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(57) Abstract

A suppository formulation for rectal or vaginal administration includes a biocompatible anionic polysaccharide material wherein at least 5% of the basic structural units of the polysaccharide are glucuronic acid.
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SUPPOSITORY FORMULATIONS COMPRISING ANIONIC POLYSACCHARIDE

Introduction

The invention relates to suppository formulations especially for rectal or vaginal administration.

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

The suppositories are adapted to be inserted into the body orifice of a human so as to allow the suppository to be in contact with tissue of the bodily orifice to facilitate transfer of suppository material therethrough.

The rectal suppositories are particularly useful for prophylaxis or treatment of haemorrhoidal disorders, especially haemorrhoidal bleeding. An analgesic and/or an antipyretic agent may also be included.

The vaginal suppositories are particularly for use in the treatment of urinary tract infections due to both gram positive and gram negative bacteria. The vaginal
mucous tissue is protected as a natural microenvironment similar to the action of lactic acid is created.

According to the invention there is provided a suppository formulation including a biocompatible anionic polysaccharide material wherein at least 5% of the basic structural units of the polysaccharide are glucuronic acid.

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

In one embodiment of the invention the polysaccharide material is polyanhydroglucuronic acid, biocompatible salts thereof, copolymers thereof or a biocompatible intermolecular complex thereof.

In a preferred 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.

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.

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

The cationic component may be a cationised natural polysaccharide. The polysaccharide may be a starch, cellulose or gum. The gum is preferably guar gum hydroxypropyltrimmonium chloride.

The cationic component may be a synthetic or semi-synthetic polyamino acid. In this case preferably the cationic component is polylysine, polyarginine, or \( \alpha, \beta \)-poly-\([N-(2-hydroxyethyl)-DL-aspartamide]\).

In one embodiment the cationic component is a synthetic anti-fibrinolytic. In this case preferably the anti-fibrinolytic may be a hexadimethrindibromide (polybren).

The cationic component may be a natural or semi-synthetic peptide.

The peptide may be a protamine, gelatine, fibrinopeptide, or derivatives thereof.

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

The anionic component is most preferably polyanhydroglucuronic acid and/or bicompatible salts and/or copolymers thereof.
In a particularly preferred embodiment 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.

The polyanhydroglucuronic acid and salts thereof preferably 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.

The content of carboxyl groups is preferably 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.

The anionic component preferably contains at most 1 per cent by weight of carbonyl groups.

The carbonyl groups are preferably intra- and intermolecular 2,6 and 3,6 hemiacetals, 2,4- hemialdals and C2-C3 aldehydes.

In a preferred embodiment the cationic component is gelatine.

In another preferred embodiment the cationic component is chitosan.

Preferably the formulation includes at least one biocompatible biologically active substance.
The formulation may alternatively or additionally include at least one biologically acceptable adjuvant.

The biologically active substance may be an anti-haemorroidal, analgesic, antipyretic, antibiotic, anti-viral, antimicrobial, anti-inflammatory and/or bacteriocidal agent.

The invention also provides a rectal suppository formulation for the prophylaxis or treatment of haemorrhoidal disorders comprising a formulation of the invention.

The invention further provides a vaginal suppository formulation for prophylaxis or treatment of urogenital disease and/or for the prophylaxis or treatment of urinary tract infections comprising a formulation of the invention.

Various pressing moulds may be used to produce suitably shaped suppositories from polyanhydroglucuronic acids and salts thereof particularly as described in co-pending application PCT IE98/00004. One advantage of suppositories prepared by this method is that the pressing method does not necessarily require use of adjuvants such as glycols, alcohols, or water, the presence of which may reduce the haemostatic activity.

The suppositories may with advantage include antibacterial components of the inorganic or organic cation type which may be bound to the COOH, OH, or both types of these groups present in the polymeric chain of polyanhydroglucuronic acids and salts thereof to form salts or complex salts. Examples, of cations which may be used for this purpose are Zn\(^{2+}\), Hg\(^{2+}\), Ag\(^{+}\), or Cu\(^{2+}\) ions, aminoglycosidic, aminoclitolic or chinolinic antibiotics, chlorohexidine or other amines having bactericidal or bacteriostatic effects. Alternatively, the suppositories may also
include pharmacologically active substances not directly bound to the polymeric chain such as herb extracts, vitamins, or even substances listed physically admixed to the polyanhydroglucuronic acids and salts thereof.

The manufacture is simple and inexpensive since is involves one single production step; no contraction or cracking of suppositories manufactured by such a pressing process has been observed.

It is also possible to apply conventional moulding techniques such as those used for manufacture of suppositories, preferably using hydrophobic bases such as cocoa butter or petroleum to prevent reduction of the haemostatic activity of the polyanhydroglucuronic acids and salts thereof.

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 immunomodululative 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 hydroxyethylmetacrylate and hydroxypropylmetacrylamide, copolymer of acrylamide, butylacrylate, maleinanhdyride, and methylmetacrylate, and the like], or else cationised natural polysaccharides such as starches, celluloses, or gums such as guar gum hydroxypropyltrimmonium chloride.

   b) Synthetic or semi-synthetic polyaminoacids such as polylysine, polargarginin, α,β-poly-[N-(2-hydroxyethyl)-DL-asparamide. Synthetic antifibrinolytics hexadimethrindibromide (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 aminoglucones 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 micrystalline 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 (tikarcillin) 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; monopropylene glycol; 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 Glucuronoglucan

Example 1:

Material: long-fibre cotton – medicinal cotton wool oxidised by N₂O₅

(proprietary)
C₆OOH 18.8 % b/w
ash content < 0.1 % b/w
Σ C=O 0.6 % b/w
20% solution Na₂CO₃ (Lachema, a.s. Neratovice)
CaCl₂.6H₂O 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)
H₂O₂ anal.grade 30% (Lachema, a.s. Neratovice)
N-HANCE 3000 guargumhydroxypropyltrimmoniumchloride
(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:

- 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: 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)

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, 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 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 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:

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Example 3:

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

C₅OOH 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% (Chemopetrol 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>
</tr>
</thead>
<tbody>
<tr>
<td>Na content</td>
<td>3.8 % b/w</td>
</tr>
<tr>
<td>$\Sigma$ C=O content</td>
<td>0.0 % b/w</td>
</tr>
<tr>
<td>COOH content</td>
<td>21.5 % b/w</td>
</tr>
<tr>
<td>N content</td>
<td>2.7 % b/w</td>
</tr>
</tbody>
</table>

Example 4:

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

- $C_6OOH$ 16.8 % b/w
- ash content < 0.15 % b/w
- $\Sigma$ C=O 2.6 % b/w

20% solution $Na_2CO_3$ (Lachema, a.s. Neratovice)
$CaCl_2 \cdot 6H_2O$ anal.grade (Lachema, a.s. Neratovice)
redistilled water (PhBs 1997)
ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)
isopropanol 99.9% (Neuberg Bretang)

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:

<table>
<thead>
<tr>
<th></th>
<th>% b/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na content</td>
<td>1.8</td>
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<tr>
<td>Σ C=O content</td>
<td>0.0</td>
</tr>
<tr>
<td>COOH content</td>
<td>10.4</td>
</tr>
<tr>
<td>N content</td>
<td>2.8</td>
</tr>
</tbody>
</table>
Example 5:

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

C₅OH  16.8 % b/w

5

ash content < 0.15 % b/w

\[ \sum C=O \]  2.6 % b/w

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

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

redistilled water (PhBs 1997)

10

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

isopropanol 99.9% (Neuberg Bretang)

H₂O₂ anal.grade 30% (Lachema, a.s. Neratovice)

gelatine (PhBs 1997)

Ambroxol (H. Mack, Germany)

15

Equipment: turbostirrer: ULTRA TURAX (Janke-Kunkel)

sulphonation flask 2 l

heater 1.5 kW

laboratory centrifuge: 4000 rpm

20

laboratory pin mill ALPINE (35 000 rpm)

thermostated water bath

pH meter PICCOLO

glass thermometer

rotary vacuum dryer or hot-air dryer

25

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:

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<th>Content</th>
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<td>Na content</td>
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<tr>
<td>Σ C=O content</td>
<td>0.0</td>
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<tr>
<td>COOH content</td>
<td>14.8</td>
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<tr>
<td>N content</td>
<td>1.9</td>
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</table>

Example 6:

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

<table>
<thead>
<tr>
<th>Content</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>
<tr>
<td>Σ C=O</td>
<td>2.6</td>
</tr>
</tbody>
</table>
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)
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:
Into a 2 l sulphonation flask equipped with a turbostirrer and a heater, 400 ml of redistilled H$_2$O were placed, 15.73 g of CaCl$_2$.6H$_2$O were added and on dissolution, 40.0 g of 20\% Na$_2$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\% H$_2$O$_2$ 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$_2$CO$_3$. 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.

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>
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<tr>
<td>Ca content</td>
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<tr>
<td>Na content</td>
<td>1.6</td>
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<tr>
<td>Σ C=O content</td>
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<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 N₂O₅ (proprietary)
C₆OOH 18.8 % b/w
ash content < 0.1 % b/w
Σ C=O 0.6 % b/w
20% solution Na₂CO₃ (Lachema, a.s. Neratovice)
5 CaCl₂.6H₂O anal.grade (Lachema, a.s. Neratovice)
demineralised water 2μS
ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)
isoopropanol 99.9% (Neuberg Bretang)
acid acetic anal.grade (Lachema, a.s. Neratovice)
10 H₂O₂ anal.grade 30% (Lachema, a.s. Neratovice)
N-HANCE 3000 guargumhydroxypropyltrimmoniumchloride
(Aqualon – Hercules)
polybren (hexadimethrinindibromide) (FLUKA)
chlorhexidindigluconate
15 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)
20 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 polybren 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>
<thead>
<tr>
<th>Component</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca content</td>
<td>3.6 % b/w</td>
</tr>
<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>18.1 % b/w</td>
</tr>
<tr>
<td>N content</td>
<td>0.35 % b/w</td>
</tr>
</tbody>
</table>
Example 8:

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

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

ash content < 0.15 \% b/w

\[ \sum \text{C}=\text{O} \quad 2.6 \% \text{ b/w} \]

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

10 \( \text{CaCl}_2 \cdot 6\text{H}_2\text{O} \) anal. grade (Lachema, a.s. Neratovice)

redistilled water (PhBs 1997)

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

isopropanol 99.9\% (Neuberg Bretang)

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

15 Chitosan, degree of deacetylation 92\% (Henkel)

Clarithromycin lactobionan (Abbott Laboratories, Italy)

Equipment: turbostirrer: ULTRA TURAX (Janke-Kunkel)

sulphonation flask 1 l

20 heater 1.5 kW

laboratory centrifuge: 4000 rpm

thermostated water bath

pH meter PICCOLO

glass thermometer

25 rotary vacuum dryer or hot-air dryer

dialysing bag (regenerated cellulose)

lyophiliser (Leybold Heraus, Germany)

laboratory pin mill ALPINE (35 000 rpm)

30
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:

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: oxidised short-fibre cotton (Linters – Temming) (proprietary)
C₆OOH  16.8 % b/w
ash content  < 0.15 % b/w
\[ \Sigma \text{C}=\text{O} \quad 2.6 \% \text{ b/w} \]

NaOH anal.grade (Lachema, a.s. Neratovice)
redistilled water (PhBs 1997)
ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)
5
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)

10 Equipment: turbostirrer: ULTRA TURAX (Janke-Kunkel)
sulphonation flask 2 l
heater 1.5 kW
laboratory centrifuge: 4000 rpm
thermostated water bath
15
pH meter PICCOLO
glass thermometer
rotary vacuum dryer or hot-air dryer

Procedure:
20 Into a sulphonation flask, 400 ml redistilled H$_2$O 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$_2$O$_2$ 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$_2$O) 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
30 BiNO$_3$.5H$_2$O in 746 ml of H$_2$O) 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>
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<tr>
<td>( \Sigma ) C=O content</td>
<td>0.0 % b/w</td>
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<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>
</tr>
</tbody>
</table>

Example 10:

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

<table>
<thead>
<tr>
<th>Component</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{C}_6\text{OOH} )</td>
<td>16.8 % b/w</td>
</tr>
<tr>
<td>ash content</td>
<td>&lt;0.15 % b/w</td>
</tr>
<tr>
<td>( \Sigma ) C=O</td>
<td>2.6 % b/w</td>
</tr>
</tbody>
</table>

20% solution Na\(_2\)CO\(_3\) (Lachema, a.s. Neratovice)
CaCl$_2$.6H$_2$O anal.grade (Lachema, a.s. Neratvice)
redistilled water (PhBs 1997)
ethanol, synthetic rectified conc. 98% (Chemopetrol Litvinov, a.s.)
isopropanol 99.9% (Neuberg Bretang)

5
H$_2$O$_2$ anal.grade 30% (Lachema, a.s. Neratvice)
gelatine (PhBs 1997)
cimetidine hydrochloride (SPOFA)

Equipment: turbostirrer: ULTRA TURAX (Janke-Kunkel)
10
sulphonation flask 2 l
heater 1.5 kW
laboratory centrifuge: 4000 rpm
thermostated water bath
pH meter PICCOLO
15
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 H$_2$O were placed, 15.73 g of CaCl$_2$.6H$_2$O were added and on dissolution, 40.0 g of 20% Na$_2$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% H$_2$O$_2$ 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$_2$CO$_3$. Furthermore, gelatine solution (10 g of gelatine in 70 g of redistilled H$_2$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 a solution of cimetidine (36 g of cimetidine
hydrochloride in 400 ml of redistilled H₂O) were added under intense 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:

<table>
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<th>Component</th>
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<td>Σ C=O content</td>
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<tr>
<td>COOH content</td>
<td>20.5</td>
</tr>
<tr>
<td>N content</td>
<td>2.1</td>
</tr>
</tbody>
</table>

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)
distilled 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 rectal suppositories from MDOC and MDOC Zn²⁺**

**MDOC = Microdispersed oxidised cellulose**

Material: Adeps neutralis (WERBA)
Trimecainum chloratum (SPOFA)
Oleum cacao (WERBA)
MDOC particle size 0.1 - 2.0μm, specific surface area 86m²,
COOH group content 22.2% b/w, Ca content 4.2 % b/w, Na
content 3.8 % b/w

MDOC Zn²⁺, Na⁺ (content Zn 8.0%, Na 4.0%)

Equipment: stainless melting tank, agitated, volume 1000 ml, input power
600W
movable support carrying a shaped blister foil

Procedure:
360 g Adeps neutralis and 132 g Oleum cacao were introduced into the melting
tank. The contents were heated to a temperature of 75°C. On melting, 3 g of
trimecainum chloratum, 90 g of MDOC Ca²⁺, Na⁺, and 15 g of MDOC Zn²⁺, Na⁺,
were gradually added under continuous agitation. After appropriate
homogenisation, the mass was cast into a shaped blister foil which serves, when
cooled down, as the suppository packaging.

Result:
Suppository of 8 mm diameter, 20 mm length, conical shape, weight 2.25 g.

Indication:
Rectal suppositories for treatment of haemorroidal bleeding.

**Example B**: *Preparation of rectal suppositories from IMC-MDOC BiO⁺
complex containing aminophenazon and allobarbital*

Material: Adeps neutralis (WERBA)
Oleum cacao (WERBA)
IMC-MDOC complex containing BiO⁺ - see Example 9
Aminophenazonum (SPOFA)
Allobarbitalum (SPOFA)

Equipment: stainless melting tank, agitated, volume 1000 ml, input power 600W movable support carrying a shaped blister foil

Procedure:
282.6 g Adeps neutralis and 122.6 g Oleum cacao were introduced into the melting tank. The contents were heated to a temperature of 75°C. On melting, 16 g of Allobarbitalum, 117.3 g of Aminophenozonum and 61.33 g of IMC-MDOC complex containing BiO⁺ were gradually added under continuous agitation. After appropriate homogenisation, the mass was cast into a shaped blister foil which serves when cooled down, as the suppository packaging.

Result:
Suppository of 8 mm diameter, 20 mm length, conical shape, weight 2.25 g.

Indication:
Combined suppositories having antihaemorrhoidal and analgetic/antipyretic effects.

**Example C: Preparation of vaginal suppositories from IMC-MDOC complex Containing gelatina, nitrofurantoin and chlorohexidine**

Material: IMC-MDOC complex – see Example 2
gelatina animalis (SIGMA)
1,2-monopropylenglykol (SIGMA)
glycerol, medicinal (MERCK)
nitrofurantoinum (SPOFA)
chlorohexidine digluconate (FEROSAN)
redistilled H₂O

Equipment: stainless melting tank, agitated, volume 1000 ml, input power 600W movable support carrying a shaped blister foil

Procedure:
78 g redistilled H₂O, 240 g medicinal glycerol and 30 g 1,2-MPG were introduced into the melting tank and the mixture was heated up to a temperature of 75°C. On melting, 30 g nitrofurantoinum and 30 g chlorohexidine were gradually added under agitation. The mixture was agitated for another 15 minutes. 102 g of gelatine animalis were introduced and after appropriate homogenisation 90 g IMC-MDOC complex were added. The resulting mixture was agitated for another 15 minutes and then cast into a shaped blister foil serving, when cooled down, as the suppository packaging.

Result:
Suppository of 8 mm diameter, 17 mm length, cylindrical shape, weight 2.0 g.

Indication:
Vaginal suppositories for use in treatment of urinary tract infections due to both gram positive and gram negative bacteria displaying a prolonged effect. The IMC-MDOC present serves to protect the vaginal mucous tissue and to create a natural microenvironment similar to the action of lactic acid.

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

1. A suppository formulation including a biocompatible anionic polysaccharide material wherein at least 5% of the basic structural units of the polysaccharide are glucuronic acid.

2. A formulation as claimed in claim 1 wherein the polysaccharide is derived from a starch, cellulose or gum, or is of microbial origin.

3. A formulation 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 formulation 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 formulation as claimed in claim 4 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.

6. A formulation as claimed in claim 5 wherein the cationic component is selected from derivatives of acrylamide, methacrylamide and copolymers thereof.
7. A formulation 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 formulation as claimed in claim 7 wherein the cationic component is a cationised natural polysaccharide.

9. A formulation as claimed in claim 8 wherein the polysaccharide is a starch, cellulose or gum.

10. A formulation as claimed in claim 9 wherein the gum is guargumhydroxypropyltrimmonium chloride.

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

12. A complex as claimed in claim 11 wherein the cationic component is polylysine, polyarginine, or α, β-poly-[(N-(2-hydroxyethyl)-DL-aspartamide].

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

14. A complex as claimed in claim 12 wherein the anti-fibrinolytic is a hexadimethrinidibromide (polybren).

15. A formulation as claimed in claim 4 wherein the cationic component is a natural or semi-synthetic peptide.
16. A formulation as claimed in claim 15 wherein the peptide is a protamine, gelatine, fibrinopeptide, or derivatives thereof.

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

18. A formulation as claimed in claim 17 wherein the aminoglucane is fractionated chitin or its de-acetylated derivative chitosan.

19. A formulation as claimed in claim 17 or 18 wherein the aminoglucane is of microbial origin or is isolated from the shells of arthropods such as crabs.

20. A formulation as claimed in any of claims 4 to 19 wherein the anionic component is polyanhydroglucuronic acid and/or bicompatible salts and/or copolymers thereof.

21. A formulation as claimed in any of claims 1 to 20 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.

22. A formulation as claimed in claim 21 wherein the polyanhydroglucuronic acid and salts thereof contain in their polymeric chain at most 0.2 per cent by weight of bound nitrogen.

23. A formulation as claimed in claim 21 or 22 wherein the molecular mass of the polymeric chain of the anionic component is from $1 \times 10^3$ to $3 \times 10^5$ Daltons.
24. A formulation as claimed in claim 23 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.

25. A formulation as claimed in any of the claims 21 to 24 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.

26. A formulation as claimed in any of claims 21 to 25 wherein the anionic component contains at most 1 per cent by weight of carbonyl groups.

27. A formulation as claimed in any of claims 21 to 26 wherein the carbonyl groups are intra- and intermolecular 2,6 and 3,6 hemiacetals, 2,4-hemialdals and C2-C3 aldehydes.

28. A formulation as claimed in claim 4 wherein the cationic component is gelatine.

29. A formulation as claimed in claim 4 wherein the cationic component is chitosan.

30. A formulation as claimed in any preceding claim including at least one biocompatible biologically active substance.

31. A formulation as claimed in any preceding claim including at least one biologically acceptable adjuvant.
32. A formulation as claimed in claim 30 wherein the biologically active substance is an anti-haemorrhoidal, analgesic, antipyretic, antibiotic, antiviral, antimicrobial, anti-inflammatory and/or bacteriocidal agent.

33. A formulation as claimed in any preceding claim which is adapted for rectal administration.

34. A formulation as claimed in any of claims 1 to 32 which is adapted for vaginal administration.

35. A rectal suppository formulation prophylaxis or treatment of haemorrhoidal disorders comprising a formulation as claimed in any of claims 1 to 32.

36. A vaginal suppository formulation for prophylaxis or treatment of urogenital disease and/or for prophylaxis or treatment of urinary tract infections comprising a formulation as claimed in any of claims 1 to 32 or 34.

37. A suppository formulation substantially as hereinbefore described with reference to the examples.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

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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)

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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**

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**Further documents are listed in the continuation of box C.**

**X** Patient family members are listed in annex.

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**Date of the actual completion of the international search**

27 October 1999

**Date of mailing of the international search report**

10/11/1999

**Name and mailing address of the ISA**

European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk, Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016

**Authorized officer**

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<td>DOMSY J.G., ET AL.: &quot;Ionic interactions between chitosan and oxidised cellulose&quot; CHITIN NAT. TECHNOL. (PROC. INT. CONF. CHITIN CHITOSAN), MEETING DATE 1985, 1986, pages 331-336, XP002119106 page 331, line 24 - line 33 page 333, line 35 - line 44</td>
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