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(54) **Formulation for controlled release of drugs by combining hydrophilic and hydrophobic agents**

Formulierung zur gesteuerten Arzneistofffreisetzung durch Kombination hydrophiler und hydrophober Stoffe

Formulation destinée à la libération contrôlée de médicaments par combinaison d'agents hydrophiles et hydrophobes

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EP-A- 0 102 265 EP-A- 0 311 065
EP-A- 0 474 098 WO-A-95/13765
WO-A-96/34599 US-A- 4 304 765

• **HOCKEL M ET AL: "PREVENTION OF
PERITONEAL ADHESIONS IN THE RAT WITH
SUSTAINED INTRAPERITONEAL
DEXAMETHASONE DELIVERED BY A NOVEL
THERAPEUTIC SYSTEM" ANNALES
CHIRURGIAE ET GYNAECOLOGIAE, vol. 76, no.
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EP 1 477 187 B9

Description**INTRODUCTION***Technical Field*

[0001] Biodegradable implants formulated for controlled, sustained drug release.

Background of the Invention

[0002] Solid pharmaceutically active implants that provide sustained release of an active ingredient are able to provide a relatively uniform concentration of active ingredients in the body. Implants are particularly useful for providing a high local concentration at a particular target site for extended periods of time. These sustained release forms reduce the number of doses of the drug to be administered, and avoid the peaks and troughs of drug concentration found with traditional drug therapies. Use of a biodegradable drug delivery system has the further benefit that the spent implant need not be removed from the target site.

[0003] Many of the anticipated benefits of delayed release implants are dependent upon sustained release at a relatively constant level. However, formulations of hydrophobic drugs with biodegradable matrices may have a release profile which shows little or no release until erosion of the matrix occurs, at which point there is a dumping of drug.

[0004] The eye is of particular interest when formulating implantable drugs, because one can reduce the amount of surgical manipulation required, and provide effective levels of the drug specifically to the eye. When a solution is injected directly into the eye, the drug quickly washes out or is depleted from within the eye into the general circulation. From the therapeutic standpoint, this may be as useless as giving no drug at all. Because of this inherent difficulty of delivering drugs into the eye, successful medical treatment of ocular diseases is inadequate.

[0005] Improved sustained release formulations which allow for a constant drug release rate are of considerable interest for medical and veterinary uses.

Relevant Literature

[0006] U.S. Patents 4,997,652 and 5,164,188 disclose biocompatible implants for introducing into an anterior chamber or posterior segment of an eye for the treatment of an ocular condition.

[0007] Heller, Biodegradable Polymers in Controlled Delivery, in : CRC Critical Reviews in Therapeutic Drug Carrier Systems, Vol. 1, CRC Press, Boca Raton, FL, 1987, pp 39-90, describes encapsulation for controlled drug delivery. Heller in: Hydrogels in Medicine and Pharmacy, N.A. Peppas ed., Vol. III, CRC Press, Boca Raton, FL, 1987, pp 137-149, further describes bioerodible polymers.

[0008] Anderson et al., Contraception (1976) 13:375 and Miller et al., J. Biomed Materials Res. (1977) 11:711, describe various properties of poly(DL-lactic acid). U.S. Patent 5,075,155 discloses sustained release formulations with lactic acid polymers and co-polymers.

[0009] EP 0 474 098 A discloses compositions comprising a hardly soluble drug, a water-soluble polymer and a biodegradable polymer.

[0010] Di Colo (1992) Biomaterials 13:850-856 describes controlled drug release from hydrophobic polymers.

SUMMARY OF THE INVENTION

[0011] According to the present invention, there is provided an implant for use in a method of treatment of ocular conditions by insertion of said implant into the vitreous chamber of the eye, said implant being suitable for sustained drug release and comprising: poly-lactate glycolic acid copolymer at a concentration of at least 20 weight percent of the implant, dexamethasone at a concentration of from 10 to 50 weight percent of the implant, and a release modulator at a concentration of from 10 to 50 weight percent of the implant, wherein the release modulator is an accelerator in the form of a hydrophilic agent having a solubility of at least 100 µg/ml in water at ambient temperature, and wherein dexamethasone is released within a therapeutic dosage that does not vary by more than about 100% for a period of at least 3 days.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012]

Figure 1A shows the release profile of a hydrophobic drug from an extended release drug delivery system. Figure

1B shows the release profile of the same drug when formulated in a drug delivery system with a release modulator. Figure 2A shows the release profile of dexamethasone in the absence or presence of the release modifier, ciprofloxacin HC1. Figure 2B shows the release of ciprofloxacin in the presence of dexamethasone. Figure 2C shows the release of ciprofloxacin in the absence of a release modifier. Figure 2D shows the release profile from a drug delivery system having combined hydrophilic and hydrophobic drugs, and further having a pharmaceutically inactive release modifier.

Figure 3 shows a cross-sectional view of an eye.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

[0013] A controlled drug release is achieved by an improved formulation of slow release biodegradable implants. The release rate of a drug from an implant is modulated by addition of a release modulator to the implant. Release of a hydrophobic agent is increased by inclusion of an accelerator in the implant, while retardants are included to decrease the release rate of hydrophilic agents. The release modulator may be physiologically inert, or a therapeutically active agent. Formulations of interest includes antiinflammatory drugs, *e.g.* glucocorticoids, NSAIDS, *etc.*, combined with an ophthalmically active agent.

[0014] The rate of release of the therapeutically active agent is controlled by the rate of transport through the polymeric matrix of the implant, and the action of the modulator. By modulating the release rate, the agent is released at a substantially constant rate within a therapeutic dosage range, over the desired period of time. The rate of release will usually not vary by more than about 100% over the desired period of time, more usually by not more than about 50%. The agent is made available at the specific site(s) where the agent is needed, and it is maintained at an effective dosage.

[0015] The transport of drug through the polymer barrier is also affected by drug solubility, polymer hydrophilicity, extent of polymer cross-linking, expansion of the polymer upon water absorption so as to make the polymer barrier more permeable to the drug, geometry of the implant, and the like. At high drug loadings, *i.e.* at a loading concentration above the theoretical percolation threshold, percolation theory predicts the potential for drug leaching from the drug delivery system matrix. In such cases release modulators are useful to slow down the leaching process.

[0016] The release modulator is an agent that alters the release of a drug from a biodegradable implant in a defined manner. It may be an accelerator or a retardant. Accelerators will be hydrophilic compounds, which are used in, combination with hydrophobic agents to increase the rate of release. Hydrophilic agents are those compounds which have at least about 100 $\mu\text{g/ml}$ solubility in water at ambient temperature. Hydrophobic agents are those compounds which have less than about 100 $\mu\text{g/ml}$ solubility in water at ambient temperature.

[0017] Therapeutically active agents that benefit from formulation with a release modulator may come from, but are not limited to, the following therapeutic classes: Ace-inhibitor, endogenous cytokines that influence basement membrane; agents that influence growth of endothelial cell adrenergic agonist or blocker, aldose reductase inhibitor, analgesic; anesthetic; antiallergic; antibacterial; antifibrotic; antifungal, *e.g.* amphotericin B; antiglaucoma; antihyper- or hypotensive; anti-inflammatory; antineoplastic; antiprotozoal; antitumor, antiviral; carbonic anhydrase inhibitor, chelating agents; cholinergic; cholinesterase inhibitor, CNS stimulant; contraceptive; dopamine receptor agonist or antagonist; estrogen; glucocorticoid; glucosidase inhibitor, releasing factor; growth hormone inhibitor, growth stimulant; hemolytic; heparin antagonist; immunomodulator, immunosuppressant; LH-RH agonist; antimitotics; NSAID; progesterone; thrombolytic; vasodilator, vasopressor, and vitamin. Among hydrophobic drugs, which typically have a slow release profile and therefore benefit from formulation with a release accelerator, are cyclosporines, *e.g.* cyclosporin A, cyclosporin G, *etc.*; vinca alkaloids, *e.g.* vincristine and vinblastine; methotrexate; retinoic acid; certain antibiotics, *e.g.* ansamycins such as rifampin; nitrofurans such as nifuroxazide; non-steroidal anti-inflammatory drugs, *e.g.* diclofenac, ketorolac, flurbiprofen naproxen, suprofen, ibuprofen, aspirin; steroids, *etc.*

[0018] Steroids are of specific interest, in particular steroidal compounds with anti-inflammatory activity, *i.e.* glucocorticoids. Glucocorticoids include the following:

21-acetoxypregnenolone	flumethasone	meprednisone
alclometasone	flunisolide	methylprednisone
algestone	fluocinolone acetonide	mometasone furoate
amcinonide	fluocinonide	prednisolone sodium 21-m-sulfobenzoate
beclomethasone	fluocortinbutyl	prednisolone 21-stearoylglycolate
betamethasone	fluocortolone	prednisolone tebutate
budemide	fluorametholone	prednisolone 21-trimethylacetate

(continued)

	chloroprednisone	fluploneacetate	prednisone
5	clobetasol	fluprednidene acetate	prednival
	clobetasone	fluprednisolone	paramethasone
	cloprednol	flurandrenolide	prednylidene
	clocortolone	formocortel	prednicarbate
10	corticosterone	halcinonide	prednylidene21-diethylaminoacetate
	cortisone	halometasone	prednisolone
	cortivasol	halopredone acetate	prednisolone 21-diethylaminoacetate
15	deffazacor	hydrocortamate	tixocortol
	desonide	diflorasone	triamcinolone
	desoximetasone	hydrocortisone	prednizolone sodium phosphate
	dexamethasone	hydrocortisone acetate	triameinolone acetonide
20	diflucortelene	hydrocortisone phosphate	prednisolone sodium succinate
	diruprednate	hydrocortisone 21-sodium succinate	triamcinolone benetonide
	enoxolone	hydrocortisone tebutate	triamcinolone hexacetonide
25	fluazacort	mazipredone	
	flucoronide	medrysone	

[0019] These hydrocortisone derivatives have been recognized of having significant therapeutic effects that are beneficial in the treatment of ocular inflammatory diseases, varying in their potency and biotolerability as function of their chemical substitutions.

[0020] The following are examples of glucocorticoids that have been used in the treatment of ocular inflammation, and are of interest for use in the subject invention: dexamethasone sodium phosphate; dexamethasone. Of these, dexamethasone is thought to be the most potent, and is therefore a good candidate for the use in an intraocular drug delivery system, because a small drug release rate is sufficient to establish therapeutic concentration levels inside the eye.

[0021] Accelerators may be physiologically inert, water soluble polymers, *e.g.* low molecular weight methyl cellulose or hydroxypropyl methyl cellulose (HPMC); sugars, *e.g.* monosaccharides such as fructose and glucose, disaccharides such as lactose, sucrose, or polysaccharides, usually neutral or uncharged, such as cellulose, amylose, dextran, *etc.* Alternatively, the accelerator may be a physiologically active agent, allowing for a combined therapeutic formulation. The choice of accelerator in such a case will be determined by the desired combination of therapeutic activities.

[0022] A category of drugs that is of interest as active release modulator in a combination are drugs with antimicrobial activity. Antibacterial drug classes that have found successful use in care of the infected eye are: aminoglycosides, amphenicols, ansamycins, lactams, lincosamides, macralides, polypeptides, tetracyclines, diaminopyrimidines, nitrofurans, quinolones and analogs, sulfonamides, sulfones, *etc.* Where one compound does not cover the range of the bacterial infection, products may combine several antibacterial drugs in one combination product. Examples of antibiotics useful in treating ocular infections include; chloramphenicol; polymyxin b, neomycin, gramicidin; neomycin; bacitracin; sulfacetamide sodium; gentamicin; ciprofloxacin; tobramycin; trimethprim sulfate; ofloxacin; erythromycin; norfloxacin; vancomycin; tetracycline; and chlortetracycline.

[0023] Antiviral drugs are also of interest. These include a number of water soluble nucleotide analogs, *e.g.* acyclovir, gancyclovir, vidarobine, azidothymidine, dideoxyinosine and dideoxycytosine.

[0024] Of particular interest as an antibacterial compound are the quinolones, which are very potent, broad spectrum antibiotics. The high activity of these drugs allows a therapeutic concentration to be reached at low levels of the drug. Examples include ciprofloxacin; norfloxacin; ofloxacin; enoxacin, lomefloxacin; fieroxacin; temafloxacin, tosufloxacin and perfloxacin.

[0025] In a preferred embodiment of the invention, the implant comprises an anti-inflammatory drug, as described above, and a release modulator, where the release modulator is an ophthalmically active agent. Certain diseases require the combined administration of drugs from different therapeutic categories. Combinations of interest include anti-inflammatory and anti-tumor; anti-inflammatory and antiviral; anti-inflammatory and antibacterial.

[0026] An example for the medical requirement of co-delivery of therapeutic agents from two different therapeutic classes is eye surgery. Eye surgery is often complicated with infection and inflammation, therefore drug products have been made available to administer an anti-inflammatory and antibacterial drug simultaneously. Of particular interest for the treatment of post-surgical eye complication is a drug delivery system delivering the combination of *e.g.* dexamethasone and ciprofloxacin. These two drugs are good candidates for intraocular drug delivery because of their high activity.

[0027] A combined anti-inflammatory drug, and antibiotic or antiviral, may be further combined with an additional therapeutic agent. The additional agent may be an analgesic, *e.g.* codeine, morphine, ketorolac, naproxen, *etc.*, an anesthetic, *e.g.* lidocaine; β -adrenergic blocker or β -adrenergic agonist, *e.g.* ephedrine, epinephrine, *etc.*; aldose reductase inhibitor, *e.g.* epalrestat, ponalrestat, sorbinil, totrestat; antiallergic, *e.g.* cromolyn, beclomethasone, dexamethasone, and flunisolide; colchicine. Anthelmintic agents, *e.g.* ivermectin and suramin sodium; antiamebic agents, *e.g.* chloroquine and chlortetracycline and antifungal agents, *e.g.* amphotericin, *etc.* may be co-formulated with an antibiotic and an anti-inflammatory drug. For intra-ocular use, anti-glaucoma agents, *e.g.* acetazolamide (dimox) befunolol, β -blockers, Ca-blockers, *etc.* in combinations with anti-inflammatory and antimicrobial agents are of interest. For the treatment of neoplasia, combination with anti-neoplastics, particularly viablastine, vincristine, interferons α , β and γ , antimetabolites, *e.g.* folic acid analogs, purine analogs, pyrimidine analogs may be used. Immunosuppressants such as azathioprine, cyclosporine and mizoribine are of interest in combinations. Also useful combinations include mitotic agents, *e.g.* carbachol, mydriatic agents such as atropine, *etc.*, protease inhibitors such as aprotinin, camostat, gabexate, vasodilators such as bradykinin, *etc.*, and various growth factors, such as epidermal growth factor, basic fibroblast growth factor, nerve growth factors, and the like.

[0028] The amount of active agent employed in the implant, individually or in combinations, will vary widely depending on the effective dosage required and rate of release from the implant. Visually the agent will be at least about 1, more usually at least about 10 weight percent of the implant, and usually not more than about 80, more usually not more than about 40 weight percent of the implant. The amount of release modulator employed will be dependent on the desired release profile, the activity of the modulator, and on the release profile of the active agent in the absence of modulator. An agent that is released very slowly will require relatively high amounts of modulator. Generally the modulator will be at least 10, more usually at least about 20 weight percent of the implant, and usually not more than about 50, more usually not more than about 40 weight percent of the implant.

[0029] Where a combination of active agents is to be employed, the desired release profile of each active agent is determined. If necessary, a physiologically inert modulator is added to precisely control the release profile. The drug release will provide a therapeutic level of each active agent.

[0030] The exact proportion of modulator and active agent will be empirically determined by formulating several implants having varying amounts of modulator. A USP approved method for dissolution or release test will be used to measure the rate of release (USP 23; NF 18 (1995) pp. 1790-1798). For example, using the infinite sink method, a weighed sample of the drug delivery device is added to a measured volume of a solution containing four parts by weight of ethanol and six parts by weight of deionized water, where the solution volume will be such that the drug concentration after release is less than 5% of saturation. The mixture is maintained at 37°C, and stirred slowly to maintain the implants in suspension. The appearance of the dissolved drug as a function of time may be followed by various methods known in the art, such as spectrophotometrically, HPLC, mass spectroscopy, *etc.* The drug concentration after 1 h in the medium is indicative of the amount of free unencapsulated drug in the dose, while the time required for 90% drug to be released is related to the expected duration of action of the dose *in vivo*. Normally the release will be free of larger fluctuations from some average value which allows for a relatively uniform release.

[0031] Normally the implant will be formulated to release the active agent(s) over a period of at least about 3 days, more usually at least about one week, and usually not more than about one year, more usually not more than about three months. For the most part, the matrix of the implant will have a physiological lifetime at the site of implantation at least equal to the desired period of administration, usually at least twice the desired period of administration, and may have lifetimes of 5 to 10 times the desired period of administration. The desired period of release will vary with the condition that is being treated. For example, implants designed for post-cataract surgery will have a release period of from about 3 days to 1 week; treatment of uveitis may require release over a period of about 4 to 6 weeks; while treatment for cytomegalovirus infection may require release over 3 to 6 months, or longer.

[0032] The implants are of dimensions commensurate with the size and shape of the region selected as the site of implantation and will not migrate from the insertion site following implantation. The implants may be rigid, or somewhat flexible so as to facilitate both insertion of the implant at the target site and accommodation of the implant. The implants may be particles, sheets, patches, plaques, fibers, microcapsules and the like and may be of any size or shape compatible with the selected site of insertion.

[0033] The implants may be monolithic, *i.e.* having the active agent homogeneously distributed through the polymeric matrix, or encapsulated, where a reservoir of active agent is encapsulated by the polymeric matrix. Due to ease of manufacture, monolithic implants are usually preferred over encapsulated forms. However, the greater control afforded by the encapsulated, reservoir-type may be of benefit in some circumstances, where the therapeutic level of the drug

falls within a narrow window. The selection of the polymeric composition to be employed will vary with the site of administration, the desired period of treatment, patient tolerance, the nature of the disease to be treated and the like. Characteristics of the polymers will include biodegradability at the site of implantation, compatibility with the agent of interest, ease of encapsulation, a half-life in the physiological environment of at least 7 days, preferably greater than two weeks, water solubility, and the like. The polymer will usually comprise at least about 10, more usually at least about 20 weight percent of the implant, and may comprise as much as about 70 weight percent or more.

[0034] Biodegradable polymeric compositions that may be employed may be organic esters or ethers, which when degraded result in physiologically acceptable degradation products, including the monomers. Anhydrides, amides, orthoesters or the like, by themselves or in combination with other monomers, may find use. The polymers will be condensation polymers. The polymers may be cross-linked or non-cross-linked, usually not more than lightly cross-linked, generally less than 5%, usually less than 1%. For the most part, besides carbon and hydrogen, the polymers will include oxygen. The oxygen may be present as carboxylic acid ester, and the like.

[0035] Copolymers of glycolic and lactic acid are of particular interest, where the rate of biodegradation is controlled by the ratio of glycolic to lactic acid. The most rapidly degraded copolymer has roughly equal amounts of glycolic and lactic acid. Homopolymers, or copolymers having ratios other than equal, are more resistant to degradation.

[0036] Particles can be prepared where the center may be of one material and the surface have one or more layers of the same or different composition, where the layers may be cross-linked, of different molecular weight, different density or porosity, or the like. For example, the center would comprise a polylactate coated with a polylactate-polyglycolate copolymer, so as to enhance the rate of initial degradation. Most ratios of lactate to glycolate employed will be in the range of about 1:0.1 to 1:1. Alternatively, the center could be polyvinyl alcohol coated with polylactate, so that on degradation of the polylactate the center would dissolve and be rapidly washed out of the implantation site.

[0037] The implants find use in the treatment of a variety of conditions in which it is convenient to employ a depot for the active agent, where the implant serves as such as a depot.

[0038] The formulation of implants for use in the treatment of ocular conditions, diseases, tumors and disorders are of particular interest. The biodegradable implants may be implanted in the vitreous cavity. Introduction of implants over an avascular region will allow for diffusion of the drug from the implant and into the inner eye and avoids diffusion of the drug into the bloodstream.

[0039] Turning now to Figure 3, a cross-sectional view of the eye is shown, illustrating the sites for implantation in accordance with the subject invention. The eye comprises a lens 16 and encompasses the vitreous chamber 3. Adjacent to the vitreous chamber 3 is the optic part of the retina 11. The retina is surrounded by the choroid 18. Between the optic part of the retina and the lens, adjacent to the vitreous, is the pars plana 19. Surrounding the choroid 18 is the sclera 8. The external surface of the eye is the cornea 9. The internal surface of the eye is the conjunctiva 6. Behind the cornea is the anterior chamber 1, behind which is the lens 16. The posterior chamber 2 surrounds the lens, as shown in the figure. Opposite from the external surface is the optic nerves, and the arteries and vein of the retina.

[0040] The implants may be administered in a variety of ways, including surgical means, injection, trocar, etc.

[0041] Other agents may be employed in the formulation for a variety of purposes. For example, buffering agents and preservatives may be employed. Water soluble preservatives which may be employed include sodium bisulfite, sodium bisulfate, sodium thiosulfate, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate, phenylmercuric nitrate, methylparaben, polyvinyl alcohol and phenylethyl alcohol. These agents may be present in individual amounts of from 0.001 to 5% by weight and preferably 0.01 to 2%. Suitable water soluble buffering agents that may be employed are sodium carbonate, sodium borate, sodium phosphate, sodium acetate, sodium bicarbonate, etc., as approved by the FDA for the desired route of administration. These agents may be present in amounts sufficient to maintain a pH of the system of between 2 to 9 and preferably 4 to 8. As such the buffering agent may be as much as 5% on a weight to weight basis of the total composition. Where the buffering agent or enhancer is hydrophilic, it may also act as a release accelerator, and will have a cumulative effect with other modulator(s). Similarly, a hydrophilic buffering agent may act as a release retardant.

[0042] The implants may be of any geometry including fibers, sheets, films, microspheres, spheres, circular discs, plaques and the like. The upper limit for the implant size will be determined by factors such as toleration for the implant, size limitations on insertion, ease of handling, etc. Where sheets or films are employed, the sheets or films will be in the range of at least about 0.5 mm x 0.5 mm, usually about 3-10 mm x 5-10 mm with a thickness of about 0.25-1.0 mm for ease of handling. Where fibers are employed, the diameter of the fiber will generally be in the range of 0.05 to 3 mm. The length of the fiber will generally be in the range of 0.5-10 mm. Spheres will be in the range of 2 μ m to 4 mm in diameter, with comparable volumes for other shaped particles.

[0043] The size and form of the implant can be used to control the rate of release, period of treatment, and drug concentration at the site of implantation. Larger implants will deliver a proportionately larger dose, but depending on the surface to mass ratio, may have a slower release rate. The particular size and geometry of an implant will be chosen to best suit the site of implantation. The vitreous chamber, is able to accommodate relatively large implants of varying geometries, having diameters of 1 to 3 mm.

[0044] In some situations mixtures of implants may be utilized employing the same or different pharmacological agents. In this way, a cocktail of release profiles, giving a biphasic or triphasic release with a single administration is achieved, where the pattern of release may be greatly varied.

[0045] Various techniques may be employed to produce the implants. Useful techniques include solvent evaporation methods, phase separation methods, interfacial methods, extrusion methods, molding methods, injection molding methods, heat press methods and the like. Specific methods are discussed in U.S. Patent 4,997,652. In a preferred embodiment, extrusion methods are used to avoid the need for solvents in manufacturing. When using extrusion methods, the polymer and drug are chosen so as to be stable at the temperatures required for manufacturing, usually at least about 85°C.

[0046] The following examples are offered by way of illustration and not by way of limitation.

EXPERIMENTAL

Example 1

Manufacture and Testing of a Drug Delivery System (DDS) without adding additional Release Modulator

[0047] Release of the hydrophobic drug dexamethasone from an extended release drug delivery system was measured. The drug delivery system was made with dexamethasone and polylactic acid/polyglycolic acid copolymer. Dexamethasone powder and a powder of polylactic acid polyglycolic acid (PLGA) copolymer were mixed thoroughly at a ratio of 50/50. The well mixed powder was filled into an extruder, and heated for 1 hour at 95°C, then extruded through a 20 gauge orifice. Six DDS of approximately 100-120 µg were cut from the extruded filaments for drug release assessment.

[0048] Each individual DDS was placed in a glass vial filled with receptor medium (9% NaCl in water). To allow for "infinite sink" conditions, the receptor medium volume was chosen so that the concentration would never exceed 5% of saturation. To minimize secondary transport phenomena, *e.g.* concentration polarization in the stagnant boundary layer, each of the glass vials was placed into a shaking water bath at 37°C. Samples were taken for HPLC analysis from each vial at defined time points. The HPLC method was as described in USP 23 (1995) pp. 1791-1798. The concentration values were used to calculate the cumulative release profiles. The release profile is shown in Figure 1A. It is seen that drug release is very slow with this DDS. Appreciable drug release begins in the fourth week after initiation, at approximately the time of polymer disintegration.

Manufacture and Testing of a DDS with HPMC Release Modifier

[0049] A drug delivery system was manufactured as described above, except that various concentrations of hydrophilic hydroxypropylmethycellulose (HPMC) were included as a release modifier. The combinations of drug, polymer and HPMC shown in Table 1 were used.

Table 1

Lot #	PLGA	HPMC	Dexamethasone	Total
XT014	3.5	1.5	5	10
XT015	2	2	5	9
XT013	1.5	1.5	5	8

[0050] The release of drug was tested as described above. The data is shown in Figure 1B. It is seen that with the addition of HPMC, there is a pronounced increase in the rate of release. Close to zero order release is observed for XT014 and XT015, where the ratio of release modulator to drug is 0.3 to 0.4. By selection of the appropriate polymer and release modifier, drug release and delivery interval can be custom-tailored to provide a release profile that is accelerated or retarded.

Example 2

Manufacture and Testing of A DDS with a Pharmaceutically Active Release Modifier

[0051] A drug delivery system was manufactured as described in Example 1, except that ciprofloxacin, a pharmaceutically active, hydrophilic compound, was included as a release modifier. The combinations of drug, polymer and HPMC shown in Table 2 were used.

Table 2

Lot #	PLGA	Release Modifier	Drug
XT029	5	-	5 dexamethasone
XT032	4	2 ciprofloxacin	4 dexamethasone
XT030 (not according to the invention)	5	-	5 ciprofloxacin

[0052] The release of dexamethasone is increased with the addition of ciprofloxacin, as shown by the data in Figure 2A. The actual drug release is almost doubled when compared to the DDS without a modifier. In addition to the benefits of increased drug delivery, there are therapeutic benefits introduced with the antibiotic activity of ciprofloxacin. The release of ciprofloxacin from the same DDS is shown in Figure 2B. The release rate is higher than that of dexamethasone. However, the overall release of ciprofloxacin is slower when co-formulated with dexamethasone than it is without dexamethasone, as shown in Figure 2C.

Example 3

Manufacture and Testing of ADDS with Multiple Release Modifiers

[0053] A drug delivery system was formulated with hydroxymethylcellulose, ciprofloxacin and dexamethasone, according to the Table 3.

Table 3

Lot #	PLGA	HPMC	Ciprofloxacin	Dexamethasone
XT035	3.4	0.4	2.4	3.8

[0054] The data show that after an initial higher release in the first day, an almost zero-order release thereafter can be observed. The overall release characteristic would be therapeutically acceptable from a therapeutic efficiency aspect.

Example 4

Manufacture and Testing of a Drug Delivery System (DDS) with a Gucoconicoid and Ganciclovir for Treatment of CMV Infection

[0055] A drug delivery system is manufactured as described in Example 1, except that ganciclovir, a pharmaceutically active, hydrophilic compound, is included as a release modifier. The combinations of drugs and polymer are as follows:

PLGA	Anti-Viral	Anti-Inflammatory
50%	-	50% dexamethasone
20 %	40% ganciclovir	40 % dexamethasone
40%	20% ganciclovir	40% dexamethasone
40 %	30% ganciclovir	30 % dexamethasone
50%	-	50% ganciclovir

[0056] The release of dexamethasone is increased with the addition of ganciclovir. In addition to the benefits of increased drug delivery, there are therapeutic benefits introduced with the antiviral activity of ganciclovir.

Example 5Manufacture and Testing of a Drug Delivery System (DDS) with a Glucocorticoid and 5-Fluorouracil for Antitumor Treatment

[0057] A drug delivery system is manufactured as described in Example 1, except that 5-fluorouracil, a pharmaceutically active, hydrophilic compound, is included as a release modifier. The combinations of drugs and polymer are as follows:

PLGA	Anti-tumor	Anti-Inflammatory
50%	-	50% dexamethasone
20 %	40 % 5-fluorouracil	40 % dexamethasone
40%	20% 5-fluorouracil	40% dexamethasone
40 %	30 % 5-fluorouracil	30 % dexamethasone
50% (not according to the invention)	-	50% 5-fluorouracil

[0058] The release of dexamethasone is increased with the addition of 5-fluorouracil. In addition to the benefits of increased drug delivery, there are therapeutic benefits introduced with the antitumor activity of 5-fluorouracil.

Example 6Manufacture and Testing of a Drug Delivery System (DDS) with an NSAID and Quinolone (not according to the invention)

[0059] A drug delivery system is manufactured as described in Example 1, except that 5-fluorouracil, a pharmaceutically active, hydrophilic compound, is included as a release modifier. The combinations of drugs and polymer are as follows:

PLGA	Quinolone	Anti-Inflammatory
50%	-	50% naproxen
20%	40% ciprofloxacin	40% naproxen
40%	20% ciprofloxacin	40% naproxen
40%	30% ciprofloxacin	30% naproxen
50%	50% ciprofloxacin	-

[0060] The release of ciprofloxacin is decreased with the addition of naproxen. In addition to the benefits of increased drug delivery, there are therapeutic benefits introduced with the combined formulation.

[0061] It is evident from the above results that biodegradable implants formulated with an active agent and release modulator provide for release kinetics where the drug is released at a constant rate over long periods of time, avoiding the need of a patient to administer drugs in much less effective ways, such as topically. The implants provide an improved method of treating ocular and other conditions, by avoiding peaks and troughs of drug release.

Claims

1. An implant for use in a method of treatment of ocular conditions by insertion of said implant into the vitreous chamber of the eye, said implant being suitable for sustained drug release and comprising:

poly-lactate glycolic acid copolymer at a concentration of at least 20 weight percent of the implant,
dexamethasone at a concentration of from 10 to 50 weight percent of the implant, and
a release modulator at a concentration of from 10 to 50 weight percent of the implant, wherein the release modulator is an accelerator in the form of a hydrophilic agent having a solubility of at least 100 µg/ml in water at ambient temperature, and
wherein dexamethasone is released within a therapeutic dosage that does not vary by more than about 100%

for a period of at least 3 days.

2. The implant of claim 1, which has a diameter of 1 to 3 mm.

5 3. The implant of claim 1, wherein the implant has a geometry selected from the group consisting of fibres, sheets, films, microspheres, spheres, circular discs, and plaques.

Patentansprüche

10 1. Implantat zur Verwendung in einem Verfahren zur Behandlung von Augenerkrankungen durch Einführen des Implantats in den Glaskörper des Auges, wobei das Implantat für eine verzögerte Arzneimittelfreisetzung geeignet ist, und umfassend:

15 ein Poly-Lactatglykolsäure-Copolymer mit einer Konzentration von mindestens 20 Gewichtsprozent des Implantats, Dexamethason mit einer Konzentration von 10 bis 50 Gewichtsprozent des Implantats und einen Freisetzungs-Modulator mit einer Konzentration von 10 bis 50 Gewichtsprozent des Implantats, wobei der Freisetzungs-Modulator ein Beschleuniger in Form eines hydrophilen Mittels ist, das eine Löslichkeit von
20 mindestens 100µg/ml in Wasser bei Umgebungstemperatur aufweist und wobei Dexamethason innerhalb einer therapeutischen Dosis freigesetzt wird, die nicht um mehr als etwa 100% für eine Dauer von mindestens 3 Tagen variiert.

25 2. Implantat nach Anspruch 1, das einen Durchmesser von 1 bis 3 mm aufweist.

3. Implantat nach Anspruch 1, wobei das Implantat eine Geometrie aufweist, ausgewählt aus der Gruppe bestehend aus Fasern, Folien, Filmen, Mikrosphären, Sphären, runden Scheiben und Platten.

Revendications

1. Implant destiné à être utilisé dans une méthode de traitement d'affections oculaires par insertion dudit implant dans la chambre vitrée de l'oeil, ledit implant étant apte à la libération prolongée de médicament et comprenant :

35 un copolymère poly-lactate-acide glycolique à une concentration d'au moins 20 pour cent en poids de l'implant, de la dexaméthasone à une concentration de 10 à 50 pour cent en poids de l'implant, et un modulateur de libération à une concentration de 10 à 50 pour cent en poids de l'implant, où le modulateur de libération est un accélérateur sous forme d'un agent hydrophile ayant une solubilité d'au moins 100 pg/ml dans l'eau à température ambiante, et
40 dans lequel la dexaméthasone est libérée suivant un régime thérapeutique qui ne varie pas de plus d'environ 100 % pendant une période de temps d'au moins 3 jours.

2. Implant suivant la revendication 1, qui a un diamètre de 1 à 3 mm.

45 3. Implant suivant la revendication 1, ledit implant ayant une géométrie choisie dans le groupe consistant en des fibres, des feuilles, des films, des microsphères, des sphères, des disques circulaires et des plaques.

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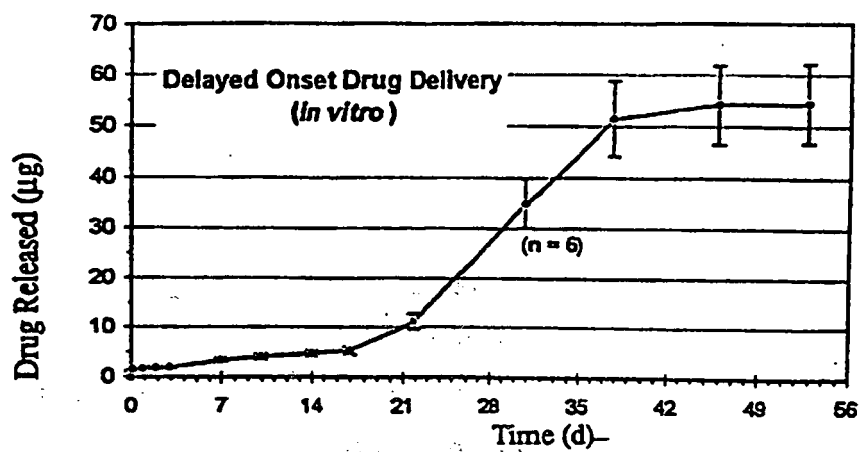


FIGURE 1A

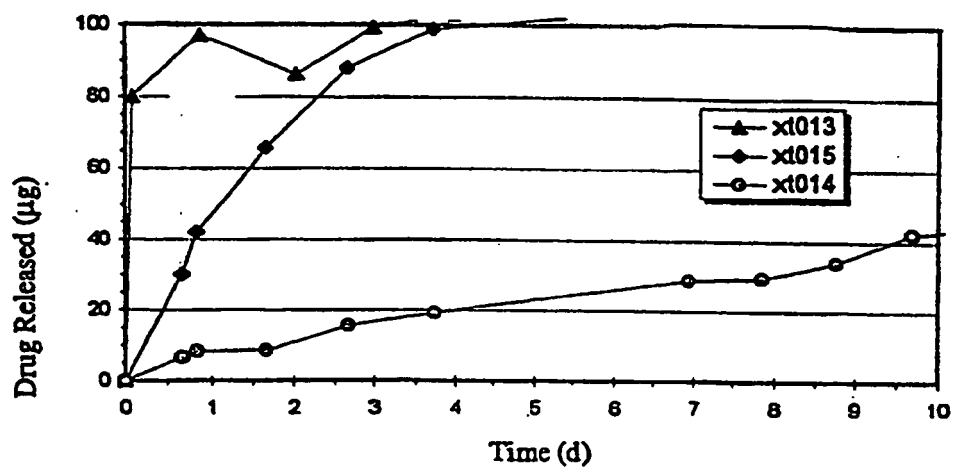


FIGURE 1B

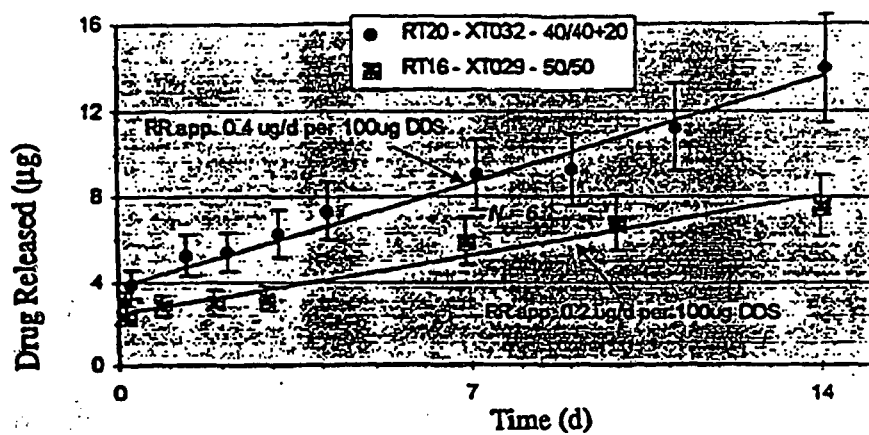


FIGURE 2A

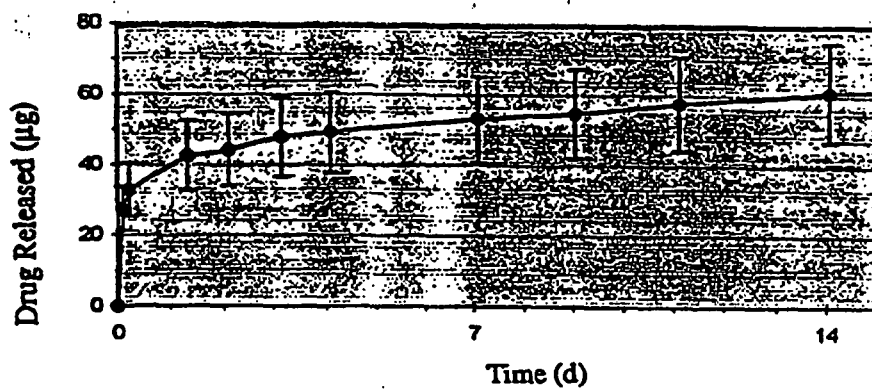


FIGURE 2B

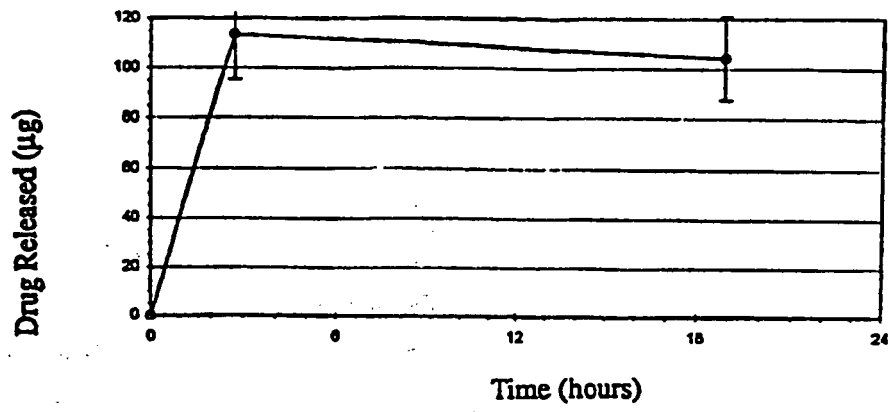


FIGURE 2C

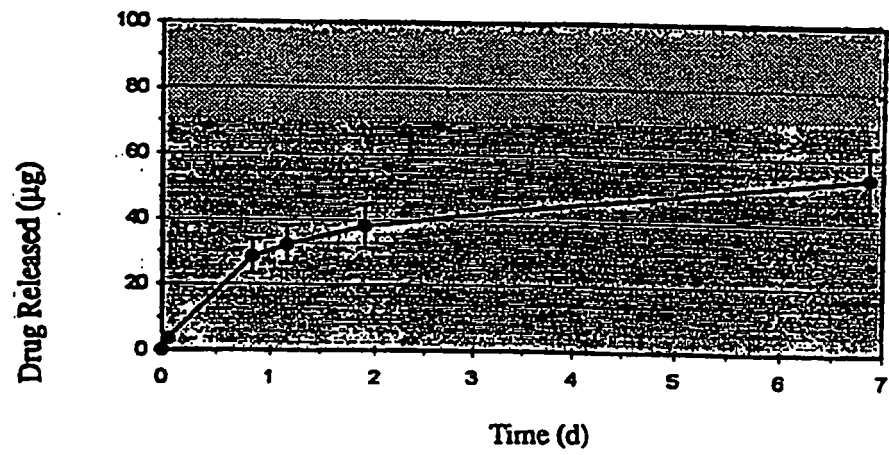


FIGURE 2D

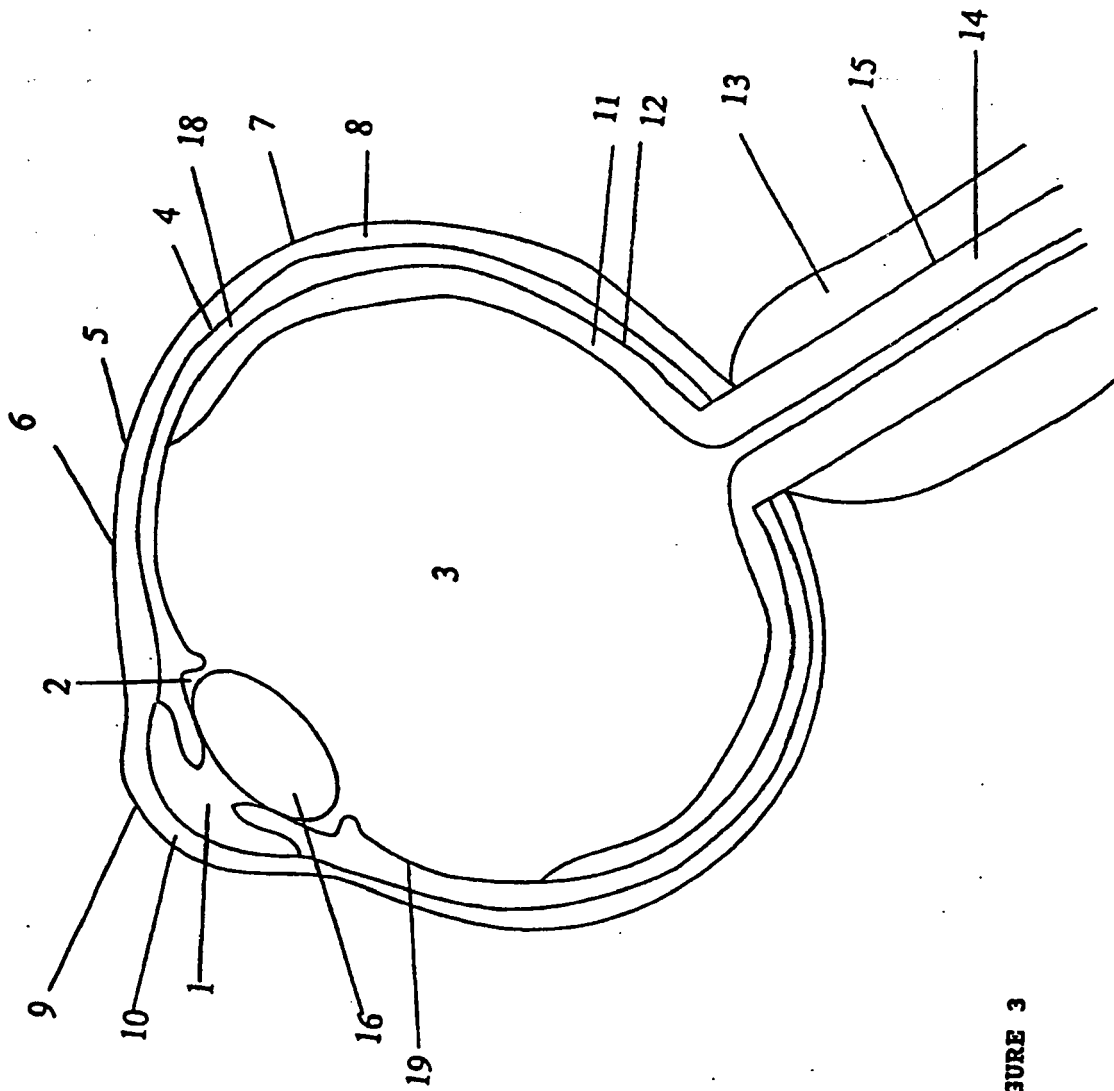


FIGURE 3

REFERENCES CITED IN THE DESCRIPTION

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