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(54) **ANTI-ULCER COMPOSITION**

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(57) **ABSTRACT**

A pharmaceutical composition for the prophylaxis or treatment of peptic ulcers includes a biocompatible anionic polysaccharide material containing glucuronic acid.

ANTI-ULCER COMPOSITION

INTRODUCTION

[0001] Peptic ulcer disease (PUD) is a broad classification for more specific conditions known as gastric or duodenal ulcers. Ulcers are clinically characterized as an erosion of the mucosal lining of the gastrointestinal tract. Duodenal ulcers are four times more common than gastric ulcers in the general population; however, among NSAID users, gastric ulcers are more common.

[0002] The etiology of PUD was originally thought to be an imbalance of several factors that included gastrointestinal secretions (gastric acid, pepsin, bile salts, and enzymes), and dietary intake (spicy foods, alcohol, caffeine). Later, it was discovered that *Helicobacter pylori* is present in more than 90% of duodenal ulcers and more than 75% of gastric ulcers not caused by NSAID use. PUD is therefore now treated as an infectious condition, cured with antibiotics. In the small percentage of PUD cases not caused by *H. pylori,* the cause can include the use of ulcerogenic drugs, mostly non-steroidal andinflammatory drugs (NSAIDs) and hypersecretory diseases.

[0003] Ulcers can be asymptomatic for an indefinite period of time. The most common symptom is pain. Weight loss and anorexia can occur in severe cases, and other non-specific symptoms include nausea, belching, bloating, abdominal distension, food intolerance, and heartburn. Complications of PUD could manifest as frequent symptoms, perforation, hemorrhage, and gastric outlet obstruction. Hemorrhage is the most common complication, occurring in an estimated 25% of cases, and sometimes is the initial presentation.

[0004] The goals of therapy for peptic ulcer disease are pain relief, ulcer healing, and eventually, complete cure. Prior to the discovery of *H. pylori,* therapy was directed at neutralizing or suppressing gastric acid secretions. Ulcer healing can occur without drug therapy, but medication promotes faster healing and reduces the potential for complications. For ulcers that are not caused by *H. pylori*—such as NSAID-induced ulcers—acid-suppressive therapy alone is recommended, along with discontinuation of the offending NSAID. If the NSAID cannot be discontinued, a histarninine-2 antagonist, proton pump inhibitor, or misoprostol type drugs are used.

[0005] As with most drugs, a number of side effects are involved in their use. Paraphrasing further a recent educational text [Bullard W., Peptic Ulcer Disease, US National Community Pharmacists Association, June 1997], the therapeutic and side effects can be summarised as follows.

[0006] Antacids provide symptomatic relief by neutralizing acid in the stomach, but their duration of action requires the patient to take multiple doses each day. Side effects are diarrhoea (mainly caused by magnesium salts), constipation (associated with aluminum salts), mineral imbalance, and alkalosis. Compliance is often a problem with this regimen.

[0007] Histamine-2 receptor antagonists, with cimetidine as the prototype, were introduced in late 70's, and ranitidine, famotidine, and nizatidine soon followed, and quickly became the most widely prescribed medications. They are highly effective in healing ulcers, however, recurrence was common, which led to the practice of maintenance therapy. These agents' most notable adverse effects are drug interactions of the cytochrome P450 system (most common with cimetidine).

[0008] Sucralfate became available to treat GI disorders in the early 80's, providing more of a barrier effect for the mucosal lining. Healing rates are similar to that to that of histarnine-2 agonists, but the dosing schedule can become cumbersome—sucralfate has to been given separately from meals, and can reduce the absorption of other medications.

[0009] Proton-pump inhibitors (PPIS) are the newer class of agents in acid-suppressive therapy. Omeprazole was released in 1989 and lansoprazole in 1995. These agents interfere with H+,K+-ATPase finction that is necessary for parietal cell acid secretion. Faster healing rates have been observed with PPIs in comparison with other therapies. However, recurrence rates are similar to the other classes of agents.

[0010] One other agent that is important in protecting the mucosa lining of the stomach is misoprostol, the first synthetic prostaglandin E1 analog for the treatment of ulcers. It is a first-line therapy for active and preventive therapy of NSAID-induced gastric ulcers. This agent is also recommended for patients who cannot or should not discontinue NSAID therapy. Diarrhoea is the most common side effect and appears to be dose-dependent. However, misoprostol is a potential abortifacient, and its use is contraindicated in women who are pregnant or trying to conceive.

[0011] Of course, PUD caused by *H. pylori* additionally requires antimicrobial therapy, but monotherapy is not recomrnended due to the potential for resistance. Antibiotic therapy should always be combined with acid-suppressive therapy when treating *H. pylori.* The most common regimen for *H. pylori* eradication is triple antibiotics (amoxicillin or tetracycline/clarithromycin, metronidazole, and bismuth subsalicylate). Compliance with triple therapy plus an antisecretory drug (known as quadruple therapy) is difficult because of the number of pills the patient must take. Therefore many dual therapy regimens have been developed and are excellent alternatives. Side effects are based on the chosen antimicrobial agents and may include nausea, taste disturbance, diarrhoea, cramps and headache.

[0012] Thus, acid-suppressive therapy is omnipresent in PUD treatment and may involve various adverse effects as well as increase the treatment expenses for the patient.

[0013] Certain other substances on a polysaccharidic basis have also been suggested for use as anti-acid agents in PUD treatment which do not seem to have been introduced into therapeutic practice as yet . These involve, for instance, the sodium salt of alginic acid as disclosed in U.S. Pat. No. 2,902,479, or more recently choline esters of acidic polysaccharides disclosed in U.S. Pat. No. 5,300,493.

[0014] The invention in particular involves the use of polyanhydroglucuronic acids and salts thereof. The term polyanhydroglucuronic acid and salts there of as used herein also includes copolymers thereof, especially with anhydroglucose. This is hereinafter referred to as PAGA.

[0015] Co-pending patent application PCT IE98/00004 describes particular polyanhydroglucuronic acids and salts thereof and a method of preparing such compounds. In

particular therefore, the term polyanhydroglucuronic acids and salts thereof includes the acids and salts referred to in this co-pending application.

Statements of Invention

[0016] We have now surprisingly established that certain anionic polysaccharides containing glucuronic acid can by themselves be applied for the purpose of PUD treatment. In particular, we have found that peroral application of suitable salts or complex salts of glucuronoglucanes, notably those bound with 1,4 β glycosidic bonds in the form of PAGA as prepared especially according to PCT IE/98/00004, and intermolecular complexes thereof with cationic polymer counterions such as, notably, gelatine or chitosan, preferably in the form of tablets, pellets, granules, or microspheres, was effective in the therapy of peptic ulcers. By analogy With the known behaviour of these glucuronoglucanes on various biological surfaces it is presumed that they can promote formation, on the inner mucosal tissue of stomach or duodenum, of an efficient protective barrier film capable of inhibiting erosion of the mucosal tissue.

[0017] In addition, this type of polymer has the advantage of being able to fulfil multiple functions in the gastrointestinal tract. Due to the bound cation(s) it can neutralise the excess acidity of the gastric acids. As an efficient haemostat it can assist in the control of eventual haemorraging complications. It can further carry active substances such as histamine-2 antagonists suppressing production of gastric acids or proton pump inhibitors.

[0018] An important advantage is that the protective film provides a long-term protection of the gastric or duodenal mucous membrane while, at the same time, releasing gradually, and in a controlled manner, the active substances bound to it. Besides H2 antagonists or proton pump inhibitors, these releasable active substances may also involve an antibiotic (such as clarithromycin) destined to eradicate *H. pylori* or the neutralising cation (such as BiO+, Al3+, Mg2+, Ca2+, Na+) or combinations thereof. The fact that the protective and therapeutically active substance—salt of PAGA or intermolecular complex thereof—can simultaneously serve as a vehicle releasing other biologically active substances and their therapeutically efficient combinations contributing to the healing process represents an essential advantage of the application of salts or complex salts of PAGA and intermolecular complexes thereof according to the invention over the commonly used drugs and therapy regimens.

[0019] Therapy using PAGA salts and intermolecular complexes thereof according to the invention thus potentially involves lower and/or less frequent dosing which brings the advantage of being less cumbersome and cost effective for the patient.

[0020] Last but not least, a major advantage is due to the inherent biocompatibility, lack of toxicity and virtual absence of adverse side effects inherent to PAGA salts and intermolecular complexes, especially when prepared according to the method of, and as explained in PCT IE/98/00004.

[0021] According to the invention there is provided a pharmaceutical composition for the prophylaxis or treatment of peptic ulcers including a biocompatible anionic polysaccharide material containing glucuronic acid.

[0022] Preferably the polysaccharide is derived from a starch, cellulose or gum, or is of microbial origin.

[0023] In one embodiment of the invention the polysaccharide material is polyanhydroglucuronic acid, biocompatible salts thereof, copolymers thereof and intermolecular complexes thereof.

[0024] Most preferably the biocompatible intermolecular polymer complex is a complex of:

[0025] an anionic component comprising a linear or branched polysaccharide chain containing glucuronic acid; and

[0026] a non protein cationic component comprising a linear or branched natural, semi synthetic or synthetic oligomer or polymer.

[0027] Preferably at least 5% of the basic structural units of the anionic component are glucuronic acid.

[0028] In one embodiment of the invention the cationic component contains nitrogen that either carries a positive charge or the positive charge is induced by contact with the polysaccharidic anionic component.

[0029] In this case preferably the cationic component is selected from derivatives of acrylamide, methacrylamide and copolymers thereof.

[0030] Ideally the cationic component is selected from polyacrylamide, copolymer of hydroxyethylmethacrylate and hydroxypropylmetacrylamide, copolymers of acrylamide, butylacrylate, maleinanhydride and/or methylmetacrylate.

[0031] The cationic component may be a cationised natural polysaccharide.

[0032] Preferably the polysaccharide is a starch, cellulose or gum.

[0033] Typically the gum is guargumhydroxypropyltriammonium chloride.

[0034] In a further embodiment of the invention the cationic component is a synthetic or semi-synthetic polyamino acid.

[0035] Preferably the cationic component is polylysin, polyarginin, or α, β-poly-[N-(2 hydroxyethyl)-DL-aspartamide].

[0036] In a further embodiment of the invention the cationic component is a synthetic anti-fibrinolytic.

[0037] Preferably the anti-fibrinolytic is a hexadimethrindibromide (polybren).

[0038] In another embodiment of the invention the cationic component is a natural or semi-synthetic peptide.

[0039] Preferably the peptide is a protamine, gelatine, fibrinopeptide, or derivatives thereof.

[0040] In a further embodiment of the invention the cationic component is an aminoglucane or derivatives thereof.

[0041] Preferably the aminoglucane is fractionated chitin or its de-acetylated derivative chitosan.

[0042] The aminoglucane may be of microbial origin or is isolated from the shells of arthropods such as crabs.

[0043] In a particularly preferred embodiment of the invention the anionic component is polyanhydroglucuronic acid and/or bicompatible salts and/or copolymers thereof.

[0044] Preferably the polyanhydroglucuronic acid and salts thereof contain in their polymeric chain from 8 to 30 percent by weight of carboxyl groups, at least 80 per cent by weight of these groups being of the uronic type, at most 5 percent by weight of carbonyl groups, and at most 0.5 percent by weight of bound nitrogen.

[0045] Ideally the polyanhydroglucuronic acid and salts thereof contain in their polymeric chain at most 0.2 percent by weight of bound nitrogen.

[0046] In a preferred embodiment the molecular mass of the polymeric chain of the anionic component is from 1×10^3 to 3×10^5 Daltons.

[0047] Preferably the molecular mass of the polymeric chain of the anionic component ranges from 5×10^3 to 1.5×10^5 Daltons.

[0048] Preferably the content of carboxyl groups is in the range of from 12 to 26 percent by weight, at least 95 percent of these groups being of the uronic type.

[0049] Ideally the anionic component contains at most 1 percent by weight of carbonyl groups.

[0050] Preferably the carbonyl groups are intra- and intermolecular 2,6 and 3,6 hemiacetals, 2,4- hemialdals and C2-C3 aldehydes.

[0051] In a preferred embodiment of the invention the cationic component is gelatine.

[0052] In another preferred embodiment of the invention the cationic component is chitosan.

[0053] The composition may include at least one biocompatible biologically active substance.

[0054] The composition may alternatively or additionally include at least one biologically acceptable adjuvant.

[0055] The composition may alternatively or additionally include at least one pharmaceutically active adjuvant.

[0056] Preferably the adjuvant is an anti-ulcer agent.

[0057] Ideally the anti-ulcer agent is an antibiotic which is active against *Helicobacter pylori* such as clarithiyromycin.

[0058] The adjuvant may be a H_2-antagonist such as cimetidine.

[0059] Alternatively the adjuvant is a combination of an antibiotic which is active against *Helicobacter pylori* and a H_2-antagonist.

[0060] The composition may include bismuth salt.

[0061] The composition may be in a form for oral administration such as a tablet, pellet, capsule, granule, or microsphere.

DETAILED DESCRIPTION

[0062] The invention will be more clearly understood from the following description thereof given by way of example only.

EXAMPLES OF POLYMER COMPLEXES OF GLUCURONOGLUCANES

Example 1

Material

[0063] long-fibre cotton—medicinal cotton wool oxidised by N_XO_y (proprietary)

[0064] C_6OOH 18.8% b/w

[0065] ash content<0.1% b/w

[0066] ΣC=O 0.6% b/w

[0067] 20% solution Na_2CO_3 (Lachema, a.s. Neratovice)

[0068] $CaCL_2.6H_2O$ anal.grade (Lachema, a.s. Neratovice)

[0069] demineralised water 2 μS

[0070] ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)

[0071] acid acetic anal.grade (Lachema, a.s. Neratovice)

[0072] H_2O_2 anal.grade 30% (Lachema, a.s. Neratovice)

[0073] N-HANCE 3000 guargumhydroxypropyltriammoniumchloride

[0074] (Aqualon—Hercules)

Equipment

[0075] mixer: bottom stirring, 150 1 (duplicator), stainless steel EXTRA S

[0076] vibrating screen: stainless steel, 150 mesh

[0077] rotary air pump: rotor diameter 150 mm

[0078] turbostirrer: ULTRA TURAX (Janke-Kunkel)

[0079] beaker: 5 1

[0080] pH meter PICCOLO

[0081] thermocouple thermometer

[0082] Procedure:

[0083] 30g of N-HANCE 3000 were placed into and 5 1 beaker and 3 1 of demineralised water 2 μS were added. Contents of the beaker were intensely stirred for 30 minutes. The pH value was adjusted to less than 4.5 by addition of an acetic acid solution leading to a viscosity rise. 60 1 of demineralised water 2 μS were introduced into a mixer. Then 3 kg of $CaCl_2.6H_2O$ anal.grade were added and the contents heated up to a temperature of 50° C. under stirring. On dissolution of the calcium chloride the stiring was interrupted and 2.7 kg of the raw oxidised cotton wool were introduced. The mixer was closed and the contents were agitated for 120 seconds. Then the pH value of the contents was adjusted by addition of a 20% solution of Na_2CO_3 to 6-6.5 and 13 kg of H_2O_2 30% were introduced. The fibre suspension was slowly agitated for 10 minutes. Then the pH value was readjusted to 4.5-5.0 and the prepared viscous solution of N-HANCE 3000 was introduced. The contents of the mixer were stirred intensely for 30 seconds. Subse-

quently 60 1 of synthetic rectified ethanol conc. 98% were introduced into the mixer. After another 15 seconds from adding the ethanol the contents of the mixer were transferred onto a vibrating screen, and the supernatant. Liquid was filtered off. The filtration cake was redispersed in the mixer in 60 1 of a mixture of 18 1 of synthetic rectified ethanol conc. 98% and 42 1 of demineralised water 2 μS. The fibre suspension was filtered again on the vibrating screen.

[0084] The isolated material thus prepared may further serve to prepare final products of the nonwoven type via a wet or dry process.

[0085] Analysis:

Ca content	4.0% b/w
Na content	1.8% b/w
Σ C=O content	0.0% b/w
COOH content	20.7% b/w

Example 2

Material

[0086] oxidised short-fibre cotton (Linters—Temming) (proprietary)

[0087] C_6OOH 16.8% b/w

[0088] ash content<0.15% b/w

[0089] ΣC=O 2.6% b/w

[0090] 20% solution Na_2CO_3 (Lachema, a.s. Neratovice)

[0091] $CaCl_2.6H_2O$ anal.grade (Lachema, a.s. Neratovice)

[0092] redistilled water (PhBs 1997)

[0093] ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)

[0094] isopropanol 99.9% (Neuberg Bretang)

[0095] H_2O_2 anal.grade 30% (Lachema, a.s. Neratovice)

[0096] gelatine (PhBs 1997)

Equipment

[0097] turbostirrer: ULTRA TURAX (Janke-Kunkel)

[0098] sulphonation flask 1 1

[0099] heater 1.5 kW

[0100] laboratory centrifuge: 4000 rpm

[0101] thermostated water bath

[0102] pH meter PICCOLO

[0103] glass thermometer

[0104] rotary vacuum dryer or hot-air dryer

[0105] Procedure:

[0106] Into a 1 1 sulphonation flask equipped with a turbostirrer and a heater, 400 ml of redistilled H_2O were placed, 15.73 g of $CaCl_2.6H_2O$ were added and on dissolution, 40.0 g of 20% Na_2CO_3 solution were introduced under stirring. Subsequently, 50 g of oxidised Linters were added to the white emulsion formed and the contents were heated up to 95° C. and the stirring intensity set to a maximum. After 10 minutes, 30 g of 30% H_2O_2 were added into the flask and the hydrolysis continued for another 10 minutes. The contents were then cooled down to 60° C. on a water bath and the pH of the system was adjusted to a value of 4.5-5.0 by addition of 20% solution. of Na_2CO_3. Furthermore, gelatine solution (10 g of gelatine in 70 g of redistilled H_2O) warmed up to 50° C. was added and let to react for another 20 minutes. The flask contents were then cooled down to 30° C. in a water bath and 626 ml of synthetic rectified ethanol conc. 98% were added gradually under intense stirring. The suspension of IMC thus formed was isolated using a laboratory centrifuge. The supernatant liquid was filtered away and the cake was redispersed into 250 ml of 50% ethanol. The system was centrifuged again and after the separation of the supernatant liquid, the IMC was redispersed into 250 ml of synthetic rectified ethanol conc. 98% and let to stay for 4 hours. It was then centrifuged again, redispersed into 99.9% isopropanol, and let to stay for a minimum of 10 hours at 20° C. The gel formed was centrifuged again and the product was dried in a rotary vacuum dryer or a hot-air dryer.

[0107] The product can be used, for instance, for microembolisation, for preparation of haemostatic dusting powders, for manufacture of polymer drugs, e.g. based on cytostatics, or for preparation of spheric particles for macroembolisation.

[0108] Analysis:

content Ca	4.4% b/w
content Na	2.7% b/w
content Σ C=O	0.0% b/w
content COOH	20.5% b/w
content N	1.8% b/w

Example 3

Material

[0109] oxidised short-fibre cotton (Linters—Temming) (proprietary)

[0110] C_6OOH 16.8% b/w

[0111] ash content<0.15% b/w

[0112] ΣC=O 2.6% b/w

[0113] NaOH anal.grade (Lachema, a.s. Neratovice)

[0114] redistilled water (PhBs 1997)

[0115] ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)

[0116] isopropanol 99.9% (Neuberg Bretang)

[0117] H_20_2 anal.grade 30% (Lachema, a.s. Neratovice)

[0118] gelatine (PhBs 1997)

Equipment

[0119] turbostirrer: ULTRA TURAX (Janke-Kunkel)

[0120] sulphonation flask 1 1

[0121] heater 1.5 kW

[0122] laboratory centrifuge: 4000 rpm

[0123] thermostated water bath

[0124] pH meter PICCOLO

[0125] glass thermometer

[0126] rotary vacuum dryer or hot-air dryer

[0127] Procedure:

[0128] Into a 1 1 sulphonation flask equipped with a turbostirrer and a heater, 400 ml of redistilled H_2O were placed, and 8 g of NaOH were added. On dissolution, 50 g of oxidised Linters were added, the contents were heated up to 70° C. and the stirring intensity set to a maximum. After 20 minutes, 40 g of 30% H_2O_2 were added into the flask, temperature was increased to 85° C., and maintained for another 10 minutes. The contents were then cooled down to 50° C. on a water bath and gelatine solution (10 g of gelatine in 70 g of redistilled H_20) warmed up to 50° C. was added to the hydrolysate. The temperature was decreased to 25-30° C. and the pH of the system was checked and adjusted to a value of 6.0-6.5. Subsequently, 626 ml of synthetic rectified ethanol conc. 98% were added gradually under intense stirring. The suspension of IMC thus formed was isolated using a laboratory centrifuge. The supernatant liquid was filtered away and the cake was redispersed into 250 ml of 50% ethanol. The system was centrifuged again and after the separation of the supematant liquid, the IMC was redispersed into 250 ml of synthetic rectified ethanol conc. 98% and let to stay for 4 hours. It was then centrifuged again, redispersed into 99.9% isopropanol, and let to stay for a minimum of 10 hours at 20° C. The gel formed was centrifuged again and the product was dried in a rotary vacuum dryer or a hot-air dryer. The product can be used, for instance, for microembolisation, for preparation of haemostatic dusting powders, for manufacture of polymer drugs, e.g. based on cytostatics, or for preparation of spheric particles for macroembolisation.

[0129] Analysis:

Na content	3.8% b/w
Σ C=O content	0.0% b/w
COOH content	21.5% b/w
N content	2.7% b/w

Example 4

Material

[0130] oxidised short-fibre cotton (Linters—Temming) (proprietary)

[0131] C_6OOH 16.8% b/w

[0132] ash content<0.15% b/w

[0133] ΣC=O 2.6% b/w

[0134] 20% solution Na_2CO_3 (Lachema, a.s. Neratovice)

[0135] $CaCl_2.6H_2O$ anal.grade (Lachema, a.s. Neratovice)

[0136] redistilled water (PhBs 1997)

[0137] ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)

[0138] isopropanol 99.9% (Neuberg Bretang)

[0139] H_2O_2 anal.grade 30% (Lachema, a.s. Neratovice)

[0140] chitosan, degree of deacetylation 92% (Henkel)

Equipment

[0141] turbostirrer: ULTRA TURAX (Janke-Kunkel)

[0142] sulphonation flask 1 1

[0143] heater 1.5 kW

[0144] laboratory centrifuge: 4000 rpm

[0145] therinostated water bath

[0146] pH meter PICCOLO

[0147] glass thermometer

[0148] rotary vacuum dryer or hot-air dryer

[0149] Procedure:

[0150] Into a sulphonation flask, 250 ml redistilled H_2O were placed, and 5 g of NaOH were added. On dissolution, 25 g of oxidised Linters were introduced under stirring, the temperature increased to 50° C. and the stirring intensity set to a maximum. After hydrolysing for 15 minutes, 35 g of 30% H_2O_2 were gradually added to the system and the temperature was maintained at 50° C. for another 20 minutes. The content were cooled down to 30° C. and 400 g of highly viscous 5% solution of chitosan were added. The flask contents were then intensely stirred for another 10 minutes, and the pH of the system was adjusted, by addition of NaOH, to a value of 7.0. Subsequently 300 ml of synthetic rectified ethanol conc. 98% were added under stirring. The suspension of IMC thus formed was isolated using a laboratory centrifuge. The supernatant liquid was filtered away and the cake was redispersed into 250 ml of 50% ethanol. The system was centrifuged again and after the separation of the supernatant liquid, the IMC was redispersed into 250 ml of synthetic rectified ethanol conc. 98% and let to stay for 4 hours. It was then centrifuged again, redispersed into 99.9% isopropanol, and let to stay for a minimum of 10 hours at 20° C. The gel formed was centrifuged again and the product was dried in a rotary vacuum dryer or a hot-air dryer.

[0151] The product can be used, for instance, for microembolisation, for preparation of haemostatic dusting powders, for manufacture of polymer drugs, e.g. based on cytostatics, or for preparation of spheric particles for macroembolisation.

[0152] Analysis:

Na content	1.8% b/w
Σ C=O content	0.0% b/w
COOH content	10.4% b/w
N content	2.8% b/w

Example 5

Material

[0153] oxidised short-fibre cotton (Linters-Temming) (proprietary)

[0154] C_6OOH 16.8% b/w

[0155] ashcontent<0.15% b/w

[0156] Σ=O 2.6% b/w

[0157] NaOH anal.grade (Lachema, a.s. Neratovice)

[0158] HCI 39% anal.grade (Lachema, a.s. Neratovice)

[0159] redistilled water (PhBs 1997)

[0160] ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)

[0161] isopropanol 99.9% (Neuberg Bretang)

[0162] H_2O_2 anal.grade 30% (Lachema, a.s. Neratovice)

[0163] gelatine (PhBs 1997)

[0164] Ambroxol (H. Mack, Germany)

Equipment

[0165] turbostirrer: ULTRA TURAX (Janke-Kunkel)

[0166] sulphonation flask 2 1

[0167] heater 1.5 kW

[0168] laboratory centrifuge: 4000 rpm

[0169] laboratory pin mill ALPINE (35 000 rpm)

[0170] thermostated water bath

[0171] pH meter PICCOLO

[0172] glass thermometer

[0173] rotary vacuum dryer or hot-air dryer

[0174] Procedure: Into a sulphonation flask, 400 ml redistilled H_2O were placed, and 8 g of NaOH were added. On dissolution, 50 g of oxidised Linters were introduced under stirring, the temperature increased to 70° C. and the stirring intensity was set to a maximum. After hydrolysing for 20 minutes, 40 g of 30% H_2O_2 were gradually added to the system and the temperature was increased to, and maintained at, 85° C. for another 10 minutes. The content were cooled down to 50° C. in a water bath, and gelatine solution (2 g of gelatine in 70 g of redistilled H_2O) warmed up to 50° C. was added to the hydrolysate. The temperature was decreased to 25-30° C. and the pH of the system was checked and adjusted to a value of 1.6-1.8 by addition of 39% HCl. Under intense stirring, a solution of Ambroxol (25g of ambroxolium hydrochloride in 500 ml of redistilled H_2O) was added gradually. After agitating for 5 minutes the pH value was adjusted to 4.3 –4.6 by adding 5% NaOH solution, and 626 ml of synthetic rectified ethanol conc. 98% were added under intense stirring. The suspension of Ambroxol containing IMC thus formed was isolated using a laboratory centrifuge. The supernatant liquid was filtered away and the cake was redispersed into, subsequently, 800 ml of 60% ethanol and 250 ml of 98% ethanol, wherein it was let to stay for a minimum of 10 hours. The system was centrfuged again and the product was dried at 40° C. in a rotary vacuum dryer or a hot-air dryer. A white to slightly yellowish powder was obtained and further desagglomerated on an Alpine pin mill. The product serves for the preparation of a mucoregulatory drug with a prolonged action.

[0175] Analysis:

Na content	4.6% b/w
Σ C=O content	0.0% b/w
COOH content	14.8% b/w
N content	1.9% b/w

Example 6

Material

[0176] oxidised short-fibre cotton (Linters—Temming) (proprietary)

[0177] C_6OOH 16.8% b/w

[0178] ash content<0.15% b/w

[0179] ΣC=O 2.6% b/w

[0180] 20% solution Na_2CO_3 (Lachema, a.s. Neratovice)

[0181] $CaCl_2.6H_2O$ anal.grade (Lachema, a.s. Neratovice)

[0182] redistilled water (PhBs 1997)

[0183] ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)

[0184] isopropanol 99.9% (Neuberg Bretang)

[0185] H_2O_2 anal.grade 30% (Lachema, a.s. Neratovice)

[0186] gelatine (PhBs 1997)

[0187] gentamycin sulphate (MERCK)

Equipment

[0188] turbostirrer: ULTRA TURAX (Janke-Kunkel)

[0189] sulphonation flask 2 1

[0190] heater 1.5 kW

[0191] laboratory centrifuge: 4000 rpm

[0192] laboratory pin nill ALPINE (35 000 rpm)

[0193] thermostated water bath

[0194] pH meter PICCOLO

[0195] glass thermometer

[0196] hot-air dryer

[0197] lyophiliser (Leibold Heraus, Germany)

[0198] Procedure:

[0199] Into a 2 1 sulphonation flask equipped with a turbostirrer and a heater, 400 ml of redistilled H_2O were placed, 15.73 g of $CaCl_2.6H_2O$ were added and on dissolution, 40.0 g of 20% Na_2CO_3 solution were introduced

under stirring. Subsequently, 50 g of oxidised Linters were added to the white emulsion formed and the contents were heated up to 95° C. and the stirring intensity set to a maximum. After 10 minutes, 30 g of 30% H_2O_2 were added into the flask and the hydrolysis was continued for another 10 minutes. The contents were then cooled down to 60° C. on a water bath and the pH of the system was adjusted to a value of 4.5-5.0 by addition of 20% solution of Na_2CO_3. Furthermore, gelatine solution (10 g of gelatine in 70 g of redistilled H_2O) warmed up to 50° C. was added and let to react for another 20 minutes. The flask contents were then cooled down to 30° C. in a water bath and 40 g of gentamycin sulphate in 600 ml of redistilled H_2O were added gradually within 10 minutes. 626 ml of synthetic rectified ethanol conc. 98% were then added gradually under intense stirring to the antibiotic containing IMC suspension formed. The suspension of IMC thus formed was isolated using a laboratory centrifuge. The supernatant liquid was filtered away and the cake was redispersed into 250 ml of 50% ethanol. The system was centrifuged again and after the separation of the supernatant liquid, the IMC was redispersed into 250 ml of synthetic rectified ethanol conc. 98% and let to stay for 4 hours. It was then centrifuged again, redispersed into 99.9% isopropanol, and let to stay for a rninimum of 10 hours at 20° C. The gel formed was centrifuged again and the product was dried in a rotary vacuum dryer or a hot-air dryer.

[0200] The product can be used, for instance, for the manufacture of a dusting powder or a powder spray for the treatment of infected wounds.

[0201] Analysis:

Ca content	2.4% b/w
Na content	1.6% b/w
Σ C=O content	0.0% b/w
COOH content	9.6% b/w
N content	2.7% b/w

Example 7

Material

[0202] long-fibre cotton—medicinal cotton wool oxidised by N_xO_y (proprietary)

[0203] C_6OOH 18.8% b/w

[0204] ash content<0.1% b/w

[0205] ΣC=O 0.6% b/w

[0206] 20% solution Na_2CO_3 (Lachema, a.s. Neratovice)

[0207] $CaCl_2.6H_2O$ anal.grade (Lachema, a.s. Neratovice)

[0208] demineralised water 2 μS

[0209] ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)

[0210] isopropanol 99.9% (Neuberg Bretang)

[0211] acid acetic anal.grade (Lachema, a.s. Neratovice)

[0212] H_2O_2 anal.grade 30% (Lachema, a.s. Neratovice)

[0213] N-HANCE 3000 guargumhydroxypropyltriammoniumchloride

[0214] (Aqualon—Hercules)

[0215] polybren (hexadimethrindibromide) (FLUKA)

[0216] chlorhexidindigluconate

Equipment

[0217] mixer: bottom stirring, 1501 (duplicator), stainless steel EXTRA S

[0218] vibrating screen: stainless steel, 150 mesh

[0219] rotary air pump: rotor diameter 150 mm

[0220] turbostirrer: ULTRA TURAX (Janke-Kunkel)

[0221] beaker: 5 1

[0222] pH meter PICCOLO

[0223] thermocouple thermometer

[0224] Procedure:

[0225] 30g of N-HANCE 3000 were placed into and 5 1 beaker and 3 1 of demineralised water 2 μS were added. Contents of the beaker were intensely stirred for 30 minutes. The pH value was adjusted to less than 4.5 by addition of an acetic acid solution leading to a viscosity rise.

[0226] 60 1 of demineralised water 2 μS were introduced into a mixer. Then 3 kg of $CaCl_2.6H_2O$ anal.grade were added and the contents heated up to a temperature of 50° C. under stirring. On dissolution of the calcium chloride the siring was interrupted and 2.7 kg of the raw oxidised cotton wool were introduced. The mixer was closed and the contents were agitated for 120 seconds. Then the pH value of the contents was adjusted by addition of a 20% solution of Na_2CO_3 to 6-6.5 and 13 kg of H_2O_2 30% were introduced. The fibre suspension was slowly agitated for 10 minutes. Then the pH value was readjusted to 4.5-5.0 and the prepared viscous solution of N-HANCE 3000 was introduced. The contents of the mixer were stirred intensely for 30 seconds. A solution of 35 g of chlorhexidine digluconate in 350 ml of demineralised water 2 μS was then introduced slowly within 10 minutes. Within another 10 minutes, a solution of polybren containing 120 g of polybrenu in 1000 ml of demineralised water 2 μS was added. Subsequently 60 1 of synthetic rectified ethanol conc. 98% were introduced into the mixer. After another 15 seconds from adding the ethanol, the contents of the mixer were transferred onto a vibrating screen, and the supernatant. Liquid was filtered off. The filtration cake was redispersed in the mixer in 60 1 of a mixture of 18 1 of synthetic rectified ethanol conc. 98% and 42 1 of demineralised water 2 μS. The fibre suspension was filtered again on the vibrating screen.

[0227] The isolated material thus prepared may further serve to prepare, via a wet or dry process, final products of the nonwoven type having an enhanced haemostatic activity and a bactericidal effect.

[0228] Analysis:

Ca content	3.6% b/w
Na content	1.9% b/w
Σ C=O content	0.0% b/w
COOH content	18.1% b/w
N content	0.35% b/w

Example 8

Material

[0229] oxidised short-fibre cotton (Linters—Temming) (proprietary)

[0230] C_6OOH 16.8% b/w

[0231] ash content<0.15% b/w

[0232] ΣC=O 2.6% b/w

[0233] 20% solution Na_2CO_3 (Lachema, a.s. Neratovice)

[0234] $CaCl_2.6H_2O$ anal.grade (Lachema, a.s. Neratovice)

[0235] redistilled water (PhBs 1997)

[0236] ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)

[0237] isopropanol 99.9% (Neuberg Bretang)

[0238] H_2O_2 anal.grade 30% (Lachema, a.s. Neratovice)

[0239] Chitosan, degree of deacetylation 92% (Henkel)

[0240] Clarithromycin lactobionan (Abbott Laboratories, Italy)

Equipment

[0241] turbostirrer: ULTRA TURAX (Janke-Kunkel)

[0242] sulphonation flask 1 1

[0243] heater 1.5 kW

[0244] laboratory centrifuge: 4000 rpm

[0245] thermostated water bath

[0246] pH meter PICCOLO

[0247] glass thermometer

[0248] rotary vacuum dryer or hot-air dryer

[0249] dialysing bag (regenerated cellulose)

[0250] lyophiliser (Leybold Heraus, Germany)

[0251] laboratory pin mill ALPINE (35 000 rpm)

[0252] Procedure:

[0253] Into a sulphonation flask, 250 ml redistilled H_2O were placed, and 5 g of NaOH were added. On dissolution, 25 g of oxidised Linters were introduced under stirring, the temperature increased to 50° C. and the stirring intensity set to a maximum. After hydrolysing for 15 minutes, 35 g of 30% H_2O_2 were gradually added to the system and the temperature was maintained at 50° C. for another 20 minutes. The content were cooled down to 30° C. and 400 g of highly viscous 2% solution of chitosan, having a pH value of 3.5, were added. The flask contents were then intensely stirred for another 10 minutes, and the pH of the system was adjusted, by addition of NaOH, to a value of 7.0. During another 10 minutes, a solution of clarithromycin (44 g of clarithromycin in 456 ml of redistilled H_2O) was introduced and the pH of the system was adjusted to a value of 7.0-7.5. Stirring was interrupted, the flask contents were transferred into a dialysing bag and dialysed against water for 48 hours. Subsequently the product was isolated by centrifugation, lyophilised, and disintegrated on the laboratory pin mill ALPINE. The product can be used, for instance, to prepare tablets or granules efficient against *Helicobacter pylori* occurring in the gastrointestinal tract.

[0254] Analysis:

Na content	4.8% b/w
Σ C=O content	0.0% b/w
COOH content	18.8% b/w
N content	0.7% b/w

Example 9

Material

[0255] oxidised short-fibre cotton (Linters—Temming) (proprietary)

[0256] C_6OOH 16.8 % b/w

[0257] ash content<0.15% b/w

[0258] ΣC=O 2.6% b/w

[0259] NaOH anal.grade (Lachema, a.s. Neratovice)

[0260] redistilled water (PhBs 1997)

[0261] ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)

[0262] isopropanol 99.9% (Neuberg Bretang)

[0263] H_2O_2 anal.grade 30% (Lachema, a.s. Neratovice)

[0264] gelatine (PhBs 1997)

[0265] $Bi(NO_3).5H_2O$ (MERCK)

Equipment

[0266] turbostirrer: ULTRA TURAX (Janke-Kunkel)

[0267] sulphonation flask 2 1

[0268] heater 1.5 kW

[0269] laboratory centrige: 4000 rpm

[0270] thermostated water bath

[0271] pH meter PICCOLO

[0272] glass thermometer

[0273] rotary vacuum dryer or hot-air dryer

[0274] Procedure:

[0275] Into a sulphonation flask, 400 ml redistilled H_2O were placed, and 8 g of NaOH were added. On dissolution, 50 g of oxidised Linters were introduced under stirring, the temperature increased to 70° C. and the stirring intensity was set to a maximum. After hydrolysing for 20 minutes, 40 g of 30% H_2O_2 were gradually added to the system and the temperature was increased to, and maintained at, 85° C. for another 10 minutes. The content were cooled down to 50° C. in a water bath, and gelatine solution (0.5 g of gelatine in 50 ml of redistilled H_2O) warmed up to 50° C. was added to the hydrolysate. The temperature was decreased to 25-30° C. and the pH of the system was checked and adjusted to a value of 1.6-1.8 by addition of 39% HCl. A freshly prepared solution of $BiNO_3$ (54 g of $BiNO_3.5H_2O$ in 746 ml of H_2O) was introduced and the temperature maintained for another 15 minutes. Then the temperature was decreased to 25-30° C. and the pH of the system was checked and readjusted to a value of 5.5-6.0. 626 ml of synthetic rectified ethanol conc. 98% were then added gradually under intense stirring. to the formed. The BiO^+ containing IMC suspension thus formed was isolated using a laboratory centrifuge. The supernatant liquid was filtered away and the cake was redispersed into 250 ml of 50% ethanol. The system was centrifuged again and after the separation of the supernatant liquid, the IMC was redispersed into 250 ml of synthetic rectified ethanol conc. 98% and let to stay for a minimum of 4 hours. It was then centrifuged again, redispersed into 99.9% isopropanol, and let to stay for a minimum of 10 hours at 20° C. The suspension formed was then centrifuged again and the product was dried in a rotary vacuum dryer or a hot-air dryer. The product can be used, for instance, to prepare dusting powders for wound treatnent or tablets for treatment of gastrointestinal tract malfunctions.

[0276] Analysis:

Na content	1.9% b/w
Σ C=O content	0.0% b/w
COOH content	20.0% b/w
N content	<0.3% b/w
Bi content	4.7% b/w

Example 10

Material

[0277] oxidised short-fibre cotton (Linters—Temming) (proprietary)

[0278] C_6OOH 16.8% b/w

[0279] ash content<0.15% b/w

[0280] ΣC=O 2.6% b/w

[0281] 20% solution Na_2CO_3 (Lachema, a.s. Neratovice)

[0282] $CaCl_2.6H_2O$ anal.grade (Lachema, a.s. Neratovice)

[0283] redistilled water (PhBs 1997)

[0284] ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)

[0285] isopropanol 99.9% (Neuberg Bretang)

[0286] H_2O_2 anal.grade 30% (Lachema, a.s. Neratovice)

[0287] gelatine (PhBs 1997)

[0288] cimetidine hydrochloride (SPOFA)

Equipment

[0289] turbostirrer: ULTRA TURAX (Janke-Kunkel)

[0290] sulphonation flask 2 1

[0291] heater 1.5 kW

[0292] laboratory centrifuge: 4000 rpm

[0293] thermostated water bath

[0294] pH meter PICCOLO

[0295] glass thermometer

[0296] rotary vacuum dryer or hot-air dryer

[0297] Procedure: Into a 11 sulphonation flask equipped with a turbostirrer and a heater, 400 ml of redistilled H_2O were placed, 15.73 g of $CaCI_2.6H_2O$ were added and on dissolution, 40.0 g of 20% Na_2CO_3 solution were introduced under stirring. Subsequently, 50 g of oxidised Linters were added to the white emulsion formed and the contents were heated up to 95° C. and the stirring intensity set to a maximum. After 10 minutes, 30 g of 30% H_2O_2 were added into the flask and the hydrolysis was continued for another 10 minutes. The contents were then cooled down to 60° C. on a water bath and the pH of the system was adjusted to a value of 4.5-5.0 by addition of 20% solution of Na_2CO_3. Furthermore, gelatine solution (10 g of gelatine in 70 g of redistilled H_2O) warmed up to 50° C. was added and let to react for another 20 minutes. The flask contents were then cooled down to 300° C. in a water bath and a solution of cimetidine (36 g of cimetidine hydrochloride in 400 nil of redistilled H_2O) were added under intens stirring. The contents were intensely agitated for 10 minutes and 800 ml of synthetic rectified ethanol conc. 98% were then added gradually. The suspension of IMC thus formed was isolated using a laboratory centrifuge. The supernatant liquid was filtered away and the cake was redispersed into 250 ml of 50% ethanol. The system was centrifuged again and after the separation of the supernatant liquid, the IMC was redispersed into 250 ml of synthetic rectified ethanol conc. 98% and let to stay for 4 hours. It was then centrifuged again, redispersed into 99.9% isopropanol, and let to stay for a minimum of 10 hours at 20° C. The gel formed was centrifuged again and the product was dried in a rotary vacuum dryer or a hot-air dryer.

[0298] The product can be used, for instance, to manufacture tablets or granulates for the treatment of the gastrointestinal tract or other non-malignant ulcerations.

[0299] Analysis:

Ca content	4.4% b/w
Na content	2.7% b/w
Σ C=O content	0.0% b/w

-continued

COOH content	20.5% b/w
N content	2.1% b/w

Example **11**

Material

[**0300**] IMC-MDOC complex (as per above Example 2)

[**0301**] [(2S;2R)-3-amino-2-hydroxy4-phenyl-butenoyl]-L-leucin (Bestatin)

[**0302**] (Boehringer Mannheim, Germany)

[**0303**] redistilled water (PhBs 1997)

[**0304**] methanol, conc. anal.grade (Chemopetrol Litvinov, a.s.)

[**0305**] diethylether (Lachema, a.s. Neratovice)

Equipment

[**0306**] turbostirrer: ULTRA TURAX (Janke-Kunkel)

[**0307**] sulphonation flask 2 1

[**0308**] laboratory centrifuge: 4000 rpm

[**0309**] hot-air dryer

[**0310**] Procedure:

[**0311**] The IMC-MDOC complex as prepared in Example 2 above was redispersed into redistilled water in a sulphonation flask using a turbostirrer. A solution of Bestatin in methanol was then added to the flask in an amount sufficient to yield a 10% b/w concentration of Bestatin in the resulting Bestatin-gelatine-MDOC complex. After thorough homogenisation, the suspension formed was isolated by centrifugation. The supernatant liquid ws filtered away and the filtration cake was redispersed into concentrated methanol again, centrifuged, redispersed in diethylether, and after being allowed to stay for 1 hour, it was dried in a hot-air dryer.

[**0312**] The product, a microdispersed form of a Bestatin-gelatine-MDOC complex, can be used, for instance, to prepare microembolisation agents used in regional chemotherapy of malignant tumours or flat dressing structures for wound treatment.

Example A Preparation of tablets and pellets from MDOC

[**0313**] MDOC=Microdispersed Oxidised cellulose.

Material

[**0314**] MDOC (Ca/Na salt of PAGA), particle size 0.1-2.0 μm, specific surface area 86 m^2/g, COOH group content 22.2% b/w, Ca content 4.2% b/w, Na content 3.8% b/w

Equipment

[**0315**] tabletting machine (KORSCH EK 0, Berlin)

[**0316**] Procedure:

[**0317**] 100 g of MDOC were introduced into do tabletting machine, and the tabletting force was set at a value of 5 kN.

[**0318**] Result:

[**0319**] The tablets prepared were smooth and cohering and had a weight of 0.5 g. Disintegration rate of the tablets in a saline F1/1 was 15 minutes at 20 C., and 8 minutes at 37° C.

Example B Preparation of tablets and pellets from IMC-MDOC complex

Material

[**0320**] IMC-MDOC complex—see Example 2

[**0321**] magnesium stearate (SIGMA)

[**0322**] ascorbic acid (MERCK)

[**0323**] α-tocoferol acetate (Slovakofarma Hlohovec)

[**0324**] ethanol synthetic rectified (Chemopetrol Litvinov, a.s.)

Equipment

[**0325**] tabletting machine (KORSCH EK 0, Berlin)

[**0326**] blender (Nautamix 300)

[**0327**] counter-flow drier BINDER

[**0328**] Procedure:

[**0329**] 10 kg of IMC-MDOC complex of composition according to Example 2 were placed into the blender, and 660 g of micronised ascorbic acid, 1660 g of α-tocoferol acetate emulgated in 2500 ml of ethanol, and 1000 g of magnesium stearate were added. The mixture was homogenised for 3 hours. It was then dried in a counter-flow drier at a temperature of 50° C. until ethanol was removed.

[**0330**] 100 g of the resulting dry powder were introduced into the tabletting machine, and the tabletting force was set at a value of 7 kN.

[**0331**] Result:

[**0332**] The tablets prepared were smooth and well cohering and had a weight of 0.5 g. Disintegration rate of the tablets in a saline F1/1 was 17 minutes at 20° C., and 8 minutes at 37° C.

Example C Preparation of tablets and pellets with IMC-MDOC complex containing clarithromycin

Material

[**0333**] IMC-MDOC complex—see Example 8

[**0334**] MDOC, particle size 0.1-2.0 μm, specific surface area 86m^2,

[**0335**] COOH group content 22.2% b/w, Ca content 4.2% b/w, Na

[**0336**] content 3.8% b/w

[**0337**] IMC-MDOC complex containing BiO^+—see Example 9

Equipment

[**0338**] laboratory mixer, bottom agitated, 4000 rpm

[**0339**] tabletting machine (KORSCH EK 0, Berlin)

[0340] Procedure:

[0341] 9.5 g of IMC-MDOC containing clarithromycin were placed into the mixer, and 12.0 g of BiO^+ salt and 78.5 g of MDOC were added. The vessel was closed, the agitation set on, and the contents were homogenised for 60 seconds. The homogenised mixture was then transferred to the storage vessel of the tabletting machine, and the tabletting force was set to a value of 7.5 kN.

[0342] Result:

[0343] The tablets prepared were smooth and cohering and had a weight of 0.5 g. Disintegration rate of the tablets in a saline F1/1 was 12 minutes at 20° C,, and 5 minutes at 37° C.

[0344] Indication: p The tablets are indicated for treatment of gastric ulcers. MDOC suppresses formation of the stomach acidity, adjust the pH value of the environment, and protects the mucous membranes by forming a gel layer. BiO+acts as a mild astringens. Clarithromycin depresses the growth of *Helicobacter pylori* beyond pathologic limits.

Example D Preparation of tablets and pellets with IMC-MDOC complex containing cimetidine

Material

[0345] MDOC, particle size 0.1-2.0 μm, specific surface area 86m^2, COOH group content 22.2% b/w, Ca content 4.2% b/w, Na content 3.8% b/w

[0346] IMC-MDOC complex containing cimetidine—see Example 10

[0347] Macrogol 400 (SIGMA)

Equipment

[0348] laboratory mixer, bottom agitated, 4000 rpm

[0349] tabletting machine (KORSCH EK 0, Berlin)

[0350] Procedure:

[0351] 63.0 g of IMC-MDOC containing cimetidine, 32.0 g of MDOC and 5.0 g of Macrogol 400 were introduced into the mixer. The vessel was closed, the agitation set on, and the contents were homogenised for 60 seconds. The homogenised mixture was then transferred to the storage vessel of the tabletting machine, and the tabletting force was set to a value of 7.5 kN.

[0352] Result:

[0353] The tablets prepared were smooth and well cohering and had a weight of 1.0 g. Disintegration rate of the tablets in a saline F1/1 was 8 minutes at 20° C., and 6 minutes at 37° C.

[0354] Indication:

[0355] The tablets are indicated for treatment of gastric ulcers. MDOC suppresses formation of the stomach acidity, adjust the pH value of the environment, and protects the mucous membranes by forming a gel layer. BiO^+ acts as a mild astringens. Cimetidine suppresses both basal and simulated secretion of the stomach acid.

Example E Preparation of granules from JMC-MDOC complex containig clarithromycin

Material

[0356] IMC-MDOC complex—see Example 8

[0357] MDOC, particle size 0.1-2.0 gm, specific surface area 86 m^2g,

[0358] COOH group content 22.2% b/w, Ca content 4.2% b/w, Na

[0359] content 3.8% b/w

[0360] IMC-MDOC complex containing BiO^+—see Example 9

[0361] ethanol synthetic rectified 98%

[0362] redistilled H_2O

Equipment

[0363] set of vibrating screens with mesh size 100, 150, 200, 250, 350, 500 μm

[0364] mixer, bottom agitated, vessel size 1000 ml, 8000 rpm, equipped with a nozzle for inlet of the granulation medium counter-flow drier BINDER

[0365] Procedure:

[0366] 100 g of MDOC were placed into the mixer, the mixer was closed and the agitation switched on. A mist of 88% aqueous solution of ethanol was gradually injected into the mixer at a rate of 10 g/45 seconds. The granulate formed was transferred to the counter-flow drier and dried at a temperature of 45° C. until the humidity content was reduced below 6% b/w. The dried granules were sieve-screened using the set of vibrating screens. The individual fractions were packaged into glass vials in amounts of 0.5-2.0 g each as required. The preparation was sterilised by γ irradiation with a dose of 25 kGy.

[0367] Indication:

[0368] The granules can be used in the treatment of gastric ulcers. MDOC suppresses formation of the stomach acidity, adjust the pH value of the environment, and protects the mucous membranes by forming a gel layer. BiO^+acts as a mild astringens. Clarithromycin depresses the growth of *Helicobacter pylori* beyond pathologic limits.

[0369] The invention is not limited to the embodiments hereinbefore described which may be varied in detail.

1. A pharmaceutical composition for the prophylaxis or treatment of peptic ulcers including a biocompatible anionic polysaccharide material containing glucuronic acid.

2. A composition as claimed in claim 1 wherein the polysaccharide is derived from a starch, cellulose or gum, or is of microbial origin, preferably the polysaccharide material is polyanhydroglucuronic acid, biocompatible salts thereof, copolymers thereof and intermolecular polymer complexes thereof.

3. A composition as claimed in claim 2 wherein the biocompatible intermolecular polymer complex is a complex of:

an anionic component comprising a linear or branched polysaccharide chain containing glucuronic acid; and

a non protein cationic component comprising a linear or branched natural, semi-synthetic or synthetic oligomer or polymer.

4. A composition as claimed in claim 3 wherein at least 5% of the basic structural units of the anionic component are glucuronic acid.

5. A composition as claimed in claim 3 wherein the cationic component contains nitrogen that either carries a positive charge or wherein the positive charge or wherein the positive charge is induced by contact with the polysaccharidic anionic component.

6. A composition as claimed in claim 5 wherein the cationic component is selected from derivatives of acrylamide, methacrylamide and copolymers thereof.

7. A complex as claimed in claim 6 wherein the cationic component is selected from polyacrylamide, copolymer of hydroxyethylmethacrylate and hydroxypropylmetacrylamide, copolymers of acrylamide, butylacrylate, maleinanhydride and/or methylmetacrylate.

8. A composition as claimed in claim 3 wherein the cationic component is a cationised natural polysaccharide, preferably the polysaccharide is a starch, cellulose or gum such as guargumhydroxypropyltriammonium chloride.

9. A composition as claimed in claim 3 wherein the cationic component is a synthetic or semi-synthetic polyamino acid, preferably the cationic component is polylysin, polyarginin, or α, β-poly-[N-(2-hydroxyethyl)-DL-aspartamide].

10. A composition as claimed in claim 3 wherein the cationic component is a synthetic anti-fibrinolytic, preferably the anti-fibrinolytic is a hexadimethrindibromide (polybren).

11. A composition as claimed in claim 3 wherein the cationic component is a natural or semi-synthetic peptide, preferably the peptide is a protamine, gelatine, fibrinopeptide, or derivatives thereof.

12. A composition as claimed in claim 3 wherein the cationic component is an aminoglucane or derivatives thereof, preferably the aminoglucane is fractionated chitin or its de-acetylated derivative chitosan, preferably the aminoglucane is of microbial origin or is isolated from the shells of arthropods such as crabs.

13. A composition as claimed in claim 3 wherein the anionic component is polyanhydroglucuronic acid [PAGA].

14. A composition as claimed in claim 13 wherein the polyanhydroglucuronic acid and salts thereof contain in their polymeric chain from 8 to 30 percent by weight of carboxyl groups, at least 80 percent by weight of these groups being of the uronic type, at most 5 percent by weight of carbonyl groups, and at most 0.5 percent by weight of bound nitrogen.

15. A composition as claimed in claim 14 wherein the polyanhydroglucuronic acid and salts thereof contain in their polymeric chain at most 0.2 percent by weight of bound nitrogen.

16. A composition as claimed in claim 14 wherein the molecular mass of the polymeric chain of the anionic component is from 1×10^3 to 3×10^5 Daltons, preferably from 5×10^3 to 1.5×10^5 Daltons.

17. A composition as claimed in claim 14 wherein the content of carboxyl groups is in the range of from 12 to 26 percent by weight, at least 95 percent of these groups being of the uronic type.

18. A composition as claimed in claim 14 wherein the anionic component contains at most 1 percent by weight of carbonyl groups.

19. A composition as claimed in claim 14 wherein the carbonyl groups ar intra- and intermolecular 2,6 and 3,6 hemiacetals, 2,4-hemialdals and C2-C3 aldehydes.

20. A composition as claimed in claim 3 wherein the cationic component is gelatine.

21. A composition as claimed in claim 3 wherein the cationic component is chitosan

22. A composition as claimed in claim 1 including at least one biocompatible biologically active substance.

23. A composition as claimed in claim 1 including at least one biologically accetable adjuvant.

24. A composition as claimed in claim 1 including at least one pharmaceutically active adjuvant.

25. A composition as claimed in claim 23 wherein the adjuvant is an anti-ulcer agent, preferably the anti-ulcer agent is an antibiotic which is active against *Helicobacter pylori,* preferably the antibiotic is clarithyromycin.

26. A composition as claimed in claim 23 wherein the adjuvant is a H_2-antagonist, preferably the adjuvant is cimetidine.

27. A composition as claimed in claim 23 wherein the adjuvant is a combination of an antibiotic which is active against *Helicobacter pylori* and a H_2-antagonist.

28. A composition as claimed in claim 22 including bismuth salt.

29. A composition as claimed in claim 1 in a form for oral administration.

30. A composition as claimed in claim 1 in the form of a tablet, pellet, capsule, granule, or microsphere

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