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(54) Titre : MICROSPHERES BIOERODABLES OU BIODEGRADABLES A LIBERATION PROLONGEE OU MICROPARTICULES EN SUSPENSION DANS UNE FORMULATION D'UN MEDICAMENT INJECTABLE A FORMATION DE DEPOT DE SOLIDIFICATION
(54) Title: TIME RELEASED BIODEGRADABLE OR BIOERODIBLE MICROSPHERES OR MICROPARTICLES SUSPENDED IN A SOLIDIFYING DEPOT-FORMING INJECTABLE DRUG FORMULATION

(57) Abrégé/Abstract:
A composite drug delivery material may be injected into an eye of a human being or mammal to provide sustained delivery of the drug. A composite drug delivery material may include a plurality of microparticles dispersed in a media composition. The microparticles may contain a drug and a coating comprising a bioerodible material or a biodegradable material, and the media composition includes the drug dispersed in a depot-forming material. The media composition may gel or solidify upon injection into the eye.
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TIME RELEASED BIODEGRADABLE OR BIOERODIBLE MICROSPHERES OR
MICROPARTICLES SUSPENDED IN A SOLIDIFYING DEPOT-FORMING
INJECTABLE DRUG FORMULATION

Inventors David A. Marsh and Hongwen M. Rivers

CROSS-REFERENCE

[00001] This application claims the benefit of U.S. Provisional Patent Application
Serial Number 61/589,681, filed on January 23, 2012, the entire disclosure of which is
incorporated herein by this specific reference.

BACKGROUND

[00002] There is a continuing need for methods of improved sustained delivery of
drugs to human beings and animals.

SUMMARY

[00003] An injectable liquid depot forming material may be used to implant a solid
sustained drug delivery device in a human being or animal without the need for making
an incision in the body. This may be useful for sensitive areas such as an eye, where
incision may be risky. Since the material may be in a liquid form, the size of the device
may not be limited by the diameter of a needle. For example, a solid implant may only
be injected if it has a cross-sectional area that allows it to pass through a needle. Thus,
a smaller needle size may be used for injectable liquid depot forming materials. It may
also provide more flexible dosing than a solid implant, since the amount of depot
material administered may be easily varied.

[00004] Some embodiments include a composite drug delivery material comprising:
a plurality of microparticles dispersed in a media composition. Microparticles may
comprise: a drug; and a coating comprising a bioerodible material or a biodegradable
material. A media composition may comprise a drug dispersed in a depot-forming
material. A media composition may be in a liquid form before administration and may
be configured to substantially increase in viscosity during or after being injected into a
body of a mammal, so that the form of the media after injection is a solid or a gel.

[00005] Methods of treating ocular diseases or injuries comprising injecting a
composite drug delivery material described herein into an eye of a mammal in need
thereof are also described.
DETAILED DESCRIPTION

[00006] Generally, composite drug delivery materials described herein comprise a plurality of microparticles dispersed in a media composition. In a given composite drug delivery material, a drug may be present in both microparticles and a media composition, or may be present in only the microparticles. A media composition may comprise a depot-forming material and a drug dispersed in the depot-forming material. A microparticle may comprise a drug, and may optionally include other materials such as a biodegradable polymer or a bioerodible polymer, and may comprise a bioerodible or a biodegradable coating. Thus, a composite drug delivery material may be an in vivo, in-situ drug delivery system. Microparticles may be comprised of drug alone or coated drug particles or coated drug-polymer particles or microspheres, wherein the coating comprises a bioerodible or biodegradable material.

[00007] Before administration, the media may be a liquid, such as a low viscosity liquid. Low viscosity may allow the media to be injected. When a media is injected into a body of a mammal, the media may substantially increase in viscosity so that the form of the media in a body is a solid or a gel. A substantial increase in viscosity includes any increase in viscosity that would substantially increase the difficulty of injecting a liquid through a needle, such as an increase of about at least about 1000 cP, at least about 10,000 cP, at least about 100,000 cP, at least about 500,000 cP, or at least about 1,000,000 cP. A solid includes a material that has a definite shape. A gel includes a material that has a definite shape under normal conditions, but which may flow upon the application of an external force greater than gravitational force.

[00008] A media composition includes any composition comprising a depot-forming material. A depot-forming material includes a material that may be in a liquid form before administration and may substantially increase in viscosity so as to form a solid or a gel during or after being injected into a body of a mammal. Examples of depot forming materials include, but are not limited to, REGEL®, sucrose acetate isobutyrate complex, poly-lactide-co-glycolide (PLGA) in an organic solution, polylactide (PLA) in an organic solution, etc.

[00009] Some depot-forming materials may comprise PLGA or PLA dissolved in an organic solvent, such as a water-soluble organic solvent. When the media composition is injected, the solvent disperses, leaving a PLGA or PLA depot immersed in an aqueous environment of physiological fluid. Since PLGA or PLA is insoluble in aqueous media, it may quickly precipitate to form a solid on contact with physiological fluid.
Examples of suitable organic solvents for a PLGA or PLA media composition may include, but are not limited, N-methyl-2-pyrrolidone, propylene glycol, dimethyl sulfoxide, tetrahydrofuran, triacetin, ethyl benzoate, benzyl benzoate, etc. In some embodiments, the organic solvent may comprise N-methyl-2-pyrrolidone, benzyl benzoate, or a combination thereof. A PLGA/N-methyl-2-pyrrolidone depot-forming material is available from Atrix Lab under the tradename ELIGARD®. A PLGA/benzyl benzoate depot forming material is available from Alza under the tradename ALZAMER®.

[00010] Some depot-forming materials may comprise sucrose acetate isobutyrate dissolved in a water miscible organic solvent such as, ethanol, benzy alcohol, etc. The solution has a low viscosity which may improve ease of administration with a small gauge needle. When injected, the sucrose acetate isobutyrate may increase in viscosity to form a gel or a solid. A sucrose acetate isobutyrate depot forming material is available from Durect under the tradename SABER®.

[00011] Some depot-forming materials may comprise a thermosensitive biodegradable triblock copolymer comprising hydrophobic PLGA blocks (A) and hydrophilic polyethylene glycol (PEG) blocks (B) with an ABA or BAB block configuration. REGEL®, developed by MacroMed, is an ABA triblock copolymer which is soluble in water. An aqueous solution of REGEL® is a free flowing liquid at 15°C, and transforms into a gel at body temperature when injected. The drug release rate may be adjusted by varying the hydrophilic/hydrophobic content, polymer concentration, molecular weight, and/or polydispersity of the triblock copolymer.

[00012] Some depot-forming materials may comprise Poloxamer 407, a triblock copolymer comprising a central hydrophobic block of polypropylene glycol that is flanked by two PEG blocks. It is a water-soluble nonionic surfactant that forms an aqueous solution with reverse-thermal gelation properties. A solution with more than 20% of the polymer exhibits a low viscosity at low temperatures, but rapidly forms a rigid semi-solid gel network at body temperature.

[00013] Some depot-forming materials may comprise GELSITE®, available from DelSite Biotech. Inc.). GELSITE® is a natural acidic polysaccharide extracted and purified from an aloe plant. The polymer, in aqueous solution, forms a gel in the presence of calcium when injected, thus entrapping a drug and providing sustained release.
[00014] A plurality of microparticles are dispersed in the media composition. The term "dispersed" includes mixing the microparticles in the media composition so that a substantial fraction of the microparticles, such as at least about 50%, at least about 80%, at least about 90%, or at least about 99%, have contact with, or are surrounded by, a media composition. Individual microparticles or clusters of microparticles may be dispersed in a media composition. Microparticles may be dispersed in an approximately homogeneous manner, or may be dispersed heterogeneously.

[00015] A microparticle includes a drug, including any compound or substance recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and any compound or substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and any substance other than food or water intended to affect the structure or any function of the body of man or other animals.

[00016] Some examples of drugs may include, but are not limited to: ace-inhibitors, endogenous cytokines, agents that influence basement membrane, agents that influence the growth of endothelial cells, adrenergic agonists or blockers, cholinergic agonists or blockers, aldose reductase inhibitors, analgesics, anesthetics, antiallergics, anti-inflammatory agents, antihypertensives, pressors, antibacterials, antivirals, antifungals, antiprotozoals, anti-infectives, antitumor agents, antimetabolites, antiangiogenic agents, tyrosine kinase inhibitors, antibiotics such as aminoglycosides such as gentamycin, kanamycin, neomycin, and vancomycin; amphenicols such as chloramphenicol; cephalosporins, such as cefazolin HCl; penicillins such as ampicillin, penicillin, carbenicillin, oxycillin, methicillin; lincosamides such as lincomycin; polypeptide antibiotics such as polymixin and bacitracin; tetracyclines such as tetracycline; quinolones such as ciproflaxin, etc.; sulfonamides such as chloramine T; and sulfonaxes such as sulfanilic acid as the hydrophilic entity, anti-viral drugs, e.g. acyclovir, gancyclovir, vidarabine, azidothymidine, dideoxyinosine, dideoxycytosine, dexamethasone, ciproflaxin, water soluble antibiotics, such as acyclovir, gancyclovir, vidarabine, azidothymidine, dideoxyinosine, dideoxycytosine; epinephrine; isofurphate; adriamycin; bleomycin; mitomycin; ara-C; actinomycin D; scopolamine; and the like, analgesics, such as codeine, morphine, ketorolac, naproxen, etc., an anesthetic, e.g. lidocaine; adrenergic agents such as α-adrenergic blockers, β-adrenergic blockers, α-adrenergic agonists such as alpha-2 adrenergic receptor agonists, β-adrenergic
agonists, e.g. ephedrine, epinephrine, timolol, brimonidine, etc.; aldose reductase inhibitor, e.g. epalrestat, ponalrestat, sorbinil, tolrestat; antiallergic, e.g. cromolyn, beclomethasone, dexamethasone, and flunisolide; colchicine, anihelminthic agents, e.g. ivermectin and suramin sodium; antiamebic agents, e.g. chloroquine and chlortetracycline; and antifungal agents, e.g. amphotericin, etc., anti-angiogenesis compounds such as anecortave acetate, retinoids such as Tazarotene, anti-glaucoma agents, such as brimonidine (ALPHAGAN® and ALPHAGAN P®), acetozolamide, bimatoprost (LUMIGAN®), Timolol, mebufenolol; memantine;; 2ME2; anti-neoplastics, such as vinblastine, vincristine, interferons; α, β and γ, antimitabolites, such as folic acid analogs, purine analogs, and pyrimidine analogs; immunosuppressants such as azathioprine, cyclosporine and mizoribine; miotic agents, such as carbachol, mydriatic agents such as atropine, etc., ranibizumab, bevacizumab, protease inhibitors such as aprotinin, camostat, gabexate, vasodilators such as bradykinin, etc., and various growth factors, such epidermal growth factor, basic fibroblast growth factor, nerve growth factors, and the like. In some embodiments the drug is timolol, brimonidine, bimatoprost, ketorolac, dexamethasone, memantine, prednisolone acetate, triamcinolone acetonide, ranibizumab, or bevacizumab. Reference to a drug includes a pharmaceutically acceptable salt or a prodrug of the drug.

[00017] In some embodiments, two or more different drugs may be used in a formulation. The drugs may be mixed together in any of the microspheres or may be mixed together in the media composition, or may be separated. For example, one set of microspheres may contain one drug and a different set of microspheres may contain a second drug. In some embodiments, a formulation comprising a first set of microspheres comprising ranibizumab or bevacizumab and a second set of microspheres comprising a different drug may be used to treat macular degeneration or diabetic retinopathy.

[00018] After the media material increases in viscosity to form a solid or a gel, microparticles and drug not part of a microparticle ("media drug") may be encapsulated in the solid or gel so that contact between physiological fluid and media drug may be limited. Over time, aqueous physiological fluid may slowly permeate the media material and release the media drug. Eventually, physiological fluid may also begin penetrating the microparticles so that drug may begin to be released from the microparticles. Media drug composition may be released up to 1 month, up to 2 months, up to 3 months, or possibly longer, after injection.
A liquid media composition, such as a low viscosity liquid media composition, may allow a drug to be delivered through a very small needle, such as about 25 gauge or about 30 gauge. Use of a small needle may reduce the risk of needle-induced serious adverse effects. Use of a small needle may be especially beneficial for injection of a formulation comprising a drug into the vitreous humor of an eye. For injection into a back of an eye area such as a vitreous humor, a smaller needle reduces the likelihood of needle-induced serious adverse effects, such as endophthalmitis, retinal separation, vitreal separation, severe pain, etc.

Injecting a low viscosity liquid media composition that solidifies or gels in vivo provides significant safety advantages over other methods of implanting solid devices. For example, injecting a sustained release liquid to solid formulation may avoid surgical implantation of a solid device of a similar size into an eye. A narrow gauge needle may minimize trauma to an eye as compared to surgical implantation, and thus may minimize loss of vitreal fluid, may decrease the probability of retinal and vitreal separation, and may greatly reduce the risk of infection such as endophthalmitis.

A solidifying or gelling media may trap microparticles and drug particles as the formulation enters the vitreous. Liquid formulations comprising microparticles or drug particles that do not undergo a phase change may “plume” and/or settle on the posterior retina, which may cause temporary blindness. Furthermore, formulations that plume may settle on the lens, where they may cause vitreous opacities or speckling. Small particles may also be endocytosed within a cell, where they are rapidly degraded and “dumped,” thereby initiating a local inflammatory response.

Penetration of microparticles may begin after a substantial amount of drug has been released from the media. If the thickness of microparticle coatings varies within a plurality of microparticles, particles with thinner coatings may begin releasing drug before particles with thicker coatings. Thus, a range of coating thickness may help to control drug release over time. A plurality of microspheres may have a variety of coating materials, such that different coating materials allow different release properties. Thus, a variety of coating materials may help to control drug release over time.

Microparticles include any particles having a size around the micron or μm range, or smaller, such as about 0.01 μm to about 1000 μm, about 1 μm to about 300 μm, about 10 μm to about 100 μm. Microparticles may be of any shape, such as
approximately spherical (e.g. microspheres), spheroid, ellipsoid, cylindrical, rod-shaped, etc.

[00024] Since microparticles are very small, they may be delivered through a very small needle, such as about 25 gauge or about 30 gauge. Use of a small needle may reduce the risk of needle-induced serious adverse effects, as explained above.

[00025] A microparticle comprises a drug, as described above, and a coating. The coating comprises a bioerodible material or a biodegradable material.

[00026] A bioerodible material includes any material that erodes in vivo. Bioerodible materials do not necessarily chemically degrade in vivo, but may disperse or dissolve in vivo in a manner that can release a therapeutically effective amount of a drug for a period that is significantly greater than the normal in vivo life of the drug. Examples of bioerodible materials include, but are not limited to, polyvinylpyrrolidine (PVP), carboxymethylcellulose (CMC), polyvinyl chloride (PVC), hydroxypropylmethylcellulose (HPMC), polyorthoester, and the like.

[00027] A biodegradable material includes a material which chemically degrades in vivo in a manner that it can release a therapeutically effective amount of drug for a period that is significantly greater than the normal in vivo life of the drug. A biodegradable material may be a single polymer or copolymer, or any combination or blend of polymers. Examples of biodegradable polymer materials may include, but are not limited to, polymers made of monomers such as esters, ethers, anhydrides, amides, orthoesters, which when degraded result in physiologically acceptable degradation products. Polymer materials may be crosslinked or non-crosslinked. If crosslinked, they may be lightly crosslinked, such as less than 5% or 1% crosslinked.

[00028] Some biodegradable polymer materials may include polymers of hydroxyaliphatic carboxylic acids, either homo- or copolymers, and polysaccharides. Included among polyesters of interest are homo- or copolymers of D-lactic acid, L-lactic acid, racemic lactic acid, glycolic acid, caprolactone, and combinations thereof. For some copolymers of glycolic and lactic acid, biodegradation may be affected by the ratio of glycolic to lactic acid.

[00029] In some embodiments, biodegradable polymer material may comprise PLA, PLGA, a polyanhydride, a polyorthoesters (POE), etc., or a combination thereof. In some embodiments, polylactide may be about 2% to about 100 %, about 2% to about 20%, about 20% to about 30%, about 30% to about 40%, about 40% to about 50%, about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about
80% to about 90%, or about 90% to about 100% of the weight of the polymer material. In some embodiments, poly(lactide-co-glycolide) may be about 2% to about 100%, about 2% to about 20%, about 20% to about 30%, about 30% to about 40%, about 40% to about 50%, about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or about 90% to about 100% of the weight of the polymer material.

**[00030]** Polylactide, polylactic acid, or PLA, includes poly (D,L-lactide), and may also be identified by CAS Number 26680-10-4 and may be represented by a formula:

![Chemical structure of polylactide](image)

**[00031]** Poly(lactic-co-glycolic)acid, poly(lactide-co-glycolide), or PLGA, includes (D,L-lactide-co-glycolide), also identified by CAS Number 26780-50-7, and may be represented by a formula:

![Chemical structure of poly(lactic-co-glycolic)acid](image)

**[00032]** Thus, PLGA comprises one or more blocks of D,L-lactide repeat units and one or more blocks of glycolide repeat units, where the size and number of the respective blocks may vary.

**[00033]** The molar percent of each monomer in poly(lactic-co-glycolic)acid (PLGA) copolymer may be 0-100%, about 15-85%, about 25-75%, or about 35-65%. In some embodiments, the D,L-lactide may be about 50% to about 75%, about 48% to about 52%, or about 50%; or about 73% to about 77%, or about 75% of the PLGA polymer on a molar basis. The balance of the polymer may essentially be glycolide repeat units.
For example, glycolide may be about 25% to about 50%, about 23% to about 27%, or about 25%; or about 48% to about 52%, or about 50% of the PLGA polymer on a molar basis. Other groups, such as terminal or capping groups may be present in small amounts. In some embodiments, PLGA copolymers are used in conjunction with polylactide polymers.

[00034] In some embodiments, a coating may comprise PLA, PLGA, PVP, CMC, PVC, HPMC, polyorthoester, a PEG, or the like.

[00035] In some embodiments, a plurality of microspheres have 3 different coatings, a first group having a PLGA coating, a second group having a PLA coating, and a third group having a POE coating.

[00036] The thickness of a coating may vary. In some embodiments, a coating may have a thickness of about 1 µm to about 5 µm, about 1 µm, about 2 µm, about 3 µm, about 4 µm, about 5 µm, or any thickness in a range bounded by, or between, any of these values.

[00037] In some embodiments, a plurality of microparticles may have several different coating thicknesses. For example, microparticles may have 2, 3, 4, 5, or more different coating thicknesses, and or types of coating materials. In some embodiments, the microparticles may have:

   a) 2 coating thicknesses such as: about 1 µm and about 2 µm, 1 µm and 3 µm, 1 µm and 4 µm, 1 µm and 5 µm, 2 µm and 3 µm, 2 µm and 4 µm, 2 µm and 5 µm, 3 µm and 4 µm, 3 µm and 5 µm, 4 µm and 5 µm, etc.;
   b) 3 coating thicknesses such as 1 µm, 2 µm, and 3 µm; 1 µm, 2 µm, and 4 µm; 1 µm, 3 µm, and 4 µm; 2 µm, 3 µm, and 4 µm; 1 µm, 2 µm, and 5 µm; 1 µm, 3 µm, and 5 µm; 2 µm, 3 µm, and 5 µm; 1 µm, 4 µm, and 5 µm; 2 µm, 4 µm, and 5 µm; 3 µm, 4 µm, and 5 µm; 1 µm, 2 µm, 3 µm, 4 µm, and 5 µm; etc.
   c) 4 coating thicknesses such as 2 µm, 3 µm, 4 µm, and 5 µm; 1 µm, 3 µm, 4 µm, and 5 µm; 1 µm, 2 µm, 4 µm, and 5 µm; 1 µm, 2 µm, 3 µm, and 5 µm; 1 µm, 2 µm, 3 µm, and 4 µm; etc.; or
   d) 5 coating thicknesses such as 1 µm, 2 µm, 3 µm, 4 µm, and 5 µm; etc.

[00038] In some embodiments, a plurality of microspheres may comprise a first microsphere type comprising a PLA coating with a thickness of about 1 µm; a second microsphere type comprising a PLA coating with a thickness of about 2 µm; a third microsphere type comprising a PLA coating with a thickness of about 3 µm; a fourth
microsphere type comprising a PLA coating with a thickness of about 4 µm; and a fifth
microsphere type comprising a PLA coating with a thickness of about 5 µm.

[00039] Some examples of about 1 µm may include, but are not limited to, 0.5 µm,
0.6 µm, 0.7 µm, 0.8 µm, 0.9 µm, 1.0 µm, 1.1 µm, 1.2 µm, 1.3 µm, 1.4 µm, etc.

[00040] Some examples of about 2 µm may include, but are not limited to, 1.5 µm,
1.6 µm, 1.7 µm, 1.8 µm, 1.9 µm, 2.0 µm, 2.1 µm, 2.2 µm, 2.3 µm, 2.4 µm, etc.

[00041] Some examples of about 3 µm may include, but are not limited to, 2.5 µm,
2.6 µm, 2.8 µm, 2.9 µm, 3.0 µm, 3.1 µm, 3.2 µm, 3.3 µm, 3.4 µm, etc.

[00042] Some examples of about 4 µm may include, but are not limited to, 3.5 µm,
3.6 µm, 3.7 µm, 3.8 µm, 3.9 µm, 4.0 µm, 4.1 µm, 4.2 µm, 4.3 µm, 4.4 µm, etc.

[00043] Some examples of about 5 µm may include, but are not limited to, 4.5 µm,
4.6 µm, 4.7 µm, 4.8 µm, 4.9 µm, 5.0 µm, 5.1 µm, 5.2 µm, 5.3 µm, 5.4 µm, etc.

[00044] In addition to a being coated with a bioerodible material or biodegradable
material, a microparticle may include a bioerodible material or a biodegradable material
inside the coating with the drug, and may thus further extend the delivery of a drug. If
the interior of a microparticle comprises a bioerodible material or a biodegradable
material, the amount may vary. In some embodiments, bioerodible material or
biodegradable material may be about 10% to about 90%, about 10% to about 30%,
about 30% to about 70%, about 30% to about 40%, about 40% to about 50%, about
50% to about 60%, about 70% to about 90%, or about 50% to about 85% of a
microparticle by weight.

[00045] The amount of drug in a microparticle may vary. In some embodiments,
drug may be about 10% to about 90%, about 10% to about 30%, about 30% to about
70%, about 30% to about 40%, about 40% to about 50%, about 50% to about 60%, or
about 70% to about 90% of a microparticle by weight.

[00046] In some embodiments, microparticles may comprise PLGA, PLA, or a
combination thereof loaded with therapeutically effective agent and a biodegradable or
bioerodible coating.

[00047] In some embodiments, a composite drug delivery material may deliver an
effective amount of the drug at the site of injection for a longer period of time than: a
composition comprising the media material and the same amount of the drug without
any microparticles and/or a plurality of microparticles comprising the same amount of
the drug without any media material.
In some embodiments, a composite drug delivery material may provide sustained release of a drug over a period of about 1 month to about 3 years, about 2 month to about 2 years, about 3 months to about 12 months, at least about 2 months, about 3 months, about 6 months, about 12 months, or more. This sustained release may reduce the risk of needle-induced serious adverse events because it may reduce the frequency of injections. Reducing the frequency of injections into an eye may reduce the risk of needle-induced serious adverse events, and may be preferred by patients. Thus, a drug delivery system that allows injections to be at least about 3 months apart, about 6 months apart, about 9 months apart, about 12 months apart, or longer, may be desirable.

In some embodiments, pseudo-zero order delivery of a drug may be obtainable over an extended period of time by varying (1) coating thickness of drug-loaded microparticles, (2) the total number of different thicknesses of coatings on drug-loaded microparticles (3), the number of microparticles within each coating group, and/or (4) the biodegradable or bioerodible polymer used to prepare the microparticle.

A composite drug delivery material may be used to treat any ocular disease or injury, including but not limited to, the following:

MACULOPATHIES/RETINAL DEGENERATION: Non-Exudative Age Related Macular Degeneration (ARMD), Exudative Age Related Macular Degeneration (ARMD), Choroidal Neovascularization, Diabetic Retinopathy, Acute Macular Neuroretinopathy, Central Serous Chorioretinopathy, Cystoid Macular Edema, Diabetic Macular Edema.


VASOCLAR DISEASES/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 Angiitis, Sickle
Cell Retinopathy and other Hemoglobinopathies, Angioid Streaks, Familial Exudative Vitreoretinopathy, Eales Disease.

[00054] TRAUMATIC/SURGICAL: Sympathetic Ophthalmia, Uveitic Retinal Disease, Retinal Detachment, Trauma, Laser, PDT, Photocoagulation, Hypoperfusion During Surgery, Radiation Retinopathy, Bone Marrow Transplant Retinopathy.


[00058] RETINAL TEARS/HOLES: Retinal Detachment, Macular Hole, Giant Retinal Tear.

[00059] TUMORS: Retinal Disease Associated with Tumors, Solid Tumors, Tumor Metastasis, Benign Tumors, for example, hemangiomas, neurofibromas, trachomas, and pyogenic granulomas, 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.


Example 1
A batch of drug-loaded microspheres is separated into 3 portions. The first portion is coated with PLGA. The second portion is coated with PLA having a second thickness. The third portion is coated with a polyorthoester [POE] having a third thickness. The POE is a poly(orthoester) polymer made by condensation polymerization of 3,9-diethylidene-2,4,8,10-tetraoxaspiro[5.5]undecane (DETOSU), cyclohexanediethanol (CDM), triethylene glycol (TEG) and 1,10-decanediol (DD). Triethylene glycol glycolide (TEG-GL) is added as a latent acid catalyst to initiate hydrolysis of the POE backbone. The POE polymer molecular weight is about 30,000 to about 35,000 Daltons. Coated microspheres from the three groups are mixed with a solidifying depot-forming media containing the same drug. Once the suspension is injected into the vitreous through a narrow gauge needle, it solidifies nearly instantly, trapping the microspheres. As the depot slowly erodes, the drug from the depot is released first. This is followed by release from the microspheres in the first group, the second group, and the third group, respectively.

Example 2

PLGA microspheres loaded with Compound 1 with PLA coatings of 1, 2, 3, 4, and 5 μm thickness respectively, are suspended in a formulation of Compound 1 in ReGel and adjusted for viscosity, pH, and ionic strength. The suspension of microspheres is then lyophilized for stability purposes and stored (the microspheres may also be lyophilized in the presence of “free” drug, so as to provide a bolus dose, if desirable, upon reconstitution and injection). After reconstitution, the formulation, maintained at 5°C, is injected through a 30 gauge needle into an animal vitreous and the formulation instantly gels at the temperature of the vitreous, ca 37°C, trapping the microspheres.

Once in the vitreous, the ReGel begins to release Compound 1. As the ReGel bioerodes, additional drug is released and the coated microspheres begin to be exposed to the aqueous environment within the vitreous. As the microspheres are exposed to the aqueous environment at 37°C, the coatings begin to bioerode.

The microspheres within the 1 μm coating have its drug-containing PLGA matrix exposed first and begin to release Compound 1. Meanwhile, microspheres with intact coating do not yet release the drug. As time continues, the coating on the microspheres within the 2 μm coating erode and begin to expose its drug-containing PLGA matrix, and drug begins to be released. Around the same time, the drug in the ReGel and the microspheres in the 1 μm coating begins to be depleted.
Sometime later, the 3 \( \mu \text{m} \) coating on a third group of microspheres is bio-removed and this group begins releasing Compound 1, as the drug release from the earlier releasing microspheres (e.g. those with 1 \( \mu \text{m} \) and 2 \( \mu \text{m} \) coatings) is depleted. This is followed, sometime later, by the erosion of the 4 \( \mu \text{m} \) and 5 \( \mu \text{m} \) coatings from the heaviest-coated microspheres, and subsequently, further drug is released.

Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about.” Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

The terms “a,” “an,” “the” and similar referents used in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of any claim. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

Groupings of alternative elements or embodiments disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

Certain embodiments are described herein, including the best mode known to the inventors for carrying out the invention. Of course, variations on these described
embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than specifically described herein. Accordingly, the claims include all modifications and equivalents of the subject matter recited in the claims as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is contemplated unless otherwise indicated herein or otherwise clearly contradicted by context.

[00070] In closing, it is to be understood that the embodiments disclosed herein are illustrative of the principles of the claims. Other modifications that may be employed are within the scope of the claims. Thus, by way of example, but not of limitation, alternative embodiments may be utilized in accordance with the teachings herein. Accordingly, the claims are not limited to embodiments precisely as shown and described.
CLAIMS

What is claimed is:

1. A composite drug delivery material comprising:
   a plurality of microparticles dispersed in a media composition;
   wherein the microparticles comprise:
   a drug; and
   a coating comprising a bioerodible material or a biodegradable
   material; and
   wherein the media composition comprises the drug dispersed in a depot-
   forming material;
   and wherein the media composition is in a liquid form before
administration and is configured to substantially increase in viscosity during or
after being injected into a body of a mammal, so that the form of the media after
injection is a solid or a gel.

2. A method of treating an ocular disease or injury comprising injecting a composite
drug delivery material according to claim 1 into an eye of a mammal in need thereof.

3. The method of claim 1 or 2, wherein a single injection of the composite drug
material provides a therapeutically effective amount of the drug for about 3 months to
about 12 months.

4. The method of any one of claims 2-3, wherein the ocular disease is macular
degeneration or diabetic retinopathy.

5. The composite drug delivery material or method of any one of the preceding
claims, wherein the composite drug delivery material is configured to deliver an
effective amount of the drug at the site of injection for a longer period of time than a
composition comprising the media material and the same amount of the drug without
any microparticles.

6. The composite drug delivery material or method of any one of the preceding
claims, wherein the composite drug delivery material is configured to deliver an
effective amount of the drug at the site of injection for a longer period of time than the
plurality of microparticles comprising the same amount of the drug without any media
material.

7. The composite drug delivery material or method of any one of the preceding
claims, wherein the drug is timolol, brimonidine, bimatoprost, ketorolac,
dexamethasone, memantine, prednisolone acetate, triamcinolone acetonide, ranibizumab, or bevacizumab.
8. The composite drug delivery material or method of any one of the preceding claims, wherein the drug is ranibizumab.
9. The composite drug delivery material or method of any one of the preceding claims, wherein the coating comprises polylactide, poly-lactide-co-glycolide, polyvinylpyrrolidone, carboxymethylcellulose, PVC, hydroxymethylpropylcellulose, polyorthoester, or a polyethylene glycol.
10. The composite drug delivery material or method of any one of the preceding claims, wherein the coating comprises polylactide.
11. The composite drug delivery material or method of any one of the preceding claims, wherein the coating has a thickness of about 1 μm to about 5 μm.
12. The composite drug delivery material or method of any one of the preceding claims, wherein the plurality of microparticles comprises:
   a first microsphere type comprising a polymer coating having a thickness of about 1 μm;
   a second microsphere type comprising a polymer coating having a thickness of about 2 μm;
   a third microsphere type comprising a polymer coating having a thickness of about 3 μm;
   a fourth microsphere type comprising a polymer coating having a thickness of about 4 μm; and
   a fifth microsphere type comprising a polymer coating having a thickness of about 5 μm.
13. The composite drug delivery material or method of any one of the preceding claims, wherein the microspheres further comprise poly-lactide-co-glycolide, polylactide, or a combination thereof loaded with drug.
14. The composite drug delivery material or method of any one of the preceding claims, wherein the depot-forming material comprises: a biodegradable copolymer comprising poly-lactide-co-glycolide blocks and polyethylene glycol blocks, a sucrose acetate isobutyrate complex, a poly-lactide-co-glycolide in an organic solution, or a polylactide in an organic solution.
15. The composite drug delivery material or method of any one of the preceding claims, wherein the polymer is a polylactide polymer.