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AN ANTILIPEMIC FORMULATION

An antilipemic composition, particularly to achieve a lowering of cholesterol levels comprises a biocompatible anionic polysaccharide material containing non-sulphated glucuronic acid.

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Introduction

The invention relates to an antilipemic composition and in particular to a composition for lowering cholesterol.

As outlined in a recent publication [Facts About Cholesterol: The Plague of Plaque, FDA Consumer magazine, January-February 1999], cholesterol, C27H45OH, is a monohydric alcohol, a sterol, widely distributed in animal tissues. It can be synthesized in the liver and is a normal constituent of bile. It is the principal constituent of most gallstones. It is important in metabolism, serving as a precursor of various steroid hormones (e.g., sex hormones, adrenal corticoids). In most individuals, however, an elevated blood level of cholesterol constitutes an increased risk of developing coronary heart disease (CHD). Scientific evidence has established that lowering definitely elevated blood cholesterol (specifically, blood levels of low-density lipoprotein cholesterol) reduces the risk of heart attacks due to CHD.

Cholesterol is needed for some important body functions, but when present in excessive amounts, it can injure blood vessels and cause heart attacks and stroke. The body needs cholesterol for digesting dietary fats, making hormones, building cell walls, and other important processes. The bloodstream carries cholesterol in particles called lipoproteins that are like blood-borne carriers delivering cholesterol to various body tissues to be used, stored or excreted. But too much of this circulating cholesterol can injure arteries, especially the coronary ones that supply the heart. This leads to accumulation of cholesterol-laden "plaque" in vessel linings, a condition called atherosclerosis. If a blood clot completely obstructs a coronary artery affected by atherosclerosis, a heart attack (myocardial infarction) or death can occur.
Lipoproteins are conjugated proteins consisting of simple proteins combined with lipid components: cholesterol, phospholipid, and triglyceride. Most plasma lipids do not circulate in an unbound state but are chemically linked with proteins. Analysis of their concentrations and proportions in the blood can provide important clues as to their role in certain diseases, particularly cardiovascular abnormalities, hypertension, atherosclerosis, and coronary artery disease. Lipoproteins are classified as very low-density (VLDL), low-density (LDL), intermediate-density (IDL) and high-density (HDL). It is thought that individuals with high blood levels of HDL are less predisposed to coronary heart disease than those with high blood levels of VLDL or LDL.

Two types of lipoproteins and their quantity in the blood are main factors in heart disease risk:

Low-density lipoprotein (LDL) - This "bad" cholesterol is the form in which cholesterol is carried into the blood and is the main cause of harmful fatty buildup in arteries. The higher the LDL cholesterol level in the blood, the greater the heart disease risk.

High-density lipoprotein (HDL) - This "good" cholesterol carries blood cholesterol back to the liver, where it can be eliminated. HDL helps prevent a cholesterol buildup in blood vessels. Low HDL levels increase heart disease risk.

One of the primary ways LDL cholesterol levels can become too high in blood is through eating too much of two nutrients: saturated fat, which is found mostly in animal products, and cholesterol, found only in animal products. Saturated fat raises LDL levels more than anything else in the diet. Several other factors such as heredity, weight, exercise, age and gender, and stress also affect blood cholesterol levels.
Cholesterol levels may be decreased by several factors, including diet, avoiding smoking, and avoiding anabolic steroids. Drugs commonly used to control cholesterol include lovastatin, niacin, gemfibrozil, clofibrate, probucol, and bile-acid resins (cholestyramine, colestipol). The decision of which drug to prescribe is based on factors such as degree of cholesterol lowering desired, side effects, and cost.

A number of substances have been applied to reduce cholesterol levels in blood. One of the early therapies involved heparin, a polysaccharide isolated from natural sources. However, the isolation process is costly and heparin therapy is therefore rather expensive at efficient doses. This led to the introduction of sulphated polysaccharides known as heparinoides. The additional sulphatation and the presence of the OSO3H groups brought about a lower efficiency and a higher toxicity compared to heparin.

Another group of polymers applied as antilipemics have been anion exchange resins of varying degree of basicity, exchanging Cl- ions for anions of bile acids. Cholestyramine and colestipol bind bile acids in the intestine and prevent their recycling through the liver. Because the liver needs cholesterol to make bile, it increases its uptake of cholesterol from the blood. These drugs are, in most cases, not resorbed from the gastrointestinal tract, but can adversely affect resorption of other drugs. Due to the rather high daily doses (up to 30 g) they may also cause gastric problems.

Antilipemic properties have also been observed for certain hormones such as gestagens. Their complex hormonal activity precludes, however, their common use in antilipemic therapy.

Nicotinic acid (niacin) lowers total and LDL cholesterol and raises HDL cholesterol. It also can lower triglycerides. Because the dose needed for treatment
is about 100 times more than the recommended daily allowance for niacin and thus can potentially be toxic, the drug must be taken under a doctor's care.

Fibric acid derivatives such as gemfibrozil and fenofibrate can also increase HDL levels, but are used mainly to lower triglycerides.

The most prominent cholesterol drugs are in the statin family, an array of powerful treatments that includes lovastatin, fluvastatin, pravastatin, simvastatin, cerivastatin, and atorvastatin. Statins work by interfering with the cholesterol-producing mechanisms of the liver and by increasing the capacity of the liver to remove cholesterol from circulating blood. Adverse side effects have also been reported recently for antilipemic drugs based on statins such as fluvastatin.

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

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

We have now found an important antilipemic effect, comparable with that of statins, in non-sulphated polysaccharides containing glucuronic acid in the polymer chain. Glucuronoglucones, notably those bound with 1,4 β glycosidic bonds in the form of PAGA as prepared, particularly, according to PCT IE/98/00004, their salts, complex salts, and intermolecular complexes thereof
with cationic polymer counterions such as, notably, gelatine or chitosan, when applied perorally, preferably in the form of tablets, pellets, granules, or microspheres, display a significant cholesterol lowering activity at relatively low daily doses of 15 to 100 mg per kg body weight.

In tests on volunteers it has been observed that the effect of increasing HDL cholesterol level, and reducing both LDL/ VLDL and total cholesterol levels was comparable with a control group of patients treated with fluvastatin with no adverse side effects reported.

It may be hypothesised that the mechanism of this effect is related to the increased supply of glucuronic acid and their oligomers to the organism during absorption and degradative clearance of the orally administered glucuronoglucane.

One advantage of the therapy based on the invention 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. This together with the low doses required reduce the potential risks to the patient compared with other types of antilipemic drugs.

A final advantage resides in the fact that PAGA salts and intermolecular complexes, especially when prepared according to the method of the earlier PCT IE/98/00004 can, in addition to their own therapeutic function, simultaneously serve as a vehicle for other antilipemic agents with potential synergic effects such as notably phospholipides, e.g. soya or egg derived lecithins, α-tocoferol, or ascorbic acid.
According to the invention there is proved an anilipemic composition including a biocompatible anionic polysaccharide material containing non-sulphated glucuronic acid.

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

In a particularly preferred embodiment the polysaccharide material is polyanhydroglucuronic acid, biocompatible salts thereof, copolymers thereof or a biocompatible intermolecular complex polymer thereof.

In an embodiment of the invention 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.

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

In one embodiment the cationic component contains nitrogen that either carries a positive charge or wherein the positive charge is induced by contact with the polysaccharidic anionic component.

In this case preferably the cationic component is selected from derivatives of acrylamide, methacrylamide and copolymers thereof.
Preferably the cationic component is selected from polyacrylamide, copolymer of hydroxyethylmethacrylate and hydroxypropylmetacrylamide, copolymers of acrylamide, butylacrylate, maleinanhydride and/or methylmetacrylate.

5 The cationic component may be a cationised natural polysaccharide.

In this case preferably the polysaccharide is a starch, cellulose or gum. The gum is preferably guargumhydroxypropyltrimmonium chloride.

10 In another embodiment the cationic component is a synthetic or semi-synthetic polyamino acid.

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

15 Alternatively the cationic component is a synthetic anti-fibrinolytic. The anti-fibrinolytic may be a hexadimethrinindibromide (polybren).

In another embodiment the cationic component is a natural or semi-synthetic peptide.

20 Preferably the peptide is a protamine, gelatine, fibrinopeptide, or derivatives thereof.

25 Alternatively the cationic component is an aminoglucane or derivatives thereof.

In this case the aminoglucane may be fractionated chitin or its de-acetylated derivative chitosan.
The aminoglucone may be of microbial origin or is isolated from the shells of arthropods such as crabs.

In an particularly preferred embodiment the anionic component is polyanhydroglucuronic acid [PAGA].

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

Ideally the polyanhydroglucuronic acid and salts thereof contain in their polymeric chain at most 0.2 per cent by weight of bound nitrogen.

The molecular mass of the polymeric chain of the anionic component is preferably from $1 \times 10^3$ to $3 \times 10^5$ Daltons.

Ideally the molecular mass of the polymeric chain of the anionic component ranges from $5 \times 10^3$ to $1.5 \times 10^5$ Daltons.

In one embodiment the content of carboxyl groups is in the range of from 12 to 26 per cent by weight, at least 95 per cent of these groups being of the uronic type.

Preferably the anionic component contains at most 1 per cent by weight of carbonyl groups.

In a preferred embodiment the carbonyl groups are intra- and intermolecular 2,6 and 3,6 hemiacetals, 2,4- hemialdals and C2-C3 aldehydes.

In another embodiment the cationic component is gelatine.
In a further embodiment the cationic component is chitosan.

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

The composition may include at least one pharmaceutically active adjuvant.

The adjuvant may be an antilipemic agent.

The antilipemic agent may be a phospholipid.

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

We have now found that by preparing polymeric intermolecular complexes (IMC) of glucuronoglucanes, notably microdispersed PAGA, prepared especially according to PCT IE 98/00004 it is possible to enhance the haemostatic effect of the final products on this basis and the properties of the temporary wound cover formed after the haemostasis is achieved such as its flexibility and resistance to cracking on movable parts of the body.

It is also possible to upgrade physicomechanical properties of the final products on this basis. Such IMCs make it possible to prepare application forms whose manufacture from a pure PAGA or their simple salts is extremely difficult. Such application forms includes non-woven textile-like structures or polymeric films. To modify or upgrade the physical mechanical properties it is sufficient to use even a relatively small amount of polymeric counterion while it is possible to obtain suitable application properties within a broad concentration range of the
components. The ratio of the glucuronoglucane to polymeric counterion can be 0.99:0.01 to 0.01:0.99.

Another advantage of glucuronoglucane based IMCs is the possibility to control their biological properties such as varying the degree of haemostatis, resorption time, or immunomodulative properties, and the like.

Polymeric cations suitable to form IMCs with glucuronoglucanes prepared for example according to PCT IE 98/00004 may roughly be subdivided to the following groups:

1. Synthetic biocompatible nitrogen-containing oligomers and polymers.

   a) Derivatives of acrylamide and methacrylamide and their copolymers [such as polyacrylamide, copolymer of hydroxyethylmethacrylate and hydroxypropylmethacrylamide, copolymer of acrylamide, butylacrylate, maleinanhdyride, and methylmetacrylate, and the like], or else cationised natural polysaccharides such as starches, cellulosises, or gums such as guargumhydroxypropyltrimmonium chloride.

   b) Synthetic or semi-synthetic polyaminoacids such as polylysin, polyarginin, α,β-poly-[N-(2-hydroxyethyl)-DL-asparamide. Synthetic antifibrinolytics hexadimethrinidibromide (polybren) can also be included in this group.

2. Natural or semi-synthetic peptides such as gelatine, protamines, or fibrinopeptides, and their derivatives.
3. Natural aminoglucanues such as fractionated chitin and its de-acetylated derivative chitosan, of microbial origin or isolated from the shells of arthropods such as crabs.

In preparing IMCs on the basis of PAGA according to the invention these three groups of substances can be combined to obtain required properties of the final product.

In general it can be said that IMCs using substances from 1a and 1b would preferably be used to prepare various types of highly absorbant biocompatible dressing materials in the form of nonwovens, films, plasters, and pads.

IMCs using the substances from 2 and 3 may serve as efficient haemostatic agents for internal applications in the microfibrillar form, in the microdispersed form as dusting powders, in the form of films, granules, tablets or non-woven textile-like structures. Those preparations also display antiadhesive properties.

We have also found out that in the form of film-like cell culture matrices the latter IMCs incorporating PAGA and salts thereof as prepared according to PCT IE 98/00004 have a favourable effect on the growth of fibroblasts and keratinocytes.

While it is also possible to create IMCs using structural scleroproteins of the collagen type as disclosed in WO 9800180A, it is preferable to use the above mentioned groups of substances because of the possibility of contamination of the final product by telopeptides, viruses or pyrogens. Collagen can affect in an uncontrolled manner, the immune response of the organism because formation of antibodies can be provoked by any portion of the collagen structure even though the main determinants occur in the terminal regions of the collagen macromolecule. Removal of telopeptides only partially solves the antigenicity problem (Michaeli et al: Science, 1969, 166, 1522).
By preparing IMCs according to the invention it is possible to essentially enhance properties of the originally prepared glucoronoglucanes such as 1,4 β PAGA. For instance an intermolecular complex salt of PAGA and gelatine in one single production step can be used to prepare final products in the form of a non woven, film, microdispersed granules, or dispersions. In contrast to collagen, suitably hydrolysed gelatine is well tolerated, has no toxicity or side effects and it is a much less costly raw material. We have found out that this complex has very good haemostatic properties being about 40% higher than the original PAGA calcium sodium salt. This is despite the fact that the gelatine itself only displays a haemostatic effect after an addition of thrombin [Schwartz S.I. et al.: Principles of Surgery, St.Louis: McGraw Hill Co, 1979, p. 122-123]. In this case the absorption in the organism can be controlled by changing the composition of the complex within the range from tens of hours to several months. With an advantage this complex with a higher haemostatic efficiency can be used as an embolisation or microembolisation product. It can also be used to prepare haemostatic layers of highly absorbent multi-layer dressings or resorbable plasters, though more costly polybren or protamines could also be applied.

An important advantage of these IMCs is the fact that the compounds can be prepared within a single manufacturing operation using the hydrolytic process described in PCT IE 98/00004 which makes these products cost effective.

These IMCs can further be modified by biologically active and/or biologically acceptable substances. Because the IMCs prepared by the present procedure are either of a microdispersed or microfibrillar nature, the active substances tend to be bound uniformly and also are uniformly released in the organism without the need for other adjuvants such as microcrystalline waxes or stearates. However, the addition of such adjuvants is not excluded.
Biologically active substances which can be incorporated into the IMC may involve, for instance, antibiotics carrying at least a weak positive charge in the molecule such as cephalosporins (cephotaxin), aminoglycosides (neomycin, gentamycin, amikacin), penicillins (tikarcilin) or macrolides (erythromycin, clarithromycin) and the like.

In cases where the calcium/sodium salt of PAGA or its IMC complexes according to the invention are used as microembolisation or embolisation agents in regional chemotherapy of malign tumours, suitable types of cytostatics such as adriamycin or derivatives of 1,4-diaminoanthrachinone can be incorporated. It is also possible to use the IMCs as detaching ligands for platinum(II) based cytostatics.

Biologically acceptable substances used for modification of the IMCs include, for instance, glycerol and its polymers (polyglycerols); mono, di, and certain triglycerides; polyethyleneglycols; monopropyleneglycol; block copolymers of polyethyleneoxides and polypropyleneoxides (Pluronic); starches; cyclodextrines; polyvinylalcohols; cellulose and its derivatives; in general, substances that, in the concentrations used, are not irritating or toxic for the living organism while being capable of further optimising the physicomechanical properties of the final product based on the IMCs according to the invention.

**Detailed Description**

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: long-fibre cotton – medicinal cotton wool oxidised by $\text{N}_2\text{O}_5$
(proprietary)

$C_6\text{OOH}$ 18.8 % b/w

ash content < 0.1 % b/w

$\Sigma C=O$ 0.6 % b/w

20% solution $\text{Na}_2\text{CO}_3$ (Lachema, a.s. Neratovice)

$\text{CaCl}_2\cdot6\text{H}_2\text{O}$ anal.grade (Lachema, a.s. Neratovice)

demineralised water 2µS

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

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

$\text{H}_2\text{O}_2$ anal.grade 30% (Lachema, a.s. Neratovice)

N-HANCE 3000 guar gum hydroxypropyltrimmonium chloride

(Aqualon – Hercules)

Equipment: mixer: bottom stirring, 150 l (duplicator), stainless steel EXTRA S

vibrating screen: stainless steel, 150 mesh

rotary air pump: rotor diameter 150 mm

turbostirrer: ULTRA TURAX (Janke-Kunkel)

beaker: 5 l

pH meter PICCOLO

thermocouple thermometer

Procedure:

30g of N-HANCE 3000 were placed into and 5 l beaker and 3 l of demineralised water 2µS 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 l of demineralised water 2μS were introduced into a mixer. Then 3 kg of CaCl₂·6H₂O anal. grade were added and the contents heated up to a temperature of 50°C under stirring. On dissolution of the calcium chloride the stirring 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 Na₂CO₃ to 6 – 6.5 and 13 kg of H₂O₂ 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. Subsequently 60 l 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 l of a mixture of 18 l of synthetic rectified ethanol conc. 98% and 42 l of demineralised water 2μS. The fibre suspension was filtered again on the vibrating screen.

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

Analysis:

<table>
<thead>
<tr>
<th>Component</th>
<th>% b/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca content</td>
<td>4.0</td>
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<tr>
<td>Na content</td>
<td>1.8</td>
</tr>
<tr>
<td>Σ C=O content</td>
<td>0.0</td>
</tr>
<tr>
<td>COOH content</td>
<td>20.7</td>
</tr>
</tbody>
</table>

Example 2:

Material: oxidised short-fibre cotton (Linters – Temming) (proprietary)

<table>
<thead>
<tr>
<th>Component</th>
<th>% b/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆OOH</td>
<td>16.8</td>
</tr>
<tr>
<td>ash content</td>
<td>&lt;0.15</td>
</tr>
</tbody>
</table>
\[ \Sigma \text{C}=\text{O} \quad 2.6 \% \text{ b/w} \]
20% solution \( \text{Na}_2\text{CO}_3 \) (Lachema, a.s. Neratovice)
\( \text{CaCl}_2.6\text{H}_2\text{O} \text{ anal.grade} \) (Lachema, a.s. Neratovice)
redistilled water (PhBs 1997)
ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)
isopropanol 99.9% (Neuberg Bretang)
\( \text{H}_2\text{O}_2 \text{ anal.grade 30\%} \) (Lachema, a.s. Neratovice)
gelatine (PhBs 1997)

10 Equipment:
turbostirrer: ULTRA TURAX (Janke-Kunkel)
sulphonation flask 1 l
heater 1.5 kW
laboratory centrifuge: 4000 rpm
thermostated water bath
pH meter PICCOLO
glass thermometer
rotary vacuum dryer or hot-air dryer

Procedure:
Into a 1 l sulphonation flask equipped with a turbostirrer and a heater, 400 ml of
redistilled \( \text{H}_2\text{O} \) were placed, 15.73 g of \( \text{CaCl}_2.6\text{H}_2\text{O} \) were added and on
dissolution, 40.0 g of 20% \( \text{Na}_2\text{CO}_3 \) 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% \( \text{H}_2\text{O}_2 \) 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 \( \text{Na}_2\text{CO}_3 \). Furthermore, gelatine solution
(10 g of gelatine in 70 g of redistilled \( \text{H}_2\text{O} \)) 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.

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.

Analysis:

<table>
<thead>
<tr>
<th>Content</th>
<th>% b/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca</td>
<td>4.4</td>
</tr>
<tr>
<td>Na</td>
<td>2.7</td>
</tr>
<tr>
<td>Σ C=O</td>
<td>0.0</td>
</tr>
<tr>
<td>COOH</td>
<td>20.5</td>
</tr>
<tr>
<td>N</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Example 3:

Material: oxidised short-fibre cotton (Linters – Temming) (proprietary)

C₈OOH 16.8 % b/w

ash content < 0.15 % b/w

Σ C=O 2.6 % b/w

NaOH anal.grade (Lachema, a.s. Neratovice)

redistilled water (PhBs 1997)

ethanol, synthetic rectified conc. 98% (Chempetrol Litvinov, a.s.)

isopropanol 99.9% (Neuberg Bretang)
H₂O₂ anal.grade 30% (Lachema, a.s. Neratovice)
gelatine (PhBs 1997)

Equipment:
- turbostirrer: ULTRA TURAX (Janke-Kunkel)
- sulphonation flask 1 l
- heater 1.5 kW
- laboratory centrifuge: 4000 rpm
- thermostated water bath
- pH meter PICCOLO
- glass thermometer
- rotary vacuum dryer or hot-air dryer

Procedure:
Into a 1 l sulphonation flask equipped with a turbostirrer and a heater, 400 ml of redistilled H₂O 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% H₂O₂ 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 H₂O) 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 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.

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.

Analysis:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Na content</td>
<td>3.8 % b/w</td>
<td></td>
</tr>
<tr>
<td>Σ C=O content</td>
<td>0.0 % b/w</td>
<td></td>
</tr>
<tr>
<td>COOH content</td>
<td>21.5 % b/w</td>
<td></td>
</tr>
<tr>
<td>N content</td>
<td>2.7 % b/w</td>
<td></td>
</tr>
</tbody>
</table>

Example 4:

Material: oxidised short-fibre cotton (Linters – Temming) (proprietary)

C₆OOH 16.8 % b/w

ash content < 0.15 % b/w

Σ C=O 2.6 % b/w

20% solution Na₂CO₃ (Lachema, a.s. Neratovice)
CaCl₂.6H₂O anal.grade (Lachema, a.s. Neratovice)
redistilled water (PhBs 1997)

ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)
isopropanol 99.9% (Neuberg Bretang)
H₂O₂ anal.grade 30% (Lachema, a.s. Neratovice)
chitosan, degree of deacetylation 92% (Henkel)
Equipment:
- turbostirrer: ULTRA TURAX (Janke-Kunkel)
- sulphonation flask 1 l
- heater 1.5 kW
- laboratory centrifuge: 4000 rpm
- thermostated water bath
- pH meter PICCOLO
- glass thermometer
- rotary vacuum dryer or hot-air dryer

Procedure:
Into a sulphonation flask, 250 ml redistilled H₂O 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% H₂O₂ 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.
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.

Analysis:

<p>| | |</p>
<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Na content</td>
<td>1.8 % b/w</td>
</tr>
<tr>
<td>( \Sigma ) C=O content</td>
<td>0.0 % b/w</td>
</tr>
<tr>
<td>COOH content</td>
<td>10.4 % b/w</td>
</tr>
<tr>
<td>N content</td>
<td>2.8 % b/w</td>
</tr>
</tbody>
</table>

10 **Example 5:**

Material: oxidised short-fibre cotton (Linters – Temming) (proprietary)

\[ \text{C}_6\text{OOH } 16.8 \text{ % b/w} \]

ash content < 0.15 % b/w

15 \[ \Sigma \text{C=O } 2.6 \text{ % b/w} \]

NaOH anal.grade (Lachema, a.s. Neratovice)

HCl 39% anal.grade (Lachema, a.s. Neratovice)

redistilled water (PhBs 1997)

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

isopropanol 99.9% (Neuberg Bretang)

\( \text{H}_2\text{O}_2 \) anal.grade 30% (Lachema, a.s. Neratovice)

gelatine (PhBs 1997)

Ambroxol (H. Mack, Germany)

25 **Equipment:** turbostirrer: ULTRA TURAX (Janke-Kunkel)

sulphonation flask 2 l

heater 1.5 kW

laboratory centrifuge: 4000 rpm

laboratory pin mill ALPINE (35 000 rpm)

30 thermostated water bath
pH meter PICCOLO
glass thermometer
rotary vacuum dryer or hot-air dryer

Procedure:
Into a sulphonation flask, 400 ml redistilled H₂O 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% H₂O₂ 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 H₂O) 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 H₂O) 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 centrifuged 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.
Analysis:

<table>
<thead>
<tr>
<th>Component</th>
<th>Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na content</td>
<td>4.6</td>
</tr>
<tr>
<td>Σ C=O content</td>
<td>0.0</td>
</tr>
<tr>
<td>COOH content</td>
<td>14.8</td>
</tr>
<tr>
<td>N content</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Example 6:

Material: oxidised short-fibre cotton (Linters – Temming) (proprietary)

- C₆OOH 16.8 % b/w
- ash content < 0.15 % b/w
- Σ C=O 2.6 % b/w
- 20% solution Na₂CO₃ (Lachema, a.s. Neratovice)
- CaCl₂·6H₂O anal.grade (Lachema, a.s. Neratovice)
- redistilled water (PhBs 1997)
- ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)
- isopropanol 99.9% (Neuberg Bretang)
- H₂O₂ anal.grade 30% (Lachema, a.s. Neratovice)
- gelatine (PhBs 1997)
- gentamycin sulphate (MERCK)

Equipment: turbostirrer: ULTRA TURAX (Janke-Kunkel)

- sulphonation flask 2 l
- heater 1.5 kW

- laboratory centrifuge: 4000 rpm
- laboratory pin mill ALPINE (35 000 rpm)
- thermostated water bath
- pH meter PICCOLO
- glass thermometer
hot-air dryer
lyophiliser (Leibold Heraus, Germany)

Procedure:

5 Into a 2 l sulphonation flask equipped with a turbostirrer and a heater, 400 ml of redistilled H₂O were placed, 15.73 g of CaCl₂.6H₂O were added and on dissolution, 40.0 g of 20% Na₂CO₃ 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% H₂O₂ 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 Na₂CO₃. Furthermore, gelatine solution (10 g of gelatine in 70 g of redistilled H₂O) 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 H₂O 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 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.
- 25 -

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

Analysis:

<table>
<thead>
<tr>
<th>Component</th>
<th>% b/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca content</td>
<td>2.4</td>
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<tr>
<td>Na content</td>
<td>1.6</td>
</tr>
<tr>
<td>(\Sigma) C=O content</td>
<td>0.0</td>
</tr>
<tr>
<td>COOH content</td>
<td>9.6</td>
</tr>
<tr>
<td>N content</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Example 7:

Material: long-fibre cotton – medicinal cotton wool oxidised by \(\text{N}_2\text{O}_y\) (proprietary)

- \(\text{C}_9\text{OOH}\) 18.8 % b/w
- ash content < 0.1 % b/w
- \(\Sigma\) C=O 0.6 % b/w

20% solution Na\(_2\)CO\(_3\) (Lachema, a.s. Neratovice)

CaCl\(_2\).6H\(_2\)O anal.grade (Lachema, a.s. Neratovice)

demineralised water 2\(\mu\)S

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

isopropanol 99.9% (Neuberg Bretang)

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

H\(_2\)O\(_2\) anal.grade 30% (Lachema, a.s. Neratovice)

N-HANCE 3000 guargumhydroxypropyltriammoniumchloride (Aqualon – Hercules)

polybren (hexadimethrin dibromide) (FLUKA)

chlorhexidindigluconate
Equipment: mixer: bottom stirring, 150 l (duplicator), stainless steel EXTRA S
vibrating screen: stainless steel, 150 mesh
rotary air pump: rotor diameter 150 mm
turbostirrer: ULTRA TURAX (Janke-Kunkel)
beaker: 5 l
pH meter PICCOLO
thermocouple thermometer

Procedure:

30g of N-HANCE 3000 were placed into and 5 l beaker and 3 l of demineralised water 2μS 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 l of demineralised water 2μS were introduced into a mixer. Then 3 kg of CaCl₂.6H₂O anal.grade were added and the contents heated up to a temperature of 50°C under stirring. On dissolution of the calcium chloride the stirring 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 Na₂CO₃ to 6 – 6.5 and 13 kg of H₂O₂ 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 2μS 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 2μS was added. Subsequently 60 l 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 l of a mixture of 18 l of synthetic rectified ethanol conc. 98% and 42 l of demineralised water 2μS. The fibre suspension was filtered again on the vibrating screen.

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.

Analysis:

<table>
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<tr>
<th>Content</th>
<th>% b/w</th>
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</thead>
<tbody>
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<tr>
<td>Na content</td>
<td>1.9</td>
</tr>
<tr>
<td>(\Sigma ) C=O content</td>
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<td>COOH content</td>
<td>18.1</td>
</tr>
<tr>
<td>N content</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Example 8:

Material: oxidised short-fibre cotton (Linters – Temming) (proprietary)

C\(_6\)OOH 16.8 % b/w

ash content < 0.15 % b/w

\(\Sigma \) C=O 2.6 % b/w

20% solution Na\(_2\)CO\(_3\) (Lachema, a.s. Neratovice)

CaCl\(_2\).6H\(_2\)O anal.grade (Lachema, a.s. Neratovice)

redistilled water (PhBs 1997)

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

isopropanol 99.9% (Neuberg Bretang)

H\(_2\)O\(_2\) anal.grade 30% (Lachema, a.s. Neratovice)

Chitosan, degree of deacetylation 92% (Henkel)

Clarithromycin lactobionan (Abbott Laboratories, Italy)
Equipment:
turbostirrer: ULTRA TURAX (Janke-Kunkel)
sulphonation flask 1 l
heater 1.5 kW
laboratory centrifuge: 4000 rpm
thermostated water bath
pH meter PICCOLO
glass thermometer
rotary vacuum dryer or hot-air dryer
dialysing bag (regenerated cellulose)
lyophiliser (Leybold Heraus, Germany)
laboratory pin mill ALPINE (35 000 rpm)

Procedure:
Into a sulphonation flask, 250 ml redistilled H₂O 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% H₂O₂ 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 H₂O) 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.
Analysis:

<table>
<thead>
<tr>
<th>Component</th>
<th>Content (b/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na content</td>
<td>4.8%</td>
</tr>
<tr>
<td>$\Sigma$ C=O</td>
<td>0.0%</td>
</tr>
<tr>
<td>COOH content</td>
<td>18.8%</td>
</tr>
<tr>
<td>N content</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

Example 9:

Material:
oxidised short-fibre cotton (Linters – Temming) (proprietary)
C$_5$OOH 16.8 % b/w
ash content < 0.15 % b/w
$\Sigma$ C=O 2.6 % b/w
NaOH anal.grade (Lachema, a.s. Neratovice)
redistilled water (PhBs 1997)
ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)
isopropanol 99.9% (Neuberg Bretang)
H$_2$O$_2$ anal.grade 30% (Lachema, a.s. Neratovice)
gelatine (PhBs 1997)
Bi(NO$_3$)$_3$.5H$_2$O (MERCK)

Equipment:
turbosirrer: ULTRA TURAX (Janke-Kunkel)
sulphonation flask 2 l
heater 1.5 kW
laboratory centrifuge: 4000 rpm
thermostated water bath
pH meter PICCOLO
glass thermometer
rotary vacuum dryer or hot-air dryer
Procedure:
Into a sulphonation flask, 400 ml redistilled H₂O 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% H₂O₂ 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 H₂O) 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 BiNO₃ (54 g of BiNO₃·5H₂O in 746 ml of H₂O) 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 treatment or tablets for treatment of gastrointestinal tract malfunctions.
Analysis:

<table>
<thead>
<tr>
<th>Component</th>
<th>Content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na content</td>
<td>1.9 b/w</td>
</tr>
<tr>
<td>Σ C=O content</td>
<td>0.0 b/w</td>
</tr>
<tr>
<td>COOH content</td>
<td>20.0 b/w</td>
</tr>
<tr>
<td>N content</td>
<td>&lt;0.3 b/w</td>
</tr>
<tr>
<td>Bi content</td>
<td>4.7 b/w</td>
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</tbody>
</table>

Example 10:

Material:
- oxidised short-fibre cotton (Linters – Temming) (proprietary)
  - C₆OOH 16.8 % b/w
  - ash content < 0.15 % b/w
- 20% solution Na₂CO₃ (Lachema, a.s. Neratovice)
- CaCl₂·6H₂O anal.grade (Lachema, a.s. Neratovice)
- redistilled water (PhBs 1997)
- ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)
- isopropanol 99.9% (Neuberg Bretang)
- H₂O₂ anal.grade 30% (Lachema, a.s. Neratovice)
- gelatine (PhBs 1997)
- cimetidine hydrochloride (SPOFA)

Equipment:
- turbostirrer: ULTRA TURAX (Janke-Kunkel)
- sulphonation flask 2 l
- heater 1.5 kW
- laboratory centrifuge: 4000 rpm
- thermostated water bath
- pH meter PICCOLO
glass thermometer
rotary vacuum dryer or hot-air dryer

Procedure:

Into a 1 l sulphonation flask equipped with a turbostirrer and a heater, 400 ml of redistilled H₂O were placed, 15.73 g of CaCl₂.6H₂O were added and on dissolution, 40.0 g of 20% Na₂CO₃ 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% H₂O₂ 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 Na₂CO₃. Furthermore, gelatine solution (10 g of gelatine in 70 g of redistilled H₂O) 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 a solution of cimetidine (36 g of cimetidine hydrochloride in 400 ml of redistilled H₂O) 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.

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

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<th>Content</th>
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<td>Na content</td>
<td>2.7 % b/w</td>
</tr>
<tr>
<td>Σ C=O content</td>
<td>0.0 % b/w</td>
</tr>
<tr>
<td>COOH content</td>
<td>20.5 % b/w</td>
</tr>
<tr>
<td>N content</td>
<td>2.1 % b/w</td>
</tr>
</tbody>
</table>

10 Example 11:

Material: IMC-MDOC complex (as per above Example 2)
[(2S;2R)-3-amino-2-hydroxy-4-phenylbutenoyl]-L-leucin (Bestatin)
(Boehringer Mannheim, Germany)
redistilled water (PhBs 1997)
methanol, conc. anal. grade (Chemopetrol Litvinov, a.s.)
diethylether (Lachema, a.s. Neratovice)

Equipment: turbostirrer: ULTRA TURAX (Janke-Kunkel)
sulphonation flask 2 l
laboratory centrifuge: 4000 rpm
hot-air dryer

Procedure:

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 was 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.

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

MDOC = Microdispersed Oxidised cellulose

Material: MDOC (Ca/Na salt of PAGA), particle size 0.1 - 2.0 μm, specific
surface area 86 m²/g, COOH group content 22.2 % b/w, Ca content
4.2 % b/w, Na content 3.8 % b/w

Equipment: tabletting machine (KORSCH EK 0, Berlin)

Procedure:
100 g of MDOC were introduced into the tabletting machine. The tabletting force
was set at a value of 5 kN.

Result:
The tablets prepared were smooth and cohesive 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.
Application Example:

A patient aged 55, displaying an increased cholesterol content in blood was treated by MDOC tablets administered orally for 50 days, at a dose of 6 tablets daily. After the treatment both LDL content and total cholesterol content were significantly reduced.

<table>
<thead>
<tr>
<th>Blood analysis</th>
<th>before treatment</th>
<th>after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>8.60 mmol/l</td>
<td>6.60 mmol/l</td>
</tr>
<tr>
<td>HDL</td>
<td>1.16 mmol/l</td>
<td>1.20 mmol/l</td>
</tr>
<tr>
<td>LDL</td>
<td>6.50 mmol/l</td>
<td>4.90 mmol/l</td>
</tr>
<tr>
<td>Triacylglycerols</td>
<td>2.70 mmol/l</td>
<td>2.40 mmol/l</td>
</tr>
</tbody>
</table>

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

Material: IMC-MDOC complex – see Example 2 (of ALPE01/C)
magnesium stearate (SIGMA)
ascorbic acid (MERCK)
α-tocoferol acetate (Slovakofarma Hlohovec)
ethanol synthetic rectified (Chemopetrol Litvinov, a.s.)

Equipment: tabletting machine (KORSCH EK 0, Berlin)
blender (Nautamix 300)
counter-flow drier (BINDER)

Procedure:

10 kg of IMC-MDOC complex of composition according to Example 2 were placed into the blender. 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 and dried in a counter-flow drier at a temperature of 50°C until the ethanol was removed.

100 g of the resulting dry powder were introduced into the tabletting machine. The tabletting force was set at a value of 7 kN.

Result:
The tablets prepared were smooth and cohesive 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.

Application Example:
A patient aged 57, displaying an increased cholesterol content in blood was treated by MDOC tablets administered orally for 50 days, at a dose of 6 tablets daily. After the treatment both LDL content and total cholesterol content were significantly reduced.

<table>
<thead>
<tr>
<th>Blood analysis:</th>
<th>before treatment</th>
<th>after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>7.70 mmol/l</td>
<td>5.70 mmol/l</td>
</tr>
<tr>
<td>HDL</td>
<td>1.16 mmol/l</td>
<td>1.30 mmol/l</td>
</tr>
<tr>
<td>LDL</td>
<td>4.40 mmol/l</td>
<td>3.30 mmol/l</td>
</tr>
<tr>
<td>Triacylglycerols</td>
<td>1.81 mmol/l</td>
<td>1.80 mmol/l</td>
</tr>
</tbody>
</table>
Example C: Preparation of granules in a fluid bed

Material: MDOC, particle size 0.1 - 2.0 μm, specific surface area 86 m²/g, COOH group content 22.2% b/w, Ca content 4.2 % b/w, Na content 3.8 % b/w

Equipment: set of vibrating screens with mesh size 100, 150, 200, 250, 350, 500 μm mixer, bottom agitated, vessel size 1000 ml, 8000 rpm, equipped with a nozzle for inlet of the granulation medium counter-flow drier (BINDER)

Procedure:
100 g of MDOC were placed into the mixer, the mixer was closed and the agitation begun. A water mist 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 to 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.

Indication:
The product may be used as a) an embolisation agent, or b) an antilipemicum.

Example D: Preparation of granules from IMC-MDOC complex

Material: IMC-MDOC complex – see Example 2
Equipment: set of vibrating screens with mesh size 100, 150, 200, 250, 350, 500μm
mixer, bottom agitated, vessel size 1000 ml, 8000 rpm, equipped with a nozzle for inlet of the granulation medium
counter-flow drier BINDER

Procedure:
100 g of MDOC were placed into the mixer, the mixer was closed and the agitation begun. Saturated water vapour 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 to 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.

Indication:
The product may be used as a) an embolisation agent, or b) an antilipemicum.

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

1. An antilipemic composition including a biocompatible anionic polysaccharide material containing non-sulphated 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.

3. A composition as claimed in claim 1 or 2 wherein the polysaccharide material is polyanhydroglucuronic acid, biocompatible salts thereof, copolymers thereof or a biocompatible intermolecular complex thereof.

4. A composition as claimed in claim 3 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.

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

6. A composition as claimed in claims 4 or 5 wherein the cationic component contains nitrogen that either carries a positive charge or wherein the positive charge is induced by contact with the polysaccharidic anionic component.
7. A composition as claimed in claim 6 wherein the cationic component is selected from derivatives of acrylamide, methacrylamide and copolymers thereof.

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

9. A composition as claimed in claim 8 wherein the cationic component is a cationised natural polysaccharide.

10. A composition as claimed in claim 9 wherein the polysaccharide is a starch, cellulose or gum.

11. A composition as claimed in claim 10 wherein the gum is guargumhydroxypropyltrimmonium chloride.

12. A complex as claimed in claim 4 wherein the cationic component is a synthetic or semi-synthetic polyamino acid.

13. A complex as claimed in claim 12 wherein the cationic component is polylys in, polyarginin, or α, β-poly-[N-(2-hydroxyethyl)-DL-aspartamide].

14. A complex as claimed in claim 4 wherein the cationic component is a synthetic anti-fibrinolytic.

15. A complex as claimed in claim 14 wherein the anti-fibrinolytic is a hexadimethrindibromide (polybren).
16. A composition as claimed in claim 4 wherein the cationic component is a natural or semi-synthetic peptide.

17. A composition as claimed in claim 15 wherein the peptide is a protamine, gelatine, fibrinopeptide, or derivatives thereof.

18. A composition as claimed in claim 4 wherein the cationic component is an aminoglucane or derivatives thereof.

19. A composition as claimed in claim 18 wherein the aminoglucane is fractionated chitin or its de-acetylated derivative chitosan.

20. A composition as claimed in claim 18 or 19 wherein the aminoglucane is of microbial origin or is isolated from the shells of arthropods such as crabs.

21. A composition as claimed in any of claims 4 to 20 wherein the anionic component is polyanhydroglucuronic acid and/or biocompatible salts and/or copolymers thereof.

22. A composition as claimed in any of claims 3 to 21 wherein the polyanhydroglucuronic acid and salts thereof contain in their polymeric chain from 8 to 30 per cent by weight of carboxyl groups, at least 80 per cent by weight of these groups being of the uronic type, at most 5 per cent by weight of carbonyl groups, and at most 0.5 per cent by weight of bound nitrogen.

23. A composition as claimed in claim 22 wherein the polyanhydroglucuronic acid and salts thereof contain in their polymeric chain at most 0.2 per cent by weight of bound nitrogen.
24. A composition as claimed in claim 22 or 23 wherein the molecular mass of the polymeric chain of the anionic component is from $1 \times 10^1$ to $3 \times 10^5$ Daltons.

25. A composition as claimed in claim 24 wherein the molecular mass of the polymeric chain of the anionic component ranges from $5 \times 10^3$ to $1.5 \times 10^5$ Daltons.

26. A composition as claimed in any of the claims 22 to 25 wherein the content of carboxyl groups is in the range of from 12 to 26 per cent by weight, at least 95 per cent of these groups being of the uronic type.

27. A composition as claimed in any of claims 22 to 26 wherein the anionic component contains at most 1 per cent by weight of carbonyl groups.

28. A composition as claimed in any of claims 22 to 27 wherein the carbonyl groups are intra- and intermolecular 2,6 and 3,6 hemiacetals, 2,4-hemialdals and C2-C3 aldehydes.

29. A composition as claimed in claim 4 wherein the cationic component is gelatine.

30. A composition as claimed in claim 4 wherein the cationic component is chitosan.

31. A composition as claimed in any preceding claim including at least one biocompatible biologically active substance.
32. A composition as claimed in any preceding claim including at least one biologically acceptable adjuvant.

33. A composition as claimed in any preceding claim including at least one pharmaceutically active adjuvant.

34. A composition as claimed in claim 31 wherein the adjuvant is an antilipemic agent.

35. A composition as claimed in claim 32 wherein the antilipemic agent is a phospholipid.

36. A composition as claimed in any preceding claim in a form for oral administration.

37. A composition as claimed in claim 34 in the form of a tablet, pellet, capsule, granule, or microsphere.

38. A composition substantially as hereinbefore described with reference to the examples.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
   IPC 7 A61K31/715 A61K31/78 A61K31/785

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 7 A61K

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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<td>PATENT ABSTRACTS OF JAPAN vol. 008, no. 126 (C-228), 13 June 1984 (1984-06-13) &amp; JP 59 038204 A (SHIYOU WA SANGYO KK), 2 March 1984 (1984-03-02) abstract</td>
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</tr>
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "L" document which may throw doubt 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.

"A" document member of the same patent family

Date of the actual completion of the International search: 19 November 1999
Date of mailing of the International search report: 03/12/1999

Name and mailing address of the ISA
European Patent Office, P.B. 5018 Patentenen 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 540-2040, Tx: 31 651 epo nl
Fax: (+31-70) 540-3016

Authorized officer: Veronese, A

Form PCT/ISA/210 (second sheet) (July 1992)
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<td>DATABASE CHEMABS 'Online!', CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US WANG, DINGGANG ET AL: &quot;Isolation, purification, analysis, and antihyperlipidemia effect of green tea polysaccharide&quot; retrieved from STN Database accession no. 115:270441 XP002123232 abstract &amp; ZHONGGOU YAOKE DAXUE XUEBAO (1991), 22(4), 225-8</td>
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<td>PATENT ABSTRACTS OF JAPAN vol. 014, no. 531 (C-0780), 21 November 1990 (1990-11-21) &amp; JP 02 221224 A (TATSUKAI YAMAGUCHI), 4 September 1990 (1990-09-04) cited in the application abstract</td>
<td>1-6,9, 18,19, 21-23,30</td>
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<td>WO 98 33822 A (SANTAR IVAN ; KISS FRANTISEK (CZ); BRIESTENSKY JIRI (CZ); ALLTRADE) 6 August 1998 (1998-08-06) cited in the application claim 22; example 6</td>
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<td>WO 98 00180 A (WATT PAUL WILLIAM ; HARVEY WILSON (GB); LORIMER ELAINE (GB); JOHNSO) 8 January 1998 (1998-01-08) claims; examples</td>
<td>1-6,17, 29</td>
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<td>BRIESTENSKY J ET AL: &quot;Production of oxidized cellulose-based sorbent as a resorbable hemostatic material&quot; STN CHEMICAL ABSTRACTS, vol. 10, no. 110, 3 April 1989 (1989-04-03), XP002120226 the whole document</td>
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<td>US 5 593 682 A (PAPAS ANDREAS M ET AL) 14 January 1997 (1997-01-14) claim 1; examples 1-10</td>
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<td>A</td>
<td>WO 95 12620 A (ALPHA BETA TECHNOLOGY ; LIANG JINSHENG (US); OSTROFF GARY R (US); Y) 11 May 1995 (1995-05-11)</td>
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<td>14-01-1997</td>
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