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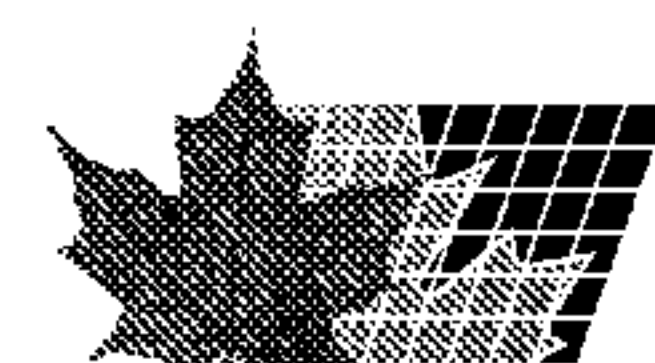
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(54) Titre : TRAITEMENT DE L'ONYCHOMYCOSE

(54) Title: TREATMENT OF ONYCHOMYCOSIS

(57) **Abrégé/Abstract:**

A flowable composition suitable for use as a controlled release implant, the composition comprising a biodegradable thermoplastic polyester that is at least substantially insoluble in aqueous medium or body fluid; a biocompatible polar aprotic solvent selected from the group consisting of an amide, an ester, a carbonate, a ketone, an ether, and a sulfonyl; wherein the biocompatible polar aprotic solvent is miscible to dispersible in aqueous medium or body fluid; and antifungal active.



ABSTRACT

[0036] A flowable composition suitable for use as a controlled release implant, the composition comprising a biodegradable thermoplastic polyester that is at least substantially
5 insoluble in aqueous medium or body fluid; a biocompatible polar aprotic solvent selected from the group consisting of an amide, an ester, a carbonate, a ketone, an ether, and a sulfonyl; wherein the biocompatible polar aprotic solvent is miscible to dispersible in aqueous medium or body fluid; and antifungal active.

TREATMENT OF ONYCHOMYCOSIS

FIELD OF THE INVENTION

5 [0001] This invention relates to compositions, devices, kits, and methods for treating onychomycosis.

BACKGROUND OF THE INVENTION

 [0002] Onychomycosis is a common dermatological condition that results from a fungal infection of the nail apparatus. The condition has a variety of clinical classifications and outcomes but often results in undesirable changes to the condition of the nail which may cause discomfort or pain to the sufferer. There are several treatments currently indicated for onychomycosis in the United States. One topical treatment is ciclopirox nail lacquer which, in two pivotal clinical trials, reported a mycologic cure rate of between 29% and 36% for mild to moderate toenail onychomycosis. The main systemic treatment for onychomycosis is terbinafine although griseofulvin and itaconazole are also approved for the condition. Terbinafine has a reported efficacy of 38% to 70% but can have unwanted side-effects. Treatment of onychomycosis can also include surgical or chemical removal of the nail plate.

SUMMARY OF THE INVENTION

 [0003] The present disclosure relates to methods, devices, compositions, and kits for treating onychomycosis. The present methods include depositing a antifungal containing composition under the nail a subject affected by onychomycosis. The present compositions include those which deliver anti-fungal agents in a controlled-release manner over a period of time. The present devices include implants for insertion under the nail that comprise an antifungal agent. The present kits include those comprising a composition or device comprising an antifungal and instructions for inserting the composition under the nail of a subject affected by onychomycosis.

 [0004] The present invention is useful for the treatment of onychomycosis. As used herein, "treatment" means any manner in which the symptoms of onychomycosis are ameliorated or otherwise beneficially altered. Treatment also encompasses prophylaxis. For example, the present invention is useful for preventing relapse in patients who have previously been cured of the condition.

[0005] As used herein, "antifungal" means a compound or mixture of compounds that kills, destroys, inhibits, or inactivates a fungus.

[0006] As used herein, the term "subject" is not limited to a specific species or sample type. For example, the term "subject" may refer to a patient, and frequently a human patient. However, this term is not limited to humans and thus encompasses a variety of mammalian species.

[0007] As used herein, "a" or "an" means "at least one" or "one or more."

DETAILED DESCRIPTION OF THE INVENTION

[0008] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. Unless otherwise specified, all patents, applications, published applications and other publications referred to herein are incorporated by reference in their entirety. If a definition set forth in this section is contrary to or otherwise inconsistent with a definition set forth in the patents, applications, published applications and other publications that are herein incorporated by reference, the definition set forth in this section prevails over the definition that is incorporated herein by reference.

[0009] The compositions of the present invention comprise an antifungal active and a pharmaceutically acceptable carrier material. The compositions herein must comprise antifungal when they are at the treatment site. However, the composition herein do not necessarily comprise antifungal before they reach the treatment site. For example, the antifungal active and the carrier material can be injected simultaneously at the treatment site so that they combine in-situ. Any suitable antifungal active may be used. Examples of antifungal actives include ciclopirox, naftifine, griseofulvin, itraconazole, terbinafine, salts and derivatives thereof, and mixtures thereof. Preferred antifungals include ciclopirox, naftifine, terbinafine, and combinations thereof.

[0010] It is preferred that the compositions herein are controlled-release compositions. That is, compositions that release antifungal active over a period of time, preferably over a period of at least 2 days, more preferably over a period of at least 7 days, even more preferably over a period of at least 10 days. Any suitable controlled-release composition may be used.

[0011] Preferred carrier materials for use herein are flowable compositions that are suitable for use as a controlled release implant for antifungals. The flowable compositions preferably include a biodegradable thermoplastic polymer that is at least substantially insoluble in an aqueous medium or body fluid. The thermoplastic polymers can be made from a variety of monomers which form polymer chains or monomeric units joined together by linking groups. These include polymers with polymer chains or backbones containing such linking groups as ester, amide, urethane, anhydride, carbonate, urea, esteramide, acetal, ketal, and orthocarbonate groups as well as any other organic functional group that can be hydrolyzed by enzymatic or hydrolytic reaction (i.e., is biodegradable by this hydrolytic action). These polymers are usually formed by reaction of starting monomers containing the reactant groups that will form these backbone linking groups. For example, alcohols and carboxylic acids will form ester linking groups. Isocyanates and amines or alcohols will respectively form urea or urethane linking groups. Preferably, the biodegradable thermoplastic polymer is selected from polyesters, polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyorthoesters, polyphosphoesters, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), and copolymers, terpolymers, or combinations or mixtures of the above materials. More preferably, the biodegradable thermoplastic is a polyester. Preferably the polyester is a polylactide, a polyglycolide, a copolymer thereof, a terpolymer thereof, or a combination thereof.

[0012] The preferred biocompatible thermoplastic polymers for use herein have a lower degree of crystallization and are more hydrophobic. Preferably, the thermoplastic polymer is substantially soluble in the organic solvents so that up to 50-60 wt% solids can be made. Preferably, the polymers used according to the invention are essentially completely soluble in the organic solvent so that mixtures up to 85-98 wt% solids can be made. Preferably the polymers are at least substantially insoluble in water so that less than 0.1 g of polymer per mL of water will dissolve or disperse in water. Preferably, the polymers used according to the invention are essentially completely insoluble in water so that less than 0.001 g of polymer per mL of water will dissolve or disperse in water.

[0013] Solvents suitable for use in the flowable composition are biocompatible and are at least slightly soluble in aqueous medium, body fluid, or water. The organic solvent preferably is at least moderately soluble, more preferably very soluble, and most preferably

soluble at all concentrations in aqueous medium, body fluid, or water. Preferably, the organic solvent has a molecular weight in the range of about 30 to about 1000.

[0014] Examples of biocompatible organic solvents that may be used to form the flowable compositions of the present invention include aliphatic, aryl, and arylalkyl linear, cyclic and branched organic compounds that are liquid or at least flowable at ambient and physiological temperature and contain such functional groups as alcohols, ketones, ethers, amides, esters, carbonates, sulfoxides, sulfones, and any other functional group that is compatible with living tissue.

[0015] Preferred biocompatible organic solvents that are at least slightly soluble in aqueous or body fluid include N-methyl-2-pyrrolidone, 2-pyrrolidone; C1 to C15 alcohols, diols, triols and tetraols such as ethanol, glycerine, propylene glycol, butanol; C3 to C15 alkyl ketones such as acetone, diethyl ketone and methyl ethyl ketone; C3 to C15 esters such as methyl acetate, ethyl acetate, ethyl lactate; C1 to C15 amides such as dimethylformamide, dimethylacetamide and caprolactam; C3 to C20 ethers such as tetrahydrofuran, or solketal; tweens, triacetin, propylene carbonate, decylmethylsulfoxide, dimethyl sulfoxide, oleic acid, and 1-dodecylazacycloheptan-2-one. Other preferred solvents are benzyl alcohol, benyl benzoate, dipropylene glycol, tributyrin, ethyl oleate, glycerin, glycofural, isopropyl myristate, isopropyl palmitate, oleic acid, polyethylene glycol, propylene carbonate, and triethyl citrate. Preferred solvents include N-methyl-2-pyrrolidone, 2-pyrrolidone, dimethyl sulfoxide, triacetin, and propylene carbonate.

[0016] Preferably the concentration of the polymer in the organic solvent according to the invention will range from about 0.01g per ml of solvent to a saturated concentration. Typically, the saturated concentration will be in the range of 80 to 95 wt% solids or 4 to almost 5 gm per ml of solvent assuming that the solvent weighs approximately 1 gm per ml.

[0017] Preferred flowable compositions are described in U.S. Pats 5,278,201; 5,324,519; and 6,395,293, the disclosures of which is incorporated herein by reference.

[0018] The compositions herein also include an antifungal active when they are at the treatment site. Any suitable concentration of active may be used. The active is preferably present in about 0.1 wt.% to about 30 wt.%, more preferably from about 1 wt.% to about 30 wt.%, even more preferably from about 5 wt.% to about 25 wt.%, of the composition.

[0019] Preferably, the flowable composition is formulated as an injectable composition. The injectable composition preferably has a volume of about 0.02 mL to about

1.0 mL or about 0.05 mL to about 0.5 mL. Preferably, the flowable composition is a liquid or a gel composition, suitable for injection under the nails of a subject.

5 **[0020]** Preferably the flowable composition is suitable for injection under the nails of a subject where it forms a pharmaceutically acceptable, solid matrix. In one aspect of the flowable composition, a biologically active agent is included and the solid implant will release the antifungal active at a controlled rate. The rate of release may be altered to be faster or slower by inclusion of a rate-modifying agent.

10 **[0021]** The present invention is also directed to biodegradable implants comprising antifungal agents and methods for producing the same. These implants are solid articles and include microcapsules, microparticles, structured articles such as sutures, staples, medical devices, stents and the like as well as monolithic implants and implant films, filamentous membranes and matrices.

15 **[0022]** Suitable microcapsules are preferably dimensioned in the order of 10 to 400 microns, and preferably are dimensioned so as to avoid causing emboli if introduced into the blood stream of a mammal. They are typically composed of a porous shell of the thermoplastic, branched polymer and a core of another material such as a bioactive agent or a bioactive agent in a diluent or carrier.

20 **[0023]** Suitable microparticles have approximately the same dimensions as microcapsules. The microparticles are typically composed of a porous matrix of the thermoplastic, branched polymer and bioactive agent. The bioactive agent is typically contained within the polymer matrix as a homogeneous dispersion or solution, or as heterogeneous domains.

25 **[0024]** Suitable structured articles have the known shapes as indicated by the information conveyed by their names. The monolithic implants are single body implants formed outside the body by solidification of the flowable composition in an aqueous medium. The differing shapes may be obtained by use of a molding or extrusion device designed to provide such shapes as the flowable composition is contacted with the solidification bath. These implants preferably have shapes suitable for insertion under the nails of a subject suffering from onychomycosis.

30 **[0025]** Suitable films may be formed by casting upon the aqueous medium or by other techniques known to provide such films.

[0026] Suitable filamentous membranes may be formed by the technique of described in copending US patent application Serial No. 09/110723, filed July 7, 1998, the disclosure of which is incorporated herein by reference.

[0027] The present invention includes methods of treating onychomycosis. Preferred methods comprise inserting a composition or device as described herein under the nail of a subject. Such an insertion is preferably in the form of an injection. Preferably the method comprises inserting a flowable composition as described hereinabove under the nail of a subject.

[0028] The present invention includes kits comprising a composition or device as described hereinabove and instructions for use of such compositions or devices. The instructions preferably comprise a description of inserting the composition or device under the nail of an onychomycosis sufferer. Preferably the kit comprises a biodegradable thermoplastic polymer, an antifungal active, and instructions for injecting the polymer and active under the nail of a subject.

[0029] In a further embodiment the kit comprises first container comprises a composition comprising a biodegradable thermoplastic polyester that is at least substantially insoluble in aqueous medium or body fluid and a biocompatible polar aprotic solvent selected from an amide, an ester, a carbonate, a ketone, an ether, and a sulfonyl; wherein the biocompatible polar aprotic solvent is miscible to dispersible in aqueous medium or body fluid; and a second container comprising an antifungal active. Preferably the containers are syringes. Preferably the kit comprises instructions. Preferably the first container can be connected to the second container.

EXAMPLES

[0030] It will be understood that the following embodiments of the present invention are intended to be illustrative of some of the possible applications or principles. Various modifications may be made by the skilled person without departing from the true spirit and scope of the invention.

EXAMPLE 1

[0031] A 360 ml teflon vessel was charged with D,L lactide (275 g), polyol (0.4-1.1 w/w %), and stannous octoate (0.045 w/w %). The mixture was heated at 145°C for 20 hours. The resulting polyester was removed from the reaction vessel and dissolved in

anhydrous dichloromethane and purified by precipitation in anhydrous methanol. The polymers were dried under vacuum at ambient temperature to remove most of the residual solvent. The resulting hard, solid masses were cooled in liquid nitrogen and cut into small pieces. The small pieces were ground in a Wiley mill to a coarse dust sufficient to pass
5 through a 6 mm screen. The resulting polymer was dried under vacuum at ambient temperature prior to final packaging.

EXAMPLE 2

[0032] The biodegradable polymer of Example 1 is dissolved in N-methyl pyrrolidone and sterilized. It is loaded into a 1 ml polypropylene syringe female luer lock fitting. Sterile terbinafine hydrochloride solution (1%) is loaded into another 1 ml syringe
10 polypropylene syringe with a male luer-lock fitting. The syringes are coupled together and mixed for 50 cycles. The formulation is drawn back into the syringe with the male coupling, the two syringes separated, and a one-half inch 20 gauge needle is attached. The contents of the syringe are then injected under the nail of a 30 year old man suffering from
15 onychomycosis.

[0033] The ordinarily skilled artisan can appreciate that the present invention can incorporate any number of the preferred features described above.

[0034] The above examples are included for illustrative purposes only and are not intended to limit the scope of the invention. Many variations to those described above are
20 possible. Since modifications and variations to the examples described above will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

[0035] Citation of the above publications or documents is not intended as an admission that any of the foregoing is pertinent prior art, nor does it constitute any admission
25 as to the contents or date of these publications or documents.

CLAIMS

1. A flowable composition suitable for use as a controlled release implant, the composition comprising:
 - 5 a. a biodegradable thermoplastic polyester that is at least substantially insoluble in aqueous medium or body fluid;
 - b. a biocompatible polar aprotic solvent selected from the group consisting of an amide, an ester, a carbonate, a ketone, an ether, and a sulfonyl; wherein the biocompatible polar aprotic solvent is miscible to dispersible in aqueous medium or
 - 10 body fluid; and
 - c. antifungal active.
2. The composition of claim 1 wherein the biodegradable thermoplastic polyester is a polylactide, a polyglycolide, a polycaprolactone, a copolymer thereof, a terpolymer thereof,
 - 15 or any combination thereof.
3. The composition of claim 1 wherein the biodegradable thermoplastic polyester is a polylactide, a polyglycolide, a copolymer thereof, a terpolymer thereof, or a combination thereof.
 - 20
4. The composition of claim 1 wherein the biocompatible polar aprotic solvent is N-methyl-2-pyrrolidone, 2-pyrrolidone, N, N-dimethylformamide, dimethyl sulfoxide, propylene carbonate, caprolactam, triacetin, or any combination thereof.
- 25 5. The composition of claim 1 wherein the antifungal active is selected from ciclopirox, naftifine, griseofulvin, itraconazole, terbinafine, salts and derivatives thereof, and mixtures thereof.
6. A method of treating onychomycosis wherein a composition comprising an antifungal
 - 30 active is deposited under the nail of the subject suffering from onychomycosis.
7. The method of claim 6 wherein the composition is a controlled release implant.

8. The method of claim 6 wherein the composition is a biodegradable thermoplastic polyester that is at least substantially insoluble in aqueous medium or body fluid.
9. The method of claim 6 wherein the composition is according to claim 1.
- 5
10. A method of treating onychomycosis comprising injecting under the nail of an affected subject a composition comprising:
 - a. a biodegradable thermoplastic polyester that is at least substantially insoluble in aqueous medium or body fluid;
 - 10 b. a biocompatible polar aprotic solvent selected from the group consisting of an amide, an ester, a carbonate, a ketone, an ether, and a sulfonyl; wherein the biocompatible polar aprotic solvent is miscible to dispersible in aqueous medium or body fluid; and
 - 15 c. antifungal active.
- 15
11. A kit comprising a composition according to claim 1 and instructions for depositing the composition under the nail of a subject suffering from onychomycosis.
12. A kit comprising a first container comprising a composition comprising a biodegradable
 - 20 thermoplastic polyester that is at least substantially insoluble in aqueous medium or body fluid and a biocompatible polar aprotic solvent selected from an amide, an ester, a carbonate, a ketone, an ether, and a sulfonyl; wherein the biocompatible polar aprotic solvent is miscible to dispersible in aqueous medium or body fluid; and a second container comprising an antifungal active