably in form of clear solution or gel, e.g. clear gel.

Filling may be effected before or after sterilization of the resulting mixture. Sterilization of the composition of the present invention and the primary package can be effected e.g. by gamma irradiation, by ethylene oxide treatment, by electron beam, by autoclaving, by microwave treatment, by filtration through a sterile filter, or by steam sterilization.

The compositions of the present invention may be packaged in conventional manner. The compositions of the present invention may be stored in single or multiple unit dosage form, e.g. closed bottles, tubes or other containers made from glass, plastic such as e.g. poly-

ethylene, polyethylene terephthalate, or polypropylene, or metal or combinations thereof. For example bottles may contain about 1 to 5 ml of the compositions of the present invention. The container may be fitted with a dropper to facilitate administration.

The compositions of the present invention may be formulated in conventional manner e.g. to be particularly adapted for topical ophthalmic use. In so far as the procedures for formulation are not particularly described herein such formulation procedures may for example be known in the art, or analogous to those known in the art or to procedures described herein. Representative procedures are disclosed in for example, Remington's Pharmaceutical Sciences, 19th Ed., Mack Publ., Co., 1995, H. Sucker et al, Pharmazeutische Technologie, 2nd Edition, Thieme, 1991, R: H. Mueller et al, Pharmazeutische Technologie: Moderne Arzneimittelformen, 2nd Edition, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1998, L. Lachman et al. The Theory and Practice of Industrial Pharmacy, 3rd Ed, 1986, and Hagers Handbuch der pharmazeutischen Praxis, 4th Ed. Vol. 7, (Springer Verlag, 1971) as well as later editions, the contents of all of which are incorporated herein by reference.

The excipients used may e.g. be those known in the art e.g in the Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete; and Handbook of Pharmaceutical Excipients, references referred to above, or analogous to those known in the art or new excipients having analogous function to those described in the art or herein.

The compositions of the present invention are useful for the temporary prevention of itching of the eye due to allergic conjunctivitis, and in particular of seasonal allergic conjunctivitis, and may be used for the treatment and prevention of signs and symptoms of seasonal allergic conjunctivitis as indicated e.g. in standard animal trials and clinical trials.

One animal test comprises a modified Draize test on three albino rabbits wherein the ocular tolerability after a single dose instillation of 50 microlitres of compositions of the present invention on the ocular surface is shown for the 15 minutes after instillation then after 1, 2 and 7 days. The tolerability was based on visual examination considering the following parameters: discomfort as judged by blinking or partial/complete closure of the eye, duration of discomfort, discharge, redness of conjunctiva (palpebral and bulbar conjunctiva), chemosis of conjunctiva (swelling), degree of opacity of cornea and area of cornea involved, and pathological influence upon iris.

A clinical trial may be effected to test the efficacy and tolerability of about 30 to 40 microlitre of compositions of the present invention containing 0.025% of ketotifen administered once a day by instillation onto the ocular surface, e.g. to the inside lower lid, to groups of, e.g. 10 to 25, healthy volunteers, or patients suffering from allergic conjunctivitis. The trial lasts e.g. 8 days.

The subjects are examined to determine the effect against conjunctivitis, e.g. fast onset of action and long duration of action and good tolerability, e.g. lack of significant irritation or reddening.

Additionally the bioavailability of the compositions of the present invention in the above trials as determined by absorption in the conjunctiva or surrounding tissues are comparable with Zaditen® administered twice a day.

The bioavailability of an addressed once-a-day ophthalmic composition was assessed with the pharmacokinetic assay described infra:
A fixed volume, e.g. 50 microliters, of the ophthalmic formulation was instilled onto the upper part of the conjunctiva of rabbits. Tears, bulbar conjunctiva, cornea and sclera were sampled after either 5, 15, 30 minutes, or, 1, 8, 16, or 20 h. Samples were extracted for ketotifen determination related to the wet weight amount of tissue or tears. Ketotifen was determined using a liquid chromatography linked to mass spectrography (LC-MS) validated method.

The exact amount of ketotifen to be administered will naturally depend on a variety of factors, e.g. choice of salt, excipients, formulation properties, and severity of the condition. Conveniently, the composition of the present invention is administered to the cornea once a day, e.g. after breakfast. Preferably from about 25 to about 75 microlitres, e.g. from about 50 to about 75 microlitres, is administered, e.g. using a dropper.

The daily dose of ketotifen to be administered is from about 1 micrograms/kg to about 5 micrograms/kg. For larger mammals, e.g. a 70 kg mammal such as a human, a dose of from about 100 to about 300 micrograms, is indicated.

Therefore, in a further aspect the present invention provides:

- a composition as described above for use in the treatment of ophthalmic diseases/disorders, for instance, treatment of inflammation, allergy, glaucoma, miosis, anaesthesia or infections caused by viruses, fungi or microorganisms,
- a composition as described above comprising ketotifen for use in the treatment of allergic conjunctivitis and, in particular, of treatment and prevention of seasonal allergic conjunctivitis, or a condition treatable by ketotifen therapy,
- a method for treating ophthalmic diseases/disorders, for instance, treatment of inflammation, allergy, glaucoma, miosis, anaesthesia or infections caused by viruses, fungi or microorganism, including a topical once-a-day administration of a composition as described above, thereby providing the therapeutic effect of the drug in said composition at the eye over about 24 hours,
- a method for treating allergic conjunctivitis, in particular for treating and preventing seasonal allergic conjunctivitis or a condition treatable by ketotifen therapy, including a once-a-day administration of a composition as described above comprising ketotifen to the eye of a patient in need thereof,
- the use of a composition as described above in the preparation of a medicament for the treatment of ophthalmic diseases/disorders, for instance, the treatment of inflammation, allergy, glaucoma, miosis, anaesthesia or infections caused by viruses, fungi or microorganisms, and
- the use of a composition as described above comprising ketotifen in the preparation of a medicament for the treatment of allergic conjunctivitis, in particular, for treatment and prevention of seasonal allergic conjunctivitis or a condition treatable by ketotifen therapy.

All percentages referred to herein are weight/weight except where otherwise indicated.

Following is a description by way of example only of compositions of the present invention.

Example 1-5:

	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5
Ketotifen hydrogen fumarate	0.0345	0.0345	0.0345	0.0345	0.0345
Poloxamer 407 (Lutrol F127) (1.1)	5.0	15.0	-	5.0	5.0
Noveon AA-1 (1.2.1)	-	0.2	0.2	-	-
Carbopol 980 (1.2.2)	-	-	-	0.2	0.2
sorbitol (2.2)	4.0	-	4.2	3.5	3.5
TRIS (3.)	-	-	0.099	0.096	0.1
benzalkonium chloride (4.1)	0.01	0.01	0.01	0.01	0.01
hydroxypropyl-γ-cyclodextrin (5.5)	-	-	-	-	2.0
Cremophor EL (5.7)	-	-	5.0	-	-
EDTA (9)	-	-	-	-	0.05
Water for injection (13.)	ad 100	ad 100	ad 100	ad 100	ad 100
Appearance*	S	OS	SP	G	OS

* S=clear solution, G= clear gel, SP= suspension, OS=Opalescent solution.

The excipients (amounts given in mg as described in table above) are added in turn to the water and the mixture stirred.

The compositions of examples 1 to 5 are stable solutions or gels. They show a good to moderate tolerability in rabbit eye and are effective against seasonal allergic conjunctivitis as administered as described above.

Claims

1. An ophthalmic composition adapted for topical once-a-day administration to the eye comprising an ophthalmic drug.

2. An ophthalmic composition according to claim 1 which is a composition comprising an ophthalmic drug and at least one polymer selected from one or more of
   i) a polyoxyethylene-polyoxypropylene co-polymer or block co-polymer, and
   ii) a cross-linked acrylic acid polymer.

3. A composition according to claim 2 further comprising one or more tonicity enhancing agent, buffer, preservative, solubilizer and/or complexing agent.

4. A composition according to claim 2 or 3 further comprising an ophthalmic carrier.

5. A composition according to anyone of claims 1 to 4, wherein the ophthalmic drug is selected from diclofenac, prednisolone, ketotifen, timolol, valsartan, griseofulvine, ascorbic acid, retinol and a pharmaceutically acceptable salt thereof.

6. A composition according to any of claims 1 to 5, wherein the concentration of the ophthalmic drug is from 0.005 to 5 %, based on the total weight of the composition.

7. A composition according to any of claims 2 to 6, wherein the concentration of the polymer components is from 0.1 to 20, preferably from 1 to 10%, based on the total weight of the composition.

8. A composition according to any of claims 1 to 7, wherein the viscosity of the composition ranges from 500 to 2000 mPa s at 20-25°C.

9. An ophthalmic composition according to claim 5 comprising ketotifen or a pharmaceutically acceptable salt thereof.

10. A composition according to claim 9 comprising ketotifen hydrogen fumarate.

11. A composition according to claim 9 or 10, wherein the concentration of ketotifen or the pharmaceutically acceptable salt thereof is from 0.005 to 0.2%, preferably from 0.02 to 0.04%, based on the total weight of the composition.

12. A composition according to any of claims 1 to 8 for use in the treatment of ophthalmic diseases/disorders, for instance, treatment of inflammation, allergy, glaucoma, miosis, anaesthesia or infections caused by viruses, fungi or microorganisms.

13. A composition according to any of claims 9 to 11 for use in the treatment of allergic conjunctivitis and, in particular, of treatment and prevention of seasonal allergic conjunctivitis, or a condition treatable by ketotifen therapy.

14. A method for treating ophthalmic diseases/disorders, for instance, treatment of inflammation, allergy, glaucoma, miosis, anaesthesia or infections caused by viruses, fungi or microorganism, including a topical once-a-day administration of a composition according to any of claims 1 to 8, thereby providing the therapeutic effect of the drug in said composition at the eye over about 24 hours.

15. A method for treating allergic conjunctivitis, in particular for treating and preventing seasonal allergic conjunctivitis or a condition treatable by ketotifen therapy, including a once-a-day administration of a composition according to any of claims 9 to 11 to the eye of a patient in need thereof.

16. The use of a composition according to any of claims 1 or 8 in the preparation of a medicament for the treatment of ophthalmic diseases/disorders, for instance, the treatment of inflammation, allergy, glaucoma, miosis, anaesthesia or infections caused by viruses, fungi or microorganisms.

17. The use of a composition according to any of claims 9 to 11 in the preparation of a medicament for the treatment of allergic conjunctivitis, in particular, for treatment and prevention of seasonal allergic conjunctivitis or a condition treatable by ketotifen therapy.