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(54) Title: DEXTRIN CONTAINING COMPOSITIONS FOR PREVENTION OF ADHESIONS

(57) Abstract: A composition for the treatment of adhesions that are formed as a result of an inflammatory response comprising an aqueous formulation containing the polysaccharide dextrin in an effective amount. The invention also discloses a method of treating adhesions that are formed as a result of an inflammatory response.

DEXTRIN CONTAINING COMPOSITIONS FOR PREVENTION OF ADHESIONS

The present invention relates to the prevention of adhesions, and in particular to adhesions formed in serous cavities such as the peritoneum, the pericardium, the plura and synovial cavities such as joints and tendons, the adhesions being formed as a result of an inflammatory response. Reference will be made hereinbelow to the prevention of adhesions in the peritoneum but it should be understood that the present invention has applicability in connection with other serous cavities in both humans and animals.

Background to the Invention

Adhesions are typically formed in response to mechanical/surgical insult. They are a well documented post-surgical event. It is known to ameliorate the condition by introducing film-forming biocompatible agents into the body cavity around the area of the wound. However, we have found surprisingly that adhesions can also occur in patients suffering from ovarian cancer who receive chemotherapeutic agents via the i.p. route. In other words the adhesions are not formed in response to post-operative events. We believe that it is the chemical insult of the chemotherapeutic agent itself, rather than the possible mechanical injury by i.p administration that induces adhesion formation in these patients. These unexpected observations, we believe, are due to an inflammatory response in these patients to the drugs which they receive. The present invention seeks to provide a composition for use in preventing adhesions that are formed as a result of the inflammatory response.

The treatment of patients with inflammation has two primary objectives, the first being to relieve pain which is typically the presenting problem, and the second is to reduce/halt the tissue-damaging process. Conventional treatment for acute and/or chronic inflammation is to administer non-steroidal anti-inflammatory drugs or glutocorticoids, however administration of these classes of pharmaceutical can cause undesired side effects in some individuals and even dependency.

Statement of the Invention

According to a first aspect of the present invention there is provided a method of preventing or reducing the incidence of adhesions in or associated with a body cavity, the adhesions being formed as a result of an inflammatory response, other than post-operative adhesions, the method comprising introducing into the body cavity an aqueous solution or suspension or gel formulation containing the polysaccharide dextrin.

Reference herein to an inflammatory response is intended to include chronic inflammatory conditions, such as and without limitation, pelvic inflammatory disease, arthritis, chronic inflammatory bowel disease, ulcerative colitis, Crohn's disease, irritable bowel syndrome and/or acute inflammatory conditions such as those induced by tissue injury the tissue injury being as a result of chemical insult.

The term "dextrin" means a glucose polymer which is produced by the hydrolysis of starch and which consists of glucose units linked together by means mainly of α-1,4 linkages. Typically dextrins are produced by the hydrolysis of starch obtained from various natural products such as wheat, rice, maize and tapioca. In addition to α-1,4 linkages, there may be a proportion of α-1,6 linkages in a particular dextrin, the amount depending on the starch starting material. Since the rate of biodegradability of α-1,6 linkages is typically less than that for α-1,4 linkages, it is preferred that, for many applications, the percentage of α-1,6 linkages is less than 10% and more preferably less than 5%.

Any dextrin is a mixture of polyglucose molecules of different chain lengths. As a result no single number can adequately characterise the molecular weight of such a polymer. Accordingly, various averages are used, the most common being the weight average molecular weight (Mw) and the number average molecular weight (Mn). Mw is particularly sensitive to changes in the high molecular weight content of a

polymer whilst Mn is largely influenced by changes in the low molecular weight content of the polymer.

It is preferred that the Mn of the dextrin is in the range of from 1,000 to 30,000 and ideally the Mw is in the range of from 3,000 to 50,000. More preferably, the Mn is from 3,000 to 8,000 and the Mw is from 5,000 to 50,000.

The term "degree of polymerisation" (DP) can also be used in connection with polymer mixtures. For a single polymer molecule, DP means the number of polymer units. For a mixture of molecules of different DP's, weight average DP and number average DP correspond to Mw and Mn. In addition, DP can also be used to characterise a polymer by referring to the polymer mixture having a certain percentage of polymers of DP greater than a particular number or less than a particular number.

It is preferred that the dextrin contains more than 15% of polymers of DP greater than 12 and, more preferably, more than 50% of polymers of DP greater than 12.

The dextrin used in the present invention is water soluble or at least forms a suspension in water or a gel formulation. The dextrin used in this invention may be in the form of either unsubstituted dextrin (as obtained by the hydrolysis of starch) or may be substituted by one or more different groups. The substituents may be negatively charged groups, for instance, sulfate groups, neutral groups, or positively charged groups, for instance, quaternary ammonium groups. In the case where the substituent group is sulfate, it is preferred that the sulfated polysaccharide contains at least one sulfate group per saccharide (glucose) unit.

The present invention also provides a composition comprising an aqueous solution or suspension or gel formulation of the polysaccharide dextrin in which the amount of dextrin is effective to prevent or reduce the incidence of adhesions that are formed as the result of an inflammatory response, other than post-operative adhesions.

The present invention further provides the use of a composition in the prevention or reduction of the incidence of adhesions that are formed as the result of an inflammatory response, other than post-operative adhesions, the composition comprising an aqueous solution or suspension or gel formulation of the polysaccharide dextrin.

The present invention further provides the use of the polysaccharide dextrin in the manufacture of a composition comprising an aqueous solution or suspension or gel formulation of dextrin for preventing or reducing the incidence of adhesions that are formed as the result of an inflammatory response, other than post-operative adhesions, in humans and animals.

Dextrin is a useful material for the production of an adhesion-preventing composition because, *inter alia*, it is non-toxic, cheap and has the ability to hold fluid in a body cavity. It is also readily metabolised within the body.

Preferably, a composition of the invention is applied to the appropriate body cavity or area before, during or after the inflammatory response.

In the instance of the inflammatory response being as a result of chemical insult by chemotherapy, the composition of the invention may be applied to the body cavity prior to the administration of the chemotherapeutic agent, alternatively it may be applied at the same time or after administration of the chemotherapeutic agent.

Preferably, the composition of the invention is co-administered in the manner as aforedescribed with one or more agent selected from the group consisting of a chemotherapeutic agent, a gene therapy agent, an antibiotic or antiviral agent or any other agent which causes an inflammatory response.

Reference herein to gene therapy agent is intended to include a viral vector the vector being an adenovirus, a retrovirus, a herpesvirus, a plasmid, a phage, a phagemid or a liposome or any other vehicle into which the gene therapy product has been inserted.

Preferably, the composition of the present invention is allowed to remain in the body cavity for a minimum of 2 to 3 days and especially over the period during which the inflammatory response is at a maximum. More preferably, the composition should remain in the body cavity for a period of up to 7 to 8 days.

Preferably, a composition of the invention should be applied to the body cavity in a volume large enough to keep the surfaces apart and/or to dilute chemotactic signals/cells involved in an inflammatory response. For the peritoneum, the volume should preferably be in the range 500-2000 ml and, more preferably, about 1000 ml-1500 ml.

Preferably, the composition should be applied to the appropriate body cavity or area in differing concentrations ideally over a concentration range of 2.5-20% and more ideally over a concentration range of 3-5% and most ideally at about 4% by weight, said concentration range is selected for a specified time span, even more ideally the concentration range is selectively altered over a period of time.

Preferably, the composition should include a concentration of dextrin which is such that the fluid largely holds in place over the period it resides in the cavity. Where a composition includes 4% by weight of dextrin then a suitable dwell period for one infusion might be of the order of 2 to 3 days. A high concentration is liable to cause ingress of fluid. A second infusion at day 3 may extend the total dwell period from 6 to 7 days.

Alternatively, a composition having a dextrin concentration of from 12 to 15% by weight may be used in a smaller volume (perhaps about 750 ml) and will be subject

to ingress of fluid. However a single infusion might be sufficient for the full 6 to 7 day period.

It will be appreciated that the concentration of the composition of the invention, the timing of administration and the dwell time are variable and may be selected according to a user's requirements. For example if a chemotherapeutic agent were to be administered over a period of several weeks then the composition of the present invention may be given for the same or extended duration of the therapy and at least until the inflammatory response had abated/ceased. The variations of a dosing regimen are not intended to limit the scope of the application.

Comparing dextrin with dextran, the latter has relatively poor biocompatibility. It is subject to immunological hypersensitivity due to its concentration in lymph nodes and its lack of metabolisability. At best, a dextran solution or suspension will act not so much to separate surfaces and therefore prevent adhesions but simply as a lubricant. Dextrin advantageously serves as an osmotic agent, which can maintain the volume of a solution in the peritoneal cavity. The continued presence of the dextrin solution within the cavity serves to separate tissues which otherwise may adhere to each other in addition to dilution of the inflammatory response.

A composition of the present invention may include any one or more of the following: a suitable lubricant such as a phosphospholipid; a calcium binding agent such as EDTA or sodium citrate; a hyaluronate; a prostacyclin or an analogue thereof; a glycocosolaminoglycan; an antibiotic agent or a material/agent which is associated with preventing an infection or build up of bacteria or foreign bodies or the like.

A composition of the present invention may also include a fibrinolytic agent or an analogue thereof, an anti-inflammatory agent or an analogue thereof, dextrin sulphate and/or methylene blue.

The present invention provides a preferred composition comprising an aqueous solution or suspension or gel formulation of dextrin, one or more phosphospholipids and hyaluronate. Such a composition is not only highly effective in preventing adhesions formed as a result of an inflammatory response, other than post operatively, but also has a good shelf life.

According to a further aspect of the invention there is provided a biocompatible, bioresorbable, and non-toxic adhesion prevention kit, the adhesions being formed as a result of an imflammatory response other than post operative adhesions, for use in humans or animals, the kit comprising an aqueous solution or suspension or gel formulation of dextrin as hereinbefore described, and optionally comprising any one or more of the preferred features as hereinbefore for co-administration with an agent that causes adhesions by inducing an inflammatory response.

Brief Description of the Drawings

The invention will now be described by way of example only with reference to the following Figures and Tables wherein:

Table 1 shows adhesion scores in adriamycin treatment groups receiving differing concentrations of icodextrin compared to controls; and

Table 2 shows the number (%) at each score in adriamycin treatment groups receiving differing concentrations of icodextrin compared to controls.

Table 3 shows overall adhesion scores in the treatment group receiving continuous 0.77 U/ml bleomycin in the presence of Ringer's lactated solution (RLS) by pump.

Table 4 shows overall adhesion scores in the treatment group receiving continuous 0.77 U/ml bleomycin in the presence of 4% icodextrin by pump.

Table 5 shows overall adhesion scores in the treatment group receiving 0.77 U/animal bleomycin as a single bolus in 15ml Ringer's lactated solution (RLS)

Table 6 shows overall adhesion scores in the treatment group receiving 0.77 U/animal bleomycin as a single bolus in 15ml 4% icodextrin.

Table 7 shows overall adhesion scores in the treatment group receiving 0.077 U/animal bleomycin as a single bolus in 15ml Ringer's lactated solution (RLS).

Table 8 shows overall adhesion scores in the treatment group receiving 0.077 U/animal bleomycin as a single bolus in 15ml 4% icodextrin.

Figure 1 represents a bar chart of number of animals with specific adhesion scores in adriamycin treatment groups receiving differing concentrations of icodextrin compared to controls;

Figure 2 represents a bar chart of the overall adhesion scores per animal in the six different treatment protocol groups receiving bleomycin.

Figure 3 represents a bar chart of the adhesion score of each animal in each of the six different treatment protocol groups receiving bleomycin.

Detailed Description of the Embodiments of the Invention

We have conducted experiments to evaluate the effect of administration three concentrations (4%, 15% or 20%) of icodextrin in comparison with a control group receiving phosphate buffered saline (PBS) on the formation of adhesions in response to i.p. adriamycin administration in rats. In addition, we provide data on the effect of adhesion formation in rats as a result of administration of bleomycin in conjunction with Ringer's lactated solution (RLS) or 4% icodextrin, either by dosing continuously by pump or as a single bolus dose.

PROTOCOL

Animals: . Female Sprague Dawley rats, 175 to 200 grams, were purchased from and quarantined in the USC Vivaria for at least 2 days prior to use. The animals were housed on a 12:12 light:dark cycle with food and water available ad libitum. Thirty animals were used for the adriamycin experiments and forty for the bleomycin experiments.

Materials: The 4% [wt/vol], 15% or 20% icodextrin were supplied by ML Laboratories PLC. The sutures used to close the muscle and skin were 4-0 Ethilon (Ethicon, Somerville, NJ). The sutures to secure the tubing and pump were 5-0 Ethilon. Alzet miniosmotic pumps (10 µl/hour, 2 ml, Model 2M1) were purchased from Alza Corporation (San Francisco, CA). Polyethylene tubing was purchased from Clay Adams (VWR, Irvine CA).

Surgical Procedure: Animals were anesthetized with a mixture of 85 mg/kg ketamine hydrochloride and 5 mg/kg Rompum intramuscularly. Following preparation for sterile surgery, a small incision was made at the midline. In animals in which a pump was placed, a polyethylene catheter (Clay Adams polyethylene tubing PE-60 ID 0.76 mm (0.030") OD 1.22 mm (0.048")) was introduced into the peritoneal cavity and sutured to the sidewall with 5-0 Ethilon. The pump was filled with 23.2 µg/ml Adriamycin (10 µl/hour over in life phase) or with 0.77 U/ml bleomycin (0.0077 U/hour) and placed in the subcutaneous space. The catheter was then attached to the pump and the midline muscle incision was closed around the catheter. Prior to closure of the last stitch, a 21-gauge catheter was introduced into the peritoneal cavity and a purse string suture was placed through the muscle around the catheter. In the adriamycin experiments, 20 ml of solution (4%, 15% or 20% icodextrin or PBS) were administered. In the bleomycin experiments 15 ml of RLS or 4% icodextrin were administered to the treatment groups as stated below. Subsequently, the skin incision was then closed with 4-0 Ethilon sutures.

Group	Bleomycin conc.	Mode of Administration	Co-administered compound
1	0.77 U/ml	Pump	RLS
2	0.77 U/ml	Pump	Icodextrin
3	0.77 U/ml	Fluid (bolus)	RLS
4	0.77 U/ml	Fluid (bolus)	Icodextrin
5	0.077 U/ml	Fluid (bolus)	RLS
6	0.077 U/ml	Fluid (bolus)	Icodextrin

Seven days after the initiation of adriamycin treatment and nine days after bleomycin treatment, the rats were euthanized by CO_2 and the extent of adhesion formation was evaluated. Adhesions were expected in the areas around the catheter, between the catheter and intestines or liver and between the lobes of the liver. The overall score was based upon the extent of adhesion formation and the number of sites involved in adhesion formation. This was a qualitative assessment based upon the appearance of the abdomen. The scoring system used to report adhesions in these studies is as follows:

0 No adhesions found in the peritoneal cavity

0.5+ Only a few, very filmy adhesions between the sidewall and catheter. Essentially no or very little fibrin-like substance covering the catheter

1.0+ Adhesions present between the sidewall and catheter with mild bowel or liver adhesions (to itself not catheter). Mild fibrin-like covering around catheter.

1.5+ Adhesions involving the liver and/or bowel and catheter. The covering on the catheter is more extensive than 1.0+.

2.0+ Adhesions as with 1.5+ with increase fibrin covering on the catheter and increased density of liver and/or bowel adhesions to catheter.

2.5+ Adhesions as described in 2.0+ but are more dense.

3.0+ More sites are involved in adhesions than in animals scored with 2.5+

4.0+ Sites (catheter to sidewall, liver, bowel and organs to themselves) as in 3.0+, but more than one site involves dense, nondissectable adhesions.

The animals were evaluated by two independent, blinded observers. If there was a disagreement as to the score, the higher one was given. Overall adhesion scores were given that took into account all of the adhesion and fibrosis scores listed above.

STATISTICAL METHODS

Non-parametric statistics were used to analyse the adriamycin data as there were 10 rats per treatment group and results were ordinal data from a scoring system.

The overall treatment effect was tested using the Kruskal-Wallis test. Further investigations in the presence of a treatment effect were to investigate each icodextrin concentration compared to the control group, using the Wilcoxon rank sum statistic.

Adriamycin Results

Ten animals pre treatment group were studied. In the control group and the 4% icodextrin group all animals were assessed for adhesion formation. In the 15% icodextrin group 1 rat was not assessed. Five (50%) of the rats in the 20% icodextrin group were euthanized early due to abdominal bulging and were not scored. The number of animals (%) at each score is presented in Table 2.

There was an overall treatment effect($p<0.001$), using the Kruskal-Wallis test. Using the Wilcoxon rank sum statistic differences between each icodextrin group and the control group were investigated. There were significant differences between the 4% icodextrin group ($p<0.01$), the 15% icodextrin group ($p<0.01$), 20% icodextrin group ($p<0.05$) and the control group. Adhesion scores were lower in all the icodextrin groups than in the control groups (Figure 1). All adhesion scores in the icodextrin groups were 1.5 or less (Table 1).

From our studies we have shown that all three icodextrin groups had significantly lower adhesion scores than the crystalloid solution and that administration of icodextrin at the end of the procedure reduced the formation of adhesions formed as a result of chemotherapy. The efficacy of the reduction of adhesion formation increased as the percentage of icodextrin was increased. However in the group of animals that received 20% icodextrin, half of the animals were euthanized early due to abdominal bulging and were not scored.

Bleomycin Results

Continuous administration of bleomycin resulted in substantial adhesions in the presence of Ringer's lactated solution (RLS), Table 3 Group 1, Rank 7.8±0.9. In the presence of icodextrin, this was significantly reduced (Table 4, Rank 3.2±1.0, p = 0.02). Administration of bleomycin in a single bolus resulted in less fibrosis (Table 5, Rank 8.0±0.0 and Table 7, Rank 6.5±1.4). However, at the higher concentration of bleomycin, administration of the chemotherapeutic in the presence of icodextrin significantly reduced adhesion formation (Table 6, Rank 3.0±0.0, p = 0.004 and Table 8, Rank 4.5±0.0, p = 0.18). The p values given are for comparison of the ranks of the most comparable RLS and icodextrin-treated groups using the Wilcoxon signed rank test. The results are tabulated below:

Bleomycin Conc	Dose Regimen	Rank Score RLS	Rank Score 4% icodextrin	P value
0.77 U/ml	pump	7.8 ± 0.9	3.2 ± 1.0	P = 0.02
0.77 U/ml	bolus	8.0 ± 0.9	3.0 ± 0.0	P = 0.004
0.077 U/ml	bolus	6.5 ± 1.4	4.5 ± 0.0	P= 0.18

In summary, the adhesiogenic effect of a high dose of bleomycin (0.77 U/ml) administered either continuously by pump in either RLS or 4% icodextrin (Groups 1 and 2) or as a single bolus dose (Groups 3 and 4) were compared. In addition a comparison between high dose (Groups 3 and 4) and a ten fold lower dose of bleomycin (0.077 U/ml; Groups 5 and 6) as a single bolus doses were compared. Our results have shown that 4% icodextrin is significantly more effective than RLS at preventing adhesion formations as a result of dosing with 0.77 U/ml bleomycin, irrespective of the dosing regimen being continous or by a single bolus. No differences between 4% icodextrin and RLS was observed at the lower dose of bleomycin (0.077 U/ml) as virtually no adhesions were formed by this concentration of bleomycin.

The dextrin composition of the present invention is therefore useful as preventing adhesion that occur as a result of chemotherapeutic injury and inflammatory responses.

Table 1.

Adhesion Scores in Rats Receiving 20 ml Phoshate Buffered Saline Solution (PBS) or icodextrin

PBS	4% icodextrin	15% icodextrin	20% icodextrin
1	0.5	0	0
1.5	0.5	0	0
1.5	0.5	0.5	0.5
2	1	0.5	0.5
2	1	1	1.5
2	1	1	
2.5	1.5	1.5	
2.5	1.5	1.5	
3	1.5	1.5	
4	1.5		

Table 2:

Number (%) at each score

Score	Control	4% icodextrin	15% icodextrin	20% icodextrin
0	0	0	2 (22%)	2 (40%)
0.5	0	3 (30%)	2 (22%)	2 (40%)
1	1 (10%)	3 (30%)	2 (22%)	0
1.5	2 (20%)	4 (40%)	3 (33%)	1 (20%)
2	3 (30%)	0	0	0
2.5	2 (20%)	0	0	0
3	1 (10%)	0	0	0
4	1 (10%)	0	0	0

Table 3: Group 1: Bleomycin 0.77 U/ml in RLS with pump

Catheter	Liver	Sidewall	Bowel	Liver-Catheter	Bowel-Catheter	Capsulation	Omentum	Horn-Catheter	Score
3	1	-	-	-	-	2	-	2	2
3	-	-	1	-	-	2	-	3	3
2	-	-	-	-	1	1	-	2	2.0
2	2	-	-	-	3	-	-	-	2.5
3	2	-	-	-	-	2	-	2	2.5

Table 4: Group 2: Bleomycin 0.77 U/ml in 4% icodextrin with pump

Catheter	Liver	Sidewall	Bowel	Liver-Catheter	Bowel-Catheter	Capsulation	Omentum	Horn-Catheter	Score
2	-	-	-	-	-	-	-	-	0.5
-	-	-	-	-	-	-	-	-	0
3	-	-	-	-	-	-	2	1	2.0
2	-	-	-	-	-	-	-	-	1
1	-	-	-	-	-	1	1**	-	1

Table 5: Group 3: Bleomycin 0.77 U/rat in RLS 15 ml IP

Catheter	Liver	Sidewall	Bowel	Liver-Catheter	Bowel-Catheter	Capsulation	Omentum	Horn-Catheter	Score
-	1*	1	-	-	-	-	-	-	0.5
-	1*	-	1	-	-	-	1**	-	0.5
-	1*	-	-	-	-	-	-	-	0.5
-	1*	-	-	-	-	-	1**	-	0.5
-	1*	-	-	-	-	-	1**	-	0.5

Table 6: Group 4: Bleomycin 0.77 U/rat in 4% icodextrin 15 ml IP

Catheter	Liver	Sidewall	Bowel	Liver-Catheter	Bowel-Catheter	Capsulation	Omentum	Horn-Catheter	Score
-	-	-	1**	-	-	-	-	-	0
-	-	-	1**	-	-	-	-	-	0
-	-	-	-	-	-	-	-	-	0
-	1*	-	-	-	-	-	-	-	0
-	-	-	1(SI+)**	-	-	-	-	-	0

+SI refers to the involvement of the small intestine.

Table7: Group 5 Bleomycin 0.077 U/rat in RLS 15 ml IP

Catheter	Liver	Sidewall	Bowel	Liver-Catheter	Bowel-Catheter	Capsulation	Omentum	Horn-Catheter	Score
-	-	-	-	-	-	-	1**	-	0
-	-	-	-	-	-	-	-	-	0
-	-	-	1**	-	-	-	1**	-	0
-	-	-	1	-	-	-	-	-	0.5
-	-	-	1	-	-	-	-	-	0.5

Table 8: Group 6: Bleomycin 0.077 U/rat in 4% icodextrin 15 ml IP

Catheter	Liver	Sidewall	Bowel	Liver-Catheter	Bowel-Catheter	Capsulation	Omentum	Horn-Catheter	Score
-	1	-	-	-	-	-	-	-	0
-	-	-	-	-	-	-	-	-	0
-	-	-	-	-	-	-	-	-	0
-	-	-	-	-	-	-	-	-	0
-	-	-	-	-	-	-	-	-	0

* refers to **fibrosis** not adhesion

** refers to **inflammation** not adhesion

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Claims

1. A composition for the treatment of adhesions that are formed as a result of an inflammatory response, other than post-operative adhesions comprising an aqueous formulation containing the polysaccharide dextrin in an effective amount.

2. A composition according to Claim 1 wherein the aqueous formulation is a solution.

3. A composition according to Claim 1 wherein the aqueous formulation is a gel.

4. A composition according to any preceding claim wherein the percentage of α-1,6 linkages in dextrin is less than 10%.

5. A composition according to Claim 4 wherein the percentage of α-1,6 linkages in dextrin is less than 5%.

6. A composition according to any preceding claim wherein the number average molecular weight (Mn) of dextrin is in the range 1,000 to 30,000.

7. A composition according to Claim 6 wherein the Mn of dextrin is in the range 3,000 to 8,000.

8. A composition according to any preceding claim wherein the weight average molecular weight (Mw) of dextrin is in the range 3,000 to 50,000.

9. A composition according to Claim 8 wherein the Mw of dextrin is from 5,000 to 50,000.

10. A composition according to any preceding claim wherein the dextrin contains more than 15% of polymers with a degree of polymerisation (DP) greater than 12.

11. A composition according to any of Claims 1-9 wherein the dextrin contains more than 50% of polymers with a degree of polymerisation (DP) greater than 12.

12. A composition according to any preceding claim wherein the dextrin is unsubstituted dextrin.

13. A composition according to any of Claims 1-11 wherein the dextrin is substituted by one or more different groups selected from the group consisting of negatively charged groups, sulfate groups, neutral groups, positively charged groups and quaternary ammonium groups.

14. A composition according to Claim 13 wherein the dextrin is sulfated dextrin containing at least one sulfate group per saccharide (glucose) unit.

15. A composition according to any preceding claim in which the dextrin is present in an amount of from 2.5-18 % by weight.

15. A composition according to Claim 15 in which the dextrin is present in an amount of from 3-5 % by weight.

17. A composition according to either of Claims 15 or 16 in which the dextrin is present in an amount of about 4 % by weight.

18. A composition according to any preceding claim which further includes a calcium binding agent.

19. A composition according to Claim 18 wherein the calcium binding agent is either EDTA or sodium citrate.

20. A composition according to any preceding claim which further includes a suitable lubricant.

21. A composition according to Claim 20 wherein the lubricant is a phospholipid.

22. A composition according to any preceding claim which further includes a hyaluronate.

23. A composition according to any preceding claim which further includes a compound selected from one or more of the following compounds, glycosolaminoglycan, an antibiotic agent, prostacyclin or an analogue thereof, a fibrinolytic agent or an analogue thereof, an anti-inflammatory agent or an analogue thereof, dextrin sulphate, a chemotherapeutic agent, gene therapy agent or vehicle and/or methylene blue.

24. A method of preventing or reducing the incidence of adhesions in or associated with a body cavity, the adhesions being formed as a result of an inflammatory response other than post-operative adhesions, the method comprising introducing into the body cavity an aqueous formulation containing the polysaccharide dextrin.

25. A method according to Claim 24 wherein the aqueous formulation is a solution or a gel.

26. A method according to either Claim 24 or 25 wherein said formulation is applied to the appropriate body cavity before administration of a chemotherapeutic or gene therapy agent

27. A method according to either Claim 24 or 25 wherein said formulation is applied to the appropriate body cavity at the same time as administering a chemotherapuetic or gene therapy agent.

28. A method according to either Claim 24 or 25 wherein said formulation is applied to the appropriate body cavity after administration of a chemotherapeutic or gene therapy agent.

29. A method according to any of Claims 24-28 wherein the composition is allowed to remain in the body cavity for a minimum of 2 to 3 days.

30. A method according to any of Claims 24-29 wherein the composition is allowed to remain in the body cavity over the period of the inflammatory response.

31. A method according to any of Claims 24-30 wherein the composition remains in the body cavity for a period of up to 7 to 8 days in order to allow restoration of non-stick surfaces (mesothelium regeneration).

32. A method according to any of Claims 24-31 wherein the composition is applied to the body cavity in a volume large enough to keep tissue surfaces apart.

33. A method according to any of Claims 24-32 wherein the volume of the composition applied to the peritoneum is in the range 500-2000 ml.

34. A method according to Claim 33 wherein the volume of the composition applied to the peritoneum is in the range 1000 ml-1500 ml.

35. A method according to any of Claims 24-34 wherein the dextrin is applied to the appropriate body cavity in differing concentrations over a concentration range of 2.5-18 % by weight.

36. A method according to Claim 35 wherein the dextrin is applied to the appropriate body cavity in differing concentrations over a concentration range of 3-5 % by weight.

37. A method according to either Claims 35 or 36 wherein the dextrin is applied to the appropriate body cavity in an amount of about 4 % by weight.

38. A method according to any of Claims 24-37 wherein the concentration range of dextrin is selectively altered over a period of time.

39. A biocompatible, bioresorbable, and non-toxic adhesion prevention kit for preventing or reducing the incidence of adhesions formed as a result of an inflammatory response, other than post-operative adhesions, in mammals, comprising an aqueous formulation of dextrin.

40. A kit according to Claim 39 wherein the aqueous formulation is a solution or a gel.

41. Use of a composition according to Claim 1 and optionally including any one or more of the features of Claims 2-23 for preventing or reducing the incidence of adhesions in or associated with a body cavity which comprises introducing into the body cavity an aqueous formulation containing the polysaccharide dextrin.

42. Products containing an aqueous formulation of the polysaccharide dextrin and any one or more of the features of Claims 18-23 as a combined preparation for use in preventing or reducing the incidence of adhesions that are formed

as a result of an inflammatory response other than post-operative adhesions, in or associated with a body cavity.

43. Use of the polysaccharide dextrin for the manufacture of a medicament for treatment of adhesions that are formed as a result of an inflammatory response other than post-operative adhesions.

44. A composition comprising dextrin and a therapeutically effective amount of a chemotherapeutic agent or gene therapy agent.

45. Use of the polysaccharide dextrin and a chemotherapeutic agent or gene therapy agent for the manufacture of a medicament for treatment of adhesions that are formed as a result of an inflammatory response, other than post-operative adhesions.

FIGURE 1


CONTROL
4% ICODEXTRIN
15% ICODEXTRIN
20% ICODEXTRIN
Adhesion scores in rats
Number of animals
Score
0
0.5
1
1.5
2
2.5
3
4
5

FIGURE 2

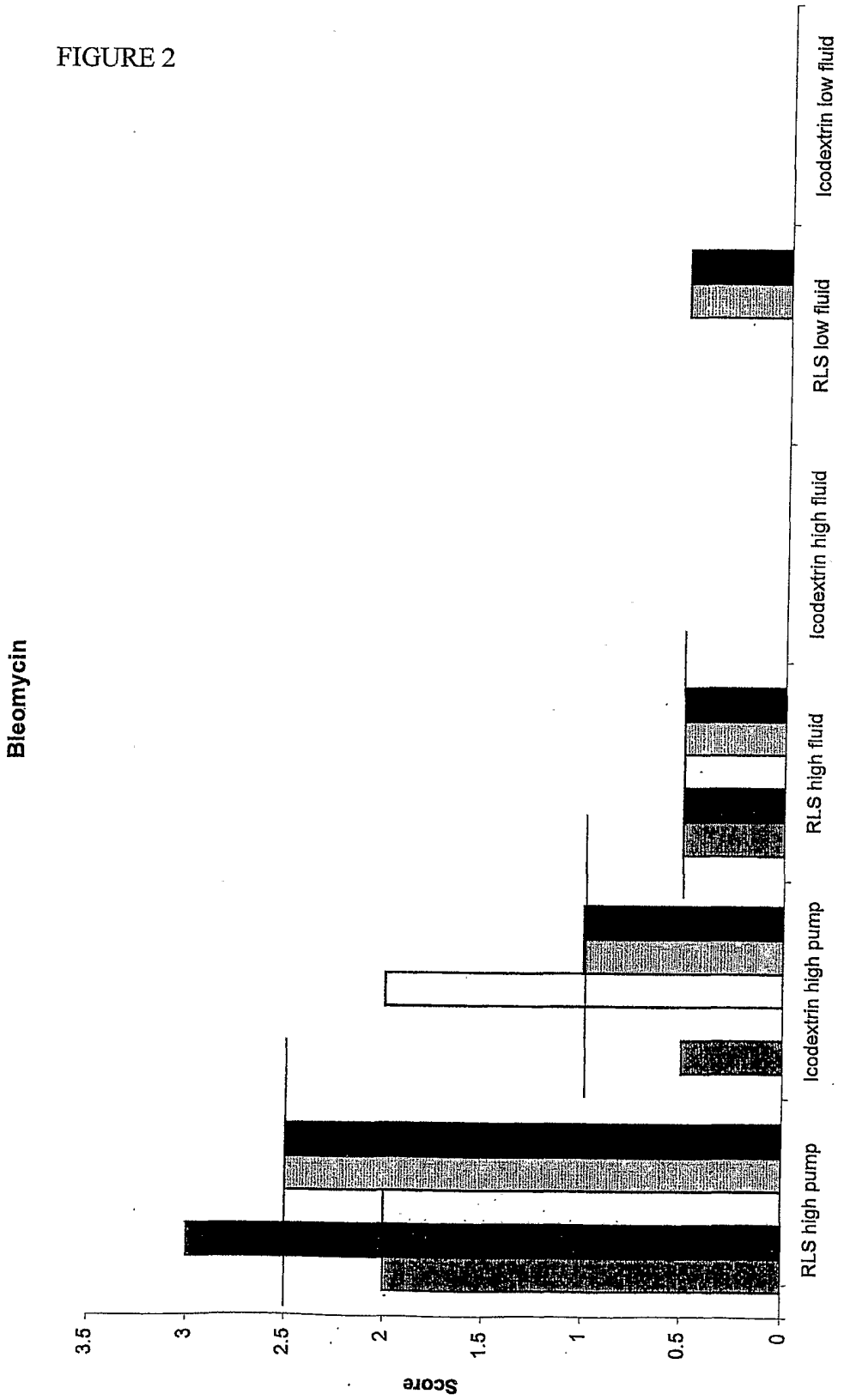
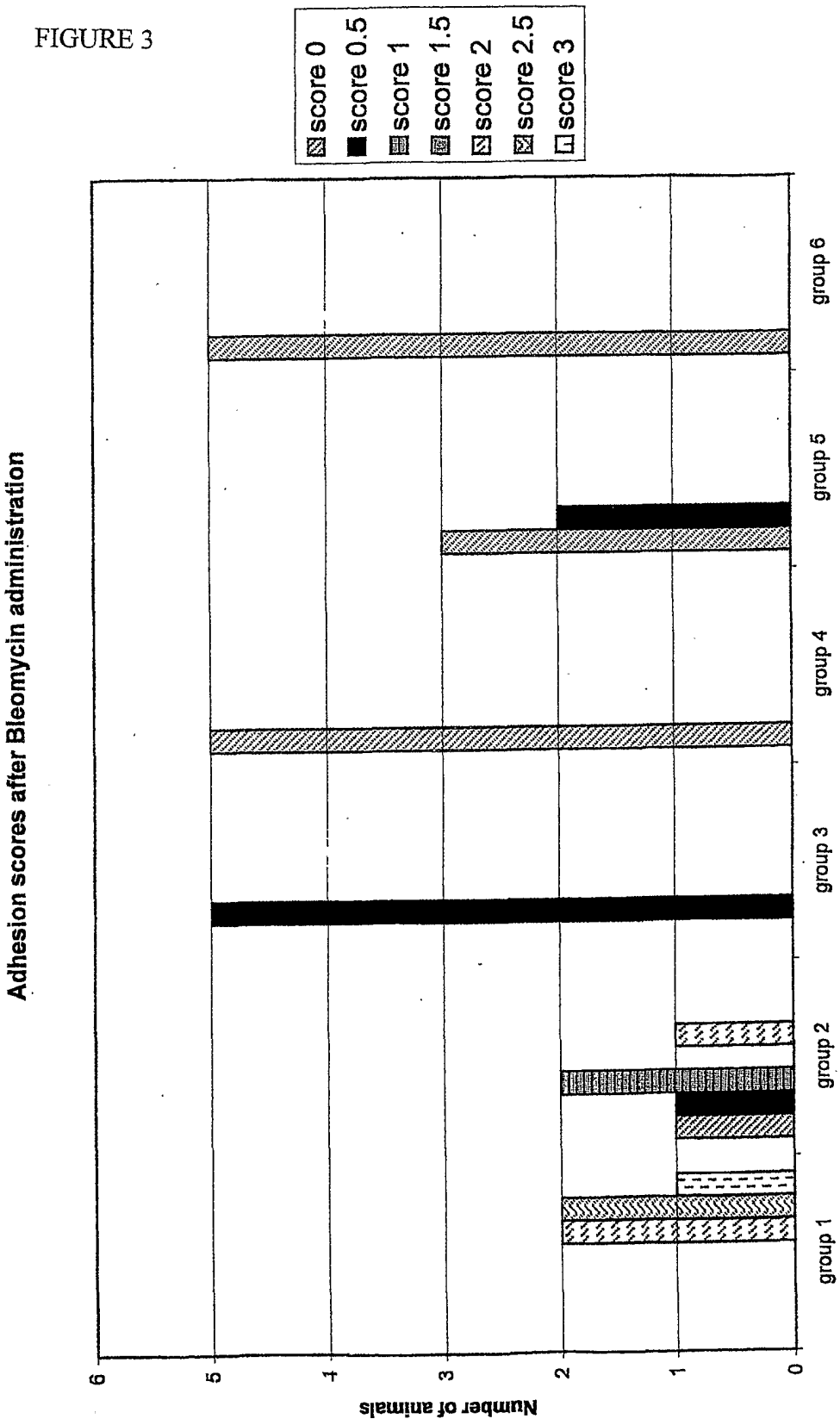

Bleomycin
Score
3.5
3
2.5
2
1.5
1
0.5
0
RLS high pump
Icodextrin high pump
RLS high fluid
Icodextrin high fluid
RLS low fluid
Icodextrin low fluid

FIGURE 3


score 0
score 0.5
score 1
score 1.5
score 2
score 2.5
score 3
Adhesion scores after Bleomycin administration
Number of animals
0
1
2
3
4
5
6
group 1
group 2
group 3
group 4
group 5
group 6

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/GB 01/00193

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/715 A61K48/00 A61P43/00

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 A61P

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)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 58168 A (BROWN COLIN ;ML LAB PLC (GB)) 18 November 1999 (1999-11-18) claims --- PEERS E ET AL: "ICODEXTRIN PROVIDES LONG DWELL PERITONEAL DIALYSIS AND MAINTENANCE OF INTRAPERITONEAL VOLUME" ARTIFICIAL ORGANS,BLACKWELL SCIENTIFIC PUBLICATIONS, INC., BOSTON,US, vol. 22, no. 1, 1998, pages 8-12, XP000945076 ISSN: 0160-564X abstract page 11, left-hand column, paragraph 2 --- -/--	1-25, 29-43 1-17,23, 39,40, 42,44

[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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 March 2001	26/03/2001

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	Seegert, K

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; March 2000 (2000-03) CONREY S ET AL: "In vitro viral vector stability and fluid dynamics of an intraperitoneal solution for delivery of gene therapy" Database accession no. prev200000227612 XP002155779 abstract & "91st Annual Meeting of the American Association for Cancer Research, San Francisco, California, USA, April 01-05,2000, March 2000" PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 41, March 2000 (2000-03), page 524	1-45
E	WO 01 12231 A (ML LAB PLC) 22 February 2001 (2001-02-22) claims	1-17,23, 39,40, 42,44

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inl tional Application No
PCT/GB 01/00193

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9958168 A	18-11-1999	AU 3833699 A	29-11-1999
		BR 9911769 A	06-02-2001
		NO 20005492 A	12-01-2001
WO 0112231 A	22-02-2001	NONE	