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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 provide an improved process for preparation of Pentosan polysulfate of formula (I) or salt thereof, comprising a step of treating xylan with chlorosulfonic acid in the presence of picoline.

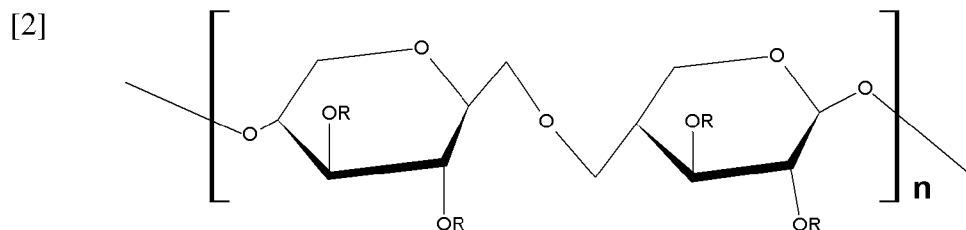
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Description

AN IMPROVED PROCESS FOR THE PREPARATION OF PENTOSAN POLYSULFATE OR SALTS THEREOF

Field of Invention

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



(I)

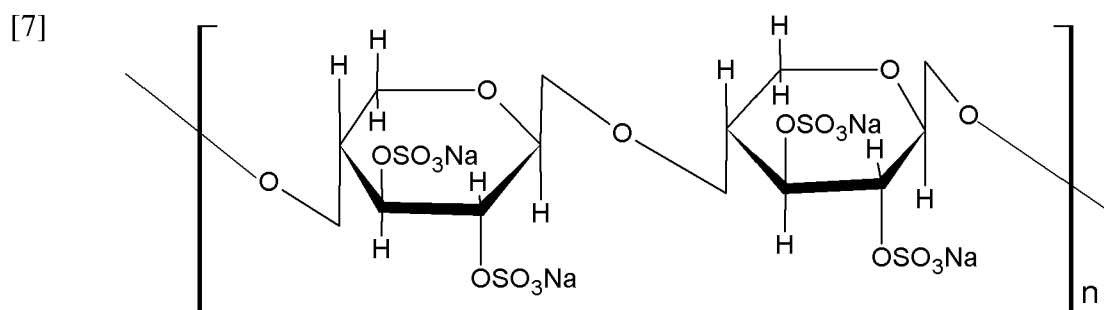
[3] or salt thereof, wherein R represents $-\text{SO}_3\text{Y}$, and Y is at least one member selected from the group consisting of H and a pharmaceutically acceptable cation such as sodium and potassium.

[4]

Background of the invention

[5]

[6] Pentosan polysulfate sodium is chemically known as Beta-D-Xylan, (1-4), 2, 3-bis (hydrogen sulphate) sodium salt having molecular weight range of 4000 to 6000 Dalton. The structural formula of Pentosan polysulfate sodium represents as below:



Pentosan Polysulfate sodium

[8] 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.

[9]

[10] 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.

[11]

[12] Pentosan polysulfate sodium is a mixture of linear polymers of Beta-1 -> 4-linked xylose, usually sulfated at the 2- and 3-positions and occasionally substituted at the 2-position with 4-*O*-methyl-alpha-D-glucuronic acid 2, 3-*O*-sulfate.

[13]

[14] 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 sulfonyl chloride and acid. After sulfation, Pentosan polysulfate is usually treated with sodium hydroxide to yield the sodium salt.

[15]

[16] Pentosan polysulfate was disclosed in US patent no. 2689848. The process wherein Xylan was 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 was dialyzed and followed the fractionation process to obtain desired product. However, the isolation of sulfuric acid ester salt of xylan provides sticky material. Moreover, this process did not provide end product with desired molecular weight.

[17]

[18] US patent no. 2689848 disclosed the process for the production of salts of sulfuric acid ester of Xylan, the steps which comprised oxidizing the aqueous solution of the salt of a sulfuric acid ester of highly polymeric xylan in an aqueous solution of H₂O₂ and H₂SO₄ to depolymerize such highly polymeric xylan ester partially, dialyzing the depolymerized product and fractionating an aqueous solution of the dialyzate with an organic water miscible solvent to obtain a fraction having a Z_{η} value between 0.0030 and 0.015 and sulfur content of 13.5 to 17%.

[19]

[20] 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 less favourable at industrial scale up.

[21]

[22] Therefore, it is necessary to develop an improved process for preparation of Pentosan polysulfate sodium which provides high yield as well as feasible at an industrial scale.

[23]

[24] Unexpectedly, the present inventors have found that reaction of Xylan with chlorosulfonic acid in the presence of picoline provides high yield and purity of sulfuric acid ester salt of xylan. This change makes the process not only easy at industrial scale but

also environmentally friendly. Moreover, the yield of sulfuric acid ester salt of xylan is being improved which in turn increased the overall yield of Pentosan polysulfate sodium having molecular weight of 4000 to 6000 Dalton.

[25]

Summary of the invention

[26]

[27] The present invention relates to an improved process for preparation of Pentosan polysulfate of formula (I) or salt thereof, comprising a step of treating xylan with chlorosulfonic acid in the presence of picoline.

[28]

Object of the invention

[29]

[30] It is therefore an object of the present invention is to provide an improved process for the preparation of Pentosan polysulfate of formula (I) or salt thereof.

[31]

[32] Another 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.

[33]

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

[35] i) treating xylan with chlorosulfonic acid in the presence of picoline followed by addition of alkali in the presence of alcoholic solvent to obtain salt of sulfuric acid ester of xylan

[36] ii) oxidizing the salt of sulfuric acid ester of xylan with the mixture of H_2SO_4 and 30% H_2O_2 followed by purification of depolymerized crude Pentosan polysulfate of formula (I) or its salt by dissolving in water and filtration through NF membrane system

[37]

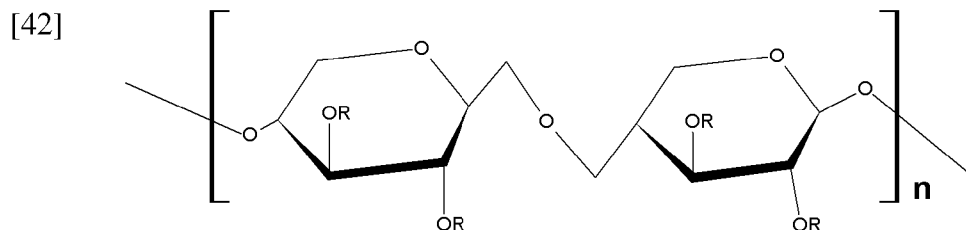
[38] A further object of the present invention is to provide an improved process for preparation of Pentosan polysulfate of formula (I) or salt thereof, comprising a step of treating xylan with chlorosulfonic acid in the presence of picoline.

[39]

Detailed description of the invention

[40]

[41] According to one aspect, present invention provides an improved process for the preparation of Pentosan polysulfate of formula (I)



[43] or salt thereof, wherein R represents $-\text{SO}_3\text{Y}$, and Y is at least one member selected from the group consisting of H and a pharmaceutically acceptable cation such as sodium and potassium.

[44]

[45] According to another aspect, present invention provides an improved process for the preparation of Pentosan polysulfate of formula (I) or salt thereof, which is operationally simple, easy to handle and applicable at an industrial scale.

[46]

[47] Yet another aspect of the present invention is to provide an improved process for preparation of Pentosan polysulfate of formula (I) or salt thereof, comprising a step of treating xylan with chlorosulfonic acid in the presence of picoline.

[48]

[49] Further aspect of the present invention is to provide an improved process for preparation of Pentosan polysulfate of formula (I) or salt thereof, comprising steps of:

[50] i) treating xylan with chlorosulfonic acid in the presence of picoline followed by addition of alkali in the presence of alcoholic solvent to obtain salt of sulfuric acid ester of xylan

[51] ii) oxidizing the salt of sulfuric acid ester of xylan with the mixture of H_2SO_4 and 30% H_2O_2 followed by purification of depolymerized crude Pentosan polysulfate of formula (I) or its salt by dissolving in water and filtration through NF membrane system

[52]

[53] The picoline in step (i) is selected from alpha-picoline, Beta-picoline, Gamma-picoline and the like or mixtures thereof.

[54]

[55] The suitable alkali in step (i) is selected from alkali metal salt of carbonate, bi-carbonate, hydroxide or mixtures thereof. The preferable is sodium hydroxide, sodium carbonate, potassium carbonate, potassium hydroxide and the like thereof. The most preferable is sodium hydroxide

[56]

[57] The suitable alcoholic solvent in step (i) is selected from methanol, ethanol, propanol, isopropanol, butanol or mixtures thereof. The most preferable is methanol.

[58]

[59] The isolation of pure pentosan polysulfate of formula (I) or its salt is carried out by the conventional methods comprising of concentrating the filtrate to obtain residue followed by crystallization from alcohol; or concentrating the filtrate to obtain the concentrate followed by spray drying or followed by lyophilizing to obtain pure Pentosan polysulfate of formula (I) or its salt.

[60]

[61] The suitable alcohol for crystallization is selected from methanol, ethanol, propanol, isopropanol, butanol or mixtures thereof. The most preferable is methanol.

[62]

[63] According to present invention, chlorosulfonic acid is added slowly to Beta-picoline at below 35-45°C. The resulting salt is heated to 60-65°C before addition of xylan and is raised the temperature to 75-80°C for 3-4 hrs. After completion of reaction, reaction mixture is cooled to room temperature and water is added and then allows standing for 12 hrs after adding chlorine dioxide solution. Subsequently this solution is allowed to flow into a mixture of methanolic sodium hydroxide solution. The reaction mixture is stirred for 30 min at room temperature. The solution is then adjusted to pH 6.5 to 7.0 by addition of glacial acetic acid. The resulting salt is isolated by filtration followed by washing with methanol and finally drying at 45-50°C to obtain Sodium salt of sulfuric acid ester of xylan.

[64]

[65] Sodium salt of sulfuric acid ester of xylan is dissolved in water and heated to 90-100°C, then addition of preheated mixture of 5N H₂SO₄ and 30% hydrogen peroxide. The reaction mixture is maintained at 90-100°C. After completion of reaction, the reaction mixture is cooled to 25-30°C followed by adjustment of pH 7.5-7.3 with 5N sodium hydroxide solution. Then the reaction mixture is subjected to the NF membrane of cut off molecular weight of 4000-6000 Dalton, filtration. The NF Membrane system is monitored the rejection of lower molecular weight material with HPLC. After the completion of filtration, the concentrate is subjected to water recovery at 50-60°C under reduced pressure. Finally residue is crystallized with methanol to get the pure Pentosan polysulfate sodium. The material is filtered and dried to get pure Pentosan polysulfate sodium.

[66]

[67] For lyophilization, the concentrate is transferred in a single neck round bottom flask and fitted to Lyophilizer (BT4KZL-105) and starts the operation of lyophilization. It takes about 24 hr to complete the lyophilization and provides Pentosan polysulfate sodium.

[68]

[69] For spray drying, the concentrate is subjected to water recovery at 40-50°C. Finally the concentrated solution is subjected to spray drying to get the Pentosan polysulfate sodium having Molecular weight 4000-6000 of Dalton.

[70]

[71] In the present invention, the filtration step as discussed hereinabove is carried out by using NF Membrane system 'PERMA' Pilot Membrane System manufactured by PERMIONIC Membranes Pvt. Ltd., 3/29, 4/19, B.I.D.C., Gorwa Estate, Vadodara-390016, Gujarat, India.

[72]

[73] The filtration of crude Pentosan polysulfate of formula (I) or its salt is carried out in following manner:

[74]

[75] The crude Pentosan polysulfate of formula (I) or its salt is dissolved in water. Feeding the resultant solution and allow it to pass through micron filter membrane system and concentrate flow meter, thereby filtering out the Pentosan polysulfate of formula (I) or its salt with desired molecular weight in the range of 4000 to 6000 Dalton.

[76]

[77] 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 of at least 4000 Dalton.

[78]

[79] Advantages of the present invention over prior art:

[80] i) The present invention provides process which is economical, operationally and industrially applicable.

[81] ii) The present invention provides cheaper as well as less time consuming process for the preparation of Pentosan polysulfate sodium.

[82] iii) The process is simple and easy to handle and does not require special handling care or critical conditions.

[83] iv) The present invention provides high yield of salt of sulfuric acid ester of xylan which is free flow in nature.

[84]

[85] The process of the present invention is described by the following examples, which are illustrative only and should not be construed so as to limit the scope of the invention in any manner.

[86]

[87] **Example-1**

[88]

[89] Chlorosulfonic acid (50 ml) was added slowly to Beta-Picoline (250 ml) while constantly stirring and cooling the solution to 30-40°C. The reaction mixture was then heated to 60-65°C and Xylan (25 gm) was added. While being constantly stirred the viscous solution was maintained at 80-85°C for 3-4 hrs. The reaction mixture cooled to room temperature and water (125 ml) was added and then allowed to stand for 12 hrs after adding chlorine dioxide solution (50 ml). Subsequently this solution was allowed to flow into a mixture of methanolic sodium hydroxide solution (550 ml). The reaction mixture was stirred for 30 min at room temperature. The solution was then adjusted to pH 6.5 to 7.0 by addition of glacial acetic acid. The resulting salt was isolated by filtration and washed with methanol and finally dried at 45-50°C. The yield of salt thus recovered was 60-65 gm.

[90]

[91] To a three neck 3 Lit round bottom flask charged sodium salt of sulfuric acid ester of Xylan (50 gm) in water (150 ml) and heated to 90-100°C, then added the preheated mixture of 5N sulfuric acid (1.5 ml) and 30% hydrogen peroxide (3ml). Monitored the reaction with HPLC, after completion of reaction till average molecular weight came about 4000-6000 Dalton, cooled the reaction mixture and solution was adjusted pH to neutral with dilute sodium hydroxide solution. Then the reaction mixture was subjected to the NF membrane of cut off molecular weight of 4000-6000 Dalton, filtration. The NF Membrane system was monitored the rejection of lower molecular weight material with HPLC. After the completion of filtration, the concentrate was subjected to water recovery at 50-60°C under reduced pressure up to 300ml. Finally residue was crystallized with methanol (225ml) to get the pure Pentosan polysulfate sodium. Filtered the material and dried it at 45-50°C under vacuum. The yield of pure Pentosan polysulfate sodium was 27.5 gm.

[92]

[93] **Example-2**

[94]

[95] Beta-picoline (11t) was added in chlorosulfonic acid (200 ml) slowly at below 35-45°C. The resulting salt was heated to 60-65°C before addition of Xylan (100 gm) and raised the temperature to 80-85°C for 4 hrs. After completion of reaction, reaction mixture was decolorized by 200ml chlorine dioxide with water (500 ml). The decolorized solution was filtered through celite bed and filtrate was neutralized with aqueous methanolic sodium hydroxide solution and crystallized with methanol to get sodium salt of sulfuric acid ester of Xylan (250 gm).

[96]

[97] To a three neck 3 It round bottom flask charged sodium salt of sulfuric acid ester of Xylan (500g) in water (1500ml) and heated to 90-100°C, then added the preheated

mixture of 5N sulfuric acid (25ml) and 30% hydrogen peroxide (250ml). Monitored the reaction with HPLC, after completion of reaction till average molecular weight came about 4000-6000 Dalton, cooled the reaction mixture and solution was adjusted pH to neutral with dilute sodium hydroxide solution. Then the reaction mixture was subjected to the NF membrane of cut off molecular weight of 4000-6000 Dalton, filtration. The NF Membrane system was monitored the rejection of lower molecular weight material with HPLC. After the completion of filtration, the concentrate was subjected to water recovery at 50-60°C under reduced pressure up to 300ml. Finally the concentrate residue was lyophilized by Lyophilizer (BT4KZL-105) for 24 hrs to get the pure Pentosan polysulfate sodium having molecular weight of 4000-6000 Dalton. Filtered the material and dried it at 45-50°C under vacuum. The yield of pure Pentosan polysulfate sodium was 225 gm.

[98]

[99]

Example-3

[100]

[101]

Chlorosulfonic acid (50 ml) was added slowly to Beta-Picoline (250 ml) while constantly stirring and cooling the solution to 30-40°C. The reaction mixture was then heated to 60-65°C and Xylan (25 gm) was added. While being constantly stirred the viscous solution was maintained at 80-85°C for 3-4 hrs. The reaction mixture cooled to room temperature and water (125 ml) was added and then allowed to stand for 12 hrs after adding chlorine dioxide solution (50 ml). If necessary filter it again. Subsequently this solution was allowed to flow into a mixture of methanolic sodium hydroxide solution (550 ml). The reaction mixture was stirred for 30 min at room temperature. The solution was then adjusted to pH 6.5 to 7.0 by addition of glacial acetic acid. The resulting salt was isolated by filtration and washed with methanol and finally dried at 45-50°C. The yield of salt thus recovered was 60-65 gm.

[102]

[103]

To a three neck 3 lt round bottom flask charged sodium salt of sulfuric acid ester of Xylan (500g) in water (1500ml) and heated to 90-100°C, then added the preheated mixture of 5N sulfuric acid (25ml) and 30% hydrogen peroxide (250ml). Monitored the reaction with HPLC, after completion of reaction till average molecular weight came about 4000-6000 Dalton, cooled the reaction mixture and solution was adjusted pH to neutral with dilute sodium hydroxide solution. Then the reaction mixture was subjected to the NF membrane of cut off molecular weight of 4000-6000 Dalton, filtration. The NF Membrane system was monitored the rejection of lower molecular weight material with HPLC. After the completion of filtration, the concentrate was subjected to water recovery at 50-60°C under reduced pressure up to 300ml. Finally the concentrated solution was subjected to spray drying to get the Pentosan polysulfate

sodium having Molecular weight 4000-6000 of Dalton. The yield of pure Pentosan polysulfate sodium was 200 gm.

Claims

[1] **We claim**

[2]

[3] 1. A process for the preparation of Pentosan polysulfate of formula (I) or salt thereof, comprising a step of treating xylan with chlorosulfonic acid in the presence of picoline.

[4]

[5] 2. A process as claimed in claim 1, wherein said picoline is selected from alpha-picoline, Beta-picoline, Gamma-picoline or mixture thereof.

[6]

[7] 3. A process as claimed in claim 1, further comprising of addition of alkali in the presence of alcoholic solvent to obtain salt of sulfuric acid ester of xylan.

[8]

[9] 4. A process as claimed in claim 3, wherein said alkali is selected from alkali metal salt of carbonate, bicarbonate, hydroxide or mixtures thereof.

[10]

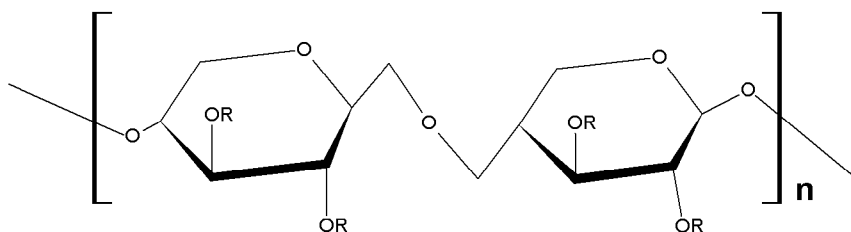
[11] 5. A process as claimed in claim 4, wherein said alkali metal salt is selected from group comprising of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate or mixture thereof.

[12]

[13] 6. A process as claimed in claim 3, wherein said alcoholic solvent is selected from methanol, ethanol, propanol, isopropanol, butanol or mixtures thereof.

[14]

[15] 7. A process for preparation of an Pentosan polysulfate of formula (I)



(I)

or salts thereof, wherein R represents $-\text{SO}_3\text{Y}$, and Y is at least one member selected from the group consisting of H and a pharmaceutically acceptable cation such as sodium and potassium, comprising steps of:

i) treating xylan with chlorosulfonic acid in the presence of picoline 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_2SO_4 and

30% H₂O₂ followed by purification of depolymerized crude Pentosan polysulfate of formula (I) or its salt by dissolving in water and filtration through NF membrane system

[16]

[17]

8. A process as claimed in claim 7, wherein said picoline in step (i) is selected from alpha-picoline, Beta-picoline, Gamma-picoline or mixture thereof.

[18]

[19]

9. A process as claimed in claim 7, wherein said alkali in step (i) is selected from alkali metal salt of carbonate, bicarbonate, hydroxide or mixtures thereof.

[20]

[21]

10. A process as claimed in claim 9, wherein said alkali metal salt is selected from group comprising of sodium hydroxide, sodium carbonate, sodium bi-carbonate, potassium hydroxide, potassium carbonate or mixture thereof.

[22]

[23]

11. A process as claimed in claim 7, wherein said alcoholic solvent in step (i) is selected from methanol, ethanol, propanol, isopropanol, butanol or mixtures thereof.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2009/050001

A. CLASSIFICATION OF SUBJECT MATTER
INV. C08B37/00

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)
C08B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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	US 2 689 848 A (ELFRIEDE HUSEMANN ET AL) 21 September 1954 (1954-09-21) cited in the application examples	1-11
A	US 4 713 373 A (BAYOL ALAIN [FR] ET AL) 15 December 1987 (1987-12-15) claims; examples	1-11
P, A	WO 2008/107906 A (ALEMBIC LTD [IN]; DESHPANDE PANDURANG BALWANT [IN]; LUTHRA PARVEN KUMA) 12 September 2008 (2008-09-12) the whole document	1-11
A	WO 88/00211 A (PHARMACIA AB [SE]) 14 January 1988 (1988-01-14) example 1	1-11



Further documents are listed in the continuation of Box C.



See patent family annex.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2009/050001

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