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Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

[Continued on next page]

(54) Title: METHOD AND COMPOSITION FOR TREATING GASTRO-ESOPHAGEAL DISORDERS

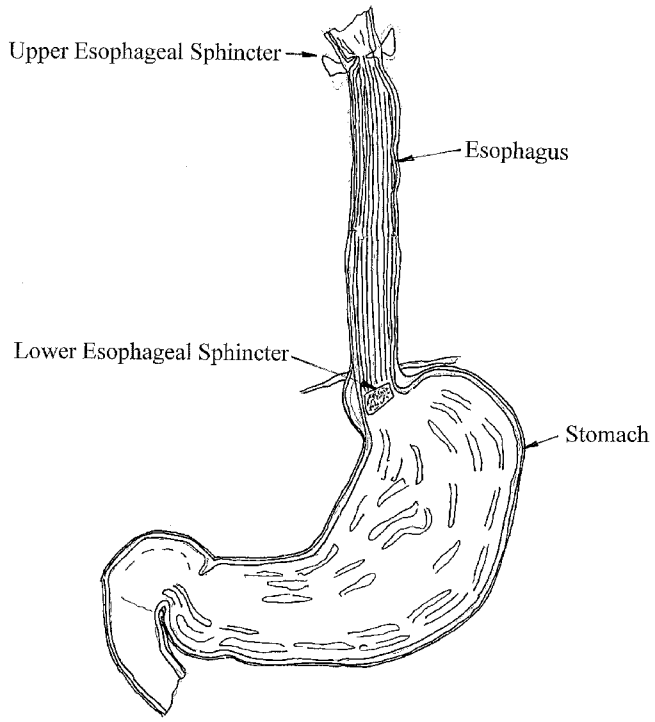

FIG. 1

(57) Abstract: An orally administered composition that includes least one alkaline agent with a pH of at least 9.0 to 12.0, mixed in an aqueous vehicle with relatively high surface tension, high viscosity and lateral adhesion properties. When mixed, a low water soluble emulsion is formed that evenly coats and partially adheres to the lower section of the esophagus and the LES and forms a relatively long acting, protective barrier and partially neutralizes gastric acid. In one embodiment, the alkaline agent is potassium hydroxide and the aqueous vehicle is made of hydroxypropyl methyl cellulose, polyethylene glycol or ethylene glycol and additional thickener agents capable of withstanding high pH environments, such as xanthan gum, croscarmellose sodium, and microcrystalline cellulose. Additional organoleptic agents, such as gum Arabic and polyethylene glycol, flavorings, such as sodium chloride, acesulfame potassium, sodium saccharine, and mint, and stabilizers such as colloidal silica made be added.

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— *of inventorship (Rule 4.17(iv))*

Published:

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

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

TITLE: METHOD AND COMPOSITION FOR TREATING GASTRO-ESOPHAGEAL DISORDERS

TECHNICAL FIELD

The present invention relates to methods and compositions for treating various gastro-esophageal disorders including esophagitis, gastro-esophageal reflux disease ('GERD'), laryngopharyngeal reflux ('LPR'), esophageal ulcers, synchronous diaphragmatic flutter ('SDF'), inadequate lower esophageal sphincter ('LES') function, and reducing esophageal infection and dysphagia due to cancer treatment side-effects.

BACKGROUND ART

Gastro-esophageal reflux disease (hereinafter referred to as 'GERD') is a chronic symptom caused by stomach acid coming up through the lower esophageal sphincter and into the esophagus. Laryngopharyngeal reflux, (hereinafter referred to as 'LPR'), is a chronic symptom caused by stomach acid coming up through the esophagus and the upper esophageal sphincter and into the larynx and nasal airway. The underlying cause of esophagitis, esophageal ulcers, and GERD is normally the inadequate closure of the lower esophageal sphincter, (hereinafter known as LES) and can also be caused or exacerbated by medical procedures such as endoscopic examinations of the esophagus and intubation of the gastro- esophageal tract. The underlying cause of LRP is normally the inadequate closure of the LES and the upper esophageal sphincter (hereinafter known as UES).

GERD and LPR sometimes cause injury to the esophagus which may include: (1) reflux esophagitis (necrosis of esophageal epithelium causing ulcers near the junction of the stomach and esophagus or LES); (2) esophageal strictures (persistent narrowing of the esophagus caused by inflammation; and (3) Barrett's esophagus (changes in the epithelial cells of the esophagus from squamous to intestinal columnar

epithelium); (4) esophageal ulcers; and even (5) esophageal adenocarcinoma (cancer), and (6) synchronous diaphragmatic flutter ('SDF'). Endoscopic examination of the esophagus and intubation of the gastro-esophageal tract, especially if pre-existing esophageal injury is present, might cause and exacerbate those injuries.

One treatment for GERD and LPR involves the use of proton pump inhibitors ("PPIs") that reduce stomach acid production. PPIs are widely used, and many patients are dependent on them. In 2010 and 2011, the U.S. Food and Drug Administration (hereinafter referred to as 'FDA') issued warning letters regarding the long term use of PPIs and many patients are fearful that their GERD and LRP symptoms will return if PPIs are discontinued.

DISCLOSURE OF THE INVENTION

It is an object of the present invention to provide a composition and alternative method for treating esophagitis, esophageal strictures, Barrett's esophagus, synchronous diaphragmatic flutter, esophageal ulcers, inflammation, and associated bacterial growth in the esophagus, GERD and LRP due to LES insufficiency or injury due to medical procedures, and improve esophageal function that has deteriorated due to cancer treatment side-effects. The method includes the use of an alkaline composition made of a sticky, highly viscous, emulsion that temporarily coats the esophageal mucosa tissue, heals inflamed esophageal tissue, reduces esophageal pain associated with inflammation and injury to the esophagus, reduces disease-causing bacteria, and also acts to neutralize the natural gastric juices in the esophagus and around the LES. The alkaline composition is formulated to coat and reside in the esophagus and around the LES a sufficient amount of time to reduce pain, reduce inflammation, improve the function of the esophageal epithelial tissue and mucosa,

and improve the function of the lower esophageal sphincter ("LES"). A typical dose is 5ml to 15ml of the alkaline composition one to three times a day depending on the severity of the esophageal injury.

More specifically, the alkaline composition includes least one alkaline agent with a pH of at least 9.0 to 12.0, mixed in an aqueous vehicle with relatively high surface tension, high viscosity and lateral adhesion properties. When mixed, a low water soluble emulsion is formed that evenly coats and partially adheres to the lower section of the esophagus and the LES and forms a relatively long acting, protective barrier and partially neutralizes gastric acid. In one embodiment, the alkaline agent is potassium hydroxide and the aqueous vehicle is made of hydroxypropyl methyl cellulose, polyethylene glycol or ethylene glycol and additional thickener agents capable of withstanding high pH environments, such as xanthan gum, croscarmellose sodium, and microcrystalline cellulose. Additional organoleptic agents, such as gum Arabic and polyethylene glycol, flavorings, such as sodium chloride, acesulfame potassium, sodium saccharine, and mint, and stabilizers such as colloidal silica may be added.

To improve adhesion to the surround tissues, the alkaline composition may also include other ingredients that are chemically compatible in higher pH environments that act as thickening agents, such as xanthan gum, and microcrystalline cellulose, croscarmellose sodium, or as organoleptic agents, such as gum Arabic and polyethylene glycol derivatives.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is an illustration of a patient's esophagus, stomach, the UES and the LES.

Fig. 2 is a table showing the anti-inflammatory and healing results from Study 1.

Fig. 3 is a table showing the anti-inflammatory and healing results of Study 2.

Fig. 4 is a table showing the bacterial count results conducted in Study 1.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention provides a method and an alkaline composition used to prevent and ameliorate pain, inflammation, bacteria colonization, and irritation to the esophagus and more serious conditions related to gastro-esophageal reflux disease ("GERD"), laryngopharyngeal reflux ("LPR"), and poor function of the lower esophageal sphincter ("LES") in adults and infants and conditions related to GERD, LPR, and LES and certain damaging side-effects in the esophagus associated with cancer treatments.

The alkaline composition is orally administered and includes least one alkaline agent with a pH of at least 9.0 to 12.0, mixed in an aqueous vehicle with relatively high surface tension, high viscosity and relatively high, lateral adhesion properties. When mixed, the alkaline composition forms an emulsion that when administered orally evenly coats and partially adheres to the lower section of the esophagus and the LES. The alkaline composition forms a relatively long acting, protective barrier that also partially neutralizes gastric acid.

In one embodiment, the alkaline agent is potassium hydroxide and the aqueous vehicle is made of hydroxypropyl methyl cellulose, polyethylene glycol or ethylene glycol and additional thickener agents capable of withstanding high pH environments, such as xanthan gum, croscarmellose sodium, and microcrystalline cellulose. Additional organoleptic agents, such as gum Arabic and polyethylene

glycol, flavorings, such as sodium chloride, acesulfame potassium, sodium saccharine, and mint, and stabilizers such as colloidal silica may be added.

Preferably, the alkaline composition uses potassium hydroxide as a strong alkaline agent that is capable of achieving the desired pH for the composition, retaining a high pH upon introduction to the esophagus. Significantly, the alkaline composition with an initial pH of 9.5 to 11.5 will, after dilution in the esophagus, provide a resulting pH of at least 9.0 in the esophagus without any negative reaction to the tissue in the esophagus. The amount of potassium hydroxide is 0.5% to 6.0% by weight, and preferably 1.0% to 5.0% by weight. In addition to potassium hydroxide, the alkaline composition may include additional alkaline agents, such as aluminum hydroxide, calcium carbonate, magnesium carbonate, and magnesium hydroxide.

Alkaline substances having long-lasting activity include alkali and alkaline earth metal hydroxides, such as sodium and potassium hydroxide, calcium carbonate and magnesium hydroxide, are suitable for use in the present invention. The rapid "antacid effect" (referring to the ability of a substance to neutralize and/or to buffer an acid) of stronger alkaline substances such as alkali and alkaline earth metal hydroxides is also used in the present invention. Alkali metal hydroxides suitable for use in the present invention include sodium hydroxide and potassium hydroxide, or a transition metal hydroxide, such as aluminum hydroxide, with potassium hydroxide being preferred for the present invention. The preferred embodiment of the present invention includes potassium hydroxide for rapid antacid effects and one or more, and preferably all, of aluminum hydroxide, calcium carbonate, and magnesium carbonate for residual acid reduction.

There are two methods for manufacturing the composition. The first method

requires the production of granules made of calcium carbonate, magnesium hydroxide, and potassium hydroxide which are coated with croscarmelose sodium and microcrystalline cellulose in 20-30% water. The granules are then dried to 3-10% water. The above steps are discussed in U.S. Patent No. 6,066,342, which is now incorporated by reference. Additional thickening agents, water and organoleptic agents may be added.

Using the second method, the granulation step above is eliminated and the ingredients are mixed together in an aqueous solution and then used to make the emulsion.

The alkaline composition is partially dissolved in water, and a thickening agent is added that increases the composition's viscosity, increases shelf life, and provides protection in a high pH environment. Suitable thickeners include xanthan gum, croscarmellose sodium (i.e. cellulose gum) and microcrystalline cellulose (i.e cellulose gel), which will withstand pH environments of up to 12.0 without substantial degradation. The composition of the present invention may alternately be compounded as a liquid suspension; however a more viscous gel or emulsion is preferred for application and coating of the esophagus. A stabilizing suspension agent such as colloidal silica may also be used.

In addition to alkaline agents and thickeners, the composition may also include inactive excipients such as organoleptic agents, such as gum Arabic and polyethylene glycol, for feel in the oral cavity and upper esophagus or flavoring agents such as sodium chloride, acesulfame-potassium, sodium-saccharine, and mint.

In each embodiment of the composition presented herein, the composition has the following physical properties: pH: 9.0 to 11.5

Specific Gravity: 1.05 to 1.15 gm/cc

Viscosity: 6,000 to 29,000 cP using small sample adapter and SC4-21/13R spindle on Brookfield DV2TRV Viscometer

Lateral Adhesion/Stickiness: 10^{-2} to 10^{-6} Newtons

When formulated into an emulsion, the alkaline composition is stable for a period in excess of one year when stored at ambient conditions, and without significant degradation of the viscosity, lateral adhesion or "stickiness" of the emulsion despite the highly alkaline environment. Lateral adhesion allows the emulsion to coat the esophageal mucosa uniformly at it flows down the esophagus. It should be understood that composition may be reformatted into a suspension, gel or paste-like substance.

The following studies were performed to demonstrate columnar epithelium tissue healing characteristics of the composition:

Study 1

In this study, ten patients with severely eroding and inflamed oral epithelial tissue were tested. A standardized test was used to establish a baseline number of bleeding points in the oral cavity. A photograph was also taken of the epithelial tissue and a bacterial sample was taken. The preferred embodiment of the composition was applied daily by each patient for 90 days. The patients then returned for examination. The average number of bleeding points was reduced from 123 to 7 after 90 days.

"Before" and "after" pictures taken of each patient indicated the epithelial tissue had returned to normal, healthy pinkish white color and the inflammation had abated after application of the emulsion. Bacteria counts of selected pathogenic bacteria were substantially reduced. All subjects reported an immediate reduction in

tissue pain and irritation upon applying the composition. The study concluded after 180 days.

Study 2

In this study, ten patients with moderately eroding oral epithelial tissue were examined. Again, a standard test established a baseline number of bleeding points in the oral cavity. The preferred embodiment of the composition as applied daily for 14 days. The patients then returned for examination. The average number of bleeding points was reduced from 44 to 20 in two weeks.

Study 3

In this study, the University Of Washington School Of Dentistry participated that conducted a double-blind, placebo-controlled, small-n format. Researchers recruited patients with moderately eroding oral epithelial tissue. Daily application of the composition resulted in significant improvement in the epithelial tissue health within two weeks.

Daily application of the preferred embodiment of the invention was associated with measurable improvement in the function of stratified squamous epithelial tissue.

The only contra-indication for the Company's emulsion is due to the presence of calcium which reduces tetracycline antibiotic absorption if both are taken at the same time. Tetracycline is a broad spectrum antibiotic that has been supplanted by several new antibiotics.

INDUSTRIAL APPLICABILITY

This invention has application in the medical industry. More specifically, in the medical treatment of esophageal and upper and lower esophageal sphincter disorders.

In compliance with the statute, the invention described herein has been described in language more or less specific as to structural features. It should be understood, however, that the invention is not limited to the specific features shown, since the means and construction shown is comprised only of the preferred embodiments for putting the invention into effect. The invention is therefore claimed in any of its forms or modifications within the legitimate and valid scope of the amended claims, appropriately interpreted in accordance with the doctrine of equivalents.

CLAIMS

We claim:

1. A method of reducing damage to the esophagus and the lower esophageal sphincter caused by physical trauma or gastric acid, comprising the administrating to a patient in need thereof an oral composition comprising:

an alkaline agent with a pH of at least 9.0 to 12.0 mixed in an aqueous vehicle that has relatively high surface tension, high viscosity, and high lateral adhesion.

2. The method as recited in Claim 1, wherein said alkaline agent is an alkali metal hydroxide.

3. The method as recited in Claim 2, wherein said alkali metal hydroxide is potassium hydroxide.

4. The method as recited in Claim 2, wherein said alkali metal hydroxide is potassium hydroxide and between 0.25% to 6.0% by weight.

5. The method as recited in Claim 1, wherein said composition further includes a thickening agent from the following group: xanthan gum, croscarmellose sodium, or microcrystalline cellulose.

6. The method as recited in Claim 2, wherein said alkali metal hydroxide is sodium hydroxide.

7. The method as recited in Claim 3, wherein said composition further includes

one or more additional alkaline agents selected from the group consisting of aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium carbonate.

8. The method as recited in Claim 5, wherein said composition includes calcium carbonate 8% to 22% by weight and magnesium hydroxide 0.1% to 3.0% by weight.

9. The method as recited in Claim 5, wherein said aqueous vehicle is made of one or more organoleptic agents from the following group: hydroxypropyl methyl cellulose, polyethylene glycol or ethylene glycol

10. The method as recited in Claim 5, wherein said composition is formulated into granules.

11. The method as recited in Claim 6, wherein said aqueous vehicle is made of one or more organoleptic agents from the following group: hydroxypropyl methyl cellulose, polyethylene glycol or ethylene glycol

12. The method as recited in Claim 1, wherein said composition is orally administered repeatedly to reduce damage or ameliorate pain.

13. The method as recited in Claim 5, wherein said composition further includes an additional alkaline agent selected from the group consisting of aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium carbonate, and mixtures thereof.

14. The method as recited in Claim 1, wherein said composition includes calcium carbonate 8% to 22% by weight and magnesium hydroxide 0.1% to 3.0% by weight.

15. The method as recited in Claim 2, wherein said composition further includes an organoleptic agrent from the following group: hydroxypropyl methyl cellulose, polyethylene glycol or ethylene glycol.

16 The method as recited in Claim 3, wherein said composition further includes a thickening agent from the following group: xanthan gum, croscarmellose sodium, or microcrystalline cellulose.

17. The method as recited in Claim 16, wherein said composition further includes an additional alkaline agent selected from the group consisting of aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium carbonate.

18. An oral composition for preventing tissue damage to lower or upper esophageal sphincters or to the esophagus caused by inflammation or gastric acid, comprising:

a. 0.25% to 6.0% by weight of an alkaline agent with a pH of at least 9.0 to 12.0 mixed in an aqueous vehicle;

b. a thickening agent stable in a pH 9.0 or greater from the following group consisting of xanthan gum, croscarmellose sodium, or microcrystalline cellulose; and,

c. a sufficient volume of a liquid vehicle to make a composition with a pH value from 9.0 to 11.5, a specific gravity from 1.05 to 1.15 gm/ml; a viscosity

from 6000 to 29,000 cP, and a lateral adhesion value from 10^{-2} to 10^{-6} Newtons.

19. The composition as recited in Claim 18, wherein said alkaline agent is an alkali metal hydroxide.

20. The composition as recited in Claim 19, further including an additional alkaline agent selected from the group consisting of aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium carbonate.

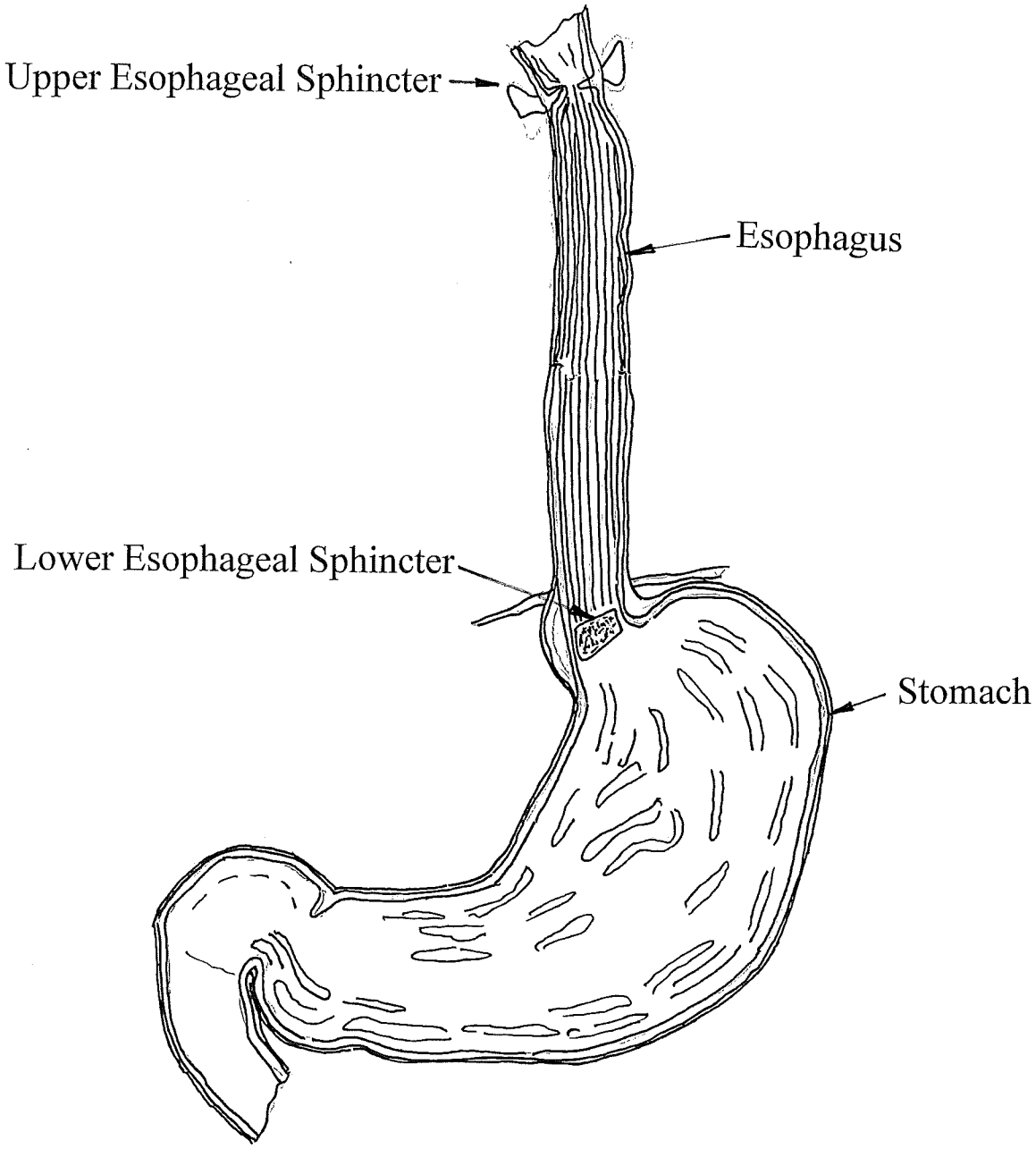
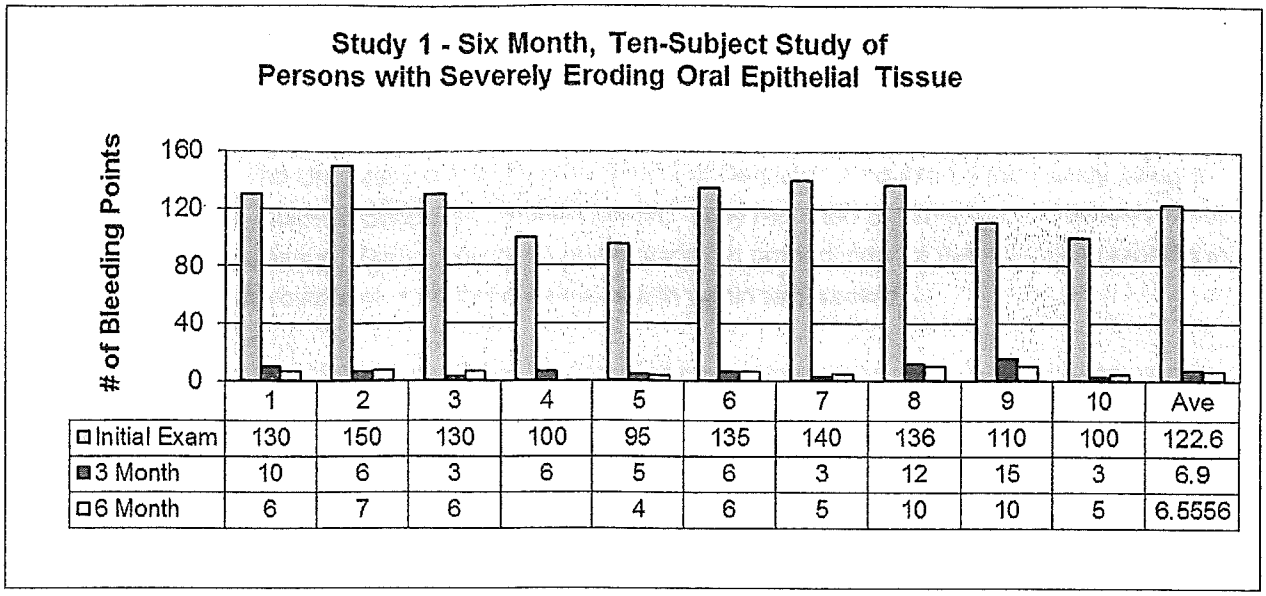
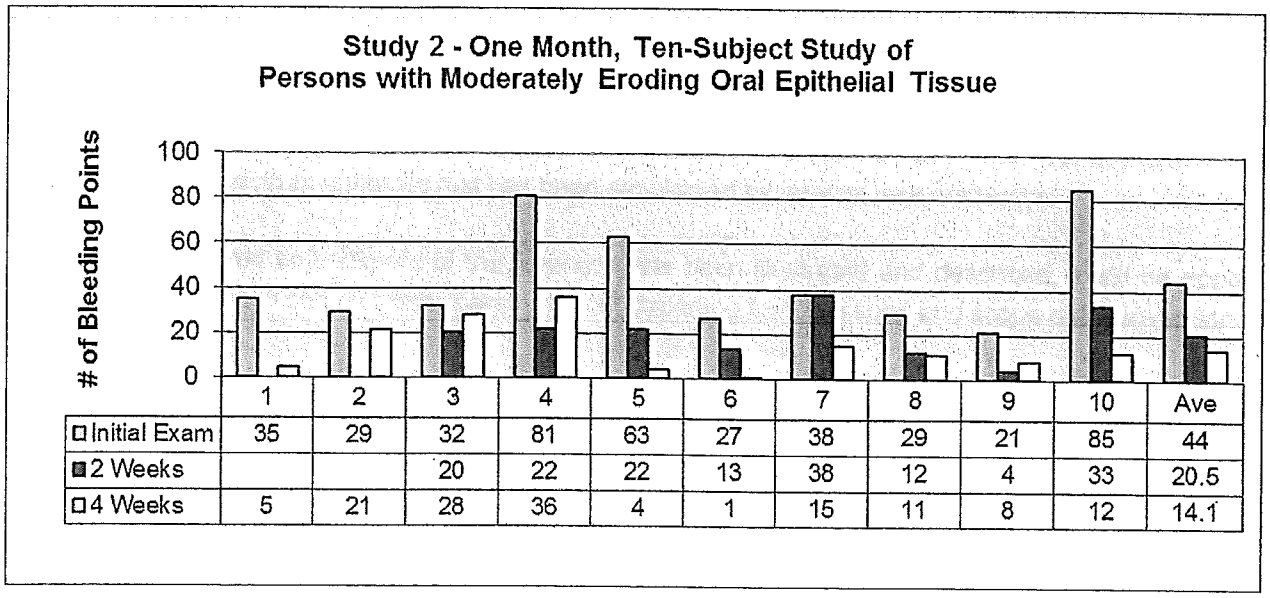

Upper Esophageal Sphincter
Esophagus
Lower Esophageal Sphincter
Stomach

FIG. 1



	1	2	3	4	5	6	7	8	9	10	Ave
Initial Exam	130	150	130	100	95	135	140	136	110	100	122.6
3 Month	10	6	3	6	5	6	3	12	15	3	6.9
6 Month	6	7	6		4	6	5	10	10	5	6.5556

FIG. 2



	1	2	3	4	5	6	7	8	9	10	Ave
Initial Exam	35	29	32	81	63	27	38	29	21	85	44
2 Weeks			20	22	22	13	38	12	4	33	20.5
4 Weeks	5	21	28	36	4	1	15	11	8	12	14.1

FIG. 3

Table 4

P. gingivalis	9.5	5.6	41%
Campylobacter sp.	12.6	7.8	38%
Eubacterium sp.	4.2	4.4	5%
Fusobacterium sp.	10.5	8.9	15%
P. micros	0	4.4	
Beta hemolytic streptococci	9.5	0	100%
Eikenella corrodens	5.3	0	100%

FIG. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/60322

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61P 1/04 (2013.01)
USPC - 424/715, 722
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)
IPC(8): A61K 9/08, 9/09, 31/715, 33/06, 47/36; A61P 1/00, 1/04 (2013.01)
USPC: 424/715, 722; 514/54, 769, 777, 819

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); ProQuest Dialog; Medline/PubMed: alkali, alkaline, aqueous, croscarmellose, esophagus, gerd, hydroxide, increase, microcrystalline, oral, raise, surface, tension, xanthan

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2002/0009478 A1 (DOBROZSI, DJ) January 24, 2002; paragraphs [0012], [0029], [0037], [0104], [0115], [0118], [0134], [0152], [0188]	1-17
Y	US 6066342 A (GUROL, IM, et al.) May 23, 2000; column 7, lines 49-51; column 12; lines 18-21; column 8, lines 56-62	1-17
Y	US 2012/0107414 A1 (LIPP, MM, et al.) May 3, 2012; paragraphs [0094], [0146], [0147]	1-17
Y	US 5681827 A (FIELD, PF) October 28, 1997; column 3, lines 25-27	6, 11
A	US 6395307 B1 (BANNING, D, et al.) May 28, 2002; columns 4-7	1-17

☐ Further documents are listed in the continuation of Box C. ☐

* 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	Date of mailing of the international search report
29 November 2013 (29.11.2013)	07 FEB 2014

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/60322

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.:
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:

Group I: Claims 1-17 are directed toward a method of reducing damage to the esophagus and the lower esophageal sphincter caused by physical trauma or gastric acid.

Group II: Claims 18-20 are directed toward an oral composition for preventing tissue damage to lower or upper esophageal sphincters or to the esophagus caused by inflammation or gastric acid.

-***-Continued Within the Next Supplemental Box-***-

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 additional fees, this Authority did not invite payment of 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.:
1-17

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

International application No.
PCT/US13/60322

-***-Continued from Box III - Observations where unity of invention is lacking-***-

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I: Claims 1-17 are directed toward a method of reducing damage to the esophagus and the lower esophageal sphincter caused by physical trauma or gastric acid.

Group II: Claims 18-20 are directed toward an oral composition for preventing tissue damage to lower or upper esophageal sphincters or to the esophagus caused by inflammation or gastric acid.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I include that has relatively high surface tension, high viscosity, and high lateral adhesion, which are not present in Group II; the special technical features of Group II include 0.25% to 6.0% by weight of an alkaline agent; a thickening agent stable in a pH 9.0 or greater from the following group consisting of xanthan gum, croscarmellose sodium, or microcrystalline cellulose; and a sufficient volume of a liquid vehicle to make a composition with a pH value from 9.0 to 11.5, a specific gravity from 1.05 to 1.15 gm/ml; a viscosity from 6000 to 29,000 cP, and a lateral adhesion value from 10-2 to 10-6 Newtons, which are not present in Group I.

The common technical features of Groups I and II are reducing damage to the esophagus and the lower esophageal sphincter caused by gastric acid; and an alkaline agent with a pH of at least 9.0 to 12.0 mixed in an aqueous vehicle.

These common technical features are disclosed by US 2009/0035393 A1 to Geibel, et al (hereinafter 'Geibel'). Geibel discloses reducing damage to the esophagus and the lower esophageal sphincter caused by gastric acid (gastric acid aids protein digestion; facilitates the absorption of iron, calcium, and vitamin B12; and prevents bacterial overgrowth; when levels of acid and proteolytic enzymes overwhelm the mucosal defense mechanisms, ulcers occur; to avoid damage that is associated with these harsh conditions, gastric acid must be finely regulated; paragraph [0006]); and an alkaline agent with a pH of at least 9.0 to 12.0 ($ZnCl_2$ concentration is alkalinized; paragraph [0013]) mixed in an aqueous vehicle (oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs; paragraph [0069]).

Since the common technical features are previously disclosed by the Geibel reference, the common features are not special and so Groups I and II lack unity.