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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))*

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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF PENTOSAN POLYSULFATE OR SALTS THEREOF

(57) Abstract: The present invention relates to an improved process for the preparation of Pentosan polysulfate of formula (I) or salt thereof, wherein R represents -SO3Y, and Y is at least one member selected from the group consisting of H and a pharmaceutically acceptable cation such as sodium, potassium, and magnesium which provides in particular to a narrow distribution low molecular weight, highly sulfated Pentosan polysulfate (in this instance a Xylan).

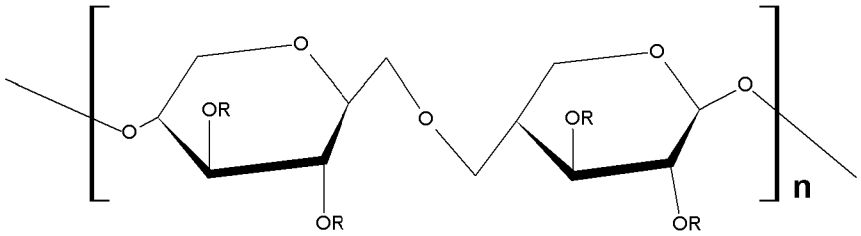
Description

Title of Invention: AN IMPROVED PROCESS FOR THE PREPARATION OF PENTOSAN POLYSULFATE OR SALTS THEREOF

[i]

Field of the Invention

[2] The present invention relates to an improved process for the preparation of Pentosan polysulfate of formula (I)



(I)

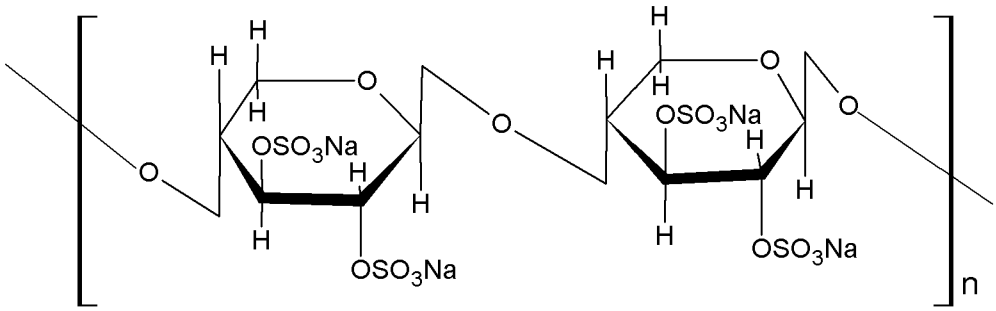
[3] or salt thereof, wherein R represents -S0 $_3$Y, and Y is at least one member selected from the group consisting of H and a pharmaceutically acceptable cation such as sodium, potassium, and magnesium which provides in particular to a narrow distribution low molecular weight, highly sulfated Pentosan polysulfate (in this instance a Xylan).

[4]

Background of the invention

[5]

[6] The structural formula of Pentosan polysulfate sodium represents as below:



Pentosan Polysulfate sodium

[7] The current pharmaceutical product containing Pentosan polysulfate sodium salt is being sold by Ortho McNeil under the tradename Elmiron ® in the form of capsules which is used for the treatment of bladder infection, interstitial cystitis and tumors.

[8]

[9] Pentosan polysulfate sodium is chemically known as β-D-Xylan, (1-4), 2, 3-bis (hydrogen sulphate) sodium salt having molecular weight range of 4000 to 6000 Dalton with special low molecular weight distribution pattern as per the CE of the innovator product i.e. Elmiron®. This CE is depicted in Fig. 2 and 3.

[10]

[11] Pentosan polysulfate sodium [37319-17-8] is a semi-synthetically produced heparin-like macromolecular carbohydrate derivative which chemically and structurally resembles glycosaminoglycans. It is a white odorless powder, slightly hygroscopic and soluble in water to 50% at pH 6.

[12]

[13] Pentosan polysulfate sodium is a mixture of linear polymers of β-l à 4-linked xylose, usually sulfated at the 2- and 3-positions and occasionally substituted at the 2-position with 4-O-methyl-a-D-glucuronic acid 2, 3-O-suflate.

[14]

[15] Pentosan polysulfate is a semi-synthetic compound whose polysaccharide backbone, xylan is extracted from the bark of the beech tree or other plant sources and then treated with sulfating agents such as chlorosulfonic acid or sulfuryl chloride and acid. After sulfation, Pentosan polysulfate is usually treated with sodium hydroxide to yield the sodium salt.

[16]

[17] Pentosan polysulfate is disclosed in US patent no. 2689848. The process wherein Xylan is treated with chlorosulfonic acid in the presence of pyridine to obtain sulfuric acid ester salt of xylan followed by oxidative depolymerisation in acidic or neutral aqueous medium to obtain depolymerised product which is dialyzed and followed the fractionation process to obtain desired product. However, this process does not provide end product with desired molecular weight.

[18]

[19] US patent 2689848 disclosed the process for the production of salts of sulfuric acid ester of Xylan, the steps which comprise oxidizing the aqueous solution of the a salt of a sulfuric acid ester of highly polymeric xylan in an aqueous solution of H_20_2 and H_2S0_4 to depolymerize such highly polymeric xylan ester partially, dialyzing the de-polymerized product and fractionating an aqueous solution of the dialyzate with an organic water miscible solvent to obtain a fraction having a Zη value between 0.0030 and 0.015 and sulfur content of 13.5 to 17%.

[20]

[21] Moreover, the process as disclosed above for the preparation of Pentosan polysulfate is tedious, costly and provides low yield of final product. Moreover, the use of cellophane tubes for dialysis makes process inapplicable at industrial scale up.

[22]

[23] Our own patent application WO 2008107906 A1 discloses improved process of Pentosan polysulfate sodium which involves use of NF membrane system for purification of crude depolymerised Pentosan polysulfate.

[24]

[25] During the research work directed towards prepration of the Pentosan polysulfate for getting the desired low molecular weight pattern our inventor observed that all above process needs improvement for achieving the desired CE pattern as it is important for molecule like Pentosan which is essentially a copolymorph and the CE pattern should identical to innovators product i.e. Elmiron® as per requirement of USFDA.

[26]

[27] Under-sulfation highly sulfated (sulfate esters) Xylan form a significant therapeutic class of pharmaceuticals in human and veterinary medicine. Sulfate esters demonstrate a broad range of clinical utility in treating various conditions including osteoarthritis, myocardial ischaemia, interstitial cystitis, cancer, and the control and treatment of virus diseases, including human immunodeficiency virus and other retroviruses.

[28]

[29] Pentosan polysulfate has been used in pharmaceutical formulations to treat osteoarthritis, as an anticoagulant or for other conditions such as interstitial cystitis, transmissible spongiform encephalopathy (TSE) and immunodeficiency virus (such as HIV/AIDS or Feline Immunodeficiency Virus (FIV)) in mammals, such as humans, food-producing and companion animals (such as feline, canine and equine). Pentosan polysulfate may also be used to treat haematomas, haemorrhoids, frostbite, burns, and multiparameter illnesses such as thrombosis and atherosclerosis.

[30]

[31] Sulfate esters of xylan, includes Pentosan polysulfate is semisynthetic. The derivation and synthesis of Pentosan polysulfate is proved to be very challenging, with production outcomes being highly variable. This directly relates to inconsistent clinical outcomes. While there are currently no reported clinical trials looking at differences in clinical outcomes of osteoarthritis treatment using more homogenous and more highly sulfated Pentosan polysulfate compared with low sulfated Pentosan polysulfate, anecdotal evidence suggests variability in clinical outcome of low sulfated Pentosan polysulfate. The main reasons that might be behind variability of molecular weight ranges during synthetic process of Pentosan polysulfate is inconsistent and high variation in the degree of sulfation of xylan.

[32]

[33] US Patent No. 4,713,373 discloses that fractions of Pentosan polysulfate with greater degrees of sulfation will have much better efficacy than those with lower sulfation.

However, in practice, it is difficult to achieve a consistently high level of sulfation at consistent positions along the chain and in a low molecular weight range. To date no-one has looked at the importance of the type and location of the sulfate groups or distinguished the chemical structure of the Pentosan polysulfate molecule produced by one manufacturing process from that produced by another. Also, the degree of sulfation within known Pentosan polysulfate formulations can vary widely, which can also lead to variability in clinical efficacy.

[34]

[35] Pentosan polysulfate as free acid or in the salt form (typically with inorganic cations such as sodium or calcium) is described in the prior art as a mixture of semi-synthetic polysulfated oligosaccharides, generally obtained from xylan. Pentosan polysulfate consists of sulfated linear 1-4 conjugated beta-D-xylopyranose units and has 4-O-methyl-D-glucuronic acid randomly attached on every eight to ten xylose units (on average).

[36]

[37] The typical number of xylose units in a Pentosan polysulfate mixture reported in the prior art has been between six and thirty. Pentosan polysulfate mixtures currently present on the market (when in the form of sodium salt at all SO_3^- groups) typically contain 15 to 17% sulfation. While the prior art describes degrees of sulfation from 15 to 20%, it is apparent from theory and experience that 20% sulfation of Pentosan polysulfate is not theoretically possible unless the sodium is substituted with hydrogen giving Pentosan hydrogen sulfate (in which case maximum sulfation is 21.9%). The highest possible degree of sulfation for physiologically active Pentosan polysulfate is 18.9 to 19%, depending on the length of the molecule. Indeed to date, there is also no substantiation in the prior art of 19% sulfation for Pentosan polysulfate, let alone higher degrees of sulfation.

[38]

[39] Differences in the manufacturing process (especially during sulfation and oxidation) can result with molecular differences of the Pentosan polysulfate molecule, such as the degree of sulfation and the position of sulfate groups on the xylan chain. It is well known that the clinical efficacy of sulfated carbohydrates can be affected by the type and position of SO_3^- groups, hence the need to fully control and characterise molecules.

[40]

[41] Prior art NMR analyses of sulfate esters (such as US Patent No 4,713,373) use NMR peak ratios to calculate degrees of sulfation. However, NMR peak ratios will not necessarily indicate the degree of sulfation of the molecule unless the calculation is made by analysis of the entire NMR spectrum.

[42]

[43] The Pentosan polysulfate prior art fails to characterise the position of SO_3^- groups (other than to describe theoretical full sulfation) or to discuss the molecular subspecies. There has been no disclosure in the prior art of where the sulfur is missing along the xylan chain when there is less than full sulfation. The prior art acknowledges that Pentosan polysulfate mixtures differ but focus only on the level of sulfation and average molecular weight as being factors that may significantly affect physiological efficacy of the Pentosan polysulfate material.

[44]

[45] Studies with heparin show the efficacy of varying molecular species (of heparin) depends on the location of the $-OSO_3^-$ groups within the molecule. Specifically, the relationship of chemical structure to activity for heparin is isolated to a pentasaccharide sequence comprising three D-glucosamine and two uronic acid units. The central D-glucosamine unit in this sequence contains a 3-O-sulfate moiety that is rare outside of this sequence. Sulfate groups on the D-glucosamines are found to be critical for retaining high anticoagulant activity, while undersulfation at less important locations seems not to affect the anticoagulant activity.

[46]

[47] Different manufacturing techniques lead to different types (chemical structures) of heparin being produced and these different structures are shown to have different clinical efficacies. By way of analogy, the molecular species of other glycan chains (including Pentosan polysulfate) vary according not only to the degree of sulfation but also according to the location of the sulfur atoms. The Pentosan polysulfate prior art does not address this in any detail.

[48]

[49] While use of Pentosan polysulfate became widespread, and to reduce batch to batch variations that could affect pharmaceutical effectiveness, the fundamental problem to overcome was production of a Pentosan polysulfate molecular species with a constant sulfur content close to or at 18 to 19%, with narrow average molecular weight range that ensures consistent physiological benefits and sulfate groups consistently attached to positions that will guarantee physiological effect. To date, there has been no discussion in the prior art regarding the relative importance of the positions of the sulfate groups on the xylan chain.

[50]

[51] Broad spectrum molecular weight Pentosan polysulfate is derived from natural sources such as xylan. In its natural form, Pentosan polysulfate consists of molecular chains of varying lengths, or molecular weights. However, like heparin, the effects of unfractionated natural Pentosan polysulfate can be difficult to predict.

[52]

[53] Clinical experience with heparin has found that by modifying heparin and making the mixture of molecules more homogenous (with a narrower molecular weight range), greater clinical efficacy, consistency and safety can be achieved. Similar experience has emerged in the clinical use of Pentosan polysulfate.

[54]

[55] However, in practice, it has been difficult to achieve consistency of the heterogeneous mixture of carbohydrates that make up Pentosan polysulfate during commercial production. This is because it has been difficult to achieve a consistent average molecular weight, consistently low molecular weight and steady but high level of sulfation.

[56]

[57] Therefore, it is necessary to develop a process for preparation of Pentosan polysulfate sodium which provides Pentosan polysulfate with a consistent average molecular weight, consistently low molecular weight and steady but high level of sulfation.

[58]

[59] Surprisingly, when the present inventors had developed improved process which involves resulfation of crude Pentosan polysulfate of formula (I) or its salt having molecular weight less than 6000 Dalton followed by purification and filtration through NF membrane system. This process of present invention provides Pentosan polysulfate of formula (I) or its salt with consistent molecular weight of less than 6000 Dalton and with steady but high level of sulfation.

[60]

[61]

Object of the invention

[62]

[63] It is therefore an object of the present invention is to provide the process for the preparation of Pentosan polysulfate of formula (I) or its salt which is operationally simple, easy to handle and applicable at an industrial scale.

[64]

[65] Another object of the present invention is to provide the process for the preparation of Pentosan polysulfate of formula (I) or its salt which provides Pentosan polysulfate of formula (I) or its salt with consistent molecular weight of less than 6000 Dalton and with steady but high level of sulfation.

[66]

[67] Yet another object of the present invention is to provide an improved process for the preparation of Pentosan polysulfate of formula (I) or salt thereof comprising:

- i) treating xylan with chlorosulfonic acid in the presence of pyridine followed by addition of alkali in the presence of alcoholic solvent to obtain salt of

sulfuric acid ester of xylan;

- ii) oxidizing the salt of sulfuric acid ester of xylan with the mixture of H_2S0_4 and 30% H_20_2 to obtain depolymerized crude Pentosan polysulfate of formula (I) or its salt by keeping the depolymerisation cut off limit of less than 6000 dalton;
- iii) resulfating depolymerized crude Pentosan polysulfate of formula (I) or its salt obtained in step (ii) with chlorosulfonic acid in the presence of pyridine followed by addition of alkali in the presence of alcoholic solvent to obtain re-sulfated depolymerized crude Pentosan polysulfate of formula (I) or its salt;
- iv) purifying resulfated depolymerized crude Pentosan polysulfate of formula (I) or its salt by dissolving it in water, followed by filtration through NF membrane system;
- v) optionally crystallizing the product obtained in the step (iv) from alcohol to obtain pure Pentosan polysulfate of formula (I) or its salt .

[68]

Summary of the invention

[69]

[70] The present invention provides an improved process for the preparation of Pentosan polysulfate of formula (I) or salt thereof, comprising:

- i) treating xylan with chlorosulfonic acid in the presence of pyridine followed by addition of alkali in the presence of alcoholic solvent to obtain salt of sulfuric acid ester of xylan;
- ii) oxidizing the salt of sulfuric acid ester of xylan with the mixture of H_2S0_4 and 30% H_20_2 to obtain depolymerized crude Pentosan polysulfate of formula (I) or its salt by keeping the depolymerisation cut off limit of less than 6000 dalton;
- iii) resulfating depolymerized crude Pentosan polysulfate of formula (I) or its salt obtained in step (ii) with chlorosulfonic acid in the presence of pyridine followed by addition of alkali in the presence of alcoholic solvent to obtain re-sulfated depolymerized crude Pentosan polysulfate of formula (I) or its salt;
- iv) purifying resulfated depolymerized crude Pentosan polysulfate of formula (I) or its salt by dissolving it in water, followed by filtration through NF membrane system;
- v) optionally crystallizing the product obtained in the step (iv) from alcohol to obtain pure Pentosan polysulfate of formula (I) or its salt .

[71]

Brief description of the drawings

[72]

[73] Figure- 1 depicts capillary electrophoresis pattern of Pentosan polysulfate sodium obtained according to process of present invention.

[74] Figure-2 depicts capillary electrophoresis pattern of innovator's Pentosan polysulfate sodium API isolated from Capsule i.e. Elmiron®.

[75] Figure-3 depicts capillary electrophoresis pattern of innovator's Pentosan polysulfate sodium Capsule i.e. Elmiron® capsule.

[76]

Detailed description of the invention

[77]

[78] Xylan is esterified with chlorosulfonic acid in presence of pyridine and Dimethyl form amide to give sulfuric acid ester of Xylan, which is isolated as sodium salt of sulfuric acid ester of Xylan by treatment with sodium hydroxide in methanol.

[79]

[80] Sodium salt of sulfuric acid ester of Xylan is subjected to oxidative depolymerization in presence of hydrogen peroxide and sulfuric acid to give crude Pentosan Polysulfate sodium. The crude Pentosan Polysulfate is isolated by addition of methanol and dried.

[81]

[82] Crude Pentosan Polysulfate Sodium is resulfonated by pyridine and chlorosulfonic acid in DMF solvent. The material is isolated by methanol and decolorized by chlorine dioxide in water. Pentosan Polysulfate sodium (crude) is purified by reverse osmosis to yield pure Pentosan Polysulfate Sodium, which is isolated by crystallization from methanol.

[83]

[84] In one embodiment, present invention provides an improved process for the preparation of Pentosan polysulfate of formula (I) or salt thereof having Capillary Electrophoresis as depicted in Fig. 1 comprising:

- i) treating xylan with chlorosulfonic acid in the presence of pyridine followed by addition of alkali in the presence of alcoholic solvent to obtain salt of sulfuric acid ester of xylan;
- ii) oxidizing the salt of sulfuric acid ester of xylan with the mixture of H_2S0_4 and 30% H_20_2 to obtain depolymerized crude Pentosan polysulfate of formula (I) or its salt by keeping the depolymerisation cut off limit of less than 6000 dalton;
- iii) resulfating depolymerized crude Pentosan polysulfate of formula (I) or its salt obtained in step (ii) with chlorosulfonic acid in the presence of pyridine followed by addition of alkali in the presence of alcoholic solvent to obtain re-sulfated depolymerized crude Pentosan polysulfate of formula (I) or its salt;

- iv) purifying resulfated depolymerized crude Pentosan polysulfate of formula (I) or its salt by dissolving it in water, followed by filtration through NF membrane system;
- v) optionally crystallizing the product obtained in the step (iv) from alcohol to obtain pure Pentosan polysulfate of formula (I) or its salt .

[85]

[86] The present invention provides an improved process for the preparation of Pentosan polysulfate of formula (I) or salt thereof comprising steps of:

- i) oxidizing the salt of sulfuric acid ester of xylan with the mixture of H_2S0_4 and 30% H_20_2 to obtain depolymerized crude Pentosan polysulfate of formula (I) or its salt by keeping the depolymerisation cut off limit of less than 6000 dalton;
- ii) resulfating depolymerized crude Pentosan polysulfate of formula (I) or its salt obtained in step (ii) with chlorosulfonic acid in the presence of pyridine followed by addition of alkali in the presence of alcoholic solvent to obtain re-sulfated depolymerized crude Pentosan polysulfate of formula (I) or its salt.

[87]

[88] The term 'alkali' used hereinabove is selected but not limited to alkali metal salt of carbonate, bicarbonate, hydroxide or mixtures thereof. The most preferable is sodium hydroxide.

[89]

[90] The alcoholic solvent is selected from methanol, ethanol, propanol, isopropanol, butanol or mixtures thereof. The most preferable is methanol.

[91]

[92] For the purpose of this specification, the meaning of the term 'NF membrane system' is nano-filtration accompanied by membrane which is capable to pass the undesired product having molecular weight less than of 6000 Dalton.

[93]

[94] The main advantage of the process of present invention is CE pattern of Pentosan polysulfate sodium obtained according to process of present invention as depicted in Fig. 1 which having molecular weight less than of 6000 Dalton is matches with CE pattern of innovator's Pentosan polysulfate sodium API isolated from Capsule as depicted in Fig. 2 as well as with CE pattern of innovator's Pentosan polysulfate sodium Capsule i.e. Elmiron® capsule.

[95]

[96] Having thus described the invention with reference to particular preferred em-bodiments and illustrative examples, those in the art would appreciate modifications to the invention as describes and illustrated that do not depart from the spirit and scope of

the invention as disclosed in the specification. The examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to limit its scope in any way. The examples do not include detailed descriptions of conventional methods. Such methods are well known to those of ordinal skill in the art and are described in numerous publications. All references mentioned herein are incorporated in their entirety.

[97]

[98] **Example 1**

[99] **Preparation of sodium salt of sulfuric acid ester of Xylan**

[100] To the four necks round bottom flask pyridine (1600 ml), and add N, N-Dimethyl formamide (1600 ml) at 25-30°C. Cool the reaction mixture to 0-5°C by using ice bath. Chlorosulfonic acid (400ml) was added drop wise to the reaction mixture and heated the reaction mixture to 60-65°C and then added Xylan (200gm) and raised the temperature up to 75-80°C after completion of reaction the reaction mixture was cooled to 25-30°C Methanol (5000 ml) was added to the reaction mixture to isolate the product. The product was filtered and washed with methanol. The isolated product was dissolved in water 500ml and decolorized with chlorine dioxide (400ml), then it was added a mixture of methanol (4000ml) and 33% Sodium hydroxide (400ml). It was then adjusted to pH to neutral with acetic acid, filtered and dried the material at 50-55° C under reduced pressure to get 240 gm sodium salt of sulfuric acid ester of xylan.

- Rsults:
- Wet weight : 950 gm
- Dry weight : 436 gm
- Yield (w/w) : 2.18 w/w

[101]

[102] **Example 2**

[103] **Preparation of Crude Pentosan Polysulfate Sodium**

[104] To a three neck 31t four necks round bottom flask charged sodium salt of sulfuric acid ester of xylan (500g) in water (1500ml) and adjust the pH to 6.0-6.5 and heated to 60-100°C, then added the preheated mixture of 5N sulfuric acid (7.50 gm) and 30 ml with water and 30% hydrogen peroxide (150ml). Monitored the reaction with HPLC, after completion of reaction till average molecular weight came about 3000-6000 Dalton, cooled the reaction mixture and solution was adjusted pH to neutral with dilute sodium hydroxide solution. Then the reaction mixture was precipitated with methanol (12.51t), filtered and dried at 50-55°C to get crude Pentosan polysulfate sodium.

- Results:
- Wet weight : 800.0 gm
- Dry weight : 440.0 gm

- Yield (w/w) : 0.88 w/w

[105]

[106] **Example 3**

[107] **Resulfonation of Crude Pentosan polysulfate sodium**

[108] To the four necks round bottom flask pyridine (2762 ml), and add N, N-Dimethyl formamide (2762 ml) at 25-30°C. Cool the reaction mixture to 0-5°C by using ice bath. Chlorosulfonic acid (709ml) was added drop wise to the reaction mixture and heated the reaction mixture to 60-65°C and then added crude Pentosan polysulfate sodium (425gm) (followed by example 2) and raised the temperature up to 75-80°C after completion of reaction the reaction mixture was cooled to 25-30°C Methanol (12750 ml) was added to the reaction mixture to isolate the product. The product was filtered and washed with methanol. The isolated product was dissolved in water (2125ml) and decolorized with chlorine dioxide (425ml). the reaction mixture pH was adjusted to pH 9.5-10.0 by using 5 N aqueous sodium hydroxide and than stir the reaction mixture for 15 minutes at 25-30°C further the reaction mixture again pH was adjusted to pH 6.5-7.0 by using acetic acid and than reaction mixture was diluted with DM water (10 liter) and charge into feeding tank with system [HPA-400 membrane]. The NF Membrane system was monitored the by HPLC till to get the low molecular weight 1.6 to 2.2%. After the completion of filtration, the concentrate was subjected to water recovery at 40-60°C under reduced pressure up to 8500ml. Finally residue was crystallized with methanol (2550ml) to get the pure Pentosan polysulfate sodium. Filtered the material and dried it at 55-60°C under vacuum. The yield of pure Pentosan polysulfate sodium was 170gm having Z h value 0.006 and Molecular weight of 6543 Dalton.

- Results:
- Wet weight : 220.0 gm
- Dry weight : 177.0 gm
- Yield (w/w) : 0.416 w/w

[109]

Claims

[Claim 1] 1] A process for the preparation of Pentosan polysulfate of formula (I) or its salt with molecular weight of less than 6000 Dalton and with high level of sulfation comprises resulfating depolymerized crude Pentosan polysulfate or its salt to obtain Pentosan polysulfate of formula (I) or its salt.

[Claim 2] 2] A process for the preparation of Pentosan polysulfate of formula (I) or salt thereof comprising steps of:

i) oxidizing the salt of sulfuric acid ester of xylan with the mixture of H_2S0_4 and H_20_2 to obtain depolymerized crude Pentosan polysulfate of formula (I) or its salt by keeping the de-polymerisation cut off limit of less than 6000 dalton;

ii) resulfating depolymerized crude Pentosan polysulfate of formula (I) or its salt obtained in step (i) with chlorosulfonic acid in the presence of pyridine, alkali and alcoholic solvent to obtain resulfated depolymerized crude Pentosan polysulfate of formula (I) or its salt.

[Claim 3] 3] A process for the preparation of Pentosan polysulfate of formula (I) or its salt thereof comprising:

i) treating xylan with chlorosulfonic acid in the presence of pyridine, sodium hydroxide and alcoholic solvent to obtain salt of sulfuric acid ester of xylan;

ii) oxidizing the salt of sulfuric acid ester of xylan with the mixture of H_2S0_4 and H_20_2 to obtain depolymerized crude Pentosan polysulfate of formula (I) or its salt by keeping the de-polymerisation cut off limit of less than 6000 dalton;

iii) resulfating depolymerized crude Pentosan polysulfate of formula (I) or its salt obtained in step (ii) with chlorosulfonic acid in the presence of pyridine, sodium hydroxide and alcoholic solvent to obtain resulfated depolymerized crude Pentosan polysulfate of formula (I) or its salt;

iv) purifying resulfated depolymerized crude Pentosan polysulfate of formula (I) or its salt by dissolving it in water, followed by filtration through NF membrane system;

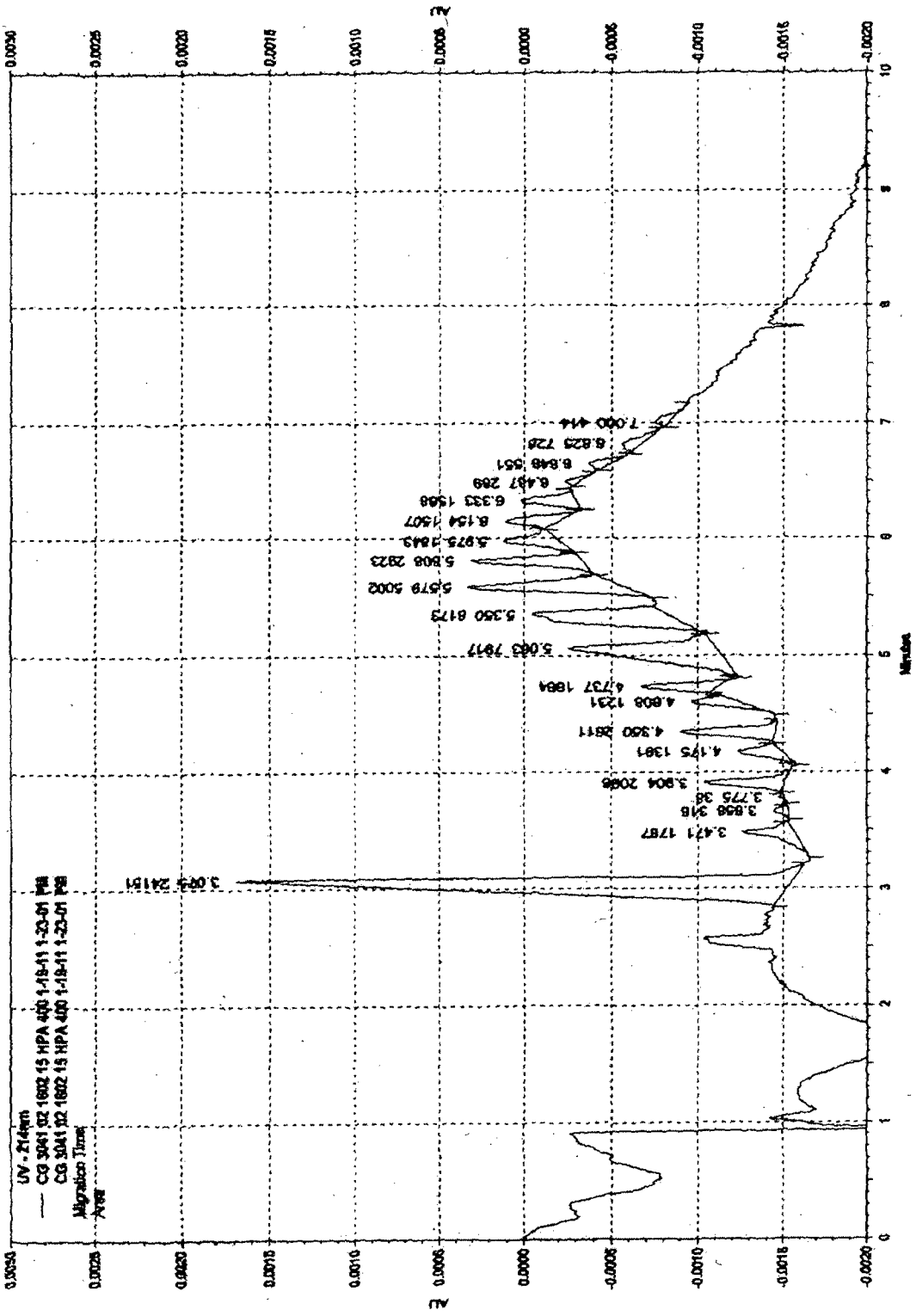
v) optionally crystallizing the product obtained in the step (iv) from alcohol to obtain pure Pentosan polysulfate of formula (I) or its salt.

[Claim 4] **4]** A process according to claim 2, wherein alkali is selected from alkali metal salt of carbonate, bicarbonate, hydroxide or mixtures thereof.

[Claim 5] **5]** A process according to claim 4, wherein alkali is sodium hydroxide.

[Claim 6] **6]** A process according to claim 2 and 3, wherein alcoholic solvent is-selected from the groupcomprising methanol, ethanol, propanol, iso-propanol, butanol or mixtures thereof.

[Claim 7] A process according to claim 5, wherein alcoholic solvent is methanol.


UV - 214nm
CG 3041 02 1602 15 HPA 400 1-19-11 1-23-01
CG 3041 02 1602 15 HPA 400 1-19-11 1-23-01
Migration Time
Area
3.094 24151
3.421 1787
3.775 34
3.856 316
3.904 2068
4.175 1361
4.320 2811
4.608 1231
4.737 1884
5.063 7917
5.350 6173
5.579 5002
5.808 2823
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6.154 1507
6.333 1568
6.487 269
6.648 551
6.825 726
7.000 414
Minutes

Fig. 1

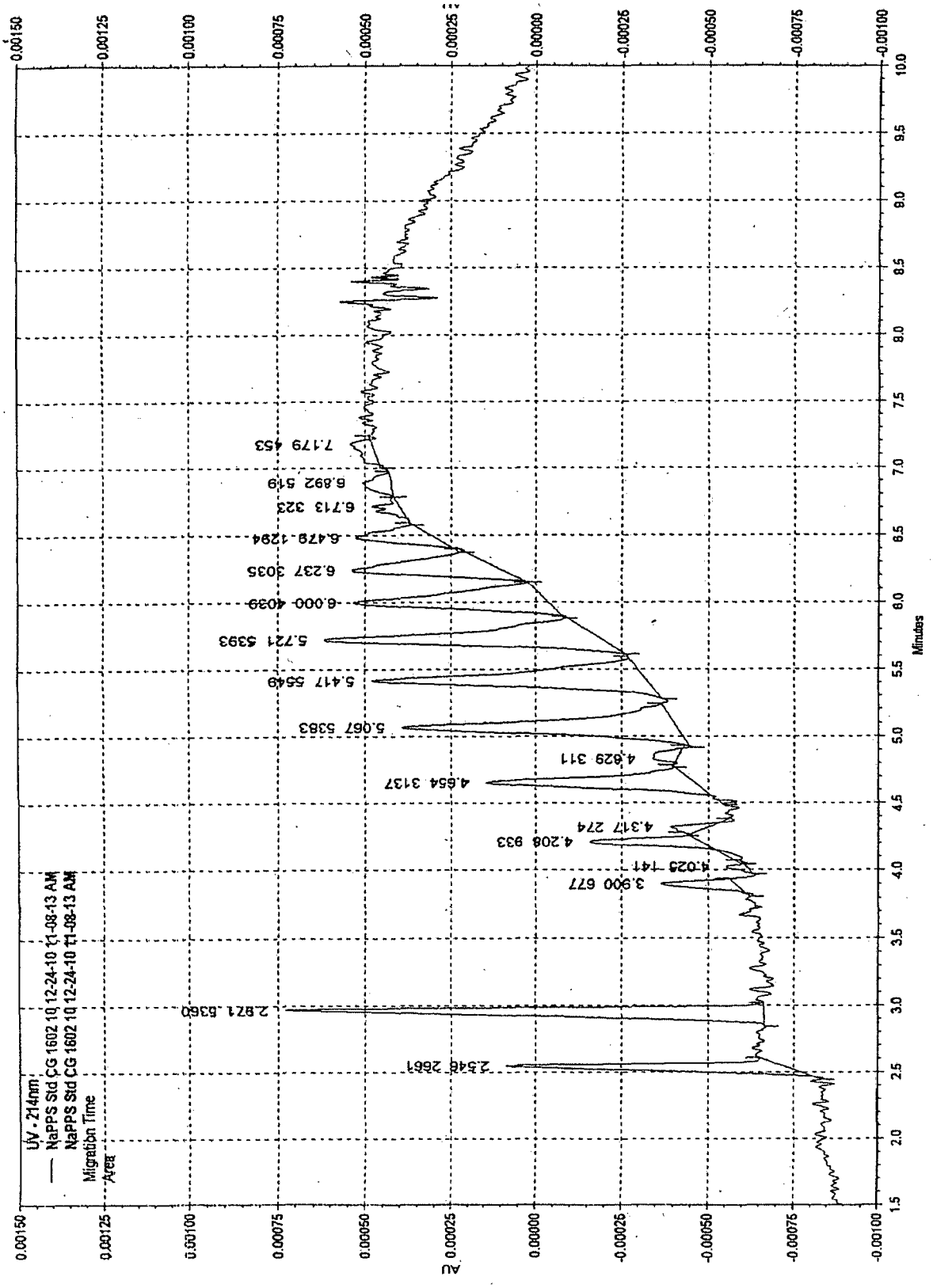
UV - 214nm
NaPPS Std CG 1602 10 12-24-10 11-08-13 AM
NaPPS Std CG 1602 10 12-24-10 11-08-13 AM
Migration Time
Area
2.548 2661
2.821 5360
3.900 677
4.023 141
4.208 933
4.317 274
4.654 3137
4.629 311
5.067 5383
5.417 5549
5.721 5393
6.000 4039
6.237 3035
6.479 1294
6.713 323
6.892 519
7.179 453
Minutes
AU

Fig. 2

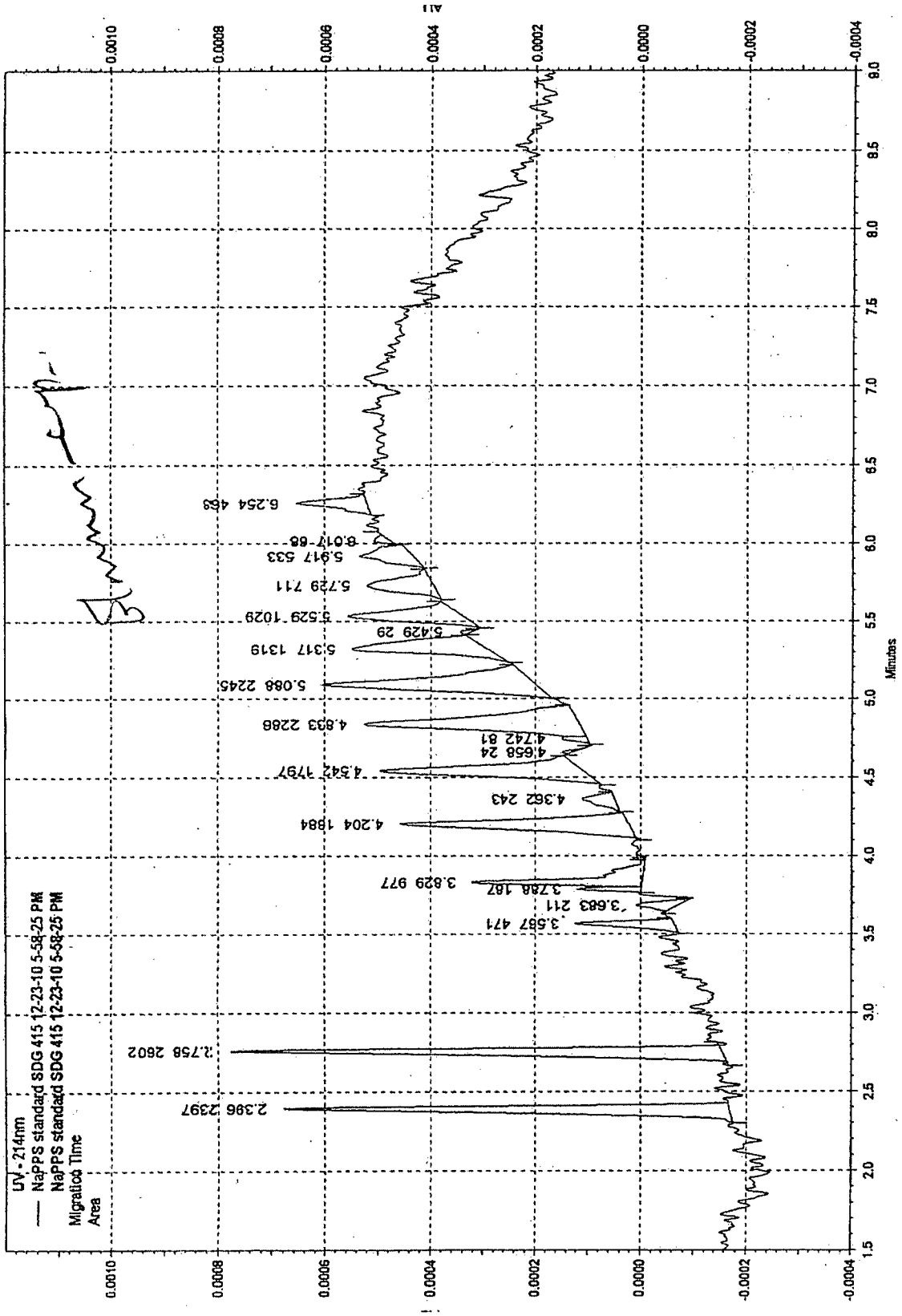
UV - 214nm
NaPPS standard SDG 415 12-23-10 5-58-25 PM
NaPPS standard SDG 415 12-23-10 5-58-25 PM
Migration Time
Area
2.396 2397
2.758 2602
3.587 471
3.663 211
3.788 187
3.829 977
4.204 1884
4.362 243
4.542 1797
4.658 24
4.742 81
4.833 2286
5.088 2245
5.317 1319
5.429 29
5.529 1029
5.729 711
5.917 533
6.017 68
6.254 463
Minutes

Fig. 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/050213

A. CLASSIFICATION OF SUBJECT MATTER
INV. C08B37/14
ADD.

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)
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 practicable, search terms used)
EPO-Internal , WPI 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 2010/000013 A1 (PARNELL LAB AUST PTY LTD [AU]; STAJIC VLADIMIR [AU]; CHEETHAM NORMAN [ ]) 7 January 2010 (2010-01-07) page 23, line 23 - line 30	1-7
X	US 4 699 900 A (BAYOL ALAIN [FR] ET AL) 13 October 1987 (1987-10-13) claim 1; examples 1,2	1-7

-/-

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"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
23 April 2012	08/05/2012

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, Fax: (+31-70) 340-3016	Lanz , Sandra

1

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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.
X	OFOSU F A ET AL: "2 Mechani sms of acti on of l ow mol ecul ar wei ght hepari ns and hepari noi ds" , BAI LLI ERE 'S CLINICAL HAEMATOLOGY, BAI LLI ERE TINDALL, LONDON , GB, vol . 3 , no. 3 , 1 July 1990 (1990-07-01) , pages 505-529 , XP026166376, ISSN : 0950-3536, D0I : 10. 1016/50950-3536(05)80016-2 [retri eved on 1990-07-01] page 511 , paragraph 1 page 518, paragraph 2 -----	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/050213

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