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(54) **Title:**
MESALAMINE SUPPOSITORY

(57) **Abstract:**
The present invention relates to a mesalamine rectal suppository designed to provide improved comfort of use. One embodiment of the invention is a mesalamine rectal suppository comprising mesalamine and one or more pharmaceutically acceptable excipients, wherein the drug load of the suppository ranges from 35% to 50%. Yet another embodiment of the invention is a mesalamine rectal suppository comprising mesalamine having a tap density ranging from about 600 to about 800 g/L (as measured by USP <616>) and a hard fat having an ascending melting point of 32 to 35.5° C. Yet another embodiment is a mesalamine rectal suppository comprising mesalamine particles and one or more pharmaceutically acceptable excipients, where the mesalamine particles have a surface area of from about 0.1 m2/g to about 2.8 m2/g (e.g., from about 0.1 m2/g to about 1.3 m2/g). Methods of preparing and methods of treatment with mesalamine suppositories are also provided. The invention further provides a method of determining a dissolution parameter (such as dissolution rate) of a mesalamine rectal suppository, such as a 1 g mesalamine suppository, by measuring its dissolution with USP Apparatus #2 at 40° C and a paddle rotation speed of 125 rpm in 0.2 M phosphate buffer at a pH of 7.5.

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(54) Title: MESALAMINE SUPPOSITORY

(57) Abstract: The present invention relates to a mesalamine rectal suppository designed to provide improved comfort of use. One embodiment of the invention is a mesalamine rectal suppository comprising mesalamine and one or more pharmaceutically acceptable excipients, wherein the drug load of the suppository ranges from 35% to 50%. Yet another embodiment of the invention is a mesalamine rectal suppository comprising mesalamine having a tap density ranging from about 600 to about 800 g/L (as measured by USP <616>) and a hard fat having an ascending melting point of 32 to 35.5° C. Yet another embodiment is a mesalamine rectal suppository comprising mesalamine particles and one or more pharmaceutically acceptable excipients, where the mesalamine particles have a surface area of from about 0.1 m^2/g to about 2.8 m^2/g (e.g., from about 0.1 m^2/g to about 1.3 m^2/g). Methods of preparing and methods of treatment with mesalamine suppositories are also provided. The invention further provides a method of determining a dissolution parameter (such as dissolution rate) of a mesalamine rectal suppository, such as a 1 g mesalamine suppository, by measuring its dissolution with USP Apparatus #2 at 40° C and a paddle rotation speed of 125 rpm in 0.2 M phosphate buffer at a pH of 7.5.

MESALAMINE SUPPOSITORY

FIELD OF THE INVENTION

The present invention relates to a mesalamine suppository designed to provide improved comfort of use, a method for manufacturing it, and methods for treating ulcerative colitis, such as active ulcerative proctitis, with it as well as a method of measuring a dissolution parameter of a mesalamine suppository.

BACKGROUND OF THE INVENTION

Inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis (UC), are characterized by chronic, relapsing intestinal inflammation. Crohn's disease and UC are believed to involve a dysregulated immune response to gastrointestinal (GI) tract antigens, a mucosal barrier breach, and/or an adverse inflammatory reaction to a persistent intestinal infection. In normal people, the GI tract luminal contents and bacteria constantly stimulate the mucosal immune system, and a delicate balance of pro-inflammatory and anti-inflammatory cells and molecules maintains the integrity of the GI tract, without eliciting severe and damaging inflammation [MacDermott, R. P., J Gastroenterology, 31:907:-916 (1996)]. It is unknown how the IBD inflammatory cascade begins, but constant GI antigen-dependent stimulation of the mucosal and systemic immune systems perpetuates the inflammatory cascade and drives lesion formation.

UC is a non-specific inflammatory disease of the colon that is of unknown cause and is characterized by diarrhea with discharge of mucus and blood, cramping abdominal pain, and

inflammation and edema of the mucous membrane with patches of ulceration. UC limited to the rectum is known as ulcerative proctitis. People suffering from chronic UC affecting the whole colon have an increased risk of colonic cancer. Furthermore, when medical therapy fails, surgical resection of affected bowel may be necessary.

In patients with more extensive disease, blood loss from the inflamed intestines can lead to anemia, and may require treatment with iron supplements or even blood transfusions. Although infrequent, the colon can acutely dilate to a large size when the inflammation becomes very severe. This condition is called toxic megacolon. Patients with toxic megacolon are extremely ill with fever, abdominal pain and distention, dehydration, and malnutrition. Unless the patient improves rapidly with medication, surgery is usually necessary to prevent colon rupture and high risk of death.

Mesalamine, 5-aminosalicylic acid (5-ASA), is often used to treat UC and is effective in reducing disease symptoms and the incidence of relapse in UC. While mesalamine is available in oral form, intrarectal administration of it has several advantages. For example, rectal administration of a drug avoids some side-effects, such as gastrointestinal disorders, due to oral administration. As mesalamine is a locally GI active drug, lower doses of the drug can be administered rectally to obtain a better or equivalent therapeutic effect as that attained with a higher dose oral formulation. The absorption of a drug orally administered may also be affected by whether it is administered before or after each meal or between meals. There is no such food effect when drugs are administered intrarectally. Intrarectal administration can be performed even during nausea, vomiting or unconsciousness, or after surgical operation.

A 1 g mesalamine suppository of a substantial size (3g) is currently marketed in the U.S. by Axcan Scandipharm Inc. as CANASA® for the treatment of active ulcerative proctitis.

There is a need for mesalamine suppositories which provide increased comfort of use.

SUMMARY OF THE INVENTION

The present inventors have discovered that the size of a mesalamine suppository can be drastically reduced (for example, by over 20% by weight) and the melting point lowered without a substantial adverse effect on its dissolution profile or its overall therapeutic efficacy. The combination of a smaller suppository and a lower melting temperature provides increased comfort of use. The inventors discovered that this result can be obtained by increasing the tap density of the mesalamine and, preferably, also lowering the melting point of the suppository base.

Generally when the drug load of a mesalamine suppository is increased, so too is the viscosity of the molten suspension which is cast to form the suppository. If the viscosity of the mesalamine suspension is too high, it cannot be cast into a suppository having acceptable content uniformity and good therapeutic properties. The inventors have surprisingly found that the viscosity of the measlamine suspension can be decreased by increasing the tap density of the mesalamine.

The inventors have also surprisingly discovered that the dissolution rate of mesalamine (a poorly soluble drug) from a suppository increases as surface area of the mesalamine particles decreases. This is contrary to the common scientific belief that the dissolution rate of a drug increases as the surface area of the drug particles increases.

One embodiment of the present invention is a mesalamine rectal suppository comprising mesalamine and one or more pharmaceutically acceptable excipients, wherein the drug load of the suppository ranges from about 35% to about 50% and preferably from about 37% to about 46%. The suppository may include from about 850 to about 1150 mg mesalamine, and preferably includes about 950 mg to about 1050 mg mesalamine (and even more preferably about 1000 mg mesalamine). According to another embodiment, the suppository includes from about 400 to about 600 mg mesalamine, and preferably includes about 450 to about 550 mg mesalamine (and even more preferably about 500 mg mesalamine). According to yet another embodiment, the suppository includes from about 1400 to about 1600 mg mesalamine, and preferably includes about 1450 to about 1550 mg mesalamine (and even more preferably about 1500 mg mesalamine). The mesalamine suppository may further include a suppository base, such as hard fat (e.g., hard fat NF).

Another embodiment of the invention is a mesalamine rectal suppository comprising from about 850 to about 1150 mg mesalamine and one or more pharmaceutically acceptable excipients, wherein the total weight of the suppository ranges from about 2250 to about 2700 mg. Preferably, the total weight of the suppository ranges from about 2250 to about 2500 mg. The amount of mesalamine in the suppository preferably ranges from about 950 mg to about 1050 mg and more preferably is about 1000 mg. The mesalamine suppository may further include a suppository base, such as hard fat (e.g., hard fat NF).

Another embodiment of the invention is a mesalamine rectal suppository comprising from about 400 to about 600 mg mesalamine and one or more pharmaceutically acceptable excipients, wherein the total weight of the suppository ranges from about 870 to about 1715 mg. Preferably, the total weight of the suppository ranges from about 980 to about 1570 mg. Preferably, the drug load is from about 35% to about 50%. The amount of mesalamine in the suppository preferably ranges from about 450 mg to about 550 mg and more preferably is about 500 mg. The mesalamine suppository may further include a suppository base, such as hard fat (e.g., hard fat NF).

Yet another embodiment of the invention is a mesalamine rectal suppository comprising from about 1400 to about 1600 mg mesalamine and one or more pharmaceutically acceptable excipients, wherein the total weight of the suppository ranges from about 2800 to about 4570 mg. Preferably, the total weight of the suppository ranges from about 3000 to about 4200 mg. Preferably, the drug load is from about 35% to about 50%. The amount of mesalamine in the suppository preferably ranges from about 1450 mg to about 1550 mg and more preferably is about 1500 mg. The mesalamine suppository may further include a suppository base, such as hard fat (e.g., hard fat NF).The mesalamine in each of the aforementioned suppositories preferably has a tap density ranging from about 600 to about 800 g/L (as measured by USP <616>) and/or a surface area of from about 0.1 to about 2.8 m^2/g (or preferably from about 0.2 to about 2.8 m^2/g, preferably from about 0.1 to about 1.3 m^2/g, or preferably from about 0.2 to about 1.3 m^2/g). According to a preferred embodiment, the mesalamine in the aforementioned suppositories is dispersed in a low melting suppository base (i.e., a suppository base having an ascending melting point of no more than 35.5° C). A preferred low melting suppository base is hard fat having an ascending melting point of 32 to 33.5° C (e.g., Witepsol® H 12 available from

Sasol Germany GmbH of Witten, Germany). Another suitable low melting suppository base is hard fat having an ascending melting point of 33.5 to 35.5° C (e.g., Witepsol® H-15 available from Sasol Germany GmbH). The dispension is preferably substantially homogenous.

Yet another embodiment of the invention is a mesalamine rectal suppository comprising mesalamine having (i) (a) a tap density ranging from about 600 to about 800 g/L (as measured by USP <616>) and/or (b) a surface area of from about 0.1 to about 2.8 m^2/g (or preferably from about 0.2 to about 2.8 m^2/g, preferably from about 0.1 to about 1.3 m^2/g, or preferably from about 0.2 to about 1.3 m^2/g) and (ii) a hard fat having an ascending melting point of 32 to 35.5° C. Typically, the mesalamine is dispersed in the hard fat. According to one preferred embodiment, the hard fat has an ascending melting point of 32 to 33.5°C. Preferably, such a dispersion is substantially homogenous. The weight ratio of mesalamine to hard fat preferably ranges from about 1:2 to about 1:1.25.

Preferably, the aforementioned suppositories each release at least about 75% by weight of the mesalamine contained in the suppository within 2 hours of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5. In one embodiment, at least about 80, 90, or 95% by weight of the mesalamine is dissolved within 2 hours. According to another embodiment, at least about 80, 85, or 90% by weight of the mesalamine is dissolved within 1 hour. According to yet another embodiment, at least 90% by weight of the mesalamine is dissolved within 30 minutes.

One preferred method for determining the dissolution profile of a suppository containing from about 400 to about 600 mg mesalamine is by USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 7 sinker turns in 0.2 M phosphate buffer at a pH of 7.5. In one embodiment, a suppository of the present invention containing from about 400 to about 600 mg (or up to about 800 mg) mesalamine releases at least about 75% by weight of the mesalamine contained in the suppository within 2 hours of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 7 sinker turns in 0.2 M phosphate buffer at a pH of 7.5. In another embodiment, at least about 80, 85, 90, or 95% by weight of the mesalamine is dissolved within 2 hours. According to another embodiment, at least about 80, 85, or 90% by weight of the mesalamine is dissolved within 1 hour.

Yet another method for determining the dissolution profile of a mesalamine suppository is by USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and from 2 to 8 sinker turns (e.g., with a wire helix) in 0.2 M phosphate buffer at a pH of 7.5. For instance, the aforementioned suppositories can release at least about 75% by weight of the mesalamine contained in the suppository within 2 hours of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and from 2 to 8 sinker turns in 0.2 M phosphate buffer at a pH of 7.5.

Yet another embodiment is a method of treating ulcerative colitis, such as active ulcerative proctitis, in a patient in need thereof by administering to the patient a mesalamine rectal suppository of the present invention. Preferably, the mesalamine suppository is administered once a day and more preferably once a day at bedtime. The suppository is also preferably retained for one to three hours or longer, if possible. The treatment can be brief, for example, once daily for three to twenty-one days, or can be longer, for example, once daily for three to six weeks.

Yet another embodiment is a method of determining a dissolution parameter (such as dissolution rate or amount of drug dissolved after a specified period of time) of a mesalamine rectal suppository, such as a 500 mg, 1 g or 1.5 g mesalamine suppository, by measuring its dissolution with USP Apparatus #2 at 40° C and a paddle rotation speed of 125 rpm in 0.2 M phosphate buffer at a pH of 7.5. A sinker can be coiled around the suppository, for example, for 2 to 8 turns of wire (e.g., wire helix). According to a preferred embodiment, a sinker is lightly coiled around the suppository, for example with only 3 turns of wire helix (for example, for a suppository containing 800 mg or more mesalamine). According to another embodiment, a sinker is coiled around the suppository with 7 turns of wire helix (for example, for a suppository containing 800 mg or less mesalamine). This dissolution method produces results which are significantly more reliable and less variable than those produced by other dissolution methods, such as methods 1 and 3 discussed in Examples 1 and 2.

Yet another embodiment is a method of preparing a mesalamine rectal suppository by (A) providing a mesalamine rectal suppository, and (B) measuring the dissolution rate of the suppository with USP Apparatus #2 at 40° C and a paddle rotation speed of 125 rpm in 0.2 M phosphate buffer at a pH of 7.5. A sinker can be coiled around the suppository, for example, for

2 to 8 turns of wire (e.g., wire helix). According to a preferred embodiment, a sinker is lightly coiled around the suppository, for example, with only 3 turns of wire helix (for example, for a suppository containing 800 mg or more mesalamine). According to another embodiment, a sinker is coiled around the suppository with 7 turns of wire helix (for example, for a suppository containing 800 mg or less mesalamine). Step (B) may include determining whether the suppository releases at least about 75% by weight of the mesalamine within 2 hours of dissolution. Step (B) may additionally or alternatively include determining whether the suppository releases at least about 85% by weight of the mesalamine within 1 hour of dissolution.

Yet another embodiment is a method of preparing a batch of mesalamine rectal suppositories (i.e., 2 or more suppositories) by (A) providing a batch of mesalamine rectal suppositories; and (B) measuring the dissolution rate of at least one suppository from the batch with USP Apparatus #2 at 40° C and a paddle rotation speed of 125 rpm in 0.2 M phosphate buffer at a pH of 7.5. A sinker can be coiled around the suppository, for example, for 2 to 8 turns of wire (e.g., wire helix). According to a preferred embodiment, a sinker is lightly coiled around the suppository, for example, with only 3 turns of wire helix (for example, for a suppository containing 800 mg or more mesalamine). According to another embodiment, a sinker is coiled around the suppository with 7 turns of wire helix (for example, for a suppository containing 800 mg or less mesalamine). Preferably, step (B) includes determining whether the suppository releases at least about 75 or 80% by weight of the mesalamine within 2 hours of dissolution (Q = 75% as described in USP 711 (30^{th} Ed.), the section entitled "immediate-release dosage forms"). Step (B) may additionally or alternatively include determining whether the suppository releases at least about 85% by weight of the mesalamine within 1 hour of dissolution. If the suppository does not meet the dissolution criterion, the batch of suppositories can be discarded.

Yet another embodiment is a method of preparing a mesalamine rectal suppository by preparing the suppository from mesalamine having (i) (a) a tap density ranging from about 600 to about 800 g/L and/or (b) a surface area of from about 0.1 to about 2.8 m^2/g (or preferably from about 0.2 to about 2.8 m^2/g, preferably from about 0.1 to about 1.3 m^2/g, or preferably from about 0.2 to about 1.3 m^2/g) with (ii) a suppository base, such as a hard fat, having an ascending

melting point of 32 to 35.5° C (e.g., 32 to 33.5° C). The inventors have found that the viscosity of a molten mixture containing mesalamine varies significantly depending on the tap density of the mesalamine used to form the molten mixture. A molten mixture having a high viscosity (e.g., greater than 5000 cps) has been found to have flow problems during suppository filling and caused small entrapped air bubbles to be molded into the surface of the suppository with content uniformity issues and resulting in an aesthetically less desirable product. The suppository may, for example, be prepared by (A) mixing the mesalamine having the aforementioned tap density with a suppository base having the aforementioned melting point, and (B) molding the mixture.

According to one embodiment, the mesalamine suppository is prepared by (A) melting the suppository base, e.g., to form a molten solution, (B) adding mesalamine to the melted suppository base, and (C) molding the mixture.

Yet another embodiment is a mesalamine rectal suppository comprising mesalamine particles and one or more pharmaceutically acceptable excipients, where the mesalamine particles have a surface area of from about 0.1 m^2/g to about 2.8 m^2/g (or preferably from about 0.2 to about 2.8 m^2/g). According to one embodiment, the drug load of the suppository preferably ranges from 35% to 50% (or from about 37% to about 46%). Preferably, the mesalamine particles have a tap density ranging from about 600 to about 800 g/L (as measured by USP <616>). The suppository can release at least about 75% by weight of the mesalamine within 2 hours of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5. In another embodiment, the suppository can release at least about 75% by weight of the mesalamine within 2 hours of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and from 2 to 8 sinker turns in 0.2 M phosphate buffer at a pH of 7.5. In yet another embodiment, the suppository can release at least about 75% by weight of the mesalamine within 2 hours of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 7 sinker turns in 0.2 M phosphate buffer at a pH of 7.5. In one embodiment, the surface area of from about 0.1 or 0.2 m^2/g to about 1.3 m^2/g. In another embodiment, the surface area of from about 1.3 m^2/g to about 2.8 m^2/g.

In one embodiment, the mesalamine suppository containing mesalamine particles having a surface area of from about 0.1 m^2/g (or 0.2 m^2/g) to about 2.8 m^2/g releases

(a) between 15.0% and 95.1% (w/w) of the mesalamine after 10 minutes of dissolution,

(b) at least 27.9% (w/w) of the mesalamine after 20 minutes of dissolution, and/or

(c) at least 32.5% (w/w) of the mesalamine after 30 minutes of dissolution, as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5. For example, the mesalamine suppository contains 1 g or 1.5 g mesalamine.

In another embodiment, the mesalamine suppository contains mesalamine particles having a surface area of from about 0.1 m^2/g (or 0.2 m^2/g) to about 1.3 m^2/g and releases

(a) at least 41.4% (w/w) of the mesalamine after 20 minutes of dissolution, and/or

(b) at least 62.3% (w/w) of the mesalamine after 30 minutes of dissolution, as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5. For example, the mesalamine suppository contains 1 g or 1.5 g mesalamine.

In yet another embodiment, the mesalamine suppository contains mesalamine particles having a surface area of from about 1.3 m^2/g to about 2.8 m^2/g and releases

(a) between 19.1% and 40.3% (w/w) of the mesalamine after 10 minutes of dissolution,

(b) between 27.9% and 70.7% (w/w) of the mesalamine after 20 minutes of dissolution, and/or

(c) between 32.5% and 94.8% (w/w) of the mesalamine after 30 minutes of dissolution,

as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5. For example, the mesalamine suppository contains 1 g or 1.5 g mesalamine.

Yet another embodiment is a mesalamine rectal suppository comprising from 1.1 to 2.5 g mesalamine particles and one or more pharmaceutically acceptable excipients, where the mesalamine particles have (i) a surface area of from about 0.1 m^2/g to about 2.8 m^2/g, (ii) a tap

density ranging from about 600 to about 800 g/L (as measured by USP <616>), or (iii) both. Preferably, the suppository releases at least about 85% by weight of the mesalamine within 1 hour of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5. The drug load in the suppository can be, for example, from 25% to 50% (for instance, 35% to 50%). The suppository can contain any of the aforementioned amounts of mesalamine, for instance, from about 400 mg to 3000 g of mesalamine. In one embodiment, the suppository contains about 400 to about 800 mg mesalamine. In another embodiment, the suppository contains from about 1.1 to about 2.5 g mesalamine.

The suppositories of the present invention (including all of the embodiments mentioned above) can include, for example, from about 400 or 500 mg to about 3 g of mesalamine. For instance, a suppository of the present invention can include 500 mg, 600 mg, 750 mg, 800 mg, or 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, or 2.5 g of mesalamine.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the viscosity of the molten mixtures prepared in Example 3 versus the tap densities of the mesalamine used to prepare the molten mixtures.

Figure 2 is a graph showing the viscosity of the molten mixtures prepared in Example 4 versus the tap densities of the mesalamine used to prepare the molten mixtures.

Figure 3 is a graph showing the viscosity of the molten mixtures prepared in Examples 3 and 4 versus the tap densities of the mesalamine used to prepare the molten mixtures.

Figures 4-9 show the dissolution profiles of mesalamine suppositories having drug loads of 33, 37, and 42% prepared from mesalamine having a tap density of 680 or 730 g/L and hard fat having an ascending melting point of 32 to 33.5° C (Witepsol® H-12) or 33.5 to 35.5° C (Witepsol® H-15).

Figure 10 shows the dissolution profiles of mesalamine suppositories having drug loads of 42 and 44% prepared from mesalamine having a tap density of 730 g/L and hard fat having an ascending melting point of 32 to 33.5° C (Witepsol® H-12).

Figure 11A is a graph showing the percentage of mesalamine dissolved after 30 minutes from mesalamine suppositories prepared in Example 7A at a drug load of 23% versus the surface

area of the mesalamine, where the dissolution was measured with USP Apparatus #2 at 37.3° C, a paddle rotation speed of 100 rpm, and 7 sinker turns in 0.2 M phosphate buffer at a pH of 7.5.

Figure 11B is a graph showing the percentage of mesalamine dissolved over time from mesalamine suppositories prepared in Example 7B at a drug load of 23%, where the mesalamine has various surface areas.

Figure 12 is a graph showing the percentage of mesalamine dissolved from mesalamine suppositories prepared in Example 8 at a drug load of 33% versus the surface area of the mesalamine.

Figure 13 is a graph showing the percentage of mesalamine dissolved over time from mesalamine suppositories prepared in Example 8 at a drug load of 33%, where the mesalamine particles in the suppositories have various surface areas.

Figure 14 is a graph showing the percentage of mesalamine dissolved over time from mesalamine suppositories prepared in Example 8 at a drug load of 42%, where the mesalamine particles in the suppositories have various surface areas.

Figure 15 is a graph showing the percentage of mesalamine dissolved over time from mesalamine suppositories prepared in Example 9 at a drug load of 39-42%, where the mesalamine particles in the suppositories have various surface areas.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term "mesalamine" refers to 5-aminosalicylic acid (5-ASA). According to one embodiment, the mesalamine has the following particle size distribution: X10 of about 5 to about 11 μm, X50 of about 25 to about 45 μm, and X90 of about 85 to about 100 μm.

The term "drug load" refers to the weight percentage of mesalamine based on the total weight of the suppository.

As used herein, the term "patient" refers to any mammal and preferably a human. The patient to be treated with mesalamine may in fact be any patient of the human population, male or female, which may be divided into children, adults, or elderly. Any one of these patient groups relates to an embodiment of the invention.

As used herein, the term "treating" refers to preventing or delaying the appearance of clinical symptoms of a disease or condition in a patient that may be afflicted with or predisposed to the disease or condition, but does not yet experience or display clinical or subclinical symptoms of the disease or condition. "Treating" also refers to inhibiting the disease or condition, i.e., arresting or reducing its development or at least one clinical or subclinical symptom thereof. "Treating" further refers to relieving the disease or condition, i.e., causing regression of the disease or condition or at least one of its clinical or subclinical symptoms. The benefit to a patient to be treated is either statistically significant or at least perceptible to the patient and/or the physician.

Symptoms of active ulcerative proctitis include, but are not limited to, abdominal pain, diarrhoea, rectal bleeding, sensation of incomplete emptying of the bowels, tenesmus, weight loss, fever, loss of appetite, tiredness, and other more serious complications, such as dehydration, anemia and malnutrition. A number of such symptoms are subject to quantitative analysis (e.g. weight loss, fever, anemia, etc.). Some symptoms are readily determined from a blood test (e.g. anemia).

Unless otherwise specified, tap density is measured by the USP tapped density test <616>.

Formulations

The mesalamine (e.g., in powder form) is typically dispersed in a suppository base, such as hard fat. The suppository base can be an oily or fatty base. Conventional suppository bases which may be employed include theobroma oil, hard fats, glycerides of fatty acids, glycerol-gelatin bases, and mixtures thereof. Suitable hard fat bases include, but are no limited to, esterified mixtures of mono-, di- and triglycerides which are obtained by esterification of fatty acids (European Pharmacopoeia, 3rd edition 1997, Deutscher Apotheker Verlag Stuttgart. p. 1022; The United States Pharmacopoeia, USP 23, NF18). Such hard fats are commercially available, for example, under the name Witepsol® (e.g. Witepsol® H12 and H15). A preferred suppository base is hard fat (e.g., hard fat NF).

Preferred hard fat bases include, but are not limited to, hard fats containing a mixture of mono-, di- and triglycerides of saturated C_{9-18} fatty acids. The hard fat base can comprise hard

fats obtained by esterification of fatty acids of vegetable origin with glycerol, a macrogol ether containing 20 to 24 oxyethylene groups in the polyoxyethylene chain, e.g., polyoxyl-20-cetostearyl ether, and glycerides, e.g., glyceryl ricinoleate.

Other suitable suppository bases include, but are not limited to, cocoa butter, lauric oil, beef tallow, hard fat, and any combination of any of the foregoing.

The drug load of the suppository is preferably 35 or 37% to 50%. According to one embodiment, the drug load ranges from about 37 to about 46%. According to another embodiment, the drug load ranges from about 39 to about 45%. According to yet another embodiment, the drug load ranges from about 41 to about 43%. For example, the suppository can contain about 1000 mg mesalamine dispersed in about 1300 to about 1500 mg of a suppository base (preferably hard fat).

The total weight of the suppository preferably ranges from about 2250 to about 2700 mg and more preferably from about 2250 to about 2500 mg. According to one embodiment, the suppository has a total weight ranging from about 2300 mg to about 2500 mg.

The suppository is preferably smooth torpedo-shaped.

The melting point of the suppository is generally sufficient to melt in the patient's body, and is typically no more than about 37° C.

Methods of Preparation

The mesalamine suppository of the present invention may be prepared as follows. The mesalamine is dispersed in a suppository base in molten form, which is then poured into a suitable mould, such as a PVC, polyethylene, or aluminum mould. For example, the mesalamine may be dispersed in the suppository base at a temperature of from about 35° C to about 50° C and preferably from about 40° C to about 44° C. The mesalamine can be milled or sieved prior to incorporation into the suppository base.

If desired, further pharmaceutically acceptable auxiliaries, such as, for example, stabilizers, consistency-improving additives or auxiliaries which bring about a uniform distribution of the mesalamine in the suppository base, can be added. Optionally the suppositories may be coated, prior to packing, for example with cetyl alcohol, macrogol or

polyvinyl alcohol and polysorbates to increase disintegration time or lubrication or to reduce adhesion on storage.

Preferably, the viscosity of a sample of the molten mesalamine dispersion is determined in-process for quality control. For example, the viscosity cut off may be about 5000 to about 10000 cps. According to one embodiment, batches of molten mesalamine dispersion having a viscosity of about 10000 cps or less would be considered acceptable while those having a viscosity over 10000 cps would not (and, therefore, may be discarded). According to another embodiment, batches of molten mesalamine dispersion having a viscosity of about 5000 cps or less would be considered acceptable.

The tap density of the mesalamine used to prepare the molten mesalamine dispersion is also preferably monitored before production to ensure that the tap density of the mesalamine is at least about 600 g/L and preferably from about 600 to about 800 g/L. Similarly, the surface area of the mesalamine used to prepare the molten mesalamine dispersion is preferably monitored before production to ensure that the surface area is in the desired range, e.g., between about 0.1 (or 0.2) and 2.8 m^2/g (or between about 0.1 (or 0.2) and 1.3 m^2/g, or between about 0.1 (or 0.2) to about 0.8 m^2/g, or between about 0.1 (or 0.2) to about 0.5 m^2/g, or between about 0.6 to about 1.0 m^2/g). Preferably, the mesalamine is not in the form of granules suitable for compaction into tablets. Rather, the mesalamine is preferably in the form of a powder of unagglomerated needle-shape crystals.

One or more sample suppositories from each batch produced are preferably tested by the dissolution method of the present invention for quality control. According to a preferred embodiment, a sample from each batch is tested to determine whether at least about 75 or 80% by weight of the mesalamine dissolves within 2 hours.

Methods of Treatment

The mesalamine suppository can be administered to treat ulcerative colitis, such as active ulcerative proctitis, in a patient in need thereof. Preferably, the mesalamine suppository is administered in sufficient quantity and frequency to reduce the symptoms of ulcerative colitis.

The mesalamine suppository can also be administered prophylactically to a patient at risk for ulcerative colitis (such as active ulcerative proctitis). Preferably, the mesalamine suppository

is administered in sufficient quantity and frequency to delay or prevent the onset of symptoms of ulcerative colitis (e.g., to delay or prevent the onset of abdominal pain, diarrhea, rectal bleeding, weight loss, fever, loss of appetite, dehydration, anemia, or malnutrition, or any combination thereof).

In the above methods, the mesalamine suppository is preferably administered once a day and more preferably once a day at bedtime. The suppository is also preferably retained for one to three hours or longer, if possible. The treatment can be brief, for example, once daily for three to twenty-one days, or can be longer, for example, once daily for three to six weeks.

The following examples illustrate the invention without limitation. All percentages are by weight unless otherwise indicated.

Example 1

The dissolution profiles of 1000 mg mesalamine suppositories (such as those prepared according to the procedure described below) were determined by three different methods (shown in Table 1 below using USP Apparatus #2). As discussed below, only the dissolution method of the present invention (method 2) produced consistent results.

Table 1

Parameter	Method 1	Method 2	Method 3
Phosphate buffer	0.05 M	0.2 M	0.2 M
Temperature	37° C	40° C	37° C
Paddle rotation speed	100 rpm	125 rpm	100 rpm
Sinker turns	7 turns	3 turns	3 turns
pH	7.5	7.5	7.5

Preparation of 1000 mg mesalamine suppositories

1000 mg mesalamine suppositories were prepared by the following procedure. Add 200.0 kg of hard fat NF (Witepsol® 15) to a mix tank. Begin heating the batch to 58 - 62° C by

recirculating steam through the tank jacket. The target temperature is 60° C. Begin mixing with the sweeps at 12 Hz as the product begins to melt. Continue heating to 58 - 62°C (target 60° C). Mix until the product is completely molten, increasing the sweeps to 60 Hz as the product melts. Mix for a minimum of 30 minutes, maintaining the temperature at 58 - 62° C using the hot box (target 60° C). Adjust the temperature of the batch to 40-44°C by recirculating tap water at approximately 34-40° C through the jacket. Maintain the batch at this temperature using the hot box (target 42° C). While adjusting the temperature, shut off the sweeps, install the prop mixer with one 7" x 7" blade and restart the sweeps to 60 Hz. Begin mixing with the prop at 12 Hz and adjust the sweeps to 30 Hz.

Slowly add 100.0 kg of mesalamine powder USP to the mix tank. During the addition of the powder, slowly increase the sweeps to 35 Hz and the prop to 35 Hz as the product level in the tank increases, minimizing aeration. The addition of the powder is performed over a 35 to 60 minute interval.

Mix for a minimum of 60 minutes. During the mix period, flush product through the bottom valve using a large pot. Continue flushing throughout the mixing interval until product appears visually uniform. Return the product to the mix tank.

Adjust the temperature of the batch to 43-45° C by recirculating tap water at approximately 50-55°C through the tank jacket or use the hot box, if necessary. Perform in-process sampling from the bottom valve of the tank taking approximately 600 g in a plastic beaker. Hook up the hot box and set it to hold the temperature of the batch at 43-45° C. Adjust the sweeps to 30-36 Hz and prop to 20-30 Hz to prevent aeration of the product.

Fill each mould. Remove 1 suppository per filling head (14 consecutive suppositories) every 25-35 minutes of operation. Fill weights of individual suppositories should be between 2.85 and 3.15 g.

Results

The dissolution profile of the 1000 mg mesalamine suppositories were determined by methods 1 and 2. The results are shown in Tables 2 and 3, respectively.

Table 2

Time	Sample 1	Sample 2	Sample 3
10 min	10.5	11.8	11.3
20 min	22.4	20.9	21.8
30 min	32.9	27.4	29.3
60 min	54.6	42.8	44.5
90 min	66.8	54.2	56.3
120 min	77.2	63	65.9
Average and SD (after 120 min)	68.70 % drug dissolved (SD = 7.50)		

Table 3

Time	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#12	Average	SD
60min	92.2	93	96.8	93.7	93.4	93.2	92.8	93.8	84	97.2	94.4	96.6	93.4	3.4
120min	97.3	97.6	98.1	97.9	95.5	98.6	98.1	97.9	97.9	98.1	97.9	98.4	97.8	0.8
240min	97.5	98.2	97.7	97.2	97	98.6	98.1	97.3	97.8	97.3	97.2	97.8	97.6	0.5

(SD = standard deviation)

The variability in the dissolution values after 120 minutes was significantly lower when measured by method 2 than when measured by method 1.

This low variability was further shown by dissolution tests using methods 2 and 3 performed on 1000 mg suppositories stored under normal (25° C and 60% relative humidity) and accelerated (30° C and 60% relative humidity) storage conditions. The results are provided in Tables 4 and 5, respectively, and show that method 2 provides reproducible dissolution values with minimal intra-lot and batch-to-batch variability.

Table 4

Batch 1 (23.5 months, 25°C / 60% RH)

Time	#1	#2	#3	#4	#5	#6	Average (%)	SD
60 min	97.8	96.8	98	99.2	98.2	98.6	98.1	0.8
120 min	98.7	98.9	98.5	99.2	98.3	98.2	98.6	0.4
240 min	98.3	98.5	98.1	98.6	97.5	987.7	98.1	0.4

Batch 2 (14.5 months, 25°C / 60% RH)

Time	#1	#2	#3	#4	#5	#6	Average (%)	SD
60 min	97.6	97.5	98.2	98.2	97.6	97.1	97.7	0.4
120 min	97.1	97.5	97.9	97.9	98.3	97.2	97.7	0.5
240 min	97.3	96.7	97.4	97.4	97.7	96.9	97.2	0.4

Batch 3 (4 months, 25°C / 60% RH)

Time	#1	#2	#3	#4	#5	#6	Average (%)	SD
60 min	98.5	96.7	91	92.2	96.7	98.2	95.6	3.2
120 min	98.9	98.7	94.4	98.7	98.7	98.6	98.0	1.8
240 min	98.5	98.2	96	97.3	97.7	97.8	97.6	0.9

Batch 4 (2.5 months, 25°C / 60% RH)

Time	#1	#2	#3	#4	#5	#6	Average (%)	SD
60 min	99.3	99.5	100.3	99.3	98.7	99.6	99.5	0.5
120 min	98.8	98.9	99.9	99.4	98.4	99.6	99.2	0.6
240 min	98.5	98.9	99.4	98.6	97.8	99.1	98.7	0.6

Batch 5 (4.5 months, 25°C / 60% RH)

Time	#1	#2	#3	#4	#5	#6	Average (%)	SD
60 min	100.8	101.7	101.3	101.4	101.3	101.4	101.3	0.3
120 min	100.2	101.4	100.9	101	101.1	101.8	101.1	0.5
240 min	100.2	100.5	100.5	100.5	100.8	101.1	100.6	0.3

Batch 6 (4.5 months, 25°C / 60% RH)

Time	#1	#2	#3	#4	#5	#6	Average (%)	SD
60 min	99.7	99.8	99.3	101.1	100	100.3	100.0	0.6

120 min	98.7	99.9	99.8	100.8	100.1	100.1	99.9	0.7
240 min	98.5	99.4	99.7	100.6	99.8	99.4	99.6	0.7

Batch 7 (4.5 months, 25°C / 60% RH)

Time	#1	#2	#3	#4	#5	#6	Average (%)	SD
60 min	99.7	99.9	99.2	100.5	99.4	99.6	99.7	0.5
120 min	100	99.7	99.6	100.4	99.1	99.7	99.8	0.4
240 min	99.7	99	99	99.5	98.7	98.8	99.1	0.4

Batch 8 (3.5 months, 30°C / 60% RH)

Time	#1	#2	#3	#4	#5	#6	Average (%)	SD
60 min	100.8	100.3	100.7	101	101	100.7	100.8	0.3
120 min	100.6	99.9	100.5	100.6	100.6	100.3	100.4	0.3
240 min	99.9	99.2	99.9	100	100	99.5	99.8	0.3

Batch 9 (3.5 months, 30°C / 60% RH)

Time	#1	#2	#3	#4	#5	#6	Average (%)	SD
60 min	100	99.9	100.2	99.7	99.8	99.8	99.9	0.2
120 min	99.7	99.4	100	99.4	100	99.5	99.7	0.3
240 min	99.3	98.8	99.4	99	99.2	98.9	99.1	0.2

Batch 10 (3.5 months, 30°C / 60% RH)

Time	#1	#2	#3	#4	#5	#6	Average (%)	SD
60 min	99.3	98.9	99.9	99.8	99.6	99.3	99.5	0.4
120 min	99.6	98.7	99.1	99.6	99.1	99.7	99.3	0.4
240 min	99.1	98.4	98.6	99.2	98.7	99.1	98.9	0.3

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Table 5

Batch number and storage conditions	Sample No. (within batch) (samples taken at 120 min)						Average	SD
	1	2	3	4	5	6		
11 6 months at 25°C / 60% RH	101.5	102.4	102.5	101.5	100.9	100.6	101.6	0.8

Batch number and storage conditions	Sample No. (within batch) (samples taken at 120 min)						Average	SD
	1	2	3	4	5	6		
12 6 months at 25°C / 60% RH	101.3	100.3	101.3	102.3	100.3	100.0	100.9	0.9
13 6 months at 25°C / 60% RH	100.4	99.7	98.6	100.3	98.8	99.8	99.6	0.8
14 25 months at 25°C / 60% RH	98.2	99.3	98.9	97.2	99.1	98.8	98.6	0.8
15 16 months at 25°C / 60% RH	92.4	98.4	97.6	97.3	96.7	92.0	95.7	2.8
16 5 months at 25°C / 60% RH	98.4	96.4	95.5	96.8	99.6	96.9	97.3	1.5
17 23 months at 25°C / 60% RH	99	98	97	100	99	81	95.7	7.3
18 23 months at 25°C / 60% RH	101	103	100	103	100	102	101.5	1.4
19 20 months at 25°C / 60% RH	101	102	101	103	100	102	101.5	1.0
20 6 months at 30°C / 60% RH	97	102	97	95	99	96	97.7	2.5
21 6 months at 30°C / 60% RH	94	94	72	81	91	106	89.7	11.8
22 6 months at 30°C / 60% RH	85	92	93	89	94	75	88.0	7.2
23 6 months at 30°C / 60% RH	85	90	97	91	96	85	90.7	5.2
24 6 months at 30°C / 60% RH	75	50	66	72	61	40	60.7	13.4

Batch number and storage conditions	Sample No. (within batch) (samples taken at 120 min)						Average	SD
	1	2	3	4	5	6		
25 6 months at 30°C / 60% RH	73	97	60	89	87	81	81.2	13.1

Samples from the three batches exhibiting the highest variability when measured according to method 3, i.e., batches 21, 24 and 25, were tested by method 2 for comparison. The results are shown in Table 6.

Table 6

Batch	Sample No. (within batch) (samples taken at 120 min)						Average	SD
	1	2	3	4	5	6		
21	100	100	100	100	101	101	100.3	0.52
24	101	101	101	101	101	102	101.2	0.41
25	100	100	101	100	99	100	100.0	0.63

These results show that method 2 produced more reliable and less variable dissolution results than method 3.

Example 2

The dissolution profiles of the 1000 mg mesalamine suppositories prepared in Example 1 were determined according to method 1 described in Example 1.

The results are shown in Table 7 below.

Table 7

1000 mg suppository
At 120 min, Average: 73% + 10.3 (SD) Range: 54.8% -97.1%

Example 3

The following experiment was conducted to determine if the tap density of the mesalamine powder starting material significantly affected the viscosity of the molten mixture used to form the suppository. Generally, a molten mixture having a viscosity greater than about 5000 to about 10000 cps was found to have flow problems during suppository filling and caused small entrapped air bubbles to be molded into the surface of the suppository with content uniformity issues and resulting in an aesthetically less desirable product.

The tap density of several lots of mesalamine were determined by USP tapped density test <616> and are shown in Table 8 below.

Table 8

Mesalamine Lot	Tapped Density (g/ml)
A	0.81
B	0.72
C	0.68
D	0.39
E	0.68
F	0.46
G	0.60

Molten mixtures were prepared by the procedure described in Example 1 using mesalamine lots A, B, and E. The molten mixtures had the viscosities reported in Table 9 below.

Table 9

Molten Mixture Lot No.	Mesalmine Lot	Mesalamine Tap Density (g/ml)	Viscosity (cps)
1	A	0.81	429
2	B	0.72	468
3	E	0.68	1010

Molten mixtures prepared from combinations of mesalamine lots C-G were prepared and had the viscosities reported in Table 10 below. The individual tap densities of each mesalamine lot were used to calculate a composite tapped density (CTD) based on the amount of each lot. The calculated CTD can be expressed by the following equation:

$$(CDF)_1 + (CDF)_2 + \ldots\ldots (CDF)_n = CTD$$

where CTD = composite tapped density; CDF = contributed density factor = % of total drug used/100 x TD; TD = measured tapped density; and n = number of drug lots used.

Table 10

Molten Mixture Lot No.	Mesalamine Lot	Measlamine used (Kg)	TD (g/ml)	CTD (g/ml)	Viscosity (cps)
4	C	82.5	0.68		
	D	17.5	0.37	0.62	1680
5	D	61.0	0.37		
	E	17.0	0.68		
	F	22.0	0.46	0.44*	13300
6	G	100.0	0.60	0.60	1730

* Note: Accuracy of the CTD of the 3 mesalamine lots used was confirmed by measuring the tap density of a separate mesalamine powder blend at the same ratio. The result was 0.43 g/ml compared to 0.44 g/ml.

The density-viscosity data from Tables 9 and 10 were combined and plotted (Figure 1) to assess the correlation for these two parameters. These data show a definite rank-order inverse relationship, with a correlation coefficient of 0.9743. Notably, a reduction in the CTD from 0.60

g/ml to 0.44 g/ml resulted in a 7 fold increase in viscosity from 1730 cps to 13300 cps (see molten mixture lot nos. 5 and 6 in Table 10).

Example 4

The procedure described in Example 3 was repeated with mesalamine lot nos. 1-8 shown in Table 11 below. The results are shown in Table 11 and Figure 2. From the correlation curve in Figure 2, a viscosity of 5000 cps corresponds to a tap density of about 0.50 g/ml.

Table 11

Mesalamine Lot No.	Tap Density (g/ml)	Viscosity (cps)
1	0.45	13845
2	0.53	1755
3	0.44	19500
4	0.36	37100
5	0.40	47500
6	0.40	26910
7	0.36	37830
8	0.37	33735

The correlation of density to viscosity is essentially rank-order and demonstrates an inverse relationship of the two parameters (correlation coefficient = 0.8803).

The tap density and viscosity data from Examples 3 and 4 (Tables 9-11) were combined and are shown graphically in Figure 3. The combined data clearly show the strong correlation (correlation coefficient = 0.9343) between the tap density of mesalamine powder and its effect on the in-process viscosity of the drug-hard fat dispersions.

Example 5

1 g mesalamine suppositories using Witepsol® H-15 or Witepsol® H-12 (hard fat NF) as the suppository base were prepared by the procedure described in Example 1 at drug loads of 33, 37, 42, and 44%. All the suppositories released at least 75% by weight of the mesalamine contained in the suppository within 2 hours of dissolution as measured with USP Apparatus #2 at

40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5 (method #2 of Table #1).

Figures 4 and 5 show the dissolution profiles of mesalamine suppositories having drug loads of 33, 37, and 42% prepared from mesalamine having a tap density of 680 g/L and Witepsol® H-15.

Figure 6 shows the dissolution profiles of mesalamine suppositories having drug loads of 33, 37, and 42% prepared from mesalamine from Supplier 2, Grade B, having a tap density of 730 g/L and Witepsol® H-15.

The in-process molten mixtures of mesalamine and hard fat used in the preparation of the suppositories described above with respect to figures 4 to 6 had the viscosities reported in Table 12 below. Suppositories could not be made from Grades C and D from supplier 2. Grades C and D were designed for compression of the mesalamine into tablets and were found to be unsuitable for the preparation of a suspension in hard fat as required for the preparation of the suppository.

Table 12

Source	Tap Density g/L	Drug Load (% w/w)	Dispersion Viscosity (Cps)
Supplier 1	0.68	33	694
		37	1131
		42	2512
Supplier 2, grade A	0.68	33	595
		37	1084
		42	2553
Supplier 2, grade B	0.73	33	515
		37	845
		42	1911
Supplier 2, grade C	0.58	33	Too Viscous
Supplier 2, grade D	0.91	33	Poor Dispersion

Figure 7 shows the dissolution profiles of mesalamine suppositories having a drug load of 42% prepared from mesalamine having a tap density of 680 g/L (supplied by Suppliers 1 and 2) or 730 g/L (Supplier 2, grade B) and Witepsol® H-15.

Figure 8 shows the dissolution profiles of mesalamine suppositories having drug loads of 33% and 42% prepared from mesalamine having a tap density of 680 g/L from supplier 1 and Witepsol® H-12 (ascending melting point of 32 to 33.5° C) or Witepsol® H-15 (ascending melting point of 33.5 to 35.5° C). It also compares suppositories having drug loads of 42% prepared with a mesalamine from supplier 2 having a tap density of 730g/ml manufactured using Witepsol® H-12 (ascending melting point of 32 to 33.5° C).

Figure 9 shows the dissolution profiles of mesalamine suppositories having a drug load of 42% prepared from mesalamine having a tap density of 680 g/L (Supplier 1) or 730 g/L (Supplier 2, grade B) and Witepsol® H-12 or Witepsol® H-15.

Figure 10 shows the dissolution profiles of mesalamine suppositories from a larger scale batch having drug loads of 42 and 44% prepared from mesalamine having a tap density of 730 g/L (Supplier 2, grade B) and Witepsol® H-12.

Example 6

High Density 1000 mg Mesalamine Suppositories

1 g mesalamine suppositories, each containing 1000 mg mesalamine (USP) and 1381 mg Witepsol® H-12 (hard fat NF), were prepared according to the following procedure.

The hard fat (Witepsol® H-12, 65.25 kg) is melted by charging it into a kettle, which is operated in automatic mode with a tank temperature of 75° C, a melting temperature of 60° C, a cooling water temperature of 48° C, a cooling air temperature of 44° C, a holding a T melting of 45 minutes, a mixing at T melting of 15 minutes, and a holding at 256 rpm for 60 minutes. When the temperature reaches 40-44° C, the mixing speed is between 60-80 rpm, and the water heating tank temperature is 71-79° C, the mesalamine from Supplier 2, grade B is slowly added over a period of 50 to 70 minutes with constant mixing at 230-270 rpm. The suspension is then mixed for 55 to 65 minutes (set point of 60 minutes) at 230-270 rpm. After the mixing time, the mixing speed is adjusted to 168-180 rpm (set point of 175 rpm).

Moulds are then filled, each mould containing 2.33-244 g of the suspension. The moulds are then cooled for 5 to 10 minutes at 20° C.

1 g suppositories heat sealed in PVC/PE containers (2.3 mL capacity per cavity) were stored for at 25 ± 2° C and 60 ± 5% relative humidity for 3 months.. The suppositories were

found to be stable and release at least 80% by weight of the mesalamine contained in the suppository within 2 hours of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5.

Example 7A

Suppositories containing 500 mg mesalamine having various surface areas, at a drug load of 23% were prepared by the procedure described in Example 1 using appropriate mixing speeds. The surface area of the mesalamine ranged from 0.395 to 2.799 m^2/g. The percentage of mesalamine dissolved at 30 minutes was measured with USP Apparatus #2 at 37.3° C, a paddle rotation speed of 100 rpm, and 7 sinker turns in 0.2 M phosphate buffer at a pH of 7.5. The results are shown in Figure 11A.

Example 7B

The percentage of mesalamine released over time was also measured for each suppository, where the dissolution was measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 7 sinker turns in 0.2 M phosphate buffer at a pH of 7.5. The results are shown in Figure 11B.

Example 8

Suppositories containing 1000 mg mesalamine having various surface areas and Witepsol® H-15 (hard fat NF), at a drug load of 33% were prepared by the procedure described in Example 1. The surface area of the mesalamine ranged from 0.268 to 2.799 m^2/g. The percentage of mesalamine dissolved at 30 minutes was measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5. The results are shown in Figure 12.

The percentage of mesalamine released after 10, 20, and 30 minutes was also measured for each suppository. The results are shown in Figure 13.

Suppositories containing mesalamine having various surface areas and Witepsol® H-12 (hard fat NF), at a drug load of 42% were prepared by the procedure described in Example 1. The surface area of the mesalamine used was 0.365, 0.731, or 1.393 m^2/g. The percentage of mesalamine released over time was measured for each suppository. The results are shown in Figure 14.

The tables below shows the minimum and maximum percentage of mesalamine dissolved as a function of surface area. The data presented in the tables originated from the 33% and 42% suppositories.

Surface area (m^2/g)	# batch	Minimum percentage of mesalamine dissolved after 10min	Minimum percentage of mesalamine dissolved after 20min	Minimum percentage of mesalamine dissolved after 30min
1.3<x<2.8	4	26%	40%	52%
0.1<x<1.3	18	36%	59%	75%

Surface area (m^2/g)	# batch	Maximum percentage of mesalamine dissolved after 10min	Maximum percentage of mesalamine dissolved after 20min	Maximum percentage of mesalamine dissolved after 30min
1.3<x<2.8	4	35%	59%	78%
0.1<x<1.3	18	77%	99%	105%

The following tables present the minimum specification based on the average value of mesalamine dissolved in the specified surface area range and the maximum specification based on the average value of mesalamine dissolved in the specified surface area range. The data presented in the tables originated from the 33% and 42% suppositories.

Surface area (m^2/g)	# batch	Minimum percentage of mesalamine dissolved after 10min	Minimum percentage of mesalamine dissolved after 20min	Minimum percentage of mesalamine dissolved after 30min
1.3<x<2.8	4	19.1%	27.9%	32.5%
0.1<x<1.3	18	15.0%	41.4%	62.3%

Surface area (m^2/g)	# batch	Maximum percentage of mesalamine dissolved after 10min	Maximum percentage of mesalamine dissolved after 20min	Maximum percentage of mesalamine dissolved after 30min
1.3<x<2.8	4	40.3%	70.7%	94.8%
0.1<x<1.3	18	95.1%	111.5%	117.0%

The tables above as well as Figures 12-14 show that the dissolution rate of the mesalamine in suppositories with a drug load of 33 and 42% is increasing with decreasing surface area. These results are contrary to the general scientific understanding that greater surface area leads to a faster dissolution by increasing the wetability and the surface contact with the dissolution medium.

Example 9

Suppositories containing between 746 and 1460 mg mesalamine having various surface areas (ranging from 0.395 to 2.799 m^2/g) and Witepsol® H-12 (hard fat NF) (a drug load of 39-42%) were prepared by the procedure described in Example 1, adjusted appropriately for the batch size and apparatus used. Moulds were filled with each mould containing around 3.5 g of the prepared suspension.

The percentage of mesalamine released after 10, 20, and 30 minutes was measured for each suppository. The results are shown in Figure 15.

All non-patent references, patents and patent applications cited and discussed in this specification are incorporated herein by reference in their entirety and to the same extent as if each was individually incorporated by reference.

CLAIMS

We claim:

1. A mesalamine rectal suppository comprising from about 400 to about 1600 mg mesalamine and one or more pharmaceutically acceptable excipients, wherein the mesalamine has a tap density ranging from about 600 to about 800 g/L (as measured by USP <616>), the drug load of the suppository ranges from 35% to 50%, and the suppository releases at least about 75% by weight of the mesalamine within 2 hours of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5.

2. The mesalamine suppository of claim 1, wherein the amount of mesalamine ranges from about 1450 to about 1550 mg.

3. The mesalamine suppository of claim 1, wherein at least one pharmaceutically acceptable excipient has an ascending melting point ranging from 32 to 33.5° C.

4. The mesalamine suppository of claim 3, wherein the pharmaceutically acceptable excipient having an ascending melting point ranging from 32 to 33.5° C is an oily or fatty base.

5. The mesalamine suppository of claim 1, wherein at least one pharmaceutically acceptable excipient is an oily or fatty base having an ascending melting point from 33 to 35.5 ° C.

6. The mesalamine suppository of claim 4, the oily or fatty base is hard fat.

7. The mesalamine suppository of claim 5, the oily or fatty base is hard fat.

8. The mesalamine suppository of claim 1, wherein the drug load ranges from about 39 to about 45%.

9. The mesalamine suppository of claim 8, wherein the drug load ranges from about 41 to about 43%.

10. The mesalamine suppository of claim 1, wherein the suppository releases at least about 80% by weight of the mesalamine within 2 hours of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5.

11. The mesalamine suppository of claim 1, wherein the suppository releases at least about 80% by weight of the mesalamine within 1 hour of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5.

12. The mesalamine suppository of claim 1, wherein the suppository releases at least 90% by weight of the mesalamine within 30 minutes of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5.

13. A method of treating active ulcerative proctitis in a patient in need thereof comprising administering the mesalamine rectal suppository of claim 1 to the patient.

14. The method of claim 13, wherein the mesalamine rectal suppository is administered once a day.

15. The method of claim 14, wherein the mesalamine rectal suppository is administered once a day at bedtime.

16. A mesalamine rectal suppository comprising from about 950 to about 1600 mg mesalamine and one or more pharmaceutically acceptable excipients, wherein the mesalamine has a tap density ranging from about 600 to about 800 g/L (as measured by USP <616>), and the suppository releases at least about 75% by weight of the mesalamine within 2 hours of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5.

17. The mesalamine rectal suppository of claim 16, wherein at least one pharmaceutically acceptable excipient is a fatty base.

18. The mesalamine rectal suppository of claim 16, wherein the amount of mesalamine ranges from about 1450 to about 1550 mg.

19. The mesalamine rectal suppository of claim 16, wherein the amount of mesalamine is about 1500 mg.

20. A mesalamine rectal suppository comprising from about 950 to about 1600 mg mesalamine and one or more pharmaceutically acceptable excipients, wherein the drug load of the suppository ranges from 35% to 46%, and the suppository releases at least about 75% by weight of the mesalamine within 2 hours of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5.

21. A mesalamine rectal suppository comprising mesalamine particles and one or more pharmaceutically acceptable excipients, wherein the mesalamine particles have a surface area of from about 0.1 m^2/g to about 2.8 m^2/g, the drug load of the suppository ranges from 35% to 50%, and the suppository releases at least about 85% by weight of the mesalamine within 1 hour of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5.

22. The mesalamine rectal suppository of claim 21, wherein the mesalamine particles have a surface area of from about 0.1 m^2/g to about 1.3 m^2/g.

23. The mesalamine rectal suppository of claim 21, wherein the suppository comprises about 500 mg mesalamine.

24. The mesalamine rectal suppository of claim 21, wherein the suppository comprises about 1 g mesalamine.

25. The mesalamine rectal suppository of claim 21, wherein the suppository comprises about 1.5 g mesalamine.

26. The mesalamine suppository of claim 21, wherein at least one pharmaceutically acceptable excipient has an ascending melting point ranging from 32 to 33.5° C.

27. The mesalamine suppository of claim 26, wherein the pharmaceutically acceptable excipient having an ascending melting point ranging from 32 to 33.5° C is an oily or fatty base.

28. The mesalamine suppository of claim 21, wherein at least one pharmaceutically acceptable excipient is an oily or fatty base having an ascending melting point from 33 to 35.5 ° C.

29. The mesalamine suppository of claim 27, the oily or fatty base is hard fat.

30. The mesalamine suppository of claim 28, the oily or fatty base is hard fat.

31. The mesalamine suppository of claim 21, wherein the drug load ranges from about 39 to about 45%.

32. The mesalamine suppository of claim 31, wherein the drug load ranges from about 41 to about 43%.

33. The mesalamine suppository of claim 21, wherein the suppository releases at least 90% by weight of the mesalamine within 30 minutes of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5.

34. The mesalamine rectal suppository of claim 22, wherein the suppository releases

(a) at least 41.4% (w/w) of the mesalamine after 20 minutes of dissolution, and

(b) at least 62.3% (w/w) of the mesalamine after 30 minutes of dissolution,

as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5.

35. A method of treating active ulcerative proctitis in a patient in need thereof comprising administering the mesalamine rectal suppository of claim 21 to the patient.

36. A mesalamine rectal suppository comprising mesalamine particles and one or more pharmaceutically acceptable excipients, wherein the mesalamine particles have a surface area of from about 0.1 m^2/g to about 2.8 m^2/g, the drug load of the suppository ranges from 35% to 50%, and the suppository releases

(a) between 15.0% and 95.1% (w/w) of the mesalamine after 10 minutes of dissolution,

(b) at least 27.9% (w/w) of the mesalamine after 20 minutes of dissolution, and

(c) at least 32.5% (w/w) of the mesalamine after 30 minutes of dissolution,

as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5.

37. The mesalamine rectal suppository of claim 36, wherein the surface area of the mesalamine particles ranges from about 1.3 m^2/g to about 2.8 m^2/g.

38. The mesalamine rectal suppository of claim 37, wherein the suppository releases

(a) between 19.1% and 40.3% (w/w) of the mesalamine after 10 minutes of dissolution,

(b) between 27.9% and 70.7% (w/w) of the mesalamine after 20 minutes of dissolution, and

(c) between 32.5% and 94.8% (w/w) of the mesalamine after 30 minutes of dissolution,

as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5.

39. A mesalamine rectal suppository comprising mesalamine particles and one or more pharmaceutically acceptable excipients, wherein the mesalamine particles have a surface area of from about 0.1 m^2/g to about 2.8 m^2/g and a tap density ranging from about 600 to about 800 g/L (as measured by USP <616>), and the suppository releases at least about 85% by weight of the mesalamine within 1 hour of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5.

40. The mesalamine rectal suppository of claim 39, wherein the surface area of the mesalamine particles ranges from about 0.1 m^2/g to about 1.3 m^2/g.

41. The mesalamine rectal suppository of claim 39, wherein the drug load of the suppository ranges from 35% to 50%.

42. The mesalamine rectal suppository of claim 39, wherein the suppository comprises about 500 mg mesalamine.

43. The mesalamine rectal suppository of claim 39, wherein the suppository comprises about 1 g mesalamine.

44. The mesalamine rectal suppository of claim 39, wherein the suppository comprises about 1.5 g mesalamine.

45. A mesalamine rectal suppository comprising from 1.1 to 2.5 g mesalamine particles and one or more pharmaceutically acceptable excipients, wherein the mesalamine particles have (i) a surface area of from about 0.1 m^2/g to about 2.8 m^2/g, (ii) a tap density ranging from about 600 to about 800 g/L (as measured by USP <616>), or (iii) both, and the suppository releases at least about 85% by weight of the mesalamine within 1 hour of dissolution as measured with USP

Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5.

46. A mesalamine rectal suppository comprising mesalamine particles and one or more pharmaceutically acceptable excipients, wherein the mesalamine particles have (i) a surface area of from about 0.1 m^2/g to about 2.8 m^2/g, (ii) a tap density ranging from about 600 to about 800 g/L (as measured by USP <616>), or (iii) both, the drug load of the suppository ranges from 25% to 50%, and the suppository releases at least about 85% by weight of the mesalamine within 1 hour of dissolution as measured with USP Apparatus #2 at 40° C, a paddle rotation speed of 125 rpm, and 3 sinker turns in 0.2 M phosphate buffer at a pH of 7.5.

47. The mesalamine rectal suppository of claim 46, wherein the suppository comprises about 400 to about 800 mg mesalamine.