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(54) METHODS FOR PREPARATION OF ANTI-ACNE FORMULATION AND COMPOSITIONS PREPARED THEREBY

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(57) **ABSTRACT**

The present invention provides methods to make solvent-microparticle (SMP) topical formulations for bioactive drugs. The formulations, which are aqueous gels containing undissolved solid drug, include a drug in a solution which can permeate the stratum corneum layer of the epidermis and the drug in an undissolved microparticulate solid form that does not readily cross the stratum corneum. The solid form is retained in or above the stratum corneum to serve as a reservoir or to provide drug action in the supracorneum zone. The fine, particulate solid component of the invention can confer a smooth, nongritty feel against the skin.

METHODS FOR PREPARATION OF ANTI-ACNE FORMULATION AND COMPOSITIONS PREPARED THEREBY

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. provisional patent application Ser. No. 61/058,751, filed on Jun. 4, 2008, and which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Formulations systems adapted for delivery of bioactive drugs to the skin and via the skin must be designed to address the barrier properties of skin and of skin-related structures, such as lesion surfaces, inflamed skin, scabs, scar tissue, and the like Formulations for drug delivery to or via skin include cosmetic, transdermal, and topical systems. The optimal delivery strategy for administering pharmaceuticals to, and via, the skin varies among various types of formulations depending upon the target tissues. Cosmetic applications, where the target tissue is the skin surface, are designed to provide for negligible drug penetration past the stratum corneum, the layer of dead cells on the surface of the epidermis. For transdermal applications, where the goal is to introduce the drug to the entire body by way of the skin, steady state, high efficiency drug delivery through the epidermal and dermal layers via the capillary bed to the bloodstream and thus systemically to the patient is preferred. However, for topical delivery, minimal systemic absorption is preferred, as the target tissue is at or near the skin surface, and topical agents may furthermore have undesirable side effects when absorbed systemically. However, the bioactive agent must nevertheless penetrate sufficiently to expose the dermal and subdermal tissue to effective doses of the agent, as the target tissue may be several millimeters below the skin surface. For instance, in the treatment of acne, the inflamed sebaceous glands are located in dermal and subdermal layers, but not in deeper musculature. In the treatment of viral lesions such as from Herpes Simplex, viral populations may be similarly located.

[0003] In order to adequately dose viable epidermis and dermis, relatively large amounts of drug must cross the intact skin barrier, i.e. the stratum corneum, or the lesional delivery barrier, i.e. scab, plaque, etc., due to the often-broad distribution of the malcondition over a substantial surface area of the body and the need to achieve effective in vivo concentrations of the bioactive drug throughout a tissue layer that can be at least several millimeters in depth. For example, acne, viral skin lesions, fungal infections, and other dermatological disease states can involve substantial areas of the body's surface. Also, it is often advantageous to be able to deliver the bioactive drug over a period of time, such that a desired level of the drug in the target tissue is achieved for a period of time sufficient to achieve the desired result, e.g., killing most of a population of infectious bacterial or fungal cells. Some dermatological conditions, such as acne, require multiple delivery strategies because they have multiple delivery requirements, such as killing skin surface bacteria while also penetrating deep into inflamed sebaceous glands to kill bacteria in that locus.

lation of the bioactive drug dapsone that is in the physical form of an aqueous gel containing dapsone both in solution and in the solid phase. Commercially available with a 5% concentration of dapsone, this gel material also includes Carbomer 980 as a thickener, methyl paraben as a preservative, diethyleneglycol monoethyl ether (DGME) as a cosolvent, and sodium hydroxide for pH adjustment. A notable feature of Aczone is that the bioactive drug dapsone is not totally dissolved in the vehicle, but also is present in microparticulate, dispersed form. Thus, the Aczone formulation is in the nature of a solvent-microparticle (SMP) topical gel formulation that contains dapsone both in dissolved form and in solid microparticulate form, which is advantageous for treatment of acne, as the dissolved material is readily and immediately available for absorption into dermal and subdermal tissue, while the solid microparticulate form persists on the surface of the skin after application and is only slowly released for absorption. It may be absorbed, for example, by dissolution in skin oils and perspiration and subsequent permeation on a molecular level. The rate of absorption of dapsone from the solid microparticulate state can be controlled, at least in part, by the specifics of the microparticulate form of the solid material, e.g., the size, size distribution, shape, surface/volume ratio, polymorphic crystalline form, and hydration or solvation of the dapsone microparticles. For example, as is well known in the art, larger particles tend to dissolve or disperse more slowly due to the lower surface area/volume ratio in comparison with smaller but similarly shaped particulates.

[0005] In U.S. Pat. Nos. 5,863,560 and 6,060,085, topical or dermatological compositions (formulations) containing bioactive drugs such as dapsone or acyclovir, and others, are provided for treatment of various skin diseases. These patents also provide methods of preparation of aqueous gels containing both dissolved and solid particulate forms of the bioactive drug, wherein the drug is at least moderately soluble in at least some organic solvents but only sparingly soluble, or insoluble, in water. These methods involve dissolving the drug in a solvent that has at least some solubility in water, then partially precipitating the drug in solid form by addition of water. This method results in the production of particulates from the sparingly soluble drug whose physical form is governed by the specifics of the technique used to carry out the precipitation, such as concentration, identity of the solvent, relative amount of water added, the presence of other ingredients, the time period over which precipitation occurs, the temperature, post-precipitation handling, and other variables. Many of these variables are likely to be influenced by the scale on which the step of precipitation is carried out, and the degree of control that can be exercised. Therefore, procedures that may work well on a small scale can nevertheless cause problems when attempting to scale up to industrial production of the topical formulation.

SUMMARY

[0006] Embodiment of the invention described herein are directed to novel methods for preparation of solvent-microparticle (SMP) topical formulations including a bioactive drug, and to the formulations prepared by various embodiments the inventive method. A specific example of a drug that is suitable for use in this type of topical SMP formulation is dapsone, which is indicated for treatment of acne, among

invention includes a bioactive agent in two physical states: a dissolved form of a drug that can permeate the stratum corneum layer of the epidermis and become available in tissues of the living dermal layer, and a solid form of a drug that does not readily cross the stratum corneum of the epidermis and thus persists on the exterior surface of the epidermis The solid form can be retained in or above the stratum corneum, where it can serve as a reservoir of a drug for eventual permeation of the skin, or can provide drug action in the supracorneum zone, for example killing bacteria disposed on the skin surface. The solid form can be of a size and form adapted to confer a smooth, soft feeling when applied topically to human skin. The solid form of the drug may be any one of multiple polymorphic forms of a single drug, or can include more than one polymorph.

[0007] In various embodiments of the invention, a method of preparing a solvent-microparticle topical gel formulation comprising a bioactive drug, wherein the formulation comprises the drug dissolved in a liquid and the drug in a microparticulate solid form dispersed in the liquid, the method comprising first forming the liquid by combining an organic solvent and water, and then contacting the drug in a microparticulate solid form with the liquid, such that the microparticulate solid form does not entirely dissolve in the liquid; and dissolving a thickener in the liquid at a concentration sufficient to form a gel, is provided.

[0008] In another embodiment of the invention, a method of preparing a solvent-microparticle topical gel formulation comprising a bioactive drug is provided wherein, prior to the step of contacting the microparticulate solid form with the liquid, forming a solution of the drug in the liquid, wherein the drug is substantially completely dissolved in the liquid.

[0009] In another embodiment, a topical SMP formulation prepared by a method of the invention is provided.

[0010] In another embodiment, a second drug can be included in a topical SMP formulation prepared by a method of the invention In various embodiments, methods of preparing a topical SMP formulation of the invention comprising a second drug are provided.

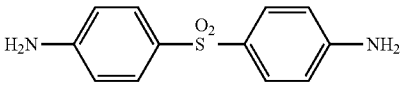
[0011] In various embodiments, the amount of the drug in microparticulate solid form dispersed in a unit volume of the liquid is no more than about six times the amount of the drug dissolved in the unit volume of the liquid.

[0012] In various embodiments, the topical composition is a semi-solid aqueous gel, wherein a drug is dissolved in the gel such that the drug has the capacity to cross the stratum corneum layer of the epidermis and become available at least in the living dermal tissue, and wherein the composition also contains the drug in a microparticulate state that does not readily cross the stratum corneum of the epidermis In various embodiments, the topical composition is a semi-solid or gel-like vehicle that can include a preservative, active surfactants or emulsifiers antioxidants, or sunscreens, or any combination thereof

[0013] In some embodiments, the solid form of the active agent is a amorphous solid. In other embodiments, the solid form of the active agent is a flake. In still other embodiments, the solid form of the active agent is a crystal. In various embodiments, the invention provides compositions with

DETAILED DESCRIPTION

[0014] As used herein, "dapsone" refers to the chemical compound dapsone having the elemental formula $C_{12}H_{12}N_2O_2S$, structure



known as bis(4-aminophenyl)sulfone, including its hydrates, solvates, tautomers, and salts; also known as 4,4'-sulfonylbis-benzeneamine, 4,4'-sulfonyldianiline, and diaphenylsulfone; and dapsone analogs; and dapsone related compounds. "Dapsone analogs" refers to chemical compounds that have similar chemical structures and thus similar therapeutic potential to dapsone such as the substituted bis(4-aminophenyl)-sulfones. "Dapsone related compounds" refers to chemical compounds that have similar therapeutic potential, but are not as closely related by chemical structure to dapsone such as the substituted 2,4-diamino-5-benzylpyrimidines.

[0015] A "drug," "active agent," "bioactive agent," or "pharmaceutical," as the terms are used herein, refer to a medicinal compound, organic, organometallic, or inorganic, that can be used for treatment of a malcondition wherein topical application of the material is medically indicated.

[0016] As used herein, "gel" refers to a colloid in a more solid form than a solution; a jelly-like material formed by the coagulation or gelation of a colloidal liquid; many gels have a fibrous matrix and fluid filled interstices: gels can be viscoelastic as well as viscous, and in various embodiments gels can resist some mechanical stress without deformation.

[0017] As used herein, the term "microparticulate" or "microparticle" refers to any solid form of an active agent, including dapsone, provided that the average particle size is on the micron scale, that is, less than 1 mm, and that there are substantially no particles of size larger than 1 mm in a sample of the solid. By "average particle size" is meant an average of the particle diameters of all the particles in a population of the particles. By "particle diameter" of an individual particle is meant, if the particle is substantially spherical, the diameter of the sphere; if the particle is elongated or of irregular shape, an average of diameters along all axes. The average particle size can be on the order of microns (1-10 microns), tens of microns (11-100 microns), or hundreds of microns (101-999 microns), or it can be submicron. Typically, average particle sizes in an SMP formulation of the invention are around 10-500 microns. The microparticulate active agent described herein can be in any solid shape, such as flakes or crystals or amorphous particles.

[0018] By the terms "dissolved" or a "solution" is meant a molecular solution of a substance, the substance being a solid in pure form at room temperature, in a liquid, wherein individual molecules of the substance are separated from each other in the liquid solution, as is well known in the art. Few if any long-lasting interactions between molecules of the substance take place in the solution phase, and the molecules of

[0019] By the terms "suspended," "suspension," "dispersed," and "dispersion" are meant a physical state wherein finely particulate solid particles are mixed with a liquid, but are not dissolved in the liquid. There are many significant and long-term associations between individual molecules of the suspended or dispersed substance within the particles. Molecules of the substances making up the liquid may permeate the particles, but the particles retain a cohesive structure, wherein aggregations of molecules of the solid substance persist. Upon standing, these particles may be acted on by the force of gravity, causing them to accumulate at the bottom of a vessel containing the suspension or dispersion.

[0020] The microparticulate solid can be any polymorph of a given drug, or can be a mixture of multiple polymorphs. It can include hydrates, solvates, tautomers, salts or molecular complexes of the drug. By a "molecular complex" of a drug is meant a form of the drug wherein the active molecule is in a defined molecular association with a carrier, for example a cyclodextrin complex of a drug. For example, when the drug is dapsone, various polymorphic forms such as Form I or Form III can be used.

[0021] The microparticulate solid may have been milled or ground to achieve smaller sized particles. As used herein, the terms "milling" and "grinding" refer to the action of breaking a solid material into smaller pieces. The grinding of solid matters occurs under exposure of mechanical forces that trench the structure by overcoming of the interior bonding forces. After the grinding the state of the solid is changed: the grain size, the grain size disposition and the. grain shape.

[0022] As used herein, "preservative" refers to any substance which prevents bacterial growth, mold growth, fermentation, oxidation, or molecular decomposition, or any combination thereof.

[0023] "Therapeutically effective amount" refers to an amount of a drug, or a combination of more than one drug or an amount of a formulation including the drug or the combination, effective to treat dermatological condition in a patient.

[0024] The term "topical" as used herein refers to the route of administration of a dermatological composition that involves direct application to the exterior body part being treated, the skin, or a lesion on the body exterior where skin has decomposed such as a scab, plaque or open sore. Typically, areas of the body suitable for application of the dermatological composition include the skin of the face, throat, neck, scalp, chest, back, ears, and other skin sites. Application to mucosal surfaces is not included in the term "topical" as used herein.

[0025] As used herein, the term "treat", "treatment", or "treating" includes prophylaxis of the specific disorder or condition, or alleviation of the symptoms associated with a specific disorder or condition and/or preventing, ameliorating, inhibiting or eliminating the symptoms.

[0026] Embodiments of the invention described herein provides topical SMP gel formulations and methods to prepare the formulations. Embodiments of the topical SMP formulations include a liquid component, the liquid component including a mixture of water and an at least partially water-soluble solvent. The solvent can be an organic solvent, for example the solvent can include diethyleneglycol monoethyl ether (DGME), N-methylpyrrolidone (NMP), N,N-dimethylformamide, N,N-dimethylacetamide (DMA), dimethylsulfoxide (DMSO), or any other substantially non-toxic solvent these solvents can be used. Additional examples include ethanol, propylene glycol, glycerol, diethyleneglycol, triethyleneglycol, polyethylene glycol, propylene carbonate, pyrrolidone, N-methyl pyrrolidone, dimethylsulfoxide, triethanolamine, 1,4-butanediol, triacetin, diacetin, dimethyl isosorbide, and the like, alone or in combination. The solvent and the water can be present in various relative amounts in the liquid. The solvent need not be miscible with water in all proportions, but when mixed at the particular ratio selected for a formulation, the water and the solvent should form a single phase. at room temperature.

[0027] Water is typically the predominant component of the liquid. For example, the solvent can make up about 10-40% of the liquid by weight, with the remainder of the liquid component as described herein being water. Deionized water or distilled water can be used in a method of the invention. The water can be sterilized, for example by ultrafiltration or by boiling, to remove any infectious organisms that could be present. The water can be substantially free of dissolved solids, such as salts or other contaminants. USP grade water can be used.

[0028] Other solvents that can be used in conjunction with water to form the liquid of the inventive method include, but are not limited to: benzyl alcohol, denatured alcohol, methanol, isopropyl alcohol, water, propanol, acetone, chlorobutanol, methyl ethyl ketone, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, butanol, butyl alcohol, diglycerides, dipropylene glycol, eugenol, diacetin, diethanolamine, monoacetin, monoglycerides, PEG vegetable oil, N,N-dimethylformamide, N-methyl formamide, N-methylacetamide, N,N-dimethylacetamide, or combinations thereof.

[0029] Glycol ethers are organic solvents that are moderately soluble to miscible with water and can be as a solvent in formation of a liquid used in a method of the invention. A glycol ether is an ether formed from at least one glycol and at least one lower alkyl alcohol. Preferably the glycol is selected from an alkylene glycol such as ethylene glycol, propylene glycol, or butylene glycol. The ether portion of the glycol ether is a radical of a lower alkyl alcohol such as a C_1 to C_6 alcohol. Preferably, the ether portion alcohol is selected from methyl alcohol, ethyl alcohol, propyl alcohol, isopropyl alcohol, butyl alcohol, or isobutyl alcohol.

[0030] Examples of glycol ethers under the classification of ethylene glycol ethers include ethylene glycol monopropyl ether (propoxyethanol), ethylene glycol monobutyl ether (butoxyethanol), diethylene glycol monoethyl ether (ethoxydiglycol, DGME), diethylene glycol monobutyl ether (butoxydiglycol), diethylene glycol monoisopropyl ether (isopropyldiglycol), and diethylene glycol monoisobutyl ether (isobutyl diglycol).

[0031] Glycol ethers under the classification of propylene glycol ethers include propylene glycol monomethyl ether, dipropylene glycol monomethyl ether (PPG-2 methyl ether), tripropylene glycol monomethyl ether (PPG-3 methyl. ether), propylene glycol n-propyl ether, dipropylene glycol n-propyl ether (PPG-2 propyl ether), propylene glycol monobutyl ether, dipropylene glycol monobutyl ether (PPG-2 butyl ether), propylene glycol monoisobutyl ether, and dipropylene glycol dimethyl ether. In one embodiment of the invention the solvent is ethoxydiglycol. In another embodiment, the solvent is methoxydiglycol. Additional suitable exemplary gly-

[0032] In one embodiment, formulations of the invention can have a glycol ether. present in about 20.0 wt. % to about 40.0 wt. %. In another embodiment, formulations of the invention cab have a glycol ether present in about 20.0 wt. % to about 35.0 wt. %. In another embodiment, formulations of the invention can have a glycol ether present in about 25.0 wt. % to about 40.0 wt. %. In yet another embodiment, formulations of the present invention can have a glycol ether present in about 25.0 wt. % to about 35.0 wt. % of the composition. More specifically, compositions of the present invention have a glycol ether present in about 25.0 wt. % of the composition.

[0033] A drug is present in the SMP formulation, both dissolved and dispersed in the liquid component. An example of a drug for use in a method of the invention is dapsone. Another example is acyclovir or ganciclovir. A drug is present in the topical SMP formulation in two distinct physical forms. First a solution or dissolved form of the drug is present in the SMP formulation, wherein the drug substance is dissolved in the liquid comprising the water and. the solvent. Therefore the drug has at least a limited solubility in the liquid of the SMP formulation. This dissolved form of the drug can permeate the stratum corneum layer of the epidermis and become available in the living dermal tissue when the formulation is applied to human skin. The second physical form of the drug in the SMP formulation is a microparticulate solid form that is not dissolved in the liquid, but rather is dispersed or suspended in the liquid of the formulation. Therefore the drug is not completely soluble in the liquid comprising water and a solvent at the concentration of drug and the composition of liquid used. The formulation can be in gel form due to the presence of a thickener as discussed below. This solid microparticulate form does not readily cross the stratum corneum of the epidermis when the formulation is applied to human skin. Instead, the solid form is retained in or above the stratum corneum to serve as a reservoir for eventual absorption through the stratum corneum into the living dermal tissue, or to provide drug action in the supracorneum zone, or both. The fine, microparticulate solid component can confer a smooth, nongritty feel against the skin. For example, flakes or amorphous solids of relatively small average particle diameter can provide a smooth skin feel or texture.

[0034] Examples of drugs that can be used in a formulation prepared by a method of the invention include, in addition to dapsone, acyclovir, and ganciclovir: salicylic acid, resorcinol, resorcinol acetate, benzoyl peroxide, sulfur, retinol, retinoic acid, citric acid, an alpha hydroxy acid, retinal, pharmaceutically acceptable salts thereof, and combinations thereof. Specifically, the active agent can be at least one of adapalene, azaleic acid, erythromycin salnacedin, inocoterone acetate, or isotretenoin anisatil.

[0035] In various embodiments of the invention, the drug can be a glucocorticoid. Glucocorticoids include, e.g., betamethasone dipropionate, betamethasone valerate, clobetasol propionate, diflorasone diacetate, halobetasol propionate, amcinonide, desoximetasone, fluocinonide, fluocinonide acetonide, halcinonide, triamcinolone acetonide, flurandrenolide, hydrocortisone valerate, hydrocortisone butyrate, mometasone furoate, aclometasone dipropionate, desonide, dexamethasone sodium phosphate, and fluocinolone acetonide.

[0036] In various embodiments of the invention, the drug

[0037] In various embodiments of the invention, the drug can be an antibiotic agent. As used herein, an "antibiotic agent" refers to any compound having activity against either Gram-positive or Gram-negative organisms (i.e., inhibits. the growth or destroys the development of either Gram-positive or Gram-negative organisms). Stedman's Medical Dictionary, Illustrated, (25th Ed.), Williams & Wilkins: Baltimore (1990) and Mosby's Medical, Nursing, & Allied Health Dictionary, (5th Ed.), Mosby: St. Louis (1998).

[0038] Any suitable antibiotic agent can be employed, provided the antibiotic. agent effectively inhibits the growth or destroys the development of either Gram-positive or Gram-negative organisms and the antibiotic agent remains stable in the formulation. Preferably, the stability is over a prolonged period of time, e.g., up to about 3 years, up to about lyear, or up to about 6 months, typically experienced in the manufacturing, packaging, shipping, and/or storage of the composition. Suitable antibiotic agents are disclosed, e.g., in Physician's Desk. Reference (PDR), Medical Economics Company (Montvale, N.J.), (53rd Ed.), 1999; Mayo Medical Center Formulary, Unabridged Version, Mayo Clinic (Rochester, Minn.), January 1998; Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals, (11th Ed.), Merck & Co., Inc. (Rahway, N.J.), 1989;. University of Wisconsin Antimicrobial Use Guide, http://www.medsch.wisc.edu/clinsci/amcg/amcg.html; Introduction on the Use of the Antibiotics Guideline, Descriptions of Specific Antibiotic Classes, Thomas Jefferson University, http://jeffline.tju.edu/CWIS/OAC/antibiotics_guide/intro.html; and references. cited therein.

[0039] Suitable classes of antibiotic agents include, e.g., β-lactams, aminoglycosides, antifungal agents, and combinations thereof. Suitable antibiotic agents include, e.g., cilastatin, clavulanic acid, folinic acid, probenecid, pyridoxine, sulbactam, dapsone, ethambutol, isoniazid, pyrazinamide, rifampin, streptomycin, capreomycin, ethionamide, para aminosalicylic acid, cycloserine, ciprofloxacin, nalidixic acid, norfloxacin, ofloxacin, imipenam, meropenem, cilistatin, cefadroxil, cefazolin, cephalexin, cephalothin, cefaclor, cefamandole, cefonicid, cefoxitin, cefuroxine, cefoperazone, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, moxalactam, cefepine, bacitracin, vancomycin, aztreonam, amoxicillin, clavulanic acid, benzathine, penicillin g, penicillin v, ampicillin, carbenicillin. indamyl, carbenicillin, mezlocillin, piperacillin, ticarcillin, cloxacillin, dicloxacillin, floxacillin, methicillin, nafcillin, oxacillin, colistmethate, polymixin b, trimethoprim, cotrimoxazole, mafenide, sulfadiazine, sodium sulfacetamide, sulfacytine, sulfadiazine, sulfamethoxazole, sulfapyridine, sulfasalazine, sulfisoxazole, chloramphenicol, clindamycin, spectinomycin, azithromycin, clarithromycin, erythrmoycin, erythromycin estolate, spiramycin, chlortetracycline, demeclocycline, doxycycline, minocycline, oxytetracycline, amikacin, kanamycin, neomycin, streptomycin, tobramycin, nitrofurantoin, griseofulvin, potassium iodide, fluconazole, itraconazole, ketoconazole, miconazole, clotrimazole, amphotericin b, nystatin, niclosamide, nifurtimox, piperazine, praziquantel, pyrantel pamoate, ascariasis, pinworm, thiabendazole, amodiaquine, chloroquine, hydroxychloroquine, mefloquine, primaquine, pyrimethamine, quinidine gluconate, fansidar, diloxanide furoate, melarsoprol, nifurtimox, paromomycin, pentamidine, sodium stibogluconate, suramin, metronidazole, foscar-

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