(51) International Patent Classification:
A61K 47/34 (2006.01) A61K 31/216 (2006.01)
A61K 9/00 (2006.01) A61K 31/4535 (2006.01)

(21) International Application Number:
PCT/EP2012/058015

(22) International Filing Date:
2 May 2012 (02.05.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
11164479.5 2 May 2011 (02.05.2011) EP

(71) Applicant (for all designated States except US): DSM IP Assets B.V. [NL/NL]; Het Overloon 1, NL-6411 TE Heerlen (NL).

(72) Inventors; and

(75) Inventors/Applicants (for US only): FRANKEN, Astrid [DE/NL]; P.O. Box 4, NL-6100 AA Echt (NL). MIHOV, George [BG/NL]; P.O. Box 4, NL-6100 AA Echt (NL). THIES, Jens Christoph [DE/NL]; P.O. Box 4, NL-6100 AA Echt (NL).

(74) Agent: VANDEVIJVER, Pascale; P.O. Box 4, NL-6100 AA Echt (NL).


Published:
— with international search report (Art. 21(3))

(54) Title: BIS-(ALPHA-AMINO-DIOL-DIESTER) CONTAINING POLYESTERAMIDE FOR OPHTALMOLOGY

(57) Abstract: The present invention relates to an ocular polymer delivery composition comprising at least one ophthalmologic agent dispersed in at least one biodegradable polymer, wherein the polymer comprises at least one of a poly (ester amide) (PEA) having a chemical formula described by structural formula (I).
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
BIS-(ALPHA-AMINO-DIOL-DI ESTER) CONTAINING POLYESTERAMIDE FOR
OPHTAMOLOGY

The present invention relates to an intraocular polymer delivery composition comprising a polyester amide (PEA). The present invention further relates to extruded or injection molded parts sized for injection via a pharmaceutical syringe needle having a bore of about 18 to 30 Gauge based on this polymer composition. The intraocular polymer delivery composition can be used to formulate biodegradable polymer delivery compositions for time release of bioactive agent's e.g. ophthalmologic therapeutic agents in a consistent and reliable manner into the exterior or interior of the eye by biodegradation of the polymer.

The present invention is also based on the premise that PEAs can be formulated as polymer delivery compositions that may incorporate a bioactive agent into the backbone of the polymer for time release into the exterior or interior of the eye in a consistent and reliable manner by biodegradation of the polymer. The intraocular polymer delivery composition may also deliver into the exterior or interior of the eye another type of bioactive agent that is dispersed in the polymer.

Delivery of drugs intraocular is a particular problem. The eye is divided into two chambers; the anterior segment which is the front of the eye, and the posterior segment which is the back of the eye. Diseases of the anterior segment are easier to treat with formulations such as eye drops because they can be applied topically. For example, glaucoma can be treated from the front of the eye. Diseases of the retina, such as diabetic retinopathy and macular degeneration, are located in the posterior segment and are difficult to treat because drugs applied topically, such as eye drops, typically do not penetrate to the back of the eye. Drugs for these disease states have customarily been delivered by injection directly into the back of the eye. Chemists, biochemists, and chemical engineers are all looking beyond traditional polymeric and other formulations to find innovative drug transport systems. Thus, there is still a need in the art for new and better polymer delivery compositions for controlled delivery of a variety of different types of bioactive agents to target specific body sites, such as the exterior and interior tissues of the eye. In particular, there is a need in the art for new and better polymer delivery compositions for a sustained and continuous delivery of an ophthalmologic agent to the anterior or posterior segment of the eye over a longer period of time, for example in treatment of chronic diseases of the front and back of the eye where a release of ophthalmologic agents during 3-6 months would be
very advantageous. It is quite important that the ophthalmologic agents are administered by controlled or sustained release technologies to attempt to increase their duration of action or reduce the toxicity of transient high general concentrations.

Polyesteramides are known in the art, in particular a-amino acid-diol-diester based polyesteramides (PEA) are known from G. Tsidlanadze, et al. J. Biomater. Sci. Polym. Edn. (2004) 15:1-24. These polyesteramides provide a variety of physical and mechanical properties as well as biodegradable profiles which can be adjusted by varying three components in the building blocks during their synthesis: naturally occurring amino acids and, therefore, hydrophobic α-amino acids, non-toxic fatty diols and aliphatic dicarboxylic acids.

Ophthalmic compositions comprising a-amino acid-diol-diester based polyesteramides are disclosed in WO2007/130477.

WO2007/130477 specifically refers to alpha-amino acid-diol-diester based polyesteramides (PEA) of formula IV,

\[
\begin{align*}
\text{R}^3 \text{R}^4 \text{R}^5 \text{R}^6 & \quad \text{Formula IV} \\
\end{align*}
\]

wherein:

- \(n\) ranges from about 5 to about 150, \(m\) ranges about 0.1 to 0.9: \(p\) ranges from about 0.9 to 0.1; \(R^1\) is independently selected from residues of \(\alpha,\omega\)-bis (4-carboxyphenoxy)(CrC\(_3\))alkane, 3,3'-alkanedioyldioxy)dicinnamic acid, 4,4'-

- (alkanedioyldioxy)dicinnamic acid, \((C_2-C_2)\)alkylene, \((C_2-C_2)\)alkenylene, saturated or unsaturated residues of therapeutic di-acids, residues of \(\alpha,\omega\)-alkylene dicarboxylates of formula (III), and combinations thereof; \(R^6\) and \(R^8\) in Formula (III) are each independently selected from \((C_2-C_2)\)alkylene and \((C_2-C_2)\)alkenylene; \(R^2\) is independently selected from hydrogen, \((C_2-C_2)\)alkyl, \((C_2-C_2)\)alkoxy, \((C_2-C_2)\)alkyl, \((C_2-C_2)\)aryl, and a protecting group; the \(R^3\)s in individual \(n\) monomers are each independently selected from hydrogen, \((C_2-C_2)\)alkyl, \((C_2-C_2)\)alkenyl, \((C_2-C_2)\)aryl, \((C_2-C_2)\)alkyl, and \(-(CH_2)_n\)alkyl; and \(R^4\) is independently selected from \((C_2-C_2)\)alkylene, \((C_2-C_2)\)alkenylene, \((C_2-C_2)\)alkoxy, \((C_2-C_2)\)alkyl, residues of saturated or unsaturated therapeutic diols, and bicyclic-fragments of 1,4:3,6-dianhydrohexitols of formula (II), and combinations thereof. A bioactive agent may covalently bind to the carboxylic group of the lysine part or may be build into the PEA backbone a therapeutic diol or diacid.
The polyesteramides as presented by general formula IV provide a plenty of possibilities to choose R1, R2, R3, R4 and the units m, p and n. No specific selection on whatever polyesteramide is disclosed in this application, neither an example is given which shows a specific polyesteramide which provides a controlled release of ophthalmologic agents over a longer period of time.

It has been recognized that it is quite difficult to select the right monomer units and m,p, n such that a PEA can be provided which shows properties of releasing ophthalmologic agents in a consistent and reliable manner over a period of at least 3 months. It has moreover been recognized that certain polyesteramides according to Formula IV have gummy and sticky like properties which makes them impossible to be processed into injectable drug delivery devices.

The object of the present invention is therefore to provide an ocular polymer delivery composition which can processed and sized for injection via a pharmaceutical syringe needle having a bore of about 18 to 30 Gauge comprising an a-amino acid-diol-diester based polyesteramide from which an ophthalmologic agent can be released in a consistent and reliable manner over a period of at least 3 months.

A further object of the present invention is to provide an ophthalmic composition comprising PEA and an ophthalmologic agent which can be processed and sized for injection via a pharmaceutical syringe needle having a bore of about 18 to 30 Gauge, and from which the release pattern is uniform and not showing a burst release in the first 24 hours.

The object of the present invention is achieved by providing an ocular polymer delivery composition sized for injection via a pharmaceutical syringe needle having a bore of about 18 to 30 Gauge, comprising at least one ophthalmologic agent dispersed in biodegradable poly (ester amide) (PEA) having a chemical formula described by structural formula (I),
Formula I

wherein

\[ m \text{ is about } 0.3-0.6, \ p \text{ is about } 0.3-0.45 \text{ and } q \text{ is about } 0.1-0.25 \text{ and wherein} \]

\[ m+p+q=1, \ m,p,q \text{ are randomly distributed, } n \text{ is about } 5-100 \text{ and} \]

\[-R_1 \text{ is } (CH_2)_5; \ (CH_2)_4 \]

\[-R_3 \text{ and } R_4 \text{ are selected from } (CH_3)2-CH-CH_2-; \]

\[-R_5 \text{ is selected from } (CH_2)_6; \]

\[-R_6 \text{ is } 1,4 :3,6\text{-dianhydrosorbitol (DAS) according to formula II} \]

\[-R_7 \text{ is a } H, \text{ benzyl protecting group or an ophthalmologic agent} \]

\[-R_8 \text{ is } (CH_2)_4 \]

Formula II:

Surprisingly it has been found that these specific elected polyesteramides of formula I can be processed and sized for injection via a pharmaceutical syringe needle having a bore of about 18 to 30 Gauge and provide unexpected properties in terms of release of ophthalmologic agents over a period of at least 3 months without showing a high burst release in the first 24 hours.

The PEA polymers as such are known in the art and disclosed in US2008/0299174. US2008/0299174 discloses the PEA polymers based on bis-(a-
amino acid)-diol-diester containing two bis-(a-amino acid)-based building blocks and shows the polymers to provide a significant improvement in mechanical properties. Incorporation of at least two linear saturated or unsaturated aliphatic diol residues into the two bis-(a amino acid)-based (e.g. bis-(a-amino acid)-diol-diester co-monomers of a PEA), increases the mechanical properties of the resulting polymer. Furthermore methods are disclosed for fixing a fixation device made of the PEA’s into the internal body site. The device biodegrades to create substantially biocompatible breakdown products while fixing the internal body site. Also biocompatible surgical devices fabricated using the PEA compositions are disclosed. The disclosure is however silent about ophthalmic compositions based on the PEA’s for the release of ophthalmologic agents on the longer term.

Accordingly, in a preferred embodiment, the invention provides ophthalmic compositions sized for injection via a pharmaceutical syringe needle having a bore of about 18 to 30 Gauge comprising PEA co-polymers of formula I wherein:

- 

m is about 0.3, p is about 0.45 and q is about 0.25; m,p,q are randomly distributed
n is about 5-100 and wherein R₁ is (CH₃)₆, R₆ and R₄ are selected from (CH₃₂)₆-CH-CH₂⁻; R₅ is selected from (CH₂)₆; R₆ is 1,4:3,6-dianhydrosoorbitol (DAS) according to formula II; R₇ is a H, benzyl protecting group or an ophthalmologic agent and R₈ is (CH₂)₄.

In a more preferred embodiment the invention provides ophthalmic compositions sized for injection via a pharmaceutical syringe needle having a bore of about 18 to 30 Gauge comprising PEA co-polymers of formula I wherein

m is about 0.3, p is about 0.45, q is about 0.25, n is about 50 and R₁ is (CH₃)₈; R₆ and R₄ are selected from (CH₃₂)₆-CH-CH₂⁻; R₅ is selected from (CH₂)₆; R₆ is 1,4:3,6-dianhydrosoorbitol (DAS); R₇ is a H, benzyl protecting group or an ophthalmologic agent and R₈ is (CH₂)₄.

The PEA co-polymers preferably have an average number molecular weight (Mn) ranging from 15,000 to 200,000 Daltons. The PEA co-polymers described herein can be fabricated in a variety of molecular weights and a variety of relative proportions of the two bis-(alpha amino acid)-containing units and optional Lysine-based monomer of the co-polymer. The appropriate molecular weight for a particular use is readily determined by one of skill in the art. A suitable Mn will be in the order of about 15,000 to about 100,000 Daltons, for example from about 30,000 to about 80,000 or from about 35,000 to about 75,000. Mn is measured via GPC in THF with polystyrene as standard.
Further properties and methods of manufacturing the PEA’s are disclosed in US2008/0299174 which is herein incorporated by reference.

It has been found that the nature of the PEA polymer plays an important role in defining the dimensional properties of the composition. The PEA’s used in the ophthalmic composition of the present invention comprises the incorporation of a bicyclic-fragment of 1,4:3,6-dianhydrohexitol as the diol residue in at least one of the two bis (a-amino acid)- based building blocks which confers a (Tg) above body temperature. By further varying the other building blocks in the PEA Tg can be adjusted. Preferably the Tg of the PEA ranges from about 40 to about 65. Tg can be measured by DSC.

Surprisingly it has been found that the release time can be tailored by varying the building blocks of the polymer and by varying the amount of the m, p, q blocks in the PEA copolymer. Moreover the polymer/ophthalmologic agent ratio plays an important role in the tuning of the release.

The ophthalmologic agent can be a therapeutic agent that is typically ophthalmically acceptable, such as steroidal or non-steroidal anti-inflammatory agents. Examples of steroidal anti-inflammatory agents include corticosteroids such as alclometasone dipropionate, amcinonide, amcinafel, amcinafide, beclamethasone, betamethasone, betamethasone dipropionate, betamethasone valerate, clobetasone propionate, chloroprednisone, clocortelone, Cortisol, cortisone, cortodoxone, difluorosone diacetate, descinolone, desonide, defluprednate, dihydroxy cortisolone, desoximetasone, dexamethasone, deflazacort, diflorasone, diflorasone diacetate, dichlorisone, esters of betamethasone, fluazacort, flucetonide, flucronidone, fludrotisone, fluorocortisone, flumethasone, flunisolide, fluocinonide, fluocinolone, fluocinolone acetonide, flucortolone, fluperolone, fluprednisolone, fluroandrenolone acetonide, fluocinolone acetonide, flurandrenolide, fluorametholone, fluticasone propionate, hydrocortisone, hydrocortisone butyrate, hydrocortisone valerate, hydrocortamate, loteprednol, medrysone, meprednisone, methylprednisone, methylprednisolone, mometasone furoate, paramethasone, paramethasone acetate, prednisone, prednisolone, prednidone, triamcinolone acetonide, triamcinolone hexacetonide, and triamcinolone, salts thereof, derivatives thereof, and mixtures thereof. As used herein, the term "derivative" refers to any substance which is sufficiently structurally similar to the material which it is identified as a derivative so as to have substantially similar functionality or activity, for example, therapeutic effectiveness, as the material when the substance is used in place of the material.
Other steroids which may be useful in the present compositions include, without limitation, glucocorticoids, androgenic steroids, estrogenic steroids, and non-estrogenic steroids.

The ophthalmologic agent may be present in an amount in the range of about 1 percent or less to about 5 percent, about 10 percent, about 20 percent, about 25 percent or about 30 percent or more (w/v) of the composition. The amount is dependent on the nature, the therapeutic dosage and the potency of a particular ophthalmologic agent.

The present ophthalmic compositions may comprise other therapeutic agents instead of or in addition to the anti-inflammatory agents disclosed herein. For example, therapeutic agents may include without limitation retinoids, prostaglandins, tyrosine kinase inhibitors, adrenoreceptor agonists or antagonists, dopaminergic agonists, cholingeric agonists, carbonic anhydrase inhibitors, guanylate cyclase activators, cannabinoids, endothelin, adenosine agonists, antianaglogenic compounds, angiostatic compounds, neuroprotectants, and the like and mixtures thereof. The therapeutic component may also include, analgesics, or antipyretics; antihistamines, antibiotics, beta blockers, anti-neoplastic agents, immunosuppressive agents, antiviral agents, antioxidants and the like and mixtures thereof.

Non-limiting examples of non-steroidal anti-inflammants, analgesics, and antipyretics, include aspirin, acetaminophen, ibuprofen, naproxen, diclofenac, etodolac, fenoprofen, indomethacin, ketoprofen, oxaprozin, piroxicam, sulindac, diflunisal, mefenamic acid, derivatives thereof, and the like and mixtures thereof.

Examples of antihistamines include, and are not limited to ketotifen, loradatine, hydroxyzine, diphenhydramine, chlorpheniramine, brompheniramine, cyproheptadine, terfenadine, clemastine, triprolidine, carboxamine, diphenylpyraline, phenindamine, azatidine, tripelemamine, dextronpheniramine, dextronpheniramine, methdilazine, and trimprazine doxylamine, pheniramime, pyrilamine, chiorcyclizine, thonzylamine, derivatives thereof, and the like and mixtures thereof. Examples of antibiotics include without limitation, cefazolin, cephradine, cefaclor, cephalixin, cefiproxime, cefoperazone, cefotetan, cefotuxime, cefotaxime, cefadroxil, cefadizidine, cephalexin, cephalothin, cefamandole, cefoxitin, cefonicid, ceforanide, ceftriaxone, cefadroxil, cephradine, cefuroxime, ampicillin, amoxicillin, cyclacillin, ampicillin, penicillin G, penicillin V potassium, pipracillin, oxacillin, bacampicillin, cloxacillin, ticarcillin, azlocillin, carbenicillin, methicillin, nafcillin, erythromycin, tetracycline, doxycycline, minocycline, aztreonam, chloramphenicol, ciprofloxacin hydrochloride,
clindamycin, metronidazole, gentamicin, lincomycin, tobramycin, vancomycin, 
polymyxin B sulfate, colistimethate, colistin, azithromycin, augmentin, 
sulfamethoxazole, trimethoprim, derivatives thereof, and the like and mixtures thereof.

Examples of beta blockers include without limitation acebutolol, 
atenolol, labetalol, metoprolol, propranolol, derivatives thereof, and the like and mixtures thereof. Examples of antineoplastic agents include without limitation adriamycin, cyclophosphamide, actinomycin, bleomycin, duanorubicin, doxorubicin, epirubicin, mitomycin, methotrexate, fluorouracil, carboplatin, carmustine (BCNU), methyl-CCNU, cisplatin, etoposide, interferons, camptothecin and derivatives thereof, 
phenesterine, taxol and derivatives thereof, taxotere and derivatives thereof, 
vindablastine, vincristine, tamoxifen, etoposide, piposulfan, cyclophosphamide, and 
fluotamide, derivatives thereof, and the like and mixtures thereof.

Examples of immunosuppressive agents include without limitation 
cyclosporine, azathioprine, tacrolimus, derivatives thereof, and the like and mixtures thereof. Examples of antiviral agents include without limitation interferon gamma, 
zidovudine, amantadine hydrochloride, ribavirin, acyclovir, valciclovir, dideoxycytidine, 
derivatives thereof, and the like and mixtures thereof.

Examples of antioxidant agents include without limitation ascorbate, 
alpha-tocopherol, manitol, reduced glutathione, various carotenoids, cysteine, uric acid, taurine, tyrosine, superoxide dismutase, lutein, zeaxanthin, cryptoxanthin, astazanthin, lycopene, N-acetyl-cysteine, carnosine, gamma- glutamylcysteine, quercitin, lactoferrin, dihydrolipoic acid, citrate, Ginkgo Biloba extract, tea catechins, bilberry extract, vitamins E or esters of vitamin E, retinyl palmitate, derivatives thereof, and the like and mixtures thereof. Other therapeutic agents include without limitation 
squalamine, carbonic anhydrase inhibitors, alpha agonists, prostamides, 
prostaglandins, antiparasitics, antifungals, derivatives thereof, and the like and mixtures thereof. Examples of prostaglandins are latanoprost, bimatoprost, tafluprost, travoprost. Further examples include aminosterols other than squalamine that have antiangiogenic activity. Another therapeutic agent may be anecortave acetate, or 
similar agents or compounds which have anti-angiogenic properties without substantial undesirable effects.

The therapeutic agent of the present compositions may include any 
and all salts, and prodrugs or precursors of the therapeutic agents, including those 
specifically identified herein.
The ophthalmic composition according to the present invention may further a second or even third ophthalmic agent.

In a further embodiment the ophthalmic composition according to the present invention may be formed of the PEA polymer as such or of a blend with one or more other polymers. Representative polymers include, but are not limited to, poly(ester amide), polyhydroxyalkanoates (PHA), poly(3-hydroxyalkanoates) such as poly(3-hydroxypropanoate), poly(3-hydroxybutyrate), poly(3-hydroxyvalerate), poly(3-hydroxyhexanoate), poly(3-hydroxyheptanoate) and poly(3-hydroxyoctanoate), poly(4-hydroxyalkanoate) such as poly(4-hydroxybutyrate), poly(4-hydroxyvalerate), poly(4-hydroxyhexanoate), poly(4-hydroxyheptanoate), poly(4-hydroxyoctanoate), poly(4-hydroxyoctanoate)-based copolymers including any of the 3-hydroxyalkanoate or 4-hydroxyalkanoate monomers described herein or blends thereof, poly(D,L-lactide), poly(L-lactide), polyglycolide, poly(D,L-lactide-co-glycolide), poly(L-lactide-co-glycolide), poly(dioxanone), poly(ortho esters), poly(trimethylene carbonate), polyphosphazenes, poly(anhydrides), poly(tyrosine carbonates) and derivatives thereof, poly(tyrosine ester) and derivatives thereof, poly(imino carbonates), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), poly(ethylene glycol) (PEG), copoly(ether-esters) (e.g. PEO/PLA), polyalkylene oxides such as poly(ethylene oxide), poly(propylene oxide), poly(ether ester), polyalkylene oxalates, poly(aspirin), biomolecules such as collagen, chitosan, alginate, fibrin, fibrinogen, cellulose, starch, collagen, dextran, dextrin, fragments and derivatives of hyaluronic acid, heparin, fragments and derivatives of heparin, glycosaminoglycan (GAG), GAG derivatives, polysaccharide, elastin, chitosan, alginate, or combinations thereof.

The present invention further relates to an extruded or injection molded parts comprising the ophthalmic composition according to the present invention. The extruded or injection molded parts are sized for injection via a pharmaceutical syringe needle having a bore of about 18 to 30 Gauge and can be used to treat, prevent, or ameliorate a medical ophthalmic condition.

As used herein, the extruded or injection molded parts may be any suitable medical substrate that can be injected in a human or veterinary patient via a pharmaceutical syringe needle having a bore of about 18-30 Gauge, preferably about 20-30 Gauge, more preferably a bore of about 22-29 Gauge, most preferably a bore of 24-28 Gauge. Examples of such medical substrates include particles, fibers, tubes or rods.
The medical substrates may be fabricated via extrusion of via injection molding or may be based on different layers of various polymers of the present invention where \( m, p \) and \( n \) vary so as to achieve a given mechanical property e.g. lubricity for ease of injectability and drug release behavior.

The present invention further relates to injectable fluids that gel or solidify upon contact with physiological fluid or at body temperature comprising the composition of the present invention. The present invention further relates to a method of delivering at least one ophthalmologic agent to the interior or exterior of the eye of a subject, said method comprising: administering the ophthalmic composition of the present invention or an injectable fluid into the interior or exterior of the eye of the subject for sustained and controlled release of the ophthalmologic agent. In at least one embodiment, the composition can be administered without accessing the subretinal space of the eye. For example, a method of treating a patient may include injecting the composition directly into the posterior chamber of the eye. In other embodiments, a method of treating a patient may comprise administering the composition to the patient by at least one of intravitreal injection, subconjunctival injection, sub-tenon injections, retrobulbar injection, and suprachoroidal injection.

Among the diseases/conditions which can be treated or addressed in accordance with the present invention include, without limitation, the following: Maculopathies/retinal degeneration such as non-Exudative Age Related Macular Degeneration (ARMD), Exudative Age Related Macular Degeneration (ARMD), wet macular degeneration. Neovascularization, Diabetic Retinopathy, Acute Macular Neuroretinopathy, Central Serous Chorioretinopathy, Cystoid Macular Edema, Diabetic Macular Edema.


Vascular disease/Exudative diseases: Retinal Arterial...
Occlusive Disease, Central Retinal Vein Occlusion, Disseminated Intravascular Coagulopathy, Branch Retinal Vein Occlusion, Hypertensive Fundus Changes, Ocular Ischemic Syndrome, Retinal Arterial Microaneurysms, Coat's Disease, Parafoveal Telangiectasis, Hemi-Retinal Vein Occlusion, Papillophlebitis, Central Retinal Artery Occlusion, Branch Retinal Artery Occlusion, Carotid Artery Disease (CAD), Frosted Branch Angitis, Sickle Cell Retinopathy and other Hemoglobinopathies, Angioid Streaks, Familial Exudative Vitreoretinopathy, Eales Disease.

Traumatic/surgical: Sympathetic Ophthalmia, Uveitic Retinal Disease, Retinal Detachment, Trauma, Laser, PDT, Photocoagulation, Hypoperfusion during surgery, Radiation Retinopathy, Bone Marrow Transplant Retinopathy.

Proliferative disorders: Proliferative Vitreal Retinopathy and Epiretinal Membranes, Proliferative Diabetic Retinopathy.

Infectious disorders: Ocular Histoplasmosis, Ocular Toxocariasis, Presumed Ocular Histoplasmosis Syndrome (POHS), Endophthalmitis, Toxoplasmosis, Retinal Diseases Associated with HIV Infection, Choroidal Disease Associated with HIV Infection, Uveitic Disease Associated with HIV Infection, Viral Retinitis, Acute Retinal Necrosis, Progressive Outer Retinal Necrosis, Fungal Retinal Diseases, Ocular Syphilis, Ocular Tuberculosis, Diffuse Unilateral Subacute Neuroretinitis, Myiasis.

Genetic disorders: Retinitis Pigmentosa, Systemic Disorders with Associated Retinal Dystrophies, Congenital Stationary Night Blindness, Cone Dystrophies, Stargardt's Disease and Fundus Flavimaculatus, Best's Disease, Pattern Dystrophy of the Retinal Pigmented Epithelium, X-Linked Retinoschisis, Sorsby's Fundus Dystrophy, Benign Concentric Maculopathy, Bietti's Crystalline Dystrophy, pseudoxanthoma elasticum.

Retinal tears/holes: Retinal Detachment, Macular Hole, Giant Retinal Tear.

Tumors: Retinal Disease Associated with Tumors, Congenital Hypertrophy of the RPE, Posterior Uveal Melanoma, Choroidal Hemangioma, Choroidal Osteoma, Choroidal Metastasis, Combined Hamartoma of the Retina and Retinal Pigmented Epithelium, Retinoblastoma, Vasoproliferative Tumors of the Ocular Fundus, Retinal Astrocytoma, Intraocular Lymphoid Tumors.
Miscellaneous: Punctate Inner Choroidopathy, Acute Posterior Multifocal Placoid Pigment Epitheliopathy, Myopic Retinal Degeneration, Acute Retinal Pigment Epithelitis and the like.

While the invention has been described with respect to various specific embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the claims.

The invention will now be further and specifically described by the following examples.

MATERIALS

PEA-III-Ac Bz polymers are used in the following examples. A more extended description of PEA-III-Ac Bz is poly-8-[(L-Leu-DAS)\textsubscript{0.45}(L-Leu-6)\textsubscript{0.3}]L-Lys(Bz)\textsubscript{0.25}-Structure is given in Formula III. The fractions indicate overall fractions of the monomers in the synthesis.

Formula III: PEA III Ac Bz

Synthesis of PEA III Ac Bz

Triethylamine (30.9 ml, 0.222 mole, 2.2eq) and N,N-dimethylformamide (53.07 ml, 0.689 mole) were added to a mixture of Di-OSu-sebacinate (39.940 g, 0.1008 mole, 1.0eq), L-leucine(6)-2TosOH (20.823 g, 0.0302 mole, 0.30eq), L-leucine-(DAS)-2TosOH (32.503 g, 0.0453 mole, 0.45eq) and L-lysine(Bz)-2TosOH (14.628 g, 0.0252 mole, 0.25eq) in a nitrogen flushed 500ml round bottomed flask equipped with an overhead stirrer at room temperature. The subsequent mixture was heated to 60°C to allow the reaction to proceed and monitored by GPC analysis in THF. After 36 hours a stable molecular weight was obtained, subsequently a portion of L-leucine(6)-2TosOH (4.338 g, 0.0063 mole) along with triethylamine (1.76 ml, 0.0126mole) and N,N-dimethylformamide (4.54 ml, 0.0590mole) was added to terminate the polymerization reaction. The mixture was heated additionally for 24 hours after which the viscous solution was further diluted with N,N-dimethylformamide (407.85g, 5.301 mole) and allowed to cool to room temperature. At room temperature
acetic anhydride (1.89 mL, 0.0199 mole) was added to acylate the amino functional end groups of the polymer. The mixture was stirred at room temperature for 24 hours. In scheme 1 the general reaction is shown.

Scheme 1: Reaction scheme for the synthesis of PEA III Ac Bz.

The obtained crude polymer mixture was precipitated in water in a 10:1 ratio (water: reaction mixture). The polymer was collected and dissolved in ethanol (500 mL, 8.57 mole) and the procedure was repeated a second time. The polymer was again dissolved in ethanol (500 mL, 8.57 mole) and precipitated in ethylacetate (5000 mL, 50.91 mole) by drop wise addition to a stirring solution. The precipitated polymer was washed with two portions ethylacetate (100 mL, 100 mole), dried and dissolved in ethanol (500 mL, 8.57 mole) and filtered over a 0.2 µm PTFE membrane filter. The filtered polymer solution was dried under reduced pressure at 65°C.

Yield 75%, Mn =50 kDa (Gel Permeation Chromatography (GPC) in THF relative to polystyrene standards. Glass transition temperatures were determined by Differential Scanning Calorimetry (DSC). Measurements were taken from second heating, with a heating rate of 10°C/min., Tg= 48°C.

Films were prepared from these polymers.
Latanoprost was purchased from Cayman Chemicals (Item # 16812, Batch 188844-14.

Ketotifen fumarate was purchased from Sifavator.

Other materials and chemicals used in this feasibility phase are generally obtained from Sigma-Aldrich and VWR/Merck. Phosphate buffered saline (PBS) was obtained from BioChrom. Tetrahydrofuran (THF) was obtained from Prolabo. Acetonitril (ACN), ethanol and phosphoric acid (H₃PO₄) were obtained from Merck. MilliQ was processed internally. Deuterated THF was obtained from Sigma Aldrich.

METHODS

For film casting, solutions were prepared in a suitable solvent resulting in solutions with viscosities low enough for solvent casting. Exact amounts of PEA-III ac Bz and API (Active Pharmaceutical Ingredient) were weighed and dissolved with a suitable solvent. The API payload is determined over the polymer weight. API payload of 10% was used. The API/polymer/solvent formulations were poured into petri dishes (4cm diameter) and covered to reduce evaporation rates of the solvent and prevent formation of air bubbles. The solvent was evaporated for 2 days at rT in a fumehood followed by 2 days @ 750mBar, 1 day @ 500mBar and 2 days at full vacuum. From the resulting films, discs were cut with diameter of 10mm and approximate thicknesses of 50-100µm.

1H NMR Measurements

A sample was prepared by dissolving -10 mg of material in 1ml of deuterated THF in a 10 ml glass vial. The sample was allowed sufficient time for complete dissolution. ¹H NMR spectra was recorded on a 300MHz Bruker Avance 300, ARX 400 NMR instrument.

HPLC quantification method

For the quantitative analysis of the release of the Latanoprost sample a Waters e2695 Alliance HPLC with a photodiode array detector was used. An isocratic HPLC method was used with an Agilent Zorbax Eclipse XBD-C18 4.6 x 250mm, 5µm column. The mobile phase was Acetonitrile / H₂O (60 / 40 containing 0.05% TFA) and the flow was 1.0 ml/min. Column temperature was set to 25°C and sample temperature to 15°C. Samples were measured at a wavelength of 210nm.
Release studies were performed in phosphate buffered saline (PBS). An accurate volume of buffer was measured into a glass vial containing the sample, with a volume depending on the

EXAMPLE I

This example describes Latanoprost stability in PEA III formulations and the release of latanoprost from PEA-III Ac Bz discs. Stability of Latanoprost in formulations and compatibility with film casting procedure was evaluated by $^1$H NMR. Analysis of spectra of initial PEA III formulations with Latanoprost as well as formulations stored @ 4°C for 3 months did not indicate any degradation of API.

Time-exchange release studies were conducted on representative discs with 10% Latanoprost. The weight per disc was around 20mg and was recorded accurately. A volume of 5mL of PBS was used for each release article. Full volume of PBS was fully exchanged at each time point. The amount of Latanoprost was measured using HPLC and the release curve in total % API is presented in Figure 1.

EXAMPLE II

Fiber extrusions were performed using a 5cc twin-screw mini-extruder.

Ketotifen fumarate and PEA-III-Ac Bz were co-dissolved in ethanol, then film-casted and allowed to dry. Films were cut in pieces and then cryo-milled. The resulting flakes were brought into the hopper at the top of the heated barrel via a steel funnel. A temperature gradient was applied to the barrel of 100°C to 130°C and 140°C from top to middle to bottom part. In-vitro release studies were performed in phosphate buffered saline (PBS). An volume of 200 ul of buffer was pipetted into a glass vial containing the sample, with a volume depending on the expected API release. The buffer was removed and replaced with fresh buffer at defined time points, typically after 1 hour, 4 hours, 1 day, 2 days, 4 days, 7 day etc. until completion of the release study. During the release study the samples were kept in glass vials at 37°C while shaking. The PBS solution with released API was transferred to HPLC vials and stored refrigerated until HPLC analysis. The release study was continued until no API was detectable anymore by HPLC or until 100% of the loaded API had been released. All release experiments were carried out with n=3 or n=4. Sink conditions were applied to avoid influence of saturation of the PBS on release kinetics. The amount of ketotifen
fumarate was measured using HPLC and the release curves in total % API is presented in Figure 2.
CLAIMS

1. An ocular polymer delivery composition sized for injection via a pharmaceutical syringe needle having a bore of about 18 to 30 Gauge, comprising at least one ophthalmologic agent dispersed in biodegradable poly (ester amide) (PEA) having a chemical formula described by structural formula (I),

\[
\begin{align*}
&\text{Formula I} \\
&\text{wherein} \\
&m \text{ is about 0.3-0.6, } p \text{ is about 0.3-0.45 and } q \text{ is about 0.1-0.25 and wherein } \\
&m+p+q=1, m, p, q \text{ are randomly distributed within formula I, } n \text{ is about 5-100 and} \\
&-R_1 \text{ is } (CH_2)_6; (CH_2)_4 \\
&-R_3 \text{ and } R_4 \text{ are selected from } (CH_3)_2-CH-CH_2^-; \\
&-R_5 \text{ is selected from } (CH_2)_6, \\
&-R_6 \text{ is } 1,4:3,6\text{-dianhydrosorbitol (DAS) according to formula II} \\
&-R_7 \text{ is a } H, \text{ benzyl protecting group or an ophthalmologic agent} \\
&-R_8 \text{ is } (CH_2)_4
\end{align*}
\]
An ocular polymer delivery composition according to claim 1 wherein
- \( m \) is about 0.3, \( p \) is about 0.45 and \( q \) is about 0.25
- the individual building blocks of ratio \( m,p \) and \( q \) are randomly distributed
along the polymer chain within formula I, \( n \) is about 5-100 and
- \( R_1 \) is \((\text{CH}_2)_{6}\)
- \( R_3 \) and \( R_4 \) are selected from \((\text{CH}_3)_2\text{-CH-CH}_2^-\);
- \( R_5 \) is selected from \((\text{CH}_2)_{6}\);
- \( R_6 \) is 1,4:3,6-dianhydrosorbitol (DAS) according to formula II
- \( R_7 \) is a H, benzyl protecting group or an ophthalmologic agent
- \( R_8 \) is \((\text{CH}_2)_{4}\)

An ocular polymer delivery composition according to claim 1 wherein
- \( m \) is about 0.6, \( p \) is about 0.3 and \( q \) is about 0.1
- the individual building blocks of ratio \( m,p \) and \( q \) are randomly distributed
along the polymer chain within formula I, \( n \) is about 5-100 and and
- \( R_1 \) is \((\text{CH}_2)_{4}\)
- \( R_3 \) and \( R_4 \) are selected from \((\text{CH}_3)_2\text{-CH-CH}_2^-\);
- \( R_5 \) is selected from \((\text{CH}_2)_{6}\);
- \( R_6 \) is 1,4:3,6-dianhydrosorbitol (DAS) according to formula II
- \( R_7 \) is a H, benzyl protecting group or an ophthalmologic agent
- \( R_8 \) is \((\text{CH}_2)_{4}\)

An ocular polymer delivery composition according to any one of the claims 1-3
wherein composition is sized for injection via a pharmaceutical syringe needle
having a bore of about 24-28 Gauge.

Particles, fibers, tubes, rods comprising the ocular polymer composition
according to any one of the claims 1-4.
6. Injectable fluid that gels or solidifies upon contact with physiological fluid or at body temperature comprising the composition according to any one of the claims 1-4.

7. A method of delivering at least one ophthalmologic agent to the interior or exterior of the eye of a subject, said method comprising: administering the composition according to any one of claims 1-4 or the injectable fluid according to claim 6 into the interior or exterior of the eye of the subject for sustained and controlled release of the ophthalmologic agent for therein.
INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/058015

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/34 A61K9/00 A61K31/216 A61K31/4535
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C08L

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

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

EPO-Internal, WPI Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

A

wo 2007/035938 A2 (MEDIVAS LLC [US]; GMURASHVI LI ZAZA D [US]; HUGHES JONATHAN MACFERRAN) 29 March 2007 (2007-03-29) cited in the application on abstract paragraphs [0093] - [0095]; claims 1, 18, 25, 26-31, 36-37, 38-40; examples 1-4, 6 Form a III

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

A: document defining the general state of the art which is not considered to be of particular relevance
E: earlier application or patent but published on or after the international filing date
L*: documents which may throw doubts on priority claim(s) or which are cited to establish the publication date of another citation or other special reason (as specified)
O: document referred to in an oral disclosure, use, exhibition or other means
P: document published prior to the international filing date but later than the priority date claimed

"I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"A" document member of the same patent family

Date of the actual completion of the international search
21 August 2012

Date of mailing of the international search report
04/09/2012

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer
Madai nska, K

Form PCT/ISA/210 (second sheet) (April 2005)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>WO 2007130477 A2</td>
<td>15-11-2007</td>
<td>NONE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1926780 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2009510197 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2008299174 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2007035938 A2</td>
</tr>
<tr>
<td>US 2006009498 Al</td>
<td>12-01-2006</td>
<td>AR 049979 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2005271700 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2011200584 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR PI0513243 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2573668 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1773350 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2216026 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2008505978 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2006009498 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2012035148 Al</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2006017347 A2</td>
</tr>
</tbody>
</table>