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.

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

In one embodiment, the present invention is directed to a solid pharmaceutical composition comprising less than or equal to 20 mg of a corticosteroid, wherein the composition has no significant systemic glucocorticoid or mineralcorticoid activity after oral administration, wherein the solid pharmaceutical composition disintegrates within 60 seconds ~~in simulated saliva~~ when tested using the USP <701> Disintegration Test, and/or which disintegrates within 60 seconds when placed in the oral cavity of a human.

In another embodiment, the present invention is directed to a liquid pharmaceutical composition comprising a corticosteroid, and a pharmaceutically acceptable substantially non-aqueous liquid.

In another embodiment, the present invention is directed to a method for treating an inflammatory condition of the gastrointestinal tract. The method comprises administering to an individual in need thereof a pharmaceutical composition of the present invention.

In yet another embodiment, the present invention is directed to a liquid pharmaceutical composition comprising a corticosteroid, a pharmaceutically acceptable aqueous or substantially non-aqueous liquid, and a pharmaceutically acceptable phase change agent dissolved or suspended in the liquid, wherein after administration to a patient, the composition undergoes a change in physical properties upon contact with the gastrointestinal tract of the patient.

In yet another embodiment, the present invention is direction to a composition in solid or liquid form additionally comprising cyclodextrins.

The compositions of the present invention are useful for various conditions including the treatment of inflammatory conditions of the gastrointestinal tract.

In another embodiment, the present invention includes a method for treating a food allergy with an identified allergen, e.g., “atopic IBS”, and “atopic bowel”.

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 or liquid 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.

Solid pharmaceutical compositions of the present invention can include, for example, an ODT (as described herein), 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.

In another embodiment, the present invention provides a liquid pharmaceutical composition comprising a corticosteroid and a pharmaceutically acceptable solvent, wherein the liquid pharmaceutical composition has no significant systemic glucocorticoid or mineralocorticoid activity. In one such embodiment the composition also includes a pharmaceutically acceptable bio-gelling polymer dissolved in the solvent, and the composition increases in viscosity upon contact with the gastrointestinal tract of an individual. In other embodiments, the liquid compositions of the present invention comprise a corticosteroid complex with a cyclodextrin, typically suspended or dissolved in a liquid carrier. The liquid compositions of the present invention may be in the form of a solution or a suspension. Liquid pharmaceutical compositions according to the present invention are compositions which are liquids at standard temperature and pressure conditions.

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.

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.

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~~ alginate gum gels, polycarboxylated vinyl polymers, pectins, xanthan gums, alginic acid, modified alginic acids, and combinations thereof.

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.

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.

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~~ purine 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,

WHAT IS CLAIMED IS:

1. An orally disintegrating solid pharmaceutical composition comprising less than or equal to about 20 mg of a topically administrable corticosteroid and at least one disintegrant, wherein the solid pharmaceutical composition has no significant systemic glucocorticoid or mineralocorticoid activity after oral administration, wherein the solid pharmaceutical composition disintegrates within 60 seconds ~~in simulated saliva fluid~~ when tested using the USP <701> Disintegration Test, and wherein upon administration the corticosteroid is deposited topically in the upper gastrointestinal tract.

2. The solid pharmaceutical composition of claim 1, wherein said solid pharmaceutical composition disintegrates within 30 seconds.

3. The solid pharmaceutical composition of claim 1, wherein said corticosteroid is selected from the group consisting of budesonide, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone, and salts, solvates and esters thereof.

4. The solid pharmaceutical composition of claim 1, further comprising an adhesive agent.

5. The solid pharmaceutical composition of claim 4, 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 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, carbomer homopolymers or copolymers, hydrophilic polysaccharide gums, maltodextrins, cross-linked ~~alignate~~ alginate gum gels, polycarboxylated vinyl polymers, pectins, xanthan gums, alginic acid, modified alginic acids, and combinations thereof.

6. The solid pharmaceutical composition of claim 1, wherein the at least one ~~further comprising a~~ 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.

7. The solid pharmaceutical composition 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.

8. The solid pharmaceutical composition of claim 1, which is substantially free of lubricant.

9. The solid pharmaceutical composition of claim 1, further comprising at least one antifungal agent.

10. The solid pharmaceutical composition of claim 9, wherein the antifungal agent is selected from the group consisting of mitotic inhibitor antifungals, pyrimidine analog antifungals, polyene antifungals, benzimidazole antifungals, imidazole antifungals, polyene antifungals, triazole antifungals, thiazole antifungals, allylamine antifungals, echinocandin antifungals, and uncategorized antifungals.

11. The solid pharmaceutical composition of claim 10, wherein the antifungal agent is selected from the group consisting of anidulafungin, caspofungin, clotrimazole, fluconazole, itraconazole, micafungin, nystatin, posaconazole, and voriconazole.

12. The solid pharmaceutical composition of claim 1, further comprising at least one antiviral agent.

13. The solid pharmaceutical composition of claim 12, wherein the antiviral agent is selected from the group consisting of interferons, nucleoside and nucl~~e~~leotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, fusion inhibitors, maturation inhibitors, ~~puridine~~ purine analogs, pyrimidine analogs, and uncategorized antiviral drugs.

14. The solid pharmaceutical composition of claim 12, wherein the antiviral agent selected from the group consisting of aciclovir, brivudine, docosanol, famciclovir, ganciclocvir, idoxuridine, penciclovir, trifluridine, tromantadine, valaciclovir, and valganciclovir.

15. The pharmaceutical composition of claim 1, wherein the pharmaceutical composition is in the form of an orally disintegrating tablet (ODT).

16. The pharmaceutical composition of claim 15, wherein the ODT comprises drug particles and rapidly dispersing granules, wherein the drug particles comprise the corticosteroid, and the rapidly dispersing granules comprise ~~a~~ the disintegrant and a sugar alcohol and/or saccharide.

17. The pharmaceutical composition of claim 16, wherein the drug particles have an average particle size of less than about 400 µm, the rapidly dispersing granules have an average particle size of less than about 300 µm, and the disintegrant and sugar alcohol and/or saccharide have an average particle size of less than about 30 µm.

18. The pharmaceutical composition of claim 16, wherein the drug particles have an average particle size of less than about 4 µm, the rapidly dispersing granules have an average particle size of less than about 300 µm~~, and the disintegrant and sugar alcohol and/or saccharide have an average particle size of less than about 30 µm~~.

19. The pharmaceutical composition of claim 16, wherein the corticosteroid is disposed over the surface of an excipient, the rapidly dispersing granules have an average particle size of less than about 300 µm~~, and the disintegrant and sugar alcohol and/or saccharide have an average particle size of less than about 30 µm~~.

20. The pharmaceutical composition of claim 4, wherein the adhesive agent and the corticosteroid are intimately associated.

21. The pharmaceutical composition of claim 20, wherein said corticosteroid is surrounded or encapsulated by the adhesive agent.

22. The pharmaceutical composition of claim 20, wherein the corticosteroid is disposed on the surface of said adhesive agent.

23. The pharmaceutical composition of claim 16, wherein the ODT comprises a lyophilized matrix, wherein the lyophilized matrix comprises the corticosteroid in combination with at least one excipient.

24. The pharmaceutical composition of claim 23, wherein the excipient is selected from the group consisting of mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, and combinations thereof.

25. The pharmaceutical composition of claim 23, wherein the ODT is in the form of a wafer or film.

26. The pharmaceutical composition of claim 16, wherein the ODT is in the form of a wafer or film.

27. An orally disintegrating tablet comprising less than or equal to about 20 mg of a corticosteroid selected from the group consisting of fluticasone, budesonide, mometasone, and salts, solvates and esters thereof, and at least one disintegrant, wherein the orally disintegrating tablet disintegrates within 60 seconds ~~in simulated saliva fluid~~ when tested using the USP <701> Disintegration Test.

28. The orally disintegrating tablet of claim 27, ~~wherein the orally disintegrating tablet~~that comprises from about ~~0.05-0.3~~2 to about 10 mg fluticasone.

~~29. A method for treating an inflammatory condition of the gastrointestinal tract comprising administering to an individual in need thereof a pharmaceutical composition according to claim 1.~~

~~30. The method of claim 29, wherein said inflammation of the gastrointestinal tract comprises inflammation of the esophagus.~~

~~31. The method of claim 29, wherein said condition is eosinophilic esophagitis.~~

~~32. The method of claim 29, wherein said inflammation comprises inflammation of the glottis, epiglottis, tonsils, or oropharynx.~~

~~33. The method of claim 29, wherein said condition is viral or bacterial pharyngitis.~~

~~34. The method of claim 29, wherein said condition is gastroesophageal reflux disease (GERD), nonerosive reflux disease (NERD) or erosive esophagitis.~~

~~35. A substantially non-aqueous liquid pharmaceutical composition comprising a corticosteroid and a pharmaceutically acceptable liquid.~~

36. The liquid pharmaceutical composition of claim 35 wherein the liquid is selected from the group consisting of pharmaceutically acceptable alcohols, oils, glycols, glycol ethers, pyrrolidones, polyethylene glycols, N-methyl-2-pyrrolidone, 2-pyrrolidone, glycerol, tetraglycol, glycerol formal, solketal, ethyl acetate, ethyl lactate, ethyl butyrate, dibutyl malonate, tributyl citrate, tri-n-hexyl acetylcitrate, diethyl succinate, diethyl glutarate, diethyl malonate, triethyl citrate, triacetin, tributyrin, diethyl carbonate, propylene carbonate, acetone, methyl ethyl ketone, dimethyl sulfoxide, dimethyl sulfone, tetrahydrofuran, caprolactam, N,N-diethyl-m-toluamide, 1-dodecylazacycloheptan-2-one, 1,3-dimethyl-3,4,5,6-tetrohydro-2(1H)-pyrimidinone, and combinations thereof.

37. The liquid pharmaceutical composition of claim 36 wherein the liquid is selected from the group consisting of alcohols, oils; glycols; glycol ethers; pyrrolidones; polyethylene glycols, glycerol and combinations thereof.

38. The liquid pharmaceutical composition of claim 37 wherein the liquid is selected from the group consisting of ethanol, glycerol, propylene glycol, glycerides, polyethylene glycol with a molecular weight between about 200 and 600, and combinations thereof.

39. The liquid pharmaceutical composition of claim 35, further comprising a phase change agent dissolved or suspended in said liquid, wherein after administration to a patient, said composition undergoes a change in physical properties of the composition upon contact with the gastrointestinal tract of said patient, whereby contact of the corticosteroid with the gastrointestinal tract of the patient is enhanced and/or prolonged.

40. The liquid pharmaceutical composition of claim 39, wherein after administration to a patient, said composition precipitates onto the mucosa of the gastrointestinal tract of the patient, whereby deposition of the corticosteroid onto the mucosa of the gastrointestinal tract is enhanced and/or prolonged.

41. The liquid pharmaceutical composition of claim 39, wherein after administration to a patient, said composition forms a gel on contact with the mucosa of the gastrointestinal tract of the patient, whereby the deposition of the corticosteroid onto the mucosa of the gastrointestinal tract is enhanced and/or prolonged.

42. The liquid pharmaceutical composition of claim 35, wherein after administration to a patient, said composition increases in viscosity upon contact with the mucosa of the gastrointestinal tract of the patient, whereby the residence time of the corticosteroid on the mucosa of the intestinal tract is prolonged.

43. The liquid pharmaceutical composition of claim 39, wherein said phase change agent is a poorly water-soluble polymer.

44. The liquid pharmaceutical composition of claim 39, wherein said phase change agent is a thermosensitive polymer whose aqueous viscosity changes in the range of about 15 – 40°C.

45. The liquid pharmaceutical composition of claim 39, wherein said phase change agent increases in viscosity upon contact with the fluids of the oropharynx..

46. The liquid pharmaceutical composition of claim 39, wherein the phase change agent is a polymer selected from the group consisting of poly(N-isopropylacrylamide), poly(ethylene glycol-(DL-lactic acid-co-glycolic acid)-ethylene glycol) and mixtures thereof.

47. The pharmaceutical composition of claim 35, wherein said corticosteroid is selected from the group consisting of budesonide, fluticasone, flunisolide, ciclesonide, mometasone, tixocortol, beclomethasone, and salts, solvates, and esters thereof.

48. The pharmaceutical composition of claim 41, wherein said liquid is water-miscible and said phase change agent is a bio-gelling polymer having a low water solubility.

49. The pharmaceutical composition of claim 48, wherein said water-miscible solvent is selected from the group consisting of ethanol, isopropyl alcohol, N-methyl-2-pyrrolidone, 2-pyrrolidone, glycerol, propylene glycol, polyethylene glycol, tetraglycol, glycerol formal, solketal, ethyl acetate, ethyl lactate, diethyl carbonate, propylene carbonate, acetone, methyl ethyl ketone, dimethyl sulfoxide, dimethyl sulfone, tetrahydrofuran, and combinations thereof.

50. The pharmaceutical composition of claim 48, wherein said bio-gelling polymer is selected from the group consisting of polylactides, polyglycolides, polycaprolactones, polydioxannones, polycarbonates, polyhydroxybutyrates, polyalkyene oxalates,

~~polyanhydrides, polyamides, polyesteramides, polyurethanes, polyacetals, polyketals, polyorthocarbonates, polyphosphazenes, polyhydroxyvalerates, polyalkylene succinates, poly(malic acid), poly(amino acids), chitin, chitosan, polyorthoesters, cellulose derivatives, cellulose esters, methacrylic acid and methacrylate polymers, and copolymers, terpolymers and mixtures thereof.~~

~~51. The pharmaceutical composition of claim 51, wherein said bio-gelling polymer is ethylcellulose.~~

~~52. The pharmaceutical composition of claim 45, wherein said increase in viscosity is at least 50%.~~

~~53. The pharmaceutical composition of claim 45, wherein said increase in viscosity is at least 100%.~~

~~54. The pharmaceutical composition of claim 45, wherein said increase in viscosity is at least 200%.~~

29. The solid composition of claim 1, formulated for topical administration to the upper gastrointestinal tract.

30. The solid composition of claim 29, wherein the upper gastrointestinal tract is further defined as the esophagus.

31. The pharmaceutical composition of claim 16, wherein the ODT further comprises a sugar alcohol, a disintegrant, and microcrystalline cellulose, wherein the drug particles comprise fluticasone, and the rapidly dispersing granules comprise a disintegrant and a sugar alcohol or saccharide or a mixture thereof.

32. The orally disintegrating tablet of claim 27, that comprises from about 0.01 mg and about 20 mg fluticasone.

33. The solid pharmaceutical composition of claim 1, that comprises from about 0.01 mg and about 20 mg fluticasone.

34. The solid pharmaceutical composition of claim 1, that comprises from about 2 to about 10 mg fluticasone.