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(54) Title: PROCESS FOR THE MANUFACTURE OF ENHANCED BIO-ADHERENT POLYMERIC COMPOSITIONS PARTICULARLY FOR COATING MUCOSAL AND EPIDERMAL EPITHELIUM

(57) Abstract: An enhanced bioadherent polymeric pharmaceutical compositions and a process for preparation of the same. The composition comprises anionic species of saccharides or sugars duly anionic by virtue of covalently bonded polarizable substituents selected from sucralfate, sucrose octasulfate and its salts, emulsified blend of a hygroscopic agent, amylopectin starch and polyhydroxyl compound in a weight to weight to weight ratio range from 1:1:10 to 1:4:8. ; one or more anti irritants selected from antacid compounds, acid reducers; proton pump inhibitors; phytotherapeutic herbals and anti-neoplastic agents. A composition comprising sucralfate or sucrose octasulfate in combination with one or more anti-irritant agents in a weight to weight ratio of between 3:1 to 1:6 of sucralfate or sucrose octasulfate to anti-irritant agent, said composition being in either liquid or solid dose form, wherein the anti-irritant agent is one or more taken from the group comprising of a) antacid compounds: b) acid reducers: c) proton pump inhibitors; d) and phytotherapeutic herbals.



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**PROCESS FOR THE MANUFACTURE OF ENHANCED BIO-ADHERENT
POLYMERIC COMPOSITIONS PARTICULARLY FOR COATING MUCOSAL AND
EPIDERMAL EPITHELIUM**

FIELD OF INVENTION

The present invention relates to enhanced bio-adherent polymeric pharmaceutical compositions particularly useful to provide protective or curative coating to the epithelial surfaces, especially in humans.

5 More particularly the present invention relates to pharmaceutical compositions with enhanced bio-adherence.

The present invention further relates to a process for the manufacture of enhanced bio-adherent polymeric compositions particularly useful to provide protective or curative coating to the epithelial surfaces, especially in humans.

10 **BACKGROUND OF INVENTION**

The epithelial surfaces are of two types. Firstly there is the mucosal type which includes those of the naso-pharynx, oro-pharynx, gastrointestinal tract, cysto-urinary and vaginal linings. Secondly, there is the epidermal type of epithelium which includes those external areas of skin directly exposed to ambient environment.

15 There is a constant need in the pharmaceutical industry for improvements on formulations that enable enhanced healing or evaluations of clinical syndromes involving ulceration of epithelium, whether on mucosal surfaces or on epidermal surfaces. The primary improvement of previously reported agents is the use of specialized concentrations of functionalized carbohydrates and anti-irritants, preferably anti-inrritants of the group comprised of antacids, acid reducers, proton pump inhibitors and phytotherapeutical herbals, more preferably carboxylic acid type of antacids, most preferable oxalate, citrate, fumarate, succinate and malate. Functionalized carbohydrates include sucrose octasulfate and sucralfate.

20 U.S. 5,447,918, specifically Example 1 and Example 12 teaches agents including sucrose octasulfate as the functionalized carbohydrates and is found in practice to have enhanced tissue adherence and coating when combined, with citrate. This observation was not limited to citrate but observed also with fumarate, succinate, malate, alpha-keto-gluturate, that is all Kreb's cycle acids (KCA).

30

In addition to this, combinations involving sucrose octasulfate or sucralfate formulated in accordance to Example 7 U.S. 5,447,918) is noted to have unimpeded absorption of cimetidine, ranitidine, nizatidine and omeprazole from the gastrointestinal (GI) tract. Typically, when cimetidine, ranitidine, nizatidine or omeprazole are given with an antacid alone or given with sucralfate alone, the absorption of such compounds from the GI tract is diminished by 15-20% (Ref 24. J Clin Gastroenterol 12 Suppl 2: S54-63, 1990). However, in practice agents combined in accordance to Example 7 formulation of U.S. 5,447,918, showed no such diminution of uptake,

However the time required to effectively treating certain disorders of the epithelium like gastro-esophageal erosions by the composition and method of US'918 is high and it requires more medication per treatment. Further disorders like non-ulcer dyspepsia or "functional dyspepsia" a heartburn-type disorder, bowel irregularity of IBS, irritable bowel syndrome, Helicobacter Pylori gastritis (without antibiotics) are not treated effectively by most gastro-intestinal drugs, including regular sucralfate, prior art sucralfate, antacids, or acid blockers such as omeprazole, rabeprazole, ranitidine and famotidine.

Thus there is need to provide method of preparation and polymeric compositions of enhanced bio-adherence which is capable to overcome the above drawbacks and at the same time provide the advantage of concomitant administration of other medication without entrapment

OBJECT OF THE INVENTION

Therefore, it is an object of the present invention to provide pharmaceutical compositions with enhanced bio-adherence

A further object is to provide pharmaceutical composition with enhanced bio-adherence.

It is further object of the present invention to provide composition adapted to effectively treat certain disorders of the epithelium at reduced time.

Another object of the present invention is to provide composition adapted to reduce the quantity of medication per treatment.

Another object of the present invention is to provide a novel pharmaceutical composition which treats symptoms such as nausea, vomiting and diarrhea.

Yet another object of the present invention is to provide a novel pharmaceutical composition of sucralfate which can be administered simultaneously with other medications without the known non-specific adsorption of these medications on sucralfate i.e entrapment.

Another object of the present invention is to provide method for preparation of pharmaceutical compositions with enhanced bio-adherence

SUMMARY OF INVENTION

According to one aspect there is provided an enhanced bioadherent polymeric pharmaceutical compositions adapted to provide selectively protective and /or curative epithelial coatings , comprising :

- i) anionic species of saccharides or sugars duly anionic by virtue of covalently bonded polarizable substituents selected from sucralfate, sucrose octasulfate and its salts,
- ii) emulsified blend of a hygroscopic agent, amylopectin starch and polyhydroxyl compound in a weight to weight to weight ratio range from 1:1:10 to 1:4:8. ;
- iii) one or more anti irritants selected from
 - a) antacid compounds,
 - b) acid reducers;
 - c) proton pump inhibitors;
 - d) phytotherapeutic herbals and
 - e) anti-neoplastic agents.

According to another aspect there is provided a composition comprising sucralfate or sucrose octasulfate in combination with one or more anti-irritant agents in a weight to weight ratio of between 3:1 to 1:6 of sucralfate or sucrose octasulfate to anti-irritant agent, said composition being in either liquid or solid dose form, wherein the anti-irritant agent is one or more taken from the group comprising of a) antacid compounds: b) acid reducers: c) proton pump inhibitors; d) and phytotherapeutic herbals:

According to another aspect of the invention there is provided a process for preparation of enhanced bioadherent polymeric pharmaceutical compositions adapted to provide selectively protective and /or curative epithelial coatings , said process comprising mixing

- 5 i) anionic species of saccharides or sugars duly anionic by virtue of covalently bonded polarizable substituents selected from sucralfate, sucrose octasulfate and its salts,
- ii) emulsifying blend of a hygroscopic agent, amyloextrin starch and poly-hydroxyl compound in a weight to weight to weight ratio range
10 from 1:1:10 to 1:4:8;
- iii) one or more anti-irritant agent selected from
 - a) antacid compounds,
 - b) acid reducers;
 - c) proton pump inhibitors;
 - 15 d) phytotherapeutic herbals and
 - e) anti-neoplastic agents.

DETAILED DESCRIPTION OF INVENTION:

According to preferred aspect of invention there is provided composition comprising sucralfate or sucrose octasulfate, anti-irritants selected from

- 20 1) antacids, such as citrate, malate, magnesium hydroxide, calcium carbonate, malgadrage, glycine, magnesium carbonate, and other Kreb's cycle acids;
- 2) acid reducers like cimetidine, ranitidine, nizatidine, and famotidine;
- 3) proton pump inhibitors omeprazole, esomeprazole, pantoprazole,
25 rabeprazole, and lansoprazole;
- 4) phytotherapeutic herbals like licorice, chamomile, saw palmetto, oryzanol, alginate, slippery elm bark and
- 5) anti-neoplastic agents

The composition of this invention is in either liquid or solid dose form
30 specifically formulated such that the weight/weight ratio for functionalized carbohydrates like sucralfate and sucrose octasulfate and the anti irritant agents

listed would range respectively from 10:1 to 1:10, preferably 5:1 to 1:6, most preferably 3:1 to 1:6 in either liquid or solid dose form.

The anti-irritant relieving agents are selected from one or more of the following group that include 1) antacids, such as citrate, malate, magnesium hydroxide, calcium carbonate, malgadrage, glycine, magnesium carbonate, Krebs' cycle acids 2) acid reducers like cimetidine, ranitidine, nizatidine, and famotidine 3) proton pump inhibitors omeprazole, esomeprazole, pantoprazole, rabeprazole, and lansoprazole 4) phytotherapeutic herbals like licorice, chamomile, saw palmetto, oryzanol, alginate, slippery elm bark and 5) anti-neoplastic agents like Vincristine, Vinblastine, 6-thioguanine, Tamoxifen, Procarbazine, Prednisone, Paclitaxel, Mercaptopurine, Mitoxantrone, Floxuridine, Altretamine, Carboplatin, Doxorubicin, Carboplatin, Chlorambucil.

The sugars are selected from monosaccharide, polysaccharides, proteosaccharides, but preferably disaccharides, specifically sucrose; the covalently bonded polarizable substituents being oxylated or aminated variety, particularly carbamic, carboxylic, sulfonic, or phosphoric type and specifically sulfate variety of polarizable substituent. A preferred anionic species embodying this component of the invention is sucrose octasulfate or any of its salts such as sucralfate which is the aluminum hydroxide salt of sucrose octasulfate.

Emulsifying agents that work well for this component of the invention are xanthum gum, poly ethylene glycol (PEG), carboxy-methylcellulose, carboxycellulose, arabin, mucilaginous, pectinaceous glycosylated proteins or proteoglycans. Starches that accommodate the purpose of this component of the invention include amyloextrins sourced from corn, maize, wheat, rice or potato. Poly hydroxyl compound that work well for this component of the invention is monosaccharide, disaccharides or polysaccharides. The emulsifying/hygroscopic agents are adapted to provide an emulsion effect of diminished chalkiness when using magnesium hydroxide.

The composition further comprises antimicrobial agents suitable for eliminating microbial-mediated processes in inflamed gastrointestinal tracts or on mucosal or epithelial surfaces.

The anti-irritant role of antacid group is three-fold. One purpose is to produce immediate neutralization of acid. A second purpose is to elevate the potency of functionalized poly/disaccharides, namely sucralfate and sucrose octasulfate, by promoting hydrogen-bonded and metal chelated polymerization of sucralfate or sucrose octasulfate in solution, which in turn when administered either orally or topically on ulcerated epithelial surfaces, higher concentrations of the functionalized poly/disaccharide would be achieved. This occurred when combining Kreb's cycle acids with sucralfate or sucrose octasulfate at weight to weight ratio 1:2 to 1:5. The third purpose is to mutually distract the antacid compounds and sucralfate or sucrose octasulfate compounds from electrostatic adsorption of concomitantly administered drugs. When both the antacid and sucralfate or sucrose octasulfate are present between weight to weight ratios of 1:2 to 1:5 [antacid to sucralfate or sucrose octasulfate], the concomitantly administered acid reducers and proton pump inhibitors do not adsorb to either the antacid or to sucralfate or sucrose octasulfate, thus remaining free in solution for uptake into the bloodstream from the GI tract.

The role of the acid reducers and proton pump inhibitors is to provide prolonged reduction in the hydrochloric acid irritant in the GI tract. The role of the phytotherapeutic herbals is to improve the mucus gel barrier in the GI tract and to diminish inflammation on ulcerated epithelium.

The compositions of the present invention improves potency of sucralfate, permits concomitant administration of antacids compounds and proton pump inhibitors or histamine-2 blockers, and relieves nausea, vomiting and diarrhea in patients who suffer from erosive as well as non-erosive gastroesophageal reflux syndrome (GERD).

Compositions of enhanced bio-adherence of present invention may be dry loose granulated, powdered, tableted or encapsulated. Compositions may be liquid in aqueous single phase, aqueous suspension or aqueous emulsion. Compositions may be in ointment or cream form with petroleum or non-petroleum base.

The compositions have enhanced bio-adherence such that when applied such compositions will coat the epithelium to effect protection or cure from noxious, erosive, inflammatory or infectious injury.

Application of compositions may be effected by oral consumptions.
5 Compositions may be applied topically in the case of epidermal epithelium or by extrusion/introduction through an orifice in the case of indwelling mucosal surfaces of urinary bladder or vaginal vault or colon.

The process of present invention comprise mixing the components as mentioned above in the given proportion. It is then tabletted, encapsulated or
10 converted to the liquid form or to the form of ointment by conventional methods.

Disclosure of the detail effects of enhanced bio-adherence, is better obtained by discussing one of the embodiments of this invention, that of high-potency sucralfate. It should be noted, however, that other embodiments have very similar results and that any practitioners skilled in the art can indeed apply
15 this invention so as to benefit from the effects of enhanced bio-adherence.

Sucralfate is of a class of cyto-therapeutic agents whose pharmacologic is solely on the basis of bio-adherence. Common drug of effects of sucralfate is due in part to its surface bio-adherence.

The following examples of this invention listed below are illustrative only;
20 they are not at all intended to limit the scope of the invention, but rather to exemplify the practicality of this invention. These examples depict potential embodiments. The preferred embodiment of the composition are those which contain sucralfate or sucrose octasulfate. It should be borne in mind, however, that other carbohydrate poly sulfonates could be used as well. Additionally that
25 the use of other KCA's such as citrate, fumarate, succinate, oxalate, malate or alpha keto glutarate could be substituted with compounds that replace the carboxylate groups with carbamide, phosphonic, phosphate or even sulfonic, sulfonate substituents.

The following examples illustrate formulations wherein in the invention acts
30 as a surface active high potency anti-irritant material.

Example 1: Liquid Formulation

Ingredients	mg/5 ml
Sucralfate or Sucrose Octasulfate	250-500
Methyl Paraben USP	5-10 mg
Propyl Paraben USP	5-10 mg
Citrate, fumarate, succinate or Malate	100-175 mg
Magnesium Hydroxide	175 mg
Calcium Carbonate	175 mg
Xanthum Gum	50 mg
Starch	50 mg
Sodium Saccharin	3.0-5.0
Sorbitol USP	200-350 mg
Flavor	q.s.
Water	5.0ml

Example 2: Liquid Formulation with Special Emulsion Formula

Ingredients	mg/5 ml
Sucralfate or Sucrose Octasulfate	250-500
Methyl Paraben USP	5-10 mg
Propyl Paraben USP	5-10 mg
Citrate, Fumarate, Succinate or Malate	100-175 mg
Simethicone	40-80
Calcium Carbonate /Magnesium Hydroxide	180 mg/150 mg
Sodium Saccharin	3.0-5.0
Starch	50-200 mg
Xanthum Gum	50 mg
Sorbitol USP	200-350 mg
Flavor	q.s.
Water	5.0ml

5

In this example the xanthum gum and starch and sucrose octasulfate are in weight ratios vary from 1:1:10 to 1:4:8 and provide for an emulsion that is particularly smooth to taste, less gritty and chalky when using magnesium hydroxide. The increase concentration of starch in the presence of xanthum gum and sucrose octasulfate appear key.

15

Example 3: Acid Reducer Formulation

Ingredients	Weight
Sucralfate or Sucrose Octasulfate	250-500 mg
Methyl Paraben USP	5-10 mg
Propyl Paraben USP	5-10 mg
Citrate, Fumarate, Succinate or Malate	100-175 mg
Cimetidine, Ranitidine, Nizatidine or Famotidine	20-400
Calcium Carbonate	175 mg
Sodium Saccharin	3.0-5.0
Sorbitol USP	200-350 mg
Flavor	q.s.
Water	5.0ml

5 **Example 4: Proton Pump Inhibitor Formulation**

Ingredients	Weight
Sucralfate or Sucrose Octasulfate	250-500 mg
Methyl Paraben USP	5-10 mg
Propyl Paraben USP	5-10 mg
Citrate, Fumarate, Succinate or Malate	100-175 mg
Omeprazole, Esomeprazole, Pantoprazole, Rabeprazole, and Lansoprazole	10-40
Calcium Carbonate	175 mg
Xanthum Gum	50 mg
Starch	50 mg
Sodium Saccharin	3.0-5.0
Sorbitol USP	200-350 mg
Flavor	q.s.
Water	5.0ml

Example 5: Phytotherapeutic Formulation

Ingredients	Weight
Sucralfate or Sucrose Octasulfate	250-500 mg
Methyl Paraben USP	5-10 mg
Propyl Paraben USP	5-10 mg
Citrate, Fumarate, Succinate or Malate	100-175 mg
Licorice, Chamomile, Saw Palmetto, Oryzonol, Alginate, Slippery Elm Bark	10-400
Calcium Carbonate	175 mg
Xanthum Gum	50 mg
Starch	50 mg
Sodium Saccharin	3.0-5.0
Sorbitol USP	200-350 mg
Flavor	q.s.
Water	5.0ml

ILLUSTRATION OF ENHANCED SUCRALFATE ADHERENCE/POTENCY

GI tract ulcers induced by ethanol in 12 laboratory rabbits was treated 1 day later by enteral administration of generic 10% sucralfate suspension (n=4), 10% sucralfate-aluminum hydroxide/magnesium hydroxide suspension (n=4) and Example No. 6 Formulation of US Patent 5,447,918 containing malate or citrate (10% sucralfate) Sucralfate Antacid Suspension (n=4) at equal volumes. At 3 hours after administration, a 1 cm square section of GI tract was examined for the content of adherent aluminum both in the ulcer crater and in surrounding normal tissue. Concentration of adherent aluminum was assayed by atomic absorption spectroscopy then correlated to sucralfate concentration.

Table 1: Enhanced Sucralfate Potency/Adherence

<u>SUCRALFATE CONCENTRATION ON G.I. LINING</u> <u>Three Hours Following Administration</u>					
<u>GENERIC</u> <u>Sucralfate</u> <u>Suspension</u>		<u>GENERIC</u> <u>Sucralfate-Antacid</u> <u>Suspension</u>		<u>GASTRAFATE</u> <u>EXAMPLE 2</u> <u>FORMULATION</u> <u>Emulsified Suspension</u>	
<u>SUCRALFATE</u>		<u>SUCRALFATE</u>		<u>SUCRALFATE</u>	
Conc $\mu\text{g}/\text{cm}^2$ on Normal GI Tract (n=4)	Conc $\mu\text{g}/\text{cm}^2$ on Ulcerated GI Tract (n=4)	Conc $\mu\text{g}/\text{cm}^2$ on Normal GI Tract (n=4)	Conc $\mu\text{g}/\text{cm}^2$ on Ulcerated GI Tract (n=4)	Conc $\mu\text{g}/\text{cm}^2$ on Normal GI Tract (n=4)	Conc $\mu\text{g}/\text{cm}^2$ on Ulcerated GI Tract (n=4)
<u>3.1</u> (+/- 0.12)	<u>3.6</u> (+/- 0.10)	<u>6.1</u> (+/- 0.31)	<u>9.4</u> (+/- 0.62)	<u>22.1</u> (+/- 0.51)	<u>82.5</u> (+/- 1.32)

Example No. 6 Formulation of US Patent 5,447,918 containing malate, (Example No. 2 above), manufactured by Sterling Foster Pharmaceutical and Glen Copel Pharmaceutical USA marketed under trade name Gastrafate Rx appear to concentrate on normal un-injured GI tract 6-7x's and 3-4x's greater than generic sucralfate suspension and sucralfate antacid suspension. Gastrafate concentrate on acid-injured GI tract 23x's greater and 8-9x's greater than generic sucralfate suspension and sucralfate antacid suspension.

Similar results were seen using sucrose octasulfate instead of sucralfate.

UNIMPEDED UPTAKE OF ACID REDUCERS

When given alone with either sucralfate or magnesium hydroxide/
aluminum hydroxide antacid, fifteen to twenty percent, 15-20%, of dissolved
5 cimetidine, ranitidine, and famotidine was not absorbed from the GI tract into the
blood stream. However when sucralfate or sucrose octasulfate was
coadministered with magnesium hydroxide/aluminum hydroxide, this diminution
of uptake of cimetidine and ranitidine disappeared. It appears sucralfate and
antacid at a weight:weight ratio of 4:1 to 2:1 mutually distract each other thus
10 allowing dissolved histamine-2 blockers to be freely absorbed from the GI tract.

Table: 2 AUC for Cimetidine and Ranitidine With Sucralfate, Magnesium Hydroxide and Aluminum Hydroxide

Compositions	AUC for Cimetidine	Compositions	AUC for Ranitidine
Cimetidine Alone	54.3	Ranitidine Alone	55.2
Sucralfate and Cimetidine	42.2	Sucralfate and Ranitidine	43.5
Sucralfate Magnesium Hydroxide, Aluminum Hydroxide (4:1) with Cimetidine	49.8	Sucralfate Magnesium Hydroxide, Aluminum Hydroxide (4:1) with Ranitidine	51.3
Sucralfate Magnesium Hydroxide, Calcium Carbonate, (2:1) with Cimetidine	54.2	Sucralfate Magnesium Hydroxide, Aluminum Hydroxide (2:1) with Ranitidine	54.9

This phenomenon most likely occurs with other co-administered
15 compounds such as proton pump inhibitors, anti-microbials, anti-seizure drugs,
and theophylline type products.

CLINICAL ILLUSTRATION OF INVENTION

In a double-blind, randomized placebo-controlled clinical trial of 50
patients, 16 with erosive GERD and 34 with non-erosive GERD, Example No. 6

Formulation of US Patent 5,447,918 containing malate (Example No. 2 above) was tested against placebo in the treatment of symptoms of GERD. Symptom relief included relief of chest pain, heartburn sensation, and acid regurgitation.

Unexpected and novel were the relief of nausea, the relief of vomiting and relief of diarrhea. See Table 3.

This same embodiment of this invention was noted to have significant comparative improvement of currently available compositions for the relief of symptoms, healing of erosions, and reduction of helicobacter pylori counts. See Table 4.

Table 3: Effects of Gastrafate Suspension vs Placebo

SYMPTOMS	Gastrafate Group	Maximum Difference Noticed	Placebo Group	Maximum Difference Noticed	Statistical Significance
Chronic Severe Heartburn	3 months-2 years		3 mths-2 years		
Number of Daily Episodes	3 or more per day		3 or more per day		
Number Completed Study	26		24		
Number with Erosive Disease	8		8		
Number with Non-erosive	18		16		
Relief of Heartburn	77% (20/26)	In 3-4 days	21% (5/24)	In 14-17 days	p<0.05
Relief of Acid Regurgitation	71% (10/14)	In 6-8 days	38% (5/13)	In 14-17 days	p<0.10
Relief of Chest Pain	82% (9/11)	In 6-8 days	50% (5/10)	In 14-17 days	p<0.04
Relief of Other Assoc'd Symptoms [Nausea Vomiting Dysphagia]	88% (14/16)	In 6-8 days	53% (8/15)	In 14-17 days	p<0.08
Relief of Irregular Bowel Movements [Loose Stools]	80% (21/26)	In 6-8 days	30% (7/24)	In 14-17 days	p<0.05

Table 4: Effects of Gastrafate Rx Suspension vs Ranitidine, Omeprazole, Antacids on Symptom Relief, Healing and Helicobacter Pylori Counts

Composition	Symptom Relief Within 12 Hours	Healing Erosions Hyperemic Irritations	Reduction of Helicobacter Pylori Counts
Magnesium & Aluminum Hydroxide 20 cc q 4-6 hours prn for 7 days	38%	40%	5%
Ranitidine 300 mg bid for 7 days	45%	50%	2%
Omeprazole 40 mg for 7 days	60%	60%	2%
Generic Sucralfate Suspension 15cc bid for 7 days	40%	45%	50%
Gastrafate Rx 15cc bid for 7days	89%	97%	98%

5 **Beneficial Effects of Enhanced Bio-Adherence**

Compositions of enhanced bio-adherence are useful in the treatment of oral, nasal, vaginal, cysto-mucosal, dermatological irritation, infection, erosions, ulcerations or lacerations. The clinical effects of enhanced bio-adherence is immediate symptomatic relief, accelerated healing, relief of conditions resulting from noxious injury to the epithelium.

The composition of the present invention was compared with those containing sucralfate and with that of the US'918. the effects of the composition were evaluated in terms of bioadherence, time taken for healing of erosions, pain improvements, relief of nausea and vomiting, bowel habits and reduction of Helicobacter pylori.

The results are provided in table 5 below.

Table 5

Invention	Bioadherence	Healing of Erosions	Pain Improvement In 1wks	Relief of Nausea & Vomiting	Relief of Bowel Habits Constipative/ Diarrhea	Reduction of Helicobacter Pylori Bacteria causative agent for Gastritis
Sucralfate	B	70% in 42days	30%	0%	0%	50%
US'918	1.5-2 x B	70% in 26days	45%	25%	0%	78%
present invention	7 – 23 x B	90% in 10days	89%	86%	75%	98%

It is found that the present invention scores over the composition with sucralfate and US '918 in the following manner:

1. Less medication required for desired healing;
 - 5 a. Less in terms of absolute amounts per dose
 - b. Less in terms of course of treatment, being reduced to
 $\frac{1}{4}$ to $\frac{1}{3}$ of the usual time required to treat erosions.
2. Unexpected addition benefits of relief of nausea, vomiting,
3. Unexpected additional benefits of relief of irregular bowel habits.
- 10 4. Non-Antibiotic method to treat Helicobacter Pylori, the causative agent for
 certain forms of gastritis.

CLAIMS

1. An enhanced bioadherent polymeric pharmaceutical compositions adapted to provide selectively protective and /or curative epithelial coatings ,
5 comprising :
- i) anionic species of saccharides or sugars duly anionic by virtue of covalently bonded polarizable substituents selected from sucralfate, sucrose octasulfate and its salts,
 - 10 ii) emulsified blend of a hygroscopic agent, amylopectin starch and poly-hydroxyl compound in a weight to weight to weight ratio range from 1:1:10 to 1:4:8. ;
 - iii) one or more anti irritants selected from
 - a) antacid compounds,
 - b) acid reducers;
 - 15 c) proton pump inhibitors;
 - d) phytotherapeutic herbals and
 - e) anti-neoplastic agents.
2. A composition comprising sucralfate or sucrose octasulfate in combination with one or more anti-irritant agents in a weight to weight ratio of between
20 3:1 to 1:6 of sucralfate or sucrose octasulfate to anti-irritant agent, said composition being in either liquid or solid dose form, wherein the anti-irritant agent is one or more taken from the group comprising of a) antacid compounds: b) acid reducers: c) proton pump inhibitors; d) and phytotherapeutic herbals.
- 25 3. A composition according to claim 1 or 2 wherein the antacid compound is selected from citrate, fumarate, succinate, malate, magnesium hydroxide, calcium carbonate, malgadrage, aluminum hydroxide, glycine, magnesium carbonate.
- 30 4. A composition according to claim 1 or 2 wherein the acid reducer is selected from cimetidine, ranitidine, nizatidine, famotidine.

5. A composition according to claim 1 or 2 wherein the proton pump inhibitor is selected from omeprazole, esomeprazole, pantoprazole, rabeprazole, lansoprazole.
6. A composition according to claim 1 or 2 wherein the phytotherapeutic
5 herbal is selected from licorice, chamomile, saw palmetto, oryzanol, alginate, slippery elm bark.
7. A composition according to claim 1 or 2 wherein the anti-neoplastic agent is selected from the group of Vincristine, Vinblastine, 6-thioguanine, Tamoxifen, Procarbazine, Prednisone, Paclitaxel, Mercaptopurine,
10 Mitoxantrone, Floxuridine, Altretamine, Carboplatin, Doxorubicin, Carboplatin, Chlorambucil.
8. A composition according to claim 1 or 2 wherein the Krebs cycle acids as selective anti-irritant agent are present at weight-weight ratio of 1:2 to 1:5 to sucralfate or sucrose octasulfate, adapted to promote hydrogen-bonded
15 and metal chelated polymerization of sucralfate and sucrose octasulfate.
9. A composition according to claim 1 or 2 wherein the anti-irritant agents selected from magnesium hydroxide, calcium carbonate, malgadrade, aluminum hydroxide, glycine, magaldrate, magnesium carbonate are present in a weight to weight ratio of 1:2 to 1:5 with sucralfate or sucrose
20 octasulfate is adapted to distract sucralfate and sucrose octasulfate and the antacid from adsorption to co-administered anti-irritants.
10. A composition according to claim 1 or 2 wherein the anti-irritant agent comprising of one or more of the agents selected from aluminum hydroxide, magnesium hydroxide, calcium carbonate, magnesium
25 carbonate, malgadrade, glycine, bismuth, citrate, fumarate, succinate, malate are present in amounts sufficient to give 10 or more milliequivalents of acid neutralizing capacity per administered dose.
11. A composition according to claim 1 comprising antimicrobial agents suitable for eliminating microbial-mediated processes in inflamed
30 gastrointestinal tracts or on mucosal or epithelial surfaces.
12. A composition of claim 1 wherein the emulsifying agent is selected from xanthum gum, starch, poly ethylene glycol (PEG), carboxy-

methylcellulose, carboxy-cellulose, algin, mucilaginous, pectinaceous glycosylated proteins or proteoglycans and adapted to provide an emulsion effect of diminished chalkiness when using magnesium hydroxide.

- 5 13.A composition as claimed in any preceding claim adapted to be administered to inflamed or ulcerated mucosa or epithelium so as to accelerate healing.
- 14.A composition as claimed in any preceding claim adapted to be administered to relieve nausea and/or vomiting and/or diarrhea.
- 10 15.A composition as claimed in any preceding claim adapted to be administered to heal erosive and non-erosive gastroesophageal reflux disorder.
- 16.A process for preparation of enhanced bioadherent polymeric pharmaceutical compositions adapted to provide selectively protective and/or curative epithelial coatings, said process comprising mixing
- 15 i) anionic species of saccharides or sugars duly anionic by virtue of covalently bonded polarizable substituents selected from sucralfate, sucrose octasulfate and its salts,
- ii) emulsifying blend of a hygroscopic agent, amylopectin starch and
- 20 poly-hydroxyl compound in a weight to weight to weight ratio range from 1:1:10 to 1:4:8,
- iii) mixture of one or more anti-irritant agent selected from
- a) antacid compounds,
- b) acid reducers;
- 25 c) proton pump inhibitors;
- d) phytotherapeutic herbals and
- e) anti-neoplastic agents.