

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11)

EP 1 165 058 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
25.05.2005 Bulletin 2005/21

(51) Int Cl.7: **A61K 31/00**, A61P 31/04,
A61P 27/02, A61K 31/7052

(21) Application number: **00918382.3**

(86) International application number:
PCT/US2000/007924

(22) Date of filing: **27.03.2000**

(87) International publication number:
WO 2000/057866 (05.10.2000 Gazette 2000/40)

(54) **AZALIDE ANTIBIOTICS FOR THE TOPICAL TREATMENT OR PREVENTION OF OCULAR INFECTIONS**

AZALID-ANTIBIOTIKA ZUR TOPISCHEN BEHANDLUNG ODER VORBEUGUNG OKULÄRER INFEKTIONEN

ANTIBIOTIQUES AZALIDES POUR LE TRAITEMENT TOPIQUE OU LA PREVENTION D'INFECTIONS OCULAIRES

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE**

(56) References cited:
**EP-A- 0 925 789 EP-A- 1 075 837
WO-A-95/09601**

(30) Priority: **31.03.1999 US 282165
02.07.1999 US 346923**

(43) Date of publication of application:
02.01.2002 Bulletin 2002/01

(73) Proprietor: **INSITE VISION INCORPORATED
Alameda, CA 94501 (US)**

(72) Inventors:
• **DAWSON, Chandler, R.
Mill Valley, CA 94941 (US)**
• **BOWMAN, Lyle, M.
Pleasanton, CA 94566 (US)**

(74) Representative: **UEXKÜLL & STOLBERG
Patentanwälte
Beselerstrasse 4
22607 Hamburg (DE)**

- **DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1997 DAWSON C R ET AL: "A comparison of oral azithromycin with topical oxytetracycline/polymyxin for the treatment of trachoma in children." Database accession no. PREV199799451696 XP002161953 & CLINICAL INFECTIOUS DISEASES, vol. 24, no. 3, 1997, pages 363-368, ISSN: 1058-4838**
- **DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1982 PATAMASUCON P ET AL: "ORAL VS. TOPICAL ERYTHROMYCIN THERAPIES FOR CHLAMYDIAL CONJUNCTIVITIS" Database accession no. PREV198375016553 XP002161954 & AMERICAN JOURNAL OF DISEASES OF CHILDREN, vol. 136, no. 9, 1982, pages 817-821, ISSN: 0002-922X**
- **DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1995 GROSS ROBERT H ET AL: "Corneal Pharmacokinetics of Topical Clarithromycin." Database accession no. PREV199598263908 XP002161955 & INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, vol. 36, no. 5, 1995, pages 965-968, ISSN: 0146-0404**

EP 1 165 058 B1

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

Description

BACKGROUND OF THE INVENTION

5 1. Field of the Invention

[0001] The present invention relates to aqueous polymeric suspension of an azalide antibiotic and the use thereof for treating or preventing infections in the eye.

10 2. Description of the Related Arts

[0002] The eye is susceptible to bacterial and parasitic infections arising from both traumatic and non-traumatic related events. Infections are a concern after ocular surgery and precautions are correspondingly taken to prevent the onset of infection. However, even without the invasive trauma of a surgical procedure, infections in the eyelids, conjunctiva, cornea, and other ocular tissues can arise.

[0003] Treating infections in ocular tissues can be challenging and/or problematic because of the difficulty in delivering an antibiotic to the affected tissue. In general, ocular infections are treated by local injection, systemic administration, or topical application of an antibiotic. The route of administration depends on the antibiotic selected, the location of the infection and the type of infection.

[0004] The simple and direct approach of topically applying the antibiotic to the exterior of the eye has several benefits, including the avoidance of side effects and the reduced chance of developing resistant strains of bacteria as compared to systemic administration. However, for a variety of reasons, many antibiotics are not amenable or suitable for topical application to the eye.

[0005] For example, in order for a topical application to be effective, the antibiotic must be able to penetrate the desired tissue. This may include penetrating the conjunctiva and the cornea. Also, the penetration rate must be sufficient to impart an effective dose. Many drugs do not possess a requisite penetration ability with regard to the tissues of the eye. It should be noted that the external layers of the eye are quite different from the tissues encountered in the stomach and intestinal tract. Thus, while a certain drug may be readily absorbed in the intestines and introduced into the blood supply for systemic administration, the same drug may be incapable of being absorbed by or passing through the substantially avascular outer layers of the conjunctiva or cornea at a minimally acceptable therapeutic concentration. The mechanism of transport or uptake of the drug is entirely different for topical administration than for oral administration.

[0006] Another concern is that the antibiotic will be toxic to the eye. A toxic response includes redness, swelling and/or discharge. Toxicity is especially problematic for topical administration because it is a concentration dependent phenomenon. The concentration ratio between tear fluid and ocular tissue in topical administration is generally in the range of about 1:500 to 1:1000, due to the penetration gradient. Thus, while a drug may be non-toxic at the minimum effective concentration, the 500% to 1000% increase in concentration associated with topical administration may well induce a toxic response. Again, the fact that oral or systemic administration shows the drug to be compatible with ocular tissue does not predict or address the toxicity issue associated with topical administration.

[0007] A further potential unsuitability of an antibiotic is the practicality of topical administration by the patient. Assuming that sufficiently high concentrations of the antibiotic can be used to achieve an effective dose within the target tissue without a toxic response, the application may nonetheless be irritating. An irritation response includes temporary burning, stinging and/or watering of the eye. Beyond whether the increased watering of the eyes washes away so much of the antibiotic composition that an effective dose is prevented, the patient may simply be resistant to complying with the dosage regimen because of the irritation. By failing to comply with the dosing regimen, the treatment efficacy is reduced or eliminated.

[0008] Some antibiotics have been found to sufficiently meet the above requirements so as to be applicable to topical administration. Examples of antibiotics that are reported to be useful in ocular topical administration include tobramycin, gentamycin, fluoroquinolone derivatives including norfloxacin, ofloxacin, and ciprofloxacin, naphthylidene, tetracyclines, and erythromycin. However, the dosing of the known topical antibiotics is usually an extensive and inconvenient regimen. Applying drops every 2 hours for the first two days and every 4 hours for the next several days is a common dosing regimen for aqueous solutions to treat ocular infections. But, such an extensive dosing regimen is inconvenient and obtaining patient compliance can be difficult. Of course, the greater the non-compliance with the regimen, the less effective the treatment.

[0009] It would be beneficial to find additional antibiotics that are capable of topical application in treating the eye. It would be further desirable to provide a topical formulation that is effective against a broad spectrum of bacteria and that can be administered in a less extensive regimen.

[0015] R¹ and R² each independently represent a hydrogen atom or a methyl group. Preferably at least one of R¹ and R² is a hydrogen atom. Azithromycin, the common name for N-methyl-11-aza-10-deoxo-10-dihydroerythromycin, corresponds to the compound of formula (I) where both R¹ and R² are a hydrogen atom. Azithromycin was disclosed in U.S. Patents 4,474,768 and 4,517,359, and is the most preferred azalide antibiotic. In particular, the dihydride form of azithromycin is especially contemplated for use in the present invention, although other forms are also suitable.

[0016] Azithromycin has been used as an oral antibiotic and is sold worldwide under the brand name Zithromax® by Pfizer Inc. Azithromycin is a broad spectrum antibiotic that is generally more effective *in vitro* than erythromycin. Moreover, because azithromycin is an azalide and thus has a ring nitrogen atom, it exhibits improved acid-stability, half-life, and cellular uptake in comparison to erythromycin. The high uptake and retention of azithromycin into cells, including phagocytic blood cells, allows the systemically administered azithromycin to be nonetheless preferentially delivered to the site of the infection. The mechanism is believed to be as follows. The ingested azithromycin is absorbed through the intestine into the blood stream from which it enters most cells of the body including, *inter alia*, the white blood cells. In response to an infection within the body, white blood cells, including those containing azithromycin, are attracted to the infectious site. When the white blood cells die, the azithromycin is released. As more and more white blood cells arrive at the infectious site and die, the concentration of azithromycin in the surrounding tissue increases, eventually surpassing the MIC. Once at the infectious site, the azithromycin remains in the tissue for a prolonged period of time, due to its long half-life, such that an effective concentration of azithromycin is present at the infected site for many days after cessation of administration.

[0017] Although azithromycin can reach many of the tissues and fluids of the eye by oral administration, it has now been discovered that azalide antibiotics in general and azithromycin in particular are amenable to topical administration on the eye. The azalide antibiotic can be supplied to the eye surface in a variety of ways, including as an aqueous ophthalmic solution or suspension, as an ophthalmic ointment, and as an ocular insert, but application is not limited thereto. Any technique and ocular dosage form that supplies an azalide antibiotic to the external eye surface is included within the notion of "topically applying." Although the external surface of the eye is typically the outer layer of the conjunctiva, it is possible that the sclera, cornea or other ocular tissue could be exposed such as by rotation of the eye or by surgical procedure and thus be an external surface.

[0018] The amount of azalide antibiotic topically supplied is effective to treat or prevent infection in a tissue of the eye. This means that the conditions of application result in a retarding or suppression of the infection. Typically at least about MIC₅₀ for the targeted bacteria or parasite is delivered to the ocular tissue by the topical application of an effective amount. More concretely, the concentration within the ocular tissue is desired to be at least about 0.25 µg/g, preferably at least 1 µg/g, and more preferably at least 10 µg/g. The amount of azalide actually supplied to the external eye surface will almost always be much higher than the tissue concentration. This reflects the penetration hold up of the azalide antibiotic by the outer tissue layers of the eye and that penetration is to some extent concentration driven. Thus, supplying greater amounts to the exterior will drive more antibiotic into the tissues.

[0019] Where a series of applications are used in the dosing regimen, it is possible that one or more of the earlier applications will not achieve an effective concentration in the ocular tissue, but that a later application in the regimen will achieve an effective concentration. This is contemplated as being within the scope of topically applying an azalide antibiotic in an effective amount. However, generally a single application, such as consisting of one or two drops, provides a therapeutically effective concentration (e.g. one that retards or suppresses the infection) of the azalide antibiotic within a tissue of the eye. Indeed, although dependent on the amount and form of the ophthalmic composition, a single application will typically provide a therapeutically effective amount of the azalide antibiotic within a tissue of the eye for at least 8, preferably 12, and more preferably at least 18 hours.

[0020] The topical application of an azalide antibiotic can be used to treat or prevent a variety of conditions associated with ocular infection. For example, conditions of the lids including blepharitis, blepharconjunctivitis, meibomianitis, acute or chronic hordeolum, chalazion, dacryocystitis, dacryoadenitis, and acne rosacea; conditions of the conjunctiva including conjunctivitis, ophthalmia neonatorum, and trachoma; conditions of the cornea including corneal ulcers, superficial and interstitial keratitis, keratoconjunctivitis, foreign bodies, and post operative infections; and conditions of the anterior chamber and uvea including endophthalmitis, infectious uveitis, and post operative infections, are a few of the tissues and conditions that can be treated by topical application of an azalide antibiotic. The prevention of infection includes pre-operative treatment prior to surgery as well as other suspected infectious conditions or contact. Examples of prophylaxis situations include treatment prior to surgical procedures such as blepharoplasty, removal of chalazia, tarsorrhaphy, procedures for the canaliculi and lacrimal drainage system and other operative procedures involving the lids and lacrimal apparatus; conjunctival surgery including removal of pterygia, pingueculae and tumors, conjunctival transplantation, traumatic lesions such as cuts, burns and abrasions, and conjunctival flaps; corneal surgery including removal of foreign bodies, keratotomy, and corneal transplants; refractive surgery including photorefractive procedures; glaucoma surgery including filtering blebs; paracentesis of the anterior chamber, iridectomy; cataract surgery; retinal surgery; and procedures involving the extra-ocular muscles. The prevention of ophthalmia neonatorum is also included.

[0021] More generally, the azalide antibiotics can be used to treat or prevent ocular infections caused by a variety

of bacteria or parasites, including but not limited to one or more of the following organisms: Staphylococcus including Staphylococcus aureus and Staphylococcus epidermidis; Streptococcus including Streptococcus pneumoniae and Streptococcus pyogenes as well as Streptococci of Groups C, F, and G and Viridans group of Streptococci; Haemophilus influenza including biotype III (H. Aegyptius); Haemophilus ducreyi; Moraxella catarrhalis; Neisseria including Neisseria gonorrhoeae and Neisseria meningitidis; Chlamydia including Chlamydia trachomatis, Chlamydia psittaci, and Chlamydia pneumoniae; Mycobacterium including Mycobacterium tuberculosis and Mycobacterium avium-intra-cellular complex as well as atypical mycobacterium including M. marinum, M. fortuitm, and M. chelonae; Bordetella pertussis; Campylobacter jejuni; Legionella pneumophila; Bacteroides bivius; Clostridium perfringens; Peptostreptococcus species; Borrelia burgdorferi; Mycoplasma pneumoniae; Treponema pallidum; Ureaplasma urealyticum; toxoplasma; malaria; and nosema.

[0022] The azalide antibiotic is applied to the exterior surface of the eye, usually in an ophthalmically acceptable composition which comprises an ophthalmically acceptable carrier and the azalide antibiotic. The ophthalmically acceptable carrier is an aqueous polymeric suspension. Generally, azalide antibiotics are poorly soluble in water. However, water solubility is improved if converted to a salt form. For example, azithromycin dihydrochloride has good water solubility. Accordingly, an aqueous solution of an azalide antibiotic can be formed and used for topical application. But, more typically, an aqueous suspension is formed of the poorly soluble or insoluble azalide antibiotic. The concentration is from about 0.01 to 2%, more typically 0.1 to 1%, for fluid compositions and 0.5 to 50% for solid dosage forms, however, the compositions are not limited thereto.

[0023] The ophthalmic compositions may contain one or more of the following: surfactants, adjuvants including additional medicaments, buffers, antioxidants, tonicity adjusters, preservatives, thickeners or viscosity modifiers, and the like. Additives in the formulation may desirably include sodium chloride, EDTA (disodium edetate), and/or BAK (benzalkonium chloride), sorbic acid, methyl paraben, propyl paraben, chlorhexidine, and sodium perborate.

[0024] A further aspect of the present invention involves the above-mentioned use of additional medicaments in combination with the azalide antibiotic. A composition comprising an azalide antibiotic, an additional medicament, and an ophthalmically acceptable carrier can advantageously simplify administration and allow for treating or preventing multiple conditions or symptoms simultaneously. The "additional medicaments," which can be present in any of the ophthalmic compositional forms described herein including fluid and solid forms, are pharmaceutically active compounds having efficacy in ocular application and which are compatible with an azalide antibiotic and with the eye. Typically, the additional medicaments include other antibiotics, antivirals, antifungals, anesthetics, anti-inflammatory agents including steroidal and non-steroidal anti-inflammatories, and anti-allergic agents. Examples of suitable medicaments include aminoglycosides such as amikacin, gentamycin, tobramycin, streptomycin, netilmycin, and kanamycin; fluoroquinolones such as ciprofloxacin, norfloxacin, ofloxacin, trovafloxacin, lomefloxacin, levofloxacin, and enoxacin; naphthyridine; sulfonamides; polymyxin; chloramphenicol; neomycin; paramomomycin; colistimethate; bacitracin; vancomycin; tetracyclines; rifampin and its derivatives ("rifampins"); cycloserine; beta-lactams; cephalosporins; amphotericins; fluconazole; flucytosine; natamycin; miconazole; ketoconazole; corticosteroids; diclofenac; flurbiprofen; ketorolac; suprofen; comolyn; lodoxamide; levocabastin; naphazoling; antazoline; and pheniraminane. These other medicaments are generally present in a pharmaceutically effective amount as is understood by workers of ordinary skill in the art. These amounts are generally within the range of from about 0.01 to 5%, more typically 0.1 to 2%, for fluid compositions and from 0.5 to 50% for solid dosage forms.

[0025] The aqueous ophthalmic compositions (suspensions) use water which has no physiologically or ophthalmically harmful constituents. Typically purified or deionized water is used. The pH is adjusted by adding any physiologically and ophthalmically acceptable pH adjusting acids, bases or buffers to within the range of about 5.0 to 8.5. Examples of acids include acetic, boric, citric, lactic, phosphoric, hydrochloric, and the like, and examples of bases include sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate, tromethamine, THAM (trishydroxymethylamino-methane), and the like. Salts and buffers include citrate/dextrose, sodium bicarbonate, ammonium chloride and mixtures of the aforementioned acids and bases.

[0026] The osmotic pressure (π) of the aqueous ophthalmic composition is generally from about 10 milliosmolar (mOsM) to about 400 mOsM, more preferably from 260 to 340 mOsM. If necessary, the osmotic pressure can be adjusted by using appropriate amounts of physiologically and ophthalmically acceptable salts or excipients. Sodium chloride is preferred to approximate physiologic fluid, and amounts of sodium chloride ranging from about 0.01% to about 1% by weight, and preferably from about 0.05% to about 0.45% by weight, based on the total weight of the composition, are typically used. Equivalent amounts of one or more salts made up of cations such as potassium, ammonium and the like and anions such as chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thio-sulfate, bisulfate, sodium bisulfate, ammonium sulfate, and the like can also be used in addition to or instead of sodium chloride to achieve osmolalities within the above-stated range. Similarly, a sugar such as mannitol, dextrose, sorbitol, glucose and the like can also be used to adjust osmolality.

[0027] A preferred form of the present invention provides achieving a sufficiently high tissue concentration with a minimum of doses so that a simple dosing regimen can be used to treat or prevent bacterial or parasitic infections. To

this end, a preferred technique involves forming or supplying a depot of azalide antibiotic in contact with the external surface of the eye. A depot refers to a source of azalide antibiotic that is not rapidly removed by tears or other eye clearance mechanisms. This allows for continued, sustained high concentrations of azalide antibiotic to be present in the fluid on the external surface of the eye by a single application. In general, it is believed that absorption and penetration are dependent on both the dissolved drug concentration and the contact duration of the external tissue with the drug-containing fluid. As the drug is removed by clearance of the ocular fluid and/or absorption into the eye tissue, more drug is provided, e.g. dissolved, into the replenished ocular fluid from the depot.

[0028] Accordingly, the use of a depot more easily facilitates loading of the ocular tissue in view of the typically slow and low penetration rate of the generally water-insoluble/poorly soluble azalide antibiotics. The depot can effectively slowly "pump" the azalide antibiotic into the ocular tissue. As the azalide antibiotic penetrates the ocular tissue it is accumulated therein and not readily removed due to its long half-life. As more azalide antibiotic is "pumped" in, the tissue concentration increases and the minimum inhibitory concentration threshold is eventually reached and/or exceeded, thereby loading the ocular tissue with azalide antibiotic. By significantly exceeding the MIC₅₀, more preferably the MIC₉₀ level, provided the toxicity limit is not exceeded, a therapeutically effective concentration will remain active in the tissue for an extended period of time due to the low clearance rate of the azalide antibiotic from the tissue. Thus, depending on the depot, one or two applications may provide a complete dosing regimen. Indeed, such a simple dosing regimen may provide a 6 to 14 day treatment concentration within the ocular tissue. A preferred dosing regimen involves one to two doses per day over a one to three day period, more preferably one or two doses in a single day, to provide in vivo at least a 6 day treatment and more typically a 6 to 14 day treatment.

[0029] A depot can take a variety of forms so long as the azalide antibiotic can be provided in sufficient concentration levels therein and is releasable therefrom and that the depot is not readily removed from the eye. A depot generally remains for at least about 30 minutes after administration, preferably at least 2 hours and more preferably at least 4 hours. The term "remains" means that neither the depot composition nor the azalide antibiotic is exhausted or cleared from the surface of the eye prior to the indicated time. In some embodiments, the depot can remain for up to eight hours or more. Typical ophthalmic depot forms include aqueous polymeric suspensions, ointments, and solid inserts. Polymeric suspensions are the most preferred form for the present invention and will be discussed subsequently.

[0030] The form is an aqueous polymeric suspension. Here, at least one of the azalide antibiotic or the polymeric suspending agent is suspended in an aqueous medium having the properties as described above. Typically the azalide antibiotic is in suspension although it is possible for the azalide antibiotic to be in solution (water soluble) or both in solution and in suspension in significant amounts generally no less than 5% in either phase (weak to moderate water solubility and relatively high total concentrations). The polymeric suspending agent is preferably a suspension (i.e. water insoluble and/or water swellable), although water soluble suspending agents are also suitable for use with a suspension of the azalide antibiotic. The suspending agent serves to provide stability to the suspension and to increase the residence time of the dosage form on the eye. It can also enhance the sustained release of the drug in terms of both longer release times and a more uniform release curve.

[0031] Examples of polymeric suspending agents include dextrans, polyethylene glycols, polyvinylpyrrolidone, polysaccharide gels, Gelrite®, cellulosic polymers like hydroxypropyl methylcellulose, and carboxy-containing polymers such as polymers or copolymers of acrylic acid, as well as other polymeric demulcents. A preferred polymeric suspending agent is a water swellable, water insoluble polymer, especially a crosslinked carboxy-containing polymer.

[0032] Crosslinked carboxy-containing polymers used in practicing this invention are, in general, well known in the art. In a preferred embodiment such polymers may be prepared from at least about 90% and preferably from about 95% to about 99.9% by weight, based on the total weight of monomers present, of one or more carboxy-containing monoethylenically unsaturated monomers (also occasionally referred to herein as carboxy-vinyl polymers). Acrylic acid is the preferred carboxy-containing monoethylenically unsaturated monomer, but other unsaturated, polymerizable carboxy-containing monomers, such as methacrylic acid, ethacrylic acid, β -methylacrylic acid (crotonic acid), cis- α -methylcrotonic acid (angelic acid), trans- α -methylcrotonic acid (tiglic acid), α -butylcrotonic acid, α -phenylacrylic acid, α -benzylacrylic acid, α -cyclohexylacrylic acid, β -phenylacrylic acid (cinnamic acid), coumaric acid (o-hydroxycinnamic acid), umbellic acid (p-hydroxycoumaric acid), and the like can be used in addition to or instead of acrylic acid.

[0033] Such polymers may be crosslinked by a polyfunctional crosslinking agent, preferably a difunctional crosslinking agent. The amount of crosslinking should be sufficient to form insoluble polymer particles, but not so great as to unduly interfere with sustained release of the azalide antibiotic. Typically the polymers are only lightly crosslinked. Preferably the crosslinking agent is contained in an amount of from about 0.01% to about 5%, preferably from about 0.1% to about 5.0%, and more preferably from about 0.2% to about 1%, based on the total weight of monomers present. Included among such crosslinking agents are non-polyalkenyl polyether difunctional crosslinking monomers such as divinyl glycol; 2,3-dihydroxyhexa-1,5-diene; 2,5-dimethyl-1,5-hexadiene; divinylbenzene; N,N-diallylacrylamide; N,N-diallylmethacrylamide and the like. Also included are polyalkenyl polyether crosslinking agents containing two or more alkenyl ether groupings per molecule, preferably alkenyl ether groupings containing terminal H₂C=C< groups, prepared by etherifying a polyhydric alcohol containing at least four carbon atoms and at least three hydroxyl groups with an

alkenyl halide such as allyl bromide or the like, e.g., polyallyl sucrose, polyallyl pentaerythritol, or the like; see, e.g., Brown U.S. Pat. No. 2,798,053. Diolefinic non-hydrophilic macromeric crosslinking agents having molecular weights of from about 400 to about 8,000, such as insoluble di-acrylates and polyacrylates and methacrylates of diols and polyols, diisocyanate-hydroxyalkyl acrylate or methacrylate reaction products of isocyanate terminated prepolymers derived from polyester diols, polyether diols or polysiloxane diols with hydroxyalkylmethacrylates, and the like, can also be used as the crosslinking agents; see, e.g., Mueller et al. U.S. Pat. Nos. 4,192,827 and 4,136,250.

[0034] The crosslinked carboxy-vinyl polymers may be made from a carboxy-vinyl monomer or monomers as the sole monoethylenically unsaturated monomer present, together with a crosslinking agent or agents. Preferably the polymers are ones in which up to about 40%, and preferably from about 0% to about 20% by weight, of the carboxy-containing monoethylenically unsaturated monomer or monomers has been replaced by one or more non-carboxyl-containing monoethylenically unsaturated monomer or monomers containing only physiologically and ophthalmically innocuous substituents, including acrylic and methacrylic acid esters such as methyl methacrylate, ethyl acrylate, butyl acrylate, 2-ethylhexylacrylate, octyl methacrylate, 2-hydroxyethyl-methacrylate, 3-hydroxypropylacrylate, and the like, vinyl acetate, N-vinylpyrrolidone, and the like; see Mueller et al. U.S. Pat. No. 4,548,990, for a more extensive listing of such additional monoethylenically unsaturated monomers.

[0035] Particularly preferred polymers are lightly crosslinked acrylic acid polymers wherein the crosslinking monomer is 2,3-dihydroxyhexa-1,5-diene or 2,3-dimethylhexa-1,5-diene. Preferred commercially available polymers include polycarbophil (Noveon AA-1) and Carbopol®. Most preferably, a carboxy-containing polymer system known by the tradename DuraSite®, containing polycarbophil, which is a sustained release topical ophthalmic delivery system that releases the drug at a controlled rate, is used in the aqueous polymeric suspension composition of the present invention.

[0036] The crosslinked carboxy-vinyl polymers used in practicing this invention are preferably prepared by suspension or emulsion polymerizing the monomers, using conventional free radical polymerization catalysts, to a dry particle size of not more than about 50 μm in equivalent spherical diameter; e.g., to provide dry polymer particles ranging in size from about 1 to about 30 μm , and preferably from about 3 to about 20 μm , in equivalent spherical diameter. Using polymer particles that were obtained by mechanically milling larger polymer particles to this size is preferably avoided. In general, such polymers will have a molecular weight which has been variously reported as being from about 250,000 to about 4,000,000, and from 3,000,000,000 to 4,000,000,000.

[0037] In the most preferred embodiment of the invention, the particles of crosslinked carboxy-vinyl polymer are monodisperse, meaning that they have a particle size distribution such that at least 80% of the particles fall within a 10 μm band of major particle size distribution. More preferably, at least 90% and most preferably at least 95%, of the particles fall within a 10 μm band of major particle size distribution. Also, a monodisperse particle size means that there is no more than 20%, preferably no more than 10%, and most preferably no more than 5% particles of a size below 1 μm . The use of a monodispersion of particles will give maximum viscosity and an increased eye residence time of the ophthalmic medicament delivery system for a given particle size. Monodisperse particles having a particle size of 30 μm and below are most preferred. Good particle packing is aided by a narrow particle size distribution.

[0038] The aqueous polymeric suspension normally contains 0.05 to 1%, preferably 0.1 to 0.5%, more preferably 0.1 to 0.5%, of the azalide antibiotic and 0.1 to 10%, preferably 0.5 to 6.5% of a polymeric suspending agent. In the case of the above described water insoluble, water-swellaible crosslinked carboxy-vinyl polymer, a more preferred amount of the polymeric suspending agent is an amount ranging from 0.5 to 2.0%, preferably from 0.5% to about 1.2%, and in certain embodiments from 0.6 to 0.9%, based on the weight of the composition. Although referred to in the singular, it should be understood that one or more species of polymeric suspending agent such as the crosslinked carboxy-containing polymer can be used with the total amount falling within the stated ranges. In one preferred embodiment, the composition contains 0.6 to 0.8 % of a polycarbophil such as NOVEON AA-1.

[0039] In one embodiment, the amount of insoluble lightly crosslinked carboxy-vinyl polymer particles, the pH, and the osmotic pressure can be correlated with each other and with the degree of crosslinking to give a composition having a viscosity in the range of from about 500 to about 100,000 centipoise, and preferably from about 1,000 to about 30,000 or about 1,000 to about 10,000 centipoise, as measured at room temperature (about 25° C) using a Brookfield Digital LVT Viscometer equipped with a number 25 spindle and a 13R small sample adapter at 12 rpm. Alternatively, when the viscosity is within the range of 500 to 3000 centipoise, it may be determined by a Brookfield Model DV-11+, choosing a number cp-52 spindle at 6 rpm.

[0040] When water soluble polymers are used as the suspending agent, such as hydroxypropyl methylcellulose, the viscosity will typically be about 10 to about 400 centipoise, more typically about 10 to about 200 centipoises or about 10 to about 25 centipoise.

[0041] Aqueous polymeric suspensions of the present invention may be formulated so that they retain the same or substantially the same viscosity in the eye that they had prior to administration to the eye. Alternatively, they may be formulated so that there is increased gelation upon contact with tear fluid. For instance, when a formulation containing DuraSite® or other similar polyacrylic acid-type polymer is administered to the eye at a pH of less than about 6.7, the polymer will swell upon contact with tear fluid since it has a higher pH (around 7). This gelation or increase in gelation

leads to entrapment of the suspended azalide antibiotic particles, thereby extending the residence time of the composition in the eye. The azalide antibiotic is released slowly as the suspended particles dissolve over time. All these events eventually lead to increased patient comfort and increased azalide antibiotic contact time with the eye tissues, thereby increasing the extent of drug absorption and duration of action of the formulation in the eye.

5 [0042] The viscous gels that result from fluid eye drops typically have residence times in the eye ranging from about 2 to about 12 hours, e.g., from about 3 to about 6 hours. The agents contained in these drug delivery systems will be released from the gels at rates that depend on such factors as the drug itself and its physical form, the extent of drug loading and the pH of the system, as well as on any drug delivery adjuvants, such as ion exchange resins compatible with the ocular surface, which may also be present.

10 [0043] The compositions used to topically deliver the azalide antibiotic of the present invention can be prepared from known or readily available materials through the application of known techniques by workers of ordinary skill in the art without undue experimentation. The azalide antibiotics used in the present invention are commercially available or readily obtained by a worker skilled in the art through known reactions techniques. In particular, the azalide antibiotics can be formed from erythromycin A, a naturally occurring compound formed during the culturing of a strain of *Streptomyces erythreus*. However, it is not required that the azalide antibiotic actually be formed from erythromycin. The azalide antibiotic can be combined with the other ingredients in the chosen dosage form by conventional methods known in the art.

20 [0044] The azalide antibiotic-containing composition is topically applied to an eye of a human or non-human animal, the latter including cows, sheep, horses, pigs, goats, rabbits, dogs, cats, and other mammals. The composition is topically applied, without limitation, to the front of the eye, under the upper eyelid, on the lower eyelid and in the cul-de-sac. The application can be as a treatment of an infection in the eye or as a preventive such as prior to surgery.

[0045] All of the percentages recited herein refer to weight percent, unless otherwise indicated. The following non-limiting examples serve to illustrate certain features of the present invention. The compositions and amounts used for Examples 1-7 are summarized in Table 1 and for Examples 9-14 in Table 2.

25 EXAMPLES 1-2

[0046] Hydroxypropylmethyl cellulose, sodium chloride, edetate sodium (EDTA), BAK and surfactant are dissolved in a beaker containing approximately 1/3 of the final weight of water and stirred for 10 minutes with an overhead stirred. 30 The azithromycin is added and stirred to disperse for 30 minutes. The solution is sterilized by autoclaving at 121°C. for 20 minutes. Alternately, the azithromycin may be dry heat sterilized and added by aseptic powder addition after sterilization. Mannitol, Poloxamer 407, and boric acid are dissolved separately in approximately 1/2 of the final weight of water and added by sterile filtration (0.22 µm filter) and stirred for 10 minutes to form a mixture. The mixture is adjusted to desired pH with 10N sodium hydroxide while stirring, brought to a final weight with water by sterile filtration and aseptically filled into multi-dose containers. 35

EXAMPLES 3-6

40 [0047] Noveon AA-1 is slowly dispersed into a beaker containing approximately 1/3 of the final weight of water and stirred for 1.5 hrs. with an overhead stirrer. Noveon AA-1 is an acrylic acid polymer available from B.F. Goodrich. Edetate sodium (EDTA), BAK, sodium chloride, and surfactant are then added to the polymer solution and stirred for 10 minutes after each addition. The polymer suspension is at a pH of about 3.0-3.5. The azithromycin is added and stirred to disperse for 30 minutes. The mixture is sterilized by autoclaving at 121° C., for 20 minutes. Alternately, the azithromycin may be dry heat sterilized and added by aseptic powder addition after sterilization. Mannitol, and boric acid, or sodium perborate, Dequest, mannitol, and boric acid are dissolved separately in approximately 1/2 of the final weight of water, added to the polymer mixture by sterile filtration (0.22 µm filter) and stirred for 10 minutes. The mixture is adjusted to the desired pH with 10N sodium hydroxide while stirring, brought to final weight with water by sterile filtration and aseptically filled into multi-dose containers. 45

50 EXAMPLE 7

[0048] Noveon AA-1 is slowly dispersed into a beaker containing approximately 1/2 of the final weight of water and stirred for 1.5 hrs. With overhead stirrer. Noveon AA-1 is an acrylic acid polymer available from B.F. Goodrich. Edetate sodium (EDTA), Poloxamer 407, and sodium chloride are then added to the polymer suspension and stirred for 10 minutes. The polymer suspension is at a pH of about 3.0-3.5. The azithromycin is added and stirred to disperse for 30 minutes. The mixture is sterilized by autoclaving at 121° C. for 20 minutes. Alternately, the azithromycin may be dry heat sterilized and added by aseptic powder addition after sterilization. Mannitol is dissolved in 1/10 of the final weight of water and sterile filtered (0.22 µm filter) in to the polymer suspension and stirred for 10 minutes. The mixture is 55

adjusted to desired pH with 10N sodium hydroxide while stirring, brought to final weight with water by sterile filtration and aseptically filled into unit-dose containers.

5
10
15
20
25
30
35
40
45
50

TABLE 1
Formulation Examples 1-7

Ingredient	1 %	2 %	3 %	4 %
Azithromycin	0.10	0.50	0.10	0.50
Hydroxypropyl Cellulose	1.50	2.00	--	--
Noveon AA-1	--	--	0.80	0.80
Sodium Chloride	0.20	0.20	0.20	0.20
Mannitol	1.50	1.50	1.50	1.50
Edetate Disodium	0.10	0.10	0.10	0.10
Poloxamer 407	0.10	0.10	0.10	0.10
Benzalkonium Chloride	0.01	0.01	0.01	0.01
Sodium Perborate	--	--	--	--
Dequest 2060S	--	--	--	--

Boric Acid	0.50	0.50	0.50	0.50
Sodium Hydroxide	q.s. to pH 7	q.s. to pH 7	q.s. to pH 6	q.s. to pH 6
Water	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

Ingredient	5 %	6 %	7 %
Azithromycin	0.50	0.50	0.10
Hydroxypropyl Cellulose	--	--	--
Noveon AA-1	0.80	0.80	0.80
Sodium Chloride	0.20	0.20	0.30
Mannitol	1.50	1.50	1.50
Edetate Disodium		0.10	0.10
Poloxamer 407	0.10	0.10	0.10
Benzalkonium Chloride	--	0.01	--
Sodium Perborate	0.10	--	--
Dequest 2060S	0.10	--	--
Boric Acid	0.50	0.50	
Sodium Hydroxide	q.s. to pH 6	q.s. to pH 7	q.s. to pH 6
Water	q.s. to 100	q.s. to 100	q.s. to 100

Example 8

[0049] An azithromycin ointment is prepared by dissolving 0.3 grams of azithromycin and 0.5 grams of chlorobutanol in a mixture containing 3.0 grams mineral oil/96.2 grams white petrolatum by stirring in a 100 ml beaker while heating sufficiently hot to dissolve both compounds. The mixture is sterile filtered through a 0.22 µm filter at a sufficient temperature to be filtered and filled aseptically into sterile ophthalmic ointment tubes.

EP 1 165 058 B1

Example 9-11

[0050] Hydroxypropylmethyl cellulose (HPMC), sodium chloride, edetate sodium (EDTA), and surfactant are dissolved in a beaker containing approximately 1/3 of the final weight of water and stirred for 10 minutes with an overhead stirrer. The mixture is sterilized by autoclaving at 121° C., for 20 minutes. The azithromycin and steroid as indicated in table 2 are dry heat sterilized and added to the HPMC-containing solution by aseptic powder addition. Mannitol, Poloxamer 407, BAK, and boric acid are dissolved separately in approximately 1/2 of the final weight of water and added by sterile filtration (0.22 um filter) and stirred for 10 minutes to form a mixture. The mixture is adjusted to desired pH with 10N sodium hydroxide while stirring, brought to a final weight with water by sterile filtration, and aseptically filled into multi-dose containers.

Examples 12-14

[0051] Noveon AA-1 is slowly dispersed into a beaker containing approximately 1/3 of the final weight of water and stirred for 1.5 hrs. with an overhead stirrer. Noveon AA-1 is an acrylic acid polymer available from B.F. Goodrich. Edetate sodium (EDTA), sodium chloride, and surfactant are then added to the polymer solution and stirred for 10 minutes after each addition. The polymer suspension is at a pH of about 3.0-3.5. The mixture is sterilized by autoclaving at 121°C. for 20 minutes. The azithromycin and steroid as indicated in table 2 are dry heat sterilized and added to the polymer suspension by aseptic powder addition. BAK, mannitol, and boric acid are dissolved separately in approximately 1/2 of the final weight of water, added to the polymer mixture by sterile filtration (0.22 um filter) and stirred for 10 minutes. The mixture is adjusted to the desired pH with 10N sodium hydroxide while stirring, brought to final weight with water and by sterile filtration and aseptically filled into multi-dose containers.

TABLE 2

Formulation Examples 9-14						
Ingredient	9 %	10 %	11 %	12 %	13 %	14 %
Azithromycin	0.10	0.10	0.10	0.10	0.10	0.10
Prednisolone Acetate	0.10	--	--	0.10	--	--
Fluorometholone	--	0.10	--	--	0.10	--
Dexamethasone	--	--	0.10	--	--	0.10
Hydroxypropyl methyl Cellulose	1.50	1.50	1.50	--	--	--
Noveon AA-1	--	--	--	0.80	0.80	0.80
Sodium Chloride	0.20	0.20	0.20	0.20	0.20	0.20
Mannitol	1.50	1.50	1.50	1.50	1.50	1.50
Edetate Disodium	0.10	0.10	0.10	0.10	0.10	0.10
Poloxamer 407	0.10	0.10	0.10	0.10	0.10	0.10
Benzalkonium Chloride	0.01	0.01	0.01	0.01	0.01	0.01
Boric Acid	0.50	0.50	0.50	0.50	0.50	0.50
Sodium Hydroxide	q.s. to pH 7	q.s. to pH 7	q.s. to pH 7	q.s. to pH 6	q.s. to pH 6	q.s. to pH 6
Water	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

[0052] The above discussion of this invention is directed primarily to preferred embodiments and practices thereof. It will be readily apparent to those skilled in the art that further changes and modifications in actual implementation of the concepts described herein can easily be made or may be learned by practice of the invention, without departing from the spirit and scope of the invention as defined by the following claims.

Claims

1. Use of an azalide antibiotic for the preparation of a pharmaceutical composition for treating an eye, wherein the

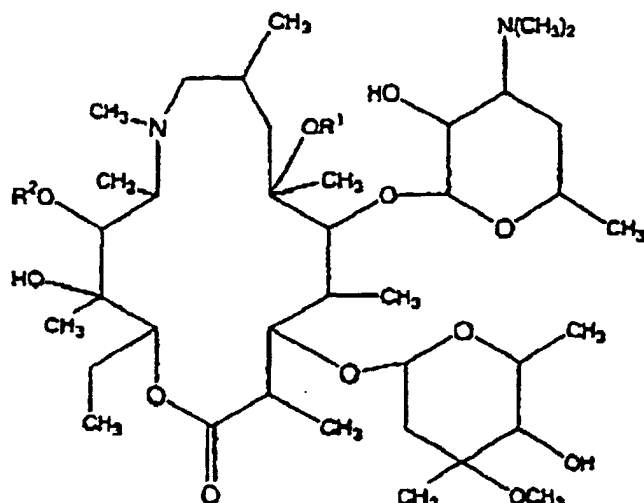
treatment comprises topically applying the composition to an eye in an amount effective to treat or prevent infection in a tissue of the eye and wherein said topical application comprises supplying a depot which is an aqueous polymeric suspension of said azalide antibiotic on the eye and wherein said aqueous suspension comprises water and 0.01% to 2.0% of an azalide antibiotic.

- 5 2. The use according to Claim 1, wherein said aqueous suspension comprises 0.01% to 1.0% of an azalide antibiotic and 0.1 to 10% of a water swellable water insoluble crosslinked carboxy vinyl polymer.
- 10 3. The use according to Claim 1 or 2, wherein said topically applied depot remains for at least 30 minutes after administration.
- 15 4. The use according to Claim 3, wherein said depot remains for at least 4 hours after administration.
- 5 5. The use according to any of Claims 1 to 4, wherein said composition further comprises an additional medicament.
- 15 6. The use according to Claim 5, wherein said additional medicament is selected from the group consisting of antibiotics, antivirals, antifungals, anesthetics, anti-inflammatory agents, and anti-allergic agents.
- 20 7. The use according to any of Claims 1 to 6, wherein the polymer is comprised of at least 90% acrylic acid monomers and 0.1% to 5% crosslinking agent.
- 25 8. The use according to Claim 7, wherein the crosslinking agent is a difunctional crosslinking agent.
9. The use according to Claim 8, wherein said crosslinking agent is selected from the group consisting of divinyl glycol, 2,3-dihydroxyhexa-1,5-diene, 2,5-dimethyl-1,5-hexadiene, divinylbenzene, N,N-diallylacrylamide, N,N-diallylmethacrylamide, and mixtures thereof.
- 30 10. The use according to any of Claims 7 to 9, wherein said polymer is a polycarbophil.
11. The use according to any of Claims 7 to 10, wherein said polymer is contained in an amount of from about 0.5 to 1.2%.
- 35 12. The use according to any of Claims 7 to 11, wherein said polymer has a monodisperse particle size distribution.
13. The use according to any of Claims 1 to 12, wherein said azalide antibiotic is azithromycin.
- 40 14. The use according to Claim 13, wherein said azalide antibiotic is azithromycin dihydrate.
15. The use according to any of Claims 1 to 14, wherein said aqueous polymeric suspension further comprises an additional medicament.
- 45 16. The use according to Claim 15, wherein said additional medicament is selected from the group consisting of amikacin, gentamycin, tobramycin, streptomycin, netilmycin, kanamycin, ciprofloxacin, norfloxacin, ofloxacin, trovafloxacin, lomefloxacin, levofloxacin, enoxacin, naphthyridine, sulfonamides, polymyxin, chloramphenicol, neomycin, paramomomycin, colistimethate, bacitracin, vancomycin, tetracyclines, rifampins, cycloserine, beta-lactams, cephalosporins, amphotericins, fluconazole, flucytosine, natamycin, miconazole, ketoconazole, corticosteroids, diclofenac, flurbiprofen, ketorolac, suprofen, comolyn, lodoxamide, levocabastin, naphazoling, antazoline, and pheniramimane.
- 50 17. The use according to any of Claims 1 to 16, wherein said eye is suffering from at least one condition selected from the group consisting of conjunctivitis, ophthalmia neonatorum, trachoma, corneal ulcers, keratitis, keratoconjunctivitis, endonhthalmitis, infectious uveitis and combinations thereof, and said amount of said azalide antibiotic is therapeutically effective to treat said condition.
- 55 18. The use according to any of Claims 1 to 17, wherein said azalide antibiotic is a compound of formula (I):

5

10

15



(I)

20

wherein R¹ and R² each independently represent a hydrogen atom or a methyl group.

19. The use according to Claim 18, wherein said azalide antibiotic is azithromycin.

25

20. The use according to any of Claims 1 to 19, wherein said application provides a therapeutically effective concentration of azalide antibiotic within a tissue of the eye for at least 8 hours.

21. The use according to Claim 20, wherein said application provides a therapeutically effective concentration of azalide antibiotic within a tissue of the eye for at least 12 hours.

30

22. The use according to Claim 21, wherein said application provides a therapeutically effective concentration of azalide antibiotic within a tissue of the eye for at least 18 hours.

23. An aqueous polymeric suspension comprising water, 0.01% to 2.0% of an azalide antibiotic.

35

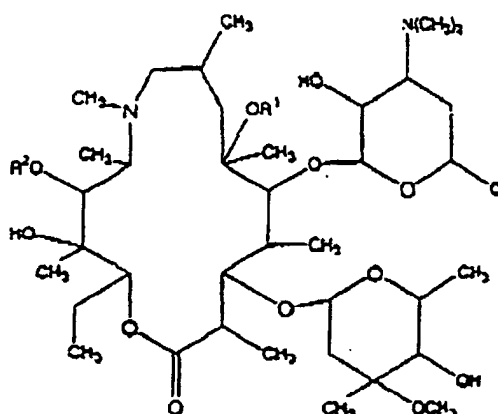
24. The suspension according to Claim 23, wherein said aqueous polymeric suspension comprises 0.01% to 1.0% of an azalide antibiotic and 0.1 to 10% of a crosslinked carboxy vinyl polymer.

25. The suspension according to Claim 23 or 24, wherein said azalide antibiotic is a compound of formula (I):

40

45

50



(I)

55

wherein R¹ and R² each independently represent a hydrogen atom or a methyl group.

26. The suspension according to Claim 23, wherein said azalide antibiotic is azithromycin and is contained in an

amount of 0.1 to 0.5%.

27. The suspension according to any of Claims 23 to 26, wherein said polymer is comprised of at least 90% acrylic acid monomers and 0.1% to 5% crosslinking agent.

28. The suspension according to any of Claims 23 to 27, wherein both the azalide antibiotic and the polymer are in suspension.

29. The suspension according to any of Claims 23 to 28, further comprising an additional medicament.

30. The suspension according to Claim 29, wherein said additional medicament is selected from the group consisting of antibiotics, antivirals, antifungals, anesthetics, anti-inflammatory agents, and anti-allergic agents.

31. The suspension according to any of Claims 29 or 30, wherein said additional medicament is contained in an amount of from 0.01 to 5.0%.

32. The suspension according to any of Claims 29 or 30, wherein said additional medicament is selected from the group consisting of amikacin, gentamycin, tobramycin, streptomycin, netilmycin, kanamycin, ciprofloxacin, norfloxacin, ofloxacin, trovafloxacin, lomefloxacin, levofloxacin, enoxacin, naphthyridine, sulfonamides, polymyxin, chloramphenicol, neomycin, paramomomycin, colistimethate, bacitracin, vancomycin, tetracyclines, rifampins, cycloserine, beta-lactams, cephalosporins, amphotericins, fluconazole, flucytosine, natamycin, miconazole, ketocozazole, corticosteroids, diclofenac, flurbiprofen, ketorolac, suprofen, comolyn, ludoxamide, levocabastin, naphazoling, antazoline, and pheniramine.

Patentansprüche

1. Verwendung eines Azalidantibiotikums zur Herstellung einer pharmazeutischen Zusammensetzung zur Behandlung des Auges, wobei die Behandlung die örtliche Applikation der Zusammensetzung an ein Auge in einer Menge umfaßt, die wirksam für die Behandlung oder Verhinderung einer Infektion in einem Gewebe des Auges ist, und wobei die örtliche Applikation das Zuführen eines Depots, daß eine wäßrige polymere Suspension eines Azalidantibiotikums ist, an das Auge umfaßt und wobei die wäßrige Suspension Wasser und 0,01% bis 2,0% eines Azalidantibiotikums umfaßt.

2. Verwendung nach Anspruch 1, bei der die wäßrige Suspension 0,01% bis 1,0% eines Azalidantibiotikums und 0,1 bis 10% eines wasserquellfähigen wasserunlöslichen vernetzten Carboxyvinylpolymers umfaßt.

3. Verwendung nach Anspruch 1 oder 2, bei der das örtlich applizierte Depot für mindestens 30 Minuten nach der Verabreichung erhalten bleibt.

4. Verwendung nach Anspruch 3, bei der das Depot für mindestens 4 Stunden nach der Verabreichung erhalten bleibt.

5. Verwendung nach einem der Ansprüche 1 bis 4, bei der die Zusammensetzung außerdem ein zusätzliches Medikament umfaßt.

6. Verwendung nach Anspruch 5, bei der das zusätzliche Medikament aus der Gruppe bestehend aus Antibiotika, antiviraler Substanzen, Antimykotika, Narkotika, entzündungshemmender Agenzien und antiallergischer Agenzien ausgewählt wird.

7. Verwendung nach einem der Ansprüche 1 bis 6, bei der das Polymer mindestens 90% Acrylsäuremonomere und 0,1% bis 5% vernetzendes Agens umfaßt.

8. Verwendung nach Anspruch 7, bei der das vernetzende Agens ein difunktionales vernetzendes Agens ist.

9. Verwendung nach Anspruch 8, bei der das vernetzende Agens aus der Gruppe bestehend aus Divinylglycol, 2,3-Dihydroxyhexa-1,5-Diol, 2,5-Dimethyl-1,5-Hexadiol, Divinylbenzol, N,N-Diallylacrylamid, N,N-Diallylmethacrylamid und Mischungen daraus ausgewählt wird.

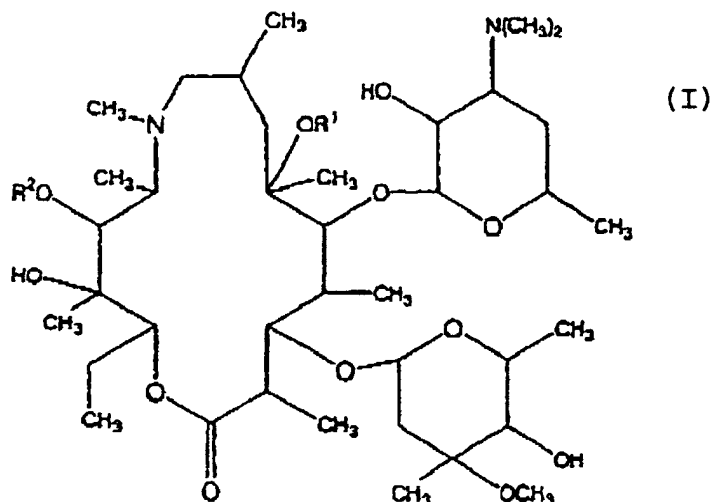
antibiotikums in einem Gewebe des Auges für mindestens 12 Stunden zur Verfügung stellt.

22. Verwendung nach Anspruch 21, bei der die Applikation eine therapeutisch wirksame Konzentration eines Azalidantibiotikums in einem Gewebe des Auges für mindestens 18 Stunden zur Verfügung stellt.

23. Eine wäßrige polymere Suspension, die Wasser und 0,01% bis 2,0% eines Azalidantibiotikums umfaßt.

24. Suspension nach Anspruch 23, bei der die wäßrige polymere Suspension 0,01% bis 1,0% eines Azalidantibiotikums und 0,1 bis 10% eines vernetzten Carboxyvinylpolymers umfaßt.

25. Suspension nach den Ansprüchen 23 oder 24, bei der das Azalidantibiotikum eine Verbindung der Formel (I) ist:



wobei R¹ und R² jeweils unabhängig ein Wasserstoffatom oder eine Methylgruppe darstellen.

26. Suspension nach Anspruch 23, bei der das Azalidantibiotikum Azithromycin ist und in einer Menge von 0,1 bis 0,5% enthalten ist.

27. Suspension nach einem der Ansprüche 23 bis 26, bei der das Polymer mindestens 90% Acrylsäuremonomere und 0,1% bis 5% vernetzendes Agens umfaßt.

28. Suspension nach einem der Ansprüche 23 bis 27, bei der sowohl das Azalidantibiotikum als auch das Polymer in Suspension vorliegen.

29. Suspension nach einem der Ansprüche 23 bis 28, die außerdem ein zusätzliches Medikament umfaßt.

30. Suspension nach Anspruch 29, bei der das zusätzliche Medikament aus der Gruppe bestehend aus Antibiotika, antiviraler Substanzen, Antimykotika, Narkotika, entzündungshemmender Agenzien und antiallergischer Agenzien ausgewählt wird.

31. Suspension nach einem der Ansprüche 29 oder 30, bei der das zusätzliche Medikament in einer Menge von 0,01 bis 5,0% enthalten ist.

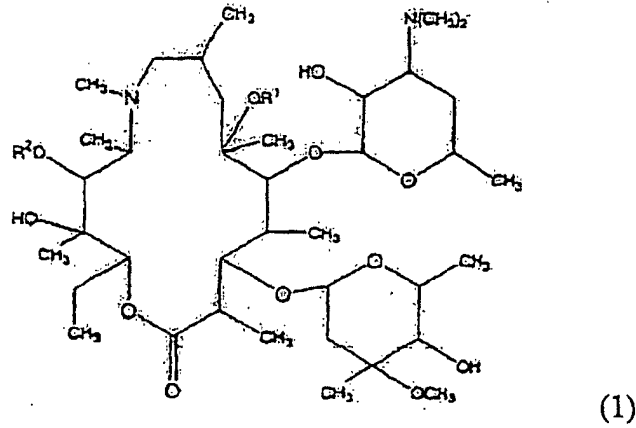
32. Suspension nach einem der Ansprüche 29 oder 30, bei der das zusätzliche Medikament aus der Gruppe bestehend aus Amikacin, Gentamycin, Tobramycin, Streptomycin, Netilmycin, Kanamycin, Ciprofloxacin, Norfloxacin, Ofloxacin, Trovafloxacin, Lomefloxacin, Levofloxacin, Enoxacin, Naphthydrin, Sulfonamiden, Polymyxin, Chloramphenicol, Neomycin, Paramomomycin, Colistimethat, Bacitracin, Vancomycin, Tetracyclinen, Rifampinen, Cycloserin, Betalactamat, Cephalosporinen, Amphotericinen, Fluconazol, Flucytosin, Natamycin, Miconazol, Ketoconazol, Kortikosteroiden, Diclofenac, Flurbiprofen, Ketorolac, Suprofen, Comolyn, Lodoxamid, Levocabastin, Naphazolin, Antazolin und Pheniramin ausgewählt wird.

Revendications

- 5 1. Utilisation d'un antibiotique azalide pour la préparation d'une composition pharmaceutique destinée à traiter un oeil, dans laquelle le traitement comprend d'appliquer de façon topique la composition au niveau d'un oeil dans une quantité efficace pour traiter ou empêcher une infection au niveau d'un tissu de l'oeil et dans laquelle ladite application topique comprend de fournir un dépôt, correspondant à une suspension polymérique aqueuse dudit antibiotique azalide sur l'oeil et dans laquelle ladite suspension aqueuse comprend de l'eau et 0.01 à 2.0% d'un antibiotique azalide.
- 10 2. Utilisation selon la revendication 1, dans laquelle ladite suspension aqueuse comprend 0.01 à 1.0% d'un antibiotique azalide, et 0.1 à 10% d'un polymère carboxy vinyl réticulé insoluble dans l'eau et gonflable dans l'eau.
- 15 3. Utilisation selon la revendication 1 ou 2, dans laquelle ledit dépôt appliqué de façon topique reste pendant au moins 30 minutes après administration.
- 20 4. Utilisation selon la revendication 3, dans laquelle ledit dépôt reste pendant au moins 4 heures après administration.
- 25 5. Utilisation selon l'une quelconque des revendications 1 à 4, dans laquelle ladite composition comprend en outre un médicament supplémentaire.
- 30 6. Utilisation selon la revendication 5, dans laquelle ledit médicament supplémentaire est choisi parmi le groupe consistant en des antibiotiques, des antiviraux, des antifongiques, des anesthésiques, des agents anti-inflammatoires et des agents anti-allergiques.
- 35 7. Utilisation selon l'une quelconque des revendications 1 à 6, dans laquelle le polymère comprend au moins 90% de monomères d'acide acrylique et 0.1% à 5% d'agent de réticulation.
- 40 8. Utilisation selon la revendication 7, dans laquelle l'agent de réticulation est un agent de réticulation di-fonctionnel.
- 45 9. Utilisation selon la revendication 8, dans laquelle ledit agent de réticulation est choisi parmi le groupe consistant en du divinyl glycol, du 2,3-dihydroxyhexa-1,5-diene, du 2,5-diméthyl-1,5-hexadiene, du divinylbenzene, du N,N-diallylacrylamide, du N,N-diallylméthacrylamide, et des mélanges de ceux-ci.
- 50 10. Utilisation selon l'une quelconque des revendications 7 à 9, dans laquelle ledit polymère est un polycarbophile.
- 55 11. Utilisation selon l'une quelconque des revendications 7 à 10, dans laquelle ledit polymère est présent dans une quantité allant d'environ 0.5 à 1.2%.
12. Utilisation selon l'une quelconque des revendications 7 à 11, dans laquelle ledit polymère présente une distribution de tailles de particules monodispersées.
13. Utilisation selon l'une quelconque des revendications 1 à 12, dans laquelle ledit antibiotique azalide est de l'azithromycine.
14. Utilisation selon la revendication 13, dans laquelle ledit antibiotique azalide est du dihydrate d'azithromycine.
15. Utilisation selon l'une quelconque des revendications 1 à 14, dans laquelle ladite suspension polymérique aqueuse comprend en outre un médicament supplémentaire.
16. Utilisation selon la revendication 15, dans laquelle ledit médicament supplémentaire est choisi parmi le groupe consistant en de la amikacine, de la gentamycine, de la tobramycine, de la streptomycine, de la netilmycine, de la kanamycine, de la ciprofloxacine, de la norfloxacine, de l'ofloxacine, de la trovafloxacine, de la lomefloxacine, de la levofloxacine, de l'enoxacine, de la naphthyridine, des sulfonamides, de la polymyxine, du chloramphenicol, de la neomycine, de la paramomomycine, du colistiméthate, de la bacitracine, de la vancomycine, des tétracyclines, des rifampicines, de la cycloserine, des beta-lactams, des cephalosporines, des amphotéricines, du fluconazole, de la flucytosine, de la natamycine, du miconazole, du ketoconazole, des corticostéroïdes, du diclofénac, du flurbiprofène, du kétorolac, du suprofène, de la comolyne, du lodoxamide, de la lévocabastine, de la naphazoline, de l'antazoline, et de la phéniramine.

17. Utilisation selon l'une quelconque des revendications 1 à 16, dans laquelle ledit oeil souffre d'au moins une condition choisie parmi le groupe consistant en une conjonctivite, une ophtalmie purulente néonatale, un trachome, un ulcère cornéen, une kératite, une kératoconjunctivite, une endophthalmitis, une uvéite infectieuse et des combinaisons de celles-ci et ladite quantité dudit antibiotique azalide est thérapeutiquement efficace pour traiter ladite condition.

18. Utilisation selon l'une quelconque des revendications 1 à 17, dans laquelle ledit antibiotique azalide est un composé de formule (1) :



dans laquelle R¹ et R² représentent chacun indépendamment un atome d'hydrogène ou un groupe méthyle.

19. Utilisation selon la revendication 18, dans laquelle ledit antibiotique azalide est de l'azithromycine.

20. Utilisation selon l'une quelconque des revendications 1 à 19, dans laquelle ladite application fournit une concentration thérapeutiquement efficace d'antibiotique azalide dans un tissu de l'oeil pendant au moins 8 heures.

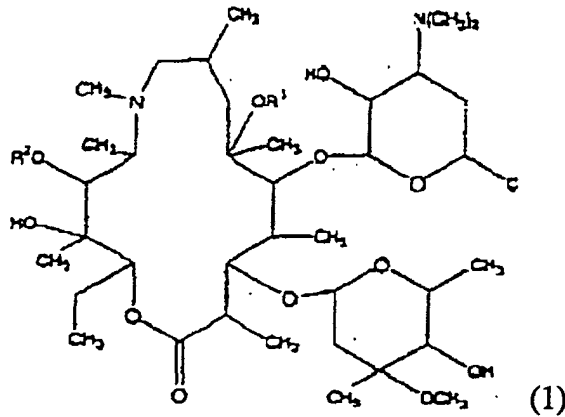
21. Utilisation selon la revendication 20, dans laquelle ladite application fournit une concentration thérapeutiquement efficace d'antibiotique azalide dans un tissu de l'oeil pendant au moins 12 heures.

22. Utilisation selon la revendication 21, dans laquelle ladite application fournit une concentration thérapeutiquement efficace d'antibiotique azalide dans un tissu de l'oeil pendant au moins 18 heures.

23. Suspension polymérique aqueuse comprenant de l'eau, 0.01% à 2.0% d'un antibiotique azalide.

24. Suspension selon la revendication 23, dans laquelle ladite suspension polymérique aqueuse comprend 0.01 à 1.0% d'un antibiotique azalide et 0.1 à 10% d'un polymère carboxy vinyl réticulé.

25. Suspension selon la revendication 23 ou 24, dans laquelle ledit antibiotique azalide est un composé de formule (1)



dans laquelle R¹ et R² représentent chacun indépendamment un atome d'hydrogène ou un groupe méthyle.

26. Suspension selon la revendication 23, dans laquelle ledit antibiotique azalide est de l'azithromycine et est présent dans une quantité allant de 0.1 à 0.5%.

27. Suspension selon l'une quelconque des revendications 23 à 26, dans laquelle ledit polymère comprend au moins 90% de monomères d'acide acrylique et 0.1% à 5% d'agent de réticulation.

28. Suspension selon l'une quelconque des revendications 23 à 27, dans laquelle à la fois l'antibiotique azalide et le polymère sont en suspension.

29. Suspension selon l'une quelconque des revendications 23 à 28, comprenant en outre un médicament supplémentaire.

30. Suspension selon la revendication 29, dans laquelle ledit médicament supplémentaire est choisi parmi le groupe consistant en des antibiotiques, des antiviraux, des antifongiques, des anesthésiques, des agents anti-inflammatoires et des agents anti-allergiques.

31. Suspension selon la revendication 29 ou 30, dans laquelle ledit médicament supplémentaire est présent dans une quantité allant de 0.01 à 5.0%.

32. Suspension selon la revendication 29 ou 30, dans laquelle ledit médicament supplémentaire est choisi parmi le groupe consistant en de la amikacine, de la gentamycine, de la tobramycine, de la streptomycine, de la netilmycine, de la kanamycine, de la ciprofloxacine, de la norfloxacine, de l'ofloxacine, de la trovafloxacine, de la lomefloxacine, de la levofloxacine, de l'enoxacine, de la naphthyridine, des sulfonamides, de la polymyxine, du chloramphenicol, de la neomycine, de la paramomomycine, du colistimethate, de la bacitracine, de la vancomycine, des tetracyclines, des rifampicines, de la cycloserine, des beta-lactams, des cephalosporines, des amphotericines, du fluconazole, de la flucytosine, de la natamycine, du miconazole, du ketoconazole, des corticostéroïdes, du diclofénac, du flurbiprofène, du kétorolac, du suprofène, de la comolyne, du lodoxamide, de la lévocabastine, de la naphazoline, de l'antazoline, et de la phéniramimane.