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(54) Title: PERITONEAL DIALYSIS SOLUTION CONTAINING MODIFIED ICODEXTRINS

(57) Abstract

The present invention provides a peritoneal dialysis solution that contains heat stable osmotic agents such as D–glucitols, gluconic acids and alkylglycosides produced the reduction, oxidation or glycosylation of icodextrine respectively. As a result, osmotic agents that are stable under autoclaving or heat sterilization conditions are provided which reduces the amount of bioincompatible materials in the sterilized peritoneal dialysis solutions. Methods of preparing the D–glucitols, gluconic acids and alkylglycosides are disclosed.

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SPECIFICATION

TITLE

"PERITONEAL DIALYSIS SOLUTION CONTAINING MODIFIED ICODEXTRINS"

BACKGROUND OF THE INVENTION

The present invention relates generally to peritoneal dialysis and solutions for the same. More specifically, the present invention relates to the use of modified icodextrins in peritoneal dialysis solutions as an osmotic agent and as an alternative to the use of glucose as an osmotic agent. The present invention also relates to methods of preparing peritoneal dialysis solutions that are stable under autoclaving conditions.

Dialysis provides a method for supplementing or replacing renal function in certain patients. Principally, hemodialysis and peritoneal dialysis are the two methods that are currently utilized.

In hemodialysis, the patient's blood is passed through an artificial kidney dialysis machine. A membrane in the machine acts as an artificial kidney for cleansing the blood. Because it is an extracorporeal treatment that requires special machinery, hemodialysis is fraught with certain inherent disadvantages such as the availability of dialysis machines and the possibility of infection and contamination.

To overcome the disadvantages associated with hemodialysis, peritoneal dialysis was developed. Peritoneal dialysis utilizes the patient's own peritoneum as a semi-permeable membrane. The peritoneum is a membranous lining of the abdominopelvic walls of the body. The peritoneum is capable of acting as a natural semi-permeable membrane because of its large number of blood vessels and capillaries.

In operation, a peritoneal dialysis solution is introduced into the peritoneal cavity utilizing a catheter. After a sufficient period of time, an exchange of solutes between the dialysate and blood is achieved. Fluid removal is achieved by providing a suitable osmotic gradient from the dialysate to the blood to permit water outflow from the blood. This allows the proper acid-base, electrolyte and fluid balance to be achieved in the blood. After an appropriate dwell period, the dialysis solution or dialysate is drained from the body through a catheter.

Conventional peritoneal dialysis solutions contain glucose as an osmotic agent to maintain the osmotic pressure of the solution higher than the physiological osmotic pressure (about 285 mOsmol/kg). Glucose is a preferred osmotic agent because it provides rapid ultrafiltration rates. However, certain disadvantages have become associated with the

use of glucose.

For example, glucose is known to decompose to 5-hydroxymethyl-furfural (5-MHF) in an aqueous solution during autoclaving or steamed sterilization. Smith, et al. AM.J. Hosp. Pharm., 34:205-206 (1977). Because 5-HMF is considered to be harmful for the peritoneum (Henderson, et al., Blood Purif., 7:86-94 (1989)), it would be desirable to have a peritoneal dialysis solution with an osmotic agent as effective as glucose but which does not produce 5-HMF or other harmful decomposition products during autoclaving or sterilization. In short, a substitute osmotic agent for glucose is needed.

One family of compounds capable of serving as osmotic agents in peritoneal dialysis solutions is icodextrins, including maltodextrins. However, while these compounds are suitable for use as osmotic agents, they are also known to degrade during heat sterilization to aldonic acids and formaldehyde. Because the presence of formaldehyde in peritoneal dialysis solutions is inappropriate due to its poor biocompatibility, the use of icodextrins, including maltodextrins as a substitute for glucose as an osmotic agent is unsatisfactory.

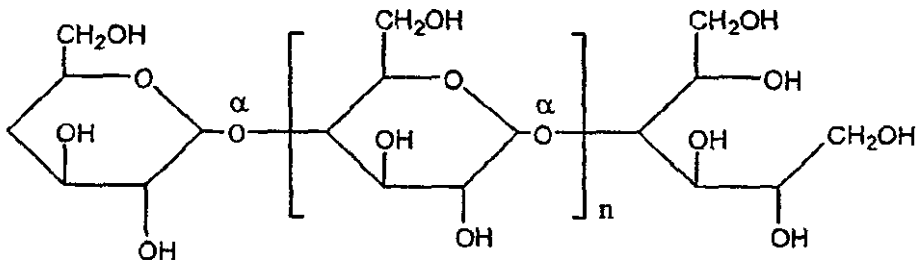
Accordingly, there is a need for an improved peritoneal dialysis solution which utilizes an osmotic agent other than glucose and which is stable under

autoclaving or steam sterilization conditions.

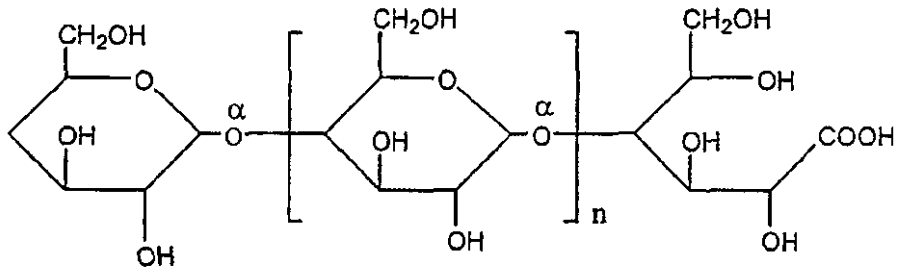
SUMMARY OF THE INVENTION

The present invention provides a solution to the aforenoted need by providing a sterilized peritoneal dialysis solution comprising a glucose polymer linked predominately by α-1,4 bonds. The term "predominately" is used because it is anticipated that within polymer molecules, other bonds such as α-1,6 bonds will be present as well, but in lesser amounts. Accordingly, as used herein, the term "predominately" means at least 85%. Thus, a glucose polymer linked predominately by α-1,4 bonds includes at least 85%, by number, α-1,4 bonds.

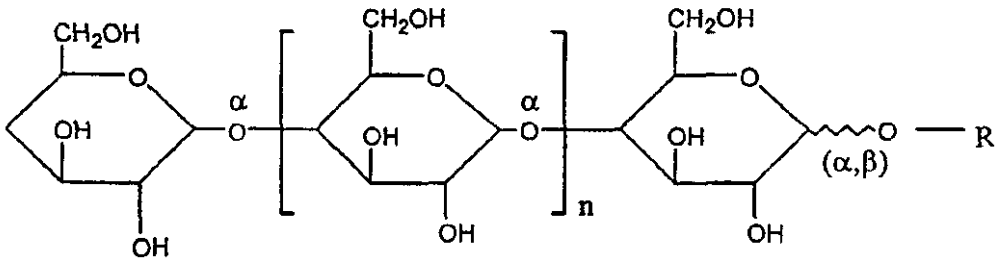
In an embodiment, the glucose polymer linked predominately by α-1,4 bonds is selected from the group consisting of D-glucitol having the formula



gluconic acid having the formula



and alkylglycoside having the formula



wherein R is selected from the group consisting of CH_3, CH_3CH_2 and $(CH_2OH)_2CH$, $CH_2(OH)CH(OH)CH_2$, and $(CH_2OH)(CHOHCH_2OH)CH$.

In an embodiment, the glucose polymers, linked predominately by α-1,4 linkages, of the peritoneal dialysis solution may include up to 10% of other linkages including, but not limited to, α-1,6 linkages.

In an embodiment, the peritoneal dialysis solution of the present invention is substantially free of formaldehyde.

In an embodiment, the peritoneal dialysis solution of the present invention is substantially free of furfurals.

In an embodiment, starch utilized as the osmotic agent is substantially free of terminal aldehyde groups.

In an embodiment, the present invention provides a method of preparing a stabilized osmotic agent of a peritoneal dialysis solution comprising the steps of providing a solution of starch dissolved in water and adding $NaBH_4$ to the solution of partially hydrolyzed starch to reduce the starch.

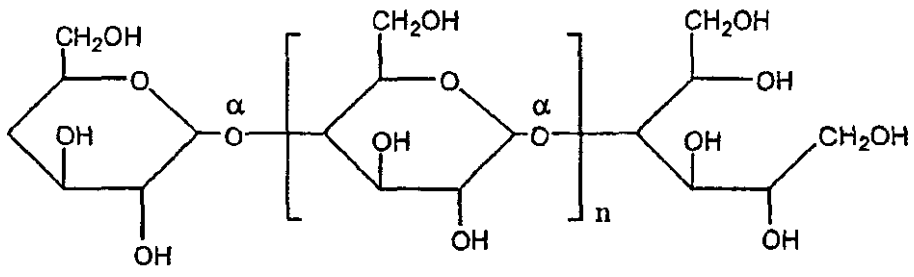
In an embodiment, the method of the present invention further comprises the step of purifying the reduced starch solution by passing the reduced starch solution through an anionic exchange resin.

In an embodiment, the dissolving and adding steps of the method of the present invention are carried out at room temperature.

In an embodiment, the method of the present invention further comprises the step of allowing the solution to scan for approximately 10 hours after the $NaBH_4$ is added to the starch solution to reduce the starch.

In an embodiment, the starch of the present invention is maltodextrin.

In an embodiment, the method of the present invention reduces maltodextrin to D-glucitol linked predominately by α-1,4 bonds and having the formula



In an embodiment, the present invention provides a method for preparing a stabilized osmotic agent of a peritoneal dialysis solution which comprises the steps of providing a solution of starch dissolved in water, providing a solution of NaOCl, and adding the NaOCl solution to the starch solution to oxidize the starch.

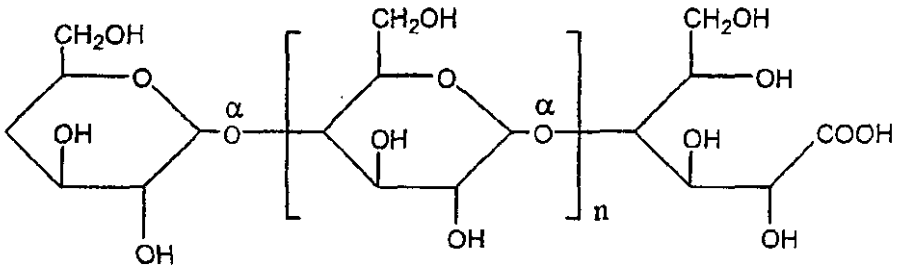
In an embodiment, the method of the present invention further comprises the step of purifying the oxidized starch solution by passing the oxidized starch solution through a gel permeation chromatograph.

In an embodiment, the oxidation of the starch is carried out at room temperature.

In an embodiment, the combined solutions are allowed to stand for approximately 2 hours.

In an embodiment, the starch is maltodextrin.

In an embodiment, the method of the present invention oxidizes the maltodextrin to a gluconic acid linked predominately by α-1,4 bonds and having the formula



In an embodiment, the maltodextrin can be oxidized electrochemically.

In an embodiment, the present invention provides a method of preparing a stabilized osmotic agent for a peritoneal dialysis solution which comprises the steps of dissolving the starch in an acid and an alcohol selected from the group consisting of methanol, butanol, glycerol or other alcohols.

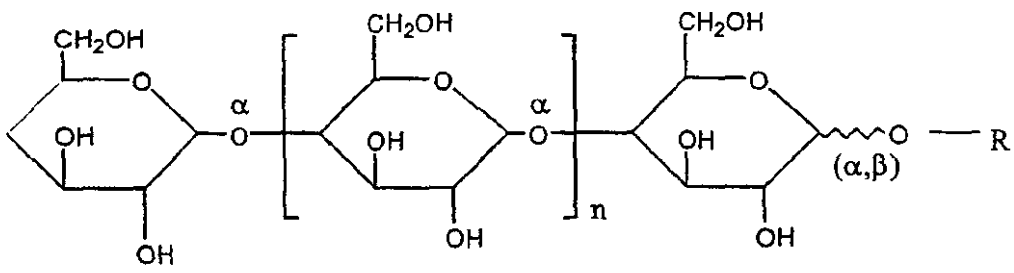
In an embodiment, the method further comprises the step of stirring the starch, alcohol and acid for 2-16 hours.

In an embodiment, the method further comprises the step of stirring the starch, alcohol and acid at a temperature of about 100°C.

In an embodiment, the starch is maltodextrin.

In an embodiment, the acid is hydrochloric acid or other acids such as sulfuric acid.

In an embodiment, the method of the present invention hydrolysizes and alkylates the starch to an alkylglycoside linked predominately by α-1,4 bonds and having the formula



and wherein R is selected from the group consisting of CH_3, CH_3CH_2 and $(CH_2OH)_2CH$. When hydrolysis is performed on starch pre-treated with periodate, R is the remnant of a glycol-split glucose unit.

It is therefore an advantage of the present invention to provide an improved peritoneal dialysis solution which is stable under autoclaving and steam sterilization conditions.

Another advantage of the present invention is that it provides an improved osmotic agent as an alternative to glucose.

Yet another advantage of the present invention is that it provides improved methods of preparing peritoneal dialysis solutions.

Yet another advantage of the present invention is that it provides improved osmotic agents for peritoneal dialysis solutions which are stable under autoclaving or steam sterilization conditions.

Additional features and advantages of the present invention are described in, and will be apparent from, the detailed description of the presently preferred embodiments and upon reference to the accompanying figures.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a graphical illustration of the ^{13}C NMR spectrum of an osmotic agent prepared by glycosylation in accordance with the present invention; and

Figure 2 is a graphical illustration of the ^{13}C NMR spectrum of an osmotic agent prepared by glycosylation in accordance with the present invention.

DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

The present invention provides a peritoneal dialysis solution with osmotic agents that are stable under autoclaving and steam sterilization conditions. The stable osmotic agents of the present invention may

be prepared by reduction, oxidation or glycosylation. When an icodextrin having reducing-end units are employed, such as maltodextrin, the reduction, oxidation or glycosylation procedures of the present invention transform the icodextrin to corresponding D-glucitols, gluconic acids and alkyglycosides respectively.

Example 1

A reduced icodextrin was prepared by starting with 15 grams of maltodextrin dissolved in 20 ml of water. One gram of $NaBH_4$ was added to the solution at room temperature and the solution was allowed to stand for 10 hours. The solution was then purified by passing it through an anionic exchange resin.

Three different maltodextrin starting materials were utilized. A low molecular weight (LMW) having a 3% degree of polymerization (DP) was utilized that contained 1% glucose, 37% maltose, 20% maltotetraose and 42% high molecular weight oligosaccharides. Second, a high molecular weight maltodextrin (HMW1) having a 14% degree of polymerization was utilized and contained 1% glucose, 2% maltose, 4% maltotetraose and 94% high molecular weight oliogosaccharides. Third, a second high molecular weight maltodextrin (HMW2) with a 9% degree of polymerization containing 1% glucose, 3% maltose, 7% maltotetraose and 90% high molecular weight oliogosaccharides was utilized. The products

and starting materials were analyzed using ^{13}C NMR spectroscopy. The signals associated with the reducing end units of the starting materials completely disappeared in the specter of the products. Some depolymerization was observed.

The products were tested for stability under sterilization conditions at neutral pH. A significant reduction of absorbance variation at 284 nm (Δ Abs) after sterilization is observed for the reduced compounds. The reduced compounds from Example 1 are listed as HMW1 red, HMW2 red and LMW red in Table 1.

Example 2

Utilizing the three different samples of maltodextrins discussed above with respect to Example 1, oxidation reactions were carried out on each sample by dissolving 15 grams of maltodextrin in 30 ml of water and combining the starch solution with an effective amount of NaOCl in 70 ml of a solution containing sodium hydroxide and having a pH of 8 ± 0.5 at a temperature of 43°C. The combined solutions were allowed to stand for approximately 2 hours and the product solution was purified by gel permeation chromatography. Again, the products were analyzed using ^{13}C NMR spectroscopy and were tested for stability under sterilization conditions as illustrated in Table 1. While the oxidation products, HMW1 ox HMW2 ox and LMW ox show contrasting results,

this is attributed to the high molecular weight oxidized products not being completely purified.

Table 1 - Absorbance (284 nm) variation after sterilization (121°C 45 min) of 5% Icodextrin and modified Icodextrin solutions

CODE	Number of experiments	ΔAbs (pH 6.5-7.5)	ΔAbs (pH 5.5)
HMW1	6	0.65±0.30	0.59±0.35
HMW1 red	6	0.31±0.10	0.20±0.07
HMW1 ox	2	1.83±0.21	1.78±0.13
HMW2	8	1.21±0.71	0.62±0.71
HMW2 red	7	0.13±0.09	0.09±0.06
HMW2 ox	4	0.76±0.31	0.79±0.19
LMW	8	1.96±0.87	1.33±0.86
LMW red	8	0.18±0.11	0.17±0.07
LMW ox	3	0.01±0.01	0.02±0.01
Reference compounds			
Glucose	4	2.54±0.78	2.36±0.96
*Glucose	2	0.98	
*D(+)-Gluconolactone	1	0.01	

*Glucose and D(+)-Gluconolactone solutions are 2.5% at pH 7
ΔAbs = difference between absorbance after and before sterilization

Example 3

In a third method of preparing stable osmotic agents in accordance with the present invention, icodextrin were glycosylated. The glycosylation reactions were performed using starch as the starting material and alcohol as the alkylating agent. Butanol and glycerol were chosen because of their

biocompatibility. The molecular weight of the reaction products depends upon the temperature, time and acid concentration used.

The hydrolysis with methanol and butanol were performed by stirring a suspension of 200 mg of starch in 540 mg of alcohol containing 60 mg of acid at a temperature of about 100°C for approximately 2 hours. The ^{13}C NMR spectrum of the two products obtained from this reaction with methanol and butanol respectively are shown in Figures 1 and 2. Table 2 presents the degree of polymerization (DP) and the percentage of non-substituted reducing ends as a function of the reaction conditions. This data was obtained from the ratio between the appropriate NMR signals (^{1}H NMR for DP values and ^{13}C NMR for the percentage of nonsubstituted reducing ends).

Table 2 - Glycosylation reaction with MeOH and ButOH

Sample No.	Alcohol	Acid M/t	D.P.	% non substituted glucose
1	MeOH	H_2SO_4	4.1	8.7
2	MeOH	HCl	5.2	11.2
3	ButOH	H_2SO_4	1.3	41.6
4	ButOH	HCl	1.4	13.0

Example 4

In the case of alcoholysis with glycerol, the reactions were performed using 1 gram of undried

starch (humidity 9%) and 2.7 grams of glycerol and stirring the mixture at 100°C with different amounts of hydrochloric acid for different time periods. Glycerol excess was eliminated by evaporation under reduced pressure and further purification was performed by gel filtration. The results are shown in Table 3.

Table 3 - Glycosylation reaction with glycerol (Standard reaction conditions: undried starch 1g, glycerol 2.7g)

Compound	Temperature °C	Time h	HCl Mol/L	Yield %	DP	% non substituted red. end
5*	80	2	1.27	n.d.	8.5	9.8
6**	100	2	1.27	96	1.4	4.8
7	100	2	1.27	n.d.	4.7	0
8	100	2	2.54	77.1	1.6	10.4
9	100	2	5.08	87.7	1.7	28.2
10	100	2	5.08	81.9	2.0	26.8
11	100	2	5.08	79.3	2.1	25.7
12	100	4	1.27	98	1.5	6.4
13	100	4	5.08	95.8	1.2	19.2
14	100	4	5.08	85.7	1.2	20.9
15	100	16	1.27	99.3	1.4	0
16***	100	16	1.27	93.1	1.2	0
17	100	16	5.08	78.9	1.0	13.4
18	100	16	5.08	79.6	1.0	0
19	100	24	5.08	82.1	1.0	4.6
20	60	16	1.27	n.d.	1.35	17.1
21	60	16	1.27	n.d.	1.10	23.9
22	80	16	0.32	88.7	1.11	13.9

23	80	16	0.32	79.4	1.10	11.3
24	80	16	0.32	89.1	1.15	10.6
25	80	16	0.64	94.2	1.04	17.9
26	80	16	0.64	n.d.	1.03	21.7
27	80	16	0.64	n.d.	1.10	9.7
28	80	16	1.27	n.d.	1.03	11.4
29	80	16	1.27	99.8	1.01	8.6
30	80	16	1.27	n.d.	1.01	4.9

* Reaction conditions: starch 200 mg, glycerol 540 mg
** Reaction conditions: starch 600 mg, glycerol 1.62 g
*** Reaction conditions: dry starch 1 g, glycerol 2.7 g

The ^{13}C NMR spectrum of the completely depolymerized product and of one with a degree of polymerization of 4.7 are shown in Figure 2. It is possible to observe the glycosidic anomeric signals α (100.9 ppm) and β (105.1 ppm), the CH_2 signals of both substituted (α = 71.3 ppm, β = 73 ppm) and non substituted (65.3 ppm) primary hydroxyl groups of glycerol, the CH signals (α = 81.5 ppm, β - 83 ppm) of secondary substituted hydroxyl group of glycerol.

The stability of one product shown in Table 3 was tested for stability under sterilization conditions and the observed variation at 284 nm is compared with that of glucose and methyl glycoside.

Table 4 - Absorbance (284 nm) variation after sterilization (121°C 45 min) of glycerol derivative and methyl glycoside

Sample	% (w/v)	number of experiments	ΔAbs neutra (pH 6.5-7.5)	ΔAbs acid (pH 5.5)
No. 6	5	4	0.46±0.32	0.35±0.15
glucose	5	3	2.43±0.9	n.d.
Methyl glycoside	2.5	1	0.01	n.d.
glucose	2.5	1	0.07	n.d.

In an in vitro test predictive of the dialytic efficiency of the osmotic agents described above, small dialysis bags with Spectra Pore membrane with a cut-off 500 Dalton (diameter 15 mm, 15 cm high) were filled with 3 ml of water solutions at different concentrations (2.5, 5.0% w/v of the samples). The bags were immersed in 200 ml of distilled water and 37°C while stirring the extra dialysis solution. At given times (0, 1, 2, 3, 4, 5, 6 hours), the increase in the volume inside the dialysis bag was evaluated by weight and expressed as a percentage increase compared to the starting volume (Δw%). The mean results are shown in Table 5 and are compared with the results for glucose and glucose-1-phosphate.

Table 5 - Volume increase in vitro dialysis test of modified icodextrins

Samples	Moles/L	N of experiments	Δwt 1h	Δwt 2h	Δwt 3h	Δwt 4h	Δwt 5h	Δwt 6h
LMW red	0.071	5	29.9	43.0	53.8	66.2	76.7	88.3
LMW ox	n.d.	5	20.2	29.2	39.3	46.0	56.4	63.4
HMW1 red	0.016	3	50.8	67.4	74.7	81.5	85.7	91.2
HMW1 ox	n.d	3	22.8	43.3	60.2	77.0	89.6	104.2
HMW2 red	0.049	3	6.7	10.0	15.7	19.2	21.2	26.3
HMW2 ox	n.d.	4	32.2	52.9	69.7	84.2	96.0	106.4
No. 6 (5%)	0.215	1	33.2	68.2	98.1	119.5	140.5	159.8
α-methyl-gluc. (5%)	0.257	1	30.9	60.7	86.5	107.9	123.2	142.0
β-methyl-gluc. (5%)	0.257	1	45	76.1	103.0	129.7	151.7	174.9
No. 6 (2.5%)	0.108	2	22.9	34.4	50.0	63.0	77.2	87.7
α-methly-gluc. (2.5%)	0.128	3	21.8	39.2	55.4	67.64	79.5	92.1
β-methly-gluc. (2.5%)	0.128	3	34.0	50.3	63.7	67.6	77.7	86.5
glucose (2.5%)	0.138	3	15.3	34.2	43.4	57.3	74.2	90.9
gluc.-1-phos. (2.5%)	0.069	3	35.8	53.6	76.3	95.9	120.1	144.1

Accordingly, the present invention provides a number of heat stable osmotic agents that provide a suitable substitute for glucose, improved peritoneal dialysis solutions containing stable osmotic agents as well as a variety of methods of producing improved peritoneal dialysis solutions.

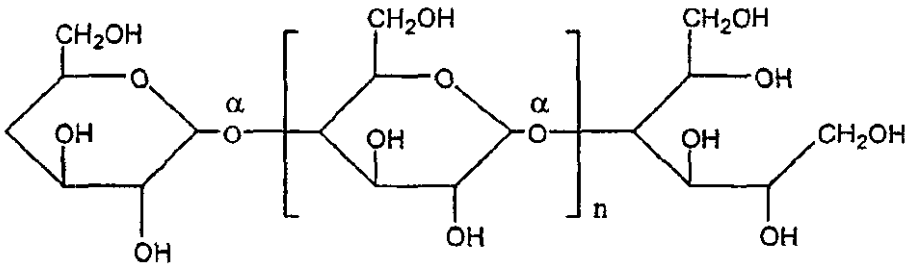
It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications may be made without departing from the spirit and scope of the

present invention and without diminishing its attendant advantages. It is, therefore, intended that such changes and modifications be covered by the appended claims.

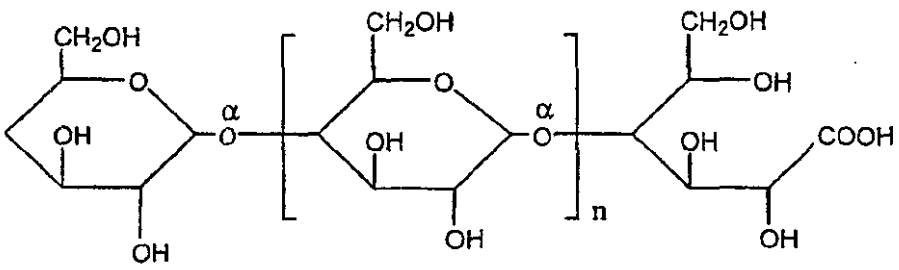
WHAT IS CLAIMED IS:

1. A sterilized peritoneal dialysis solution comprising:

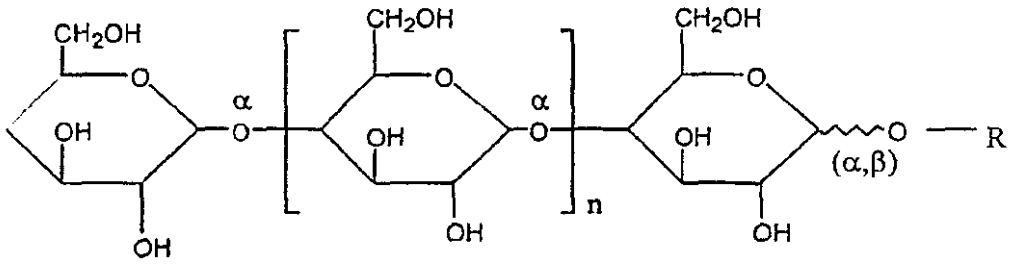
a starch comprising a glucose polymer linked by bonds and selected from the group consisting of D-glucitol having the formula:



gluconic acid having the formula



and alkylglycoside having the formula



wherein R is selected from the group consisting of CH_3, CH_3CH_2, $(CH_2OH)_2CH$, $CH_2(OH)CH(OH)CH_2$, and $[CH_2(OH)CH(OH)CH_2(OH)]CH$ and wherein the bonds linking the polymer include at least 85%, by number, α-1,4 bonds.

2. The peritoneal dialysis solution of claim 1 wherein the solution is absent of formaldehyde.

3. The peritoneal dialysis solution of claim 1 wherein the solution is absent of furfurals.

4. The peritoneal dialysis solution of claim 1 wherein the partially hydrolyzed starch is absent of

terminal aldehyde groups.

5. A method of preparing a stabilized osmotic agent for a peritoneal dialysis solution comprising the following steps:

providing a solution of starch dissolved in water;

adding $NaBH_4$ to the starch solution to reduce the starch.

6. The method of claim 5 further comprising the step of

purifying the reduced starch solution by passing the reduced starch solution through an anionic exchange resin.

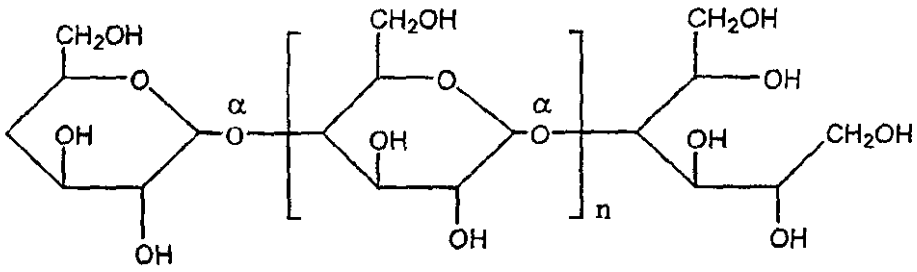
7. The method of claim 5 wherein the dissolving and adding steps are carried out at room temperature.

8. The method of claim 6 further comprising the following step after the adding step and prior to the purifying step:

allowing the solution to stand for about 10 hours.

9. The method of claim 5 wherein the starch is maltodextrin.

10. The method of claim 5 wherein the starch is reduced to an icodextrin linked predominately by α-1,4 bonds and having the formula:



11. A method of preparing a stabilized osmotic agent for a peritoneal dialysis solution comprising the following steps:

providing a solution of starch dissolved in water;

providing a solution of NaOCl;

adding the NaOCl solution to the starch solution to oxidize the starch.

12. The method of claim 11 further comprising the step of

purifying the oxidized starch solution by passing the oxidized starch solution through a gel permeation chromatograph.

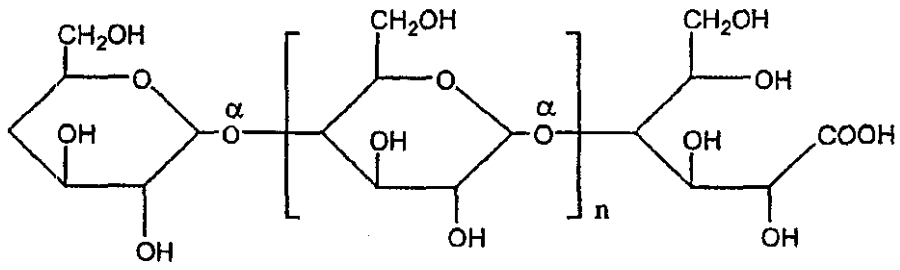
13. The method of claim 11 wherein the adding step is carried out at room temperature.

14. The method of claim 12 further comprising the following step after the adding step and prior to the purifying step:

allowing the solution to stand for about 2 hours.

15. The method of claim 11 wherein the starch is maltodextrin.

16. The method of claim 11 wherein the starch is oxidized to an icodextrin linked predominately by α-1,4 bonds and having the formula:



17. A method of preparing a stabilized osmotic agent for a peritoneal dialysis solution comprising the following steps:

dissolving starch in an acid and an alcohol selected from the group consisting of methanol, butanol and glycerol.

18. The method of claim 17 further comprising the step of

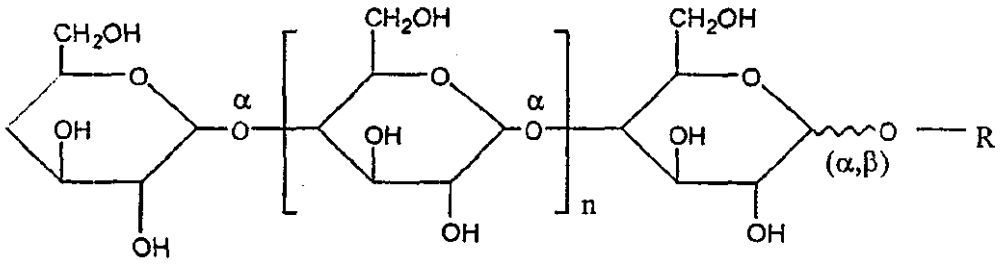
stirring the starch, alcohol and acid for about 2 hours.

19. The method of claim 17 wherein the stirring step is carried out at a temperature of about 100°C.

20. The method of claim 17 wherein the starch is maltodextrin.

21. The method of claim 17 wherein the acid is HCl.

22. The method of claim 17 wherein the starch is glycosylated to an icodextrin linked predominately by α-1,4 bonds and having the formula:



wherein R is selected from the group consisting of CH_3, CH_3CH_2 and $(CH_2OH)_2CH$.

FIG. 1

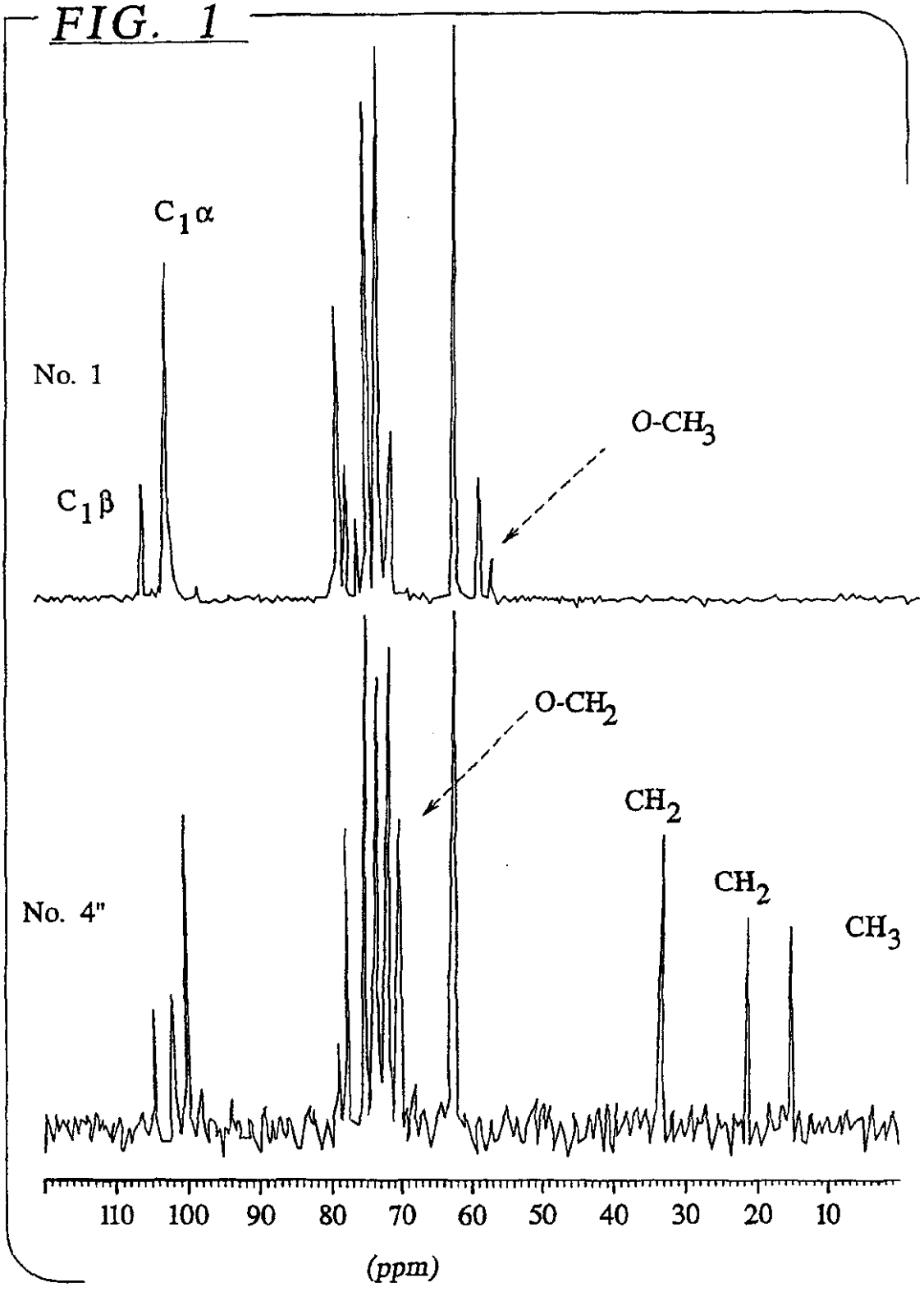
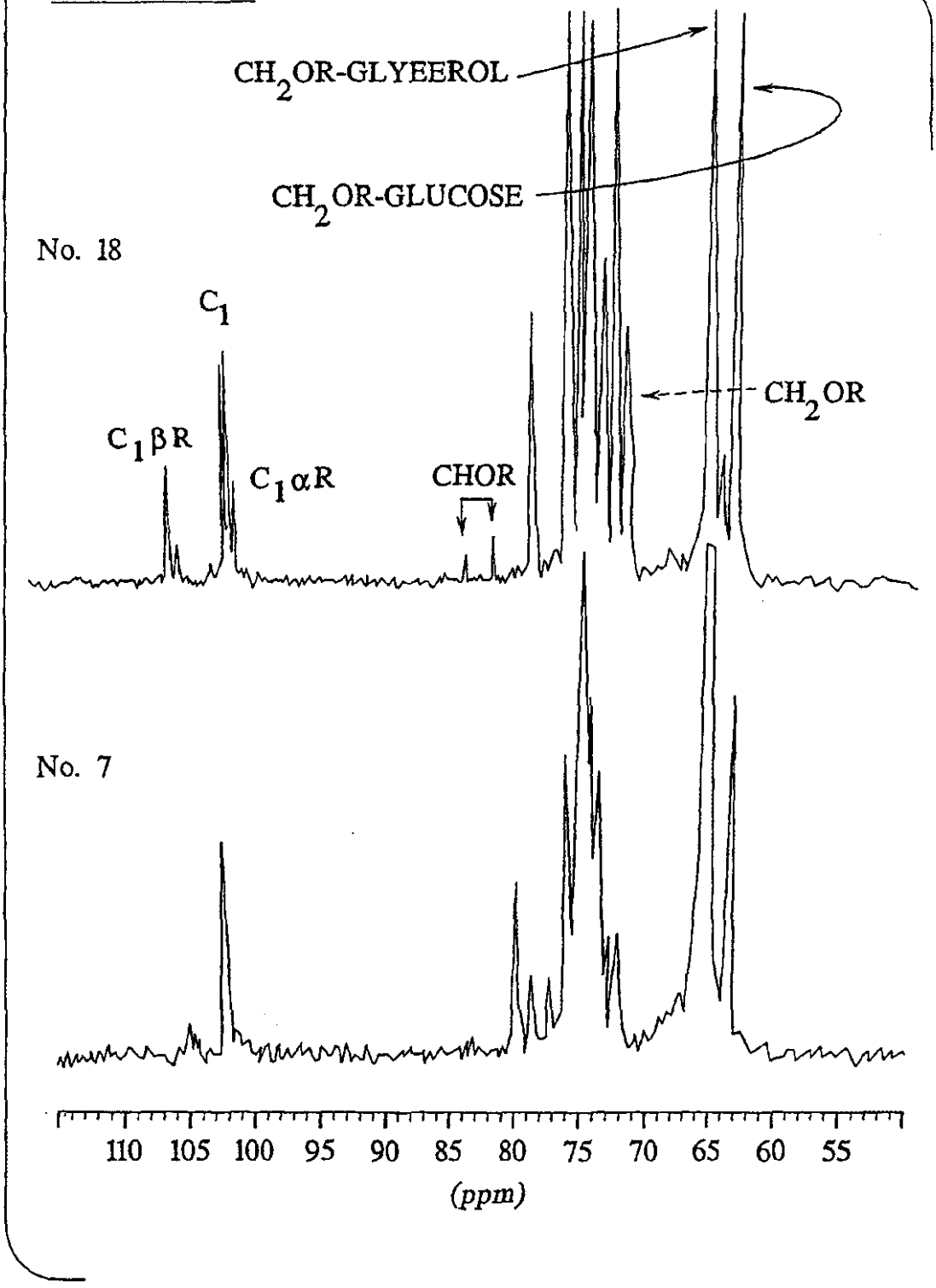

$C_1\alpha$
No. 1
$C_1\beta$
O-CH_3
O-CH_2
CH_2
CH_2
CH_3
No. 4"
110 100 90 80 70 60 50 40 30 20 10
(ppm)

FIG. 2


CH2OR-GLYEEROL
CH2OR-GLUCOSE
No. 18
C1
C1βR
C1αR
CHOR
CH2OR
No. 7
110 105 100 95 90 85 80 75 70 65 60 55
(ppm)

[19]中华人民共和国国家知识产权局

[51]Int. Cl[7]
A61K 31/715
A61P 7/08

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[85]进入国家阶段日期 2000.8.4
[71]申请人 巴克斯特国际有限公司
地址 美国伊利诺伊州
[72]发明人 A·纳吉 E·佩特雷拉 G·托里
B·卡素
[74]专利代理机构 中国专利代理(香港)有限公司
代理人 罗 宏 王其灏

权利要求书4页 说明书12页 附图页数2页

[54]发明名称 含有改进的ICODEXTRINS的腹膜透析溶液

[57]摘要

本发明提供了一种含有热稳定性的渗透剂的腹膜透析溶液,所述 的渗透剂诸如分别通过还原、氧化或糖基化 icodextrine 产生的 D－ 山梨醇类、葡糖酸类和烷基苷类。结果是提供了在高压灭菌或加热灭 菌条件下保持稳定的渗透剂,这可减少灭菌腹膜透析溶液中没有生物兼容性的物质的量。本发明还公开了制备 D－山梨醇类、葡糖酸类和烷 基苷类的方法。

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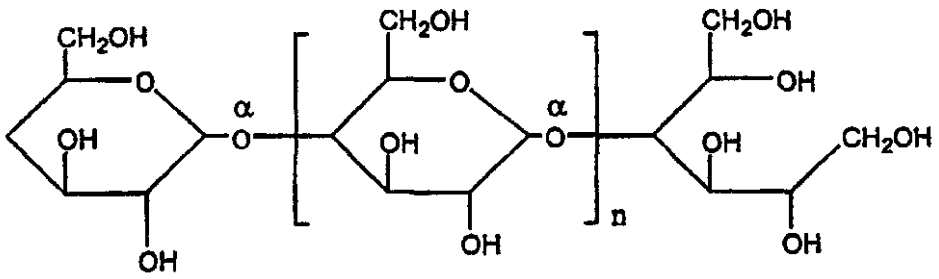
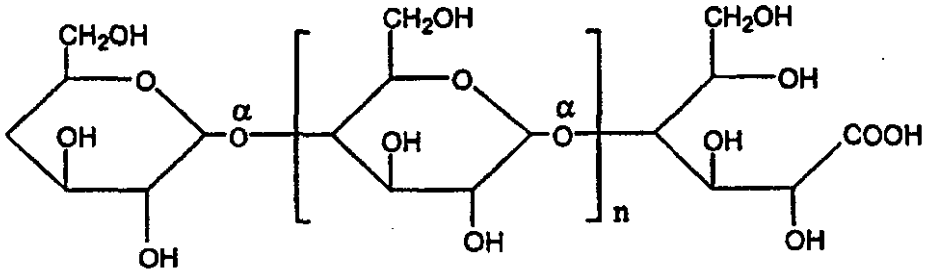
权　利　要　求　书

1. 一种灭菌的腹膜透析溶液，包括：

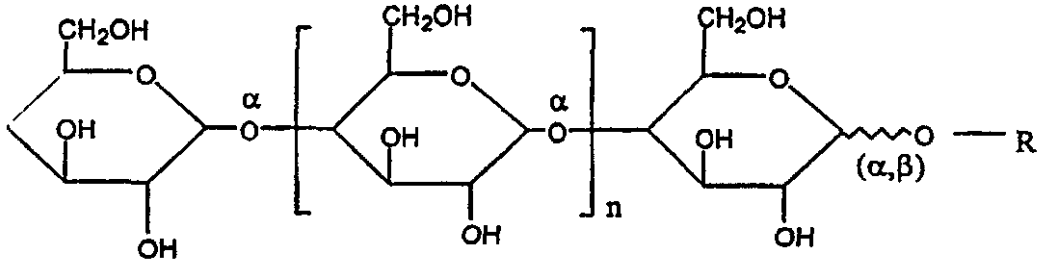
含有通过键连接并选自具有下列通式的 D-山梨醇：



具有下列通式的葡糖酸：



和具有下列通式的烷基苷组成的组的葡萄糖聚合物的淀粉：



其中 R 选自 CH_3、CH_3CH_2、$(CH_2OH)_2CH$、$CH_2(OH)CH(OH)CH_2$ 和 $[CH_2(OH)CH(OH)CH_2(OH)]CH$ 组成的组且其中所述的连接聚合物的键包括按数量计总计至少 85％的α-1,4 键。

2. 权利要求 1 的腹膜透析溶液，其中所述的溶液不含甲醛。

3. 权利要求 1 的腹膜透析溶液，其中所述的溶液不含糖醛类。

4. 权利要求 1 的腹膜透析溶液，其中部分水解的淀粉不含末端醛基。

5. 一种制备用于腹膜透析溶液的稳定渗透剂的方法，包括下列步骤：

提供一种溶于水的淀粉溶液；

向所述的淀粉溶液中添加 $NaBH_4$ 以还原淀粉。

6. 权利要求 5 的方法，进一步包括下列步骤：

通过使所述还原的淀粉溶液通过阴离子交换树脂而纯化所述的还原的淀粉溶液。

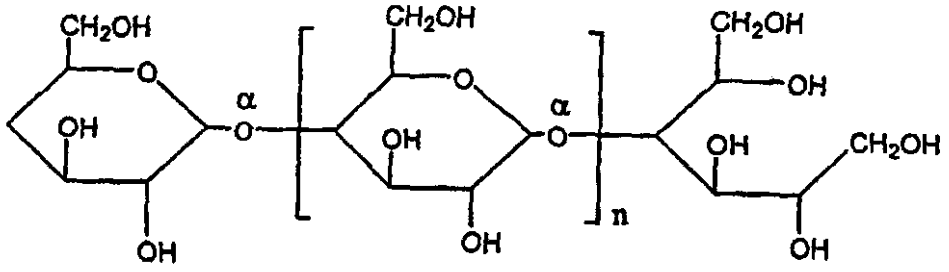
7. 权利要求 5 的方法，其中所述的溶解和添加步骤在室温下进行。

8. 权利要求 6 的方法，在添加步骤后和纯化步骤前进一步包括下列步骤：

使所述溶液稳定约 10 小时。

9. 权利要求 5 的方法，其中所述的淀粉是麦芽糖糊精。

10. 权利要求 5 的方法，其中将所述的淀粉还原成主要由α-1,4 键连接的 icodextrin 并具有下列通式：



11. 一种制备用于腹膜透析溶液的稳定渗透剂的方法，包括下列步骤：

提供溶于水的淀粉溶液；

提供 NaOCl 溶液；

将 NaOCl 溶液添加到淀粉溶液中以氧化所述的淀粉.

12.权利要求 11 的方法，进一步包括下列步骤:

通过使所述氧化的淀粉溶液通过凝胶渗透层析而纯化所述的氧化的淀粉溶液.

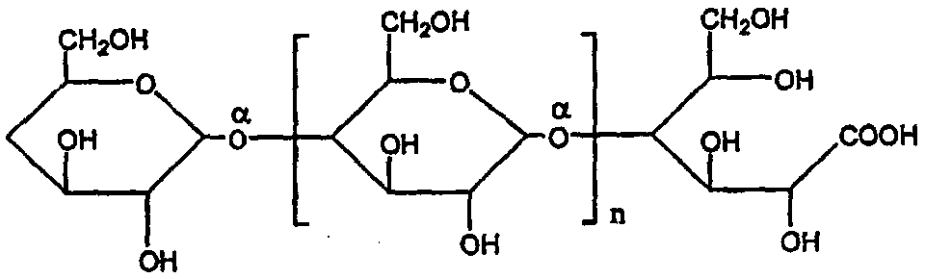
13.权利要求 11 的方法，其中所述的添加步骤在室温下进行.

14.权利要求 12 的方法，在添加步骤后和纯化步骤前进一步包括下列步骤:

使所述溶液稳定约 2 小时.

15.权利要求 11 的方法，其中所述的淀粉是麦芽糖糊精.

16.权利要求 11 的方法，其中将所述的淀粉氧化成主要由α-1,4 键连接的 icodextrin 并具有下列通式:



17.一种制备用于腹膜透析溶液的稳定渗透剂的方法，包括下列步骤:

在酸和醇中溶解淀粉，所述的醇选自甲醇、丁醇和丙三醇组成的组.

18.权利要求 17 的方法，进一步包括下列步骤:

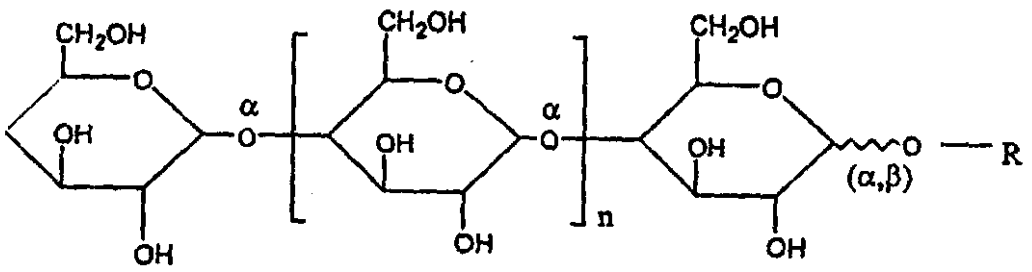
将所述的淀粉、醇和酸搅拌约 2 小时.

19.权利要求 17 的方法，其中所述的搅拌步骤在约 100℃的温度下进行.

20.权利要求 17 的方法，其中所述的淀粉是麦芽糖糊精.

21.权利要求 17 的方法，其中所述的酸是 HCl.

22.权利要求 17 的方法，其中将所述的淀粉糖基化成主要由α-1,4 键连接的 icodextrin 并具有下列通式:



其中 R 选自 CH_3、CH_3CH_2 和 $(CH_2OH)_2CH$ 组成的组。

00·08·04

说　明　书

含有改进的 ICODEXTRINS 的腹膜透析溶液

发明背景

本发明一般涉及腹膜透析和用于同样目的的溶液．更具体地说，本发明涉及将腹膜透析溶液中的改进的 icodextrins 用作渗透剂和作为替代将葡萄糖用作渗透剂的另一种选择．本发明还涉及在高压灭菌条件下保持稳定的腹膜透析溶液的制备方法．

透析为某些患者提供了补充或恢复肾功能的方法．一般来说，血液透析和腹膜透析是目前使用的两种方法．

在血液透析中，患者的血液流过人工肾脏透析仪．仪器中的膜起清洁血液的人工肾脏的作用．因为它是一种需要特殊仪器的体外治疗方法，所以血液透析伴随有某些内在的缺陷诸如透析仪的可用性和感染与污染的可能性．

为了克服与血液透析相关的缺陷，开发了腹膜透析．腹膜透析使用患者自身的腹膜作为半透膜．腹膜是身体腹骨盆壁的膜性衬层．腹膜能够起天然半透膜的作用，这是因为其中存在大量血管和毛细管的原因．

在操作中，使用一种导管将腹膜透析溶液引入腹腔．在一段足够的时间期限后，进行透析液与血液之间的交换．通过提供一种从透析液到血液的合适的渗透梯度而实现液体的流动以便使水从血液中流出．这使得在血液中实现合适的酸-碱、电解质和流体平衡成为可能．在一段延续期限后，透析溶液或透析液通过导管从身体中流出．

常规的腹膜透析溶液含有葡萄糖作为渗透剂以便维持高于生理渗透压（约 285mOsmol/kg）的所述溶液的渗透压．葡萄糖是一种优选的渗透剂，因为它可提供快速的超滤速度．然而，某些缺陷已经开始变得与葡萄糖的应用有关．

例如，公知葡萄糖在高压灭菌或蒸气灭菌过程中在水溶液中可分解成 5-羟甲基糠醛（5-MHF）．Smith 等《美国医院药物杂志》（AM. J. Hosp. Pharm.），34: 205-206（1977）．因为将 5-MHF 看作是对腹膜有害的（Henderson 等《现有纯化》（Blood Purif.），7:86-94

（1989）），所以理想的情况是在高压灭菌或蒸气灭菌过程中使腹膜透析溶液含有与葡萄糖同样有效的渗透剂而不会产生 5-MHF 或其它有害的分解产物．简言之，需要替代葡萄糖的渗透剂．

能够在腹膜透析溶液中用作渗透剂的一类化合物是 icodextrins、包括麦芽糖糊精．然而，尽管这些化合物适合用作渗透剂， 但是还公知它们在加热灭菌过程中会降解成醛糖糖酸类和甲醛．因为在腹膜透析溶液中存在的甲醛因其生物相容性极差而不适用，所以将 icodextrins 、包括麦芽糖糊精用作替代葡萄糖的渗透剂是不能令人满意的．

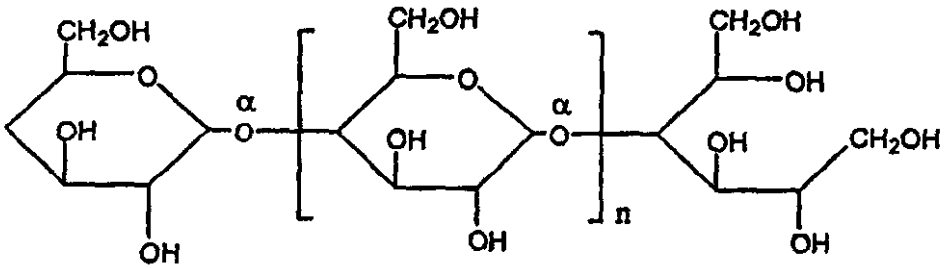
因此，存在一种对改进的腹膜透析溶液的需求，该溶液使用不是葡萄糖的渗透剂并且在高压灭菌或蒸气灭菌条件下保持稳定．

发明概括

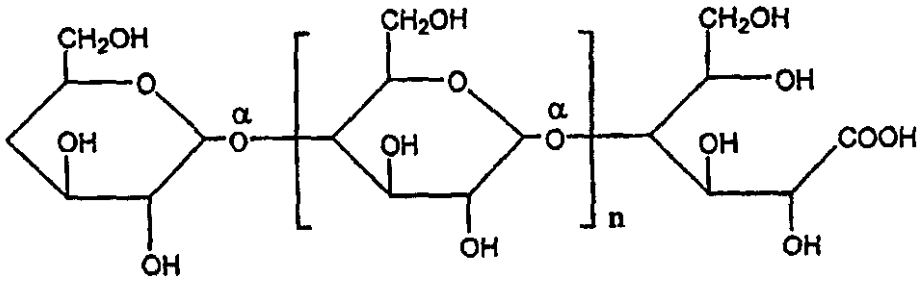
本发明通过提供一种含有主要由α-1,4 键连接的葡萄糖聚合物的灭菌腹膜透析溶液而提供了满足上述需求的溶液．使用术语“主要”是因为预计在聚合物分子内同样也存在其它键诸如α-1,6 键，但是数量较少．因此，本文所用的术语“主要”指的是至少为 85%．由此，主要由α-1,4 键连接的葡萄糖聚合物包括总计至少 85% 的α-1,4 键．

在一个实施方案中，主要由α-1,4 键连接的葡萄糖聚合物选自下列物质组成的组:

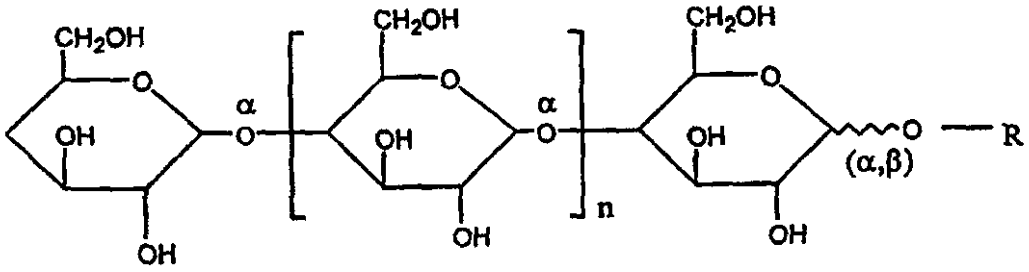
具有下列通式的 D-山梨醇（D-glucitol）:



具有下列通式的葡糖酸:



和具有下列通式的烷基苷:



其中 R 选自 CH_3、CH_3CH_2 和（CH_2OH）$_2CH$、CH_2（OH）CH（OH）CH_2、和（CH_2OH）（$CHOHCH_2OH$）CH 组成的组.

在一个实施方案中，腹膜透析溶液中主要由α-1,4 键连接的葡萄糖聚合物可以包括达 10% 的其它键包括但不限于α-1,6 键.

在一个实施方案中，本发明的腹膜透析溶液基本上不含甲醛.

在一个实施方案中，本发明的腹膜透析溶液基本上不含糖醛.

在一个实施方案中，用作渗透剂的淀粉基本上不含末端醛基.

在一个实施方案中，本发明提供了制备腹膜透析溶液的稳定的渗透剂的方法，该方法包括下列步骤：提供一种溶于水的淀粉溶液并向所述的部分水解的淀粉溶液中添加 $NaBH_4$ 以还原所述淀粉.

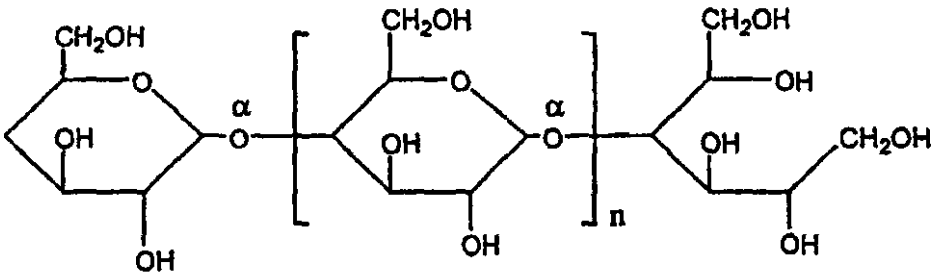
在一个实施方案中，本发明的方法进一步包括通过使所述还原的淀粉溶液通过阴离子交换树脂而纯化所述的还原的淀粉溶液的步骤.

在一个实施方案中，本发明方法的溶解和添加步骤在室温下进行.

在一个实施方案中，本发明的方法进一步包括下列步骤：在将 $NaBH_4$ 添加到所述淀粉溶液以还原淀粉后使所述溶液观察约 10 分钟。

在一个实施方案中，本发明的淀粉是麦芽糖糊精。

在一个实施方案中，本发明的方法将麦芽糖糊精还原成主要由 α-1,4 键连接的 D-山梨醇并具有下列通式：



在一个实施方案中，本发明提供了制备腹膜透析溶液的稳定的渗透剂的方法，该方法包括下列步骤：提供溶于水的淀粉溶液；提供 NaOCl 溶液；并将 NaOCl 溶液添加到淀粉溶液中以氧化所述的淀粉。

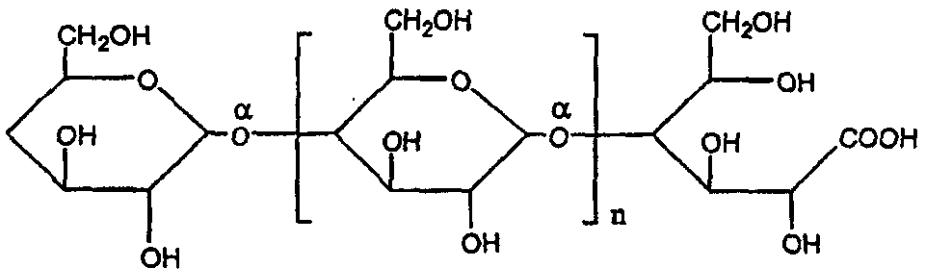
在一个实施方案中，本发明的方法进一步包括通过使所述氧化的淀粉溶液通过凝胶渗透层析而纯化所述氧化的淀粉溶液的步骤。

在一个实施方案中，所述淀粉的氧化在室温下进行。

在一个实施方案中，使混合的溶液稳定约 2 小时。

在一个实施方案中，所述的淀粉是麦芽糖糊精。

在一个实施方案中，本发明的方法将麦芽糖糊精氧化成主要由 α-1,4 键连接的葡糖酸并具有下列通式：



在一个实施方案中，可以以电化学方式氧化麦芽糖糊精.

在一个实施方案中，本发明提供了制备用于腹膜透析溶液的稳定的渗透剂的方法，该方法包括在酸和醇中溶解淀粉的步骤，所述的醇选自甲醇、丁醇、丙三醇或其它醇类组成的组.

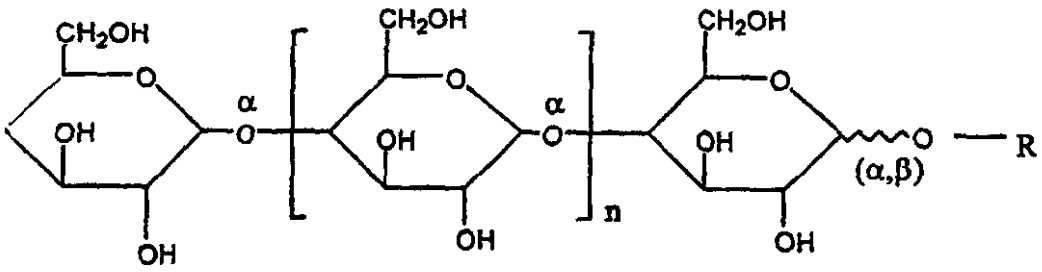
在一个实施方案中，本方法进一步包括将所述的淀粉、醇和酸搅拌 2－16 小时的步骤.

在一个实施方案中，本方法进一步包括在约 100℃的温度下搅拌所述的淀粉、醇和酸的步骤.

在一个实施方案中，所述的淀粉是麦芽糖糊精.

在一个实施方案中，所述的酸是盐酸或其它酸类诸如硫酸.

在一个实施方案中，本发明的方法将所述的淀粉水解并烷基化成主要由α-1,4 键连接的烷基苷并具有下列通式:



且其中 R 选自 CH_3、CH_3CH_2和（CH_2OH）$_2CH$ 组成的组. 当对用高碘酸预处理的淀粉进行水解时，R 是乙二醇裂解的葡萄糖单位的残基.

因此本发明的优点在于提供了一种改进的在高压灭菌和蒸气灭菌条件下能够保持稳定的腹膜透析溶液.

本发明的另一个优点在于提供了一种改进的渗透剂作为葡萄糖的替代物.

本发明的另一个优点在于提供了腹膜透析溶液的改进的制备方法.

本发明的另一个优点在于提供了在高压灭菌和蒸气灭菌条件下保持稳定的用于腹膜透析溶液的改进的渗透剂.

本文描述了本发明的其它特征和优点且从对目前优选的实施方

案的具体描述并参照附图中可以看出这些优点和特征是显而易见的.

附图的简要说明

附图 1 是通过按照本发明的糖基化制备的渗透剂的 ^{13}C NMR 光谱的图解说明; 且

附图 2 是通过按照本发明的糖基化制备的渗透剂的 ^{13}C NMR 光谱的图解说明.

当前优选实施方案的具体描述

本发明提供了含有在高压灭菌和蒸气灭菌条件下保持稳定的渗透剂的腹膜透析溶液. 本发明的稳定的渗透剂可以通过还原、氧化或糖基化来制备. 当使用带有还原端单位的 icodextrin 诸如麦芽糖糊精时, 本发明的还原、氧化或糖基化将 icodextrin 分别转化成相应的 D-山梨醇类、葡糖酸类和烷基苷类.

实施例 1

通过从将 15 克麦芽糖糊精溶于 20ml 水开始制备还原的 icodextrin. 在室温下将 1 克的 $NaBH_4$ 加入所述溶液并使所述溶液稳定 10 小时. 然后通过使之通过阴离子交换树脂来纯化所述溶液.

使用三种不同的麦芽糖糊精原料. 使用具有 3% 聚合度 (DP) 的低分子量 (LMW) 的麦芽糖糊精, 它包括 1% 的葡萄糖、37% 的麦芽糖、20% 的麦芽四糖和 42% 的高分子量寡糖类. 第二, 使用具有 14% 聚合度的高分子量麦芽糖糊 (HMW1) 并包括 1% 的葡萄糖、2% 的麦芽糖、4% 的麦芽四糖和 94% 的高分子量寡糖类. 第三, 使用具有 9% 聚合度的第二种高分子量的麦芽糖糊精 (HMW2), 它含有 1% 的葡萄糖、3% 的麦芽糖、7% 的麦芽四糖和 90% 的高分子量寡糖类. 使用 ^{13}C NMR 光谱分析产物和原料. 与所述原料的还原端单位相关的信号在产物的光谱中完全消失. 观察到了某些解聚作用.

在中性 pH 的灭菌条件下检测产物的稳定性. 对所述还原的化合物观察灭菌后在 284nm (Δ Abs) 处的显著减少的吸收度的变化. 将

来自实施例 1 中的还原的化合物列为表 1 中的 HMW1 red、HMW2 red 和 LMW red.

实施例 2

在 43℃的温度下，使用相应于实施例 1 的上述三种不同的麦芽糖糊精样品，通过将 15 克麦芽糖糊精溶于 30ml 水并将所述淀粉溶液与有效量的 NaOCl 溶于 70ml 含有氢氧化钠并具有 pH 为 8±0.5 的所得溶液合并而对各样品进行氧化反应．使合并的溶液稳定约 2 小时并通过凝胶渗透层析纯化产物溶液．此外，使用 ^{13}C NMR 光谱分析产物并在如表 1 中所说明的灭菌条件下检测产物的稳定性．尽管氧化产物 HMW1 ox 、HMW2 ox 和 LMW ox 表现出相反的结果，但是认为是由高分子量的未完全纯化的氧化产物所造成的．

表 1－5％Icodextrin 和改进的 Icodextrin 溶液灭菌（121℃，45 分钟）后的吸收度（284nm）变化

代码	实验次数	Δ Abs（pH 6.5-7.5）	Δ Abs（pH 5.5）
HMW1	6	0.65±0.30	0.59±0.35
HMW1 red	6	0.31±0.10	0.20±0.07
HMW1 ox	2	1.83±0.21	1.78±0.13
HMW2	8	1.21±0.71	0.62±0.71
HMW2 red	7	0.13±0.09	0.09±0.06
HMW2 ox	4	0.76±0.31	0.79±0.19
LMW	8	1.96±0.87	1.33±0.86
LMW red	8	0.18±0.11	0.17±0.07
LMW ox	3	0.01±0.01	0.02±0.01
参照化合物			
葡萄糖	4	2.54±0.78	2.36±0.96
*葡萄糖	2	0.98	
*D（+）-葡糖酸内酯	1	0.01	

*葡萄糖和 D（＋）-葡糖酸内酯溶液在 pH 为 7 时是 2.5％

Δ Abs－灭菌后和灭菌前之间吸收度的差异

实施例 3

在按照本发明制备稳定的渗透剂的第三种方法中，使 icodextrin 糖基化．使用淀粉作为原料和醇作为烷基化剂进行糖基化反应．选择丁醇和丙三醇，因为它们具有生物相容性．反应产物的分子量取决于温度、时间和所用的酸的浓度．

通过将 200mg 淀粉溶于含有 60mg 酸的 540mg 醇所得到的悬浮液在约 100℃下搅拌约 2 小时来进行使用甲醇和丁醇的水解．从分别使用甲醇和丁醇的该反应中获得的两种产物的 ^{13}C NMR 光谱如附图 1 和 2 中所示．表 2 表示了作为反应条件函数的聚合度（DP）和未取代还原端的百分比．从合适的 NMR 信号（DP 值的 ^{1}H NMR 与未取代还原端的百分比的 ^{13}C NMR）间的比例获得这一数据．

表 2－使用 MeOH 和 ButOH 的糖基化反应

样品号	醇	酸 M/l	D.P.	未取代葡萄糖的%
1	MeOH	H_2SO_4	4.1	8.7
2	MeOH	HCl	5.2	11.2
3	ButOH	H_2SO_4	1.3	41.6
4	ButOH	HCl	1.4	13.0

实施例 4

就使用丙三醇醇解的情况而言，使用 1 克未干燥的淀粉（湿度 9%）和 2.7 克的丙三醇并在 100℃下与不同量的盐酸搅拌不同的时间期限来进行该反应．通过在减压条件下蒸发来去除过量的丙三醇并通过凝胶过滤进一步进行纯化．结果如表 3 中所示．

表 3－使用丙三醇的糖基化反应（标准反应条件：未干燥的淀粉 1g，丙三醇 2.7g）

化合物	温度℃	时间:小时	HCl Mol/L	产率%	DP	未取代还原端的%
5*	80	2	1.27	未测出	8.5	9.8
6**	100	2	1.27	96	1.4	4.8
7	100	2	1.27	未测出	4.7	0
8	100	2	2.54	77.1	1.6	10.4
9	100	2	5.08	87.7	1.7	28.2
10	100	2	5.08	81.9	2.0	26.8
11	100	2	5.08	79.3	2.1	25.7
12	100	4	1.27	98	1.5	6.4
13	100	4	5.08	95.8	1.2	19.2
14	100	4	5.08	85.7	1.2	20.9
15	100	16	1.27	99.3	1.4	0
16***	100	16	1.27	93.1	1.2	0
17	100	16	5.08	78.9	1.0	13.4
18	100	16	5.08	79.6	1.0	0
19	100	24	5.08	82.1	1.0	4.6
20	60	16	1.27	未测出	1.35	17.1
21	60	16	1.27	未测出	1.10	23.9
22	80	16	0.32	88.7	1.11	13.9
23	80	16	0.32	79.4	1.10	11.3
24	80	16	0.32	89.1	1.15	10.6
25	80	16	0.64	94.2	1.04	17.9
26	80	16	0.64	未测出	1.03	21.7
27	80	16	0.64	未测出	1.10	9.7
28	80	16	1.27	未测出	1.03	11.4
29	80	16	1.27	99.8	1.01	8.6
30	80	16	1.27	未测出	1.01	4.9

*反应条件：淀粉 200mg，丙三醇 540mg

**反应条件：淀粉 600mg，丙三醇 1.62g

***反应条件：干淀粉 1g，丙三醇 2.7g

完全解聚的产物和具有 4.7 聚合度的产物的 ^{13}C NMR 光谱如附图 2 中所示．能够观察到糖苷异头信号α（100.9 ppm）和β（105.1 ppm）、丙三醇的两种取代的（α＝71.3 ppm，β＝73ppm）和未取代的（65.3 ppm）伯羟基的 CH_2 信号、丙三醇的仲取代的羟基的 CH 信号（α＝81.5 ppm，β＝83ppm ）．

将表 3 中所示的一种产物的稳定性用来检测在灭菌条件下的稳定性并将在 284nm 处观察到的变化与葡萄糖和甲基苷的变化进行比较．

表 4－丙三醇衍生物和甲基苷灭菌（121℃，45 分钟）后吸收度（284nm）的变化

样品	%（w/v）	实验次数	ΔAbs 中性（pH 6.5-7.5）	ΔAbs 酸（pH 5.5）
6 号	5	4	0.46±0.32	0.35±0.15
葡萄糖	5	3	2.43±0.9	未测出
甲基苷	2.5	1	0.01	未测出
葡萄糖	2.5	1	0.07	未测出

在预测上述渗透剂的透析有效性的体外试验中，使带有以 500 道尔顿截断值的光谱孔膜的小型透析袋（直径 15mm，15cm 高）充满 3ml 的不同浓度的水溶液（2.5，5.0％w/v 的样品）．将该袋浸入 200ml 的蒸馏水并在 37℃时搅拌过量的透析溶液．在给定的时间（0、1、2、3、4、5、6 小时）时，通过重量评估透析袋内的体积增加量并将其表示为与起始体积之比的百分比（Δw％）．将平均结果表示在表 5 中并与葡萄糖和葡萄糖-1-磷酸的结果进行比较．

表 5 - 改进的 icodextrins 的体外透析试验的体积增加量

样品	摩尔/L	实验次数	Δw%1 小时	Δw%2 小时	Δw%3 小时	Δw%4 小时	Δw%5 小时	Δw%6 小时
LMW red	0.071	5	29.9	43.0	53.8	66.2	76.7	88.3
LMW ox	未测出	5	20.2	29.2	39.3	46.0	56.4	63.4
HMW1 red	0.016	3	50.8	67.4	74.7	81.5	85.7	91.2
HMW1 ox	未测出	3	22.8	43.3	60.2	77.0	89.6	104.2
HMW2 red	0.049	3	6.7	10.0	15.7	19.2	21.2	26.3
HMW2 ox	未测出	4	32.2	52.9	69.7	84.2	96.0	106.4
6 号 (5%)	0.215	1	33.2	68.2	98.1	119.5	140.5	159.8
α-甲基-葡萄糖 (5%)	0.257	1	30.9	60.7	86.5	107.9	123.2	142.0
β-甲基-葡萄糖 (5%)	0.257	1	45	76.1	103.0	129.7	151.7	174.9
6 号 (2.5%)	0.108	2	22.9	34.4	50.0	63.0	77.2	87.7
α-甲基-葡萄糖 (2.5%)	0.128	3	21.8	39.2	55.4	67.64	79.5	92.1
β-甲基-葡萄糖 (2.5%)	0.128	3	34.0	50.3	63.7	67.6	77.7	86.5
葡萄糖 (2.5%)	0.138	3	15.3	34.2	43.4	57.3	74.2	90.9
葡萄糖-1-磷酸 (2.5%)	0.069	3	35.8	53.6	76.3	95.9	120.1	144.1

因此，本发明提供了大量热稳定性的作为葡萄糖的合适替代物的渗透剂、含有稳定的渗透剂的改进的腹膜透析溶液以及产生改进的腹膜透析溶液的各种方法。

可以理解对目前本文所述的优选实施方案进行各种改变和修改对于本领域技术人员来说是显而易见的。可以进行这类改变和修改而

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不会脱离本发明的实质和范围且不会减少其附带的优点．因此这类改变和修改属于所附权利要求的范围．

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说　明　书　附　图

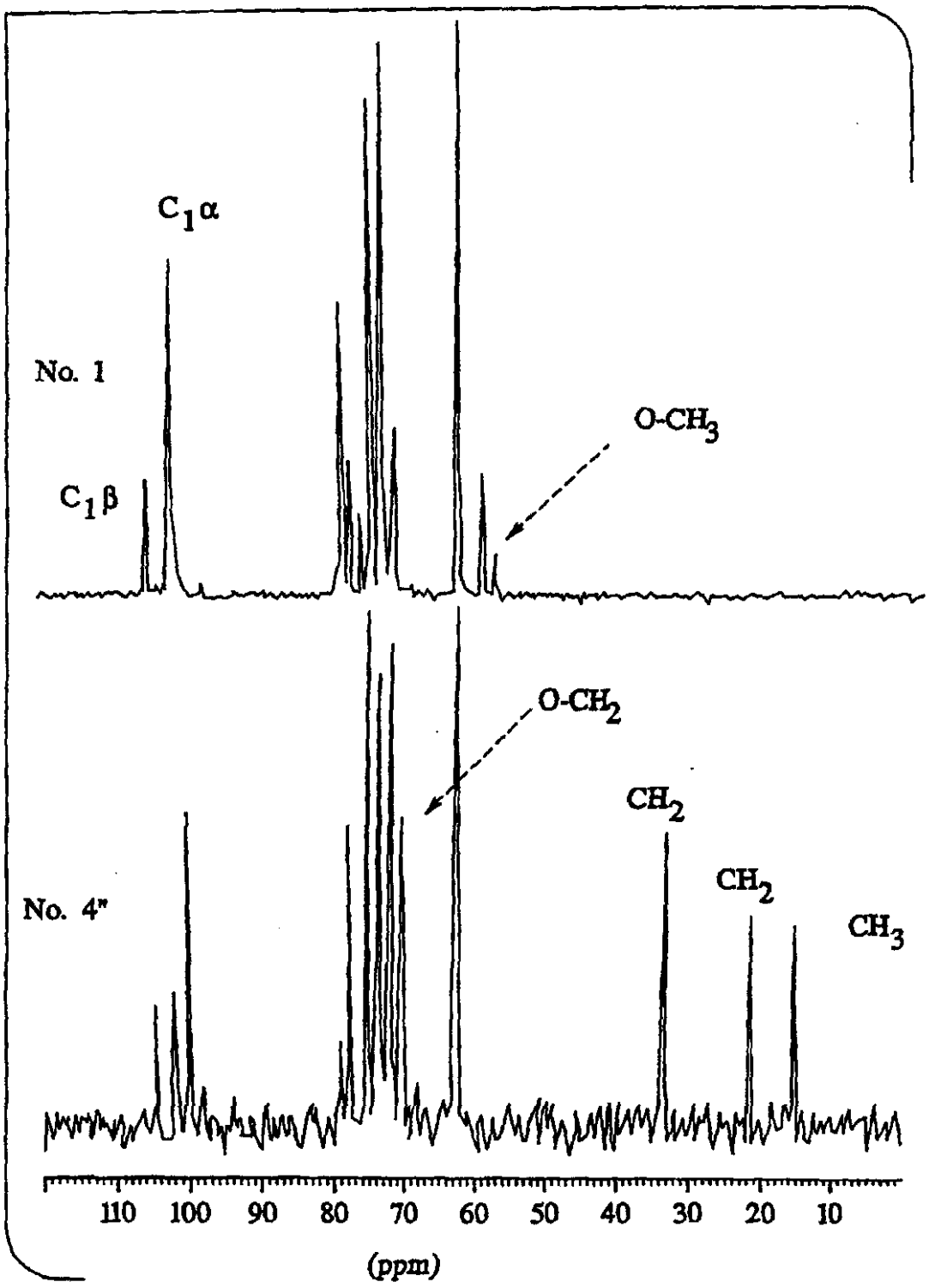

图　1

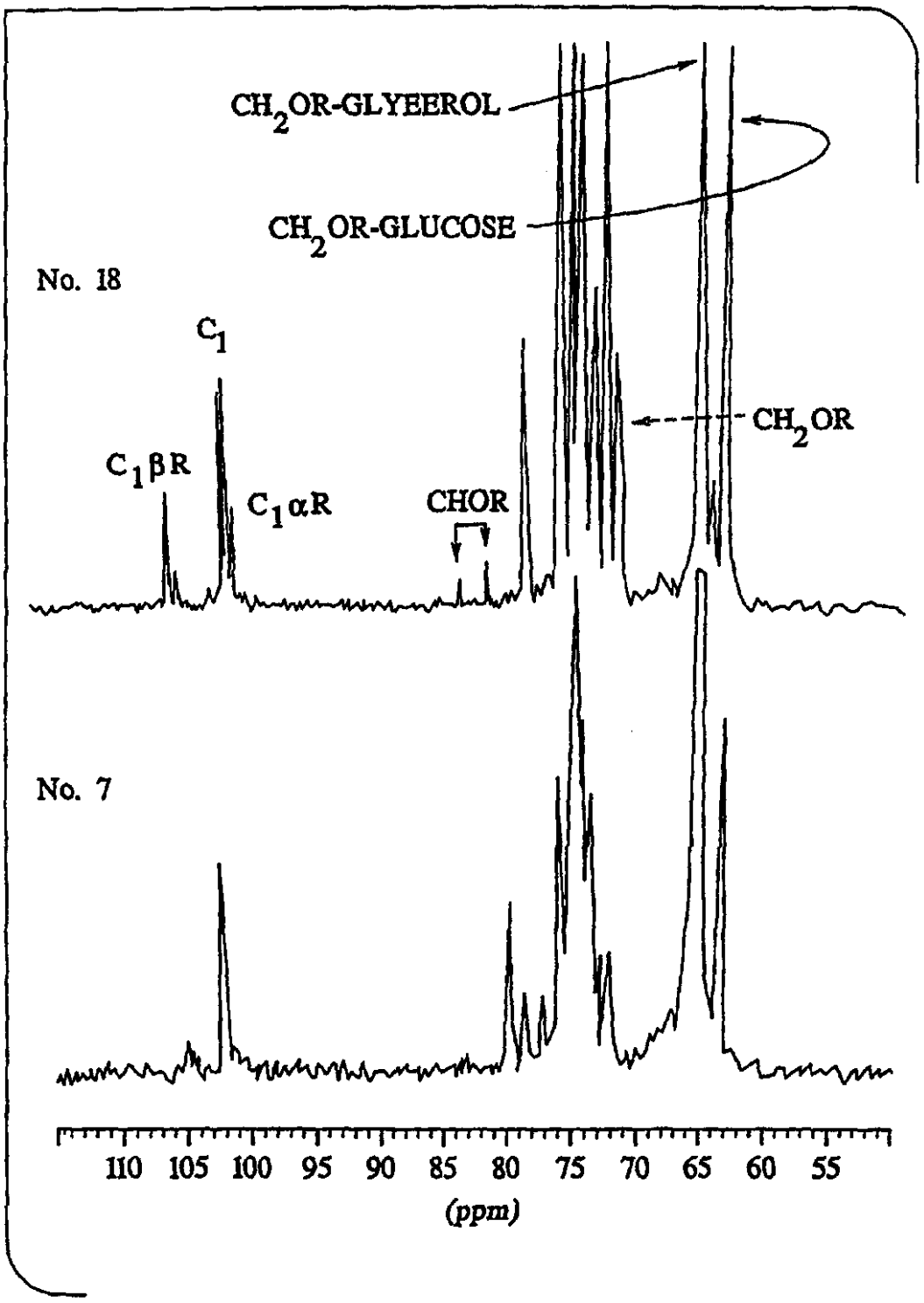
CH2OR-GLYEEROL
CH2OR-GLUCOSE
No. 18
C1
C1βR
C1αR
CHOR
CH2OR
No. 7
110 105 100 95 90 85 80 75 70 65 60 55
(ppm)

图 2