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(54) **ORALLY ADMINISTERED CORTICOSTEROID COMPOSITIONS**

ORAL VERABREICHTE CORTICOSTEROID-ZUSAMMENSETZUNGEN

COMPOSITIONS DE CORTICOSTÉROÏDES ADMINISTRÉES PAR VOIE ORALE

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(56) References cited:
EP-A1- 1 595 533 **WO-A2-2010/144865**
US-A1- 2003 099 701 **US-A1- 2004 106 663**
US-A1- 2005 009 848 **US-A1- 2007 059 361**
US-A1- 2009 123 550 **US-A1- 2009 169 620**

- **BOWER ET AL.: 'Manifestations and Treatment of Laryngeal Sarcoidosis.' AM REV RESPIR DIS. vol. 122, no. 2, August 1980, pages 325 - 332, XP008155963**
- **WEI ET AL.: 'Efficacy of Single-Dose Dexamethasone as Adjuvant Therapy for Acute Pharyngitis. The Laryngoscope.' vol. 112, no. 1, January 2002, pages 87 - 93, XP008155940**

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Dr. Falk Pharma **Ex. 1003**
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Description

TECHNICAL FIELD OF THE INVENTIONS

[0001] This invention relates to orally administered corticosteroid compositions, useful for the treatment of conditions associated with inflammation of the gastrointestinal tract.

BACKGROUND OF THE INVENTION

[0002] A quick-disintegrating tablet in the buccal cavity is described in US 2003/0099701. There are currently no approved topically administered anti-inflammatory medications for the treatment of conditions associated with inflammation of the upper portion of the gastrointestinal tract. One such condition, eosinophilic esophagitis (EE), is an inflammatory condition of the esophagus. It is characterized histologically by a proliferation of eosinophils. The disease is painful, leads to difficulty swallowing and predisposes patients to food impaction and other complications.

[0003] Experimental and "off-label" treatments for EE include directing steroid medications formulated and approved for inhalation to the back of the throat such that they are not appreciably inhaled, and instructing the patient to rinse their mouth immediately after administration and not to swallow food or water for two hours after administration. Rinsing is recommended because residual drug in the mouth and throat can lead to candiasis infection, and swallowing is contraindicated because it may wash drug away from the esophagus. Aqueous corticosteroid preparations intended for oral inhalation through nebulization are also mixed with sugars to produce a thickened and sweetened liquid for administration.

[0004] Off-label treatments for EE also include administration of corticosteroid tablets containing steroids such as prednisolone. However, systemic administration of corticosteroids is associated with a number of known and undesirable side-effects. For example, oral prednisolone can produce generalized suppression of immune function, and in children, particularly troubling side-effects from long term systemic exposure include growth retardation, which may lead to a reduction in adult height.

[0005] There is therefore a need in the art for orally administered corticosteroid formulations which provide topical (rather than systemic) treatment of inflammation of the gastrointestinal tract, particularly inflammation of the upper gastrointestinal tract, such as EE.

SUMMARY OF THE INVENTION

[0006] In a first aspect, there is provided an orally dispersing tablet comprising less than or equal to 20 mg of budesonide or a solvate or ester thereof, and at least one pharmaceutically acceptable ingredient which facilitates the dispersal of the tablet in the oral cavity, wherein the tablet is suitable for topical administration of budesonide in the upper gastrointestinal tract.

[0007] The compositions of the present invention are useful for various conditions including the treatment of inflammatory conditions of the gastrointestinal tract. Accordingly, the present invention also provides an orally dispersing tablet of the first aspect, for use in treating inflammatory conditions of the gastrointestinal tract in an individual.

DETAILED DESCRIPTION OF THE INVENTION

[0008] The term "drug", "active" or "active pharmaceutical ingredient" as used herein includes a pharmaceutically acceptable and therapeutically effective compound (e.g., corticosteroid), pharmaceutically acceptable salts, stereoisomers and mixtures of stereoisomers, solvates (including hydrates), and/or esters thereof (e.g., of corticosteroid).

[0009] The terms "orally disintegrating tablet", "orally dispersing tablet", or "ODT" refer to a solid dosage form of the present invention, which disintegrates rapidly in the oral cavity of a patient after administration, without chewing. The rate of oral disintegration can vary, but is significantly faster than the rate of oral disintegration of conventional solid dosage forms or chewable solid dosage forms (i.e., tablets or capsules) which are intended to be swallowed immediately after administration. ODT compositions of the present invention can contain pharmaceutically acceptable ingredients which swell, dissolve or otherwise facilitating the disintegration or dissolution of the ODT composition. Such ingredients can include pharmaceutical a disintegrant, a sugar alcohol, a saccharide, or a mixture thereof, a water-soluble binder, a meltable solid (e.g., a wax), which can release the corticosteroid upon entering the stomach, etc.

[0010] The term "about", as used herein to refer to a numerical quantity, includes "exactly". For example, "about 60 seconds" includes 60 seconds, exactly, as well as values close to 60 seconds (e.g., 50 seconds, 55 seconds, 59 seconds, 61 seconds, 65 seconds, 70 seconds, etc.). When the term "about" is used in reference to a range of values, the term "about" refers to both the minimum and maximum value of the range (e.g., "about 1-50 μm" means "about 1 μm to about 50 μm").

[0011] The term "adhesive agent", as used herein refers to agents which promote adhesion of the corticosteroid to biological surfaces, and includes, but is not limited to bio-adhesive agents. Adhesive agents can include compounds which adhere to the oropharyngeal mucosa, as well as compounds which increase the residence time of the compositions of the present invention on the oropharyngeal mucosa of a patient.

[0012] The term "intimately associated", as used herein to describe the spatial relationship between two or more components of a composition refers to components that are intimately mixed, such as for example in mixtures, coatings and matrices.

[0013] The term "having no significant systemic gluco-

corticoid or mineralocorticoid activity", as used herein refers to corticosteroid compositions which do not provide a generalized effect in the body through absorption into the circulation, but do provide local effects through topical contact with a diseased tissue. Corticosteroids which have high systemic glucocorticoid potencies when administered orally include e.g., hydrocortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, betamethasone, etc.) or mineralocorticoid potencies (e.g., alsosterone). Exemplary corticosteroids having no significant systemic glucocorticoid or mineralocorticoid activity include, but are not limited to budesonide, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone and tixocortol.

[0014] Unless indicated otherwise, all percentages and ratios are calculated by weight. Unless indicated otherwise, all percentages and ratios are calculated based on the total composition.

[0015] The solid pharmaceutical compositions of the present invention are suitable for topical administration of a corticosteroid to the gastrointestinal tract, for example the upper gastrointestinal tract such as the esophagus. Topical administration of a corticosteroid for conditions associated with inflammation of the gastrointestinal tract is desirable because it results in fewer side-effects than systemic corticosteroid administration. Such side-effects are reduced still further with the use of corticosteroids which do not have significant systemic glucocorticoid or mineralocorticoid activity because of their reduced systemic exposure.

[0016] The pharmaceutical compositions of the present invention are suitable for treating inflammatory conditions of the gastrointestinal tract, for example inflammatory conditions of the upper gastrointestinal tract such as the esophagus. Thus, the present invention includes treating inflammatory conditions of the gastrointestinal tract by administering to a patient in need thereof a solid pharmaceutical composition of the present invention. Inflammatory conditions of the gastrointestinal tract which may be treated according to the present invention include inflammation of the esophagus, inflammation of the glottis, inflammation of the epiglottis, inflammation of the tonsils, inflammation of the oropharynx, eosinophilic esophagitis, gastroesophageal reflux disease (GERD), non-erosive reflux disease (NERD), erosive esophagitis, Barrett's esophagus, eosinophilic gastroenteritis, hyper-eosinophilic syndrome, corrosive (caustic) chemical esophagitis, radiation-induced esophagitis, chemotherapy-induced esophagitis, transient drug-induced esophagitis (also known as medication esophagitis), persistent drug-induced esophagitis, Crohn's disease of the esophagus, scleroderma, and scleroderma sine scleroderma, systemic lupus erythematosus, systemic vasculitides, leukocytoclastic vasculitis, polyarteritis nodosa, Churg-Strauss syndrome, rheumatoid vasculitis, and pseudomembranous esophagitis.

[0017] In other embodiments, the pharmaceutical compositions of the present invention are suitable for treating inflammatory conditions of the gastrointestinal tract such as an autoimmune disease, Behcet's syndrome, Kawasaki disease, X-linked lymphoproliferative syndrome; an infectious viral disease caused by one or more of the following viruses: Adenoviridae, Coronaviridae, Coxsackie virus, Herpes simplex, HIV, Influenza (Type A), Lassa virus, Epstein-Barr virus, Parainfluenza, or Respiratory syncytial virus; an infectious bacterial disease caused by one or more of the following bacteria: Arcanobacterium hemolyticum, Chlamydia (Chlamydophila), Corynebacterium, Francisella tularensis, Group A, C, G Streptococcus, S. pneumoniae, S. pyogenes, Haemophilus influenza type B, Mycoplasma pneumonia, Neisseria gonorrhea, Multiple (e.g. peritonsillar cellulitis/abscess); an infectious fungal disease caused by Candida (e.g. Candida albicans) or Histoplasma (e.g. H capsulatum); inflammation caused by injury or an irritant selected from the group consisting of an airway foreign body, chloroacetophenone, chlorobenzylidene malononitrile, chronic smoke exposure, morpholine, sulfuryl fluoride, and scalded throat; lepidopterism, Seasonal allergic pharyngitis, and Stevens-Johnson syndrome; or periodic fever; etc.

[0018] In one embodiment, the present invention relates to a method for treating inflammation of the esophagus comprising administering to a patient in need thereof a pharmaceutical composition of the present invention. In one such embodiment, the present invention includes a method for treating eosinophilic esophagitis comprising administering to a patient in need thereof a pharmaceutical composition of the present invention.

[0019] In another embodiment, the present invention relates to a method for treating gastroesophageal reflux disease (GERD), nonerosive reflux disease (NERD) or erosive esophagitis comprising administering to an individual in need thereof a pharmaceutical composition of the present invention.

[0020] In another embodiment, the present invention relates to a method for treating a food allergy with an identified allergen, e.g., "atopic IBS", and "atopic bowel".

[0021] In one embodiment, the present invention provides a solid pharmaceutical composition which comprises less than or equal to 20 mg of a corticosteroid, wherein the composition has no significant systemic glucocorticoid or mineralocorticoid activity, and wherein the solid pharmaceutical composition disintegrates within 60 seconds in simulated saliva when tested using the USP <701> Disintegration Test. In another embodiment, the solid pharmaceutical compositions of the present invention disintegrate within 60 seconds in the oral cavity of the patient, e.g. human. In still other embodiments, the solid pharmaceutical compositions of the present invention disintegrate within 30 seconds in simulated saliva (using the USP <701> Disintegration Test), or in the oral cavity of a patient. In still other embodiments, the solid pharmaceutical compositions of the present invention topically provide a therapeutically effective amount of a corticosteroid to inflamed tissues of the gastrointestinal

tract, after oral administration to a patient in need thereof.

[0022] The orally dispersing tablets of the present invention can include, for example, a wafer, a film, or other solid dosage form which disintegrates or dissolves rapidly in the mouth to form a solution or dispersion of a corticosteroid, which can readily be swallowed.

[0023] In another embodiment, the compositions of the present invention include a bioadhesive agent, which is a lipid or a mixture of lipids. Such lipids or lipid mixtures may undergo a phase transition on contact with wetted biological surfaces to form an adhesive film. Examples of such lipids include mixtures of so-called membrane and non-membrane lipids which will typically form lamellar and non-lamellar structures, such as hexagonal or cubic phases, respectively. Examples of such lipids are glycerphospholipids such as phosphatidyl choline, and diacyl glycerols such as glycerol dioleate. Such self-organizing structures demonstrate superior spreading and adhesion to biological surfaces and have the advantage or being pharmaceutically acceptable materials. Advantageously the active agent, e.g. a corticosteroid may be dissolved in the lipid component.

[0024] The corticosteroid which is included in the pharmaceutical compositions of the present invention is budesonide, or a solvate or ester thereof.

[0025] The amount of corticosteroid present in the pharmaceutical compositions of the present invention will, in general, be selected so as to maximize the therapeutic benefit from topical administration while minimizing systemic absorption. In the case of solid pharmaceutical compositions of the present invention, the amount of corticosteroid in the composition is less than or equal to 20 mg. In one embodiment the amount of corticosteroid in the pharmaceutical composition is between about 0.01 mg and about 20 mg. In another embodiment the amount of corticosteroid in the pharmaceutical composition is between about 1 mg and about 15 mg. In still another embodiment the amount of corticosteroid in the pharmaceutical composition is between about 2 mg and about 10 mg. In yet another embodiment the amount of corticosteroid in the pharmaceutical composition is between about 2 mg and about 5 mg. In still other embodiments, the amount of corticosteroid is about 0.01 mg, about 0.02 mg, about 0.03 mg, about 0.04 mg, about 0.05 mg, about 0.06 mg, about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 90 mg, or about 20 mg, inclusive of all ranges and subranges therebetween.

[0026] Typical amounts of corticosteroid in the solid pharmaceutical compositions of the present invention include about 0.25 mg, about 0.5 mg, about 1 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 mg, about 4 mg, about 4.5 mg and about 5 mg.

[0027] Upon administration of a solid pharmaceutical composition of the present invention to an individual, the composition disintegrates in the patient's oral cavity. In one embodiment, the composition of the present invention is in the form of an ODT comprising drug containing particles (e.g., a corticosteroid as described herein optionally coated or combined with an adhesive agent as described herein), combined with rapidly dispersing microgranules. Rapidly dispersing microgranules can be prepared as described in US 2005/0232988 or US 20010014340 by granulating a disintegrant having an average particle size of not more than about 30 μm with a sugar alcohol and/or saccharide having an average particle size of not more than about 30 μm. The granulation can be carried out, for example, in a high shear granulator with approximately 20-25% water as the granulating fluid, and if needed wet milled and dried to produce rapidly dispersing microgranules having an average particle size of not more than about 300 μm (e.g., about 175-300 μm).

[0028] The ratio of the disintegrant to the sugar alcohol, saccharide, or mixture thereof in the rapidly dispersing microgranules ranges from about 90/10 to about 99/01, for example about 90/10, about 91/9, about 92/8, about 93/7, about 94/6, about 95/5, about 96/4, about 97/3, about 98/2, about 99/1, inclusive of all values, ranges, and subranges therebetween.

[0029] The ratio of the rapidly dispersing microgranules to drug-containing particles ranges from about 5/1 to about 1/1, including about 5/1, 4/1, 3/1, 2/1, 1/1, inclusive of all values, ranges, and subranges therebetween.

[0030] The corticosteroid containing particles of the ODT dosage form should also have a small enough particle size such that after disintegration of the ODT in the oral cavity of the patient, a smooth, easy-to-swallow suspension results. In most embodiments in which the pharmaceutical compositions of the present invention is provided as an ODT dosage form, the average particle size of the taste-masked non-opioid analgesic/opioid analgesic drug-containing microparticles is not more than about 400 μm, or in some embodiments not more than about 300 μm.

[0031] The ODT dosage form as described herein may also include pharmaceutically acceptable excipients typically used in disintegrating tablet formulations such as microcrystalline cellulose and spray dried mannitol (compressible diluents), croscarmellose sodium or crospovidone (super disintegrant), coloring agents, and optionally magnesium stearate or sodium stearyl fumarate (lubricant intragranularly mixed or used externally to lubricate die and punch surfaces).

[0032] Tablet dosage forms, including ODT dosage forms, comprising the pharmaceutical composition of the present invention have a low friability, e.g., less than about 1%, (e.g., less than about 0.9%, less than about 0.8%, less than about 0.7%, less than about 0.6%, less than about 0.5%, less than about 0.4%, less than about 0.3%, etc., inclusive of all ranges and subranges therebetween) in order to have sufficient durability to withstand handling, shipping, and/or packaging in push-through

blister packaging.

[0033] A non-limiting list of suitable disintegrants for the rapidly dispersing microgranules includes crospovidone (cross-linked PVP), sodium starch glycolate, cross-linked sodium carboxymethylcellulose, calcium silicate, and low substituted hydroxypropyl cellulose. The amount of disintegrant in the ODT is typically in the range of about 1 % to about 10% by weight.

[0034] A non-limiting list of suitable sugar alcohols includes mannitol, sorbitol, xylitol, maltitol, arabitol, ribitol, dulcitol, iditol, isomalt, lactitol, erythritol and combinations thereof. A non-limiting list of suitable saccharides includes lactose, sucrose, maltose, and combinations thereof. The amount of sugar alcohol and/or saccharide in the ODT ranges from about 30% to about 70% by weight.

[0035] Pharmaceutically acceptable excipients include fillers, diluents, glidants, disintegrants, binders and lubricants. Other pharmaceutically acceptable excipients include acidifying agents, alkalizing agents, preservatives, antioxidants, buffering agents, chelating agents, coloring agents, complexing agents, emulsifying and/or solubilizing agents, flavors, perfumes, humectants, sweetening agents and wetting agents.

[0036] Examples of suitable fillers, diluents and/or binders include lactose (e.g. spray-dried lactose, α-lactose, β-lactose, Tabletose®, various grades of Pharmatose®, Microtose® or Fast-Flo®), microcrystalline cellulose (various grades of Avicel®, Ceolus®, Elcema®, Vivacel®, Ming Tai® or Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), low molecular weight hydroxypropyl methylcellulose (HPMC) (e.g. Methocel E, F and K from Dow Chemical, Metolose SH from Shin-Etsu, Ltd), hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylhydroxyethylcellulose and other cellulose derivatives, sucrose, agarose, sorbitol, mannitol, dextrins, maltodextrins, starches or modified starches (including potato starch, maize starch and rice starch), calcium phosphate (e.g. basic calcium phosphate, calcium hydrogen phosphate, dicalcium phosphate hydrate), calcium sulfate, calcium carbonate, sodium alginate and collagen.

[0037] Examples of suitable diluents include e.g. calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, powdered cellulose, dextrans, dextrin, dextrose, fructose, kaolin, lactose, mannitol, sorbitol, starch, pregelatinized starch, sucrose and sugar.

[0038] Examples of suitable disintegrants include e.g. alginic acid or alginates, microcrystalline cellulose, hydroxypropyl cellulose and other cellulose derivatives, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, starch, pregelatinized starch, and carboxymethyl starch (e.g. Primogel® and Explotab®).

[0039] Specific examples of glidants and lubricants include stearic acid, magnesium stearate, calcium stearate or other metallic stearates, talc, waxes and glycerides, light mineral oil, PEG, glyceryl behenate, colloidal silica, hydrogenated vegetable oils, corn starch, sodium stearyl fumarate, polyethylene glycols, alkyl sulfates, sodium benzoate and sodium acetate.

[0040] Other excipients include e.g. flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, antioxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents and agents for modified release.

[0041] Other functional excipients such as cyclodextrins may be used, for example as taste-masking agents (e.g., by means of their complexation with the corticosteroid). Cyclodextrins may also be used as a carrier and/or a dispersant to facilitate delivery and distribution of the corticosteroid at the intended site of therapeutic activity.

[0042] Compositions of the present invention in the form of an ODT disintegrate into corticosteroid containing particles while sugar alcohol/saccharide-containing granules included within the composition rapidly dissolve, thereby forming a smooth suspension that can be readily swallowed.

[0043] Other corticosteroid-containing orally disintegrating or orally dissolving tablet dosage forms such as wafers or films can also be used. For example, wafers can include dried or lyophilized compositions such as orally disintegrating or dissolving dosage forms prepared using Zydis® lyophilization technology (e.g., as described in U.S. Patent No. 6,316,027), containing a corticosteroid as the active pharmaceutical ingredient. Film dosage forms can include edible films such as those described in US 6,596,298 or US 6,740,332, containing a corticosteroid as the active pharmaceutical ingredient.

[0044] The rate of disintegration of the compositions of the present invention in the oral cavity of an individual can be in the order of about 60 seconds or less, about 50 seconds or less, about 40 seconds or less, about 30 seconds or less, about 20 seconds or less, or about 10 seconds or less.

[0045] The rate of disintegration of the solid pharmaceutical compositions of the present invention can be measured using various in vitro test methods, for example the USP <701> Disintegration Test. When using the USP <701> Disintegration Test, the rate of disintegration of the compositions of the present invention typically is about 60 seconds or less, about 45 seconds or less, about 30 seconds or less, about 20 seconds or less, or about 10 seconds or less.

[0046] In other embodiments, the solid pharmaceutical compositions of the present invention can have any rate of disintegration or dissolution in the oral cavity of a patient which provides a therapeutically effective amount of corticosteroid to the inflamed tissues of the gastrointestinal tract. For example, in some embodiments, solid pharmaceutical compositions according to the present invention include compositions that provide about 0.5 mg

to about 20 mg of the corticosteroid to the inflamed tissues of the gastrointestinal tract after oral administration.

[0047] In one embodiment, the solid pharmaceutical compositions of the present invention include an adhesive agent. Suitable adhesive agents include sucrose aluminum sulfate complex, chitosan and derivatives thereof (e.g., trimethylchitosan, chitosan salts), polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, hydroxypropyl cellulose, cross-linked or uncross-linked polyacrylates, cross-linked polyacrylates, acidic cross-linked or uncross-linked polyacrylates, polyacrylic acid homopolymers or copolymers, aminoalkyl methacrylate copolymers, methacrylic acid/methylmethacrylate copolymer, alkylacrylate/alkylmethacrylate copolymers, ammoniomethacrylate copolymers, Eudragit® polymers (E, L, S, NE, RL, and RS grades), carbomer homopolymers or copolymers, hydrophilic polysaccharide gums, maltodextrins, cross-linked alignate gum gels, polycarboxylated vinyl polymers, pectins, xanthan gums, alginic acid, modified alginic acids, and combinations thereof.

[0048] In certain embodiments of the solid pharmaceutical compositions of the present invention, the corticosteroid and the adhesive agent are intimately associated. In one such embodiment the solid pharmaceutical composition comprises corticosteroid surrounded or encapsulated by the adhesive agent. In another such embodiment the solid pharmaceutical composition comprises corticosteroid disposed on the surface of the adhesive agent. In still other embodiments, the solid pharmaceutical composition comprises corticosteroid mixed or granulated with the adhesive agent.

[0049] Topical administration of a corticosteroid to the oral cavity of individuals has been associated with candidiasis infection. Consequently, in one embodiment pharmaceutical compositions of the present invention include an antifungal agent. Suitable antifungal agents include, but are not limited to mitotic inhibitor antifungals, pyrimidine analog antifungals, polyene antifungals, benzimidazole antifungals, imidazole antifungals, polyene antifungals, triazole antifungals, thiazole antifungals, allylamine antifungals, echinocandin antifungals, and other "uncategorized" antifungals recognized in the art that do not fall within any of the above categories (e.g., tolnaflate and ciclopirox). For example, suitable antifungal agents which may be included in the solid pharmaceutical compositions of the present invention include abafungin, amorolfine, anidulafungin, bifonazole, butenafine, butoconazole, candicin, caspofungin, ciclopirox, clotrimazole, econazole, fenticonazole, filipin, fluconazole, flucytosine, griseofulvin, isavuconizole, isoconazole, itraconazole, ketoconazole, micafungin, miconazole, miconazole nitrate, naftifine, natamycin, nystatin, oxiconazole, posaconazole, pramiconazole, ravuconazole, rimocidin, setaconizole, sulconazole, terbafine, terconazole, tioconazole, tolnaftate, undecylenic acid, and voriconazole.

[0050] In another embodiment, pharmaceutical compositions of the present invention include an antiviral agent. Antiviral agents which may be included in the solid pharmaceutical compositions of the present invention include interferons, nucleoside and nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, fusion inhibitors, maturation inhibitors, guanosine analogs, puridine analogs, pyrimidine analogs, and other "uncategorized" antiviral drugs recognized in the art which do not fall within any of the above classes (e.g. foscarnet and miltefosine). For example, suitable antifungal agents which may be included in the solid pharmaceutical compositions of the present invention include abacavir, aciclovir (also known as acyclovir), adefovir, amantadine, amdoxovir, amprenavir, aplaviroc, apricitabine, arbidol, atazanavir, bevirimat, BMS-488043, boceprevir, brivudine, cidofovir, DCM205, docosanol, delavirdine, didanosine, durunavir, efavirenz, elvitegravir, elvucitabine, emtricitabine, enfuvirtide, epigallocatechin gallate, etravirine, famciclovir, fosamprenavir, ganciclocvir, globoidnan A, griffithsin, ibalizumab, idoxuridine, indinavir, lamivudine, lopinavir, loviride, maraviroc, nelfinavir, nevirapine, oseltamivir, pegylated interferon α-2a, pegylated interferon α-2b, penciclovir, peramivir, plerixafor, PRO 140, racivir, raltegrvir, ritonavir, ribavirin, rimantadine, rlipivirine, saquinavir, stampidine, stavudine, tenofovir, tipranavir, TNX-355, trifluridine, tromantadine, valaciclovir, valganciclovir, vicriviroc, vidarabione, viramidine, vivecon, zalcitabine, zanamivir, and zidovudine.

[0051] In one embodiment, the solid pharmaceutical compositions of the present invention comprise corticosteroid-containing granules. The corticosteroid-containing granules may be granules comprising corticosteroid crystals and a film-forming binder, e.g., prepared by granulation. The corticosteroid crystals can have an average particle size ranging from about 1-300 μm, for example about 1-50 μm, about 1-100 μm, about 1-150 μm, about 1-200 μm, about 1-250 μm, about 50-100 μm, about 50-150 μm, about 50-200 μm, about 50-250 μm, about 50-300 μm, about 100-150 μm, about 100-200 μm, about 150-200 μm, about 150-250 μm, about 150-300 μm, about 200-250 μm, about 200-300 μm, or about 250-300 μm.

[0052] In another embodiment, the corticosteroid may be in the form of crystals. Such crystals may have an average size in the sub-micron range (e.g., average particle size of about < 1 μm), or may be nanoparticles (e.g., average particle size in the range of about 1-100 nm).

[0053] In yet another embodiment, the corticosteroid may be present in amorphous form, for example in association with a stabilizing agent which limits drug recrystallization, e.g., polyvinylpyrrolidone (PVP) (including homo- and copolymers of polyvinylpyrrolidone and homopolymers or copolymers of N-vinylpyrrolidone); crospovidone; gums; cellulose derivatives (including hydroxypropyl methylcellulose (HPMC), hydroxypropyl methylcellulose phthalate, hydroxypropyl cellulose, ethyl cellulose, hydroxyethylcellulose, sodium carboxymethyl

cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose, and others); dextran; acacia; homo- and copolymers of vinyllactam, and mixtures thereof, cyclodextrins; gelatins; hypromellose phthalate; sugars; polyhydric alcohols; polyethylene glycol (PEG); polyethylene oxides; polyoxyethylene derivatives; polyvinyl alcohol; propylene glycol derivatives and the like, sodium lauryl sulphate, Tween® surfactants, Eudragit® polymers; and combinations thereof.

[0054] The film-forming binder may comprise any suitable binder used in granulation. Non-limiting examples of suitable film-forming binders include water-soluble, alcohol-soluble or acetone/water soluble binders, e.g. polyvinylpyrrolidone (PVP), corn starch, polyethylene oxide, polyethylene glycol, hydroxypropyl methylcellulose (HPMC), methylcellulose, or hydroxypropylcellulose (HPC). The amount of film-forming binder in the corticosteroid-containing granules can range from about 0.5% to about 10%, including about 0.5%-1%, about 0.5%-2%, about 0.5%-5%, about 0.5%-7%, about 1%-2%, about 1%-5%, about 1%-7%, about 1%-10%, about 2%-5%, about 2%-7%, about 2%-10%, about 5%-7%, about 5%-10%, and about 7%-10%.

[0055] The corticosteroid-containing granules of the present invention may also include other pharmaceutically acceptable ingredients, for example, fillers or diluents. Non-limiting examples of other pharmaceutically acceptable ingredients for the corticosteroid-containing granules include, for example, mannitol, lactose, microcrystalline cellulose, potassium sulfate, calcium phosphate, modified starch, and mixtures thereof. The amount of other pharmaceutically acceptable ingredients (e.g. fillers or diluents) in the corticosteroid-containing granules can range from about 5%-80%, including about 5%-70%, about 5%-60%, about 5%-50%, about 5%-40%, about 5%-30%, about 5%-20%, about 5%-15%, about 5%-10%, about 10%-70%, about 10%-60%, about 10%-50%, about 10%-40%, about 10%-30%, about 10%-20%, about 10%-15%, about 20%-70%, about 20%-60%, about 20%-50%, about 20%-40%, about 20%-30%, about 20%-25%, about 30%-70%, about 30%-60%, about 30%-50%, about 30%-40%, about 30%-35%, about 40%-70%, about 40%-60%, about 40%-50%, about 40%-45%, about 50%-70%, about 50%-60%, about 50%-55%, about 60%-70%, or about 60%-65%.

[0056] In another embodiment, the corticosteroid-containing granules of the present invention can be in the form of corticosteroid-layered beads. Corticosteroid-layered beads comprise a core, e.g. a pharmaceutically acceptable sugar bead, coated with a corticosteroid layer. Such corticosteroid-layered beads can be prepared, for example, by dissolving or suspending corticosteroid in a polymeric binder solution, which is then sprayed or coated onto inert particles (e.g., sugar spheres or cellulose spheres (Celphere®)). Suitable polymeric binders include any of those disclosed herein, for example starches, modified celluloses (e.g., hydroxypropylcellulose, carboxymethylcellulose sodium), alginic acid, polyvinyl pyrrolidone (povidone), and mixtures thereof. The amount of corticosteroid in the corticosteroid layer, and the thickness of the corticosteroid layer can be modified to provide a therapeutically effective dose of corticosteroid. The corticosteroid-containing layer comprises about 90%-99% corticosteroid, and about 1% to about 10% binder.

[0057] The corticosteroid-containing granules of the present invention can be prepared by any suitable method. For example, the corticosteroid-containing granules can be prepared by granulation of corticosteroid crystals, one or more disintegrants, and one or more fillers (e.g., sugar alcohol, saccharide and/or microcrystalline cellulose) in a high shear granulator or a fluid-bed granulator using a solution of one or more polymeric binders, and dried in fluid bed equipment or on trays in a conventional oven to produce the corticosteroid-containing granules.

[0058] The solid pharmaceutical compositions of the present invention may include rapidly dispersing granules comprising a disintegrant and a sugar alcohol and/or a saccharide. The disintegrant-containing granules can include disintegrants or so-called super-disintegrants, e.g. crospovidone (crosslinked PVP), sodium starch glycolate, crosslinked sodium carboxymethyl cellulose, low substituted hydroxypropylcellulose, and mixtures thereof. The amount of disintegrant in the rapidly dispersing granules can range from about 1 %-10%, or about 5%-10% of the total weight of the rapidly dispersing granules, including all ranges and subranges therebetween.

[0059] Sugar alcohols are hydrogenated forms of carbohydrates in which the carbonyl group (i.e., aldehyde or ketone) has been reduced to a primary or secondary hydroxyl group. Non-limiting examples of suitable sugar alcohols for the rapidly dispersing granules of the pharmaceutical compositions of the present invention include e.g. arabitol, isomalt, erythritol, glycerol, lactitol, mannitol, sorbitol, xylitol, maltitol, and mixtures thereof. The term "saccharide" is synonymous with the term "sugars" includes monosaccharides such as glucose, fructose, the lactose, and ribose; and disaccharides such as sucrose, lactose, maltose, trehalose, and cellobiose. In one embodiment, non-limiting examples of suitable saccharides for use in the compositions of the present invention include e.g. lactose, sucrose, maltose, and mixtures thereof. In another embodiment, the rapidly dispersing granules comprise at least one disintegrant in combination with a sugar alcohol. In another embodiment, the rapidly dispersing granules comprise at least one disintegrant in combination with a saccharide. In yet another embodiment, the disintegrant-containing granules comprise at least one disintegrant in combination with a sugar alcohol and a saccharide. The amount of sugar alcohol and/or saccharide in the rapidly dispersing granules ranges from about 99%-90%, or about 95%-90% of the total weight of the disintegrant-containing granules, including all ranges and subranges therebetween. In one embodiment, the average particle size of a sugar alcohol

and/or saccharide is 30 μm or less, for example about 1-30 μm, about 5-30 μm, about 5-25 μm, about 5-20 μm, about 5-15 μm, about 5-10 μm, about 10-30 μm, about 10-25 μm, about 10-20 μm, about 10-15 μm, about 15-30 μm, about 15-25 μm, about 15-20 μm, about 20-30 μm, about 20-25 μm, or about 25-30 μm.

[0060] The corticosteroid-containing particles (e.g., crystals, granules, or drug-layered beads) of the solid pharmaceutical compositions of the present invention can also be coated with a taste-masking layer to improve the palatability of the composition. The corticosteroid-containing particles can be taste-masked by coating the corticosteroid-containing particles (e.g., crystals, granules, or drug-layered beads) with a water-insoluble polymer. Non-limiting examples of suitable water-insoluble polymers for the taste-masking layer include ethylcellulose, polyvinyl acetate (PVA), cellulose acetate (CA), cellulose acetate butyrate (CAB), methacrylate copolymers, such as those available under the tradename "EUDRAGIT" (e.g., type RL, RS, and NE30D), and combinations thereof.

[0061] In one embodiment, the water-insoluble polymer is ethylcellulose having a viscosity of about 90-110 cps when tested in an Ubbelohde viscometer as a 5 weight % 80:20 toluene/ethanol solution at 25°C.

[0062] In one embodiment, the solid pharmaceutical compositions of the present invention comprise about 25-35% of corticosteroid crystals, microencapsulated with a taste-masking layer comprising a water-insoluble polymer (e.g., ethylcellulose); about 60-70% of rapidly-dispersing granules (e.g., comprising crospovidone and mannitol); about 5% of additional disintegrant (e.g., crospovidone); about 1% of one or more flavors, and about 0.5%-1% of a sweetener (e.g., sucralose).

[0063] The method of producing drug-layered beads may comprise dissolving or suspending corticosteroid in a polymeric binder solution and layering onto inert particles (50-100 mesh or 150-300 μm in diameter) such as sugar spheres or cellulose spheres (e.g., Celphere® CP-203) using a fluid-bed coater equipped with a bottom-spray Wurster insert. These corticosteroid-coated beads can then be taste-masked by fluid-bed coating or by solvent coacervation as described herein.

[0064] In another embodiment, the compositions of the present invention can comprise corticosteroid particles (e.g., crystals), coated with a taste-masking layer. The taste-masking layer (as described herein) can be applied to the corticosteroid particles by any suitable method, for example coacervation or fluidized bed coating methods. Alternatively, the compositions of the present invention can comprise a corticosteroid complexed with a cyclodextrin.

[0065] The method of preparing the compositions of the present invention may include a taste-masking step. The taste-masked corticosteroid-containing particles of the compositions of the present invention (e.g., corticosteroid crystals, corticosteroid-containing microgranules or drug-layered beads) can be prepared by various methods, including solvent coacervation with a water-insoluble polymer such as ethylcellulose. The water-insoluble polymer (e.g., ethylcellulose), a phase-inducer (e.g., polyethylene), and corticosteroid are loaded into a coacervation tank containing cyclohexane. The mixture in the tank is heated to about 80°C to dissolve the ethylcellulose, and then slowly cooled under controlled conditions thereby causing phase-induced microencapsulation of corticosteroid particles by the ethylcellulose. Microencapsulation or coacervation refers to the process of applying a membrane by phase separation for imparting taste-masking (or sustained release) properties. Upon reaching ambient temperature, the suspension of microencapsulated corticosteroid particles are filtered, washed with fresh cyclohexane and dried to reduce residual solvent levels within acceptable limits (e.g., <4,000 ppm), in one embodiment less than 1,000 ppm. The coating weight of the microencapsulated corticosteroid particles can range from about 5% to about 30% including about 10%, 15%, 20%, and 25%, inclusive of all ranges and subranges therebetween. Examples of such a coacervation process are disclosed in U.S. Pat. Nos. 5,252,337, 5,639,475, 6,139,865 and 6,495,160.

[0066] Alternatively, the coacervation solution can comprise a mixture of the water-insoluble polymer (e.g., ethylcellulose) and a water-insoluble or gastrosoluble pore-former (e.g., calcium carbonate). The ratio of water-insoluble polymer to pore-former can range from about 50/50 to 95/05, including about 55/45, about 60/40, about 65/35, about 70/30, about 75/25, about 80/20, about 85/15, and about 90/10, including all ranges and subranges therebetween. The coating weight of the microencapsulated corticosteroid particles can range from about 5% to about 30% including about 10%, 15%, 20%, and 25%, inclusive of all ranges and subranges therebetween. In one embodiment, the coacervation step comprises suspending the drug-containing particles in a solution of water-insoluble ethylcellulose at 80°C in the coacervation tank. During the cooling cycle, the micronized pore-former is introduced into the tank at a temperature of about 58°C, while constantly stirring the suspension to uniformly distribute the pore-former in the microcapsule-membrane, at the forming/hardening phase. Examples of such a coacervation process are disclosed in U.S. Patent Publication No. US 2006/0105038.

[0067] In one embodiment, the solid pharmaceutical composition of the present invention is in the form of an orally disintegrating tablet (ODT) comprising drug particles and rapidly dispersing granules, wherein the drug particles comprise the corticosteroid, and the rapidly dispersing granules comprise a disintegrant and a sugar alcohol and/or saccharide. The drug particles may comprise, for example, corticosteroid crystals with or without a coating, corticosteroid-layered beads or granulates of corticosteroid with one more additional components. In certain embodiments the ODT is in the form of a wafer or film (for example those described in US 6,534,549, US 7,125,564, etc.).

[0068] In one embodiment of the present invention the solid composition comprises a lyophilized matrix, wherein the lyophilized matrix comprises corticosteroid and an excipient. Suitable excipients include mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, and combinations thereof.

[0069] The amount of corticosteroid-containing granules in the solid compositions of the present invention can range from about 5% to about 50%, including about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, and about 50%, inclusive of all values, ranges, and sub-ranges therebetween. In one embodiment, the composition of the present invention is an ODT comprising about 30% by weight of cortico steroid-containing granules.

[0070] One method for producing pleasant tasting corticosteroid ODT formulations of the present invention, comprising corticosteroid microparticles with a mean particle size of about 100-400 μm, comprises (i) preparing drug-containing cores having corticosteroid crystals with a desired mean particle size, e.g., as microgranules, corticosteroid particles (e.g., crystals), or as drug-layered beads, (ii) preparing granules comprising a disintegrant, a sugar alcohol and/or a saccharide, and (iii) compressing a blend comprising the corticosteroid microparticles and the disintegrant granules, optionally with pharmaceutically acceptable flavorant(s), sweetener(s), other disintegrant(s), colorant(s) and/or compression aides such as microcrystalline cellulose in sufficient quantities into the ODT form using a tablet press, such as a rotary tablet press equipped with an external lubrication system to lubricate the punches and dies prior to compression. These ODT tablets rapidly disintegrate upon exposure to the saliva in the mouth into a smooth, easy-to-swallow suspension with no gritty aftertaste.

[0071] A method for preparing ODT formulations of the present invention comprising corticosteroid microparticles with a mean particle size of about 100-400 μm can also include a unit process for taste-masking the corticosteroid-containing particles (e.g., corticosteroid crystals, corticosteroid-containing granules or drug-layered beads) by coacervation or fluid bed coating prior to blending and compression into ODT tablets. For example, corticosteroid crystalline material with an average particle size range of about 1-200 μm, more particularly about 50-150 μm can be coated with a taste-masking layer by either fluid-bed coating or solvent coacervation in accordance with other aspects of the invention. Corticosteroid crystalline material with a mean particle size of about 5-50 μm can also be taste-masked by solvent coacervation as described herein.

[0072] In another embodiment, the compositions of the present invention can be orally disintegrating tablets prepared by mixing corticosteroid microgranules or taste-masked corticosteroid microparticles, one or more flavoring agents, a sweetener, rapidly-dispersing microgranules, microcrystalline cellulose, and an additional disintegrant, and compressing this mixture into orally disintegrating tablets. The orally disintegrating tablets formed thereby rapidly disintegrate on contact with saliva in the buccal cavity, and have a pleasant taste (good creamy mouth feel) and provide rapid, substantially-complete release of the dose in the stomach.

[0073] In yet another embodiment, the compositions of the present invention may be orally disintegrating tablets formed by compressing a composition comprising corticosteroid-containing particles, rapidly-dispersing granules, and optionally flavoring agents, sweeteners, and other pharmaceutically acceptable excipients in a tablet press equipped with an externally lubricating system to pre-lubricate dies and punches, thereby providing a tablet formulation otherwise free of lubricant. The orally disintegrating tablets thus produced typically exhibit sufficient hardness and sufficiently low friability to be suitable for packaging in HDPE bottles and push-through film backed or peel-off paper backed blister packs using conventional equipment for storage, transportation and commercial distribution.

[0074] A method of manufacturing orally disintegrating tablets of the present invention may comprise the following steps: (a) preparing corticosteroid-containing microgranules by granulating crystalline corticosteroid material having an average particle size of about 5-50 μm and one or more diluents/fillers such as lactose, mannitol, microcrystalline cellulose and mixtures thereof, with a polymeric binder in a high-shear granulator or a fluid-bed coater; (b) granulating one or more sugar alcohols and/or saccharides, each having an average particle diameter of not more than about 30 μm, with a disintegrant such as crospovidone, using water or an alcohol-water mixture in a conventional granulator, and drying the granulate in fluid-bed equipment or a conventional oven to produce rapidly-dispersing microgranules with an average particle size of not more than about 400 μm, as described in U.S. Patent Publication No. US 20050232988; (c) blending the corticosteroid microgranules of step (a) with one or more flavoring agents, a sweetener, microcrystalline cellulose, additional disintegrant, and the rapidly-dispersing microgranules of step (b); and (d) compressing the blend of step (c) into tablets using e.g. a conventional rotary tablet press equipped with an external lubrication system to pre-lubricate the dies and punches.

[0075] A method of manufacturing orally disintegrating tablets of the present invention may comprise the following steps: a) preparing a drug-containing core particle (e.g., corticosteroid crystals, drug-layered beads, or corticosteroid-containing microgranules) by granulating the drug and optionally one or more diluents/fillers such as lactose, mannitol, microcrystalline cellulose and mixtures thereof with a polymeric binder in a high-shear granulator or a fluid-bed coater, or drug-layering on an inert particle (60-100 mesh sugar sphere or cellulose sphere, e.g., Celphere® CP-203) from a solution/suspension comprising a polymeric binder and the drug in a fluid-bed coater and optionally applying a seal-coat (e.g., Opadry® Clear); b) taste-masking core particles by microencap-

sulation, e.g. by solvent coacervation or fluid-bed coating with a water-insoluble polymer such as ethylcellulose, or with a mixture of a water-insoluble functional polymer and a water-soluble/gastrosoluble pore-former (e.g., ethylcellulose and sodium chloride or calcium carbonate at a ratio ranging from about 50/50 to 95/5) to produce pleasant-tasting microparticles with a desired particle size distribution (e.g., an average particle size of not more than about 400 μm, or an average particle size of not more than about 300 μm); c) granulating one or more sugar alcohols and/or saccharides, each of which has an average particle diameter of not more than about 30 μm, with a disintegrant such as crospovidone, as disclosed herein; d) blending the taste-masked microparticles of step (b) with one or more flavoring agents, a sweetener, microcrystalline cellulose, additional disintegrant, and rapidly-dispersing microgranules of step (c); and e) compressing the blend of step (d) into tablets using e.g. a conventional rotary tablet press equipped with an external lubrication system to pre-lubricate the dies and punches.

EXAMPLE (COMPARATIVE)

[0076] Fluticasone Propionate Microgranules A: Mannitol 25 (91.2% w/w) and Crospovidone XL-10 (4.8% w/w) at a ratio of 95/5 are co-milled individually by passing the mixture through a Comil® milling apparatus, equipped with 0.225" spacers, at a speed of about 1400-1500 rpm. The mannitol, crospovidone, and fluticasone propionate (4% w/w) crystalline material are blended for about 3-5 minutes to mix the ingredients. A Glatt GPCG-3 fluid-bed apparatus equipped with a top spray granulation chamber and a granulation bowl is charged with the pre-blend of mannitol, crospovidone, and fluticasone propionate (batch size: 1500 g) and granulated by spraying purified water (nozzle: 1.2 mm tip) at an atomization pressure of about 1.25 bar and at a spray rate of 30-50 mL/min and an outlet temperature of >70°C and at a product temperature of >33°C. The wet mass is dried until the moisture level (the percent loss on drying) is less than about 1%.

[0077] Tableting: A Hata production tablet press equipped with a vacuum transfer system, tablet de-duster, a metal detector, and a Matsui Ex-lube system were set up according to standard operating procedures. Magnesium stearate was used as a processing aid, i.e., to externally lubricate the punch and die surfaces and was therefore present in only trace amounts on the tablets. The weight range for the tablets was typically ±5% of the target tablet weight. The Ex-lube system was started to ensure that the lubricant was spraying properly when the tablet press was running. The tableting parameters, such as fill depth (mm), precompression position (mm or kN) and main compression position (mm or kN) were adjusted on the press in order to produce 4 mg tablets that meet the exemplary specifications listed below:

TABLE: Tablet Parameters

Parameter	Target	Range
Weight (mg)	100	95-105
Thickness (mm)	2.4	2.0-2.8
Hardness (N)	28	8-48
Friability	NMT 0.6%	1.0%
Weight 10 tablets (g)	1.0g	0.96-1.04

[0078] Following the successful set-up, the press was run in 'Automatic Mode' until completion. During the run, tablets were sampled periodically to ensure that the tablets produced would meet the specifications listed above.

[0079] The tablets are tested in the USP <701> Disintegration test and disintegrate in about 60 seconds or less.

Claims

1. An orally dispersing tablet comprising less than or equal to 20 mg of budesonide or a solvate or ester thereof, and at least one pharmaceutically acceptable ingredient which facilitates the dispersal of the tablet in the oral cavity, wherein the tablet is suitable for topical administration of budesonide in the upper gastrointestinal tract.

2. The orally dispersing tablet of claim 1, wherein said tablet disintegrates within 60 seconds in simulated saliva fluid when tested using the USP <701> Disintegration Test.

3. The orally dispersing tablet of claim 2, wherein said tablet disintegrates within 30 seconds.

4. The orally dispersing tablet of any one of claims 1-3, further comprising an adhesive agent, wherein the adhesive agent is selected from the group consisting of sucrose aluminum sulfate complex, chitosan and derivatives thereof, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, hydroxypropyl cellulose, cross-linked or uncross-linked polyacrylates, cross-linked polyarylates, acidic cross-linked or uncross-linked polyacrylates, polyacrylic acid homopolymers or copolymers, aminoalkyl methacrylate copolymers, methacrylic acid/methylmethacrylate copolymer, alkylacrylate/alkylmethacrylate copolymers, ammoniomethacrylate copolymers, carbomer homopolymers or copolymers, hydrophilic polysaccharide gums, maltodextrins, cross-linked alginate gum gels, polycarboxylated vinyl polymers, pectins, xanthan gums, alginic acid, modified alginic acids, and combinations thereof.

5. The orally dispersing tablet of claim 4, wherein the adhesive agent and the budesonide or solvate or ester thereof are intimately associated.

6. The orally dispersing tablet of claim 1, wherein the at least one pharmaceutically acceptable ingredient is at least one disintegrant.

7. The orally dispersing tablet of claim 6, wherein the at least one disintegrant is selected from the group consisting of crospovidone, sodium starch glycolate, crosslinked carboxymethyl cellulose, low-substituted hydroxylpropylcellulose, mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, and combinations thereof.

8. The orally dispersing tablet of claim 1, further comprising an excipient selected from the group consisting of mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, cyclodextrin, and combinations thereof.

9. The orally dispersing tablet of claim 1, which is free of lubricant.

10. The orally dispersing tablet of claim 6, wherein the tablet comprises drug particles and rapidly dispersing granules, wherein the drug particles comprise the budesonide or solvate or ester thereof, and the rapidly dispersing granules comprise the at least one disintegrant and a sugar alcohol and/or saccharide.

11. The orally dispersing tablet of claim 10, wherein the drug particles have an average particle size of less than 400 μm, the rapidly dispersing granules have an average particle size of less than 300 μm, and the disintegrant and sugar alcohol and/or saccharide have an average particle size of less than 30 μm; or wherein the budesonide or solvate or ester thereof is disposed over the surface of an excipient, the rapidly dispersing granules have an average particle size of less than 300 μm, and the disintegrant and sugar alcohol and/or saccharide have an average particle size of less than 30 μm.

12. The orally dispersing tablet of claim 10 or claim 11, wherein the tablet comprises a lyophilized matrix, wherein the lyophilized matrix comprises the budesonide or solvate or ester thereof in combination with at least one excipient.

13. The orally dispersing tablet of claim 12, wherein the excipient is selected from the group consisting of mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, and combinations thereof.

14. The orally dispersing tablet of claim 6, comprising less than or equal to 20 mg of budesonide or a solvate or ester thereof, and the at least one disintegrant, wherein the tablet disintegrates within 60 seconds in simulated saliva fluid when tested using the USP <701> Disintegration Test.

15. The orally dispersing tablet of claim 14, wherein the tablet comprises 0.05-0.3 mg budesonide.

16. An orally dispersing tablet as claimed in claim 1 for use in treating an inflammatory condition of the gastrointestinal tract.

17. The orally dispersing tablet for use according to claim 16, wherein said inflammatory condition of the gastrointestinal tract comprises inflammation of the esophagus, eosinophilic esophagitis, or inflammation of the glottis, epiglottis, tonsils, or oropharynx.

18. The orally dispersing tablet of claim 1 comprising from 0.01 mg to 20 mg budesonide.

19. The orally dispersing tablet of claim 1 comprising from 2 mg to 20 mg budesonide.

Patentansprüche

1. Oral dispergierende Tablette, umfassend weniger als oder gleich 20 mg Budesonid oder eines Solvats oder Esters davon und mindestens einen pharmazeutisch akzeptablen Bestandteil, der die Dispersion der Tablette in der Mundhöhle ermöglicht, wobei die Tablette für die topische Verabreichung von Budesonid im oberen Gastrointestinaltrakt geeignet ist.

2. Oral dispergierende Tablette nach Anspruch 1, wobei die Tablette innerhalb von 60 Sekunden in simulierter Speichelflüssigkeit zerfällt, wenn sie unter Verwendung des USP <701>-Zerfallstests getestet wird.

3. Oral dispergierende Tablette nach Anspruch 2, wobei die Tablette innerhalb von 30 Sekunden zerfällt.

4. Oral dispergierende Tablette nach einem der Ansprüche 1-3, ferner umfassend ein Bindemittel, wobei das Bindemittel ausgewählt ist aus der Gruppe bestehend aus Sucrose-Aluminiumsulfat-Komplex, Chitosan und Derivaten davon, Polyvinylpyrrolidon, Methylcellulose, NatriumCarboxymethylcellulose, Hydroxypropylcellulose, quervernetzten oder nicht quervernetzten Polyacrylaten, quervernetzten Polyarylaten, sauren quervernetzten oder nicht quervernetzten Polyacrylaten, Polyacrylsäure-Homopolymeren oder -Copolymeren, Aminoalkylmethacrylat-Copolymeren, Methacrylsäure-/Methylmethacrylat-Copolymer, Alkylacrylat-/Alkylmethacrylat-Copolymeren, Ammonio-Methacrylat-Co-

polymeren, Carbomer-Homopolymeren oder - Copolymeren, hydrophilen Polysaccharid-Gummis, Maltodextrinen, quervernetzten Alginatgummigelen, polycarboxylierten Vinylpolymeren, Pektinen, Xanthangummis, Alginsäure, modifizierten Alginsäuren und Kombinationen davon.

5. Oral dispergierende Tablette nach Anspruch 4, wobei das Bindemittel und das Budesonid oder das Solvat oder der Ester davon eng verbunden sind.

6. Oral dispergierende Tablette nach Anspruch 1, wobei der mindestens eine pharmazeutisch akzeptable Bestandteil mindestens ein Sprengmittel ist.

7. Oral dispergierende Tablette nach Anspruch 6, wobei das mindestens eine Sprengmittel ausgewählt ist aus der Gruppe bestehend aus Crospovidon, Natriumstärkeglykolat, quervernetzter Carboxymethylcellulose, gering substituierter Hydroxylpropylcellulose, Mannit, Xylitol, Sorbitol, Maltol, Maltit, Laktose, Sucrose, Maltose und Kombinationen davon.

8. Oral dispergierende Tablette nach Anspruch 1, ferner umfassend einen Hilfsstoff, der ausgewählt ist aus der Gruppe bestehend aus Mannit, Xylitol, Sorbitol, Maltol, Maltit, Laktose, Sucrose, Maltose, Cyclodextrin und Kombinationen davon.

9. Oral dispergierende Tablette nach Anspruch 1, die frei von Schmiermittel ist.

10. Oral dispergierende Tablette nach Anspruch 6, wobei die Tablette Arzneimittelteilchen und rasch dispergierende Körnchen umfasst, wobei die Arzneimittelteilchen das Budesonid oder das Solvat oder den Ester davon umfassen, und die rasch dispergierenden Körnchen das mindestens eine Sprengmittel und einen Zuckeralkohol und/oder ein Saccharid umfassen.

11. Oral dispergierende Tablette nach Anspruch 10, wobei die Arzneimittelteilchen eine durchschnittliche Teilchengröße von weniger als 400 μm haben, die rasch dispergierenden Körnchen eine durchschnittliche Teilchengröße von weniger als 300 μm haben und das Sprengmittel und der Zuckeralkohol und/oder das Saccharid eine durchschnittliche Teilchengröße von weniger als 30pm haben; oder wobei das Budesonid oder das Solvat oder der Ester davon über der Oberfläche eines Hilfsstoffs angeordnet ist, die rasch dispergierenden Körnchen eine durchschnittliche Teilchengröße von weniger als 300 μm haben und das Sprengmittel und der Zuckeralkohol und/oder das Saccharid eine durchschnittliche Teilchengröße von weniger als 30 μm haben.

12. Oral dispergierende Tablette nach Anspruch 10 oder Anspruch 11, wobei die Tablette eine lyophilisierte Matrix umfasst, wobei die lyophilisierte Matrix das Budesonid oder das Solvat oder den Ester davon in Kombination mit mindestens einem Hilfsstoff umfasst.

13. Oral dispergierende Tablette nach Anspruch 12, wobei der Hilfsstoff ausgewählt ist aus der Gruppe bestehend aus Mannit, Xylitol, Sorbitol, Maltol, Maltit, Laktose, Sucrose, Maltose und Kombinationen davon.

14. Oral dispergierende Tablette nach Anspruch 6, umfassend weniger als oder gleich 20 mg Budesonid oder eines Solvats oder Esters davon und das mindestens eine Sprengmittel, wobei die Tablette innerhalb von 60 Sekunden in simulierter Speichelflüssigkeit zerfällt, wenn sie unter Verwendung des USP <701>-Zerfallstests getestet wird.

15. Oral dispergierende Tablette nach Anspruch 14, wobei die Tablette 0,05-0,3 mg Budesonid umfasst.

16. Oral dispergierende Tablette, wie in Anspruch 1 beansprucht, zur Verwendung bei der Behandlung eines Entzündungszustands des Gastrointestinaltrakts.

17. Oral dispergierende Tablette zur Verwendung nach Anspruch 16, wobei der Entzündungszustand des Gastrointestinaltrakts eine Entzündung der Speiseröhre, eine eosinophile Ösophagitis oder eine Entzündung der Glottis, Epiglottis, Tonsillen oder Oropharynx umfasst.

18. Oral dispergierende Tablette nach Anspruch 1, umfassend von 0,01 mg bis 20 mg Budesonid.

19. Oral dispergierende Tablette nach Anspruch 1, umfassend von 2 mg bis 20 mg Budesonid.

Revendications

1. Comprimé à dispersion orale comprenant 20 mg ou moins de 20 mg de budésonide ou d'un solvate ou ester de celui-ci et au moins un ingrédient pharmaceutiquement acceptable qui facilite la dispersion du comprimé dans la cavité orale, le comprimé convenant pour l'administration topique de budésonide dans le tractus gastro-intestinal supérieur.

2. Comprimé à dispersion orale selon la revendication 1, ledit comprimé se délitant en moins de 60 secondes dans du liquide salivaire simulé lorsqu'il est testé à l'aide de l'essai de délitement <701> de la pharmacopée des États-Unis.

3. Comprimé à dispersion orale selon la revendication 2, ledit comprimé se délitant en moins de 30 secondes.

4. Comprimé à dispersion orale selon l'une quelconque des revendications 1-3, comprenant en outre un agent adhésif, l'agent adhésif étant choisi dans le groupe constitué par le complexe saccharose-sulfate d'aluminium, le chitosane et les dérivés de celui-ci, la polyvinylpyrrolidone, la méthylcellulose, la carboxyméthylcellulose sodique, l'hydroxypropylcellulose, les polyacrylates réticulés ou non réticulés, les polyarylates réticulés, les polyacrylates réticulés ou non réticulés acides, les homopolymères ou copolymères de poly(acide acrylique), les copolymères de méthacrylate d'aminoalkyle, un copolymère d'acide méthacrylique/méthacrylate de méthyle, les copolymères d'acrylate d'alkyle/méthacrylate d'alkyle, les copolymères d'ammoniométhacrylate, les homopolymères ou copolymères carbomères, les gommes de polysaccharides hydrophiles, les maltodextrines, les gels de gomme d'alginate réticulé, les polymères vinyliques polycarboxylés, les pectines, les gommes de xanthane, l'acide alginique, les acides alginiques modifiés et les associations de ceux-ci.

5. Comprimé à dispersion orale selon la revendication 4, l'agent adhésif et le budésonide ou le solvate ou ester de celui-ci étant intimement associés.

6. Comprimé à dispersion orale selon la revendication 1, l'au moins un ingrédient pharmaceutiquement acceptable étant au moins un délitant.

7. Comprimé à dispersion orale selon la revendication 6, l'au moins un délitant étant choisi dans le groupe constitué par la crospovidone, le glycolate d'amidon sodique, la carboxyméthylcellulose réticulée, l'hydroxypropylcellulose à faible degré de substitution, le mannitol, le xylitol, le sorbitol, le maltol, la maltitol, le lactose, le saccharose, le maltose et les associations de ceux-ci.

8. Comprimé à dispersion orale selon la revendication 1, comprenant en outre un excipient choisi dans le groupe constitué par le mannitol, le xylitol, le sorbitol, le maltol, le maltitol, le lactose, le saccharose, le maltose, la cyclodextrine et les associations de ceux-ci.

9. Comprimé à dispersion orale selon la revendication 1, qui est exempt de lubrifiant.

10. Comprimé à dispersion orale selon la revendication 6, le comprimé comprenant des particules de médicament et des granules à dispersion rapide, les particules de médicament comprenant le budésonide ou le solvate ou ester de celui-ci et les granules à dispersion rapide comprenant l'au moins un délitant et un alcool de sucre et/ou un saccharide.

11. Comprimé à dispersion orale selon la revendication 10, les particules de médicament ayant une taille moyenne de particule inférieure à 400 μm, les granules à dispersion rapide ayant une taille moyenne de particule inférieure à 300 μm et le délitant et l'alcool de sucre et/ou le saccharide ayant une taille moyenne des particules inférieure à 30 μm ; ou le budésonide ou le solvate ou ester de celui-ci étant disposé sur la surface d'un excipient, les granules à dispersion rapide ayant une taille moyenne de particule inférieure à 300 μm et le délitant et l'alcool de sucre et/ou le saccharide ayant une taille moyenne des particules inférieure à 30 μm.

12. Comprimé à dispersion orale selon la revendication 10 ou la revendication 11, le comprimé comprenant une matrice lyophilisée, la matrice lyophilisée comprenant le budésonide ou le solvate ou ester de celui-ci en association avec au moins un excipient.

13. Comprimé à dispersion orale selon la revendication 12, l'excipient étant choisi dans le groupe constitué par le mannitol, le xylitol, le sorbitol, le maltol, le maltitol, le lactose, le saccharose, le maltose et les associations de ceux-ci.

14. Comprimé à dispersion orale selon la revendication 6, comprenant 20 mg ou moins de 20 mg de budésonide ou d'un solvate ou ester de celui-ci, et l'au moins un délitant, le comprimé se délitant en moins de 60 secondes dans du liquide salivaire simulé lorsqu'il est testé à l'aide de l'essai de délitement <701> de la pharmacopée des États-Unis.

15. Comprimé à dispersion orale selon la revendication 14, le comprimé comprenant 0,05-0,3 mg de budésonide.

16. Comprimé à dispersion orale selon la revendication 1 destiné à être utilisé en traitement d'un trouble inflammatoire du tractus gastro-intestinal.

17. Comprimé à dispersion orale destiné à être utilisé selon la revendication 16, ledit trouble inflammatoire du tractus gastro-intestinal comprenant une inflammation de l'oesophage, une oesophagite à éosinophiles ou une inflammation de la glotte, de l'épiglotte, des amygdales ou de l'oropharynx.

18. Comprimé à dispersion orale selon la revendication 1 comprenant de 0,01 mg à 20 mg de budésonide.

19. Comprimé à dispersion orale selon la revendication 1 comprenant de 2 mg à 20 mg de budésonide.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 20030099701 A **[0002]**
- US 20050232988 A **[0027] [0074]**
- US 20010014340 A **[0027]**
- US 6316027 B **[0043]**
- US 6596298 B **[0043]**
- US 6740332 B **[0043]**
- US 5252337 A **[0065]**
- US 5639475 A **[0065]**
- US 6139865 A **[0065]**
- US 6495160 B **[0065]**
- US 20060105038 A **[0066]**
- US 6534549 B **[0067]**
- US 7125564 B **[0067]**