**PCT** WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
**A61L 25/00, 15/22, 15/60**

**A1**

(11) International Publication Number: **WO 98/40110**

(43) International Publication Date: 17 September 1998 (17.09.98)

(21) International Application Number: PCT/GB98/00494

(22) International Filing Date: 5 March 1998 (05.03.98)

(30) Priority Data:
9704807.8 7 March 1997 (07.03.97) GB

(71) Applicant *(for all designated States except US)*: POLY-BIOMED LIMITED [GB/GB]; Sheffield Technology Park, 60 Shirland Lane, Sheffield S9 3SP (GB).

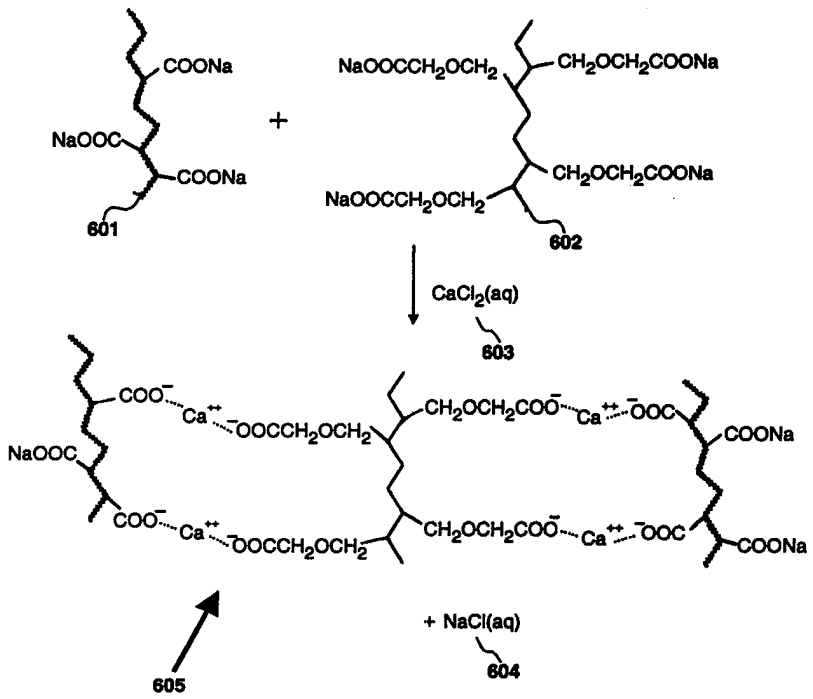
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: AL–LAMEE, Kadem, Gayad [GB/GB]; 64 Broomfield, Leeds SL16 7AD (GB). TAKTAK, Yousef, Samih [GB/GB]; Barncroft, Farley, Matlock, Derbyshire DE4 5LR (GB).

(74) Agent: ATKINSON, Ralph; Atkinson & Co., P.O. Box 1205, Sheffield S9 3UR (GB).

(81) Designated States: AL, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*
*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: WOUND DRESSING GEL




(57) Abstract

A gel for use in dressing a wound and a process for the manufacture of a gel are disclosed. The gel comprises a monovalent salt of a polygalacturonic acid derivative (such as sodium pectate), a carboxy–polysaccharide (such as a monovalent salt of a carboxycellulose derivative or a monovalent salt of an alginic acid derivative) and multivalent ions providing ionic cross–links between the monovalent salt and the carboxy–polysaccharide.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **AL** | Albania | **ES** | Spain | **LS** | Lesotho | **SI** | Slovenia |
| **AM** | Armenia | **FI** | Finland | **LT** | Lithuania | **SK** | Slovakia |
| **AT** | Austria | **FR** | France | **LU** | Luxembourg | **SN** | Senegal |
| **AU** | Australia | **GA** | Gabon | **LV** | Latvia | **SZ** | Swaziland |
| **AZ** | Azerbaijan | **GB** | United Kingdom | **MC** | Monaco | **TD** | Chad |
| **BA** | Bosnia and Herzegovina | **GE** | Georgia | **MD** | Republic of Moldova | **TG** | Togo |
| **BB** | Barbados | **GH** | Ghana | **MG** | Madagascar | **TJ** | Tajikistan |
| **BE** | Belgium | **GN** | Guinea | **MK** | The former Yugoslav Republic of Macedonia | **TM** | Turkmenistan |
| **BF** | Burkina Faso | **GR** | Greece | | | **TR** | Turkey |
| **BG** | Bulgaria | **HU** | Hungary | **ML** | Mali | **TT** | Trinidad and Tobago |
| **BJ** | Benin | **IE** | Ireland | **MN** | Mongolia | **UA** | Ukraine |
| **BR** | Brazil | **IL** | Israel | **MR** | Mauritania | **UG** | Uganda |
| **BY** | Belarus | **IS** | Iceland | **MW** | Malawi | **US** | United States of America |
| **CA** | Canada | **IT** | Italy | **MX** | Mexico | **UZ** | Uzbekistan |
| **CF** | Central African Republic | **JP** | Japan | **NE** | Niger | **VN** | Viet Nam |
| **CG** | Congo | **KE** | Kenya | **NL** | Netherlands | **YU** | Yugoslavia |
| **CH** | Switzerland | **KG** | Kyrgyzstan | **NO** | Norway | **ZW** | Zimbabwe |
| **CI** | Côte d'Ivoire | **KP** | Democratic People's Republic of Korea | **NZ** | New Zealand | | |
| **CM** | Cameroon | | | **PL** | Poland | | |
| **CN** | China | **KR** | Republic of Korea | **PT** | Portugal | | |
| **CU** | Cuba | **KZ** | Kazakstan | **RO** | Romania | | |
| **CZ** | Czech Republic | **LC** | Saint Lucia | **RU** | Russian Federation | | |
| **DE** | Germany | **LI** | Liechtenstein | **SD** | Sudan | | |
| **DK** | Denmark | **LK** | Sri Lanka | **SE** | Sweden | | |
| **EE** | Estonia | **LR** | Liberia | **SG** | Singapore | | |

# WOUND DRESSING GEL

## Field of Invention

The present invention relates to a gel for use in dressing a wound and to a process for making a gel.

## Background

Hydrogels are known for the treatment of cuts, abrasions, burns and similar wounds and consist of a matrix of polymers with a water content of up to 96%. Known hydrogel dressings exhibit less than ideal adherence characteristics and need to be covered with a secondary dressing, and the fluid or bacterial permeability of the gel depends upon the nature of the dressing used. Hydrogels are absorbent and semi-transparent and prior to application they may be refrigerated, such that the cooling effect contributes to the relief of pain.

A hydrogel for use as a wound dressing is described in International Patent Publication No. WO 92/16245, consisting of a water insoluble, water swellable cross-linked cellulose derivative, water and a polyol component. The gel described in this publication is primarily directed to the removal of necrotic tissue, as it reduces the need for the use of a chemical debriding agent or surgical excision. Thus, the known gel provides a dressing which can combine the actions of debriding and cleansing, independent upon the extent of necrosis. Furthermore, the dressing is capable of breaking down necrotic tissue and retaining resultant debris.

However, a problem with known hydrogels, for application as wound dressings, is that their adherency tends to be less than ideal. Furthermore, there is a tendency for these known compounds to disintegrate in the wound and to cause maceration to the skin around the wound.

## Summary of The Invention

According to a first aspect of the present invention, there is

provided a gel for use in dressing a wound, comprising a monovalent salt of a polygalacturonic acid derivative, another carboxy-polysaccharide and multivalent ions providing ionic cross-links between said monovalent salt and said other carboxy-polysaccharide.

Preferably, the salt of polygalacturonic acid derivative is sodium pectate. Preferably, the carboxy-polysaccharide is a monovalent salt of a carboxycellulose derivative, or a monovalent salt of an alginic acid derivative.

In a preferred embodiment, the salts include ions of sodium, potassium or ammonium.

Preferably, said carboxy-polysaccharide is sodium carboxymethylcellulose, or sodium alginic acid.

According to a second aspect of the present invention, there is provided a process for making a gel, comprising steps of: preparing a solution including a water soluble salt of a polygalacturonic acid derivative and a water soluble salt of another carboxy-polysaccharide; preparing a cross-linking agent in the form of a solution; and blending said solution of cross-linking agent with said water soluble salts to form a gel by effecting formation of ionic bonds between said salts.

**Brief Description of the Drawings**

Figure 1 shows an overview for the preparation of a hydrogel, including a gel preparation step;

Figure 2 details the gel preparation step identified in Figure 1, including the preparation of sodium pectate solution and the preparation of sodium carboxymethylcellulose solution;

Figure 3 details a sodium pectate polymer;

Figure 4 details a sodium carboxymethylcellulose polymer;

Figure 5 details a sodium alginic acid polymer;

Figure 6 illustrates the formation of cross-linkages between the polymers illustrated in Figure 3 and 4, when reacted with calcium chloride;

Figure 7 illustrates the formation of cross-linkages between the polymers illustrated in Figures 3 and 5, when reacted with calcium chloride;

Figure 8 illustrates, in two dimensions, a portion of gel composed of cross-linked polymers as detailed in Figure 6 or Figure 7.

Figure 9 illustrates the application of the gel produced by the process shown in Figure 1 applied to a wound.

**Detailed Description of The Preferred Embodiments**

The invention will now be described by way of example only with reference to the previously identified drawings.

An overview for the preparation of a hydrogel is shown in Figure 1. Initially, ingredients are required or taken from store at step 101, whereafter at step 102 a gel is prepared. At step 103 propane-1,2 diol is added to the gel to enhance its physical characteristics and to act as a preservative. Optionally, thereafter and as indicated at step 104, further medicaments may be added for particular applications. At step 105 the gel is sterilised by being maintained at a temperature of 121°C for a duration of at least twenty minutes. Thereafter, at step 106, the gel is packaged for subsequent application within a medical environment.

Step 102 for the preparation of the gel is detailed in Figure 2. Amounts described relate to a typical batch and may clearly be scaled during the manufacturing process to result in appropriate amounts being made. The amounts illustrated in Figure 2 require 7.8 kilograms (7.5 litres) of propane-1,2 diol being added at step 103, as illustrated in Figure 1.

The gel produced at step 102 essentially consists of a first carboxy-polysaccharide cross-linked with a second carboxy-polysaccharide, wherein the cross-linking is facilitated by the presence of multivalent ions. In the preferred embodiment, the preparation of which is illustrated in Figure 2, the first carboxy-polysaccharide is sodium pectate and the second carboxy-polysaccharide is sodium carboxymethylcellulose. Sodium pectate suitable for the invention is for example supplied by Citrus Colloids Limited wherein

no specific trade name is available, the compound interchangeably being called sodium pectate, sodium polypectate or sodium polygalacturonate. Similarly, suitable sodium carboxymethylcellulose powder is supplied by Hercules Limited under the Trade Name "Blanose Cellulose Gum", type 7H3SXF. 1.5 kilograms of sodium pectate powder 201 are dissolved in deionised water 202 to produce sodium pectate solution 204. A similar solution is made from 2 kilograms of sodium carboxymethylcellulose powder 203 to produce sodium carboxymethylcellulose solution 205. Deionised water is also added to 0.5 kilograms of calcium chloride powder 207 to produce calcium chloride solution 208, where the total weight of deionised water used for solutions 204, 205 and amounts to 42.5 kilograms.

The sodium pectate solution 204 is mixed with the sodium carboxymethylcellulose solution 205 to produce a homogeneous solution shown at 206. The gel is then produced at 209 by adding, in a stepwise process with continual mixing, the calcium chloride solution 208, resulting in the establishment of cross-linkages produced by ionic bonding. Thus, in the preferred embodiment, the sodium ions of the carboxy-polysaccharides are attracted to the chloride ions of the calcium chloride to produce sodium chloride with the bivalent calcium ions attracting the carboxy groups of different and/or like polymers, thereby producing the ionic cross-linkages. The carboxy-polysaccharide salts are monovalent and may be sodium, potassium or ammonium for example. In the preferred embodiment as described above, sodium is the preferred salt.

In the above preferred embodiment the amount of cross-linking agent used is such that the gel exhibits characteristics suitable for adherence to a highly exudating wound. Reducing the amount of said agent produces gels of successively lower viscosity which are suitable for different applications and practices. For example in some countries less viscous gels are preferred for treatment of deep highly exudating wounds and thus a gel according to the present invention which is suitable for these requirements can be made by reducing the amount of cross-linking agent used.

Incorporation of additional medicaments as described is facilitated in the invention through carboxy groups that are not incorporated into cross-linked ionic bonds. This is in addition to the simple trapping of said medicaments in the gel matrix. These medicaments may consist of an anti-bacterial agent, an anti-fungal agent, an anti-mycotic agent, an anaesthetic, an additional debriding agent or an anti-inflammatory agent. Alternatively, other agents may be added, such as a growth factor, an enzyme such as Lysozyme or a proteinase and nutrients such as vitamins, amino acids or trace elements. For example, it is known that the addition of zinc ions may be beneficial to assist in the healing process.

A sodium pectate polymer molecule is illustrated in Figure 3, in which the unit bounded by braces 301 is repeated to produce the polymer chain, typically consisting of more than 100 monomer units. Each monomer unit includes a sodium carboxy group 302 and it is the process of replacement of the sodium atoms of these groups which presents an ionised component for cross-linking with other polymer molecules.

A sodium carboxymethylcellulose polymer is shown in Figure 4, where again the repeating monomer is enclosed with braces 401. Each repeating monomer section includes cyclic components with each said component incorporating a sodium carboxymethyl group extending from each cyclic group. Again, some of the sodium atoms are removed thereby ionising the monomer units to facilitate the creation of cross-bonds with other polymers.

A sodium alginic acid polymer is shown in Figure 5, again having sodium carboxy groups from which a sodium atom may be removed to facilitate the creation of ionic cross-bonding.

The formation of cross-bonds or links between a sodium pectate polymer of the type shown in Figure 3 and a sodium carboxymethylcellulose polymer, of the type shown in Figure 4, is illustrated in Figure 6. Sodium pectate polymers 601 are placed in solution with sodium carboxymethylcellulose polymers 602. Aqueous calcium chloride 603 is added thereby placing calcium and chloride ions into the solution containing

both sodium pectate and sodium carboxymethylcellulose polymers. The sodium ions present within the original polymers 601 and 602 are attracted to the chloride ions to produce aqueous sodium chloride 604, with the resulting free carboxy groups of the two polymers being attracted to the bivalent calcium ions. However, given that two carboxy groups are required in order to balance with each calcium ion, cross-linkages are formed between adjacent polymer strands, resulting in the production of the cross-lined hydrogel 605.

A similar reaction is shown in Figure 7 in which a sodium alginic acid polymer 702, functionally similar to polymer 602, reacts with a sodium pectate polymer 701. Again, aqueous calcium chloride 703 is added, resulting in the substitution of the monovalent sodium ions for bivalent calcium ions to produce an alternative cross-linked hydrogel 704 and sodium chloride 705.

A cross-linked hydrogel 605 is also shown in Figure 8. As shown in Figure 8, each polymer such as polymer 801 for example, may include a plurality of ionic cross-linkages and the total number of cross-linkages (802, 803 and 804 for polymer 801) within the gel will influence the viscosity of the gel, which, as previously stated, may be adjusted to satisfy particular medical applications and preferences.

The reactions shown in Figure 6 and Figure 7 consist of a first carboxy-polysaccharide forming a cross-linkage with a second carboxy-polysaccharide. However, as shown in Figure 8, cross-linkages are also formed between carboxy-polysaccharides of the same type. Two sodium carboxymethylcellulose polymers, 805 and 806 have a cross-link 807 and similarly two sodium pectate polymers 808 and 809 have two cross-links 810 and 811. As described above a cross-link such as cross-link 804 comprises a calcium ion 812 and two carboxy groups 813 and 814, one group being supplied from each polymer. Each carboxy-polysaccharide should have at least one link to another carboxy-polysaccharide and it is not necessary for all of the potential bonding sites to be exploited. Two unused potential bonding sites (sodium carboxy groups) include 815 and 816 for example.

This in turn facilitates the possibility of other groups being bound using a similar mechanism. However, not all of the bonding sites should be exploited for cross-linking otherwise there is a tendency for the gel to become hard and brittle.

The packaged gel identified at step 106 may be kept in storage for a period in the region of two years, provided that storage temperatures do not exceed 25°C.

The gel is particularly useful for application to relatively deep wounds, of the type illustrated at Figure 9. Wounds 901, in this example taking the form of a severe and deep dermal ulceration in a patient's arm 902 are often highly exudating or dry. The gel is therefore applied into the wound in order to prevent or at least reduce the amount of fluid oozing out of the wound site if highly exudating or to donate fluid if the wound is dry, and primarily to assist in the healing of the wound, aid removal of unwanted matter and to facilitate the prevention of undesirable contamination. Other wound categories applicable to this gel include, but are not restricted to, Stage I, II or III pressure ulcers, dermal ulcers, donor sites, second degree burns, abrasions, blisters and chronic wounds.

Prior to application of the dressing, the wound itself is irrigated with sterile saline solution, whereafter excess liquid is removed by an antiseptic swab. Gel, which may have been stored in a tube or sachet etc is squeezed into the wound to a minimum depth of 5mm, whereafter any excess gel is discarded. The tendency of the gel is to adhere to the wound, but it is necessary to apply a secondary dressing so as to maintain a moist, infection free environment. A further advantage of the invention is that the gel maintains structural integrity and thus does not readily disintegrate in environments such as highly exudating wounds. Removal of the dressing is simple and is facilitated by the fact that the dressing remains intact.

The tendency of the gel will be to remove excess liquid from its environment while ensuring that the environment does not dry out and thus remains moist. If the wound site is or becomes dry, the gel will tend to donate

liquid to its environment ensuring that an equilibrium is maintained between the gel itself and its surrounding tissue.

The example given in the description of this embodiment concerning the proportions of the mixture may be varied to suit particular applications. In general, the carboxy-polysaccharide components, such as sodium pectate and sodium carboxymethylcellulose in the preferred embodiment, comprise at least 0.1% by weight of the total weight of the packaged gel.

The production process as descried herein involves reactions and processes which take place at normal ambient temperatures. However, in some applications, it may be desirable to apply additional heating and/or other methods to the system in order to improve production times. An important advantage of the process described for making a gel according to the invention is that the carboxy-polysaccharides used as starting materials are water soluble. This facilitates mixing of components which in turn reduces costs in large scale processing.

The present invention is further illustrated by the following example of laboratory scale synthesis. A gel of the invention having the following composition was made:

| Material | Weight | % by Weight |
|---|---|---|
| Sodium pectate | 15g | 2.78 |
| Sodium carboxymethylcellulose (Blanose 7H3SXF) | 20g | 3.70 |
| Calcium chloride | 5g | 0.93 |
| Propylene glycol (Propane-1,2 diol) | 78g | 13.89 |
| Deionised water | 425g | 78.70 |

15g of sodium pectate are stirred in 200ml of deionised water at room temperature, until fully dissolved. Similarly, 20g of sodium carboxymethylcellulose are stirred in 200ml of deionised water, until fully dissolved. The two solutions are then mixed together until a homogeneous

solution is formed. 5g of calcium chloride are dissolved in 25ml of deionised water, and added stepwise to the above solution. The mix is then homogenised carefully resulting in the formation of a highly viscous gel. Finally, 75ml of propylene glycol are added to the gel with continuous mixing, to ensure that a homogeneous gel is formed. The gel is then steam sterilised at 121°C for twenty minutes in an autoclave.

## Claims

1. A gel for use in dressing a wound, comprising a monovalent salt of a polygalacturonic acid derivative, another carboxy-polysaccharide and multivalent ions providing ionic cross-links between said monovalent salt and said other carboxy-polysaccharide.

2. A gel according to claim 1, wherein said salt of polygalacturonic acid derivative is sodium pectate.

3. A gel according to claim 1, wherein said carboxy-polysaccharide is a monovalent salt of a carboxycellulose derivative.

4. A gel according to claim 1, wherein said carboxy-polysaccharide is a monovalent salt of an alginic acid derivative.

5. A gel according to claim 1, wherein said salts include ions of sodium, potassium or ammonium.

6. A gel according to claim 1, wherein said carboxy-polysaccharide is sodium carboxymethylcellulose.

7. A gel according to claim 1, wherein said carboxy-polysaccharide is sodium alginic acid.

8. A gel according to claim 1, wherein said multivalent ions are divalent.

9. A gel according to claim 8, wherein said divalent ions are ions of calcium or magnesium.

**10.** A gel according to claim 1, further comprising a polyol or diol component.

**11.** A gel according to claim 10, wherein said polyol or said diol component includes propane-1,2 diol.

**12.** A gel according to claim 1, wherein said monovalent salt and said carboxy-polysaccharides collectively comprise at least 0.1 percent by weight of the gel.

**13.** A gel according to claim 1, wherein said gel is steam sterilised at a temperature greater than one hundred degrees centigrade.

**14.** A gel according to claim 1, further comprising at least one of the following components: an antibacterial agent; an anti-fungal agent; an anti-mycotic agent; an anaesthetic, an additional debriding agent; an anti-flammatory agent; a growth factor; an enzyme such as lysozyme or protanase and/or simple nutrients such as vitamins, amino acids and trace elements such as a source of zinc ions.

**15.** A gel according to claim 14, wherein carboxy-polysaccharide carboxy groups are not all incorporated in said cross-linked ionic bonds and one or more of said additional components binds to said carboxy groups that a not incorporated in said cross-links.

**16.** A process for making a gel, comprising steps of:

preparing a solution including a water soluble salt of a polygalacturonic acid derivative and a water soluble salt of another carboxy-polysaccharide;

preparing a cross-linking agent in the form of a solution; and

blending said solution of cross-linking agent with said water soluble

salts to form a gel by effecting formation of ionic bonds between said salts.

**17.** A process according to claim 16, wherein said carboxy-polysaccharide is a monovalent salt of a carboxycellulose derivative.

**18.** A process according to claim 16, wherein said carboxy-polysaccharide is a monovalent salt of an alginic acid derivative.

**19.** A process according to claim 16, wherein said salt of a polygalacturonic acid derivative is sodium pectate.

**20.** A process according to claim 16, wherein said salt of a carboxy-polysaccharide is sodium carboxymethylcellulose.

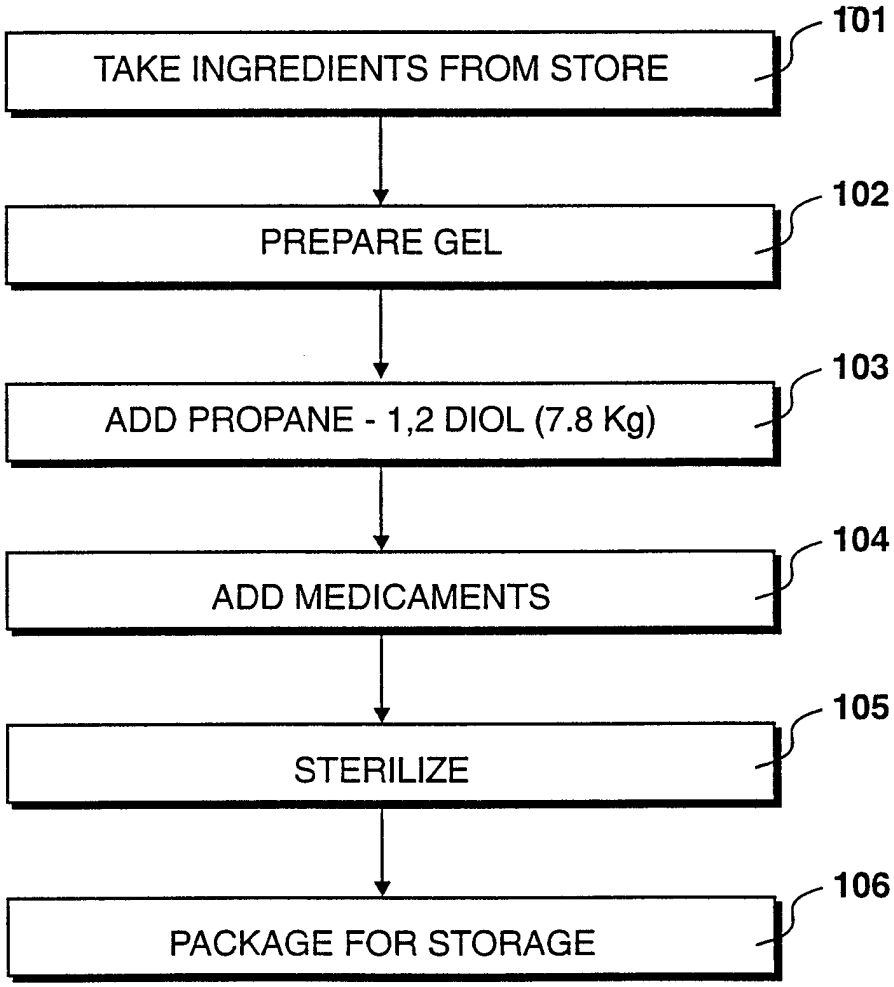

TAKE INGREDIENTS FROM STORE
101
PREPARE GEL
102
ADD PROPANE - 1,2 DIOL (7.8 Kg)
103
ADD MEDICAMENTS
104
STERILIZE
105
PACKAGE FOR STORAGE
106

Figure 1

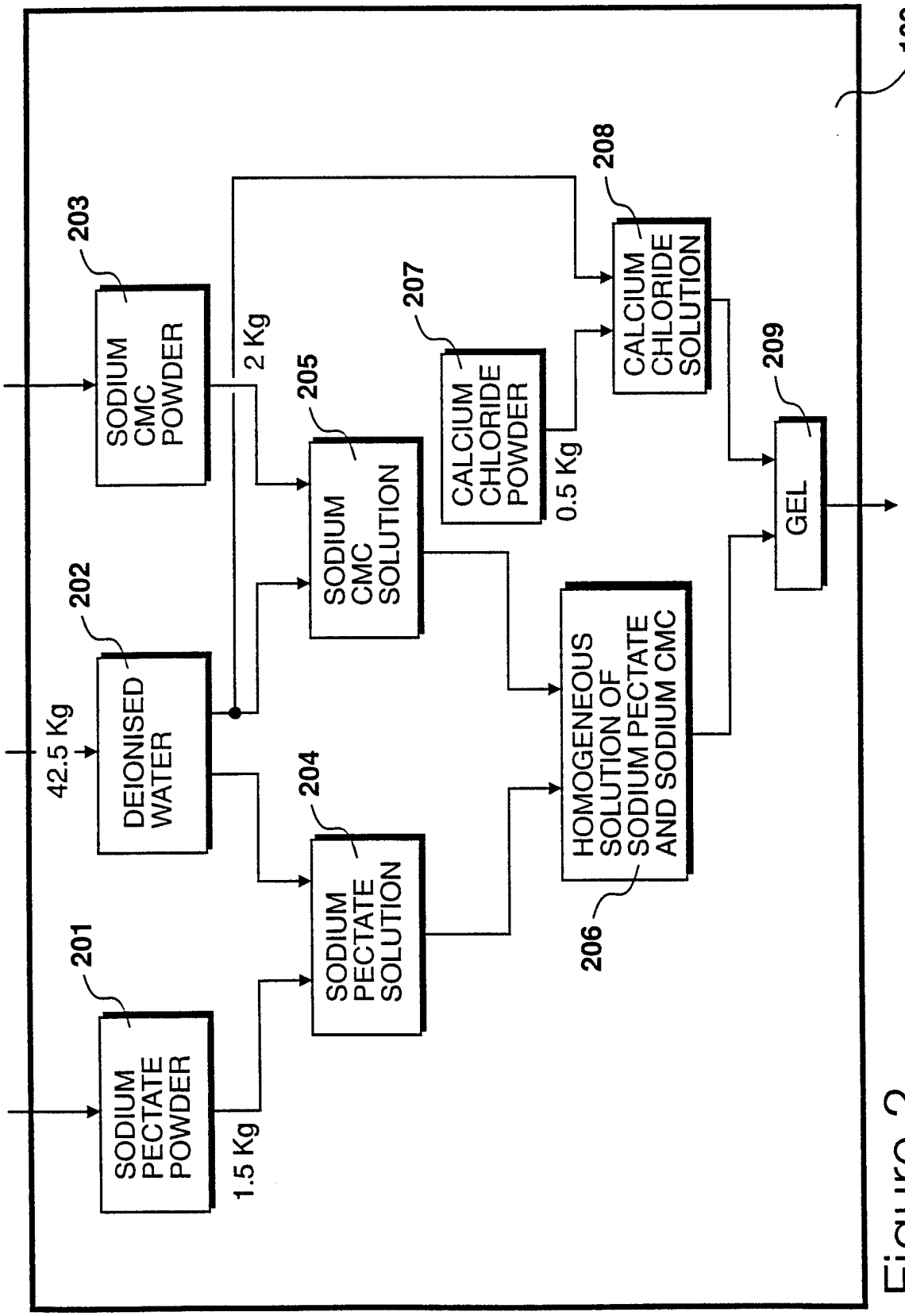

102
SODIUM CMC POWDER
203
2 Kg
SODIUM CMC SOLUTION
205
CALCIUM CHLORIDE POWDER
207
0.5 Kg
CALCIUM CHLORIDE SOLUTION
208
GEL
209
42.5 Kg
DEIONISED WATER
202
SODIUM PECTATE POWDER
201
1.5 Kg
SODIUM PECTATE SOLUTION
204
HOMOGENEOUS SOLUTION OF SODIUM PECTATE AND SODIUM CMC
206

Figure 2

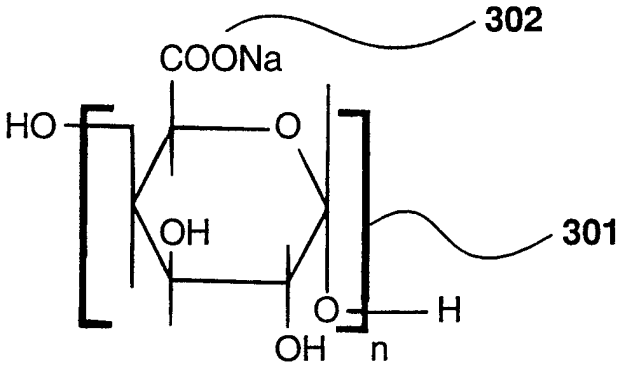



Figure 3

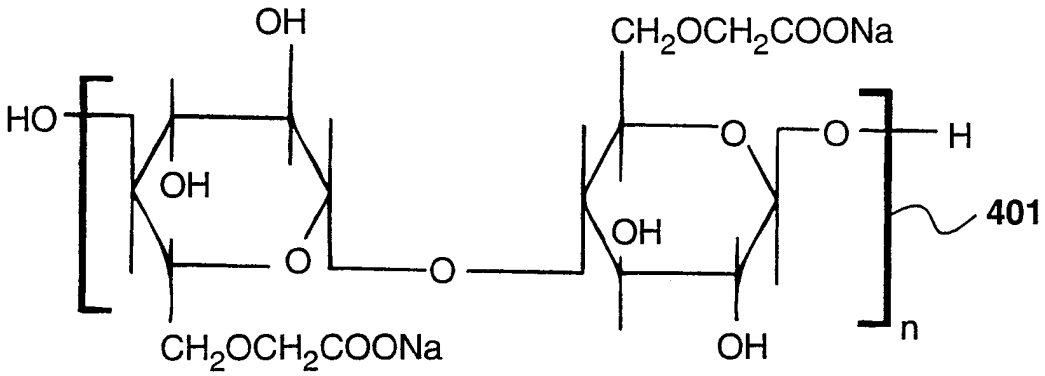



Figure 4

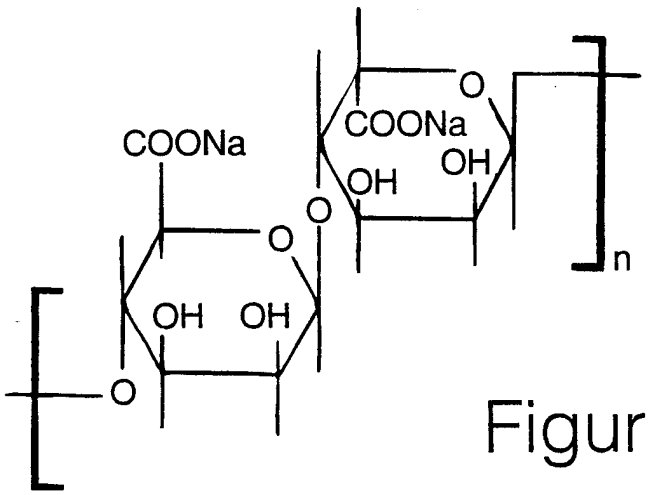



Figure 5

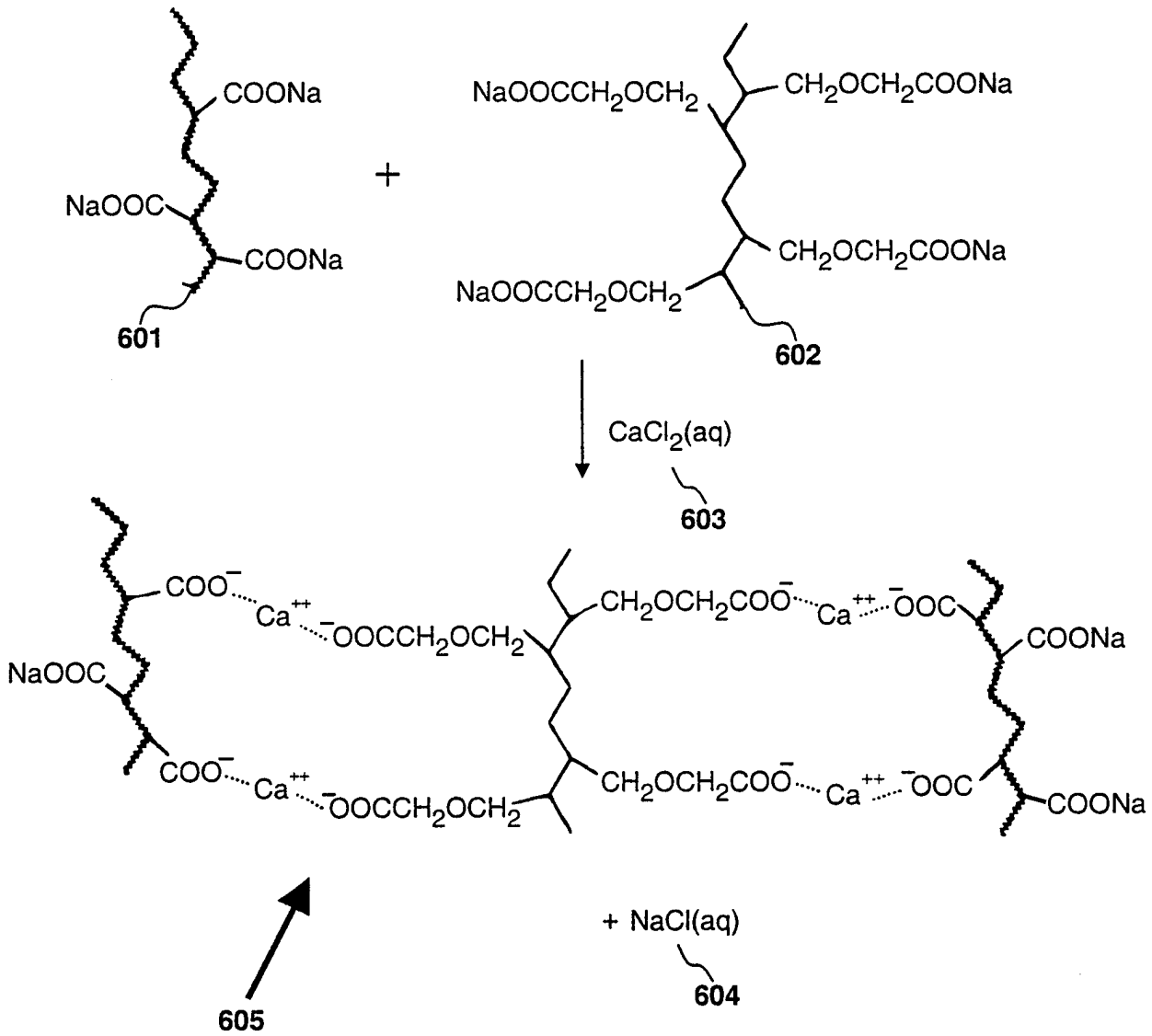

COONa
NaOOC
COONa
601
+
NaOOCCH2OCH2
CH2OCH2COONa
CH2OCH2COONa
NaOOCCH2OCH2
602
CaCl2(aq)
603
COO−
Ca++
−OOCCH2OCH2
CH2OCH2COO−
Ca++
−OOC
COONa
NaOOC
COO−
Ca++
−OOCCH2OCH2
CH2OCH2COO−
Ca++
−OOC
COONa
605
+ NaCl(aq)
604

Figure 6

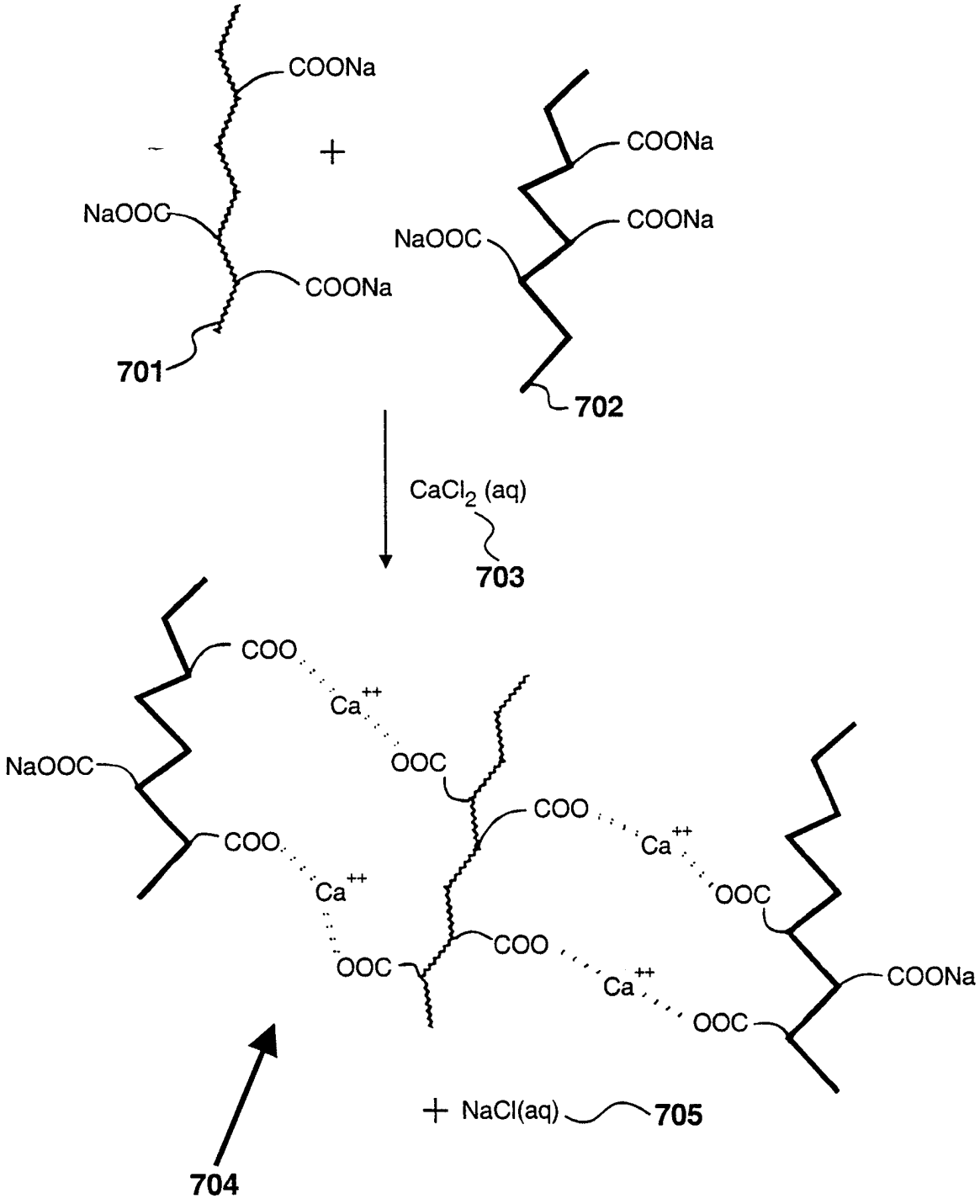

COONa
NaOOC
COONa
701
COONa
COONa
NaOOC
702
CaCl2 (aq)
703
COO
Ca++
NaOOC
OOC
COO
Ca++
COO
Ca++
OOC
COO
Ca++
OOC
COONa
OOC
+ NaCl(aq)
705
704

Figure 7

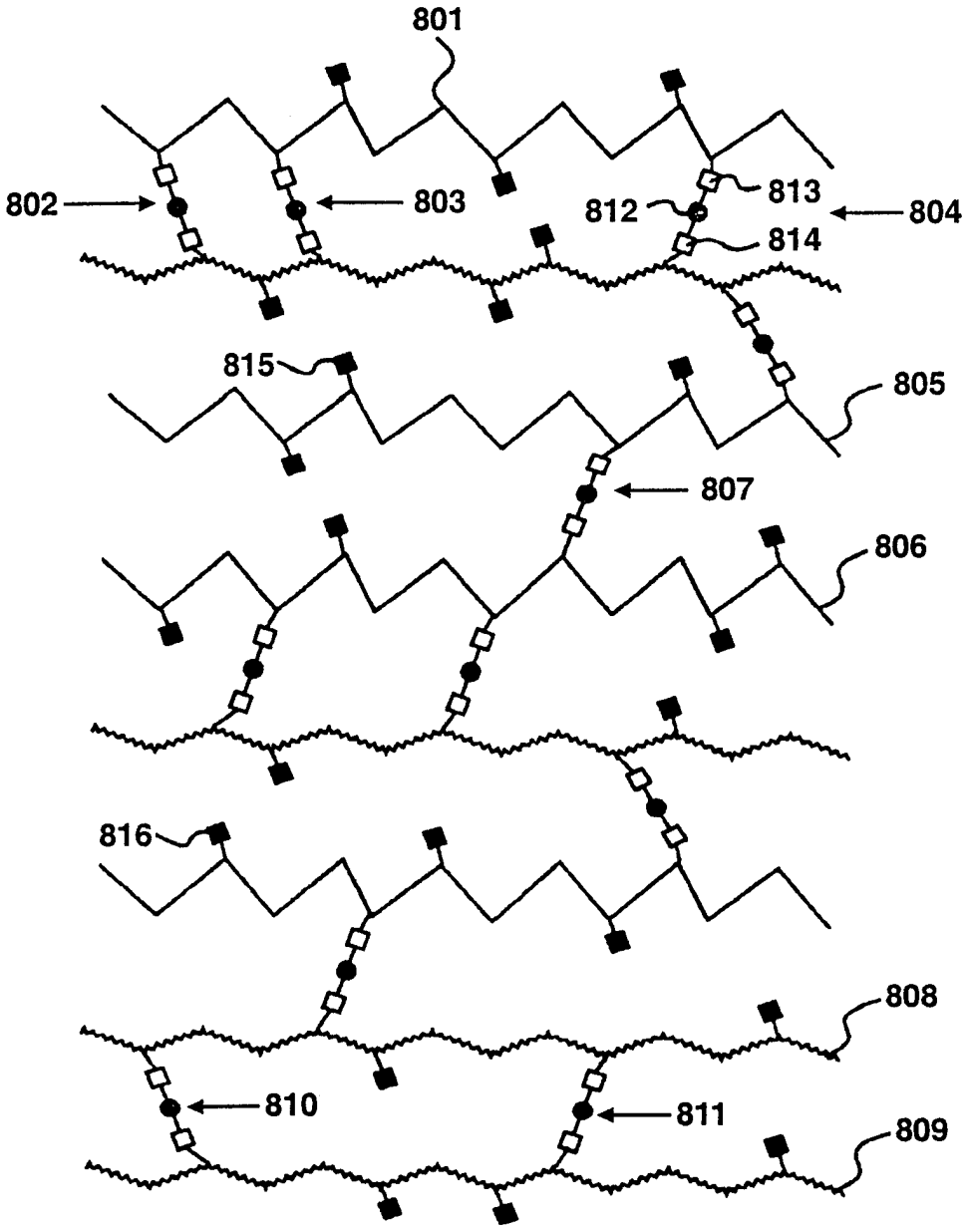



Figure 8

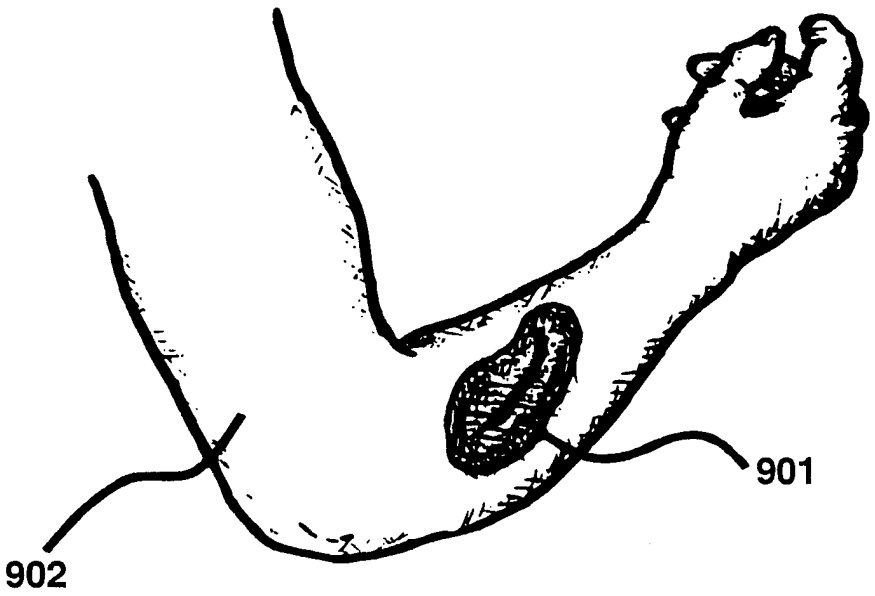



Figure 9

# INTERNATIONAL SEARCH REPORT

Ir. ational Application No
PCT/GB 98/00494

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L25/00 A61L15/22 A61L15/60

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 6 A61L C08B

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

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 97 03710 A (INNOVATIVE TECH LTD ;GILDING DENNIS KEITH (GB); QIN YIMIN (GB)) 6 February 1997 see claims; example 1 --- | 1-20 |
| X | GB 696 608 A (IRVING LEONARD OCHS AND PRESTON LEONARD VELTMAN) 2 September 1953 see claims; examples --- | 1 |
| Y | EP 0 567 311 A (SQUIBB BRISTOL MYERS CO) 27 October 1993 see claims; examples 1-3 --- | 1-20 |
| Y | EP 0 666 081 A (SQUIBB BRISTOL MYERS CO) 9 August 1995 see claims; examples --- | 1-20 |
| | -/-- | |

[X] Further documents are listed in the continuation of box C.

[X] 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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 27 July 1998 | 06/08/1998 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| 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 | ESPINOSA, M |

1

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Ir. ıational Application No
PCT/GB 98/00494

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ˚ | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | WO 96 10106 A (INNOVATIVE TECH LTD ;QIN YIMIN (GB); GILDING KEITH DENNIS (GB)) 4 April 1996 see claims; examples | 1-20 |
| A | WO 96 13282 A (INNOVATIVE TECH LTD ;QIN YIMIN (GB); GILDING KEITH DENNIS (GB)) 9 May 1996 see claims; examples 1,2 | 1 |
| A | EP 0 302 536 A (SQUIBB & SONS INC) 8 February 1989 see claims | 1 |
| A | WO 95 03786 A (FIDIA ADVANCED BIOPOLYMERS SRL ;BENEDETTI LUCA (IT); CALLEGARO LAN) 9 February 1995 see claims | 1 |
| A | US 4 292 972 A (PAWELCHAK JOHN M ET AL) 6 October 1981 see claims | 1 |

1

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 98/00494

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9703710 A | 06-02-1997 | AU 6525296 A | 18-02-1997 |
| | | EP 0848621 A | 24-06-1998 |
| GB 696608 A | | FR 1043022 A | 05-11-1953 |
| | | US 2726982 A | 13-12-1955 |
| EP 0567311 A | 27-10-1993 | US 5503847 A | 02-04-1996 |
| | | AU 3703593 A | 28-10-1993 |
| | | CA 2094533 A | 23-10-1993 |
| | | JP 6009373 A | 18-01-1994 |
| | | NZ 247431 A | 27-11-1995 |
| | | NZ 272995 A | 29-01-1997 |
| EP 0666081 A | 09-08-1995 | CA 2140827 A | 25-07-1995 |
| WO 9610106 A | 04-04-1996 | AU 3530695 A | 19-04-1996 |
| | | EP 0783605 A | 16-07-1997 |
| | | GB 2307687 A | 04-06-1997 |
| | | JP 10506442 T | 23-06-1998 |
| WO 9613282 A | 09-05-1996 | AU 3706695 A | 23-05-1996 |
| | | EP 0788378 A | 13-08-1997 |
| | | GB 2309909 A | 13-08-1997 |
| EP 0302536 A | 08-02-1989 | AU 569031 B | 21-01-1988 |
| | | AU 1356583 A | 27-10-1983 |
| | | BR 8301958 A | 20-12-1983 |
| | | CA 1220422 A | 14-04-1987 |
| | | DE 3382538 A | 07-05-1992 |
| | | DE 3382643 A | 24-12-1992 |
| | | DK 175783 A,B, | 23-10-1983 |
| | | EG 17028 A | 30-03-1991 |
| | | EP 0092999 A | 02-11-1983 |
| | | IE 60457 B | 13-07-1994 |
| | | IN 159044 A | 14-03-1987 |
| | | JP 2014984 C | 02-02-1996 |
| | | JP 6013045 B | 23-02-1994 |
| | | JP 58190446 A | 07-11-1983 |
| | | US 4538603 A | 03-09-1985 |
| | | US 4728642 A | 01-03-1988 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 98/00494

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9503786 A | 09-02-1995 | IT 1263394 B | 05-08-1996 |
| | | AU 7534194 A | 28-02-1995 |
| | | EP 0716596 A | 19-06-1996 |
| US 4292972 A | 06-10-1981 | AT 10064 T | 15-11-1984 |
| | | AU 557569 B | 24-12-1986 |
| | | AU 7256281 A | 18-03-1982 |
| | | CA 1146469 A | 17-05-1983 |
| | | EP 0044624 A | 27-01-1982 |
| | | JP 1040855 B | 31-08-1989 |
| | | JP 1556187 C | 23-04-1990 |
| | | JP 57047355 A | 18-03-1982 |