Corticosteroid Containing Orally Disintegrating Tablet Compositions for Eosinophilic Esophagitis

CROSS-RELATED APPLICATIONS

This application claims the benefit under 35 USC §119(e) of U.S. Provisional Patent Application Ser. No.: 61/874,450 filed September 6, 2013, disclosure of which is herein incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

This invention relates to orally administered low dose, topically acting corticosteroid compositions, useful for the treatment of conditions associated with inflammation of the esophagus.

BACKGROUND OF THE INVENTION

Esophageal inflammation disorders such as eosinophilic esophagitis (EoE) characterized by high levels of eosinophils in the esophagus, as well as basal zonal hyperplasia, are gaining increased recognition in children and adults. Many aspects of the disease remain unclear including its etiology, natural history, and optimal therapy. EoE affects all age groups but most frequently individuals between 20 and 50 years of age. Symptoms of EoE often mimic those of gastroesophageal reflux disease (GERD) and include vomiting, dysphagia, pain and food impaction. The common occurrence regarding misdiagnosis of EoE for GERD often results in delayed treatment in patients with EoE. 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, particularly the inflammatory conditions of the esophagus, *i.e.*, EoE. The disease is painful, leads to difficulty swallowing and predisposes patients to food impaction and other complications. Although systemic treatments with corticosteroids such as prednisolone are effective, they are associated with significant adverse effects such as suppression of the hypothalamo-pituitary–adrenal (HPA) axis as reflected in salivary cortisol levels, generalized suppression of immune function, and particularly in children, troubling side-effects from long term systemic exposure include growth retardation, which may lead to a reduction in adult height.

In contrast, twice-daily treatments of EoE include directing steroid medications through a metered dose inhaler (MDI) to the back of the throat such that they are not appreciably inhaled, and instructing the patient to keep the mouth closed during the "puff and swallow" treatment and rinse the 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 candidiasis infection, and swallowing is contraindicated because it may wash drug away from the esophagus. In another study, 50% of fluticasone propionate (FP)-treated patients achieved histologic remission compared with 9% of patients receiving placebo ($P = 0.047$). FP decreased esophageal eosinophil levels, with a more pronounced effect in non-allergic individuals. However, this therapy is particularly problematic for younger children and those with developmental delay, who are unlikely to utilize this puff and swallow technique effectively.

In another randomized, double-blind, placebo-controlled trial performed to evaluate the effect of oral 1 mg budesonide viscous solution (0.5-mg respule dissolved along with five 1-g packets of sucralose in 10-15 mL fluid) dosed twice daily vs. placebo in adolescent and adult patients with active EoE for 15 days, the pretreatment and post treatment disease activities were assessed clinically, endoscopically, and histologically. The primary end point was reduced mean numbers of eosinophils in the esophageal epithelium (number per high-power field [hpf] = esophageal eosinophil load). A 15-day course of treatment with budesonide is well tolerated and highly effective in inducing a histologic and clinical remission in adolescent and adult patients with active EoE. A 15-day course of therapy significantly decreased the number of eosinophils in the esophageal epithelium in patients given budesonide (from 68.2 to 5.5 eosinophils/hpf; $P < 0.0001$); but not in the placebo group (from 62.3 to 56.5 eosinophils/hpf; $P = 0.48$). Dysphagia scores significantly improved among patients given budesonide compared with those given placebo (5.61 vs 2.22; $P < 0.0001$). White exudates and red furrows were reversed in patients given budesonide, based on endoscopy examination. This dosage form has not been FDA approved for commercial use, and the oral administration is going to be messy and likely to produce inconsistent results.

When oral solid dosage forms with a drug load of $\leq 5\%$ by weight are required, the drug is either micronized and co-processed by blending with at least one carrier excipient or granulating in a fluid bed or high shear granulator by spraying preferably a solution of the drug to achieve

blend uniformity/homogeneity of the blend and subsequently, content uniformity in the finished dosage units per regulatory requirements (FDA's Draft Guidance for Industry "Powder blend and finished dosage units - stratified in-process dosage unit sampling and assessment" October 2003). Many micronized drugs show a tendency to segregate and form larger particles in the blend in order to reduce their high surface energy, resultant segregation and agglomeration could cause resurfacing of the blend non-uniformity/inhomogeneity issues set out to resolve in the first place. Segregation and agglomeration in the blends containing especially poorly water soluble, low-dose drugs must be avoided not only during powder blending but also until processed into finished dosage forms, capsules or tablets, to achieve and maintain desired blend uniformity/homogeneity and/or to avoid high dissolution variability. Segregation of drug particles, especially in direct compression blends, is equipment and material dependent. It is thus very challenging to achieve acceptable blend homogeneity during direct compression blending of a low-dose drug with suitable pharmaceutically acceptable excipients (*i.e.*, at a drug content of < 5% by weight in the blend) and maintain the blend homogeneity until processing into finished dosage forms (e.g., tablets or capsules) (McGinity J. W. et al. Dissolution and uniformity properties of ordered mixes of micronized griseofulvin and a directly compressible excipient. Drug Development and Industrial Pharmacy 1985; 11(4): 891-900; Yalkowsky S.H. and Bolton S. Particle size and content uniformity. Pharmaceutical Research. 1990; 7(9): 962-966; Ahmad H. and Shah N. Formulation of low dose medicines-Theory and Practice. *Amer. Pharm. Rev.* 2000; 3 (3): 1-5; Mahmoudi Z. N. et al. The influence of filler in blend uniformity of micronized drugs. Contributed poster, AAPS Annual Meeting (USA) 2010; Mahmoudi Z. N. et al. Effect of drug particle size on blend segregation and content uniformity. Contributed poster, AAPS Annual Meeting (USA) 2011).

WO 2011041509 discloses the preparation of an orally administrable pharmaceutical composition containing a topically acting corticosteroid in an amount of less than 20 mg. Although there is no specific discussion of how to achieve acceptable blend uniformity in the working example of the compression blend which contains fluticasone propionate at only 4% by weight, which will be translated into achieving acceptable content uniformity of the ODTs, the fact that fluticasone is granulated with suitable pregranulated excipients, such as rapidly dispersing microgranules comprising mannitol and crospovidone, suggests that the granulation of fluticasone has been performed for the purpose of achieving acceptable content uniformity in the

finished tablets. However, the micronized topically acting corticosteroid particles may be present in the agglomerated granules and as such may not be readily exposed to the inflamed EoE tissues upon oral administration for rapid induction of remission of EoE.

There is therefore a need for low-dose corticosteroid compositions having acceptable blend uniformity/homogeneity during blending of a topically acting corticosteroid with suitable pharmaceutically acceptable excipients as a carrier (*i.e.*, at a drug content of < 5%, especially at <3% by weight in the blend) and maintain the blend homogeneity until processing into finished unit dosage forms (e.g., tablets or capsules), which while exhibiting high content uniformity are suitable for oral administration in patients to provide topical (rather than systemic) treatment of inflammation of the of the upper gastrointestinal tract, particularly eosinophilic esophagitis (EoE) since the micronized, topically acting corticosteroid particles having been adsorbed largely on the surface of the carrier are capable of rapidly inducing remission of EoE.

SUMMARY OF THE INVENTION

The present invention is directed to an oral solid pharmaceutical composition comprising a low-dose topically acting corticosteroid and at least one pharmaceutically acceptable carrier for adsorption of the drug, wherein the drug is in an amount of less than about 5% (weight of drug/weight of composition), particularly less than 3% by weight and the composition has no significant systemic glucocorticoid or mineralocorticoid activity after oral administration in humans. The blend of a corticosteroid with the carrier has high blend uniformity/drug homogeneity which is translated into content uniformity of finished unit tablets.

The composition of the invention which can be formulated as an orally disintegrating tablet (hereafter referred to as an ODT) that disintegrates within 30 seconds when tested using the USP <701> Disintegration Test, and/or disintegrates within 60 seconds when placed in the oral cavity of a human.

The present invention is also directed to a process for making low dose pharmaceutical compositions comprising adsorbing a topically acting corticosteroid optionally micronized onto at least one pharmaceutically acceptable carrier such as silicified microcrystalline cellulose by blending for a sufficiently long time and passing through a de-segregating/comminuting mill at least once before blending with other pharmaceutically acceptable excipients, and then formulating the resulting blend into a suitable unit dose presentation, e.g., tableting.

The present invention discloses a method of preparing pharmaceutical compositions comprising especially poorly water soluble, low-dose, micronized drugs and at least one pharmaceutically acceptable carrier which must be blended for a sufficiently long time using a suitable blender-comminuting mill combination, thereby avoiding segregation-agglomeration of the drug particles in the blend not only during powder blending but also until processed into finished dosage forms, capsules or tablets, to achieve and maintain desired high blend uniformity / homogeneity and/or to achieve high content uniformity of the finished dosage units and also to avoid high dissolution variability.

The compositions of the present invention are useful for treatment of various conditions including the inflammatory conditions of the gastrointestinal tract. Accordingly, the present invention also provides a method for treating inflammatory conditions of the upper gastrointestinal tract in an individual, particularly in the esophagus (eosinophilic esophagitis) via topical action with minimal systemic absorption and concomitant corticosteroid related side-effects. The method comprises administering to an individual to treat eosinophilic esophagitis a pharmaceutical composition of the present invention comprising topically acting optionally micronized corticosteroid particles adsorbed onto silicified microcrystalline cellulose. Alternatively, the compositions of the present invention may comprise a water soluble or water-swellable pharmaceutically acceptable excipient, such as bio-gelling or bioadhesive polymer that will enhance bioadherence of the corticosteroid to the inflammed esophageal mucosa.

DETAILED DESCRIPTION OF THE FIGURE

FIG. 1 shows the sampling locations in a blender for taking representative samples as per draft FDA Guidance (FDA's Draft Guidance for Industry "Powder blend and finished dosage units - stratified in-process dosage unit sampling and assessment" October 2003).

DETAILED DESCRIPTION OF THE INVENTION

The invention is directed to a solid pharmaceutical composition which comprises a corticosteroid in an amount of less than about 5% (weight of drug/weight of composition) and at least one pharmaceutically acceptable carrier for adsorption of the drug, wherein the composition has no significant systemic glucocorticoid or mineralocorticoid activity, and wherein the solid pharmaceutical composition disintegrates within 30 seconds when tested using the USP <701>

disintegration method. The composition disintegrates in about 60 seconds or less on contact with saliva in the oral cavity of a subject or patient in need thereof.

The solid pharmaceutical composition of the present invention provides a therapeutically effective amount of a topical corticosteroid to inflamed tissues of the upper gastrointestinal tract, particularly to the esophageal inflamed tissues.

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall have the following meanings.

The term "drug", "active" or "active pharmaceutical ingredient" as used herein includes a pharmaceutically acceptable and topically acting corticosteroid, pharmaceutically acceptable salts, esters, solvates (including hydrates), polymorphs, stereoisomers, and/or prodrugs, and mixtures thereof. The terms "salts" refers to the product formed by the reaction of a suitable inorganic or organic acid with the "free base" form of the drug. Suitable acids include those having sufficient acidity to form a stable salt, for example acids with low toxicity such as the salt approved for use in humans or animals. Non-limiting examples of acids that may be used to form salts of a orally active drug, include inorganic acids, e.g., HCl, H_3PO_4 H_2SO_4. Non-limiting examples of organic acids include alkyl sulfonic acids and propionic acid.

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.

The term "about", as used herein to refer to a numerical quantity, includes "exactly". For example, "about 30 seconds" includes 30 seconds, exactly, as well as values close to 30 seconds (e.g., 25 seconds, 29 seconds, 31 seconds, 35 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").

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.

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.

The term "having no significant systemic glucocorticoid 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). Corticosteroids which typically have systemic glucocorticoid or mineralocorticoid activity when administered orally can also be used in the diluted compositions of the present invention, wherein the systemic uptake of the corticosteroid is reduced or suppressed.

Suitable topically acting corticosteroids which may be included in the pharmaceutical composition of the present invention include budesonide, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone, tixocortol and salts, or esters and mixtures thereof.

In a particular embodiment, the composition of the present invention comprises fluticasone. In other embodiments, the composition of the present invention comprises budesonide. In certain other embodiments, the composition of the present invention comprises ciclesonide.

In one embodiment, the corticosteroid may be in the form of crystals having a mean particle size of about 100 μm or less, about 75 μm or less, about 50 μm or less, more particularly about 25 μm or less, or about 15 μm or less. A particular embodiment of the invention is where the corticosteroid is micronized in order to achieve a mean particle size of less than about 10 μm, less than about 8 μm or less, less than about 6 μm, or particularly, less than about 4 μm. Alternatively, such crystals may have an average size in the sub-micron range (e.g., average particle size of about <1 μm), *i.e.*, may be as nanoparticles (e.g., average particle size in the range of about 1-100 nm).

In another embodiment, the corticosteroid may be present in an amorphous form, for example in association with a stabilizing agent which limits drug recrystallization, e.g., polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose, hydroxyethylcellulose; Soluplus®, Kollidon® VA64, sodium lauryl sulphate, Tween surfactants, Eudragit® EPO polymer, and mixtures thereof.

The amount of corticosteroid present in the pharmaceutical compositions of the present invention is selected so as to maximize the therapeutic benefit from topical administration while minimizing side effects from systemic absorption. In the case of solid pharmaceutical compositions of the present invention, the amount of corticosteroid in the composition is less than about 5% w/w (weight of drug/ weight of composition). In one embodiment the amount of corticosteroid in the pharmaceutical composition is less than about 4%. In another embodiment it is less than about 3%. In yet another embodiment it is less than about 2%, less than about 1.5%, less than about 1%, less than about 0.5% by weight or less. In one embodiment the amount of corticosteroid in the pharmaceutical composition is between about 0.50 mg and about 18 mg. In still another embodiment the amount of corticosteroid in the pharmaceutical composition is between about 0.75 mg and about 12 mg. In yet another embodiment the amount of corticosteroid in the pharmaceutical composition is between about 1.5 mg and about 9 mg. In still other embodiments, the amount of corticosteroid is about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.15 mg, about 0.1 mg, about 0.2 mg, about 0.25 mg, about 0.3 mg, about 0.35 mg, about 0.4 mg, about 0.45 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.75 mg, about 0.8 mg, about 1 mg, about 1.5 mg, about 2 mg, about 3 mg, about 4 mg, about 4.5 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 12 mg, about 18 mg, inclusive of all ranges and sub-ranges there between.

In the embodiment of the invention the rapidly disintegrating composition of the invention may comprise pharmaceutically acceptable excipients which swell, dissolve or otherwise facilitate disintegration of the ODT composition forming a smooth viscous suspension containing micronized corticosteroid particles to coat inflammatory esophageal mucosa to treat eosinophilic esophagitis. In certain embodiments of the present invention the total weight of the dosage form is kept in the range of from 300 to 900 mg to incorporate as much rapidly dispersing microgranules comprising at least one sugar alcohol in combination with at least one

disintegrant, as possible to maximize eosinophilic esophagitis surface coating with micronized corticosteroid. In another embodiment, the rapidly dispersing microgranules comprise at least one disintegrant in combination with a sugar alcohol and/or 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 sub-ranges there between. In one embodiment, the average particle size of a sugar alcohol and/or saccharide is about 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.

In one embodiment of the invention the dosage form has total weight of 300 mg and contain about 0.05 mg (0.16%), about 0.75 mg (0.25% w/w), about 1.5 mg (0.5% w/w), about 3 mg (1% w/w), about 4.5 mg (1.5%) , about 6 mg (2% w/w), about 9 mg (3% w/w), about 12 mg (4% w/w), about 16 mg (5%) of the corticosteroid.

In another embodiment of the invention the dosage forms has total weight of 600 mg and contain about 0.75 mg (0.125% w/w), about 1.5 mg (0.25% w/w), about 3 mg (0.5% w/w), about 4.5 mg (0.75%), about 6 mg (0.1% w/w), about 9 mg (1.5% w/w), about 12 mg (2% w/w), about 18 mg (3% w/w) of the corticosteroid. In one embodiment of the invention the topically acting corticosteroid is fluticasone propionate and it is in the range of about 0.05 to about 15 mg in the pharmaceutical composition at a drug content of from about 0.16% to 5% by weight of the composition.

In another embodiment the fluticasone propionate is in the range of about 0.75 to about 4.5 mg in the composition at a drug content of from about 0.25% to 1.5% by weight in the composition.

In another embodiment the fluticasone propionate is in the range of 0.05 to about 18 mg in the composition at a drug content of from about 0.125% to 5% by weight in the composition.

The pharmaceutically acceptable carrier used in the mixture of the present invention is suitable for adsorption of the drug, it should have the properties of an excellent carrier for dry blends providing blend flowability and workability and preventing the segregation. It may concur in providing corticosteroid content uniformity. It is selected from the group consisting of

microcrystalline cellulose, silicified microcrystalline cellulose, pregelatinized starch, corn starch, colloidal silica, or amorphous magnesium aluminum silicate (commercially available as VEEGUM™ or NEUSILIN™). It is preferably silicified microcrystalline cellulose which is composed of intimately associated microcrystalline cellulose and colloidal silicon dioxide particles, (PROSOLV® SMCC: MCC, 98% and CSD, 2%). The use of this ingredient in the composition of the invention improves the flow and blending properties of the corticosteroid mixture; improved blend uniformity/homogeneity and physical stability of the formulations during storage until their final processing into finished dosage forms such as tablets or capsules, *i.e.*, to avoid or minimize potential de-mixing and segregation of corticosteroid microparticles is also achieved. The presence of this carrier in admixture with the active also ensures reproducibility of preparations of the composition of the invention (in particular with the applied technology of direct tableting). In one embodiment of the present invention a low-dose corticosteroid blend with the carrier showing high blend uniformity, low-segregation potential and excellent flowability is disclosed. This blend is particularly suitable for producing a rapidly disintegrating diluted corticosteroid composition. In one embodiment of the invention the blend comprises fluticasone propionate adsorbed on silicified microcrystalline cellulose, and rapidly dispersing microgranules.

The rate of disintegration of the compositions of the present invention in the oral cavity of an individual can be on 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.

The rate of disintegration of the solid pharmaceutical compositions of the present invention measured using the USP <701> Disintegration Test 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.

In addition to the corticosteroid and the carrier, the blend of the compositions or the oral dosage forms of the present invention may contain further pharmaceutically acceptable ingredients which swell, dissolve or otherwise facilitate disintegration. Such ingredients can include disintegrant, a sugar alcohol, a saccharide, or a mixture thereof, a water-soluble

polymeric binder, a bio-gelling or a bioadhesive polymer, which can retain the corticosteroid particle adhered onto the inflamed esophageal tissues longer than in its absence.

In one embodiment, the present invention provides a solid pharmaceutical composition comprising a corticosteroid and a pharmaceutically acceptable bio-gelling polymer which enables longer retention of the corticosteroid at the inflamed esophageal tissues. The ingredient herein called "bio-gelling polymer" or "bio-adhesive agent" is an agent which promote adhesion of the corticosteroid to biological surfaces, especially the inflamed mucosa through gelling under GI tract physiological conditions, for example, upon contact with physiological fluids and/or at physiological temperature, and includes, but is not limited to the bio-gelling polymers listed below.

The bio-gelling polymer may be a thermosensitive polymer. Suitable thermosensitive polymers include polyacrylamides, such as poly(N-isopropylacrylamide), as well as poly(ether-ester) copolymers, such as poly(ethylene glycol-(DL-lactic acid-co-glycolic acid)-ethylene glycol). Such thermosensitive polymers can partially or fully cover the inflamed esophageal tissues while keeping the corticosteroid particle(s) close or in intimate contact with the inflamed tissues, thereby increasing the topical contact of the corticosteroid with the inflamed tissues.

In one embodiment, the composition of the present invention includes a bioadhesive agent such as a lipid or a polymer. Examples of such lipids are glycerphospholipids such as phosphatidyl choline, and diacyl glycerols such as glycerol dioleate. Examples of bioadhesive polymers include chitosan, polyorthoesters, and copolymers, terpolymers and mixtures thereof.

In another embodiment, the solid pharmaceutical compositions of the present invention include an adhesive agent. Suitable adhesive agents include sucrose aluminum sulfate complex, chitosan and derivatives such as trimethylchitosan, polyvinylpyrrolidone, methylcellulose, hydroxypropyl cellulose, cross-linked polyacrylic acid copolymers, polyvinylpyrrolidone, vinylpyrrolidone-polyvinyl acetate copolymer (*e.g.*, Kollidon® VA 64 from BASF), Soluplus®, poly(ethylene glycol 6000 - vinylcaprolactam - vinyl acetate) (13:57:30) copolymer from BASF), polyvinyl alcohol, polyethylene oxide, polyamide, alginic acid and its salts, carrageenan, xanthan gum, ammoniomethacrylate copolymers, CARBOPOL polymers, maltodextrins, pectins, sucralose, 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.

In certain embodiments of the present invention, the solid pharmaceutical composition includes any solid dosage form which disintegrates rapidly in the mouth to form a suspension of powdered corticosteroid, which is hypothesized to coat or adhere onto the inflamed esophageal mucosa when swallowed.

In one embodiment, the composition of the present invention is in the form of an ODT. The ODT comprises the drug is in amount less than about 5% (weight of drug/weight of composition) and a pharmaceutically acceptable carrier, wherein the composition has no significant systemic glucocorticoid or mineralocorticoid activity after oral administration in humans. The drug particles, (e.g., a corticosteroid as described herein optionally coated or optionally combined with an adhesive agent as described herein) are combined with rapidly dispersing microgranules. Rapidly dispersing microgranules comprise a sugar alcohol, a saccharide, or a mixture thereof and a disintegrant alone or a disintegrant in combination with a pharmaceutically acceptable additive with multi-functional activity (e.g., pregelatinized starch, hydroxypropylcellulose or the like).

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.

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 sub-ranges there between.

The amount of sugar alcohol and/or saccharide in the ODT ranges from about 30% to about 70% by weight.

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.

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 sub-ranges there between.

The corticosteroid particles are typically adsorbed onto the carrier. The process for the preparation includes repeatedly mixing corticosteroid and carrier so that the blend is adsorbed onto the carrier. Corticosteroid is typically micronized (mean particle size of less than 10 μm) for the following reasons. Firstly, the finished dosage form (such as the ODT) is designed to rapidly disintegrate on contact with saliva in the oral cavity. In order to accomplish this, the dosage form (ODT) should have preferably a minimum of 100 mg of rapidly dispersing

microgranules, irrespective of the dose of corticosteroid (for example, 0.1 mg, 1 mg, 10 mg or 20 mg). Secondly, in order to achieve blend uniformity/homogeneity in the blend and content uniformity of the finished unit dosage forms, a homogeneous distribution could be achieved by incorporating the micronized drug particles in silicified microcrystalline cellulose alone or in combination with rapidly dispersing microgranules by at least once blending and milling as described in examples of different embodiments of the present invention. The first option of incorporating the drug in the silicified microcrystalline cellulose will largely prevent segregation of corticosteroid microparticles during transient storage until final processing into finished dosage forms, capsules or tablets exhibiting high content uniformity and/or low dissolution variability.

Rapidly dispersing granules or granulate can be prepared as described in U.S. 2005/0232988 or U.S. 2003/0215500 by granulating a disintegrant 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). Rapidly dispersing microgranules can alternatively be prepared as described in U.S. 13/310,632 by granulating a sugar alcohol, a saccharide, or a mixture thereof and a disintegrant in combination with a pharmaceutically acceptable additive with multi-functional activity (e.g., starch, hydroxypropylcellulose or the like) at a low level of 0.5-3.0% by weight in a fluid-bed granulator.

The rapidly dispersing microgranules present in the ODT help rapid disintegration of the tablet when placed in the oral cavity, creating a smooth suspension containing the corticosteroid drug particles. It is desirable to incorporate sufficient amount of rapidly dispersing microgranules to coat extensively the esophageal mucosa. This creates a content uniformity problem in these low-dose ODTs (for example, 300 mg ODT containing 12 mg or less of a corticosteroid). Typically, this problem is overcome by granulation, which involves spraying a dilute solution of the corticosteroid on to an excipient powder bed. The drug particles are embedded in the granules and consequently may not become exposed to the inflamed mucosa, resulting in being poorly efficacious. It has been surprisingly observed possible not only to

achieve desired content uniformity but also enhance the probability of largely keeping the corticosteroid drug particles exposed to the inflamed mucosa by adsorbing micronized topically acting corticosteroid drug particles onto the pharmaceutically acceptable carrier (such as silicified microcrystalline cellulose) prior to blending with rapidly dispersing microgranules and other excipients and compressing into ODTs.

The dosage form as described herein may also include pharmaceutically acceptable excipients typically used in disintegrating tablet formulations such as fillers, diluents, glidants, disintegrants, binders and lubricants.

Examples of suitable fillers, diluents and/or binders include lactose (e.g. spray-dried lactose, such as FAST-FLO®), microcrystalline cellulose (various grades of Avicel®, CEOLUS®), hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), low molecular weight hydroxypropyl methylcellulose (HPMC) (e.g., Methocel™ E, F and K from Dow Chemical, MetholoseE 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. The preferred filler for the composition of the invention is mannitol such as spray dried mannitol.

Examples of suitable disintegrants include crospovidone (cross-linked PVP), sodium starch glycolate, cross-linked sodium carboxymethylcellulose, calcium silicate, and low substituted hydroxypropyl cellulose. The preferred disintegrant for the composition of the invention is cropovidone.

Specific examples of glidants and lubricants include stearic acid, magnesium stearate, calcium stearate or other metallic stearates, talc, glyceryl behenate, colloidal silica, corn starch, and optionally magnesium stearate or sodium stearyl fumarate (lubricant intragranularly mixed or used externally to lubricate die and punch surfaces). The preferred glidant for the composition of the invention is colloidal silica and preferred lubricant is sodium stearyl fumarate.

The solid pharmaceutical compositions of the present invention can include other dosage forms besides an ODT, a wafer, a film, or other solid dosage form which disintegrates rapidly in

the mouth to form a suspension or dispersion of a corticosteroid, which can readily be swallowed to coat the mucosal surface of eosinophilic esophagitis.

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. Pat. No. 6,316,027), containing a corticosteroid as the active pharmaceutical ingredient. Film dosage forms can include edible films such as those described in U.S. Pat. No. 6,596,298 or U.S. Pat. No. 6,740,332, containing a corticosteroid as the active pharmaceutical ingredient. In one embodiment of the present invention the solid composition comprises a lyophilized matrix, wherein the lyophilized matrix comprises corticosteroid, the carrier and excipient. Suitable excipients include mannitol, xylitol, sorbitol, maltol, maltitol, lactose, sucrose, maltose, and combinations thereof.

Topical administration of a corticosteroid to the oral cavity of individuals has been associated with candidiasis infection. While the invention is designed so as be less prone to promoting such an infection, however in another embodiment of the invention, the pharmaceutical composition may 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 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 alpha-2a, pegylated interferon alpha-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.

Tablet dosage forms, including ODT dosage forms, comprising the low dosage strength of a topically acting corticosteroid and a pharmaceutically acceptable carrier, wherein the drug is in amount less than about 5% (weight drug/weight of composition), have no significant systemic glucocorticoid or mineralocorticoid activity after oral administration in humans, disintegrate in less than about 30 sec (USP method), and have a low friability in order to have sufficient durability to withstand handling, shipping, and/or packaging in push-through blister packaging. Friability is 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 sub-ranges there between).

Different preparation processes can be applied to prepare blends of a corticosteroid with suitable carrier having blend homogeneity, *i.e.,* acceptable blend uniformity and also content uniformity suitable for tableting. Blending the above ingredients can be achieved both by dry mixing or by granulation.

The present invention further discloses the method of manufacturing oral composition, such as compression or compressible blend at a drug load of from about 0.5% to about 3% by weight wherein it is challenging to achieve and maintain acceptable blend uniformity until the compression or compressible blend is processed into final unit dosage forms (e.g., orally disintegrating tablets) exhibiting acceptable content uniformity. The method comprises the following steps:

1) preparing the rapidly dispersing microgranules or granulate;

2) preparing the preblend 1 comprising charging a V-blender with one quarter of silicified microcrystalline cellulose (SMCC, a pharmaceutically acceptable carrier), micronized corticosteorid, colloidal silicon dioxide (a glidant) and another quarter of SMCC and blending the contents for 10 minutes;

3) preparing the preblend 2 comprising charging a high shear granulator with a free flowing filler (such as spray dried mannitol), preblend 1, remaining half of SMCC, disintegrant (such as crospovidone), and sweetener (sucralose powder) and blending the contents for 10 minutes at an impeller speed of 300±50 rpm and a chopper speed of 1500±50 rpm;

4) preparing the final compressible blend comprising charging a V-blender with one half of the rapidly dispersing granules of step 1, lubricant (such as sodium stearyl fumarate), the pre-blend 2 of step 3, and remaining half of rapidly dispersing granules of step 1and blending for 30 minutes, sampled and further blended for 10 ± 1 minutes to achieve acceptable blend uniformity/homogeneity as per regulatory requirements;

5) preparing the orally disintegrating tablets comprising the compressible blend of step 4, which exhibit acceptable content uniformity as per regulatory requirements.

In one embodiment, the method of manufacturing orally disintegrating tablets is performed by repeated dry blending and milling. The method comprises the following steps:

1) preparing the rapidly dispersing microgranules or granulate with an average particle size of not more than about 400 μm by 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) in presence of water or an alcohol-water mixture and then drying the granulate (fluid-bed equipment or a conventional oven);

2) preparing the milled preblend 1 by blending the pharmaceutically acceptable carrier (such as silicified microcrystalline cellulose), micronized corticosteroid and glidant (such as colloidal silicon dioxide) in a V-blender for 10 minutes at 25±1 rpm and then milling through a comminuting mill equipped with a 024R screen (30 Mesh opening) at approximately 2400±100 rpm;

3) preparing the milled preblend 2 by blending half of free flowing mannitol, preblend 1 from step 2, disintegrant (crospovidone), and sweetener (sucralose powder) in a V-blender for 10 minutes at 25±1 rpm and then milling through a comminuting mill equipped with a 024R screen at a speed of 2400±100 rpm, and rinsing the mill with remaining half of free flowing mannitol;

4) preparing the compressible blend by blending the rapidly dispersing granules of step 1, lubricant (such as sodium stearyl fumarate), the milled preblend 2 of step 3, rinsed free flowing mannitol) for total time of 40 minutes;

5) preparing the tablets by compressing the compressible blend of step 4.

The repeated dry blending and milling process is the preferred process for the preparation of the compositions of the invention.

In the process of the invention the different steps and the order of addition of individual components is important to achieve as acceptable blend uniformity/homogeneity in the compressible blend, as well as acceptable content uniformity of the finished dosage units as per regulatory requirements. The tablets obtained with the above process have the appearance, disintegration time, hardness and friability appropriate and suitable for ODTs to withstand attrition during transport in bulk containers, commercial packaging in blisters or bottles, and transport of primary/secondary packaged products for commercial distribution and end use and the purpose of the invention. Moreover, the tablets manufactured and then packaged in blisters are highly stable at accelerated and long-term ICH stability conditions.

The solid pharmaceutical compositions of the present invention are suitable for oral administration of a topically acting corticosteroid to treat inflamed tissues of the upper gastrointestinal tract, for example the esophagus. The use of a topically acting corticosteroid for treating conditions associated with inflammation of the gastrointestinal tract is desirable because it results in fewer side-effects than a highly systemically acting corticosteroid.

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, hypereosinophilic 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, and pseudomembranous esophagitis.

In one specific embodiment, the pharmaceutical compositions of the present invention are suitable for treating inflammatory conditions of the upper gastrointestinal tract, particularly eosinophilic esophagitis.

Thus, the present invention includes pharmaceutical composition for use as medicaments in the treatment of inflammatory conditions of the gastrointestinal tract.

The invention also includes the method of administering to a patient in need thereof a solid pharmaceutical composition of the present invention. In one 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. Upon administration of a solid pharmaceutical composition of the present invention to an individual, the composition disintegrates in the patient's oral cavity. In another embodiment, the present invention includes 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. 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".

From the foregoing description and the experimental part, it can be seen that the present invention provides several important advantages. The described invention provides low dose oral compositions comprising a corticosteroid and a pharmaceutical carrier characterized by high content uniformity and stability, the composition and dosage forms wherein the corticosteroid microparticles are present largely at or near the surface of the carrier and are therefore likely to

be suitably positioned for the topical treatment of inflammation of gastroenteric tract, particularly EoE, upon disintegration of the corticosteroid ODT in the oral cavity of a patient and swallowing of the resultant viscous suspension.

EXPERIMENTS

METHODS

Bulk/tapped density is measured according to USP <616> method 1.

Particle size distribution (PSD) is measured on samples of 5-10 mg with ATM sonic sifter.

Flowability is tested using Sotax flow tester on about 110 g of materials employing standard six pre-vibration /vibration mode; the flow property is expressed as a flow index (α'/α_{ref}) and as Carr's index.

Water content is determined using Karl Fisher titration or LOD is measured according to USP<921> 1a method.

Blend Uniformity Testing: Blend uniformity testing is carried out by withdrawing 6 random samples using a sampling thief from different locations of the final direct compression blend contained in the V- or twin shell blender as shown in FIG. 1. Samples collected are tested for their drug contents using an HPLC stability-indicating method.

Content Uniformity of ODTs: Orally disintegrating tablets are randomly sampled at the beginning, middle and end of each compression run, 10 tablets are tested for their content uniformity using the HPLC stability-indicating method.

Disintegration is performed according to USP<701> method. *Friability* is measured according to USP<1216> method.

EXAMPLES

Example 1: Rapidly Dispersing Microgranules

Rapidly dispersing microgranules are prepared following the procedure disclosed in US Patent Application Publication No. U.S. 2003/0215500 published November 20, 2003, the contents of which are hereby incorporated by reference in its entirety for all purposes. Specifically, D-mannitol (152 kg) with an average particle size of approximately 20 μm or less

(PEARLITOL® 25 from Roquette, France) is blended with 8 kg of cross-linked povidone (Crospovidone® XL-10 from ISP) in a high shear granulator (GMX 600 from Vector), granulated with purified water (approximately 32 kg), wet-milled using a Comil from Quadro, and finally tray-dried to provide microgranules having an LOD (loss on drying) of less than about 1.0%. Alternatively, the wet milled granules are dried in a fluid-bed dryer to provide microgranules having an LOD of less than 1.0% by weight. The dried granules are sieved and oversize material is again milled to produce rapidly dispersing microgranules with an average particle size in the range of approximately 175-300 microns.

D-mannitol with a median particle size of < 20 μm (93parts) and Crospovidone (5 parts) are granulated by spraying the starch solution (2 parts of Starch 1500® from Colorcon) in a top spray fluid-bed granulator and dried for a loss on drying of <1.0%. The dried granules are sieved through a 20 mesh sieve, and oversized granules are milled and sieved, if needed to produce alternate rapidly dispersing granules.

Example 2: Blend preparation by high shear process for 1.5 mg fluticasone ODT; batch 1

A preblend 1 is first prepared by blending one quarter of silicified microcrystalline cellulose (SMCC commercially available as PROSOLV® HD90), micronized fluticasone propionate, colloidal silicon dioxide, and another quarter of SMCC in a 1 quart V-blender for 10 ± 1 minutes (see Table 1 for weights of individual components of compressible blends of ODTs, 1.5 and 3 mg). A second preblend (preblend 2) is prepared: 10 L granulation bowl of a high shear granulator, PMA 1 is charged with spray-dried mannitol (PARTECK® M200), preblend 1, remaining half of SMCC, crospovidone and sucralose powder. Blending is performed for 10 ± 1 minutes at an impeller speed of 300±50 rpm and a chopper speed of 1500±50 rpm to produce preblend 2. One half of rapidly dispersing microgranules, sodium stearyl fumarate, preblend 2 and the remaining half of rapidly dispersing microgranules are blended in a 8 qt V-shell blender and sampled for blend uniformity at 30 and 40 minutes. The final blend is sampled for bulk/tapped density, particle size distribution (PSD), flowability and moisture testing.

Table 1: Compositions of compressible blends of Fluticasone ODTs, 1.5 and 3 mg

Ingredients (mg)	Fluticasone ODTs							
ODT Batch#	1.5 mg batch 1		1.5 mg batch 2	1.5 mg batch 3	1.5 mg batch 4	3 mg batch 5		3 mg batch 6
	(%/tablet)	(mg/tablet)	(mg/tablet)	(mg/tablet)	(mg/tablet)	(%/tablet)	(mg/tablet)	(mg/tablet)
Micronized Fluticasone Propionate USP	0.50	1.50	1.50	1.50	1.50	1.0	3.00	3.00
Colloidal Silicon Dioxide NF	0.30	0.90	0.90	0.90	0.90	0.30	0.90	0.90
Silicified Microcrystalline Cellulose NF	10.00	30.00	30.00	30.00	30.00	10.00	30.00	30.00
Crospovidone NF	7.50	22.50	22.50	22.50	22.50	7.50	22.50	22.50
Sucralose NF	0.40	1.20	1.20	1.20	1.20	0.40	1.20	1.20
Spray-dried Mannitol USP	30.30	90.90	90.90	90.90	89.40	29.80	89.40	87.90
Rapidly Dispersing Granules	50.00	150.00	150.0	150.0	150.0	50.00	150.0	150.0
Sodium Stearyl Fumarate NF	1.00	3.00	3.00	3.00	4.50	1.00	3.00	4.50
Total	100.00	300.0	300.0	300.0	300.0	100.00	300.0	300.0

Example 3: Blends preparation by repeated blending and milling for 1.5 and 3 mg fluticasone ODT; batch 2, 3, 5

A preblend 1 (see Table 1 for weights of individual components of compressible blends of ODTs, 1.5 and 3 mg) is prepared by charging a 2 quart V-blender sequentially with half of SMCC, micronized fluticasone propionate, colloidal silicon dioxide and the remaining half of SMCC and blending for 10 ± 1 minutes. The preblend 1 is passed through a QUADRO Comil fitted with a 024R screen (30 mesh opening) at approximately 2400±100 rpm. Preblend 2 is prepared: half of spray-dried mannitol, milled preblend 1, crospovidone, and sucralose powder are blended in a 4 quart V-blender for 10 ± 1 minutes and milled through the 024R screen. The Comil is rinsed by passing the remaining half of spray-dried mannitol through a 024R screen. Half of rapidly dispersing microgranules, sodium stearyl fumarate, milled preblend 1, rinsed mannitol and the remaining half of rapidly dispersing granules are blended and sampled for blend uniformity at 30 and 40 minutes. The final blends are sampled for testing of bulk/tapped density, particle size distribution (PSD), flowability, and moisture content.

Example 4: Blend uniformity results of blends of examples 2 and 3

Test results for the compressible blends of Examples 2 and 3 are presented in Table 2. The compression blends, ODT 1.5 mg (batch 1) and ODT 1.5 mg (batch 2), which have been processed using two different combinations of equipment – V-blender-high shear granulator and V-blender-comminuting mill- show similar blend physical (powder) properties such as bulk and tapped densities, particle size distributions, flow properties, and blend uniformity values, excepting that the 30-minute blended batch shows a slightly higher %RSD.

Table 2: Physical/Blend uniformity test results for Fluticasone ODT, 1.5 and 3 [illegible] ds

Test	Parameters		Blend Batch #					
			1.5 mg batch 1	1.5 mg batch 2	1.5 mg batch 3	3 mg batch 5	1.5 mg batch 4	3 mg batch 6
Bulk/Tap Density USP <616> Method I	Bulk Density		0.57	0.57	0.57	0.57	0.57	0.58
	Tapped Density		0.71	0.71	0.72	0.70	0.78	0.77
Particle Size Analysis	Sieve #	Particle Size (µm)	% Retained	% Retained	% Retained	% Retained	% Retained	% Retained
	20	840	0.62	0.39	0.36	0.61	0.6	0.4
	40	425	16.08	14.05	17.32	18.08	18.9	20.2
	60	250	13.37	12.00	14.57	14.62	13.8	14.8
	80	180	9.70	10.33	10.07	10.21	10.7	12.0
	100	150	6.60	5.84	7.90	8.37	6.2	5.5
	200	75	22.61	24.62	19.83	21.24	20.0	20.0
	Pan	20	31.01	32.77	29.95	26.86	29.8	27.1
LOD USP <921>1a			1.0	1.0	1.0	0.9	1.0	1.1
Flow Results	Parameters							
	Flow Angle		67.9	69	55.7	55.9	68.5	67.3
	Flow Index		0.83	0.84	0.68	0.68	0.84	0.82
	Flow Quality		Good	Good	Medium	Medium	Good	Good
Blend Uniformity	Blending time		30 min	40 min	30 min	40 min	30 min	40 min	40 min	40 min
	Minimum, %		94.8	94.5	93.2	93.4	95.8	101.0	94.7	97.3
	Maximum, %		105.1	100.4	98.6	99.9	102.8	104.8	99.4	101.1
	Mean, %		99.3	97.2	95.7	97.0	98.9	102.0	97.4	99.5
	%RSD		3.6	2.2	2.0	2.9	2.7	1.4	1.0	1.5
Content Uniformity	Mean						101.5	101.1	100.6	100.7
	±SD						3.7	1.5	2.0	1.0
	AV						8.8	3.7	4.7	2.4

Table 3: Stratified Blend uniformity results for Fluticasone ODT Compression Blends

Sampling Location	Label Claim (%)							
	1.5 mg 101		1.5 mg 201		1.5 mg301	3 mg 101		3 mg 201
	30 min	40 min	30 min	40 min	40 min	30 min	40 min	40 min
Top Left	98.9	96.0	95.9	99.9	94.7	100.6	101.5	98.0
Middle Left	105.1	94.5	93.2	93.4	98.2	100.0	101.6	99.9
Bottom Left	101.2	97.8	95.5	99.0	95.5	102.8	104.8	97.3
Top Right	94.8	95.9	94.1	93.6	98.5	96.4	101.7	101.1
Middle Right	98.3	100.4	98.6	98.2	99.4	95.8	101.0	99.5
Bottom Right	97.4	98.7	96.8	97.6	97.8	98.0	101.6	100.9
Maximum	105.1	100.4	98.6	99.9	99.4	102.8	104.8	101.1
Minimum	94.8	94.5	93.2	93.4	94.7	95.8	101.0	97.3
Mean	99.3	97.2	95.7	97.0	97.4	98.9	102.0	99.5
RSD	3.6%	2.2%	2.0%	2.9%	1.9%	2.7%	1.4%	1.5%

Example 5: Compression of ODTs of Examples 2 and 3

The compression blends of Examples 2 and 3 are compressed using a rotary tablet press, Manesty Beta Press equipped with 8 punch die sets of 9.5 mm round, plain, flat-faced radius edge tooling. The average tablet weight is about 300 mg. The main compression force used is maintained at 5-6 KN, with a pre-compression force set at 2 ±0.2 kN for compression runs (except where noted). During the compression, the tablet press instrumentation by SMI is used to measure press speed and compression force. During tableting, tablets are periodically sampled for visual inspection of 'appearance', in-process measurements of weight, thickness, hardness and friability. Additional tablets are also samples as 'composite samples' for analytical

testing. Details of compression parameters and tablet properties are shown in Table 4. Tablets appears as round tablets they are also tested for assay, potency, content uniformity, dissolution (greater than 90% release after 45 minutes for all batches); they have friability not more than 0.4%, hardness of about 4 kP, disintegration time less than 30 sec.

Example 6: Confirmatory compression blend and ODT batches (ODT 1.5 mg: batch 3, 3 mg: batch 5)

Blend batches preparation by a twice repeated blending and milling process (repeated process of blending in the V-shell blender in conjunction with the milling using the Comil) for 1.5 and 3.0 mg fluticasone ODTs compression blends (see Table 1 for compositions, and Tables 2 and 3 for Physical/Blend uniformity test results and Stratified Blend uniformity results, respectively). Although bulk and tapped density values, particle size distributions blend uniformity values for the confirmatory compression blends are similar to those of the corresponding attributes of the ODT compression blend batch, ODT 1.5 mg (batch 2), the estimated flow properties of both ODT 1.5 mg (batch 3) and ODT 3 mg (batch 5) are not very good. Both compression blend batches are compressed using the same Beta Press equipped with the same set of tooling, and under comparable compression parameters. During compression of both compression blends, some picking and/or sticking to the punches is observed. Details of compression parameters and tablet properties are shown in Table 4.

Example 7: Blends preparation by repeated blending and milling for 1.5 and 3 mg fluticasone ODT, Lubricant at 1.5% by weight, batches 4 and 6

Fluticasone compression blend batches are prepared by first preparing preblend 1 and preblend 2 as disclosed in Example 3, then blending the components of the final blend without incorporating the lubricant for 35 minutes and further blending for 5 minutes following the addition of the lubricant (sodium stearyl fumarate at 1.5% by weight). The final blends are sampled for testing of bulk and tapped density, particle size distribution (PSD), flowability, moisture content, blend uniformity, and stratified blend uniformity of both batches. Results are reported in Tables 2 and 3.

Example 8: Compression of ODTs of Example 7

Both batches are compressed using the same rotary tablet press, same set of tooling and under similar compression conditions as disclosed above.

Table 4: Compaction process conditions and chemical/physical test results for Fluticasone ODTs

	1.5 mg tablet				3 mg tablet	
Compression parameters	**1.5 mg batch 1**	**1.5 mg batch 2**	**1.5 mg batch 3**	**1.5 mg batch 4**	**3 mg batch 5**	**3 mg batch 6**
Compression force (kN)	5.1-5.5	5.1-6.0	5.3-5.8	5.5-6.0	5.1	4.7-6.0
Precompression force (kN)	2.1-2.2	2.2	2.0-2.2	0	2.0	0
Results						
Average weight (mg)	304.3±3.2	305.4±3.4	303.8±0.7	304.7±3.3	307±2.1	301.8±2.1
Hardness min-max (kp)	3.23-4.01	3.0-3.9	2.67-4.12	2.8-3.6	3.00-3.85	3.0-4.2
Thickness min-max (mm)	4.059-4.149	4.02-4.23	4.09-4.21	4.13-4.19	4.28-4.33	3.99-4.15
Friability (%)	0.29	0.24	0.63	0.64	0.52	0.27
Disintegration - Start (sec)	12	13	12	12	10	14
Disintegration - End (sec)	14	14	12	24	16	15
Assay % label claim	n.p.	100.0	n.p.	99.2	103.8	101.6
Related Substances (%)	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.
Unknown	n.p.	n.p.	n.p.	<0.10	<0.10	<0.10
Unknown	n.p.	0.11	n.p.	n.p.	n.p.	n.p.

Total	n.p.	0.11	n.p.	<0.10	<0.10	<0.10
Dissolution (% at x minutes)						
10	63	52	69	67	54	54
20	79	81	86	83	73	73
30	87	91	93	89	84	82
45	92	95	96	93	91	88
60	95	96	98	94	94	90

n.p. --> not performed

Example 9: Stability testing

Fluticasone ODT batches 2 (1.5 mg) and 5 (3 mg) are packaged in 30 cc (30 tablets per bottle) HDPE bottles, with rayon coil and 0.5 g pouch dessicant (Sorb-it ½ g packet) included. All ODTs are stable at accelerated conditions (40°C/75% RH) for a period of 6 months, as well as at long-term stability conditions (25°C/60% RH) for a period of 9 months as shown in Tables 5 and 6. The physical properties, such as appearance, hardeness, friability, and disintegration time at all stability conditions are also comparable to the initial values of Fluticasone ODTs, 1.5 and 3 mg.

Table 5: Stability data for Fluticasone ODT batch 2 (1.5 mg)

Test/Method	**Batch 2, 1.5 mg**					
	Time = Initial		Time = 6 months 40°C/75%RH		Time = 9 months 25°C/60%RH	
Physical Appearance/ Visual	White round tablets		White round tablets		White round tablets	
Moisture	1.0%		1.9 %		1.8 %	
Disintegration	16 sec		25 sec		18 sec	
Friability	0.3%		0.6%		0.1%	
Hardness (kP)	Min: 2.2 Max: 3.6 Mean: 3.0		Min: 1.4 Max: 3.3 Mean:2.5		Min: 2.7 Max: 4.3 Mean:3.4	
Potency (%)	1: 100.0 2: 100.0 Mean: 100.0		1: 100.0 2: 100.2 Mean: 100.1		1: 99.5 2: 98.3 Mean: 98.9	
Related Substances,	RRT	%RS	RRT	%RS	RRT	%RS
Unknown	-	-	0.89	0.14	1.66	0.10

Unknown	0.75		0.11			0.90		0.13			-		-		
Total (%)	0.11					0.27					0.10				
Dissolution															
Minutes	10	20	30	45	60	10	20	30	45	60	10	20	30	45	60
Minimum (%)	61	82	90	93	95	66	84	92	96	97	66	83	90	93	94
Maximum (%)	67	86	94	97	99	68	86	93	97	99	69	85	91	95	96
Mean (%)	64	85	92	95	97	67	85	92	96	98	67	84	91	94	95
%RSD	3.3	2.1	1.7	1.7	1.7	1.0	0.7	0.7	0.8	0.8	1.8	0.9	0.8	0.8	0.8

Table 6: Stability data for Fluticasone ODT batch 5 (3 mg)

Test/Method	**Batch 5, 3 mg**					
	Time = Initial		Time = 6 months 40°C/75%RH		Time = 9 months 25°C/60%RH	
Physical Appearance/ Visual	White round tablets		White round tablets		White round tablets	
Moisture Content	0.9%		1.3%		1.8%	
Disintegration Time	17 sec		17 sec		15 sec	
Friability	1.2%		1.6%		1.1%	
Hardness (kP)	Min: 1.9 Max: 3.5 Mean: 2.6		Min: 1.3 Max: 3.7 Mean: 2.5		Min: 1.7 Max: 3.0 Mean: 2.4	
Potency (%)	1: 103.6 2: 103.9 Mean: 103.8		1: 99.8 2: 97.4 Mean: 98.6		1: 100.7 2: 100.1 Mean: 100.4	
Related	RRT	%RS	RRT	%RS	RRT	%RS

Substances,															
Unknown	0.89		<0.1			0.89			0.14		1.66			0.13	
Unknown	-		-			0.90			0.13		-			-	
Total (%)	< 0.1					0.27					0.13				
Dissolution															
Minutes	10	20	30	45	60	10	20	30	45	60	10	20	30	45	60
Minimum (%)	57	78	87	92	94	47	64	72	78	80	56	76	85	91	93
Maximum (%)	61	81	90	95	97	56	76	89	97	101	59	78	89	96	99
Mean (%)	59	79	88	94	96	53	73	84	91	94	58	77	86	93	95
%RSD	3.1	1.7	1.4	1.4	1.3	6.1	6.4	7.0	7.4	7.6	1.5	1.2	1.7	2.0	2.2

Example 10: Preparation of Clinical Trial Materials, batches C1, C2

Clinical trial batches (Fluticasone propionate ODTs, 1.5 and 3 mg with 1.5% by weight of sodium stearyl fumarate) are prepared by a repeated blending - milling -blending process followed by compression as disclosed in Examples 7 and 8. The in-process testing results and the analytical results of the clinical batches are presented in Table 7 and Table 8, respectively. The compression blend batches show physical (powder) properties similar to that of the feasibility batches, except that the clinical batches have more finer particles passing through 100 mesh sieve (67-76% particles are < 150 μm in size) as compared to 47-57% finer particles in the feasibility batches. However, this has not affected the tableting properties of the clinical batches significantly: in batch C-2 (3 mg) a slightly higher %RSD in content uniformity and excellent blend uniformity results are observed.

Table 7: Physical/Blend uniformity test results for Clinical Trial Batches 1.5 and 3 mg

Test/Method	Test Parameter		1.5 mg Blend		3 mg Blend	
			1.5001	1.5002	3.0001	3.0002
Bulk/ Tap Density USP <616> Method I	Bulk Density (g/cc)		0.56	0.56	0.56	0.56
	Tapped Density (g/cc)		0.75	0.75	0.75	0.74
	Hausner Ratio		1.34	1.34	1.34	1.32
	Carr's Index		25.14	25.41	25.56	24.44
Particle Size Analysis	Size#	Particle Size (µm)	% Retained	% Retained	% Retained	% Retained
	20	840	0.50	0.80	0.20	0.70
	40	425	2.90	3.30	2.30	3.40
	60	250	6.00	10.60	5.10	9.90
	80	180	8.90	11.40	9.30	10.80
	100	150	5.50	6.00	6.10	5.70
	200	75	23.20	23.40	24.40	21.40
	Pan	< 75	53.00	44.50	52.60	48.10
LOD (USP <921>1a			1.3	1.2	1.6	1.2
Blend Uniformity	Minimum (%)		97.4	94.0	96.4	94.1
	Maximum (%)		98.1	97.0	99.1	96.2
	Mean (%)		97.9	96.1	98.1	95.8
	% RSD		0.3	1.2	0.9	0.9

Table 8: Physical/Blend uniformity test results for Clinical Trial Batches of Fluticasone ODTs, 1.5 and 3 mg

Parameter	ODT 1.5 mg C1	ODT 1.5 mg C2	ODT 3 mg C1	ODT 3 mg C2
Physical Appearance / Visual	White round tablets	White round tablets	White round tablets	White round tablets
Moisture Content	1.9%	1.2%	1.8%	1.3%
Disintegration Time	15 sec	18 sec	16 sec	19 sec
Friability	0.1%	0.0%	0.4%	0.3%
Hardness, kP	Min: 3.1 Max: 5.1 Mean: 3.9	Minimum: 3.9 Maximum: 5.4 Mean: 4.6	Minimum: 2.8 Maximum: 4.3 Mean: 3.4	Minimum: 3.5 Maximum: 4.9 Mean: 4.3
Potency (%)	1: 98.3 2: 99.2 Mean: 98.8	1: 95.4 2: 96.1 Mean: 95.8	1: 98.3 2: 99.6 Mean: 99.0	1: 98.1 2: 97.9 Mean: 98.0
Related Substance (%)	%RS at RRT	%RS at RRT	%RS at RRT	%RS at RRT
Individual Impurity (NMT 0.5%)	<0.1% at 0.89	< 0.10	< 0.10	< 0.10
Total (NMT 1.5%)	<0.1% at 0.90	< 0.10	< 0.10	< 0.10
Content Uniformity of Dosage units – Minimum (%)	97.0	93.2	98.3	96.1
- Maximum	99.3	97.9	100.4	98.5
- Mean	98.1	96.3	99.2	97.5
- % RSD	2.3	6.1	1.7	3.7
% Mean Dissolved / 60 min	96%	95%	94%	93%

Example 11: Stability data for Clinical Trial Batches, Fluticasone ODTs, 1.5 and 3 mg

Fluticasone ODT batches, 1.5 mg and 3 mg are packaged in 30 c't (30 tablets per bottle) HDPE bottles, with rayon coil and 0.5 g pouch dessicant (Sorb-it ½ g packet) included. All ODTs are stable at accelerated conditions (40°C/75% RH) for a period of 9 months, as well as at long-term stability conditions (25°C/60% RH) for a period of 24 months as shown in Table 9. The physical properties, such as appearance, hardness, friability, and disintegration time at all stability conditions are also comparable to the initial values of Fluticasone ODTs, 1.5 and 3 mg.

Table 9: Stability data for Clinical Trial Batches Fluticasone ODTs, 1.5 and 3 mg

ODT Batch#	ODTs, 1.5 mg		ODTs, 3 mg	
Parameter	Time: Initial	Time: 24 months at 25°C/60%RH	Time: Initial	Time: 24 months at 25°C/60%RH
Physical Appearance / Visual	White round tablets	White round tablets	White round tablets	White round tablets
Moisture Content	2.2%	2.1%	2.4%	2.0%
Disintegration Time	0-5 sec	0-5 sec	0-5 sec	0-5 sec
Friability	0.03%	0.12%	0.02%	0.50%
Hardness, kP	Min: 3.6 Max: 6.1 Mean: 4.8	Min: 3.8 Max: 5.9 Mean: 5.0	Min: 4.0 Max: 5.9 Mean: 4.7	Min: 3.3 Max: 6.2 Mean: 4.8
Potency (%)	1: 100.8 2: 100.3 Mean: 100.6	1: 99.7 2: 99.8 Mean: 99.7	1: 100.3 2: 101.3 Mean: 100.8	1: 100.0 2: 100.0 Mean: 100.0
Related Substances	%RS at RRT	%RS at RRT	%RS at RRT	%RS at RRT
Unknown	<0.1% at 0.89	-	<0.1% at 0.89	-
Unknown	<0.1% at 0.90	-	<0.1% at 0.90	-
Total	<0.1	<QL	<0.1	<QL
% Mean Dissolved / 60 min	96%	95%	94%	93%

Example 12: Clinical tests

A proof of concept study is conducted for clinical batches ODT-FT 1.5 mg and 3 mg dose strengths in patients with a diagnosis of EoE aged 12 years to 55 years.

The doses utilized are 1.5 mg administered twice daily and 3.0mg administered once daily. The study also included a placebo arm. Each arm enrolls 8 subjects. Findings of efficacy analyses demonstrate a positive signal for efficacy with the greatest response seen histologically in the decrease of peak eosinophil count per high power field (a hallmark of the disease and indicator of treatment response). Both 1.5 mg and 3 mg treatment groups are clearly more efficacious than placebo histologically. The percent of subjects with at least 30% decrease in the overall EoE symptom severity, as measured by patient questionnaire, also shows numerical superiority of the two FT-ODTs over placebo. Endoscopic improvements are also seen with changes in furrowing and vascularity showing the greatest differentiation of FT-ODTs from placebo, indicating a positive anti-inflammatory effect of the formulations.

Overall, the FT-ODTs of the invention demonstrate improvements in histology, overall symptoms and overall endoscopic activity.

Example 13: Preparation of Blends for 0.75, 4.5 and 6 mg Fluticasone ODTs - Batches 7 to 9

Fluticasone compression blend batches at a drug load of 0.25% by weight are prepared by first preparing preblend 1 and preblend 2 as disclosed in Example 3. A preblend 1 (see Table 10 for weights of individual components of compression blends of ODTs, 0.75mg, 4.5mg and 6mg) is prepared by charging a 2 quart V-blender sequentially with half of SMCC, micronized fluticasone propionate, colloidal silicon dioxide and the remaining half of SMCC and blending at 25 rpm for 10 ± 1 minutes. The preblend 1 is passed through a QUADRO Comil fitted with a 024R screen (30 mesh opening) at approximately 2400±100 rpm. Preblend 2 is prepared: half of spray-dried mannitol, milled preblend 1, crospovidone, and sucralose powder are blended in a 32 quart V-blender at 25 rpm for 10 ± 1 minutes and milled through the 024R screen. The Comil is rinsed by passing the remaining half of spray-dried mannitol through a 024R screen. Half of rapidly dispersing microgranules, milled preblend 1, rinsed mannitol and the remaining half of rapidly dispersing granules are blended in a 32 quarts V-blender at 25 rpm, without incorporating

the lubricant, for 35 minutes and further blended for 5 minutes following the addition of the lubricant (sodium stearyl fumarate at 1.5% by weight).

Example 14: Preparation of Blends for 1.5mg Fluticasone ODTs at Batch Size: 30 kgs; batch 10

The manufacturing process for the fluticasone compression blend batch at a lower drug load of 0.5% by weight is scaled up to a semi-industrial scale of 30 kgs. The process essentially consists of first preparing preblend 1 and preblend 2 as disclosed in Example 3. A preblend 1 (see Table 10 for weights of individual components of compressible blends of ODTs, 1.5mg) is prepared by charging a 32 quart V-blender sequentially with half of SMCC, micronized fluticasone propionate, colloidal silicon dioxide and the remaining half of SMCC and blending at 25 rpm for 10 ± 1 minutes. The preblend 1 is passed through a QUADRO Comil fitted with a 024R screen (30 mesh opening) at approximately 2400±100 rpm. Preblend 2 is prepared: half of spray-dried mannitol, milled preblend 1, crospovidone, and sucralose powder are blended in a Galley blender with 113L tote at 12 rpm for 20 ± 1 minutes and milled through the 024R screen. The Comil is rinsed by passing the remaining half of spray-dried mannitol through a 024R screen. Half of rapidly dispersing microgranules, milled preblend 1, rinsed mannitol and the remaining half of rapidly dispersing granules are blended at 12 rpm for up to 40 minutes.

The final blends in Example 13 and 14 are sampled and subjected to in-process testing as per United States Pharmacopeia requirements and analytical testing of bulk and tapped density, particle size distribution (PSD), flowability, blend uniformity and moisture content. This is the first time, a direct compression ODT blend batch at a drug load of 0.25% by weight is manufactured using the procedure established for the blend at a drug load of 0.5% by weight. No technical issues have been encountered during the manufacture. The results reported in Table 11 show acceptable physical characteristics. Although the blend uniformity data indicate a uniform distribution of the active, a low potency is evident in Batch 7 with the lowest drug load, probably due to a loss of the active during blending/milling. During the semi-industrial scale compression blending process prior to incorporating the lubricant, the blends sampled at 20, 30 and 40 minutes show acceptable blend uniformity values as shown below.

Blend Uniformity (% Label Claim)	Sampling Time	20 min	30 min	40 min
	Mean (%)	101.4	99.1	98.3
	Minimum (%)	99.3	97.2	95.9
	Maximum (%)	104.3	100.6	100.1
	RSD (%)	1.4	1.4	1.3

Example 15: Compression of ODTs of Example 13 and 14

Batches of ODTs, 0.75mg, 4.5mg and 6mg are compressed using the same rotary tablet press (Beta Press) equipped with the same force feeder and same set of tooling (B-size tooling, 9.5 mm round flat faced radius edge) and under similar compression conditions as disclosed previously for ODTs, 1.5mg or 3mg. The compressed tablets of 0.75mg, 4.5mg and 6mg meet the specifications for tablet weight, disintegration time, friability, hardness and thickness. The physical properties of the tablets are similar and comparable to the other dose strengths. The potency and content uniformity results for the 0.75mg ODTs indicate a low potency confirming the low blend uniformity results reported above.

ODTs, 1.5mg are compressed using the industrial tablet press, Korsch XL 400 equipped with D tooling, 9.5 mm round, flat faced radius edge, operated at 1015 tablets per minutes. The compressed tablets are observed to meet all specifications for tablet weight, disintegration time, friability, hardness and tablet thickness. The physical properties of the tablets are similar and comparable to the same dose strength or other dose strengths produced at small scale. The potency and content uniformity results confirm the blend uniformity results, resulting ODTs meeting all product specifications. The results of the scale up batch have shown that the current small scale process at a drug load of 0.5% by weight or higher, is scalable. The comparable /similar results obtained between dose strengths and consistency in results between batch sizes at least at a drug load of 0.5% by weight or higher, indicate a robust, suitable direct compression manufacturing process for ODT dose strengths ranging from 1.5mg to 6mg or at a drug load of from 0.5% to 2% by weight. This low end drug load has been possible in the past only by spray

granulation, by spraying the drug solution while granulating tablet components excepting the lubricant.

Table 10: Compositions of compression blends of Fluticasone ODTs, 0.75mg (Batch 7), 4.5mg (Batch 8), 6mg (Batch 9) and 1.5mg (Batch 10)

Ingredients (mg)	Fluticasone ODTs				
ODT Batch#	0.75mg batch 7		4.5mg batch 8	6.0mg batch 9	1.5mg batch 10
	(%/tablet)	(mg/tablet)	(mg/tablet)	(mg/tablet)	(mg/tablet)
Micronized Fluticasone Propionate USP	0.25	0.75	4.50	6.00	1.50
Colloidal Silicon Dioxide NF	0.30	0.90	0.90	0.90	0.90
Silicified Microcrystalline Cellulose NF	10.00	30.0	30.00	30.00	30.00
Crospovidone NF	7.50	22.50	22.50	22.50	22.50
Sucralose NF	0.40	1.20	1.20	1.20	1.20
Spray-dried Mannitol USP	30.05	90.15	86.40	84.90	89.40
Rapidly Dispersing Granules	50.00	150.00	150.00	150.0	150.0
Sodium Stearyl Fumarate NF	1.50	4.50	4.50	4.50	4.50
Total	100.00	300.0	300.0	300.0	300.0

Table 11: Physical/Blend uniformity test results for Fluticasone ODT, 0.75mg, 4.5mg and 6mg Compression Blends

Test	Parameters		Blend Batch #		
			0.75 mg batch 7	4.5 mg batch 8	6.0 mg batch 9
Bulk/Tap Density USP <616> Method I	Bulk Density		0.56	0.55	0.55
	Tapped Density		0.75	0.73	0.75
	Hausner Ratio		1.33	1.33	1.35
Particle Size Analysis	Sieve #	Particle Size (µm)	% Retained	% Retained	% Retained
	20	840	0.6	0.6	0.6
	40	425	10.0	9.8	7.6
	60	250	16.9	16.7	15.1
	80	180	20.2	19.2	18.5
	100	150	9.3	9.3	9.4
	200	75	25.2	26.9	28.4
	Pan	20	17.8	17.5	20.5
LOD USP <921> (KF)			1.4	1.8	1.5
Flow Results	Flow Angle		82.6	83.9	83.2
	Flow Index		1.01	1.02	1.01
	Flow Quality		Very Good	Very Good	Medium
Blend Uniformity	Blending time		Blend (40 min) After Lubrication		
	Mean, %		91.3	97.1	98.7
	Minimum, %		88.5	94.7	94.7
	Maximum, %		94.1	98.7	100.4
	%RSD		2.2	1.3	2.1

Table 12: Compaction process conditions and chemical/physical test results for Fluticasone ODTs

	ODTs			
Compression parameters	**0.75 mg batch 7**	**4.5 mg batch 8**	**6 mg batch 9**	**1.5 mg batch 10**
Compression force (kN)	5.3-5.6	5.0-5.2	5.2-5.3	4.8-5.1
Precompression force (kN)	2.0	1.5-1.7	1.5	1.3-1.4
Average weight, mg (%RSD)*	302.3 (0.56)	301.9 (0.84)	300.6 (0.54)	301.2 (0.76)
	297.3 (0.58)	301.7 (0.94)	303.6 (0.42)	302.2 (0.40)
	296.4 (0.40)	303.2 (0.77)	299.6 (0.76)	302.1 (0.33)
Hardness min-max (kp)*	3.70 (2.4-5.9)	3.35 (3.0-3.9)	4.34 (3.8-4.8)	5.45 (4.9-5.8)
	3.57 (2.4-5.9)	3.72 (2.8-4.4)	3.13 (2.3-3.4)	4.92 (3.8-5.5)
	2.95 (2.8-3.2)	3.75 (3.1-4.6)	3.14 (2.1-4.0)	4.91 (4.6-5.4)
Thickness min-max (mm)	4.15-4.41	4.01-4.12	4.01-4.19	4.01-4.04
Friability (%) Start/Middle/End	0.2/0.2/0.3	0.5/0.2/03	0.5/0.5//0.3	0.0/0.1/0.0
Disintegration - Start (sec)	10	15	15	12
Disintegration - End (sec)	10	14	16	14
Assay % label claim	95.5-95.6	98.6	99.3-100.1	97.2-99.3
Related Substances (%) - RRT				
Unknown 0.79		ND	ND	0.18
Unknown 0.89/0.90		ND/0.10	ND/ND	<0.10/ 0.11
Unknown 1.58 / 1.84		ND/ND	ND/ND	<0.10/ <0.10
Total		0.10	<0.10	0.29
Time	% Dissolved			
10 Min	58 (1.9)	46 (2.6)	46 (3.1)	64 (2.5)
20 Min	72 (1.1)	74 (15.2)	66 (1.1)	82 (0.9)
30 Min	79 (0.9)	85 (8.8)	77 (1.2)	90. (1.2)
45 Min	84 (0.8)	89 (2.8)	86 (1.5)	93 (1.0)
60 Min	86 (0.6)	92 (1.0)	91 (1.4)	95 (1.0)

** --> Tested at Start, Middle and End of compression; ND --> not detected*

Stability of Fluticasone ODTs batch 7 (0.75 mg), batch 8 (4.5) and batch 9 (6 mg) is testes; these batches are packaged in 30 cc (30 tablets per bottle) HDPE bottles, with rayon coil and 0.5 g silica pouch dessicant (Sorb-it ½ g packet) included. All ODTs are stable at accelerated conditions (40°C/75% RH) for a period of 6 months, as well as at long-term stability conditions (25°C/60% RH) for a period of 9 months; all values measured at given time points (T= 0, 1 month, 2 months, 3 months, 6 months, 9 months) are within the acceptance criteria (disintegration: NMT 30 sec, assay: NLT 90.0% and NMT 110.0%, each impurity: NMT 0.5%, total impurity: NMT 1.5%). The physical properties, such as appearance, hardeness, friability, and disintegration time at all stability conditions are also comparable to the initial values of the corresponding Fluticasone ODTs.

While the invention has been described in connection with the specific embodiments herein, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to that the invention pertains and as may be applied to the essential features hereinbefore set forth and as follows in the scope of the appended claims.

MCSLLP

CLAIMS

1. A pharmaceutical composition in the form of an orally disintegrating tablet for oral administration comprising:

a. a topically acting corticosteroid or pharmaceutically acceptable salt, ester, or polymorph adsorbed onto silicified microcrystalline cellulose;

b. rapidly dispersing microgranules; wherein the topically acting corticosteroid is present in an amount of 5% or less by weight in the composition.

2. The pharmaceutical composition of claim 1, wherein the orally disintegrating tablet disintegrates within 30 seconds when tested using the USP <701> method for disintegration time.

3. The pharmaceutical composition of claim 1, wherein the orally disintegrating tablet disintegrates within 60 seconds on contact with saliva in the oral cavity of a patient in need thereof.

4. The pharmaceutical composition of claim 1, 2, or 3, wherein the rapidly dispersing microgranules comprise a sugar alcohol, or a saccharide, or a mixture thereof and at least one disintegrant.

5. The pharmaceutical composition of claim 4, wherein the sugar alcohol or saccharide and the disintegrant are present in a ratio of sugar alcohol or saccharide to disintegrant from 90:1 0 to 99:1.

6. The pharmaceutical composition of claim 1, 2, 3, 4, or 5, wherein said corticosteroid is selected from the group consisting of budesonide, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone, and salts, solvates, esters, and mixtures thereof.

7. The pharmaceutical composition of claim 6, wherein said corticosteroid is fluticasone.

8. The pharmaceutical composition of claim 7, wherein said corticosteroid is fluticasone propionate.

9. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7, or 8, wherein the topically acting corticosteroid is in an amount of about 3% or less by weight in the composition.

10. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7, or 8, wherein the topically acting corticosteroid is in an amount of about 1.5% or less by weight in the composition.

11. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7, or 8, wherein the topically acting corticosteroid is in an amount of about 1% or less by weight in the composition.

12. The pharmaceutical composition of claim l, 2, 3, 4, 5, 6, 7, or 8, wherein the topically acting corticosteroid is in an amount of about 0.5% or less by weight in the composition.

13. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7, or 8, wherein the topically acting corticosteroid is in an amount of about 4.5 mg in the composition.

14. The pharmaceutical composition of claim 1, 2, 3, 4, 5, or 6, wherein the topically acting corticosteroid is in an amount of about 3 mg in the composition.

15. The pharmaceutical composition of claim 1, 2, 3, 4, 5, or 6, wherein the topically acting corticosteroid is in an amount of about 1.5 mg in the composition.

16. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7, or 8, wherein the topically acting corticosteroid is in an amount of about 6 mg in the composition.

17. The pharmaceutical composition of claim 1, 2, 3, 4, 5, or 6, wherein the topically acting corticosteroid is fluticasone propionate in the range of 0.05 to about 15 mg in the composition at a drug content of from about 0.16% to 5% by weight of the composition.

18. The pharmaceutical composition of claim 1, 2, 3, 4, 5, or 6, wherein the topically acting corticosteroid is fluticasone propionate in the range of 0.75 to about 4.5 mg in the composition at a drug content of from about 0.25% to 1.5% by weight in the composition.

19. The pharmaceutical composition of claim 1, 2, 3, 4, 5, or 6, wherein the topically acting corticosteroid is fluticasone propionate in the range of 0.05 to about 18 mg in the composition at a drug content of from about 0.125% to 5% by weight in the composition.

20. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19, wherein the corticosteroid is micronized with a particle size of not more than 50 microns.

21. The pharmaceutical composition of claim 20, wherein the corticosteroid has a mean particle size of not more than 10 microns.

22. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21, wherein the composition further comprises an adhesive agent.

23. The pharmaceutical composition of claim 22, wherein the adhesive agent is selected from the group consisting of sucrose aluminum sulfate complex, chitosan and derivatives thereof, polyvinylpyrrolidone, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl ethylcellulose, sodium carboxymethylcellulose, cross-linked polyacrylic acid, cross-linked polyacrylates, aminoalkyl methacrylate copolymers, carbopol polymers, hydrophilic polysaccharide gums, maltodextrins, pectins, xanthan gums, alginic acid, modified alginic acids, and combinations thereof.

24. The pharmaceutical composition of claim 4 or 5; or claim 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23 when dependent on claim 4 or 5; wherein the disintegrant is selected from the group consisting of crospovidone, sodium starch glycolate, crosslinked carboxymethyl cellulose, and low substituted hydroxylpropylcellulose.

25. The pharmaceutical composition of claim 4 or 5; or claim 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 or 23 when dependent on claim 4 or 5; or claim 24, wherein the sugar alcohol or saccharide is selected from the group consisting of sucralose, lactose, sucrose, maltose, mannitol, sorbitol, xylitol, maltitol, and mixtures thereof.

26. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25, further comprising a free flowing sugar alcohol or saccharide selected from the group consisting of spray-dried mannitol, spray-dried lactose, and combinations thereof.

27. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26, further comprising a lubricant selected from the group consisting of magnesium stearate, stearic acid, sodium stearyl fumarate, glyceryl behenate, and a mixture thereof.

28. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27, further comprising at least one antifungal agent.

29. The pharmaceutical composition of claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, or 27, further comprising at least one antiviral agent.

30. The pharmaceutical composition of claim 4 or 5; or claim 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 or 23 when dependent on claim 4 or 5; claim 24 or 25; or claim 26, 27, 28, or 29 when dependent on claim 4 or 5, wherein the rapidly dispersing microgranules further comprise an additive and wherein the ratio of sugar alcohol or saccharide to disintegrant to the additive is from 88:10:2 to 98.5:1:0.5.

31. The pharmaceutical composition of claim 30, wherein the additive is selected from the group consisting of pregelatinized starch, hydroxypropylcellulose.

32. The pharmaceutical composition of claim 4 or 5; or claim 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 or 23 when dependent on claim 4 or 5, claim 24or 25; or claim 26, 27, 28, 29 when dependent on claim 4 or 5, or claim 30, or 31, wherein the corticosteroid has an average particle size of less than about 10 μm, the rapidly dispersing microgranules have an average particle size of less than about 300 μm, and the sugar alcohol and/or saccharide has an average particle size of less than about 30 μm.

33. The pharmaceutical composition of claim 32, wherein the corticosteroid is fluticasone propionate with a particle size of less than 5 microns, the rapidly dispersing microgranules consist of mannitol and crospovidone, the free-flowing sugar alcohol is spray-dried mannitol, and the lubricant is sodium stearyl fumarate.

34. The pharmaceutical composition according to any one of claims 1 to 33 for use in medicine.

35. The pharmaceutical composition according to any one of claims 1 to 33 for use in a method for treating an inflammatory condition of the gastrointestinal tract, wherein the pharmaceutical composition is for administering to an individual in need thereof.

36. The pharmaceutical composition for the use of claim 35, wherein said condition of the gastrointestinal tract comprises inflammation of the esophagus.

37. The pharmaceutical composition for the use of claim 36, wherein said condition is eosinophilic esophagitis.

38. The pharmaceutical composition for the use of claim 37, wherein said condition comprises inflammation of the glottis, epiglottis, tonsils, or oropharynx.

39. The pharmaceutical composition for the use of claim 35, wherein said condition is viral or bacterial pharyngitis, gastroesophageal reflux disease (GERD), nonerosive reflux disease (NERD) or erosive esophagitis.

40. Use of: a. a topically acting corticosteroid or pharmaceutically acceptable salt, ester or polymorph adsorbed on to silicified microcrystalline cellulose, wherein the topically acting corticosteroid or pharmaceutically acceptable salt, ester of polymorph is present in an amount of 5% or less by weight in the composition;and

b. rapidly dispersing microgranules; in the preparation of a pharmaceutical composition in the form of an orally disintegrating tablet for oral administration for treating an inflammatory condition of the gastrointestinal tract.

41. Use according to claim 40, wherein the orally disintegrating tablet disintegrates within 30 seconds when tested using the USP <701> method for disintegration time.

42. Use according to claim 40, wherein the orally disintegrating tablet disintegrates within 60 seconds in contact with saliva in the oral cavity of a patient in need thereof.

43. Use according to any one of claims 40 to 42, wherein the rapidly dispersing microgranules comprise a sugar alcohol, or a saccharide, or a mixture thereof and at least one disintegrant.

44. Use according to claim 43, wherein the sugar alcohol or saccharide and the disintegrant are present in a ratio of sugar alcohol or saccharide to disintegrant from 90:1 0 to 99:1.

45. Use according to any one of claims 40 to 44, wherein said corticosteroid is selected from the group consisting of budesonide, fluticasone, flunisolide, ciclesonide, mometasone, beclomethasone, and salts, solvates, esters, and mixtures thereof.

46. Use according to claim 45, wherein said corticosteroid is fluticasone.

47. Use according to claim 46, wherein said corticosteroid is fluticasone propionate.

48. Use according to any one of claims 40 to 47, wherein the topically acting corticosteroid is in an amount of about 3% or less by weight in the composition.

49. Use according to any one of claims 40 to 47, wherein the topically acting corticosteroid is in an amount of about 1.5% or less by weight in the composition.

50. Use according to any one of claims 40 to 47, wherein the topically acting corticosteroid is in an amount of about 1% or less by weight in the composition.

51. Use according to any one of claims 40 to 47, wherein the topically acting corticosteroid is in an amount of about 0.5% or less by weight in the composition.

52. Use according to any one of claims 40 to 47, wherein the topically acting corticosteroid is in an amount of about 4.5 mg in the composition.

53. Use according to any one of claims 40 to 45, wherein the topically acting corticosteroid is in an amount of about 3 mg in the composition.

54. Use according to any one of claims 40 to 45, wherein the topically acting corticosteroid is in an amount of about 1.5 mg in the composition.

55. Use according to any one of claims 40 to 47, wherein the topically acting corticosteroid is in an amount of about 6 mg in the composition.

56. Use according to any one of claims 40 to 45, wherein the topically acting corticosteroid is fluticasone propionate in the range of 0.05 to about 15 mg in the composition at a drug content of from about 0.16% to 5% by weight of the composition.

57. Use according to any one of claims 40 to 45, wherein the topically acting corticosteroid is fluticasone propionate in the range of 0.75 to about 4.5 mg in the composition at a drug content of from about 0.25% to 1.5% by weight in the composition.

58. Use according to any one of claims 40 to 45, wherein the topically acting corticosteroid is fluticasone propionate in the range of 0.05 to about 18 mg in the composition at a drug content of from about 0.125% to 5% by weight in the composition.

59. Use according to any one of claims 40 to 58, wherein the corticosteroid is micronized with a particle size of not more than 50 microns.

60. Use according to claim 59, wherein the corticosteroid has a mean particle size of not more than 10 microns.

61. Use according to any one of claims 40 to 60, wherein the composition further comprises an adhesive agent.

62. Use according to claim 61, wherein the adhesive agent is selected from the group consisting of sucrose aluminum sulfate complex, chitosan and derivatives thereof, polyvinylpyrrolidone, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl ethylcellulose, sodium carboxymethylcellulose, cross-linked polyacrylic acid, cross-linked polyacrylates, aminoalkyl methacrylate copolymers, carbopol polymers, hydrophilic polysaccharide gums, maltodextrins, pectins, xanthan gums, alginic acid, modified alginic acids, and combinations thereof.

63. Use according to any one of claim 43 or 44; or claim 45 to 62 when dependent on claim 43 or 44 wherein the disintegrant is selected from the group consisting of crospovidone, sodium starch glycolate, crosslinked carboxymethyl cellulose, and low substituted hydroxylpropylcellulose.

64. Use according to any one of claim 43 or 44; or claim 45 to 62 when dependent on claim 43 or 44; or claim 63, wherein the sugar alcohol or saccharide is selected from the group consisting of sucralose, lactose, sucrose, maltose, mannitol, sorbitol, xylitol, maltitol, and mixtures thereof.

65. Use according to any one of claims 40 to 64, wherein the pharmaceutical composition further comprising a free flowing sugar alcohol or saccharide selected from the group consisting of spray-dried mannitol, spray-dried lactose, and combinations thereof.

66. Use according to any one of claims 40 to 65, wherein the pharmaceutical composition further comprising a lubricant selected from the group consisting of magnesium stearate, stearic acid, sodium stearyl fumarate, glyceryl behenate, and a mixture thereof.

67. Use according to any one of claims 40 to 66, wherein the pharmaceutical composition further comprising at least one antifungal agent.

68. Use according to any one of claims 40 to 66, wherein the pharmaceutical composition further comprising at least one antiviral agent.

69. Use according to any one of claim 43 or 44; or claims 45 to 62 when dependent on claim 43 or 44; claim 63 or 64; or claim 65 to 68 when dependent on claim 43 or 44, wherein the rapidly dispersing microgranules further comprise an additive and wherein the ratio of sugar alcohol or saccharide to disintegrant to additive is from 88:10:2 to 98.5:1:0.5.

70. Use according to claim 69, wherein the additive is selected from the group consisting of pregelatinized starch, hydroxypropylcellulose.

71. Use according to any one of claim 43 or 44; or claims 45 to 62 when dependent on claim 43 or 44; claim 63 or 64; or claims 65 to 68 when dependent on claim 43 or 44; or claim 69 or 70, wherein the corticosteroid has an average particle size of less than about 10 μm, the rapidly dispersing microgranules have an average particle size of less than about 300 μm, and the sugar alcohol and/or saccharide has an average particle size of less than about 30 μm.

72. Use according to claim 71, wherein the corticosteroid is fluticasone propionate with a particle size of less than 5 microns, the rapidly dispersing microgranules consist of mannitol and crospovidone, the free-flowing sugar alcohol is spray-dried mannitol, and the lubricant is sodium stearyl fumarate.

73. A method of preparing the pharmaceutical composition of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, comprising the steps of:

a) preparing the rapidly dispersing microgranules;

b) preparing a preblend 1 by blending silicified microcrystalline cellulose, corticosteroid, and glidant;

c) preparing a preblend 2 by blending filler, the preblend 1 of step b, disintegrant, and sweeteners;

d) preparing the final compressible blend, by blending the rapidly dispersing granules of step a, lubricant, the preblend 2 of step c, filler;

e) preparing the tablet by compressing the blend of step d.

74. The method of claim 73 comprising the steps of:

a) preparing the rapidly dispersing microgranules;

b) preparing preblend 1 by blending silicified microcrystalline cellulose, micronized fluticasone propionate and colloidal silicon dioxide;

c) preparing preblend 2 by blending mannitol, the preblend 1 of step b, crospovidone, and sucralose powder;

d) preparing the final compressible blend, by blending the rapidly dispersing granules of step a, sodium stearyl fumarate, the preblend 2 of step c, sugar alcohol, or rinsed mannitol;

e) preparing the tablet by compressing the blend of step d.

75. The method of claim 73 comprising the steps of:

a) preparing the rapidly dispersing microgranules;

b) preparing preblend 1 comprising charging a blender with one quarter of the silicified microcrystalline cellulose, corticosteroid, glidant, and another quarter of the silicified microcrystalline cellulose and blending the contents;

c) preparing preblend 2 comprising charging a high shear granulator with a free flowing filler, preblend 1, remaining half of the silicified microcrystalline cellulose, disintegrant, and sweetener and blending the contents;

d) preparing the final compressible blend comprising charging a blender with one half of the rapidly dispersing granules of step a, lubricant, the preblend 2 of step c, and remaining half of the rapidly dispersing granules of step a and blending;

e) preparing the orally disintegrating tablets by compressing the compressible blend of step d.

76. The method of claim 75 comprising the step of:

a) preparing the rapidly dispersing microgranules;

b) preparing preblend 1 comprising charging a blender with one quarter of silicified microcrystalline cellulose (SMCC), micronized fluticasone propionate, colloidal silicon dioxide and another quarter of (SMCC) and blending;

c) preparing preblend 2 comprising charging a high shear granulator with spray-dried mannitol, preblend 1, remaining half of SMCC, crospovidone, and sucralose powder and blending;

d) preparing the final compressible blend comprising charging a V-blender with one half of the rapidly dispersing granules of step a, sodium stearyl fumarate, the preblend 2 of step c, and remaining half of rapidly dispersing granules of step a and blending;

e) preparing the orally disintegrating tablets by compressing the compressible blend of step d.

77. The method of claim 73 comprising the steps of:

a) preparing the rapidly dispersing microgranules or granulate with an average particle size of not more than about 400 μm by 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 in the presence of water or an alcohol-water mixture and then drying the granulate;

b) preparing a milled preblend 1 by blending silicified microcrystalline cellulose, corticosteroid and glidant in a blender and then milling through a comminuting mill equipped with an screen with a 30 Mesh opening;

c) preparing the milled preblend 2 by blending half of free flowing mannitol, preblend 1 from step b, disintegrant, and sweetener in a blender and then milling through a comminuting mill equipped with a screen with a 30 Mesh opening, and rinsing the mill with remaining half of free flowing mannitol;

d) preparing the compressible blend by blending the rapidly dispersing granules of step a, lubricant, the milled preblend 2 of step c, rinsed with free flowing mannitol;

e) preparing the orally disintegrating tablets by compressing the compressible blend of step d.

78. The method of claim 77 comprising the steps of:

a) preparing the rapidly dispersing microgranules or granulate with an average particle size of not more than about 400 μm by granulating one or more sugar alcohols and/or

saccharides, each having an average particle diameter of not more than about 30 μm, with crospovidone in presence of water or an alcohol-water mixture and then drying the granulate;

b) preparing a milled preblend 1 by blending silicified microcrystalline cellulose, micronized fluticasone proprionate and colloidal silicon dioxide in a blender and then milling through a comminuting mill equipped with an screen with a 30 Mesh opening;

c) preparing the milled preblend 2 by blending half of free flowing mannitol, preblend 1 from step b, crospovidone, and sucralose powder in a blender and then milling through a comminuting mill equipped with a screen with a 30 Mesh opening, and rinsing the mill with remaining half of free flowing mannitol;

d) preparing the compressible blend by blending the rapidly dispersing granules of step a, sodium stearyl fumarate, the milled preblend 2 of step c, rinsed with free flowing mannitol;

e) preparing the orally disintegrating tablets by compressing the compressible blend of step d.