COMPOSITIONS FOR THE TREATMENT OF INFLAMMATION OF THE GASTROINTESTINAL TRACT

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ABSTRACT (57)
Provided herein are methods for preventing or alleviating the symptoms of and inflammation associated with inflammatory diseases and conditions of the gastrointestinal tract, for example, those involving the esophagus. Also provided herein are pharmaceutical compositions useful for the methods of the present invention.
Total Oesophageal Retention

M0
M2
M1
M3

% Retention

Time [minutes]

FIGURE 1
COMPOSITIONS FOR THE TREATMENT OF INFLAMMATION OF THE GASTROINTESTINAL TRACT

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 60/987,720, filed Nov. 13, 2007; U.S. Provisional Application No. 61/012,012, filed December 06, 2007; U.S. Provisional Application No. 61/015,998, filed December 21, 2007; U.S. Provisional Application No. 61/019,818, filed Jan. 8, 2008; U.S. Provisional Application No. 61/034,941, filed Mar. 7, 2008; U.S. Provisional Application No. 61/035,348, filed Mar. 10, 2008; U.S. Provisional Application No. 61/054,103, filed May 16, 2008; U.S. Provisional Application No. 61/054,104, filed May 16, 2008; U.S. Provisional Application No. 61/054,105, filed May 16, 2008; U.S. Provisional Application No. 61/054,106, filed May 16, 2008; U.S. Provisional Application No. 61/054,107, filed May 16, 2008; and U.S. Provisional Application No. 61/090,658, filed Aug. 20, 2008, which applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Esophageal inflammation disorders are gaining increased recognition in both adults and children. One example is eosinophilic esophagitis (EE), which is an emerging, and fast-growing disorder characterized by high levels of eosinophils in the esophagus, as well as basal zone hyperplasia. EE is thought to be provoked, in at least a subset of patients, by food allergies or airborne allergen exposure (1-5, 144). EE diagnosis is often associated with other hypersensitivity disorders, including asthma, rhinitis, and other food and aeroallergen inhalant sensitivities (39-40). Diagnosis is often made, e.g., in young children and depends on the finding of 15 to 20 or more to 24 or more eosinophils per high power field (eos/hpf) within esophageal mucosal biopsies (6-12).

[0003] In parallel with other atopic disorders, the incidence of EE appears to be increasing (15, 35). The disorder may present with reflux-like symptoms, pain and dysphagia, clinical symptoms similar to the presentation of gastroesophageal reflux disease (“GERD”) (42). Symptoms of EE include, for example, abdominal pain, chest pain, choking, difficulty swallowing, failure to thrive, nausea, reflux not relieved by standard anti-flux therapy, skin rash or hives, vomiting, and weight loss. In one series, 15% of EE patients had concurrent developmental delay (45).

[0004] Although EE is becoming more frequently diagnosed throughout developing countries (7, 8, 13-16) many aspects of the disease remain unclear including its etiology, natural history and optimal therapy. Symptoms of EE often mimic those of GERD and include vomiting, dysphagia, pain and food impaction (8, 14, 17-20). However, treatment of EE and GERD differ and it is important to distinguish between them, particularly as untreated EE may be associated with esophageal narrowing in 10-30% of cases (14, 18, 20, 21). The overlap of GERD and EE symptoms is common; failure to respond to high PPI GERD treatment may be one diagnostic guideline for EE (42). The common occurrence regarding misdiagnosis of EE for GERD often results in delayed treatment for patients with EE (42).

[0005] Long term systemic steroid therapy can result in significant secondary side effects on growth and bone development. Although treatment with anti-IL-5 monoclonal antibody has been reported to be successful in EE, this therapy is currently not approved for use in children (36).

[0006] Current treatments include elimination diets (22, 23), and elemental formulas (2, 24). Identifying true inciting food allergens can be difficult and elemental formulas are often unpalatable, thereby making dietary interventions complicated (1, 22). Improvised puff and swallow techniques may be difficult for patients, especially smaller children, and especially children with developmental delays, to perform efficiently. This may result in a lesser than effective dose of a topical steroid being delivered to the esophagus.

SUMMARY OF THE INVENTION

[0007] Certain embodiments of the present invention provide a method of treating, preventing or alleviating inflammation of the gastrointestinal tract comprising orally administering to an individual in need thereof a composition comprising a corticosteroid, a preservative, a choking agent, an isotonic agent, a surfactant, and an excipient that increases the interaction of the composition with a mucosal layer. In some embodiments, the corticosteroid is, by way of non-limiting example, budesonide. In specific embodiments, the corticosteroid is present in the composition in an amount of about 0.01 mg to about 1.0 mg of corticosteroid per gram of composition. In some embodiments, the corticosteroid is present in the composition in an amount of about 0.01 mg to about 1.0 mg of corticosteroid per mL of composition.

[0008] In certain embodiments, the present invention provides for methods of administering about 5 mL to about 50 mL of the corticosteroid containing composition to the individual.

[0009] In some embodiments, the preservative is, by way of non-limiting example, potassium sorbate. In specific embodiments, the preservative is present in the composition in an amount of about 0.0002% to about 0.5% w/w of the composition. In some embodiments, the choking agent is, by way of non-limiting example, disodium edetate. In specific embodiments, the choking agent is present in the composition in an amount of about 0.0005% to about 0.1% w/w of the composition. In certain embodiments, the isotonic agent is, by way of non-limiting example, polysorbate 80. In specific embodiments, the surfactant is present in the composition in an amount of about 0.0005% to about 2% w/w of the composition. In certain embodiments, the excipient that increases the interaction of the composition with a mucosal layer is a viscosity modifier and/or modifier. In specific embodiments, the viscosity modifier and/or modifier is selected from, by way of non-limiting example, microcrystalline cellulose, carboxymethyl cellulose sodium and a combination thereof. In more specific embodiments, the viscosity modifier and/or modifier is a combination of microcrystalline cellulose and carboxymethyl cellulose sodium. In some embodiments, the viscosity modifier and/or modifier is present in the composition in about 0.01% to about 3.0% w/w of the composition. In certain embodiments, the viscosity modifier and/or modifier is Avicel® RC-591.

[0010] In some embodiments, the composition has a first and a second excipient. In specific embodiments, the second excipient is selected from an excipient that increases the interaction of the composition with a mucosal layer, a binder, a filler, a disintegrant, a diluent, a carrier, a vehicle and combinations thereof. In other embodiments, the second excipient that increases the interaction of the composition with a
mucosal layer is a second viscosity modulator and/or modifier. In some embodiments, the second excipient is a vehicle (including a diluent) and is present in the composition in an amount of about 50% to about 99.5% w/w of the composition. In specific embodiments, the vehicle is selected from, by way of non-limiting example, a liquid vehicle, a solid vehicle and combinations thereof. In some embodiments, the vehicle is a solid vehicle and is selected from, by way of non-limiting example, tule, bentonite, kaolin calcium carbonate, and combinations thereof. In certain embodiments, the vehicle is a liquid vehicle and is selected from, by way of non-limiting example, water, ethanol, an organic solvent, an oil (e.g., corn oil) and combinations thereof. In specific embodiments, the corticosteroid containing composition is formulated as a micronized suspension of the corticosteroid in an aqueous vehicle.

In some embodiments, the corticosteroid containing composition has a target pH of about 4.5. In certain embodiments, the target pH of the composition is attained by adding a pH adjusting agent to the composition. In specific embodiments, the pH adjusting agent is, by way of non-limiting example, hydrochloric acid or sodium hydroxide.

In certain embodiments, the corticosteroid containing composition also contains, by way of non-limiting example, a sweetener, a flavoring agent or a combination thereof.

In specific embodiments of the present invention, the corticosteroid containing composition contains budesonide as the corticosteroid, potassium sorbate as the preservative, disodium edetate as the chelating agent, dextrose as the isotonic agent, polysorbate 80 as the surfactant, a combination of microcrystalline cellulose and carboxymethyl cellulose sodium as the excipient that increases the interaction of the composition with a mucosal layer, and hydrochloric acid as the pH adjusting agent. In more specific embodiments, the corticosteroid containing composition contains about 0.01 mg to about 1.0 mg of budesonide per ml. of composition, about 0.0002% to about 0.5% w/w of potassium sorbate, about 0.0005% to about 0.1% w/w of disodium edetate, about 0.002% to about 2% w/w of polysorbate 80, and about 0.01% to about 3.0% w/w of a combination of microcrystalline cellulose and carboxymethyl cellulose sodium. In still more specific embodiments, the composition is further comprises an aqueous vehicle. In some embodiments, the corticosteroid containing composition is formulated as a micronized suspension of the budesonide in the aqueous vehicle. In yet more specific embodiments, the composition has a pH of about 4.5. In some embodiments, the composition comprises a second excipient that increases the interaction of the composition with a mucosal layer.

In certain embodiments, a pharmaceutical composition described comprises or a method described herein comprises administering (e.g., per day or per dose) to an individual about 0.1 mg to about 20 mg corticosteroid, about 1 to about 2 mg corticosteroid, about 2 to about 3 mg corticosteroid, or about 0.25- to about 2.5 mg, or about 0.25 to about 3 mg of corticosteroid. In certain embodiments, the methods described herein of treating, preventing or alleviating inflammation of the gastrointestinal tract include treating, preventing or alleviating inflammation of the esophagus. In certain embodiments, the individual has been diagnosed with (or has inflammation associated with), by way of non-limiting example, esophagitis, inflammatory bowel disease involving the esophagus, Crohn’s disease, esophageal inflammation secondary to caustic/irritant ingestion, persistent/recurrent esophageal strictures of any cause and including caustic/irritant ingestion, pill-induced esophagitis, systemic diseases, congenital diseases or post-surgery inflammation. In specific embodiments, the individual has been diagnosed with (or has inflammation associated with), by way of non-limiting example, eosinophilic esophagitis. In some embodiments, the individual has been diagnosed with (or has inflammation associated with), by way of non-limiting example, gastroesophageal reflux disease (GERD), nonerosive reflux disease (NERD), or erosive esophagitis. It is to be understood that disclosure of treating an individual diagnosed with or inflammation associated with a certain inflammatory disorder includes a method of treating, preventing or alleviating inflammation associated with the certain inflammatory disorder.

In certain embodiments, the individual treated with the methods disclosed herein is a child or infant. In some embodiments, the child less than 19 years old, less than 16 years old, 12 years old, 8 years old, 6 years old, 4 years old, or 2 years old. In other embodiments, the individual is an adult.

INCORPORATION BY REFERENCE

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

FIG. 1 illustrates the percent amount of composition present in the esophagus as a function of time following oral administration (by measuring the amount of radiolabel present in the esophagus).

DETAILED DESCRIPTION OF THE INVENTION

In certain embodiments, the present invention is directed to methods and pharmaceutical compositions for treating, preventing or alleviating the symptoms of and inflammation associated with inflammatory diseases involving the gastrointestinal tract, including the upper gastrointestinal tract (e.g., inflammatory diseases involving pre-colonic gastrointestinal inflammation), esophagus, stomach and/or digestive tract. Provided herein are methods of treating, preventing or alleviating, for example, esophageal inflammation in an individual. In certain embodiments, these methods comprise orally administering to said individual a corticosteroid in association with at least one excipient that increases the interaction of the composition with a surface of the gastrointestinal tract (e.g., the mucosa and/or epithelium of the gastrointestinal tract or a surface of said gastrointestinal tract, such as the esophagus). In some embodiments, the viscosity modulator and/or modifier provides an increased viscosity and the increased viscosity of the composition allows the composition to be in contact with the esophagus for an extended period of time following administration.
An individual suitable for treatment with the compositions disclosed herein may, for example, have been diagnosed with a disease or condition including, but not limited to, eosinophilic esophagitis, inflammatory bowel diseases involving the esophagus, Crohn’s disease, esophageal inflammation secondary to caustic/irritant ingestion, persistent/recurrent esophageal stricture of any cause and including caustic/irritant ingestion, pill-induced esophagitis, celiac disease, intermediate esophagitis, epithelial hyperplasia, basal cell hyperplasia, elongated papillae, dilated vessels in papillae, fungal esophagitis, viral esophagitis, bacterial esophagitis, corrosive esophagitis, radiation esophagitis, chemotherapy esophagitis, graft vs host disease, a skin disease with esophageal involvement, bullous pemphigoid, pemphigus vulgaris, epidermolysis bullosa, Stevens-Johnson syndrome, Behçet’s disease, sarcoidosis, idiopathic esophagitis, eosinophilic gastritis, Ménetrier’s disease, parasitic gastritis, lymphocytic esophagitis, inflammatory bowel disease-associated esophagitis, parasitic gastritis, lymphocytic esophagitis, inflammatory bowel disease-associated esophagitis, eosinophilic duodenitis, functional dyspepsia, systemic diseases, congenital diseases or post-surgery inflammation. The composition may also be used in treating other gastrointestinal disorders, including stomach and duodenal ulcers, hyperactive acidic discharge disorders, such as Zollinger-Ellison syndrome and laryngeal disorders.

Provided herein are methods for treating, preventing and alleviating any chronic inflammatory or malignant state that involves the gastrointestinal tract, such as the esophagus, and responds to steroid therapy. The methods of the present invention are useful, for example, for treating, preventing and alleviating inflammation and/or symptoms associated with eosinophilic esophagitis, inflammatory bowel diseases involving the esophagus, Crohn’s disease, esophageal inflammation secondary to caustic/irritant ingestion, persistent/recurrent esophageal strictures of any cause and including caustic/irritant ingestion, pill-induced esophagitis, systemic diseases, congenital diseases, Epidermolysis bullosa, and post-surgery inflammation. The present methods are also useful for treating, preventing or alleviating symptoms and/or inflammation associated with other diseases or conditions of the gastrointestinal tract, for example, the upper gastrointestinal tract, where it is beneficial to target a particular target site, rather than provide systemic therapy. Also provided herein are pharmaceutical compositions useful in the methods of the present application. As used herein, inflammation and/or symptoms associated with a disorder or disease disclosed herein includes inflammation and/or symptoms associated with, caused by and/or resulting from the disorder or disease.

As used herein, unless otherwise stated, the use of the terms “a”, “an” and “the” include both singular and multiple embodiments. As used herein, the term “individual” includes any animal. In some embodiments, the animal is a mammal. In certain embodiments, the mammal is a human. In specific embodiments, the human is an adult. In other embodiments, the human is a child. In yet other embodiments, the human is an infant. As used herein, the phrase “method of treating” or “method for treating” encompasses methods of preventing, reducing the incidences of, providing prophylactic treatment, treating and alleviating. As used herein, the phrase “an effective amount” and “a therapeutically effective amount” is an amount sufficient to elicit a change in the symptoms of or inflammation associated with gastrointestinal diseases, including but not limited to esophageal inflammation. As used herein, the term “or” includes “and” and “or.”

Methods and Compositions

In certain embodiments, the corticosteroids used in the present invention include topical steroids including, for example, budesonide. In some embodiments, corticosteroids are selected from, by way of non-limiting example, beclometasone, ciclesonide, clobetasol, fluticasone, mometasone, necobetasol, prednisolone, scopolamine, fluticasone propionate, halobetasol, hydrocortisone, hydrocortisone butyrate, hydrocortisone valerate, mometasone furoate, mometasone, prednisolone, budesonide, or fluticasone. In a specific embodiment, the corticosteroid is budesonide.

Provided herein are methods and pharmaceutical compositions for treating, preventing or alleviating the symptoms of, and inflammation associated with, inflammatory diseases of the gastrointestinal tract, including but not limited to the esophagus.

In certain embodiments, a corticosteroid (e.g., budesonide) that is administered in oral form, in a formulation with increased fluid viscosity, is delivered to the esophagus in an effective dose to reduce the inflammation of the esophagus.

In one aspect, an exemplary corticosteroid is budesonide. Budesonide, 16,17-(butylenediabse(oxyl))-11,21-dihydroxy-, (11β,16α)-pregna-1,4-diene-3,20-dione, is a corticosteroid sometimes used in inhaled form to treat pulmonary conditions.

In certain embodiments, the pharmaceutical composition described herein includes one or more excipients. Excipients useful herein include, by way of non-limiting example, binders, fillers, lubricants, isotonic agents, surfactants, antioxidants (e.g., chelating agents), preservatives, buffers, pH adjusting agents, solvents, flavoring agents, coloring agents, sweeteners, excipients that increase the interaction of the composition with a surface of the gastrointestinal tract (e.g., the mucosa and/or epithelium of the gastrointestinal tract or of a specific site of the gastrointestinal tract, such as the esophagus) and combinations thereof. Excipients that increase the interaction of the composition with the surface of the gastrointestinal tract (e.g., the mucosa and/or epithelium of the gastrointestinal tract or of a specific site of the gastrointestinal tract, such as the esophagus) include excipients that modulate and/or modify (e.g., enhance) the viscosity of the composition, excipients that impart a mucoadhesive characteristic to the composition, and excipients that enhance the absorption of the composition through a surface of the gastrointestinal tract (e.g., the mucosa and/or epithelium of the gastrointestinal tract or of a specific site of the gastrointestinal tract).
tract, such as the esophagus). In some embodiments wherein the composition is a suspension, surfactants are utilized in order to obtain an efficient dispersion of corticosteroid (e.g., budesonide) particles in the suspension.

**0030** Sweeteners include, by way of non-limiting example, sucrose, lactose, glucose, fructose, arabinose, xylose, ribose, mannose, galactose, dextrose, sorbose, sorbitol, mannitol, maltose, cellobiose, xylitol and the like. Flavoring agent include, by way of non-limiting example, peppermint, wintergreen, grape and cherry.

**0031** In some embodiments, surfactants include, by way of non-limiting example, polysorbates (e.g., polysorbate 80), Tween® 80, poloxamers, polyoxymethylene alkyl ethers, polyoxymethylene castor oil derivatives and combinations thereof. In a specific embodiment, the surfactant is polysorbate 80.

**0032** In certain embodiments, an isotonic agent includes, by way of non-limiting example, dextrose, glycerin, mannitol, sodium chloride, potassium chloride and combinations thereof. In specific embodiments, the isotonic agent is dextrose (e.g., dextrose anhydrous).

**0033** In some embodiments, antioxidants or chelating agents include, by way of non-limiting example, edetate (e.g., disodium edetate) (EDTA). As used herein, "edetate" includes all compounds of Formula I wherein each R is independently selected from an H and a negative charge (e.g., as a salt or as a disassociated salt or acid). In certain embodiments, edetate is selected from, by way of non-limiting example, disodium edetate, calcium edetate, ethylenediaminetetraacetic acid and the like.

![Formula I](image)

**0034** Preservatives include, by way of non-limiting example, benzalkonium chloride, methylparaben, propylparaben, potassium sorbate and sodium benzoate. In specific embodiments, the preservative is potassium sorbate.

**0035** In some embodiments, the compositions comprise an excipient that increases the interaction of the composition with a surface of the gastrointestinal tract (e.g., the mucosa and/or epithelium of the gastrointestinal tract or of a specific site of the gastrointestinal tract, such as the esophagus). In certain embodiments, the excipient or excipients chosen increase the interaction of the composition with the surface of the gastrointestinal tract (e.g., the mucosa and/or epithelium of the gastrointestinal tract or of a specific site of the gastrointestinal tract, such as the esophagus) by at least 1.02 fold, by at least 1.05 fold, by at least 1.1 fold, by at least 1.2 fold, by at least 1.25 fold, by at least 1.5 fold, by at least 2 fold, by at least 3 fold, by at least 4 fold, by at least 5 fold, by at least 10 fold, or by at least 20 fold. In certain embodiments, the increased interaction of the composition is an at least 1.02 fold, by at least 1.05 fold, by at least 1.1 fold, by at least 1.2 fold, by at least 1.25 fold, by at least 1.5 fold, by at least 2 fold, by at least 3 fold, by at least 4 fold or by at least 5 fold of interaction of the composition with the esophagus that occurs following passing of the bolus of the composition being swallowed. In certain embodiments, these increases are measured and compared to the measure of an otherwise similar composition lacking the excipient or excipients that increase the interaction of the composition with the surface of the gastrointestinal tract. In certain instances, increased interaction of the composition is measured as a function of the amount of composition present in the esophagus (e.g., after the bolus has passed through the esophagus). In specific instances, the amount of composition present in the esophagus is measured in any suitable manner, e.g., by radiolabeling the composition and measuring the amount of the composition in the esophagus utilizing gamma scintigraphy. An increase in the interaction of the composition with the surface of the gastrointestinal tract (e.g., the mucosa and/or epithelium of the gastrointestinal tract or of a specific site of the gastrointestinal tract, such as the esophagus) may be measured by measuring the retention time of the material along a length of a surface of the gastrointestinal tract (e.g., the mucosa and/or epithelium of the gastrointestinal tract or of a specific site of the gastrointestinal tract, such as the esophagus), wherein the retention time is increased in the presence of the excipient as compared to its absence. In some embodiments, a portion composition is retained on the esophagus after oral administration (e.g., after initial swallowing) for at least 5 seconds, for at least 6 seconds at least 10 seconds, for at least 12 seconds, for at least 15 seconds, for at least 30 seconds, for at least 60 seconds, for at least 2 minutes, for at least 4 minutes, for at least 10 minutes, for at least 15 minutes, for at least 30 minutes, or the like. In certain embodiments, the portion of the composition that is retained on or within the esophagus is at least 1%, at least 2%, at least 3%, at least 4%, at least 5%, at least 6%, at least 7%, at least 8%, at least 9%, at least 10%, at least 15%, at least 20%, at least 30%, at least 40%, at least 50%, or the like. In certain embodiments, the composition is retained on the esophagus after oral administration for about 15 seconds to about 120 seconds, or for about 30 to about 90 seconds. In another embodiment, an increased interaction may be measured by the decrease in physiological manifestations or symptoms of the disease or ailment to be treated, including a decrease in total eosinophil counts in a particular gastrointestinal tissue sample.

**0036** In specific embodiments, following oral administration of a composition described herein to the esophagus (e.g., following initial swallowing or drinking of the composition), at least 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 95% by weight of the corticosteroid or composition administered is present within the esophagus (e.g., as measured by gamma scintigraphy) after at least 5 seconds, 10 seconds, 15 seconds, 20 seconds, 25 seconds, 30 seconds, 40 seconds, 45 seconds, 50 seconds, or 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55 or 60 minutes following application of the composition to the esophagus. In certain instances, even small differences (e.g., increases) in adherence times (e.g., residence times) between formulations can result in therapeutically significant or clinically significant results or improvements.

**0037** In one aspect of the invention, the use of the excipients may act to decrease the quantity of active agents needed to elicit a response in the absence of the excipients. In some embodiments, the excipients may decrease the amount of corticosteroid used, for example, from about 1 to about 3 mg of budesonide in the absence of excipient to about 500 μg to
about 2 mg of budesonide in the presence thereof. Accordingly, the compositions provided herein may provide an additional advantage of decreasing the amount of active agent needed to treat subjects afflicted with inflammatory diseases involving the gastrointestinal tract, including the esophagus, stomach and/or digestive tract.

[0038] In certain embodiments, the corticosteroid is administered in combination with an excipient that enhances the viscosity of the composition. It is to be understood that in various embodiments of the present invention, the viscosity of the oral dosage form is at a level that is sufficient to deliver an effective amount of the composition to the site of gastrointestinal inflammation, e.g., the esophagus. In some embodiments, the effective amount of the composition delivered to the esophagus is at an amount sufficient to coat the esophagus, and thereafter deliver the composition to the affected areas, including by way of example only, the lower esophagus, the esophageal-stomach juncture, the stomach and/or the duodenum. In certain embodiments, the viscosity of the oral dosage form is such that when administered orally, it is not so thick as to cause difficulty in swallowing, cause gagging, or be unpalatable. Those of ordinary skill in the art can determine the viscosity of the compositions provided herein, and may thus determine appropriate ranges. In certain embodiments, the viscosity of the oral dosage form is a viscosity that is sufficient to provide exposure of the corticosteroid to the esophagus for a sufficient period of time such that the symptoms of and/or inflammation associated with inflammatory diseases involving the gastrointestinal tract, including the esophagus, are reduced following administration of the corticosteroid containing oral dosage form.

[0039] One method for determining sufficient viscosity, may include monitoring changes in the interaction of the composition with a surface of the gastrointestinal tract (e.g., the mucosa and/or epithelium of the gastrointestinal tract or of a specific site of the gastrointestinal tract, such as the esophagus), including but not limited to measuring changes in residence or retention time of the composition in the absence and presence of the excipient. Another method for determining whether the composition is sufficiently viscous is by determining whether the inflammation of the esophagus is reduced after treatment with the composition.

[0040] Viscosity may be, for example, measured at room temperature, at about 20-25 degrees Celsius, or at about 37 degrees Celsius to mimic body temperature. The viscosity of a liquid generally decreases as the temperature is raised. In various embodiments of the present invention, the viscosity of the composition described herein is any viscosity suitable for delivery of the corticosteroid to the inflamed portion of the gastrointestinal tract. In some embodiments, the viscosity of the composition is at least about 2 centipoise (cP), at least about 25 cP, or at least about 50 cP. In some embodiments, the viscosity of the composition is at least about 100 cP. In one aspect the viscosity of the composition is from about 25 centipoise (cP) to about 800 cP, measured with a Brookfield viscometer at 25 degrees Celsius, more preferably at about 50 cP to about 800, or about 300 cP to about 800 cP. In another aspect, the viscosity of the composition may range from about 250 cP to about 600 cP or about 400 cP to about 600 cP. In specific embodiments, the viscosity of the formulation is about 100 cP, measured with a Brookfield viscometer at 25 degrees Celsius (e.g., equipped with an ultra low adapter).

[0041] Viscosity can also be determined by any method that will measure the resistance to shear offered by the substance or preparation. Many viscometers are available to those in the pharmaceutical field, and include those built by, for example, Brookfield.

[0042] In some embodiments, the viscosity of the composition is measured at room temperature (about 25 degrees C.) with a shear rate of about 13.2 sec^-1. In certain embodiments, provided herein is a composition having a viscosity under such conditions that is at least about 2 centipoise (cP); at least about 25 cP; at least about 30 cP; at least about 35 cP; at least about 40 cP; at least about 45 cP; at least about 50 cP; at least about 200 cP; at least about 225 cP; at least about 250 cP; at least about 300 cP; or at least about 400 cP. In some embodiments, the viscosity of the composition under such conditions is about 50 cP to about 250,000 cP; about 50 cP to about 70,000 cP; about 50 cP to about 25,000 cP; about 50 cP to about 10,000 cP; about 50 cP to about 3,000 cP; about 50 cP to about 2,000 cP; about 250 cP to about 250,000 cP; about 250 cP to about 70,000 cP; about 250 cP to about 25,000 cP; about 250 cP to about 10,000 cP; about 250 cP to about 3,000 cP; or about 250 cP to about 2,000 cP. In one aspect, the viscosity of the composition, as measured at 25 degrees Celsius, is from about 25 centipoise (cP) to about 800 cP, about 50 cP to about 800, or about 300 cP to about 800 cP (e.g., measured by a Brookfield viscometer). In another aspect, the viscosity of the composition under such conditions may range from about 100 cP to about 200 cP; about 200 cP to about 300 cP; about 250 cP to about 600 cP or about 400 cP to about 600 cP. In specific embodiments, the viscosity of the formulation measured under such conditions is about 30 cP, about 40 cP, about 100 cP, about 200 cP, about 300 cP, about 400 cP, about 500 cP, or about 250,000 cP.

[0043] In some embodiments, the viscosity of the composition is measured at room temperature (about 25 degrees C.) with a shear rate of about 15 sec^-1 (e.g., with a gap between the spindle and the sample chamber wall of about 6 mm or greater). In certain embodiments, provided herein is a composition having a viscosity under such conditions that is at least about 150 centipoise (cP); at least about 160 cP; at least about 170 cP; at least about 180 cP; at least about 190 cP; or at least about 200 cP. In some embodiments, the viscosity of the composition under such conditions is about 150 cP to about 250,000 cP; 160 cP to about 250,000 cP; 170 cP to about 250,000 cP; 180 cP to about 250,000 cP; or 190 cP to about 250,000 cP.

[0044] Viscosity-enhancing excipients that may be used in pharmaceutical compositions described herein include, but are not limited to, acacia (gum arabic), agar, aluminum magnesium silicate, sodium alginate, sodium steinate, bladder wrack, bentonite, carbomer, carrageenan, Carbopol, xanthan, cellulose, microcrystalline cellulose (MCC), ceratonia, chondrus, dextrose, furcellaran, gelatin, Ghatti gum, guar gum, hectorite, lactose, sucrose, maltodextrin, mannitol, sorbitol, honey, maize starch, wheat starch, rice starch, potato starch, gelatin, sterculia gum, xanthan gum, polyethylene glycol (e.g. PEG 2004500), gum tragacanth, ethyl cellulose, ethyl hydroxyethyl cellulose, ethylmethyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, poly(hydroxyethyl methacrylate), oxypolygelatin, pectin, polyethylene, povidone, propylene carbonate, methyl vinyl ether/maleic anhydride copolymer (PVM/MA), poly(methoxyethyl methacrylate), poly(methoxymethoxylethyl methacrylate), hydroxypropyl cellulose,
hydroxypropylmethyl-cellulose (HPMC), sodium carboxymethyl-cellulose (CMC), silicon dioxide, polyvinylpyrrolidone (PVP; povidone), Splenda® (dextrose, maltodextrin and sucralose) or combinations thereof. In one non-limiting example, the viscosity-enhancing excipient is Splenda®. In specific embodiments, the viscosity-enhancing excipient is a combination of MCC and CMC (e.g., Avicel® RC-591 manufactured by FMC Corporation; colloid forming attrited mixture of microcrystalline cellulose and carboxymethylcellulose sodium, NF, BP; Avicel® RC-591 product brochure, RC-591 (5/99) is hereby incorporated by reference in its entirety). In more specific embodiments, a composition described herein comprises a first viscosity enhancing agent (e.g., Avicel® 3 RC-591) and a second viscosity enhancing agent (e.g., Splenda®).

[0045] Mucoadhesive agents including, but not limited to, at least one soluble polyvinylpyrrolidone polymer (PVP); a water-swellable, but water-insoluble, fibrous, cross-linked carboxy-functional polymer; a crosslinked poly(acrylic acid) (e.g., Carbopol 947P); a carbomer homopolymer; a carbomer copolymer; a hydrophilic polysaccharide gum, maltodextrin, a cross-linked alginate gum gel, a water-dispersible polycarboxylated vinyl polymer, at least two particulate components selected from the group consisting of titanium dioxide, silicon dioxide, and clay, or a mixture thereof. The mucoadhesive agent may be used in combination with a viscosity increasing excipient, or may be used alone to increase the interaction of the composition with the esophagus. In one non-limiting example, the mucoadhesive agent is maltodextrin. Those of ordinary skill in the art will recognize that the mucoadhesive character imparted to the composition should be at a level that is sufficient to deliver an effective amount of the composition to, for example, the esophagus in an amount that may coat the esophagus, and thereafter deliver the composition to the affected areas, including by way of example only, the lower esophagus, the esophageal-stomach juncture, the stomach and/or the duodenum. Also, the mucoadhesiveness should be at a level that may be given orally, i.e. allows a patient to swallow, limits a gagging reaction, and is palatable. Those of ordinary skill in the art can determine the mucoadhesive characteristics of the compositions provided herein, and may thus determine appropriate ranges. One method for determining sufficient mucoadhesiveness may include monitoring changes in the interaction of the composition with a surface of the gastrointestinal tract (e.g., the mucosa and/or epithelium of the gastrointestinal tract or of a specific site of the gastrointestinal tract, such as the esophagus), including but not limited to measuring changes in residence or retention time of the composition in the absence and presence of the excipient. Another method for determining whether the composition is sufficiently mucohesive is by determining whether the inflammation of the esophagus is reduced after treatment with the corticosteroid. As used herein, a mucoadhesive agent is an agent that adheres to a gastrointestinal surface (e.g., either or both of a gastrointestinal epithelia or mucosa).

[0046] Mucoadhesive agents have been described, for example, in U.S. Pat. Nos. 6,638,521; 6,562,363; 6,509,028; 6,348,502; 6,319,513; 6,306,789; 5,814,330; and 4,900,552, each of which is hereby incorporated by reference in its entirety.

[0047] In one non-limiting example, the mucoadhesive agent is maltodextrin. Maltodextrin is a carbohydrate produced by the hydrolysis of starch that may be derived from corn, potato, wheat or other plant products. Maltodextrin may be used either alone or in combination with other mucoadhesive agents to impart mucoadhesive characteristics on the compositions disclosed herein. In one embodiment, a combination of maltodextrin and a carboxyl polymer are used to increase the mucoadhesive characteristics of the composition disclosed herein. In some embodiments, any composition or formulation described herein comprises greater than 7% w/w, greater than about 8% w/w, greater than about 9% w/w, greater than about 10% w/w, greater than about 11% w/w, greater than about 12% w/w, greater than about 13% w/w, greater than about 14% w/w, greater than about 15% w/w, greater than about 16% w/w, greater than about 17% w/w, greater than about 18% W/W, greater than about 19% w/w, greater than about 20% w/w, greater than about 21% w/w, greater than about 22% w/w, greater than about 23% w/w, greater than about 24% w/w, greater than about 25% w/w, greater than about 26% w/w, greater than about 27% w/w, greater than about 28% w/w, greater than about 29% w/w or greater than about 30% w/w of maltodextrin. In specific embodiments, the maltodextrin is substantially dissolved in a liquid vehicle of the composition or formulation. In certain embodiments, the maltodextrin has a dextrose equivalents (DE) of greater than 4, greater than 5, greater than 10, greater than 11, greater than 12, greater than 13, greater than 14, greater than 15, about 14 to about 10, about 4 to about 9, about 4 to about 8, about 11 to about 20, about 12 to about 19, about 13 to about 18, or about 14 to about 16. In specific embodiments, the first maltodextrin has a DE of about 4 to about 10, about 4 to about 9, or about 4 to about 8 and the second maltodextrin has a DE of about 10 to about 20, about 12 to about 19, or about 13 to about 18. In some embodiments, at least one maltodextrin utilized in a composition described herein has a molecular weight high enough to increase the solubility of a corticosteroid, or to increase the suspendability of a corticosteroid particle.

[0048] In another non-limiting example, a mucoadhesive agent can be, for example, at least two particulate components selected from titanium dioxide, silicon dioxide, and clay, wherein the composition is not further diluted with any liquid prior to administration and the level of silicon dioxide, if present, is from about 3% to about 15%, by weight of the composition. Silicon dioxide, if present, may be selected from the group consisting of fumed silicon dioxide, precipitated silicon dioxide, coagulated silicon dioxide, gel silicon dioxide, and mixtures thereof. Clay, if present may be kaolin minerals, serpentine minerals, smectites, illite or a mixture thereof. For example, clay can be laponite, bentonite, hectorite, saponite, montmorillonites or a mixture thereof.

[0049] In specific embodiments, provided herein are compositions comprising a viscosity enhancing agent and a mucoadhesive agent. In specific embodiments, the composition comprises about 0.005% (w/w) to about 3% (w/w) of a viscosity enhancing excipient (e.g., a CMC/MCC combination having a ratio as described herein), and about 1% (w/w) to about 30% (wsw) of a mucoadhesive agent (e.g., maltodextrin).

[0050] Examples of absorption enhancing include, but are not limited to, acylcarboxamides, surfactants, sodium lauryl sulfate, saponins, bile salts or bile acids including but not limited to cholic acid, chylcholic acid, deoxycholic acid, glycocholic acid, taurocholic acid, chenodeoxycholic acid, lithocholic acid, ursodeoxycholic acid, ursodiol, o xoacetic acid, lagodeoxycholic acid, glycodeloxycholic acid,
glycochenodeoxycholic acid, dehydrocholic acid, hyocholic acid, hyodeoxycholic acid, or combinations thereof, dihydrofuisorides, fatty acid derivatives, chitosan, carboxol, cellulosic agents, sterols, including but not limited to alcohols structurally related to steroids, including but not limited to cholestanol, coprostanol, cholesterol, epicholesterol, ergosterol, ergocalciferol, or combinations thereof, starch, dextran, cyclodextrin, or combinations thereof. Absorption enhancing agents may act by increasing absorption of the active agent, including corticosteroids and acid inhibitors, through a surface of the gastrointestinal tract (e.g., the mucosa and/or epithelium of the gastrointestinal tract or of a specific site of the gastrointestinal tract, such as the esophagus). Examples of absorption enhancing agents are disclosed in WO 2005/113098, which is hereby incorporated by reference in its entirety.

0051 The compositions contemplated herein may also include a combination of excipients that are viscosity enhancing agents, mucosalhesive agents and/or absorption enhancing agents. Moreover, an excipient may exhibit multiple characteristics, i.e., may be both a viscosity enhancing agent and a mucosalhesive agent. The composition may also include excipients that do not impart characteristics of viscosity enhancing, mucosalhesive agents or absorption enhancing activity.

0052 In certain embodiments, the pharmaceutical compositions provided herein is used to treat, prevent or alleviate inflammatory diseases involving the gastrointestinal tract, including the esophagus, stomach and/or digestive tract. In specific embodiments, the pharmaceutical composition is in liquid form. Liquid forms include, by way of non-limiting example, solutions, suspensions, syrups, slurries, dispersions, colloids and the like. In specific embodiments, the liquid is a suspension.

0053 The methods and compositions of the present invention are used by individuals of any age. By “individual” is meant any animal, for example, a mammal, or, for example, a human, including, for example, patients in need of treatment. In some embodiments, the individual is a human adult. In other embodiments, the individual is a human child or infant. In certain embodiments, the human child or infant is less than 16 years old, less than 12 years old, less than 8 years old, less than 6 years old, less than 4 years old or less than 2 years old.

0054 Formulations

0055 While the compositions of the present invention will typically be used in therapy for human patients, in certain embodiments, they are used in veterinary medicine to treat similar or identical diseases. In some embodiments, the compositions are used, for example, to treat mammals, including, but not limited to, primates and domesticated mammals. In some embodiments, the compositions are used, for example, to treat herbivores. The compositions of the present invention include geometric and optical isomers.

0056 Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredient or ingredients are contained in an effective amount to achieve its intended purpose. In light of the detailed disclosure provided herein, determination of the effective amounts is well within the capability of those skilled in the art. It is expected that a skilled pharmacologist may adjust the amount of drug in a pharmaceutical composition or administered to a patient based upon standard techniques well known in the art.

0057 The exact dosage will depend upon the route of administration, the form in which the composition is administered, the subject to be treated, the age, body weight/height of the subject to be treated, and the preference and experience of the attending physician. In certain embodiments, the optimal concentration of the corticosteroid in the composition depends upon the specific corticosteroid used, the characteristics of the patient, and the nature of the inflammation for which the treatment is sought. In various embodiments, these factors are determined by those of skill in the medical and pharmaceutical arts in view of the present disclosure.

0058 Generally, a therapeutically effective dose is desired. A therapeutically effective dose refers to the amount of the corticosteroid that results in a degree of amelioration of symptoms and inflammation related to the status of such symptoms prior to treatment. The dosage forms containing effective amounts are within the scope of the instant invention. In various embodiments, the amount of corticosteroid (e.g., budesonide) used in a method or in a composition disclosed herein is from about 2.5 to 400 μg/kg of body weight per day, or for example, in the range of 5 to 300 μg/kg per day, or for example in the range of 5 to 200 μg/kg per day, or for example in the range of 5 to 100 μg/kg per day, or for example in the range of 10 to 100 μg/kg per day, or for example in the range of 10-50 μg/kg per day, or for example in the range of 10-100 μg/kg/day, or for example in the range of 5-50 μg/kg/day, or in an illustrative embodiment in the range of 10-60 μg/kg/day. In some embodiments, the amount of corticosteroid (e.g., budesonide) used in a method or in a composition disclosed herein includes, by way of non-limiting example, 250 μg to 3 mg, or 500 μg to 3 mg, or 500 μg to 2 mg, or 1 mg to 3 mg. In an illustrative embodiment, the dosage is provided in a sufficient volume to allow the composition to reach the esophagus in an effective amount.

0059 In an illustrative embodiment, a dosage or amount (including a divided dose) of corticosteroid is provided in a composition of sufficient volume to allow any of the compositions disclosed herein to reach the targeted and/or inflamed portion of the gastrointestinal tract, including, e.g., the esophagus, in an effective amount. In some embodiments, the effective amount of the composition delivered to the esophagus is an amount sufficient to coat or at least partially coat the esophagus, and deliver the composition to the affected areas, including by way of example only, the lower esophagus, the esophageal-stomach juncture, the stomach and/or the duodenum. In certain embodiments, a composition described herein as a volume of, for example about 1-20 mL, or for example about 1-50 mL, or for example about 1-40 mL, or for example about 1-30 mL, or for example about 1-25 mL, or for example about 5-25 mL, or for example about 10-20 mL, or for example about 10 mL, or for example about 15 mL, or for example about 20 mL, or for example about 1-15 mL, or for example about 1-10 mL, or for example about 2-8 mL, or for example about 3-7 mL, or for example about 4-6 mL, or for example about 5 mL, or for example about 6-14 mL, or for example about 8-12 mL, or for example about 9-11 mL, or for example about 10 mL. In more specific embodiments, about 0.25 mg to about 6 mg, about 0.375 mg, about 0.5 mg, about 0.75 mg, about 1 mg, about 1.25 mg, about 1.5 mg, about 2 mg of corticosteroid (e.g., budesonide) is formulated into a single or unit dose of a pharmaceutical composition described herein, the single or unit dose having a total volume of about 1-20 mL, or for example about 10-20 mL, or for example about 10 mL, or for example about 15 mL, or for
example, about 20 mL, or for example about 1-15 mL, or for example about 1-10 mL, or for example about 2-8 mL, or for example about 3-7 mL, or for example, about 4-6 mL, or for example, about 5 mL, or for example about 6-14 mL, or for example about 8-12 mL, or for example, about 9-11 mL, or for example, about 10 mL. As discussed herein, “liquid” encompasses slurries, solutions, suspensions, dispersions or any combination thereof, depending on the solubilities and amounts of the individual components and the vehicles and solvents used. In some embodiments, an appropriate palatable dosage is in a volume sufficient to coat or at least partially coat the esophagus, and in an illustrative embodiment, the volume is sufficient to coat or at least partially coat the esophagus and deliver the corticosteroid to the affected areas, including by way of example only, the lower esophagus, the esophageal-stomach juncture, the stomach, the duodenum and/or within 3 cm of the Z-line. The composition may be delivered, for example, four times a day, three times a day, twice a day, once a day, every other day, three times a week, twice a week, or once a week. The dosage may, for example, be divided into multiple doses throughout the day, or be provided, for example, in four, three, two, or one dose a day. In certain instances, administration more frequent administration (e.g., b.i.d. versus once a day) provides for a shorter overall therapy or a quicker onset of symptom resolution. In one illustrative example, the dose is provided once a day.

In certain embodiments, a dose or composition described herein is administered with food. In some embodiments, a dose or composition described herein is administered without food. In certain embodiments, a dose or composition described herein is administered in a fed or fasted state. In some embodiments, a dose or composition described herein is administered in the morning, in the afternoon, in the evening, at night, or a combination thereof. In some embodiments, the dose is administered at night. In another aspect, the dose is administered about 30 minutes prior to bed, with no food or water given after administration of the compositions herein. In yet another embodiment of the instant invention, the dose is administered prior to bedtime, wherein after administration of the composition, the patient or individual is in a substantially supine position for at least 30 minutes, at least 1 hour, at least 2 hours, at least 4 hours or at least 8 hours.

In some embodiments, provided herein are methods of treating, preventing, or alleviating inflammation or symptoms associated with inflammation of the gastrointestinal tract, e.g., the esophagus, comprising administering to an individual in need thereof a single unit dose of a pharmaceutical composition described herein from a multidose container. In specific embodiments, administering a single unit dose from a multi-dose container comprises (1) shaking a multidose container, the multidose container comprising at least one unit dose of a pharmaceutical composition described herein; (2) pouring a single unit dose from the multidose container into an administration device (e.g., a device suitable for administering to a human individual, such as a spoon, cup or syringe); and (3) administering the single unit dose to the individual in need thereof. In more specific embodiments, shaking of the multidose container occurs until the fluid therein has a viscosity suitable for pouring (e.g., easy pouring). Some specific embodiments, the process further comprises waiting after pouring the single unit dose and prior to administering the single unit dose to the individual in need thereof. In specific embodiments, the wait time is a time sufficient to allow the viscosity of composition to achieve a desired level, e.g., a viscosity to improve the coating capabilities of the composition. In some embodiments, the wait time is, e.g., about 3 seconds, or more; about 5 seconds, or more; about 10 seconds, or more; about 15 seconds, or more; about 20 seconds, or more; about 25 seconds, or more; about 30 seconds, or more; about 40 seconds, or more; about 45 seconds, or more; about 50 seconds, or more; or about 60 seconds, or more. In other specific embodiments, the composition is administered immediately following pouring the composition into the administration device. In some embodiments, the process comprises shaking the multidose container well.

In some embodiments, provided herein is a multiple unit container comprising about 2 to about 180, about 10 to about 60, about 14, or about 50 unit doses of any pharmaceutical composition described herein. In more specific embodiments, each dose comprises about 1 mL to about 25 mL, about 1 mL to about 20 mL, about 7 mL to about 25 mL, about 10 to about 20 mL, about 15 mL to about 20 mL, about 3 to about 7 mL, about 5 mL to about 8 mL to about 12 mL, or about 10 mL. In still more specific embodiments, each dose comprises about 0.1 to about 20 mg, about 0.1 to about 10 mg, about 0.1 to about 7.5 mg, about 0.1 to about 5 mg, about 0.3 to about 4 mg, about 0.25 to about 2.5 mg, about 0.3 to about 2 mg, about 0.5 to about 1 mg, about 0.7 to about 1.5 mg, about 0.375 mg, about 0.75 mg, about 1 mg, about 1.25 mg, about 1.5 mg or about 2 mg of corticosteroid. In certain embodiments, provided herein is a multiple unit container comprising about 10 mL to about 1500 mL, about 50 mL to about 600 mL, about 150 mL, about 300 mL, about 600 mL, or about 1,200 mL of any pharmaceutical composition described herein. In specific embodiments, the multidose container comprises about 330 mL or about 55 mL of a composition described herein. In some embodiments, a kit provided herein comprises any multidose container as described herein, a pharmaceutical composition as described herein (e.g., in a volume described), and a delivery or metered device (e.g., a syringe, a cup, a spoon, or the like). In specific embodiments, the delivery or metered device is incorporated into the container (e.g., a nebulizer, an aerosolizer, a pump, or the like). In some embodiments, the delivery or metered device is separate from the container. In certain embodiments, the pharmaceutical composition contained within any of the multiple unit containers described herein is physically and chemically stable.

In some embodiments, the corticosteroid is budesonide and the composition comprises about 0.01 mg to about 1.0 mg of budesonide/g of composition. In some embodiments, the composition comprises about 0.1 mg to about 1.0 mg of budesonide/g of composition. In certain embodiments, the composition comprises about 0.3 mg to about 0.6 mg of budesonide/g of composition. In specific embodiments, the composition comprises about 0.4 mg or 0.44 mg of budesonide/g of composition. In certain specific embodiments, the composition comprises about 3.8 mg/8.6 g of composition. In some embodiments, the composition comprises about 0.01 mg to about 1.0 mg of budesonide/mL of composition (about 0.001 to about 0.1% w/w). In some embodiments, the composition comprises about 0.1 mg to about 10.0 mg of budesonide/mL of composition (about 0.01 to about 1.0% w/w). In certain embodiments, the composition comprises about 0.3 mg to about 0.8 mg of budesonide/mL of composition (about 0.03 to about 0.08% w/w). In specific embodiments, the composition comprises about 0.6 to about 0.7 mg of budesonide...
mL of composition (about 0.06 to about 0.07% w/w). In more specific embodiments, the composition comprises about 0.63 mg of budesonide/mL of composition (about 0.063% w/w).

[0064] In one embodiment, the corticosteroid-containing composition comprises budesonide, a viscosity enhancing agent, a preservative, an antioxidant (including, e.g., a chelating agent), an isotonic agent, a surfactant, an aqueous vehicle, an optional pH adjusting agent and an optional sweetener. In certain embodiments, the composition is a liquid. In specific embodiments, the liquid composition is a suspension.

[0065] In certain embodiments, a viscosity enhancing agent is present in about 0.005% to about 3.0% w/w of the composition. In certain embodiments, a viscosity enhancing agent is present in about 0.1% to about 3.0% w/w of the composition. In specific embodiments, a viscosity enhancing agent is a combination of microcrystalline cellulose and carboxymethyl cellulose (e.g., carboxymethyl cellulose sodium), such as Avicel RC-591. In more specific embodiments, the combination of MCC and CMC are present in an amount of about 0.05% to about 2.5% w/w (or about 0.5% to about 2.5% w/w) of the composition. In some embodiments, a viscosity enhancing agent is selected from, by way of non-limiting example, xanthan gum at about 0.03% to about 3% w/w (or about 0.3% to about 3% w/w), carbomer at about 0.01% to about 2% w/w (or about 0.1% to about 2% w/w), guar gum at about 0.03% to about 2% w/w (or about 0.3% to about 2% w/w), or RPMC at about 0.05% to about 3.0% w/w (or about 0.5% to about 3.0% w/w) of the composition. In some embodiments, one or more additional viscosity enhancing agents are added so as to provide a viscosity as described herein. Alternatively, the amount of the aforementioned viscosity enhancing agent present in the composition is increased so as to provide a viscosity as described herein. In some embodiments, the CMC/MCC combination (e.g., Avicel® RC-591) is present in the composition in an amount of about 1 mg/mL to about 150 mg/mL, 1 mg/mL to about 75 mg/mL, or about 5 mg/mL to about 40 mg/mL. In certain embodiments, the CMC/MCC mixed weight ratio is between about 1/99 and about 99/1, or about 20/80 and about 5/95, or about 15/85 and about 10/90. In a specific embodiment, the CMC is NaCMC and the CMC/MCC mixed weight ratio is about 11/89.

[0066] In some embodiments, surfactants include, by way of non-limiting example, polysorbates (e.g., polysorbate 80), poloxamers, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives and combinations thereof. In certain embodiments, surfactants are present in an amount of about 0.0005% to about 2% w/w (or about 0.005% to about 2% w/w) of the composition. In a specific embodiment, the surfactant is polysorbate 80. In specific embodiments, polysorbates are present in an amount of about 0.0005% to about 2% w/w (or about 0.005% to about 2% w/w) of the composition. In some embodiments, poloxamers are present in an amount of about 0.001% to about 2% w/w (or about 0.1% to about 2% w/w) of the composition, polyoxyethylene alkyl ethers are present in an amount of about 0.001% to about 1% w/w (or about 0.01% to about 1% w/w) of the composition, and/or polyoxyethylene castor oil derivatives are present in an amount of about 0.001% to about 1% w/w (or 0.01% to about 1% w/w) of the composition.

[0067] In certain embodiments, an isotonic agent includes, by way of non-limiting example, dextrose, glycerin, mannitol, sodium chloride, potassium chloride and combinations thereof. In specific embodiments, the isotonic agent is dextrose (e.g., dextrose anhydrous). In certain embodiments, the isotonic agent is included in any suitable amount, such as, by way of non-limiting example, between about 0.5 mg and about 0.5 g per gram of composition. In specific embodiments, the isotonic agent is included in an amount of about 10 mg and about 100 mg or about 40 mg to about 60 mg per gram of composition.

[0068] In some embodiments, chelating agents include, by way of non-limiting example, disodium edetate (EDTA). In certain embodiments, the chelating agent is present in an amount of about 0.0005% to about 0.1% w/w (or about 0.005% to about 0.1% w/w) of the composition.

[0069] Preservatives include, by way of non-limiting example, benzalkonium chloride, methylparaben, propylparaben, potassium sorbate and sodium benzoate. In specific embodiments, the preservative is potassium sorbate. In some embodiments, the preservative is present in an amount of about 0.0002% to about 0.5% w/w (or about 0.002% to about 0.5% w/w) of the composition. In specific embodiments, benzalkonium chloride is present in an amount of about 0.0002% to about 0.02% w/w (or about 0.002% to about 0.02% w/w) of the composition, methylparaben is present in an amount of about 0.005% to about 0.25% w/w (or about 0.05% to about 0.25% w/w) of the composition, propylparaben is present in an amount of about 0.001% to about 0.2% w/w (or about 0.01% to about 0.2% w/w) of the composition, potassium sorbate is present in an amount of about 0.005% to about 2.0% w/w (or about 0.05% to about 2.0% w/w) of the composition, and/or sodium benzoate is present in an amount of about 0.1% to about 0.5% w/w (or about 0.1% to about 0.5% w/w) of the composition.

[0070] Sweeteners include, by way of non-limiting example, sucralose, sucrose, lactose, glucose, fructose, arabinose, xyllose, ribose, mannose, galactose, dextrose, sorbitol, mannitol, maltose, cellulose, xylitol, honey and the like. In general, when utilized, the sweetener is utilized in an amount sufficient to at least partially mask the taste of the composition and/or the corticosteroid (e.g., budesonide).

[0071] In some embodiments, the corticosteroid-containing composition comprises micronized budesonide, microcrystalline cellulose, carboxymethyl cellulose sodium, dextrose anhydrous, polysorbate 80, disodium edetate, potassium sorbate, water, optionally hydrochloric acid and optionally one or more additional excipient. In specific embodiments, the composition has a pH of about 4.5. In a specific embodiment, at least one of the optional excipients is a sweetener, a flavoring agent, or a combination thereof.

[0072] In specific embodiments, the composition administered comprises a micronized suspension of budesonide in an aqueous medium. In some specific embodiments, microcrystalline cellulose and carboxymethyl cellulose sodium, dextrose anhydrous, polysorbate 80, disodium edetate, potassium sorbate, and purified water are contained in the aqueous medium. In more specific embodiments, hydrochloric acid is added to adjust the pH to a target of about 4.5. In certain embodiments, the compositions provided herein are prepared utilizing any suitable source of active agents. In some embodiments, corticosteroid (e.g., budesonide) used in the compositions described herein are neat corticosteroid (e.g., budesonide). In some embodiments, the neat corticosteroid (e.g., budesonide) is neat, bulk corticosteroid. In certain embodiments, the neat corticosteroid (e.g., budesonide) is powder corticosteroid (e.g., budesonide). In specific embodi-
ments, the neat corticosteroid (e.g., budesonide) is micronized corticosteroid (e.g., budesonide). In an exemplary embodiment, the composition comprises Rhinocort Aqua® (manufactured by AstraZeneca; Rhinocort Aqua® Nasal Spray; 32 mcg of budesonide per spray and 120 metered sprays after initial priming; package insert 30516-00, Rev. 01/05, is hereby incorporated by reference in its entirety), an optional diluent, and an optional sweetener. In some embodiments, the diluent is any carrier suitable for oral administration, including, by way of non-limiting example, water, ethanol, and combinations thereof. In a specific embodiment, the diluent is water. In some embodiments, the composition comprises Rhinocort Aqua®, an additional viscosity enhancing agent (e.g., Splenda), an optional diluent, and an optional sweetener and/or flavoring agent. In some embodiments, a composition useful herein includes a composition comprising a composition described in U.S. Pat. No. 6,291,445, U.S. Pat. No. 6,866,346, or U.S. Pat. No. 6,986,904, an optional additional viscosity enhancing agent or “thickener”, an optional diluent, and an optional sweetener and/or flavoring agent. In some embodiments, the composition comprises Rhinocort Aqua® and a diluent wherein the Rhinocort Aqua® and diluent are present in a ratio between about 1:0.5 and about 1:100. In more specific embodiments, the diluted Rhinocort Aqua® composition further comprises an excipient that increases the interaction of the composition with a surface of the gastrointestinal tract (e.g., a viscosity enhancing agent).

In some embodiments, initial treatment continues, for example, for about 3 days to 2 weeks for an acute condition, or about 4 weeks to about 16 weeks for a chronic condition, or about 8 weeks to about 12 weeks for a chronic condition. In various embodiments, longer therapy is needed, such as, for example, therapy similar to chronic therapy for persistent asthma. In some aspects of the present invention, patients are, for example, treated for up to 6 months, or up to one year. In certain aspects, maintenance treatments last up to longer than one year. In some embodiments, patients are treated on a maintenance basis or on an as needed basis during a problematic episode, depending on the severity of the condition. In certain embodiments, patients are treated on a rotating treatment basis, where treatment is provided for a period of time and then the patient is taken off of the drug for a period before treatment resumes again. When the drug, the patient may be given no treatment, treatment with another medication, dietary therapy, or treatment with a reduced dosage. In certain embodiments, patients are given treatment with a higher dose of the composition until a desired reduced disease state is achieved, and then continued on a lower dose of the composition. In certain embodiments, a patient combines treatment with a composition described herein with a treatment with another medication, and/or dietary therapy. In certain embodiments, patients are given treatment with a higher dose of the composition until a desired reduced disease state is achieved, and then continued on a lower dose of the composition.

In various embodiments, the compositions of the present invention include pharmaceutically acceptable salts. Pharmaceutically acceptable salts are generally well known to those of ordinary skill in the art and include, by way of non-limiting example, acetate, atosylate, benzenesulfonate, besylate, benzate, bicarbonate, bitartrate, bromide, calcium edetate, carnosylate, carbonate, citrate, edetate, edisylate, esolate, esylate, fumarate, glucuronate, glutamate, glycollyarsanilate, hexylresorcinate, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, nucate, napsylate, nitrate, pamoate (embonate), pantolactate, phosphate/diphosphate, polygalacturate, sulicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, or teoclate. Other pharmaceutically acceptable salts may be found in, for example, Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000). In specific embodiments, pharmaceutically acceptable salts include, for example, acetate, benzoate, bromide, carbonate, citrate, gluconate, hydrobromide, hydrochloride, maleate, mesylate, napsylate, pamoue (embonate), phosphate, sulicylate, succinate, sulfate, or tartrate. In certain embodiments, such salts are used for any of the corticosteroids described herein.

In certain embodiments, the compositions are formulated into liquid or solid dosage forms and administered systemically or locally. In some embodiments, the agents are delivered, for example, in a timed- or sustained-release form as is known to those skilled in the art. Techniques for formulation and administration may be found in Remington: The Science and Practice of Pharmacy (20th ed.) Lippincott, Williams & Wilkins (2000). In specific embodiments, the composition is formulated as a liquid dosage form. In more specific embodiments, the liquid dosage form is a suspension of micronized corticosteroid (e.g., budesonide) particles.

In addition to the active or actives, various embodiments of the present invention provide for pharmaceutical compositions that contain suitable pharmaceutically acceptable excipients and auxiliaries. For example, in some embodiments, pharmaceutically acceptable excipients and/or auxiliaries are used to formulate the corticosteroids herein disclosed for the practice of the invention into dosages suitable for systemic administration within the scope of the invention. In some embodiments, the corticosteroid is formulated readily using pharmaceutically acceptable excipients and/or auxiliaries well known in the art into dosages suitable for oral administration. Such excipients and/or auxiliaries enable the compositions of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated.

In certain embodiments, pharmaceutical preparations for oral use are obtained by combining an aqueous formulation of a corticosteroid (e.g., budesonide) with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. In certain embodiments, solid oral dosage forms (e.g., tablets, dragee cores, capsules, push-fit capsules, soft capsules, lozenges, etc.) are formulated such that the dosage forms substantially dissolve or disintegrate in the mouth and/or esophagus. In some embodiments, solid oral dosage forms are formulated such that the dosage forms substantially dissolve or disintegrate prior to reaching the stomach. In certain embodiments, an oral dosage form has substantially dissolved or disintegrated if at least 50%, by weight, of the dosage form has dissolved or disintegrated. In other embodiments, a substantial dissolution or disintegration includes at least 60%, 70%, 80%, 90% or 95% by weight. Suitable excipients include, by way of non-limiting example, fillers such as sugars or starches, including dextrose, lactose, maltodextrin, sucrose, saccharose, mannitol, or sorbitol; cellulose preparations, for
In certain embodiments, the aqueous formulation comprises budesonide, a viscosity enhancing agent, a preservative, a chelating agent, an isotonic agent, a surfactant, an optional pH adjusting agent and an optional sweetener. In more specific embodiments, the aqueous formulation comprises budesonide, microcrystalline cellulose and carboxymethyl cellulose sodium, dextrose anhydrous, polysorbate 80, disodium edetate, potassium sorbate, and hydrochloric acid to adjust the pH to a target of about 4.5 (e.g., Rhinocort Aquan®). In some embodiments, prior to mixing the aqueous suspension with the solid excipients, the aqueous solvent is removed (e.g., by evaporation). Disintegrating agents are optionally added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate. In some embodiments, the pharmaceutical compositions used herein include excipients suitable for rendering the dissolving tablet palatable, such as sweeteners or flavoring agents.

In some embodiments, the pharmaceutical compositions described herein are in liquid form. Appropriate excipients for use in liquid form pharmaceutical compositions include, for example, those that increase the liquid viscosity of the liquid composition. Optional excipients also include, by way of non-limiting example, those that render the liquid composition palatable. Optional excipients include, by way of non-limiting example, sugars, including dextrose, lactose, sucrose, sucralose, maltodextrin, mannitol, or sorbitol; honey or combinations thereof.

Dragee cores are provided with suitable coatings. In some embodiments, concentrated sugar solutions are used for this purpose, which optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments are optionally added to the tablets or dragee coatings for identification or to characterize different combinations of active corticosteroid doses.

In various embodiments, pharmaceutical preparations that are used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. In some embodiments, the push-fit capsules contain the active ingredient or ingredients admixed with a filler, binder, lubricant, stabilizer or a combination thereof. Fillers include, by way of non-limiting example, lactose. Binders include, by way of non-limiting example, starches. Lubricants include, by way of non-limiting example, talc and magnesium stearate. In soft capsules, the corticosteroids may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols (PEGs). In addition, stabilizers are optionally added.

In one embodiment, the present invention provides for a corticosteroid that has a low bioavailability. Due to the low bioavailability, the corticosteroid is used in certain embodiments of the invention, the corticosteroid remains in the gastrointestinal tract, for example, in the esophagus. In some embodiments, the low bioavailability results in decreased systemic side effects and complications, allowing patients with chronic conditions to receive treatment for longer periods of time.

Diseases

In certain embodiments, diseases or conditions that are treated, prevented, or exhibit an alleviation of symptoms by administering a composition described herein include any disease or condition that involves inflammation of the gastrointestinal tract, including the esophagus, stomach and/or digestive tract. This includes, by way of non-limiting example, any chronic inflammatory or malignant state that involves the gastrointestinal tract (e.g., the esophagus, stomach and/or digestive tract) and responds to steroid therapy. The methods of the present invention are useful, for example, for treating, preventing and alleviating the symptoms of eosinophilic esophagitis, inflammatory bowel diseases involving the esophagus, Crohn's disease, celiac disease, epithelial hyperplasia, basal cell hyperplasia, elongated papillae, dilated vessels in papillae, fungal esophagitis, viral esophagitis, bacterial esophagitis, corrosive esophagitis, radiation esophagitis, chemotherapy esophagitis, graft vs. host disease, a skin disease with esophageal involvement, bullous pemphigoid, pemphigus vulgaris, epidermolysis bullosa, Stevens-Johnson syndrome, Behcet's disease, sarcoidosis, idiopathic esophagitis, eosinophilic gastritis, Ménétrier's disease, parasitic gastritis, lymphocytic esophagitis, inflammatory bowel disease-associated esophagitis, parasitic gastritis, lymphocytic esophagitis, inflammatory bowel disease-associated esophagitis, eosinophilic duodenitis, functional dyspepsia, acute esophageal inflammation secondary to caustic/irritant ingestion, persistent/recurrent esophageal strictures secondary to caustic/irritant, conditions due to ingestion, systemic diseases, congenital diseases, and post-surgery inflammation. The methods of the present invention are also useful, for example, for treating, preventing and alleviating the symptoms of gastroesophageal reflux disease (GERD), non-erosive reflux disease (NERD) and/or erosive esophagitis.

It will be appreciated that reference herein to treatment extends to prophylaxis as well as the treatment of inflammation or other symptoms.

In certain embodiments, provided herein is a method of treating, preventing or alleviating inflammation of the gastrointestinal tract, including the esophagus, stomach and/or digestive tract, in an individual comprising orally administering to said individual any of the compositions described herein. In certain embodiments, oral administration includes the oral administration of a solid dosage form (e.g., tablets, dragee cores, capsules, push-fit capsules, soft capsules etc.) that is formulated such that the dosage form substantially dissolves or disintegrates in the mouth and/or esophagus. In some embodiments, solid oral dosage forms are formulated such that the dosage forms substantially dissolve or disintegrate prior to reaching the stomach. In certain embodiments, an oral dosage form has substantially dissolved or disintegrated if at least 50%, by weight, of the dosage form has dissolved or disintegrated. In other embodiments, substantial dissolution or disintegration includes at least 60%, 70%, 80%, 90% or 95% by weight. In certain embodiments, the oral dosage form is a liquid (e.g., a slurry, suspension, syrup, dispersion, solution, etc.)

In one aspect, a patient is administered a topical corticosteroid such as, for example, budesonide.

In some embodiments, the inflammation treated by the methods and compositions described herein is associated with eosinophilic inflammation and/or neutrophil inflammation. In some embodiments, individuals (e.g., patients) to be treated with compositions described herein include those that have been diagnosed eosinophilic esophagitis, an inflammatory bowel disease involving the esophagus, Crohn's disease, celiac disease, epithelial hyperplasia, basal cell hyper-
plasia, elongated papillae, dilated vessels in papillae, fungal esophagitis, viral esophagitis, bacterial esophagitis, corrosive esophagitis, radiation esophagitis, chemotherapy esophagitis, eosinophilic esophagitis, cosinophilic gastritis, idiopathic esophagitis, cosmetic disease, Behçet’s disease, sarcoidosis, parasitic gastritis, lymphocytic esophagitis, inflammatory bowel disease-associated esophagitis, parasitic gastritis, lymphocytic esophagitis, inflammatory bowel disease-associated esophagitis, eosinophilic diathesis, functional dyspepsia, esophageal inflammation secondary to caustic/irritant ingestion, persistent/recurrent esophageal strictures of any cause and including caustic/iritant ingestion, pill-induced esophagitis, systemic diseases, congenital diseases or post-surgery inflammation. In one non-limiting example, the patient has eosinophilic esophagitis. In some embodiments, the patient (e.g., patients) to be treated with the compositions described herein include those that have been diagnosed with gastroesophageal reflux disease (GERD), nonerosive reflux disease (NERD) and/or erosive esophagitis. In some embodiments, the patient is an adult. In other embodiments, the patient is a child or infant. In various aspects, a patient is a child or infant less than 16 years old, less than 12 years old, less than 7 years old, less than 6 years old, less than 4 years old or less than 2 years old.

In some embodiments, a composition is in a unit dose formulation for oral administration of a patient. In some embodiments, a unit dose of the corticosteroid is administered from a metered dose device, such as a metered dose inhaler. In certain aspects, from about 0.1 mg to about 20 mg, or about 0.25 to about 5 mg, or about 0.25 to about 2.5 mg/day or about 2 to 5 mg/day/day) corticosteroid per day is administered to the patient. In some embodiments, the corticosteroid is present in a unit dose in an amount of between about 0.1 mg and about 20 mg, or about 0.25 mg to about 5 mg. In some embodiments, the amount of corticosteroid administered daily or in a unit dose is between about 0.5 mg and about 4 mg. In some embodiments, the amount of corticosteroid administered daily or in a unit dose is between about 0.5 mg and about 3 mg. In other embodiments, the amount of corticosteroid present in a unit dose or administered daily is between about 1 and about 3 mg, or between about 1 and about 2 mg, or between about 2 and about 3 mg.

In some embodiments, the corticosteroid is present in a pharmaceutical composition described herein in an effective amount. In some embodiments, an effective amount is an amount sufficient to reduce inflammation or symptoms of inflammation associated with an inflammatory disease or condition of the gastrointestinal tract (e.g., the esophagus) as compared to the level of inflammation or symptoms of inflammation associated with an inflammatory disease prior to administration of the effective amount. In certain embodiments, effective amount is an amount sufficient to maintain a reduction in inflammation or symptoms of inflammation achieved in any manner including, but not limited to, by the administration of an effective amount sufficient to achieve such a reduction. In some embodiments, the effective amount (per day or per dose) is about 100 µg to about 20 mg, about 300 µg to about 4 mg, about 50 mg to about 500 mg, about 50 µg to about 200 mg, about 50 µg to about 100 mg, about 50 µg to about 50 mg, about 0.05 mg to about 20 mg, about 0.05 mg to about 15 mg, about 0.05 mg to about 10 mg, about 0.05 mg to about 7.5 mg, about 0.05 mg to about 5 mg, about 0.25 mg to about 3 mg, about 0.25 mg to about 2.5 mg, about 0.5 mg to about 3 mg, about 0.5 mg to about 2 mg, about 0.5 mg to about 1 mg, about 0.5 mg to about 5 mg, about 0.5 mg to about 4 mg, about 1 mg to about 4 mg, about 1 mg to about 3 mg, about 2 mg to about 3 mg, or about 2 mg to about 4 mg.

In specific embodiments, the effective amount of corticosteroid is about 0.05 mg, about 0.1 mg, about 0.25 mg, about 0.3 mg, about 0.35 mg, about 0.4 mg, about 0.57 mg, about 0.375 mg, about 0.7 mg, about 0.8 mg, about 0.75 mg, about 1 mg, about 1.25 mg, about 1.3 mg, about 1.5 mg, about 2 mg, about 2.5 mg, about 3 mg, about 3.5 mg, about 4 mg, about 4.5 mg, about 5 mg, about 5.5 mg, about 6 mg, about 6.5 mg, about 7 mg, or about 7.5 mg or more.

In some embodiments, the volume of a composition or dose of a composition described herein is an amount sufficient to substantially coat (e.g., at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 98% or at least 99% of) the length of the esophagus of an individual to whom the composition is administered. In certain embodiments, the volume of a composition or dose of a composition described herein is about 0.05 mL/cm esophageal length to about 1 mL/cm esophageal length, about 0.1 mL/cm esophageal length to about 0.8 mL/cm esophageal length, about 0.2 mL/cm esophageal length to about 0.6 mL/cm esophageal length, or about 0.3 mL/cm esophageal length to about 0.5 mL/cm esophageal length, wherein the esophageal length is the esophageal length of the individual to whom the composition is administered. In some embodiments, the volume of a composition or dose of a composition described herein is based on the esophageal length of an individual (e.g., male, female, or both) that is in the 50th percentile of height for their age. Therefore, in some embodiments, the volume of a composition or dose of a composition described herein is about 0.05 mL/cm esophageal length to about 1 mL/cm esophageal length, about 0.1 mL/cm esophageal length to about 0.8 mL/cm esophageal length, about 0.2 mL/cm esophageal length to about 0.6 mL/cm esophageal length, about 0.3 mL/cm esophageal length to about 0.5 mL/cm esophageal length, about 0.32 mL/cm esophageal length to about 0.41 mL/cm esophageal length, or about 0.3 mL/cm esophageal length to about 0.46 mL/cm esophageal length, wherein the esophageal length is the esophageal length of an individual having a height in the 50th percentile for the age of the individual to whom the composition is administered. In certain instances, esophageal length is the actual esophageal length of the individual or is calculated based on the equation: esophageal length=1.048 (cm)+(0.167*height(cm)). In certain instances, for example, the 50th percentile height (CDC 2000) for male children age 2 is 87 cm, age 3 is 95 cm, age 4 is 102 cm, age 5 is 109 cm, age 6 is 115 cm, age 7 is 122 cm, age 8 is 128 cm, age 9 is 134 cm, age 10 is 139 cm, age 11 is 144 cm, age 12 is 149 cm, age 13 is 156 cm, age 14 is 164 cm, age 15 is 170 cm, age 16 is 174 cm, age 17 is 175 cm, and age 18 is 176 cm.

Furthermore, in certain embodiments, the amount of a therapeutic agent (e.g., a corticosteroid such as budesonide) in a composition or a dose of a composition described herein is about 0.005 mg/cm esophageal length to about 0.3 mg/cm esophageal length, about 0.008 mg/cm esophageal length to about 0.2 mg/cm esophageal length, about 0.01 mg/cm esophageal length to about 0.15 mg/cm esophageal length, or about 0.015 mg/cm esophageal length to about 0.1
mg/cm esophageal length, wherein the esophageal length is the esophageal length of the individual to which the composition is administered. In some embodiments, the volume of a composition or dose of a composition described herein is based on the esophageal length of an individual (e.g., male, female, or both) that is in the 50th percentile for their age. Therefore, in some embodiments, the amount of a therapeutic agent (e.g., a corticosteroid such as budesonide) in a composition or dose of a composition described herein is about 0.005 mg/cm esophageal length to about 0.3 mg/cm esophageal length, about 0.008 mg/cm esophageal length to about 0.2 mg/cm esophageal length, about 0.01 mg/cm esophageal length to about 0.15 mg/cm esophageal length, or about 0.015 mg/cm esophageal length to about 0.1 mg/cm esophageal length, wherein the esophageal length is the esophageal length of an individual having a height in the 50th percentile for the age of the individual to whom the composition is administered.

[0092] In some embodiments, any pharmaceutical composition or dose of a pharmaceutical composition described herein is provided or administered in a volume sufficient to provide a bolus when orally administered to an individual. In certain embodiments, the composition has a volume that does not systemically deliver excessive amounts of the active agent. In some embodiments, the pharmaceutical composition or dose is provided in a volume sufficient to provide a bolus when administered to an individual, wherein the size of the bolus at the distal end of the esophagus (e.g., the size of the bolus prior, e.g., immediately prior, to entering or passing the lower esophageal sphincter) is less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, less than 50%, less than 45%, less than 40%, less than 35%, less than 30%, less than 25%, less than 20%, less than 15%, less than 10%, or less than 5% of size of the bolus that entered the esophagus (e.g., the size of the bolus after, e.g., immediately after, passing the upper esophageal sphincter). In some embodiments, the size of the bolus is determined as a measure of diameter of volume. In certain embodiments, diameter of the sphincter can be determined using gamma scintigraphy techniques. In specific embodiments, the volume of the composition or dose is adjusted given the length and/or diameter of the esophagus of the individual to whom the composition or dose is administered.

[0093] The entirety of each patent, patent application, publication and reference referenced herein is hereby incorporated by reference. Citation of the above patents, patent applications, publications and documents is not an admission that any of the foregoing is pertinent prior art, nor does it constitute any admission as to the contents or date of these publications or documents.

[0094] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and systems similar or equivalent to those described herein can be used in the practice or testing of the present invention, the methods, devices, and materials are now described. All publications mentioned herein are incorporated herein by reference for the purpose of describing and disclosing the processes, systems, and methodologies which are reported in the publications which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

[0095] Modifications may be made to the foregoing without departing from the basic aspects of the invention. Although the invention has been described in substantial detail with reference to one or more specific embodiments, those of ordinary skill in the art will recognize that changes may be made to the embodiments specifically disclosed in this application, and yet these modifications and improvements are within the scope and spirit of the invention. The invention illustratively described herein suitably may be practiced in the absence of any elements not specifically disclosed herein. Thus, for example, in each instance herein any of the terms “comprising”, “consisting essentially of”, and “consisting of” may be replaced with either of the other two terms. Thus, the terms and expressions which have been employed are used as terms of description and not of limitation, equivalents of the features shown and described, or portions thereof, are not excluded, and it is recognized that various modifications are possible within the scope of the invention.

[0096] In some embodiments, the dose or volume of a composition administered herein is adjusted based on the efficacy of treatment. In certain embodiments, a diagnosis of eosinophilic esophagitis is achieved by administering a composition described herein and determining the efficacy of the treatment. In certain embodiments, a composition described herein and separately determined to be effective in treating eosinophilic esophagitis is utilized. Efficacy of treatment can be determined in any suitable manner including, e.g., symptom score assessment, gastrointestinoscopy (e.g., esophagogastrroduodenoscopy), gastrointestinal (e.g., esophageal) biopsy, histological evaluation, or a combination thereof. Processes of diagnosing eosinophilic esophagitis and/or determining efficacy of treatment include any suitable process including, by way of non-limiting example, processes as set forth in Aceves et al., J Allergy Clin Immunol, February 2008; abstract 270, or Aceves et al., Am J Gastroenterol., October 2007, 102(10):2271-9, both of which are incorporated herein in their entirety.

[0097] In some embodiments, a process for determining efficacy of a treatment (e.g., for eosinophilic esophagitis) described herein is a clinical symptom score assessment comprising (i) administering a composition described herein to an individual diagnosed with or suspected of having eosinophilic esophagitis; and (ii) evaluating one or more symptom of the individual. In certain embodiments, prior to administering the composition, the process comprises evaluating the one or more symptom of the individual. Symptoms that are optionally scored include, by way of non-limiting example, nausea, vomiting, pain, and heartburn. Total score or change in score is optionally utilized to diagnose a disorder and/or determine efficacy of treatment.

[0098] In certain embodiments, a process for determining efficacy of a treatment described herein comprises (i) administering a composition described herein to an individual diagnosed with or suspected of suffering from inflammation of the gastrointestinal tract (e.g., eosinophilic esophagitis); (ii) endoscopy the gastrointestinal surface of the individual; (iii) biopsying the gastrointestinal surface tissue; and (iv) evaluating the biopsied tissue and optionally determining an endoscopy score of the tissues biopsied. In specific embodiments, the process further comprises comparing the evaluated
biopsied tissue and/or the endoscopy score obtained prior to administration of the composition to the biopsied tissue and/or endoscopy score subsequent to administration of the composition.

[0099] In some embodiments, provided herein is a process of diagnosing an individual with gastrointestinal inflammation by (i) detecting and/or measuring symptoms of the individual prior to administering to the individual a composition described herein; (ii) administering to the individual any composition described herein; (iii) detecting and/or measuring symptoms of the individual following administration of the composition; and (iv) comparing the symptoms measured or detected prior to and following administration of a composition described herein. If the symptoms exhibited by the individual are reduced (e.g., by a statistically significant or clinically relevant amount), a positive diagnosis occurs. In specific embodiments, the process of diagnosing an individual with gastrointestinal inflammation is diagnosing an individual with eosinophilic esophagitis.

EXAMPLE 1

[0100] This example illustrates the increased interaction between a composition described herein and the esophagus when compared to a radiolabeled oral composition made by combining Pulmicort Respules® (4 mL) with 99mTc pertechnetate, and diluting with saline to about 7-8 mL (M0). The M0 composition has a viscosity of about 1 cp at 13.2 sec^-1. Also administered to a population of healthy individuals was a radiolabeled budesonide composition (Rhinocort Aquat®, M1), which has a viscosity of about 39 at 13.2 sec^-1. Increased interaction of the budesonide composition was determined by measuring the amount of radiolabel present in the esophagus following oral administration of the M1 budesonide composition. FIG. 1 illustrates the percent amount of composition present in the esophagus as a function of time following oral administration (by measuring the amount of radiolabel present in the esophagus).

[0101] The area under the curve (AUCr) of the percent of the dose administered as a function of time (% dose-time (min)) was determined from the time of 50% swallow (i.e., 50% of the administered dose had passed from the mouth), until esophageal activity had peaked and fallen to 10% of the peak value. The area under the curve from t=0 min to t=1 min (AUCr,1); and from t=0 min to t=2 min (AUCr,2) was also determined. These results (including the ratio of the non-viscous sample to the viscous sample) are set forth below:

<table>
<thead>
<tr>
<th>Formulation</th>
<th>AUCr,1</th>
<th>AUCr,2</th>
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<td>geometric mean</td>
</tr>
<tr>
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</tr>
<tr>
<td>M1</td>
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</table>

EXAMPLE 2

[0102] This example details the efficacy and safety of once daily and twice daily use of budesonide formulations described herein in 5 mL, 7 mL, 10 mL, 12 mL, 15 mL, or 17.5 mL doses in inducing and maintaining remission of disease activity in children with EE. A number of children (e.g., 20 per budesonide dose frequency, amount, and volume) are evaluated to determine the highest eosinophil count (eos/hpf) and the mean highest eosinophil count for the group. Evaluation of the highest eosinophil count (eos/hpf) and the mean highest eosinophil count for the group is also determined following therapy. Symptom scores and mean symptom scores are also determined before and after therapy.

[0103] In some instances, individuals who received previous therapy with proton pump inhibitor, elimination diet based upon skin or blood allergy testing, or elimination diet or refused elimination diet, but continued to have ≥24 eos/hpf on esophageal biopsy are included in the review. Patients are defined as having food or allergen sensitization if RAST and/or skin prick testing are positive. No changes are made to longstanding therapy used for treating chronic conditions such as asthma or eczema and none of the children receive concurrent immunomodulatory treatment.

[0104] Endoscopy is performed using the Olympus P160 endoscope (by RD) and pan-esophageal, gastric and duodenal biopsies are taken. Eosinophilic esophagitis is diagnosed when ≥24 eos/hpf are found in at least one of the esophageal sites biopsied. Two mucosal biopsies re taken from the proximal esophagus (3 cm below the criopharyngeus muscle), distal esophagus (3 cm above the gastroesophageal junction (GEJ), and mid-esophagus (midpoint between the criopharyngeus muscle and the GEJ). Biopsies are processed routinely and evaluated by a pediatric pathologist (RN). The highest number of eosinophils per x400 high power field are counted. Basal zone hyperplasia (BZH) is reported when basal zones extend towards the luminal surface of the epithelium (>25% of epithelial thickness).

[0105] Follow-up endoscopy with biopsies are taken after 34 months treatment. Counting the highest number of eos/hpf within biopsies determined the response to therapy and patients are categorized into responders (0-7 eos/hpf), partial-responders (8-23 eos/hpf) and non-responders (≥24 eos/hpf).

[0106] An EE Endoscopy Score is devised to compare findings before and after treatment. It is calculated from procedure reports and photographs. Four categories, (1) pallor and diminished vascular markings; (2) furrowing with "thickened" mucosa; (3) white mucosal plaques; (4) concentric rings or strictures. For each category, one point is allocated if 1 or 2 esophageal sites are involved, and two points for pan-esophageal involvement. The maximum score is 8.

[0107] Patients receive a formulation described herein for between 0.25 and 2 mg daily and are instructed not to ingest any solids or liquids for 30 minutes afterwards. No dietary changes are made in patients already on dietary restrictions.

[0108] A modified symptom score based on children with acid-peptic disease is used routinely in the EE clinic. The symptom categories include (1) heartburn or regurgitation; (2) abdominal pain or unexplained irritability in younger children; (3) nausea or vomiting; (4) anorexia or early satiety; (5) dysphagia or odynophagia; (6) nocturnal waking with symptoms; (7) gastrointestinal bleeding (previous 4 months). Each category scored 0-2 points with a maximum of 14 points. Zero points are awarded if the symptom is absent; one point if the symptom is mild, did not interfere with daily activities; 2 points if the symptoms are severe enough to interrupt daily activities. Previous GI bleeding is considered mild (1 point) if there is no associated hemodynamic compromise or anemia, and severe (2 points) if bleed is multiple, caused anemia, or required blood transfusion.

[0109] All statistical analysis is carried out using NCSS Statistical Software Package. Two-tailed p values are calcu-
lated using paired t-tests to compare the means of patient values for eos/hpf, EE Endoscopy Scores and Symptom Scores before and after budesonide therapy. Two-tailed unpaired t-tests are utilized in order to compare variables grouped by responders versus non-responders. Spearman’s correlation coefficients are generated using GraphPad Prism software. Results with p values <0.05 are considered statistically significant. Both mean and median statistics are generated; both are equivalent and mean statistics are presented.

[0110] Subjects. Chart reviews are undertaken on a number of children. All children have >24 eos/hpf on repeat esophageal biopsy before starting therapy.

[0111] Treatment. Patients received formulations described herein for a designated amount of time (e.g., 1 week, 2 weeks, 1 month, 2 months, 3 months, 4 months, 6 months, or the like) before repeat endoscopy. Various patients received budesonide in amounts ranging from 0.25 to 2 mg/day.

[0112] Histology. Before treatment the mean highest eosinophil count is measured for all patients, including distal, mid and proximal esophageal sites. All sites are likewise evaluated over the designated amount of time, and again if desired.

[0113] Upper Gastrointestinal Endoscopy. Before treatment, the mean EE Endoscopy Score for all patients is determined. Following treatment the mean EU Endoscopy Score is repeated. Decreases in endoscopy scores (e.g., of >95%, >90%, >85%, >75%, >50%, >25%, or the like) in an individual indicate successful treatment.

[0114] Symptom Score. Before treatment the mean symptom score for all patients is determined. It is again determined following treatment. Decreases in symptom scores (e.g., of >95%, >90%, >85%, >75%, >50%, >25%, or the like) in an individual indicate successful treatment (alone or in combination with the above referenced decreases in endoscopy scores).

[0115] Adults: these parameters are repeated in adults to determine efficacy and safety therein.

EXEMPLARY EXAMPLE 3

[0116] This example details the efficacy and safety of once daily and twice daily use of budesonide in a formulation described herein in inducing and maintaining remission of disease activity in individuals (children and/or adults) with GERD. Doses of 0.1 mg, 1.2 mg, 2.3 mg, 3.4 mg, 4.5 mg, and 5.6 mg per daily dose are administered once a day, b.i.d. or t.i.d. in volumes of 3, 5, 7, 10, 12, 15, or 17.5 mL. A number of individuals (e.g., 20 per budesonide dose frequency, amount, and volume) are evaluated to determine the symptoms prior to therapy, during therapy and following therapy. Administration is conducted for 7 days, 14 days, and 28 days. Primary Outcome Measures include complete resolution of heartburn and regurgitation (e.g., no more than one day with either mild heartburn or regurgitation over the seven days prior to the assessment time-point). Secondary Outcome Measures include: Number of days with heartburn (daytime and nighttime); Number of days with regurgitation (daytime and nighttime); Number of heartburn and regurgitation-free days (24 hrs); Composite score of heartburn and regurgitation frequency and severity; Time to resolution of symptoms of heartburn/regurgitation; Severity of additional GERD symptoms; Quality of Life (assessed using PAGI-QOL) to PGIC (Patient Global Impression of Change); Complete resolution of heartburn; Complete resolution of regurgitation; Average severity of heartburn (daytime and nighttime); Average severity of regurgitation (daytime and nighttime). These symptoms are scored (e.g., assigning a 3 to the most severe symptoms and a 0 to a lack of symptoms) and utilized to determine the efficacy of the treatment.

[0117] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

REFERENCES


What is claimed is:

1. A method of treating, preventing or alleviating inflammation of the gastrointestinal tract comprising orally administering to an individual in need thereof a composition comprising a corticosteroid, a preservative, a chelating agent, an isotonic agent, a surfactant, and an excipient that increases the interaction of the composition with a surface of the gastrointestinal tract.
2. The method of claim 1, wherein the corticosteroid is budesonide.

3. The method of claim 1, wherein the corticosteroid is present in the composition in an amount of about 0.01 mg to about 1.0 mg of corticosteroid per gram of composition.

4. The method of claim 1, wherein the corticosteroid is present in the composition in an amount of about 0.01 mg to about 1.0 mg of corticosteroid per mL of composition.

5. A method of claim 4, wherein the method comprises administering about 5 mL to about 50 mL of the composition to the individual.

6. The method of claim 1, wherein the preservative is potassium sorbate.

7. The method of either of claims 1 or 6, wherein the preservative is present in the composition in an amount of about 0.0002% to about 0.5% w/w of the composition.

8. The method of claim 1, wherein the chelating agent is edetate.

9. The method of claim 1, wherein the chelating agent is present in the composition in an amount of about 0.0005% to about 0.1% w/w of the composition.

10. The method of claim 1, wherein the isotonic agent is dextrose.

11. The method of claim 1, wherein the surfactant is polysorbate 80.

12. The method of claim 1, wherein the surfactant is present in the composition in an amount of about 0.0005% to about 2% w/w of the composition.

13. The method of claim 1, wherein the excipient that increases the interaction of the composition with a surface of the gastrointestinal tract is a viscosity enhancing agent.

14. The method of claim 13, wherein the viscosity enhancing agent is selected from microcrystalline cellulose, carboxymethyl cellulose sodium and a combination thereof.

15. The method of claim 14, wherein the viscosity enhancing agent is a combination of microcrystalline cellulose and carboxymethyl cellulose sodium.

16. The method of claim 13, wherein the viscosity enhancing agent is present in the composition in about 0.01% to about 3.0% w/w of the composition.

17. The method of claim 15, wherein the viscosity enhancing agent is a combination of a CMC and MCC.

18. The method of claim 1, wherein the composition is formulated as a micronized suspension of the corticosteroid in an aqueous vehicle.

19. The method of claim 1, wherein the composition has a target pH of about 4.5.

20. The method of claim 19, wherein the target pH of the composition is attained by adding a pH adjusting agent to the composition.

21. The method of claim 20, wherein the pH adjusting agent is hydrochloric acid.

22. The method of claim 1, wherein the composition further comprising a sweetener, a flavoring agent or a combination thereof.

23. The method of claim 1, wherein the composition comprises:
   a. about 0.01 mg to about 1.0 mg of budesonide per mL of composition;
   b. about 0.0002% to about 0.5% w/w of potassium sorbate;
   c. about 0.0005% to about 0.1% w/w of disodium edetate;
   d. about 0.0005% to about 2% w/w of polysorbate 80; and
   e. about 0.01% to about 3.0% w/w of a combination of microcrystalline cellulose and carboxymethyl cellulose sodium.

24. The method of claim 1, comprising administering about 0.1 mg to about 20 mg of corticosteroid per day.

25. The method of claim 1, wherein the inflammation of the gastrointestinal tract is inflammation of the esophagus.

26. The method of claim 1, wherein the inflammation of the gastrointestinal tract is eosinophilic esophagitis, an inflammatory bowel disease involving the esophagus, Crohn’s disease, celiac disease, intermediate esophagitis, epithelial hyperplasia, basal cell hyperplasia, elongated papillae, dilated vessels in papillae, fungal esophagitis, viral esophagitis, bacterial esophagitis, corrosive esophagitis, radiation esophagitis, chemotherapy esophagitis, graft vs. host disease, a skin disease with esophageal involvement, bullous pemphigoid, pemphigus vulgaris, epidermolysis bullosa, Stevens-Johnson syndrome, Behcet’s disease, sarcoidosis, idiopathic esophagitis, eosinophilic gastritis, Méniétrier’s disease, parasitic gastritis, lymphocytic esophagitis, inflammatory bowel disease-associated esophagitis, parasitic gastritis, lymphocytic esophagitis, inflammatory bowel disease-associated esophagitis, eosinophilic duodenitis, functional dyspepsia, esophageal inflammation secondary to caustic/irritant ingestion, persistent/recurrent esophageal strictures of any cause and including caustic/irritant ingestion, pill-induced esophagitis, systemic diseases, congenital diseases or post-surgery inflammation.

27. The method of claim 25, wherein the individual has eosinophilic esophagitis.

28. The method of claim 25, wherein the individual has been diagnosed with gastroesophageal reflux disease (GERD), nonerosive reflux disease (NERD), or erosive esophagitis.

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