The present invention provides systems and methods for ocularly delivering a triamcinolone acetonide agent to a subject. In one aspect, for example, a method is provided for treating or preventing an ocular condition in a subject for which triamcinolone acetonide is effective. Such a method may include ocularly administering a triamcinolone acetonide agent to the subject in order to treat or prevent the condition. Although any administration technique is contemplated, in some aspects a triamcinolone acetonide agent may be delivered to eye tissue via ocular iontophoresis.
OCULAR DELIVERY OF TRIAMCINOLONE ACETONIDE PHOSPHATE AND RELATED COMPOUNDS

PRIORITY DATA

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 11/238,144, filed on Sep. 27, 2005, which claims the benefit of U.S. Provisional Patent Application Ser. No. 60/623,150, filed on Oct. 27, 2004, both of which are incorporated herein by reference. This application is also a continuation-in-part of U.S. patent application Ser. No. 11/238,104, filed on Sep. 27, 2005, which claims the benefit of U.S. Provisional Patent Application Ser. No. 60/623,150, filed on Oct. 27, 2004, both of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to systems, methods, and devices for the minimally invasive or noninvasive delivery of an active agent. Accordingly, the present invention involves the fields of chemistry, pharmaceutical sciences, and medicine, particularly ophthalmology.

BACKGROUND OF THE INVENTION

[0003] Posterior and intermediate eye diseases that require ocular drug delivery to prevent blindness include uveitis, bacterial, and fungal endophthalmitis, age-related macular degeneration, viral retinitis, and diabetic retinopathy, among others. For example, the reported incidence of posterior uveitis is more than 100,000 people in the United States. If left untreated, uveitis leads to blindness. It is responsible for about 10 percent of all visual impairment in the U.S. and is the third leading cause of blindness worldwide.

[0004] Treatments of intermediate and posterior uveitis are complicated by the inaccessibility of the posterior eye to topically applied medications. Current therapy for intermediate and posterior uveitis requires repeated periocular injections and/or high-dose systemic therapy with corticosteroids. Injections are usually preferred to systemic drug administration because the blood/retinal barrier impedes the passage of most drugs from the systemically circulating blood to the interior of the eye. Therefore large systemic doses are needed to treat intermediate and posterior uveitis, which often result in systemic toxicities including immuno-suppression, adrenal suppression, ulcerogenesis, fluid and electrolyte imbalances, fat redistribution and psychological disorders.

[0005] Endophthalmitis affects approximately 10,000 people in the United States each year. Endophthalmitis is typically caused by gram-positive bacteria after ocular surgery or trauma, but it can also be fungal or viral in nature. The current method of treating endophthalmitis is direct injection of antimicrobials into the vitreous. Intravitreal injections are necessary because periocular injections and systemic administration do not deliver efficacious amounts of antibiotics to the target sites in the eye. Age-related macular degeneration (AMD) is the leading cause of irreversible loss of central vision in patients over the age of 50. AMD affects more than 15 million people worldwide.

[0006] Treatments of posterior eye diseases require intravitreal and periocular injections or systemic drug administration. Systemic administration is usually not preferred because of the resulting systemic toxicity as discussed above. While intravitreal and periocular injections are preferable to systemic administration, the half-life of most injected compounds in the vitreous is relatively short, usually on the scale of just a few hours. Therefore, intravitreal injections require frequent administration. The repeated injections can cause pain, discomfort, intraocular pressure increases, intraocular bleeding, increased chances for infection, and the possibility of retinal detachment. The potential complication of periocular injections is accidental perforation of the globe, which causes pain, retinal detachment, ocular hypertension, and intraocular hemorrhage. Other possible complications of periocular injections include pain, central retinal artery/vein occlusion, and intraocular pressure increases. Therefore, these methods of ocular drug delivery into the posterior of the eye have significant limitations and major drawbacks. In addition, injections are very poorly accepted by patients. These methods also involve high healthcare cost due to the involvement of skilled and experienced physicians to perform the injections.

[0007] As such, devices, systems, and methods which are capable of minimally invasively, or non-invasively delivering drugs, particularly to the interior of the eye, continue to be sought.

SUMMARY OF THE INVENTION

[0008] Accordingly, the present invention provides systems and methods of noninvasively delivering a triamcinolone acetone agent to a subject. In one aspect, for example, a method is provided for treating or preventing an ocular condition in a subject for which triamcinolone acetone is effective. Such a method may include administering a triamcinolone acetone agent to an eye of the subject in order to treat or prevent the condition. Although any triamcinolone acetone agent would be considered to be within the scope of the present claims, in one aspect nonlimiting examples may include triamcinolone acetone, triamcinolone acetone phosphate, and combinations thereof. In one specific aspect the triamcinolone acetone agent may include triamcinolone acetone phosphate. In another specific aspect, the triamcinolone acetone agent may include triamcinolone acetone. In some aspects it may be beneficial to co-administer triamcinolone acetone with a solubilizing agent.

[0009] A variety of administration techniques are contemplated to administer the triamcinolone acetone agent to an eye of the subject. In one aspect, for example, administering the triamcinolone acetone agent may occur by iontophoretic administration. In another aspect, the administration of the triamcinolone acetone agent may occur by passive diffusion.

[0010] Additionally, numerous conditions may be prevented or treated by ocularly delivering a triamcinolone acetone agent to a subject. In one aspect, for example, the condition may include macular edema, age related macular degeneration, anterior, intermediate, and posterior uveitis, HSV retinitis, diabetic retinopathy, bacterial, fungal, or viral endophthalmitis, eye cancers, glioblastomas, glaucoma, glaucomatous degradation of the optic nerve, and combinations thereof.

[0011] It may further be beneficial to co-administer a vasoconstricting agent with the triamcinolone acetone...
agent. Nonlimiting examples of vasoconstricting agents may include naphazoline, tetrahydrozoline, phenylephrine, ephedrine, norepinephrine, dopamine, dobutamine, colterol, ethyl-norepinephrine, isoproterenol, isethaniline, metaproterenol, terbutaline, metaraminol, phenylephrine, tyramine, hydroxyamphetamine, ritodrine, prenalol, methoxamine, oxymethazoline, albuterol, amphetamine, methamphetamine, benzphetamine, ephedrine, phenylpropanolamine, methadone, phentermine, fenfluramine, propylhexedrine, diethylpropion, phenmetrazine, phendimetrazine, and combinations thereof. In one specific aspect, the vasoconstricting agent may include oxymethazoline.

[0012] The present invention also provides a system for treating or preventing an ocular condition in a subject for which a triamcinolone acetonide is effective. Such a system may include an ocular device having a drug reservoir and a triamcinolone acetonide agent disposed within the drug reservoir. Although the ocular device may include any type of device, in one aspect the ocular device may be an iontophoretic ocular device. Additionally, in one aspect the ocular device may further include an enhancer reservoir configured to contain an enhancing agent. In one specific aspect the enhancer reservoir may contain a vasoconstricting agent.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG. 1 is a front view of an iontophoretic ocular device in accordance with an aspect of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0014] Before the present systems and methods for ocular drug delivery are disclosed and described, it is to be understood that this invention is not limited to the particular process steps and materials disclosed herein, but is extended to equivalents thereof, as would be recognized by those ordinarily skilled in the relevant arts. It should also be understood that terminology employed herein is used for the purpose of describing particular embodiments only and is not intended to be limiting.

[0015] It must be noted that, as used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural forms unless the context clearly dictates otherwise. Thus, for example, reference to “a polymer” includes reference to one or more of such polymers, and “an excipient” includes reference to one or more of such excipients.

DEFINITIONS

[0016] In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set forth below.

[0017] As used herein, “formulation” and “composition” may be used interchangeably herein, and refer to a combination of two or more elements, or substances. In some embodiments a composition may include an active agent, an excipient, or a carrier to enhance delivery or depot formation.

[0018] As used herein, “active agent,” “bioactive agent,” “pharmaceutically active agent,” and “pharmaceutical,” may be used interchangeably to refer to an agent or substance that has measurable specified or selected physiologic activity when administered to a subject in a significant or effective amount. It is to be understood that the term “drug” is expressly encompassed by the present definition as many drugs and prodrugs are known to have specific physiologic activities. These terms of art are well-known in the pharmaceutical, and medicinal arts. Examples of drugs useful in the present invention include without limitation, steroids, antibacterials, antivirals, antifungals, antiparasitics, anti-metabolites, immunosuppressive agents, angiopatic inhibitors, ICAM inhibitors, antibodies, protein kinase C inhibitors, chemotherapeutic agents, neuroprotective agents, nucleic acid derivatives, aptamers, proteins, enzymes, peptides, and polypeptides.
be combinatory therapies or adjunctive therapies for the prevention and treatment of a disease.

[0024] As used herein, “carrier” or “inert carrier” refers to a substance with which a drug may be combined to achieve a specific dosage formulation for delivery to a subject. In the some aspects of the present invention, the carriers used may or may not enhance drug delivery. As a general principle, carriers must not react with the drug in a manner which substantially degrades or otherwise adversely affects the drug, except that carriers may react with a drug to prevent it from exerting a therapeutic effect until the drug is released from the carrier. Further, the carrier, or at least a portion thereof must be suitable for administration into a subject along with the drug. Additionally, the carrier may be used to increase the solubility of the drug, and thus act as a solubilizer. Nonlimiting examples may include charged or polar micelles, cyclodextrins, etc.

[0025] As used herein, “eye” and “ocular” refer to the peripheral visual organ of a subject.

[0026] As used herein, “sclera” refers to the sclera tissue in the eye or the conjunctiva between the limbus and the fornix on the surface of the eye, which is the white part of the eye. “Sclera” is also used in referring to other eye tissues.

[0027] As used herein, “subject” refers to a mammal that may benefit from the administration of a composition or method as recited herein. Most often, the subject will be a human but can be of other animals such as dogs and cats.

[0028] As used herein, “administration,” and “administering” refer to the manner in which an active agent, or composition containing such, is presented to a subject. As discussed herein, the present invention may include numerous administration techniques, including iontophoretic delivery, injections, topical application, etc.

[0029] As used herein, “noninvasive” refers to a form of administration that does not rupture or puncture a biological membrane or structure with a mechanical means across which a drug or compound of interest is being delivered. A number of noninvasive delivery mechanisms are well recognized in the transdermal arts such as patches, and topical formulations. Many of such formulations may employ a chemical penetration enhancer in order to facilitate noninvasive delivery of the active agent. Additionally, other systems or devices that utilize a non-chemical mechanism for enhancing drug penetration, such as iontophoretic devices are also known.

[0030] As used herein, “depot” refers to a temporary mass inside a biological tissue or system, which includes a drug that is released from the mass over a period of time. In some aspects, a depot may be formed by the interaction of an active agent with a depot forming agent, such as a complexing ion which will form an active agent complex that is less soluble than the active agent by itself, and thus precipitate in vivo.

[0031] As used herein, the term “body surface” refers to an outer tissue surface of the subject such as tissue surfaces encountered in ocular and transdermal delivery, or mucosal tissues lining a body cavity such as the mouth for buccal delivery or vaginal tract for vaginal delivery. The term “skin” refers to an outer tissue surface of the subject. It is therefore intended that skin also refer to mucosal and epithelial tissues, as well as the outer surfaces of the eye.

[0032] As used herein, the term “electrode assembly” refers to an assembly of at least one electrode and at least one reservoir.

[0033] As used herein, the term “reservoir” refers to a body or a mass that may contain a depot forming agent, an active agent, or an enhancing agent. As such, a reservoir may include any structure that may contain a liquid, as well as solid structures made up of the agent to be delivered. In some cases, an electrode may be considered to be a reservoir.

[0034] As used herein, the term “reacting” refers to any force, change in environmental conditions, presence or encounter of other chemical agent, etc. that alters the active agent. For example, “reacting” between the active agent and the depot forming agent can be physical or chemical interactions.

[0035] As used herein, the term “precipitate” refers to anything less than fully solubilized. As such, a precipitate can include not only crystals, but also gels, semi-solids, increased molecular weight, etc.

[0036] As used herein, the term “substantially” refers to the complete or nearly complete extent or degree of an action, characteristic, property, state, structure, item, or result. For example, an object that is “substantially” enclosed would mean that the object is either completely enclosed or nearly completely enclosed. The exact allowable degree of deviation from absolute completeness may in some cases depend on the specific context. However, generally speaking the nearness of completion will be so as to have the same overall result as if absolute and total completion were obtained. The use of “substantially” is equally applicable when used in a negative connotation to refer to the complete or near complete lack of an action, characteristic, property, state, structure, item, or result. For example, a composition that is “substantially free of” particles would either completely lack particles, or so nearly completely lack particles that the effect would be the same as if it completely lacked particles. In other words, a composition that is “substantially free of” an ingredient or element may still actually contain such item as long as there is no measurable effect thereof.

[0037] As used herein, the term “about” is used to provide flexibility to a numerical range endpoint by providing that a given value may be “a little above” or “a little below” the endpoint.

[0038] As used herein, a plurality of items, structural elements, compositional elements, and/or materials may be presented in a common list for convenience. However, these lists should be construed as though each member of the list is individually identified as a separate and unique member. Thus, no individual member of such list should be construed as a de facto equivalent of any other member of the same list solely based on their presentation in a common group without indications to the contrary.

[0039] Concentrations, amounts, and other numerical data may be expressed or presented herein in a range format. It is to be understood that such a range format is used merely for convenience and brevity and thus should be interpreted flexibly to include not only the numerical values explicitly
recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. As an illustration, a numerical range of "about 1 to about 5" should be interpreted to include not only the explicitly recited values of about 1 to about 5, but also include individual values and sub-ranges within the indicated range. Thus, included in this numerical range are individual values such as 2, 3, and 4 and sub-ranges such as from 1-3, from 2-4, and from 3-5, etc., as well as 1, 2, 3, 4, and 5, individually. This same principle applies to ranges reciting only one numerical value as a minimum or a maximum. Furthermore, such an interpretation should apply regardless of the breadth of the range or the characteristics being described.

The Invention

[0040] The present invention provides methods, systems, devices, and formulations for administering triamcinolone acetonide agents to an eye of a subject for the treatment or prevention of various ocular conditions. The inventors have found that an effective method of delivering triamcinolone acetonide agents to a subject is through ocular administration techniques. Iontophoretic ocular administration may also be particularly effective for the delivery of charged triamcinolone acetonide agents, such as triamcinolone acetonide phosphate.

[0041] In one detailed aspect, for example, a method for treating or preventing an ocular condition in a subject for which triamcinolone acetonide is effective is provided. Such a method may include administering a triamcinolone acetonide agent to an eye the subject in order to treat or prevent the condition. Various triamcinolone acetonide agents are contemplated for ocular administration, including without limitation, triamcinolone acetonide, triamcinolone acetonide phosphate, and combinations thereof. In one specific aspect the triamcinolone acetonide agent may include triamcinolone acetonide phosphate. In another specific aspect, the triamcinolone acetonide agent may include triamcinolone acetonide. Furthermore, in some aspects utilizing triamcinolone acetonide, it may be necessary to solubilize the triamcinolone acetonide in a solubilizing agent to increase the effectiveness of ocular administration. It is considered that one of ordinary skill in the art would understand methods and agents for solubilizing triamcinolone acetonide once in possession of the present specification, and as such, solubilizers will not be discussed in detail.

[0042] Although any condition may be treated for which triamcinolone acetonide agents are effective, nonlimiting examples may include conditions such as inflammation, edema, neovascularization, angiogenesis, neoplastic conditions, fibroplastic conditions, immunosuppressive conditions, infections, metabolic and/or constitutional irregularities of tissue, etc. Though numerous conditions would benefit from the methods and devices of the present invention, they are particularly well suited for the treatment of ocular diseases because of the relatively high permeability of the eye tissues and the large aqueous compartments in the eye. Additionally, triamcinolone acetonide agents may be delivered as direct, combinatory, and adjuvantic therapies. Specific ocular conditions for which triamcinolone acetonide agents are effective may include, without limitation, macular edema, age related macular degeneration, anterior, intermediate, and posterior uveitis, HSV retinitis, diabetic retinopathy, bacterial, fungal, or viral endophthalmitis, eye cancers, glioblastomas, glaucoma, glaucomatous degradation of the optic nerve, and combinations thereof.

[0043] A number of specific iontophoretic devices and configurations may be suitably used to deliver a triamcinolone acetonide agent into the subject's tissue, all of which are suitable for use in the present invention. Ocular iontophoresis techniques are well suited for the delivery of triamcinolone acetonide agents to a subject, particularly for the treatment of eye diseases and other eye conditions. Prior methods for treating ocular conditions such as inflammation included systemically administering drugs such as a triamcinolone acetonide to a subject. Such systemic administration has proven difficult for a number of reasons, including side effects from the large doses of drug required to treat the eye due to the blood/retinal barrier that impedes the passage of most systemically circulating drugs into the interior of the eye. High doses of systemically administered drugs often increase the incidence of many side effects. It should be noted that, although ocular iontophoretic techniques are discussed and exemplified herein, iontophoresis of a triamcinolone acetonide agent to any tissue of the subject would be considered to be within the scope of the present invention.

[0044] Specific examples of useful iontophoretic techniques include, without limitation, alternating current (AC), direct current (DC), AC with superimposed DC offset, electroporation, etc. In practice, two iontophoretic electrodes are used in order to complete an electrical circuit. In traditional transscleral iontophoresis, for example, at least one of the electrodes is considered to be an active iontophoretic electrode, while the other may be considered as a return, inactive, or indifferent electrode. In such cases, the active electrode is typically placed on an eye surface and the compound of interest is transported at the active electrode across the tissue as a permeant when a current is applied to the electrodes through the tissue. Compound transport may occur as a result of a direct electrical field effect (e.g., electrophoresis), an indirect electrical field effect (e.g., electroosmosis), electrically induced pore or transport pathway formation (electroporation), or a combination of any of the foregoing. Examples of currently known iontophoretic devices and methods for ocular drug delivery may be found in U.S. Pat. Nos. 6,319,240; 6,539,251; 6,579,276; 6,607,668, and PCT Publication Nos. WO 03/03989 and WO 03/043689, each of which is incorporated herein by reference. It may also be beneficial for the application sritis to be sealed with a sealant following delivery of the triamcinolone acetonide agent. This procedure may protect the tissue in which iontophoretic administration occurred. Sealants may include any known to one of ordinary skill in the art, including gels, glues and impermeable polymers or resinous membranes.

[0045] For optimal iontophoretic delivery of the triamcinolone acetonide agent into the eye, the methods and systems of the present invention can further include placing a permselective material in ion-conducting relation to the eye surface. An electric current of AC, DC, or AC with superimposed DC can be used to drive the agent through the permselective material to the eye. The permselective material hinders iontophoretic transport of a competing ion and
increases the transference efficiency of the agent during iontophoresis. As a result, the agent and carriers are delivered iontophotorectally into the eye more efficiently than without the permselective material. For example, more efficient iontophotorectic transport can be achieved by placing the permselective material against the current driving electrode (e.g., Ag/AgCl) between the electrode and the reservoir chamber to prevent the products of electrochemical reactions generated at the electrode surface (e.g., Ag or Cl ions) from moving into the reservoir. Another example is to place the permselective material between the body surface and the reservoir to prevent the migration of the active agent and endogenous ions into depot forming agent reservoir or vice versa the depot forming agent and endogenous ions into the active agent reservoir during iontophoresis.

[0046] Any permselective material capable of hindering iontophotorectic transport of a competing ion during iontophotorectic transport of the triamcinolone acetoneide agent may be used in conjunction with the invention. The permselective material may be provided in any of a number of forms, such as those described in Applicant’s copending U.S. patent application Ser. No. 10/371,148, entitled “Methods and Systems For Controlling and/or Increasing Iontophoretic Flux”, which is incorporated herein by reference. By way of example, and without limitation, the permselective material may be provided in a liquid, partially liquid, gelled, partially solid, or fully solid state. In some instances, the permselective material may be supported by a support structure such as an additional membrane having sufficient porosity and chemical inertness so as to avoid interfering with the performance of the permselective material, yet having sufficient mechanical integrity for ease in handling. The material can also be provided in the form of a membrane having a surface size and/or shaped for direct contact with the eye or other tissue, or it may be shaped for direct contact with the current driving electrode (e.g., Ag/AgCl). In other instances, the permselective material may be comprised of a polyelectrolyte, which can be a single molecule or an aggregate of molecules having ions or ionizable groups.

[0047] The triamcinolone acetoneide agent may be iontophotorectically administered into the subject’s eye at nearly any location on the eye in accordance with the present invention. However, in one aspect, the triamcinolone acetoneide agent may be delivered to the top of the eye. In another aspect, delivery may be made to the bottom of the eye. In yet another aspect, delivery may be made at, or near the back of the eye. In an additional aspect, delivery may be made to the side of the eye. In a further aspect, delivery may be made simultaneously to different locations of the eye, for example opposite sides of the eye using separate non-invasive delivery devices or separate reservoirs on the same device. It is preferable to deliver the triamcinolone acetoneide agent to a location or locations in the eye that will provide sufficient amount of the drugs to their sites of action for the prevention or treatment of an eye disease or other eye conditions. For example, to deliver the triamcinolone acetoneide agent to the anterior and posterior chambers of the eye, the preferred site of iontophoresis application is near the limbus. For the delivery of the triamcinolone acetoneide agent to the back of the eye, the preferred site to deliver the carriers will be in the sclera or in the vitreous. In the sclera, the agent will be carried to the back of the eye by the blood vasculature system in the eye. In the vitreous, the agent will diffuse to the back of the eye passively.

[0048] In addition to effective delivery, in some cases iontophoresic administration of triamcinolone acetoneide agents may allow the in vivo generation of a sustained release depot. For example, triamcinolone acetoneide phosphate may react with endogenous depot forming agents within the subject’s tissue to form a sustained release depot. Such a depot may be created inside the tissue or in an organ of the subject, from which the triamcinolone acetoneide agent is released on a sustained basis. One example of an organ where such an administration method may be beneficial is the eye. It should be noted, however, that it is intended that the scope of the present claims cover all tissues where aspects of the present invention may be effectively carried out.

[0049] Endogenous depot forming agents will, of course, not come into contact with the active agent until administration occurs. Thus an in-vivo reaction between the triamcinolone acetoneide agent and the endogenous depot forming agent will cause the triamcinolone acetoneide agent or a derivative thereof to form a depot. In one aspect such a depot forming mechanism may be a change in the solubility of the triamcinolone acetoneide agent, thus causing precipitation and subsequent depot formation. This depot of triamcinolone acetoneide agent complex is then able to deliver the therapeutic compound to the subject over time.

[0050] As a sustained release mechanism, it will be recognized that the depot formulation of the present invention generally has an in-vivo solubility that is lower than that of the triamcinolone acetoneide agent by itself. In this way, as the triamcinolone acetoneide agent dissolves out of the depot over time, a sustained therapeutic effect may be obtained. Further, since the triamcinolone acetoneide agent in the depot may be unable to have a therapeutic effect until released therefrom, the solubility properties of the depot limit potential toxicity or overdose concerns that would normally arise when delivering a sufficient amount of drug to last over a prolonged period.

[0051] This method is particularly suited for iontophoresic transport of a triamcinolone acetoneide agent and sustaining its level in the eye by means of sustained release of the agent in the eye for the treatment of anterior, intermediate, and posterior eye disease. In addition to iontophoresis, the triamcinolone acetoneide agent may be delivered by any means known to one of ordinary skill in the art, including sonophoresis, electroporation, passive diffusion, etc. As an example of passive diffusion, a triamcinolone acetoneide agent such as triamcinolone acetoneide phosphate could be applied to a scleral or corneal lens and allowed to diffuse passively into the eye. Such passive diffusion may be further facilitated by the coadministration of permeation enhancers, vasoconstrictors, etc.

[0052] As has been described, the triamcinolone acetoneide agent used may be a prodrug, or in prodrug form. Prodrugs for nearly any desired active agent will be readily recognized by those of ordinary skill in the art. Additionally, prodrugs with high electromobility which metabolize into drugs with a low aqueous solubility may be advantageously used as both the drug and the depot forming agent. In this case, the prodrug may be iontophotorectically delivered and then precipitate into a depot in-vivo upon the metabolism (e.g. enzymatic cleavage) of the prodrug into the drug.

[0053] In yet another aspect, an electrically mobile prodrug of a low solubility drug, as is the case with triamci-
nolone acetonide and triamcinolone acetonide phosphate, can be used to create a sustained release system in the eye. Because the triamcinolone acetonide phosphate prodrug has high electronegativity, it is effectively delivered into the eye. The prodrug then converts into the lower solubility triamcinolone acetonide in the eye and the lower solubility drug precipitates in the eye. The drug in solid state in the eye will be slowly released into the eye and provide an ocular sustained release condition.

[0054] As has been discussed, in one aspect an endogenous depot forming agent may facilitate the creation of a depot upon administration of the triamcinolone acetonide agent. Examples of such agents may include without limitation, various enzymes, ascorbate, lactate, citrate, various amino acids, calcium, magnesium, zinc, iron, chlorite, fluoride, as well as ions found in the tissues and vitreous of the eye. In such cases, the presence of such a substance inside the body may be relied upon in order to form the depot and once the triamcinolone acetonide agent has been delivered. Alternatively, such substances may be delivered to the body if they are not thought to be present in sufficient concentration to form a depot.

[0055] As has also been described, triamcinolone acetonide is generated from the metabolism and hydrolysis of triamcinolone acetonide phosphate. Due to the low aqueous solubility of triamcinolone acetonide, the precipitation of triamcinolone acetonide in the tissue provides a sustained release system after the delivery of triamcinolone acetonide phosphate. However, triamcinolone acetonide phosphate may be cleared quickly from the delivery site and may not provide long enough residence in the tissue for the metabolism and hydrolysis of triamcinolone acetonide phosphate. In one aspect, therefore, triamcinolone acetonide phosphate can first be precipitated by a counterion in the tissue, which has higher aqueous solubility than that of triamcinolone acetonide. The triamcinolone acetonide phosphate-counterion complex has low enough solubility to provide tissue residence for triamcinolone acetonide phosphate-to-triamcinolone acetonide conversion. When triamcinolone acetonide phosphate is released from the precipitate depot, triamcinolone acetonide phosphate is converted to triamcinolone acetonide. The solubility of triamcinolone acetonide is low and will precipitate in the tissue to provide further sustained release capability. In another aspect, the precipitating process can result in ion-drug complexes in the form of a gel or aggregation. The gel or aggregation allows enzyme degradation and conversion to occur before gel clearance. Gel formation has been observed when dexamethasone phosphate (a prodrug of dexamethasone) or triamcinolone acetonide phosphate was mixed with calcium ions. Various non-endogenous depot forming agents and techniques for forming such depots may be found in U.S. patent application Ser. Nos. 11/238,144 and 11/238,104, both filed on Sep. 27, 2005, and both of which are incorporated herein by reference.

[0056] In some cases, the treatment of a condition may be hampered by the in-vivo movement of the triamcinolone acetonide agent in the tissue. It is therefore contemplated that various means for restricting or slowing such movement may improve the effectiveness of treatment. In one aspect, the in-vivo movement may be restricted by constriction of the blood vessels exiting an area in which localized treatment is desired, such as in the eye. Such constriction may be induced by the administration of a vasoconstricting agent. A vasoconstrictor may be administered actively by iontophoretic or other means, or it may be delivered passively. Specific non-limiting examples of vasoconstricting agents may include α-agonists such as naphazoline, and tetrahydrozoline, sympathomimetics such as phenylephrine, epinephrine, norepinephrine, dopamine, dobutamine, col,trol, ethylnorepinephrine, isoproterenol, isethorinan, metaproterenol, terbutaline, metenaminol, phenylephrine, tyramine, hydroxyamphetamine, nitroprone, prazosin, methoxamine, oxymethazoline, albuterol, amphetamine, metamphetamine, benzphetamine, cephedrine, phenylpropanolamine, methemeterine, phentermine, fenfluramine, propylhexedrine, diethylpropion, phenmetrazine, phenidemetrizine, and combinations thereof. In one specific aspect the vasoconstricting agent may be oxymethazoline. Vasoconstricting agents can be administered either before or concurrently with the administration of the triamcinolone acetonide agent. Though administration of the vasoconstrictor may occur following administration of the triamcinolone acetonide agent, the results may be less effective than prior or concurrent administration. Additionally, in some aspects, the vasoconstricting agent may have the same polarity as the triamcinolone acetonide agent and may be administered concurrently.

[0057] Additionally, a wide variety of additional drugs may be co-administered to the eye of a subject with the triamcinolone acetonide agent. Of course, selection of a specific additional drug and the specific form of that drug will depend on a variety of considerations, such as the specific condition to be treated or prevented, the specific carrier to be used, the duration of the desired treatment, and any overriding health considerations of the subject, such as allergies to certain medications. However, as a general matter, a number of specific additional drugs are known as useful in treating one or more of the conditions recited herein, including without limitation, steroids, steroid derivatives such as aminosteroids, antibacterials, antis, anti-fungals, antiproteo, antinotolactols, antinertolactols, VEGF inhibitors, ICAM inhibitors, antibodies, protein kinase C inhibitors, chemotherapeutic agents, neuroprotective agents, nucleic acid derivatives, aptamers, proteins, enzymes, peptides, poly peptides. More specific examples include without limitation dexamethasone phosphate, squalamine, anjikacin, oligonucleotides, Fl, peptides, PEG-oligonucleotides, salicylate, tropicanide, methotrexate, 5-fluorouracil, and diclofenac. Finally, various other compounds may be co-administered with the triamcinolone acetonide agent, including various permeation enhancers that are well known in the art.

[0058] The present invention also encompasses systems and devices for administering triamcinolone acetonide agents into the tissue of a subject. In one aspect, for example, a system for treating or preventing a condition in a subject for which triamcinolone acetonide is effective is provided. Such a system may include an iontophoretic device having a drug reservoir, and a triamcinolone agent disposed within the drug reservoir. In one specific aspect, such a system may be configured for ocular iontophoretic delivery of a triamcinolone acetonide agent. As is shown in FIG. 1, for example, such a system may include an ocular iontophoretic device 10 including at least one drug reservoir 12 and a triamcinolone acetonide agent contained within the drug reservoir. The ocular iontophoretic device 10 further
includes an active electrode 14 to provide an electrical current to the drug reservoir 12 configured to thus iontophoretically drive the triamcinolone acetonide agent into the eye. The active electrode 14 is electrically coupled to a power supply 16 with an electrical lead 18. The power supply may also function to regulate the electrical current delivered to the active electrode. Additionally, the system may further include a return electrode 20 to complete an electrical circuit. The return electrode 20 may complete the electrical circuit by contacting any surface of the subject’s body, including the surface of an eye, an eyelid, a portion of the face or ear, or any other bodily surface that would allow the completion of such a circuit.

Various device configurations are contemplated that allow the iontophoretic administration of a triamcinolone acetonide agent through the tissue of a subject in order to treat or prevent various conditions. For example, devices may be constructed wherein the active electrode and the return electrode are in an integrated single unit. In one aspect, the active electrode and the return electrode may be configured adjacent one another within the integrated single unit. Alternatively, devices may be constructed as a collection of separate electrode assemblies that function as a single unit. Additionally, the shape of the device may be configured to conform to the tissue surface through which the triamcinolone acetonide agent will be delivered. In ocular aspects, therefore, the device may be configured to conform to an eye surface. In such a configuration, the active electrode and/or the reservoir may be in contact with various tissue structures in the eye, such as the conjunctiva. In one aspect, a portion of the device may cover the cornea and the reservoir may be in contact with the conjunctiva. The portion covering the cornea provides a better fit of the device onto the eye. In another aspect, the device may extend into the cul-de-sac under the eyelids for the same purpose. The portion of the device in the cul-de-sac can also hold the active electrode in contact with the conjunctiva for administering the triamcinolone acetonide agent.

Depending on the configuration of the device, the active electrode and the return electrode may require electrical isolation from one another at the body surface in order to direct the electrical current through the tissue rather than between the electrodes at the interface with the body surface. In one aspect, such electrical isolation can be accomplished by applying a temporary sealant between the electrodes at the body surface. In addition to directing electrical current through the tissue, such a sealant may also advantageously function to temporarily affix and hold the electrodes and/or the device in place on the body surface. Sealants may be any useful insulative material known to one skilled in the art, for example, and without limitation, gels, waxes, adhesives, impermeable polymeric or resinous materials, etc.

The reservoir according to aspects of the present invention is designed to hold a triamcinolone acetonide agent prior to administration through the body surface of a subject. Various iontophoretic reservoir materials are known to those skilled in the art, and all are considered to be within the scope of the present invention.

A dose controller may be used to control the supply of electrical current applied across the electrodes. Such a controller may be programmed to provide different dosing intervals for the triamcinolone acetonide agent and any other co-administered compound. Co-administration may occur concurrently, or in an alternating fashion. The dose controller allows the switching back and forth of the electric current across multiple active electrodes to control the delivery of the triamcinolone acetonide agent and any co-administered compound. In some aspects such as system may also be utilized to reduce the duration of the electric current passage to thus minimize possible adverse effects due to the application of the electric current. Different electric current protocols can be carried out utilizing these electrodes to provide effective administration and co-administration of triamcinolone acetonide agents and other compounds.

The active electrodes of the present invention are designed to deliver electrical current across the reservoir to iontophoretically deliver the agent located therein. The electrodes can be of any material or manufacture known to one skilled in the art. Various examples include metal electrodes, conductive glass electrodes, etc. A single electrode may be coupled to a single reservoir or to multiple reservoirs depending on the particular configuration of a given electrode assembly.

**EXAMPLE**

The following example is intended to be merely illustrative of the various aspects of the invention disclosed herein and is not intended in any way to limit the scope of the claimed invention. Other aspects of the invention that are considered equivalent by those skilled in the art are also within the scope of this invention.

Example 1

This example describes the non-invasive delivery of a triamcinolone acetonide agent into the eyes of rabbits. In this study, an ocular device was placed on the eyes of rabbits. The electrode chamber of the device was positioned on the conjunctiva near the pars plana. The triamcinolone acetonide agent in the electrode chamber was 0.5 M triamcinolone acetonide phosphate. The delivery of the active agent was achieved by applying a constant direct electric current of two milliamperes across the electrode chamber for 15 minutes, thus delivering the triamcinolone acetonide agent. Six groups of 2 to 3 rabbits with each group assigned to the different time point (10-min, 4-hour, or 1-day) were used. At 10 minutes, 4 hours, and 1 day after the iontophoresis applications, the animals were euthanized and the eyes were enucleated for triamcinolone acetonide and triamcinolone acetonide phosphate assays. The assay procedures involved extracting these compounds from the conjunctiva, sclera, and vitreous humor with a pH-adjusted organic solvent and HPLC analysis. The amounts of the active agent in the eye after the iontophoresis applications are shown in Table 1.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Total amounts of triamcinolone acetonide and triamcinolone acetonide phosphate in the eye.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Immediate release iontophoresis</td>
</tr>
<tr>
<td>10 min</td>
<td>0.4 mg</td>
</tr>
<tr>
<td>4 hours</td>
<td>0.01 mg</td>
</tr>
<tr>
<td>24 hours</td>
<td>0 mg</td>
</tr>
</tbody>
</table>
Example 2

This example describes the non-invasive delivery of a sustained release triamcinolone acetonide agent into the eyes of rabbits using a depot forming agent. In this study, an ocular device of side-by-side active and depot forming agent chambers was placed on the eyes of rabbits. The electrode chambers of the device were positioned on the conjunctiva near the pars plana. The active and depot forming agents were 0.5 M triamcinolone acetonide phosphate and 1.0 M dodecyl ammonium, respectively. The delivery of the sustained release system was achieved by applying a constant direct electric current of two milliamperes across the side-by-side chambers for 15 minutes, in which the active agent was delivered from the cathode and the depot forming agent was from the anode. Six groups of 2 to 3 rabbits with each group assigned to the different time point (10 min, 4 hour, or 1 day) were used. At 10 minutes, 4 hours, and 1 day after the iontophoresis applications, the animals were euthanized and the eyes were enucleated for triamcinolone acetonide and triamcinolone acetonide phosphate assays. The assay procedure involved extracting these compounds from the conjunctiva, sclera, and vitreous humor with a pH-adjusted organic solvent and HPLC analysis. The amounts of the active agent in the eye after the iontophoresis applications are shown in Table 2, along with the data from Example 1.

<table>
<thead>
<tr>
<th>Total amounts of triamcinolone acetonide and triamcinolone acetonide phosphate in the eye.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained release system delivered by iontophoresis</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>10 min</td>
</tr>
<tr>
<td>4 hours</td>
</tr>
<tr>
<td>24 hours</td>
</tr>
</tbody>
</table>

It should be understood that the above-described arrangements are only illustrative of the application of the principles of the present invention. Numerous modifications and alternative arrangements may be devised by those skilled in the art without departing from the spirit and scope of the present invention. Thus, while the present invention has been described above with particularity and detail in connection with what is presently deemed to be the most practical and preferred embodiments of the invention, it will be apparent to those of ordinary skill in the art that numerous modifications, including, but not limited to, variations in size, materials, shape, form, function and manner of operation, assembly and use may be made without departing from the principles and concepts set forth herein.

What is claimed is:

1. A method for treating or preventing an ocular condition in a subject for which triamcinolone acetonide is effective, comprising:
   administering a triamcinolone acetonide agent to an eye of the subject in order to treat or prevent the condition.
2. The method of claim 1, wherein the triamcinolone agent is a member selected from the group consisting of triamcinolone acetonide, triamcinolone acetonide phosphate, and combinations thereof.
3. The method of claim 2, wherein the triamcinolone agent is triamcinolone acetonide phosphate.
4. The method of claim 2, wherein the triamcinolone agent is triamcinolone acetonide.
5. The method of claim 4, wherein the triamcinolone acetonide is coadministered with a solubilizing agent.
6. The method of claim 1, wherein administering the triamcinolone acetonide agent further includes ocular iontophoretic administration.
7. The method of claim 1, wherein the condition is a member selected from the group consisting of ocular edema, age related macular degeneration, anterior, intermediate, and posterior uveitis, HSV retinitis, diabetic retinopathy, bacterial, fungal, or viral endophthalmitis, eye cancers, glaucomatous degeneration of the optic nerve, and combinations thereof.
8. The method of claim 1, further comprising co-administering a vasoconstricting agent with the triamcinolone acetonide agent.
9. The method of claim 8, wherein the vasoconstricting agent is a member selected from the group consisting of naphazoline, tetrahydrozoline, phenylethylamine, ephedrine, norepinephrine, dopamine, dobutamine, colterol, ethylhexylpropranolol, isoproterenol, isethanor, metaproterenol, terbutaline, metenamminol, phenylephrine, tyramine, hydroxyamphetamine, ritodrine, prenalor, methoxamine, oxymethazoline, albuterol, amphetamine, methamphetamine, benzphetamine, ephedrine, phenylpropanolamine, methemetermine, phentermine, fenfluramine, propylxcedrine, diethylpropion, phenthimetazime, phenidimetrazine, and combinations thereof.
10. The method of claim 9, wherein the vasoconstricting agent is oxymethazoline.
11. A system for treating or preventing a condition in a subject for which triamcinolone acetonide is effective, comprising:
   an ocular device having a drug reservoir; and
   a triamcinolone agent disposed within the drug reservoir.
12. The system of claim 11, wherein the triamcinolone agent is a member selected from the group consisting of triamcinolone acetonide, triamcinolone acetonide phosphate, and combinations thereof.
13. The system of claim 12, wherein the triamcinolone agent is triamcinolone acetonide phosphate.
14. The system of claim 11, wherein the ocular device is an iontophoretic ocular device.
15. The system of claim 14, further comprising a permselective material functionally coupled to the drug reservoir.
16. The system of claim 11, wherein the ocular device further includes an enhancer reservoir configured to contain an enhancing agent.
17. The system of claim 16, wherein the enhancer reservoir contains a vasoconstricting agent.
18. The system of claim 17, wherein the vasoconstricting agent is a member selected from the group consisting of naphazoline, tetrahydrozoline, phenylethylamine, ephedrine, norepinephrine, dopamine, dobutamine, colterol, ethylhexylpropranolol, isoproterenol, isethanor, metaproterenol, terbutaline, metenamminol, phenylephrine, tyramine, hydroxyamphetamine, ritodrine, prenalor, methoxamine, oxymethazoline, albuterol, amphetamine, methamphetamine, benzphetamine, ephedrine, phenylpropanolamine, methemetermine, phentermine, fenfluramine, propylxcedrine, diethylpropion, phenthimetazime, phenidimetrazine, and combinations thereof.
19. The system of claim 18, wherein the vasoconstricting agent is oxymethazoline.

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