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(54) **DERMATOLOGIC SOFT GEL COMPOSITIONS**

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(57) **ABSTRACT**

Orally administrable softgels or soft gelatin capsules and fill compositions therefore for use in treating various dermatological conditions. These compositions are also particularly useful for treating children or patients of at least 55 years of age.

DERMATOLOGIC SOFT GEL COMPOSITIONS

[0001] This application claims priority to U.S. Provisional Patent Application Ser. No. 60/537,288, filed on Jan. 20, 2004, the contents of which are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present subject matter relates to orally administrable softgels or soft gelatin capsules and fill compositions therefore for use in treating various dermatological conditions. These compositions are particularly useful for treating children, patients of at least 55 years of age, and females.

BACKGROUND OF THE INVENTION

[0003] The topical administration of various pharmacologically active agents to treat various dermatological disorders has long been known in the art. The accessibility of the skin and the opportunity it provides for application of topical preparations over a prolonged period of time have resulted in an increasing use of topical drug delivery systems over the past number of years. Typically, these topical dosage forms can be in liquid, semisolid, or solid form.

[0004] Drugs have typically been applied to the skin in this manner to elicit one or more of four general effects: an effect on the skin surface, an effect within the stratum corneum, a more deep-seated effect requiring penetration into the epidermis and dermis, or a systemic effect resulting from delivery of a sufficient amount of drug through the epidermis and the dermis to the vasculature to produce therapeutic systemic concentrations.

[0005] However, the penetration of a drug into the viable epidermis and dermis when applied in a topical dosage form may sometimes be difficult to achieve. Further, even if drug penetration is achieved, the drug may only be delivered to the local area where the composition is applied, rather than regionally or systemically. Accordingly, topical compositions are generally not optimal in treating many dermatological disorders that exhibit certain regional or systemic effects.

[0006] Topical pharmaceutical dosage forms may have the further disadvantage of exhibiting side effects on application, such as irritation to sensitive skin areas. Such irritation is often due to the presence of preservatives to maintain the stability of the active agent in the topical dosage form. Maintaining drug stability in topical compositions at times can be a very difficult endeavor, making preservatives a very common and necessary ingredient in many topical compositions.

[0007] Further, topical compositions at times have to remain in contact with the skin for an extended period of time to release sufficient amounts of the active agent to the skin and exert the desired pharmacological effect against a dermatological disorder. However, it may be difficult to formulate a topical composition that remains on the skin for this extended period of time without wearing or rubbing off during the wearers regular daily activities. Further, topical compositions that are sufficiently robust to remain on the skin for extended periods of time often have disadvantages in that they may not be readily absorbed by the skin, they

[0008] To overcome some of these problems associated with certain topical treatments of dermatological disorders, many drugs may be administered in an oral dosage form. The most common oral dosage forms are tablets and capsules. Tablets and capsules may be prepared from the compression of solid ingredients, in powder form or otherwise. However, an oral dosage form such as a tablet or capsule formed via compression oftentimes results in a large amount of degradates of the active ingredient.

[0009] Further, solid oral dosage forms may cause irritation upon administration due to the presence of the active agent in a powdery, crystal form. This powdery, crystal form of the active ingredient likewise may make it difficult to achieve an optimal, controlled dissolution and absorption of the active agent after administration. It is oftentimes difficult to attain a consistent bioavailability of the active agent due to this powdery crystal form.

[0010] Most tablets also require the use of a diluent, or a bulking agent, to make the tablet a practical size for compression. Similarly, tablets oftentimes contain other excipients such as binders, lubricants, glidants, and disintegrants to permit formation of the tablet, as well as to aid in drug delivery. However, the presence of these additional ingredients may have an adverse effect on both the patient and the stability of the active ingredients, depending on the agent used.

[0011] Additionally, certain hard tablets and capsules are poor delivery devices for hydrophobic drugs. Hydrophobic drugs generally do not dissolve readily in water, gastric fluid, or intestinal fluid. When they are compounded in solid dosage forms, the dissolution rate may be slow, absorption may vary, and the bioavailability may be incomplete.

[0012] Hard tablets and hard capsules are also difficult for certain patients, particularly certain young and old patients, as well as female patients, to swallow. This is due to their hard, compact nature, which results in a rough exterior that may easily get caught in the mouth or throat. Accordingly, there remains a need for an additional dosage form easily administrable to young, old, and female human patients that is effective for the treatment of dermatological disorders.

[0013] Soft gel capsules, or softgels, are known in the art as alternative dosage forms to those described above, but not necessarily for the treatment of dermatological disorders. For example, U.S. Pat. No. 5,587,149 discloses such a softgel formulation for water-soluble active ingredients, such as ascorbic acid (vitamin C), where the fill material comprises an emulsion of which a first phase includes polyethylene glycol (into which the water-soluble active ingredient is dissolved) and the second phase includes a silicone fluid.

[0014] Likewise, U.S. Pat. No. 6,251,426 discloses a soft gelatin capsule that contains a highly concentrated solution of ibuprofen. However, this patent does not disclose the ability of softgels to deliver active agents useful in treating dermatological disorders.

[0015] U.S. Pat. No. 5,200,191 discloses a softgel composition containing retinol for topical application to the skin. The disclosed softgel provides a single use method for dispensing the product, wherein the softgel contains a twist-

agent in the disclosed softgel is applied topically to the skin, this dosage form is very similar to the topical dosage forms previously discussed.

[0016] One oral softgel known in the art for the treatment of dermatological disorders is Accutane®, a softgel available from Hoffmann-La Roche, New Jersey, containing the active ingredient isotretinoin, a known retinoid. The soft gel dosage form is used to protect the isotretinoin during manufacturing, as retinoids as a class of compounds must be protected from oxygen to prevent oxidation. However, this softgel composition does not possess any advantages over, e.g., a topical composition containing isotretinoin with respect to the actual delivery of the drug to a patient. In fact, since the isotretinoin is contained in the Accutane® softgel in a liquid suspension, it has a half life after administration of about 90 hours, resulting in a high possibility of adverse side effects.

[0017] Accordingly, there remains a need in the art for methods of treating certain dermatological disorders by administering a composition that can effectively deliver an active agent to the body for the treatment of the dermatological disorder. Such a method would provide an alternative to topical dosage forms and compressed oral dosage forms such as tablets and capsules by effectively administering a drug orally for the treatment of dermatological disorders. There further remains a need for treating dermatological disorders in young, old, and female patients by administering an oral composition that is easily and readily taken by these patient groups. The present subject matter addresses these needs.

SUMMARY OF THE INVENTION

[0018] The present subject matter relates generally to a method of treating a dermatological disorder in a mammal. This method is achieved by administering to the mammal a soft gel capsule providing a therapeutically effective amount of a pharmacologically active agent. The soft gel capsule preferably comprises an internal, non-aqueous liquid phase and an external gelatin and/or soft cellulose layer. The internal, non-aqueous liquid phase may comprise a solution or suspension of the pharmacologically active agent having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of the pharmacologically active agent. This purity and concentration of degradation product(s) of the active agent are preferably sufficient to permit safe treatment of the dermatological disorder and provide improved bioavailability of the pharmacologically active agent.

[0019] In a preferred embodiment, the pharmacologically active agent is selected from the group consisting of antibiotics, antiinfectives, antimycotic agents, steroids, antihistamines, antiparasitic agents, immunomodulators, antisense agents, antiviral agents, treatments for hypo- and hyper-skin pigmentation disorders, antipsoriatic agents, keratolytic agents, immunosuppressants, DNA synthesis inhibitors, cytotoxic agents, antithyroid agents, monoclonal antibody regulators, TNF alpha antagonists, immunoglobulins, metabolic regulators, antiangiogenic agents, kinase regulators, hormones, photodynamic agents, protease inhibitors, anxiolytics, cell growth regulators, enzymes, prostaglandins,

[0020] In another preferred embodiment, the present subject matter relates to a method of treating a dermatological disorder in a mammal, comprising:

[0021] orally administering to said mammal a soft gel capsule providing improved bioavailability of a pharmacologically active agent comprising:

[0022] an internal, non-aqueous liquid phase comprising a solution or suspension of a single, hydrophobic, pharmacologically active agent effective to treat said dermatological disorder having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said hydrophobic pharmacologically active agent, wherein said purity and concentration of degradation product(s) are sufficient to permit safe treatment of said dermatological disorder; and

[0023] an external gelatin layer comprising gelatin, soft cellulose, or a mixture thereof and additional components selected from the group consisting of an additional gelling agent, a plasticizer, water, a colorant, an antioxidant, a flavorant, and mixtures thereof;

[0024] wherein said hydrophobic pharmacologically active agent is selected from the group consisting of antiinfectives, steroids, a salt thereof, a derivative thereof, and mixtures thereof.

[0025] In yet another preferred embodiment, the present subject matter relates to a method of treating a dermatological disorder in a mammal, comprising:

[0026] orally administering to said mammal a soft gel capsule providing improved bioavailability of a pharmacologically active agent comprising:

[0027] an internal, non-aqueous liquid phase having a pH of from about 3 to about 9 when combined with an aqueous medium comprising a solution or suspension of a single, hydrophobic, pharmacologically active agent effective to treat said dermatological disorder and one or more fatty acids or derivatives thereof selected from the group consisting of omega-3 fatty acids, DHA, docosapentaenoic acid, tetracosapentaenoic acid, tetracosahexaenoic acid, monounsaturated fatty acids, polyunsaturated fatty acids, saturated fatty acids, trans fatty acids, derivatives thereof, and mixtures thereof, said single pharmacologically active agent comprising a hydrophobic antiinfective agent or a salt or derivative thereof having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said hydrophobic antibiotic agent, wherein said purity and concentration of degradation product(s) are sufficient to permit safe treatment of said dermatological disorder; and

[0028] an external gelatin layer comprising gelatin and additional components selected from the group consisting of an additional gelling agent, a plasticizer, water, a colorant, an antioxidant, a flavorant, and mixtures thereof.

[0029] In still another preferred embodiment, the present

[0030] orally administering to said mammal a soft gel capsule providing improved bioavailability of doxycycline or a salt or derivative thereof comprising:

[0031] an internal, non-aqueous liquid phase having a pH of from about 3 to about 9 when combined with an aqueous medium comprising a solution or suspension of doxycycline or a salt or derivative thereof as a sole active ingredient effective to treat said dermatological disorder and one or more fatty acids or derivatives thereof selected from the group consisting of omega-3 fatty acids, DHA, docosapentaenoic acid, tetracosapentaenoic acid, tetracosahexaenoic acid, monounsaturated fatty acids, polyunsaturated fatty acids, saturated fatty acids, trans fatty acids, derivatives thereof, and mixtures thereof, said doxycycline having a purity of at least 95% and a concentration of degradation product(s) less than about 5% of the starting concentration of said doxycycline, wherein said purity and concentration of degradation product(s) are sufficient to permit safe treatment of said dermatological disorder; and

[0032] an external gelatin layer comprising gelatin and additional components selected from the group consisting of an additional gelling agent, a plasticizer, water, a colorant, an antioxidant, a flavorant, and mixtures thereof.

[0033] In an alternative preferred embodiment, the present subject matter relates to a method of treating a dermatological disorder in a mammal, comprising:

[0034] orally administering to said mammal a soft gel capsule providing improved bioavailability of a hydrophobic pharmacologically active agent comprising:

[0035] an internal, non-aqueous liquid phase comprising a solution or suspension of a single hydrophobic pharmacologically active agent or a salt or derivative thereof effective to treat said dermatological disorder and one or more fatty acids or derivatives thereof selected from the group consisting of omega-3 fatty acids, docosahexaenoic acid (DHA), docosapentaenoic acid, tetracosapentaenoic acid, tetracosahexaenoic acid, monounsaturated fatty acids, polyunsaturated fatty acids, saturated fatty acids, trans fatty acids, derivatives thereof, and mixtures thereof, said hydrophobic pharmacologically active agent having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said hydrophobic pharmacologically active agent, wherein said purity and concentration of degradation product(s) are sufficient to permit safe treatment of said dermatological disorder; and

[0036] an external gelatin layer comprising gelatin and additional components selected from the group consisting of an additional gelling agent, a plasticizer, water, a colorant, an antioxidant, a flavorant, and mixtures thereof.

[0037] In a further alternative embodiment, the present subject matter relates to a method for treating a human

[0038] orally administering to said human patient in need thereof a soft gel capsule providing improved bioavailability of a pharmacologically active agent comprising:

[0039] an internal, non-aqueous liquid phase comprising a solution or suspension of a pharmacologically active agent having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said pharmacologically active agent and one or more fatty acids or derivatives thereof, wherein said purity and concentration of degradation product(s) are sufficient to permit safe treatment of said human patient and provide improved bioavailability of said pharmacologically active agent; and

[0040] an external gelatin and/or soft cellulose layer;

[0041] wherein said pharmacologically active agent is selected from the group consisting of antibiotics, antiinfectives, antimycotic agents, steroids, antihistamines, antiparasitic agents, immunomodulators, antisense agents, antiviral agents, treatments for hypo- and hyper-skin pigmentation disorders, antipsoriatic agents, keratolytic agents, immunosuppressants, DNA synthesis inhibitors, cytotoxic agents, antithyroid agents, monoclonal antibody regulators, TNF alpha antagonists, immunoglobulins, metabolic regulators, antiangiogenic agents, kinase regulators, hormones, photodynamic agents, protease inhibitors, anxiolytics, cell growth regulators, enzymes, prostaglandins, peptides, analgesics, salts thereof, derivatives thereof, and mixtures thereof.

[0042] In yet another alternative embodiment, the present subject matter relates to a method of treating a dermatological disorder in a human patient having an age in excess of at least 55 years, comprising:

[0043] orally administering to said human patient in need thereof a soft gel capsule providing improved bioavailability of a tetracycline comprising:

[0044] an internal, non-aqueous liquid phase having a pH of from about 3 to about 9 when combined with an aqueous medium comprising a solution or suspension of a tetracycline or a salt or derivative thereof as a sole active ingredient effective to treat said dermatological disorder and one or more fatty acids or derivatives thereof selected from the group consisting of omega-3 fatty acids, docosahexaenoic acid (DHA), docosapentaenoic acid, tetracosapentaenoic acid, tetracosahexaenoic acid, monounsaturated fatty acids, polyunsaturated fatty acids, saturated fatty acids, trans fatty acids, derivatives thereof, and mixtures thereof, said tetracycline having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said tetracycline, wherein said purity and concentration of degradation product(s) are sufficient to permit safe treatment of said human patient; and

[0045] an external gelatin layer comprising gelatin and additional components selected from the group consisting of an additional gelling agent, a plasti-

[0046] In still another preferred embodiment, the present subject matter relates to a soft gel capsule suitable for oral administration to a human and providing improved bioavailability of a dermatologically effective active agent comprising:

[0047] an internal, non-aqueous liquid phase having a pH of from about 3 to about 9 when combined with an aqueous medium comprising a solution or suspension of a dermatologically effective active agent or a salt or derivative thereof and one or more fatty acids or derivatives thereof selected from the group consisting of omega-3 fatty acids, DHA, docosapentaenoic acid, tetracosapentaenoic acid, tetracosahexaenoic acid, monounsaturated fatty acids, polyunsaturated fatty acids, saturated fatty acids, trans fatty acids, derivatives thereof, and mixtures thereof, said dermatologically active agent having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said dermatologically active agent, wherein said purity and concentration of degradation product(s) are sufficient to permit safe treatment of said human patient; and

[0048] an external gelatin layer comprising gelatin and additional components selected from the group consisting of an additional gelling agent, a plasticizer, water, a colorant, an antioxidant, a flavorant, and mixtures thereof.

[0049] In a further preferred embodiment, the present subject matter relates to a soft gel capsule suitable for oral administration to a human and providing improved bioavailability of a tetracycline comprising:

[0050] an internal, non-aqueous liquid phase having a pH of from about 3 to about 9 when combined with an aqueous medium comprising a solution or suspension of a tetracycline or a salt or derivative thereof as a sole active ingredient effective to treat a dermatological disorder and one or more fatty acids or derivatives thereof selected from the group consisting of omega-3 fatty acids, docosahexaenoic acid (DHA), docosapentaenoic acid, tetracosapentaenoic acid, tetracosahexaenoic acid, monounsaturated fatty acids, polyunsaturated fatty acids, saturated fatty acids, trans fatty acids, derivatives thereof, and mixtures thereof, said tetracycline having a purity of at least 90% and a concentration of degradation product(s) less than about 10% of the starting concentration of said tetracycline, wherein said purity and concentration of degradation product(s) are sufficient to permit safe treatment of said human patient; and

[0051] an external gelatin layer comprising gelatin and additional components selected from the group consisting of an additional gelling agent, a plasticizer, water, a colorant, an antioxidant, a flavorant, and mixtures thereof.

DETAILED DESCRIPTION OF THE INVENTION

[0052] Definitions

treated. The term administering as used herein excludes providing a composition to a patient either intravenously or via inhalation.

[0054] As used herein, a "controlled release" refers to a release rate that is different from the pharmacologically active agent's normal release rate. Accordingly, this term indicates that the release rate of the pharmacologically active agent has been modified to achieve a delayed, sustained, or extended release in comparison to the agent's normal release rate.

[0055] As used herein, "degradation products" refers to the product(s) produced by decomposition of one or more of the active ingredients of the present compositions.

[0056] The phrase "effective amount", as used herein, means an amount of a composition or component thereof sufficient enough to positively modify the disorder to be treated but low enough to avoid secondary infections that cause a need for additional treatments beyond those contemplated herein. Effective amounts will vary with the particular disorder or disorders being treated, the severity of the disorder, the duration of the treatment, the specific components of the composition being used, the weight, tolerance, and other physical attributes of the patient being treated, and like factors as are known by health-care providers, including physicians.

[0057] As used herein, a "hard" oral dosage form refers to a solid oral drug delivery system formed for example via compression, direct or otherwise, granulation, and/or spray drying. For example, such a hard oral dosage form can be formed by compression of one or more powdery substances. Hard tablets, caplets, and pellets included in capsules are non-limiting examples of such hard oral dosage forms.

[0058] As used herein, "pharmaceutically acceptable salts" refers to salts of the active compound(s) which possess the same pharmacological activity as the active compound(s) and which are neither biologically nor otherwise undesirable. A salt can be formed with, for example, organic or inorganic acids. Non-limiting examples of suitable acids include acetic acid, acetylsalicylic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzoic acid, benzenesulfonic acid, bisulfic acid, boric acid, butyric acid, camphoric acid, camphorsulfonic acid, carbonic acid, citric acid, cyclopentanepropionic acid, digluconic acid, dodecylsulfic acid, ethanesulfonic acid, formic acid, fumaric acid, glyceric acid, glycerophosphoric acid, glycine, glucoheptanoic acid, gluconic acid, glutamic acid, glutaric acid, glycolic acid, hemisulfic acid, heptanoic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, hydroxyethanesulfonic acid, lactic acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthylanesulfonic acid, naphthylic acid, nicotinic acid, nitrous acid, oxalic acid, pelargonic, phosphoric acid, propionic acid, saccharin, salicylic acid, sorbic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid, thioglycolic acid, thiosulfuric acid, tosylic acid, undecylenic acid, naturally and synthetically derived amino acids.

[0059] If organic bases are used, poorly volatile bases are preferably employed, for example low molecular weight

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