



(51) International Patent Classification:

A61K 31/5375 (2006.01) A61K 9/06 (2006.01)
A61K 31/137 (2006.01) A61K 9/08 (2006.01)
A61K 9/70 (2006.01)

(21) International Application Number:

PCT/US2016/049304

(22) International Filing Date:

29 August 2016 (29.08.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/211,525 28 August 2015 (28.08.2015) US
62/284,788 9 October 2015 (09.10.2015) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: HEMORRHOID PREPARATION AND SHEETS

Manufacture of Hemorrhoid Composition

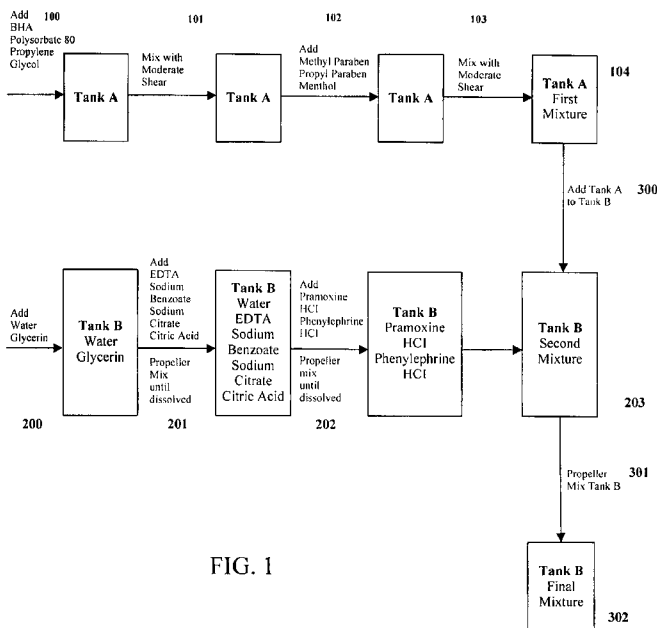


FIG. 1

(57) Abstract: A pharmaceutical composition for the treatment of hemorrhoids, sheets, methods of making and using the same.



BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present invention relates to pharmaceutical compositions for the treatment of hemorrhoids, sheets for applying the composition, methods of making and using the same.

Description of the Related Art

[0002] Hemorrhoids are swollen veins in the anal canal. Veins can swell inside the anal canal to form internal hemorrhoids or near the opening of the anus to form external hemorrhoids. Patients may have both. Excess pressure on the veins in the pelvic and rectal area can cause hemorrhoids. Normally, tissue inside the anus fills with blood to help control bowel movements. Increased pressure during bowel movements can cause the veins in this tissue to swell and stretch leading to hemorrhoids. Diarrhea or constipation also may lead to straining and can increase pressure on veins in the anal canal. Pregnant women can get hemorrhoids during the last 6 months of pregnancy because of increased pressure on the blood vessels in the pelvic area. Straining during labor can make hemorrhoids worse. Being overweight can also lead to hemorrhoids. WebMD Hemorrhoids Guide (2015).

[0003] Common symptoms of both internal and external hemorrhoids include: bleeding during bowel movements, discomfort, skin irritation, itching, rectal pain. Internal hemorrhoids often are small, swollen veins in the wall of the anal canal. External hemorrhoids can get irritated and clot under the skin, causing a hard painful lump called a thrombosed, or clotted, hemorrhoid.

[0004] Current medicines that can help relieve symptoms of hemorrhoids include ointments, wipes, suppositories, and nonprescription pain relievers. WebMD Hemorrhoids Guide (2015).

[0005] Ointments that protect the skin, such as zinc oxide or petroleum jelly, can prevent further injury and reduce itching by forming a barrier over hemorrhoids. Medicated ointments may contain 1% or 2.5% hydrocortisone that may relieve inflammation and itching. Other products contain a local anesthetic that numbs the anal region for relief of pain associated with hemorrhoids. WebMD Hemorrhoids Guide (2015).

[0006] Suppositories, Preparation H® or Tucks® (formerly Anusol), may last for 7 to 10 days to relieve irritation and to lubricate the anal canal during bowel movements. Some of these products contain substances that can harm anal tissues if they are used for too long. WebMD Hemorrhoids Guide (2015).

pain. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) such as Motrin® (ibuprofen) and Aleve® (naproxen) can offer patients relief from pain and swelling. WebMD Hemorrhoids Guide (2015).

[0008] Commercially-available products for the treatment of hemorrhoids include Preparation H® Wipes which have 50% Witch Hazel (astringent) as an active ingredient and aloe barbadensis leaf juice, anhydrous citric acid, capryl/capramidopropyl betaine, diazolidinyl urea, glycerin, methyl paraben, propylene glycol, propyl paraben, purified water, and sodium citrate as inactive ingredients. Similarly, Preparation H® Medicated Wipes for Women which have 20% Witch Hazel (astringent) as an active ingredient and aloe barbadensis leaf juice, anhydrous citric acid, capryl/capramidopropyl betaine, chamomilla recutita (matricaria) flower extract, cucumis sativus (cucumber) fruit extract, diazolidinyl urea, dipropylene glycol, DMDM hydantoin, edetate disodium, fragrance, glycerin, methylisothiazolinone, methyl paraben, PEG-75 shea butter glycerides, phenoxyethanol, polysorbate 20 (Polyoxyethylene (20) sorbitan monolaurate), propylene glycol, propyl paraben, purified water, sodium citrate, and vitamin E acetate as inactive ingredients. Preparation H® Maximum Strength Pain Relief Cream which comprises 14.4% glycerin, 0.25% phenylephrine HCl, 1% pramoxine HCl, and 15% white petrolatum. Preparation H® Wipes; Preparation H® Medicated Wipes for Women; and Preparation H® Maximum Strength Pain Relief Cream product information (2015).

[0009] Tucks® Medicated Cooling pads comprise 50% Witch Hazel (astringent) as an active ingredient and water, glycerin, alcohol, propylene glycol, sodium citrate, diazolidinyl urea, citric acid, methyl paraben, and propyl paraben as inactive ingredients. Tucks® Medicated Cooling pads product information (2015).

[0010] Nelsons Medicated Wipes comprise *Aesculus Hippocastanum* - 6 C, *Calendula Officinalis* - 6 C, *Collinsonia Canadensis* - 6 C, *Hamamelis Virginiana* - 6 C, *Paeonia Officinalis* - 6 C as active ingredients and aloe vera, butylparaben, citric acid, diazolidinyl urea, disodium cocoamphodiacetate, ethylparaben, glycerin, isobutylparaben, methyl paraben, phenoxyethanol, polysorbate 20, propylene glycol, propyl paraben, purified water, sodium hydroxide, and tocopherol as inactive ingredients. Nelsons Medicated Wipes product information (2015).

[0011] CVS® Maximum Strength Formula Medicated wipes comprise 50% Witch Hazel (astringent) as an active ingredient and aloe barbadensis leaf juice, 2-bromo-2-nitropropane-1,3-

lanolin, propylene glycol, sodium citrate, and water as inactive ingredients. CVS Pharmacy website (2015).

[0012] Walgreens® Pre-Moistened Medicated Wipes comprise 50% Witch Hazel (astringent) as an active ingredient and alcohol, citric acid, glycerin, phenoxyethanol, potassium sorbate, purified water, and sodium citrate as inactive ingredients. Walgreens Website (2015).

[0013] The commercially available preparations may not provide sufficient relief to patients with hemorrhoids. Accordingly, there is a need in the art for an improved hemorrhoid treatment preparation.

BRIEF SUMMARY OF THE INVENTION

[0014] In numerous embodiments, this invention provides a pharmaceutical composition comprising an analgesic, vasoconstrictor, emollient, and cooling agent.

[0015] In one embodiment, the analgesic may be pramoxine hydrochloride, benzocaine; benzyl alcohol, dibucaine, dibucaine hydrochloride, dyclonine hydrochloride, lidocaine, pramoxine hydrochloride, tetracaine, tetracaine hydrochloride, or a mixture thereof.

[0016] In most embodiments of this invention, the analgesic is pramoxine hydrochloride. In numerous embodiments of this invention, the analgesic may be in an amount of about 0.5% to about 2.0% by weight of the composition. In various embodiments of this invention, the analgesic may be in an amount of about 0.75%, 1.0%, 1.25%, or 1.50% by weight of the composition. In most embodiments of this invention, the analgesic may be benzocaine at about 5 to 20 percent by weight; benzyl alcohol at about 1 to 4% by weight; dibucaine at about 0.25 to 1% by weight; dibucaine hydrochloride at about 0.25 to 1% by weight; dyclonine hydrochloride at about 0.5 to 1% by weight; lidocaine at about 2 to 5% by weight; pramoxine hydrochloride at about 1% by weight; tetracaine at about 0.5 to 1% by weight; tetracaine hydrochloride at about 0.5 to 1%; or a mixture thereof.

[0017] The compositions of this invention may comprise water as a solvent.

[0018] In most embodiments of this invention, the composition may comprise mixtures of water, glycerin, propylene glycol, and/or low molecular weight polyethylene glycols (PEGs) as a solvent. In many embodiments, the composition may comprise about 10–40% glycerin by weight, preferably 10%, 15%, 20%, 25%, 30%, 35%, or 40% glycerin by weight, more

about 1–10% propylene glycol by weight, preferably about 1%, 1.5%, 2%, 2.5%, 3%, 5%, 6%, 7%, 8%, 9%, or 10% propylene glycol by weight, more preferably about 2% propylene glycol by weight. In particular embodiments, the composition may comprise about 1–5% polyethylene glycol by weight, preferably about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, or 5% polyethylene glycol by weight, more preferably about 2% polyethylene glycol by weight.

[0019] In some embodiments, the said polyethylene glycol may have an average molecular weight of 100–600. In many embodiments, the polyethylene glycol may be PEG100, PEG200, PEG300, PEG400, PEG 500, PEG600 or a mixture thereof. In many embodiments, the polyethylene glycol may be PEG400, PEG600, or a mixture thereof. In many embodiments, the composition may comprise a mixture of water:propylene glycol:PEG in a ratio of 1:1:1 to 3:2:1. In many embodiments, the composition may comprise a mixture of water:propylene glycol:PEG100 in a ratio of 1:1:1. In many embodiments, the composition may comprise a mixture of water:propylene glycol:PEG600 in a ratio of 3:2:1.

[0020] In particular embodiments, the solvent may be in an amount of about 70% to about 90% by weight of the composition. In particular embodiments, the solvent may be in an amount of about 71%, 72%, 73%, 74%, or 75% by weight of the composition.

[0021] In most embodiments of this invention, the vasoconstrictor may be ephedrine sulfate, epinephrine, epinephrine hydrochloride, phenylephrine hydrochloride, or a mixture thereof. In particular embodiments, the vasoconstrictor may be phenylephrine hydrochloride. In many embodiments, the vasoconstrictor may be in an amount of about 0.005% to about 1.25% by weight of the composition. In particular embodiments, the vasoconstrictor may be in an amount of about 0.20%, 0.25%, 0.30%, or 0.35% by weight of the composition. In particular embodiments, the vasoconstrictor may be an amount of about 0.1 to 1.25% by weight. In particular embodiments, the vasoconstrictor may be ephedrine sulfate at about 0.1 to 1.25% by weight; epinephrine at about 0.005 to 0.01% by weight; epinephrine hydrochloride at about 0.005 to 0.01% by weight; phenylephrine hydrochloride at about 0.25%; or a mixture thereof. In another embodiment, the vasoconstrictor may be epinephrine in an amount of about 0.10% to about 0.50% by weight of the composition.

[0022] In many embodiments, the emollient may be glycerin, propylene glycol, dipropylene glycol, hexylene glycol, butylene glycol, or a combination thereof. In many embodiments, the

many embodiments, the emollient may be in an amount of about 1.0% to about 40% by weight of the composition. In particular embodiments, the emollient may be in an amount of about 2.0%, 5.0%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% by weight of the composition.

[0023] In many embodiments, the composition may comprise a surfactant which is preferably a nonionic surfactant. In many embodiments, the nonionic surfactant may be ethoxylated castor oil, Polysorbate 20, Polysorbate 60, Polysorbate 80, or a combination thereof. In many embodiments, the composition may comprise a surfactant which is Polysorbate 80 (polyethylene glycol sorbitan monooleate).

[0024] In many embodiments, the surfactant may be in an amount of about 0.5% to about 5% by weight of the composition. In particular embodiments, the surfactant may be in an amount of about 1.0%, 1.5%, 2.0%, 3.0%, 3.5%, or 5.0% by weight of the composition.

[0025] In many embodiments, the cooling agent may be menthol, eucalyptol, camphor, juniper tar, or a combination thereof. In many embodiments, the cooling agent may be menthol. In many embodiments, the cooling agent may be in an amount of about 0.05% to about 0.1% by weight of the composition. In particular embodiments, the cooling agent may be in an amount of about 0.05%, 0.06%, 0.07%, 0.08%, or 0.09% by weight of the composition.

[0026] In many embodiments, the composition may further comprise an antioxidant, acidulant, preservative, chelating agent, or a combination thereof.

[0027] In many embodiments, the antioxidant may comprise butylated hydroxyanisole, butylated hydroxyl toluene, propyl gallate, or a combination thereof. In many embodiments, the antioxidant may be in an amount about 0.01% to about 0.10% by weight of composition. In particular embodiments, the antioxidant may be in an amount about 0.03%, 0.04%, 0.05%, 0.06%, or 0.07% by weight of composition.

[0028] In many embodiments, the acidulant may be sodium citrate, citric acid, or a combination thereof. In many embodiments, the acidulant may be in an amount about 0.10% to about 0.50% by weight of composition. In particular embodiments, the acidulant may be in an amount about 0.20%, 0.25%, 0.30%, 0.35%, or 0.40% by weight of composition.

[0029] In many embodiments, the preservative may be sodium benzoate, methyl paraben, propyl paraben, or a combination thereof. In many embodiments, the preservative may be in an amount about 0.01% to about 0.25% by weight of composition. In particular embodiments, the

0.18%, 0.20%, or 0.25% by weight of composition.

[0030] In many embodiments, the chelating agent may be disodium EDTA. In many embodiments, the chelating agent may be in an amount about 0.05% to about 0.20% by weight of composition. In particular embodiments, the chelating agent may be in an amount about 0.08%, 0.09%, 0.10%, 0.11%, 0.12%, or 0.13% by weight of composition.

[0031] In many embodiments of the method of this invention, the pharmaceutical composition described herein will not contain petrolatum.

[0032] In many embodiments of the method of this invention, the pharmaceutical composition described herein will not contain witch hazel.

[0033] In many embodiments of the method of this invention, the pharmaceutical composition described herein will not contain cetyl alcohol.

[0034] In many embodiments of the method of this invention, the pharmaceutical composition described herein may be formulated as a suspension.

[0035] In a further embodiment, the invention provides for a pharmaceutical composition comprising a solvent, emollient, analgesic, vasoconstrictor, antioxidant, acidulant, surfactant, preservative, chelating agent, and a cooling agent/penetrating agent. In another embodiment, the pharmaceutical composition may comprise water, glycerin, pramoxine hydrochloride, phenylephrine hydrochloride, propylene glycol, butylated hydroxyanisole, trisodium citrate dihydrate, TWEEN[®] 80 (Polysorbate 80), citric acid (anhydrous), sodium benzoate, disodium EDTA, methyl paraben, propyl paraben, and L-menthol crystals. In a particular embodiment, the pharmaceutical composition may comprise about 73% water by weight, 20% glycerin by weight, 1% pramoxine hydrochloride by weight, 0.25% phenylephrine hydrochloride by weight, 2% propylene glycol by weight, 0.05% butylated hydroxyanisole by weight, 0.35% trisodium citrate dihydrate by weight, 2% TWEEN[®] 80 (Polysorbate 80) by weight, 0.25% citric acid (anhydrous) by weight, 0.1% sodium benzoate by weight, 0.1% disodium EDTA by weight, 0.18% methyl paraben by weight, 0.02% propyl paraben by weight, and 0.07% L-menthol crystals by weight.

[0036] In many embodiments of this invention, a cream may comprise the pharmaceutical composition described herein. In many embodiments of this invention, a lotion may comprise the pharmaceutical composition described herein.

composition described herein. In certain embodiments, the sheet may comprise absorbent cellulose based fibers, absorbent synthetic fibers, or a mixture thereof. The fibers may be cross-linked. The absorbent cellulosic fiber may be in sheet form, fluff form, or a combination thereof. The absorbent cellulose fiber may be in the form of a stabilized resin-bonded or thermal-bonded non-woven mat. The absorbent cellulose fiber may be a wood pulp fiber obtained from a Kraft or sulfite chemical process. The wood pulp fiber may be obtained from a hardwood cellulose pulp, a softwood cellulose pulp, or a combination or mixture thereof. The composition may be applied to the sheet to provide from about 0.001 weight % to about 600% weight % composition on fiber, based on the total weight of the fiber. The composition may be applied to the sheet to provide from about 6.0 gram solution per sheet of cloth.

[0038] In many embodiments of this invention, a method of making a sheet may comprise applying the pharmaceutical composition described herein to absorbent fibers. The composition may be applied by spraying, dipping, or rolling. The composition may be applied by a puddle press, size press, or a blade-coater.

[0039] In many embodiments of this invention, a method of making the pharmaceutical composition described herein may comprise (a) mix BHA, polysorbate 80, and propylene glycol for form a first mixture; (b) add methyl paraben, propyl paraben, and menthol to said first mixture to form a second mixture; (c) mix water and glycerin to form a third mixture; (d) add EDTA, sodium benzoate, sodium citrate, and citric acid to said third mixture to form a fourth mixture; (e) add pramoxine HCl and phenylephrine HCl to said fourth mixture to form a fifth mixture; and (f) add said second mixture to said fifth mixture to form a hemorrhoid treatment composition.

[0040] In many embodiments of this invention, a method of treating hemorrhoids may comprise administering one or another embodiment of the pharmaceutical composition described herein a patient in need thereof. The composition is applied by the patient to the source of the pain, redness or swelling. This area of application may be the hemorrhoid itself or the tissue adjacent to the hemorrhoid.

[0041] In many embodiments of this invention, a method of treating hemorrhoids comprises applying the sheet described herein to a hemorrhoid on patient in need thereof.

vasoconstrictor, and a cooling agent.

[0043] In one embodiment, the use of a composition comprising analgesic, solvent, vasoconstrictor, emollient, surfactant, and cooling agent, may be used in the manufacture of a composition for treating hemorrhoids.

DESCRIPTION OF THE DRAWINGS

[0044] **Figure 1** depicts an exemplary flow chart of manufacturing hemorrhoid treatment compositions.

DETAILED DESCRIPTION OF EXEMPLARY EMBODIMENTS

[0045] Commercially available hemorrhoid treatment preparations provide partial relief to hemorrhoid sufferers. Further, commercially available hemorrhoid treatment preparations have lipophilic skin protectants which delay the action of the anorectal drugs. Specifically, the addition of oleaginous additives such as shark liver oil, garlic oil, petrolatum, mineral oil, stearyl alcohol, cetyl alcohol, and tocopherol have occlusive properties that delay the onset of water soluble drugs and are often uncomfortable for patients to use due to greasiness.

[0046] The hemorrhoid treatment compositions described herein comprise multiple ingredients, which may include analgesic, vasoconstrictor, hydrophilic skin protectant, penetration enhancer, especially hydrophilic penetration enhancer, surfactant, and cooling agent. The hemorrhoid treatment compositions described herein may comprise about 1% pramoxine HCl (analgesic), 0.25% phenylephrine HCl (vasoconstrictor), 20% glycerin (hydrophilic skin protectant), 2% propylene glycol (hydrophilic penetration enhancer), 2% TWEEN® 80 (polyethylene glycol sorbitan monooleate), 0.07% D.L-menthol (cooling agent/penetration agent), and water to balance. *See, e.g.*, Table 1.

[0047] The inherent solubility parameter of skin lipids (δ_s) is about $10 \text{ (cal/cm}^3)^{1/2}$, where water the δ_v is 23.4. The inherent solubility parameter for lipophilic ingredients of prior art preparations include shark liver oil/squalene ($\delta_v = 6.19$), petrolatum ($\delta_v = 7.3$), mineral oil ($\delta_v = 7.09$), stearyl alcohol ($\delta_v = 8.90$), and cetyl alcohol ($\delta_v = 8.94$) which are added to provide skin protection. These lipophilic skin protectants have occlusive properties that can act to delay the onset of action for water soluble drugs, especially when the inflamed area is located deep inside

propylene glycol ($\delta v = 14.5$) and glycerin ($\delta v = 16.26$) are capable of distributing within the stratum corneum and increasing the flux (enhancing penetration) of water soluble drugs, thereby acting as penetration enhancers. Menthol ($\delta v = 9.94$) is capable of distributing with the stratum corneum and increasing the flux of water soluble drugs.

[0048] A single agent may act as both cooling agent and penetration enhancer, *e.g.*, menthol. Obata, *et al.* reported that percutaneous absorption of hydrophilic diclofenac sodium was substantially enhanced in the presence of l-menthol. Obata, *et al.* Drug Design, Del., 6, 319, 1990. The combined effect of menthol and ethanol as skin penetration enhancers was also studied by Kobayashi, *et al.* Pharm Res., 11, 96, 1994.

[0049] The inventors surprisingly discovered that menthol acts synergistically both as a cooling agent and a penetration enhancer to improve the delivery of water soluble active ingredient through the mucous membrane of a hemorrhoid. The menthol is preferably solubilized in a micro-emulsion of a surfactant, *e.g.*, TWEEN® 80 (polyethylene glycol sorbitan monooleate). Other surfactants that may be used are nonionic surfactants such as ethoxylated castor oil, Polysorbate 20 (Polyoxyethylene (20) sorbitan monolaurate), and/or Polysorbate 60 (polyoxyethylene (60) sorbitan monostearate). The hemorrhoid treatment compositions described herein improve the efficacy of the hemorrhoid preparation through the synergistic action of analgesic (*e.g.*, pramoxine HCl), vasoconstrictor (*e.g.*, phenylephrine HCl) and penetration enhancer (*e.g.*, methanol, propylene glycol, and glycerin). Further, the hemorrhoid treatment compositions described herein do not contain lipophilic skin protectants that slow down the action of the water soluble drugs.

[0050] The pharmaceutical compositions described herein may comprise water, glycerin, propylene glycol, and/or low molecular weight polyethylene glycols (PEGs) as a solvent. For example, the pharmaceutical compositions described herein may comprise about 10–40% glycerin by weight. The pharmaceutical compositions described herein may comprise, 10%, 15%, 20%, 25%, 30%, 35%, or 40% glycerin by weight, preferably about 20% glycerin by weight. The pharmaceutical compositions described herein may comprise about 1–10% propylene glycol by weight. The pharmaceutical compositions described herein may comprise, about 1%, 1.5%, 2%, 2.5%, 3%, 5%, 6%, 7%, 8%, 9%, or 10% propylene glycol by weight, preferably about 2% propylene glycol by weight. The pharmaceutical compositions described

pharmaceutical compositions described herein may comprise, about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, or 5% polyethylene glycol, preferably PEG400, by weight, preferably about 2% polyethylene glycol, preferably PEG400, by weight.

[0051] Analgesics that may be used in compositions of this invention include but are not limited to benzocaine; benzyl alcohol; dibucaine; dibucaine hydrochloride; dyclonine hydrochloride; lidocaine; pramoxine hydrochloride; tetracaine; tetracaine hydrochloride; or a mixture thereof.

[0052] A preferred analgesic is pramoxine HCl.

[0053] The analgesics may be in an amount of about 0.25 to 20% by weight. For example, benzocaine may be at about 5 to 20% by weight; benzyl alcohol may be at about 1 to 4% by weight; dibucaine may be at about 0.25 to 1% by weight; dibucaine hydrochloride may be at about 0.25 to 1% by weight; dyclonine hydrochloride may be at about 0.5 to 1% by weight; lidocaine may be at about 2 to 5% by weight; pramoxine hydrochloride may be at about 1 percent by weight; tetracaine may be at about 0.5 to 1% by weight; tetracaine hydrochloride may be at about 0.5 to 1%; or a mixture thereof.

[0054] The A preferred analgesic is pramoxine HCl may be in an amount of about 0.5% to about 2.0% by weight of the composition. For example, pramoxine HCl may be in an amount of about 0.75%, 1.0%, 1.25%, or 1.50% by weight of the composition.

[0055] Vasoconstrictors used in compositions of this invention include ephedrine sulfate, epinephrine, epinephrine hydrochloride, phenylephrine hydrochloride, or a mixture thereof. The vasoconstrictor may be present in an amount of about 0.005 to 1.25% by weight. The vasoconstrictor may be ephedrine sulfate at about 0.1 to 1.25% by weight; epinephrine at about 0.005 to 0.01% by weight; epinephrine hydrochloride at about 0.005 to 0.01 % by weight; phenylephrine hydrochloride at about 0.25% ; or a mixture thereof.

[0056] A preferred vasoconstrictor is phenylephrine HCl. The preferred vasoconstrictor phenylephrine HCl may be in an amount of about 0.10% to about 0.50% by weight of the composition. For example, the compositions described herein may comprise phenylephrine HCl in an amount of about 0.20%, 0.25%, 0.30%, or 0.35% by weight of the composition.

[0057] The compositions of this invention may comprise an emollient.

Examples of suitable emollients are dipropylene glycol, hexylene glycol, butylene glycol which are used at percentages low enough to ensure solubility in the preparation.

[0059] The emollient may be propylene glycol. The emollient may be glycerin.

[0060] The emollient may be in an amount of about 1.0% to about 40% by weight of the composition. The emollient may be in an amount of about 2.0%, 5.0%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% by weight of the composition. For example, the composition may comprise about 1-40% glycerin by weight of the composition, preferably about 2.0%, 5.0%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% by weight of the composition. The composition may comprise about 1-40% propylene glycol by weight of the composition, preferably about 2.0%, 5.0%, 10%, 15%, 20%, 25%, 30%, 35%, or 40% by weight of the composition.

[0061] The compositions described herein may further comprise an antioxidant, acidulant, preservative, chelating agent, or a combination thereof.

[0062] The compositions of this invention will typically comprise acidulants, such as citric acid and sodium citrate, as well as preservatives, such as methyl paraben, propyl paraben, sodium benzoate, diazolidinyl urea, and butylated hydroxyanisole. The compositions may also include chelating agents. Compositions of this invention also comprise an aqueous solvent.

[0063] The antioxidant may be butylated hydroxyanisole, butylated hydroxyl toluene, propyl gallate, or a combination thereof. The antioxidant, preferably butylated hydroxyanisole, may be in an amount about 0.01% to about 0.10% by weight of composition, preferably about 0.03%, 0.04%, 0.05%, 0.06%, or 0.07% by weight of composition.

[0064] The acidulant may be sodium citrate, citric acid, or a combination thereof.

[0065] The acidulant may be in an amount about 0.10% to about 0.50% by weight of composition, preferably in an amount about 0.20%, 0.25%, 0.30%, 0.35%, or 0.40% by weight of composition.

[0066] For example, the composition may comprise water as a solvent. The composition may comprise a mixture of water/glycerin/propylene glycol/low molecular weight polyethylene glycols (PEGs) as a solvent. The composition may comprise a solvent is in an amount of about 70% to about 90% by weight of the composition. For example, the composition may comprise a solvent, preferably water, that is in an amount of about 71%, 72%, 73%, 74%, or 75% by weight of the composition.

amount of about 70% to about 90% by weight of the composition. For example, the solvent may be in an amount of about 71%, 72%, 73%, 74%, or 75% by weight of the composition.

[0068] The pharmaceutical composition may comprise mixtures of water, glycerin, propylene glycol, and/or low molecular weight polyethylene glycols (PEGs) as a solvent. The pharmaceutical composition may comprise about 10–40% glycerin by weight, preferably 10%, 15%, 20%, 25%, 30%, 35%, or 40% glycerin by weight, more preferably about 20% glycerin by weight. The pharmaceutical composition may comprise about 1–10% propylene glycol by weight, preferably about 1%, 1.5%, 2%, 2.5%, 3%, 5%, 6%, 7%, 8%, 9%, or 10% propylene glycol by weight, more preferably about 2% propylene glycol by weight. The pharmaceutical composition may comprise about 1–5% polyethylene glycol by weight, preferably about 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5%, or 5% polyethylene glycol by weight, more preferably about 2% polyethylene glycol by weight.

[0069] The polyethylene glycol may have an average molecular weight of 100–600. The polyethylene glycol may be PEG100, PEG200, PEG300, PEG400, PEG 500, PEG600 or a mixture thereof. The polyethylene glycol may be PEG400, PEG600, or a mixture thereof. Ratio of the mixtures depend on the average molecular weight of PEG where the number denotes the molecular unit, *e.g.*, PEG 400 has an average molecular weight of 400. In the compositions described herein, water soluble PEGs can vary from PEG 100 to PEG 600. As the molecular weight of the PEG increases, the proportion of the PEG in the mixture may decrease. For example, the ratio of a suitable mixture of water: propylene glycol: PEG 100 = 1:1:1 and the ratio of a suitable mixture of water: propylene glycol: PEG 600 = 3:2:1. The pharmaceutical composition may comprise a mixture of water:propylene glycol:PEG in a ratio of 1:1:1 to 3:2:1. For example, the water:propylene glycol:PEG100 may be a ratio of 1:1:1. The water:propylene glycol:PEG600 may be a ratio of 3:2:1.

[0070] The solvent may be in an amount of about 70% to about 90% by weight of the composition. For example, the solvent may be in an amount of about 71%, 72%, 73%, 74%, or 75% by weight of the composition.

[0071] The compositions described herein may comprise a nonionic surfactant. The nonionic surfactant may be ethoxylated castor oil, Polysorbate 20, Polysorbate 60, Polysorbate 80, or a combination thereof. The surfactant may be Polysorbate 80 (polyethylene glycol sorbitan

monooleate), may be in an amount of about 0.5% to about 5% by weight of the composition, preferably in an amount of about 1.0%, 1.5%, 2.0%, 3.0%, 3.5%, or 5.0% by weight of the composition.

[0072] Cooling agents used in the compositions of this invention include menthol, eucalyptol, camphor, juniper tar, or a combination thereof. A preferred cooling agent is menthol.

[0073] The cooling agent, preferably menthol, may be an amount of about 0.05% to about 0.1% by weight of the composition, preferably about 0.05%, 0.06%, 0.07%, 0.08%, or 0.09% by weight of the composition.

[0074] The preservative is a pharmaceutically-acceptable preservative suitable for topical use. For example, the preservative may be sodium benzoate, methyl paraben, propyl paraben, or a combination thereof. The preservative may be in an amount about 0.01% to about 0.25% by weight of composition. For example, the preservative may be in an amount about 0.01%, 0.02%, 0.03%, 0.05%, 0.10%, 0.15%, 0.16%, 0.18%, 0.20%, or 0.25% by weight of composition.

[0075] The chelating agent may be disodium EDTA in an amount about 0.05% to about 0.20% by weight of composition, preferably in amount about 0.08%, 0.09%, 0.10%, 0.11%, 0.12%, or 0.13% by weight of composition.

[0076] The compositions described herein do not contain petrolatum. The compositions described herein do not contain witch hazel. The compositions described herein do not contain acyclic alcohol or a monohydric aliphatic alcohol. The compositions described herein do not contain cetyl alcohol. The compositions described herein may be formulated as a suspension, cream, lotion, or applied to a sheet.

[0077] The hemorrhoid treatment compositions described herein have rapid onset action because, in part, it is a solution and not a cream which reaches the affected areas faster than a petrolatum-containing cream. Also, the hemorrhoid treatment compositions described herein contain menthol which has instant cooling action that provides the patient rapid relief from pain associated with hemorrhoids. Also, the hemorrhoid treatment compositions described herein comprise a penetration enhancer— menthol —that allows for better access of the active ingredients to the inflamed tissue. The hemorrhoid treatment compositions described herein use glycerin (*e.g.*, 20%) and not petrolatum which gives the compositions better skin protectant effect. The hemorrhoid treatment compositions described herein has a rapid synergistic effect

a dual penetration enhancer/cooling agent that causes the active agents to penetrate the affected area and provide long lasting relief from the pain and discomfort of hemorrhoids. Menthol, a penetration agent, improves the analgesic action of the pramoxine HCl as a topical analgesic and phenylephrine HCl as a topical vasoconstrictor. The improvement in action is related to the fact that neutral molecules such as menthol have the exact solubility characteristics that improve the passage of ionic molecules through mucous membranes.

[0078] Also, the hemorrhoid treatment compositions described herein do not contain any petrolatum and are non-greasy with a better feel after application. Additionally, the microemulsion created by the addition of at least 2% w/w TWEEN[®] 80 forms micelles that solubilize menthol.

[0079] A clear microemulsion is inherently stable due to the formation of submicron sized micelles that are also referred to as isotropic solutions. The surfactants which make up microemulsions are too large themselves to penetrate into the dermis.

[0080] The hemorrhoid treatment preparations described herein may be formulated as a suppository, topical solution, ointment, cream, or impregnated into a wipe. Further, the hemorrhoid treatment preparations described herein may be delivered by a pump spray, squeeze tube (with or without nozzles), or disposable applicators. The dose may be metered by the pump spray or disposable applicator. In certain embodiments, the composition of this invention may be produced by mixing menthol with surfactant(s) and preservatives, then adding this mixture to an aqueous solution which contains all of the other ingredients of the composition. Figure 1 shows an exemplary manufacturing scheme. This final mixture may then be impregnated into a non-woven sheet for use as a wipe.

[0081] A sheet may be impregnated with the composition described herein. The sheet may be absorbent cellulose based fibers, absorbent synthetic fibers, or a mixture thereof. Further, the fibers of the sheet may be cross-linked. The cellulosic absorbent fiber may be in sheet form, fluff form, or a combination thereof. The absorbent cellulose fiber may be in the form of a stabilized resin-bonded or thermal-bonded non-woven mat. The absorbent cellulose fiber may be a wood pulp fiber obtained from a Kraft or sulfite chemical process. The wood pulp fiber may be obtained from a hardwood cellulose pulp, a softwood cellulose pulp, or a combination or mixture

spraying, rolling, or a combination thereof.

[0082] Preferred cloths are those which are dispersible. Dispersibility is a desirable characteristic for cloths due to the concern about the potential blockage of sewer drains and septic systems. Specific tests proposed by the National Sanitary Association are performed in order for a cloth to be designated as "dispersible".

[0083] Proceeding now to a description of the drawing, FIG 1 shows an exemplary method of manufacturing the composition described herein. The composition is formulated as two separate formulations **104**, **203** and then mixed together into a final composition **302**. BHA is added to polysorbate 80 and propylene glycol **100**. This composition is mixed with moderate shear **101**. Then methyl paraben, propyl paraben, and menthol are added **102**. This mixture is then mixed with moderate shear **103** to form a first mixture **104**.

[0084] The amount of shear should be sufficient to create a vortex in the solution such that the BHA, methyl paraben, propyl paraben, and menthol will be dissolved in a reasonable period of time, preferably less than 1 hour. This amount of mixing can be achieved with a 6"-12" propeller mixer running at 600 – 1200 RPM. For example, in a 100 gallon tank a 6" blade running at 600 RPM may be used to achieve dissolution in about 1 hour. As the size of the tank increases, the mixer speed and/or the size of the blade may need to be increased in order to achieve adequate mixing in a reasonable amount of time, preferably less than 1 hour. For example, the mixer speed may be increased to 1200 RPM and the size of the blade may be increased to 12" in order to achieve dissolution in about 1 hour.

[0085] Ross, Silverson, or Gaulin mixers may be used. For example, moderate shear may be 400 rpm (rotations per minute) of the 4 blade rotor head against a static stator with a 10 micron gap allowing the mixture to pass through in a Ross® High Shear Mixer (Laboratory Model). The time required for mixing will depend upon the size of the batch and the number of passes through the mixer head in one hour, usually at least 3 – 5 passes per hour are required to achieve dissolution. Slight heating will accelerate the mixing process, but heat is not required to achieve mixing.

[0086] In a separate tank, water and glycerin are added together **200**. Then EDTA, sodium benzoate, sodium citrate, citric acid are added and propeller mixed until dissolved **201**. Then pramoxine HCl, phenylephrine HCl are added and the mixture is propeller-mixed until dissolved

mixture **203** and propeller mixed in the reaction vessel that held the second mixture **301**. This produces the final formulation **302**, a composition for treating hemorrhoids.

[0087] Further embodiments of the present invention will now be described with reference to the following examples. The examples contained herein are offered by way of illustration and not by any way of limitation.

EXAMPLE 1

[0088] Table 1—Non-optimal hemorrhoid treatment preparation

Ingredient	Ingredient Function	% w/w
water	solvent	51.70%
glycerin	emollient	42.61%
pramoxine hydrochloride	analgesic	1.00%
phenylephrine hydrochloride	vasoconstrictor	0.25%
propylene glycol	emollient	2.00%
butylated hydroxyanisole	antioxidant	0.05%
trisodium citrate dihydrate	acidulant	0.35%
TWEEN [®] 80 (Polysorbate 80)	surfactant	1.30%
citric acid (anhydrous)	acidulant	0.25%
sodium benzoate	preservative	0.10%
disodium EDTA	chelating agent	0.10%
Methyl paraben	preservative	0.18%
Propyl paraben	preservative	0.02%
Eucalyptol	cooling agent/ penetrating agent	0.02%
L-menthol crystals	cooling agent/ penetrating agent	0.07%

[0089] Clear microemulsions are inherently stable solutions. The preparation shown in Table 1 was made with 1.3% w/w TWEEN[®] 80 and was not clear, therefore the microemulsion was not completely formed. Some of the menthol and eucalyptol remained undissolved. Also, is preparation was found to be sticky while drying on the skin.

EXAMPLE 2

[0090] Table 2—Non-optimal hemorrhoid treatment preparation

Ingredient	Ingredient Function	% w/w
water	solvent	74.11%
glycerin	emollient	20.00%

phenylephrine hydrochloride	vasoconstrictor	0.25%
propylene glycol	emollient	2.00%
butylated hydroxyanisole	antioxidant	0.02%
trisodium citrate dihydrate	acidulant	0.35%
TWEEN [®] 80 (Polysorbate 80)	surfactant	1.50%
citric acid (anhydrous)	acidulant	0.25%
sodium benzoate	preservative	0.10%
disodium EDTA	chelating agent	0.10%
Methyl paraben	preservative	0.18%
Propyl paraben	preservative	0.02%
Eucalyptol	cooling agent/ penetrating agent	0.02%
L-menthol crystals	cooling agent/ penetrating agent	0.07%

[0091] As shown in Table 2, a preparation was made with 1.5% w/w TWEEN[®] 80 and was initially clear, but became cloudy over time. Compared to the preparation of Table 1, the preparation of Table 2 was less sticky while drying on the skin.

EXAMPLE 3

[0092] Table 3—Exemplary hemorrhoid treatment preparation of this invention

Ingredient	Ingredient Function	% w/w
water	solvent	73.63%
glycerin	emollient	20.00%
pramoxine hydrochloride	analgesic	1.00%
phenylephrine hydrochloride	vasoconstrictor	0.25%
propylene glycol	emollient	2.00%
butylated hydroxyanisole	antioxidant	0.05%
trisodium citrate dihydrate	acidulant	0.35%
TWEEN [®] 80 (Polysorbate 80)	surfactant	2.00%
citric acid (anhydrous)	acidulant	0.25%
sodium benzoate	preservative	0.10%
disodium EDTA	chelating agent	0.10%
Methyl paraben	preservative	0.18%
Propyl paraben	preservative	0.02%
L-menthol crystals	cooling agent/ penetrating agent	0.07%

clear, and maintained clarity over the shelf life of two years. Compared to the preparation of Table 1, the preparation of Table 3 was less sticky while drying on the skin.

[0094] All publications (*e.g.*, Non-Patent Literature), patents, patent application publications, and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All such publications (*e.g.*, Non-Patent Literature), patents, patent application publications, and patent applications are herein incorporated by reference to the same extent as if each individual publication, patent, patent application publication, or patent application was specifically and individually indicated to be incorporated by reference.

[0095] While the foregoing invention has been described in connection with this preferred embodiment, it is not to be limited thereby but is to be limited solely by the scope of the claims which follow.

WHAT IS CLAIMED IS:

1. A composition for treating hemorrhoids, comprising:
an analgesic,
a vasoconstrictor,
an emollient, and
a cooling agent,
wherein the composition does not comprise a lipophilic skin protectant.

2. A composition for treating hemorrhoids, consisting of:
an analgesic,
a vasoconstrictor,
an emollient,
a cooling agent,
optionally, a solvent,
optionally, an acidulant,
optionally, an antioxidant,
optionally, a preservative, and
optionally, a chelating agent,
wherein the composition does not comprise a lipophilic skin protectant.

3. A composition for treating hemorrhoids, consisting of:
pramoxine hydrochloride,
phenylephrine hydrochloride,
glycerin,
propylene glycol,
menthol,
water,
polysorbate 80,
sodium citrate,
citric acid,

butylated hydroxyanisole,
sodium benzoate,
methyl paraben,
propyl paraben, and
disodium EDTA,

wherein the composition does not comprise a lipophilic skin protectant.

4. The composition for treating hemorrhoids of any of the preceding claims, wherein the analgesic comprises pramoxine hydrochloride,
the vasoconstrictor comprises phenylephrine hydrochloride;
the emollient comprises glycerin and propylene glycol,
the cooling agent comprises menthol,
the solvent comprises water,
the non-ionic surfactant comprises polysorbate 80,
the acidulant comprises sodium citrate and citric acid,
the antioxidant comprises butylated hydroxyanisole,
the preservative comprises sodium benzoate, methyl paraben and propyl paraben, and
the chelating agent comprises disodium EDTA.

5. The composition for treating hemorrhoids of any of the preceding claims, wherein the analgesic is present in an amount of 0.25-20% by weight,
the vasoconstrictor is present in an amount of 0.005-1.25% by weight;
the emollient is present in an amount of 1.0-40% by weight,
the cooling agent is present in an amount of 0.05-0.1% by weight,
the solvent is present in an amount of 70-90% by weight,
the non-ionic surfactant is present in an amount of 0.5-5.0% by weight,
the acidulant is present in an amount of 0.10-0.50% by weight,
the antioxidant is present in an amount of 0.01-0.10% by weight,
the preservative is present in an amount of 0.01-0.25% by weight, and

the chelating agent is present in an amount of 0.05-0.20% by weight.

6. The composition for treating hemorrhoids of any of the preceding claims, wherein the analgesic comprises at least one member selected from the group consisting of benzocaine, benzyl alcohol, dibucaine, dibucaine hydrochloride, diclonine hydrochloride, lidocaine, pramoxine hydrochloride, tetracaine and tetracaine hydrochloride.
7. The composition for treating hemorrhoids of any of the preceding claims, wherein the analgesic is present in an amount of 0.25-20% by weight.
8. The composition for treating hemorrhoids of any of the preceding claims, wherein the analgesic is present in an amount of 0.5-2.0% by weight.
9. The composition for treating hemorrhoids of any of the preceding claims, wherein the vasoconstrictor comprises at least one member selected from the group consisting of ephedrine sulfate, epinephrine, epinephrine hydrochloride and phenylephrine hydrochloride.
10. The composition for treating hemorrhoids of any of the preceding claims, wherein the vasoconstrictor is present in an amount of 0.005-1.25% by weight.
11. The composition for treating hemorrhoids of any of the preceding claims, wherein the vasoconstrictor is present in an amount of 0.10-0.50% by weight.
12. The composition for treating hemorrhoids of any of the preceding claims, wherein the emollient comprises at least one member selected from the group consisting of dipropylene glycol, hexylene glycol, butylene glycol, propylene glycol and glycerin.

13. The composition for treating hemorrhoids of any of the preceding claims, wherein the emollient is present in an amount of 1.0-40% by weight.
14. The composition for treating hemorrhoids of any of the preceding claims, wherein the cooling agent comprises at least one member selected from the group consisting of menthol, eucalyptol, camphor and juniper tar.
15. The composition for treating hemorrhoids of any of the preceding claims, wherein the cooling agent is present in an amount of 0.05-0.1% by weight.
16. The composition for treating hemorrhoids of any of the preceding claims, further comprising a solvent.
17. The composition for treating hemorrhoids of any of the preceding claims, wherein the solvent comprises at least one member selected from the group consisting of water, glycerin, propylene glycol and polyethylene glycol.
18. The composition for treating hemorrhoids of any of the preceding claims, wherein the solvent is present in an amount of 70-90% by weight.
19. The composition for treating hemorrhoids of any of the preceding claims, further comprising a non-ionic surfactant.
20. The composition for treating hemorrhoids of any of the preceding claims, wherein the non-ionic surfactant comprises at least one member selected from the group consisting of ethoxylated castor oil, polysorbate 20, polysorbate 60 and polysorbate 80.
21. The composition for treating hemorrhoids of any of the preceding claims, wherein the non-ionic surfactant is present in an amount of 0.5-5.0% by weight.

22. The composition for treating hemorrhoids of any of the preceding claims, further comprising an acidulant.
23. The composition for treating hemorrhoids of any of the preceding claims, wherein the acidulant comprises at least one member selected from the group consisting of sodium citrate and citric acid.
24. The composition for treating hemorrhoids of any of the preceding claims, wherein the acidulant is present in an amount of 0.10-0.50% by weight.
25. The composition for treating hemorrhoids of any of the preceding claims, further comprising an antioxidant.
26. The composition for treating hemorrhoids of any of the preceding claims, wherein the antioxidant comprises at least one member selected from the group consisting of butylated hydroxyanisole, butylated hydroxyl toluene and propyl gallate.
27. The composition for treating hemorrhoids of any of the preceding claims, wherein the antioxidant is present in an amount of 0.01-0.10% by weight.
28. The composition for treating hemorrhoids of any of the preceding claims, further comprising a preservative.
29. The composition for treating hemorrhoids of any of the preceding claims, wherein the preservative comprises at least one member selected from the group consisting of methyl paraben, propyl paraben, sodium benzoate, diazolidinyl urea and butylated hydroxyanisole.
30. The composition for treating hemorrhoids of any of the preceding claims, wherein the preservative is present in an amount of 0.01-0.25% by weight.

31. The composition for treating hemorrhoids of any of the preceding claims, further comprising a chelating agent.
32. The composition for treating hemorrhoids of any of the preceding claims, wherein the chelating agent comprises disodium EDTA.
33. The composition for treating hemorrhoids of any of the preceding claims, wherein the chelating agent is present in an amount of 0.05-0.20% by weight.
34. The composition for treating hemorrhoids of any of the preceding claims, wherein the analgesic comprises pramoxine hydrochloride,
the vasoconstrictor comprises phenylephrine hydrochloride;
the emollient comprises glycerin, and
the cooling agent comprises menthol.
35. The composition for treating hemorrhoids of any of the preceding claims, further comprising a solvent,
a non-ionic surfactant,
an acidulant,
an antioxidant,
a preservative, and
a chelating agent.
36. The composition for treating hemorrhoids of any of the preceding claims, wherein the solvent comprises water, propylene glycol and polyethylene glycol.
37. The composition for treating hemorrhoids of any of the preceding claims, wherein the water, propylene glycol and polyethylene glycol are present in a ratio of 3:2:1.

38. The composition for treating hemorrhoids of any of the preceding claims, wherein the water, propylene glycol and polyethylene glycol are present in a ratio of 1:1:1.
39. The composition for treating hemorrhoids of any of the preceding claims, wherein the composition is formulated as a member selected from the group consisting of a solution, a suppository, an ointment or an impregnated sheet.
40. The composition for treating hemorrhoids of any of the preceding claims, wherein the composition is not a cream.
41. The composition for treating hemorrhoids of any of the preceding claims, wherein the composition is clear.
42. The composition for treating hemorrhoids of any of the preceding claims, wherein the cooling agent is solubilized as a microemulsion.
43. The composition for treating hemorrhoids of any of the preceding claims, wherein the composition does not comprise petrolatum, witch hazel, cetyl alcohol, acyclic alcohols nor monohydric aliphatic alcohols.
44. A sheet for treating hemorrhoids, wherein the sheet is impregnated with a composition of any of the preceding claims.
45. The sheet for treating hemorrhoids of any of the preceding claims, wherein the sheet is dispersible.
46. A method of making the composition for treating hemorrhoids of any of the preceding claims, comprising:
adding an antioxidant to a non-ionic surfactant and a first emollient in a first tank, to form a first mixture;

mixing the first mixture;
adding a first preservative and a cooling agent to the first mixture in the first tank,
to form a second mixture;
mixing the second mixture;
adding a solvent to a second emollient, different from the first emollient, in a
second tank, to form a third mixture;
adding a chelating agent, a second preservative, different from the first
preservative, and an acidulant to the third mixture in the second tank, to form a fourth
mixture;
mixing the fourth mixture;
adding an analgesic and a vasoconstrictor to the fourth mixture in the second
tank, to form a fifth mixture;
mixing the fifth mixture;
adding the second mixture to the fifth mixture in the second tank, to form a final
mixture;
mixing the final mixture to form the composition for treating hemorrhoids.

47. The method of making a composition for treating hemorrhoids of any of the preceding claims, wherein the antioxidant comprises butylated hydroxyanisole, the non-ionic surfactant comprises polysorbate 80, the first emollient comprises propylene glycol, the first preservative comprises a mixture of methyl paraben and propyl paraben, the cooling agent comprises menthol, the solvent comprises water, the second emollient comprises glycerin, the chelating agent comprises EDTA, the second preservative comprises sodium benzoate, the acidulant comprises a mixture of sodium citrate and citric acid, the analgesic comprises pramoxine hydrochloride, and the vasoconstrictor comprises phenylephrine hydrochloride.

48. The composition of any of the preceding claims for use in treating hemorrhoids.
49. The sheet of any of the preceding claims for use in treating hemorrhoids.

Manufacture of Hemorrhoid Composition

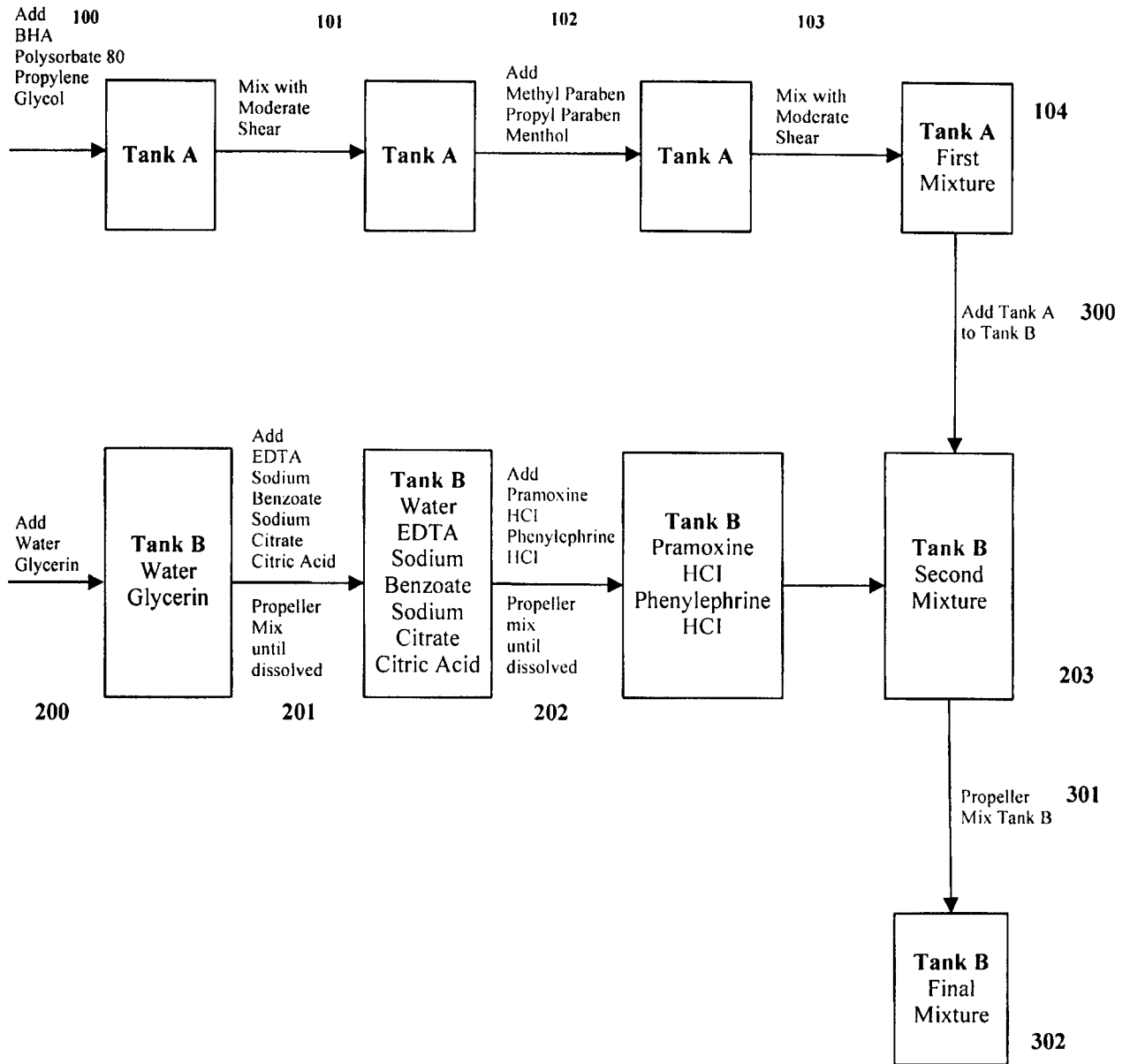


FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/049304**A. CLASSIFICATION OF SUBJECT MATTER****A61K 31/5375(2006.01)i, A61K 31/137(2006.01)i, A61K 9/70(2006.01)i, A61K 9/06(2006.01)i, A61K 9/08(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 31/5375; A61K 31/137; A61K 31/24; A61K 33/44; A61K 8/89; A61K 9/70; A61K 9/08; A61K 9/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: hemorrhoids, analgesic, vasoconstrictor, emollient, cooling agent

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2014-0256688 A1 (PERITECH PHARMA LTD.) 11 September 2014 See abstract; paragraphs [0136], [0141]-[0144], [0152], [0154], [0246]; and table 1.	1,2
Y		3,4
Y	US 2006-0004094 A1 (AGISIM, G. R. et al.) 05 January 2006 See abstract; and paragraphs [0035]-[0038], [0041], [0050], [0051].	3,4
A	US 2006-0034825 A1 (CHARRON, D.) 16 February 2006 See the whole document.	1-4
A	US 2007-0027152 A1 (CLARK, K. L. et al.) 01 February 2007 See the whole document.	1-4
A	US 2002-0192273 A1 (BUSEMAN, T. et al.) 19 December 2002 See the whole document.	1-4

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

05 December 2016 (05.12.2016)

Date of mailing of the international search report

05 December 2016 (05.12.2016)

Name and mailing address of the ISA/KR

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/049304

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.: 5-49
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2016/049304

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2014-0256688 A1	11/09/2014	AU 2014-229497 A1 CA 2904507 A1 CN 105142611 A EP 2968133 A2 EP 2968133 A4 JP 2016-510807 A KR 10-2015-0136077 A US 2014-255521 A1 US 2014-255522 A1 US 2015-272957 A1 US 9072747 B2 WO 2014-140925 A2 WO 2014-140925 A3	24/09/2015 18/09/2014 09/12/2015 20/01/2016 09/03/2016 11/04/2016 04/12/2015 11/09/2014 11/09/2014 01/10/2015 07/07/2015 18/09/2014 30/07/2015
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