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- Declarations under Rule 4.17:**
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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF PENTOSAN POLYSULFATE SODIUM

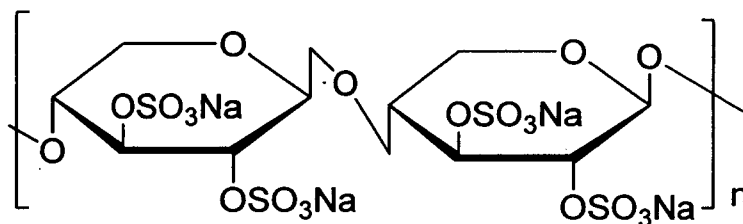
(57) Abstract: The present invention relates to provide an improved process of preparation of Pentosan Polysulfate Sodium of Formula (I) comprising a step of purifying the depolymerized aqueous solution by diluting with excess of water followed by diafiltration through membrane system.



AN IMPROVED PROCESS FOR THE PREPARATION OF PENTOSAN POLYSULFATE SODIUM

FIELD OF INVENTION

5 The present invention discloses an improved process for the preparation of Pentosan Polysulfate Sodium and also disclosed an improved process for the isolation of compound of Formula I.

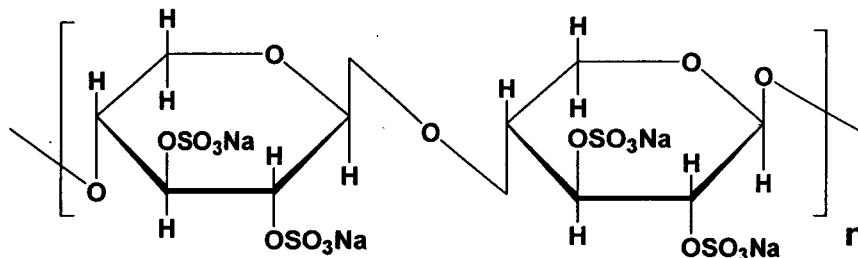


Pentosan Polysulfate Sodium (Formula I)

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BACKGROUND OF THE INVENTION

Pentosan Polysulfate Sodium is chemically known as β -D-Xylan, (1-4), 2,3 -bis (hydrogen Sulfate) sodium salt having molecular range of 4000-6000 Dalton and has the following structural formula:



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Pentosan Polysulfate Sodium

Pentosan Polysulfate Sodium is a semi-synthetically produced heparin like macromolecular carbohydrate derivative which chemically and structurally resembles glycosaminoglycans. It has anticoagulant and fibrinolytic effects. It is a white odorless powder, slightly hygroscopic and soluble in water upto 50% at pH-6.

Pentosan Polysulfate is produced from a chemical solution of polysaccharides (e.g. Xylan) extracted from the bark of the beech tree or other plant sources which is then treated with sulfating agents such as chlorosulfonic acid or sulfonyl chloride and an acid. After sulfation, Pentosan Polysulfate is usually treated with sodium hydroxide to yield the sodium salt. Pentosan Polysulfate is most commonly used as an oral formulation to treat interstitial cystitis in humans and as an injectable drug to treat osteoarthritis in companion animals. It has also been used for treatment of hematomas,

hemorrhoids, frostbites, burns and multiparameter illnesses such as thrombosis and atherosclerosis.

Pentosan Polysulfate is disclosed in US patent no. 2689848. The same patent disclosed the process for the production of salts of sulfuric ester of xylan, the steps comprising oxidizing the aqueous solution of the a salt of sulfuric acid ester of highly polymeric xylan in an aqueous solution of H_2O_2 and H_2SO_4 to depolymerize such highly polymeric xylan ester partially, dialyzing the depolymerized product and fractioning an aqueous mixture of the dialyzate with an organic water miscible solvent to obtain a fraction having a ZD value between 0.0030 and 0.015 (The value of ZD is proportional to the degree of polymerization and consequently, serves as an index of the molecular weight or length of the chain of the xylan sulphuric acid esters) and sulfur content of 13.5 to 17%. The process as disclosed therein does not describe about the molecular weight of product after getting step-2 or even of final product. The patent only characterized the final product by ZD value and sulfur content.

US 4713373 disclosed novel xylan sulfates having a sulfation degree between 1.5 and 2.0 and an apparent molecular weight from about 2000-5000. The process disclosed the ultra filtration technique for the preparation of above claimed compound. Moreover the process does not provide the desired pentosan polysulfate sodium with molecular weight of 4000 to 6000 Dalton specifically.

WO2008107906 disclosed process for the preparation of Pentosan Polysulfate and an amorphous form of Pentosan Polysulfate sodium with molecular weight of about 3000 to 10000 Dalton. In the process xylan treated 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. Oxidizing the salt with the mixture of H_2SO_4 and 30% H_2O_2 to obtain depolymerized crude pentosan polysulfate Sodium of Formula (I). Purifying depolymerized crude pentosan polysulfate sodium by filtration through NF membrane system. Lyophilizing the product to obtain amorphous form of pentosan polysulfate sodium. Moreover the process does not provide the desired pentosan polysulfate sodium with molecular weight of 4000 to 6000 Dalton specifically

WO2009087581 disclosed process for the preparation of Pentosan Polysulfate or salt thereof comprising a step of 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. Oxidizing the salt with the mixture of

H₂SO₄ and 30% H₂O₂ to obtain depolymerized crude pentosan polysulfate of Formula (I) or its salt, purifying depolymerized crude pentosan polysulfate of Formula (I) or its salt by filtration through NF membrane system.

WO 2009047699 also described a process for the preparation of an amorphous form of Pentosan Polysulfate Sodium comprising steps of dissolving crude pentosan polysulfate sodium having a molecular weight of 4000 to 6000 Dalton in water (step I) followed by spray drying the solution to obtain amorphous Pentosan Polysulfate Sodium.

Thus the prior processes described above for the preparation of Pentosan Polysulfate Sodium is tedious and costly. So, there is a need in the art to develop a process for preparation of Pentosan Polysulfate Sodium which provides good yield, simple, convenient, economical and easily applicable at an industrial scale.

We herein disclosed a purification method of Pentosan Polysulfate Sodium Formula (I) by diluting the aqueous solution with excess of water followed by Dia-filtration through membrane system and isolation of resulting mixture provides high yield with desired molecular weight of 4000-6000 Dalton.

OBJECTS OF THE INVENTION

An object of the present invention is to provide an improved process for preparing Pentosan Polysulfate Sodium.

It a further object of the present invention to provide a process for purification of Pentosan Polysulfate Sodium using suitable technique.

It a further object of the present invention to provide an improved process for isolation of Pentosan Polysulfate Sodium using suitable solvents.

The above and other embodiments are further described in the following paragraphs.

DETAILED DESCRIPTION

The above and other objects of the present invention are achieved by an improved process for preparing Pentosan Polysulfate Sodium of Formula (I), comprising steps of:
i) reacting xylan with chlorosulfonic acid in the presence of pyridine followed by addition of alkali in the presence of alcoholic solvent to obtain sodium salt of sulfuric acid ester of xylan.

ii) depolymerizing the salt of sulfuric acid ester of xylan with the mixture of H_2SO_4 and an oxidizing agent to obtain depolymerized crude Pentosan Polysulfate Sodium of Formula (IV)

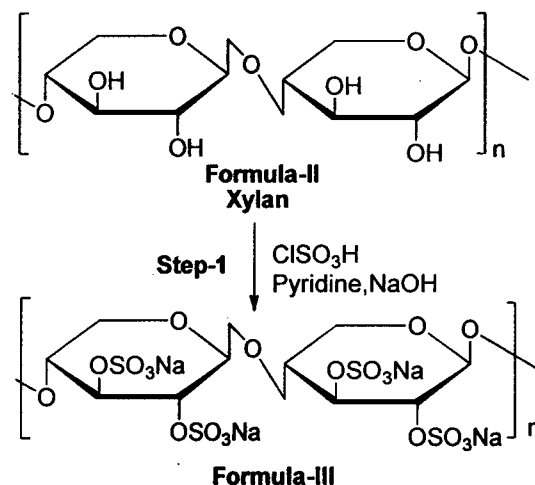
iii) purifying the depolymerized aqueous solution of Formula (IV) by diluting with excess of water followed by diafiltration through suitable membrane system

iv) isolation of the product obtained in the step-(iii) from suitable solvents to obtain pure Pentosan Polysulfate Sodium of Formula (I)

Accordingly, the invention provides a process for the preparation of Pentosan Polysulfate sodium of Formula (I) as depicted following steps:

The steps comprises:

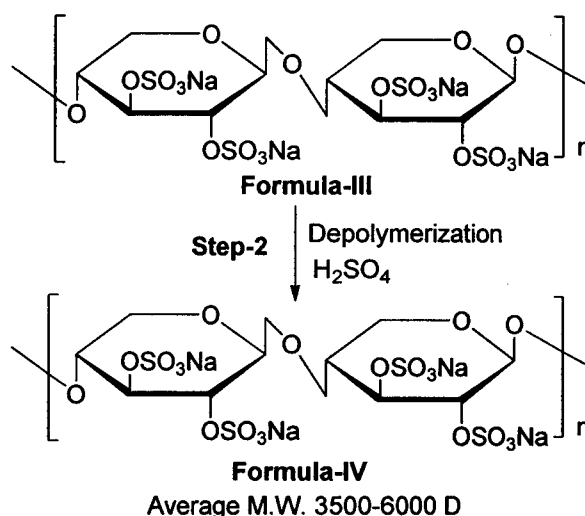
i) reacting xylan with chlorosulfonic acid in the presence of pyridine followed by addition of suitable alkali in the presence of suitable alcoholic solvent to obtain sodium salt of sulfuric acid ester of xylan Formula III



The suitable solvent used in **step-(i)** may be selected from (C_1 - C_5) alcohols such as methanol, ethanol, propanol, isopropanol, butanol or mixtures thereof. The most preferably is methanol.

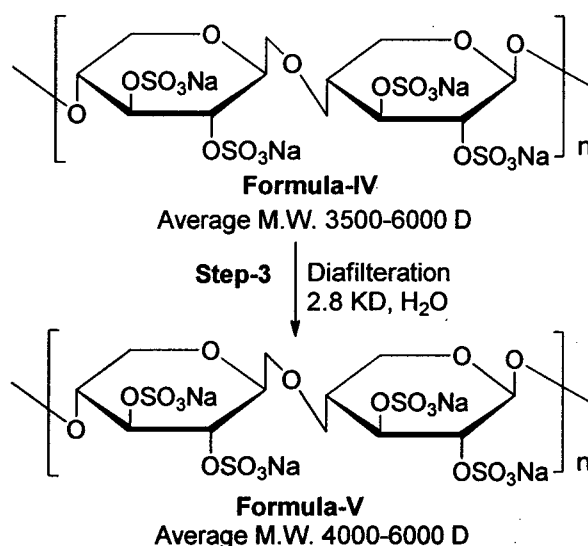
The suitable alkali used in **step-(i)** is selected from alkali metal salt of carbonates, bicarbonates, hydroxide or mixtures thereof. The most preferably is sodium hydroxide.

ii) reacting the compound of Formula (III) with a mixture of suitable oxidizing agents and H_2SO_4 to obtain the depolymerized compound of Formula (IV)



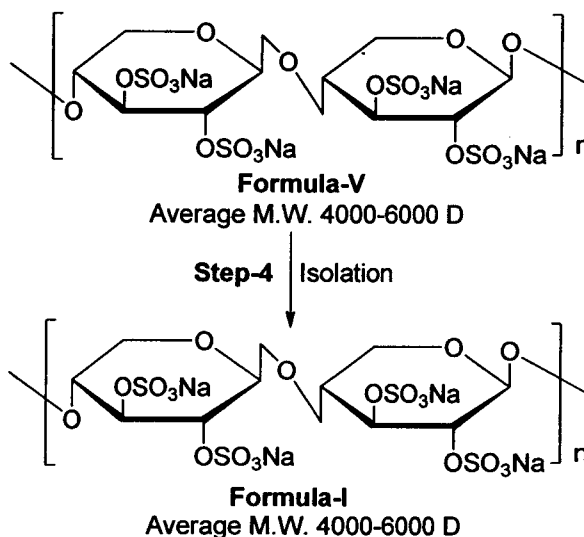
The suitable oxidizing agent used in **step-(ii)** may be selected from peroxides such as hydrogen peroxides and the like; halogenated oxidizing agents such as sodium hypochlorite, sodiumhypobromide & the like; metallic oxidizing reagents such as osmium tetroxide, chromates, permanganates, tungstates & the like; periodic acids or salts of periodic acids such as sodium metaperiodate, potassium metaperiodate & the likes either independently or in a suitable mixtures thereof.

- iii) purifying the depolymerized aqueous solution of Formula (IV) obtained in **step-(ii)** by diluting with excess of water to 0.25 – 2.5 % followed by Dia-filtration through suitable membrane system to obtain compound of formula (V)



- Suitable diafiltration membranes as are known in the art may be used. The diafiltration can be done continuously or discontinuously. Such techniques are well within the ability of a skilled person. For the present invention the suitable membrane

- system in the filtration step as discussed herein is carried out by using pure flow-U30S ultra filtration membrane. This advanced thin film composite ultra filtration membrane has a filtration range of less than 4 KD, preferably 1 KD - 4 KD and more preferably 2.8 KD nominal MWCO (Molecular wt. cut off). It removes most of bivalent ions,
- 5 inorganic salts and unreacted low molecules of solute.
- iv) isolation of the compound of Formula (V) in suitable solvent to obtain compound of Formula (I)



The suitable solvent for isolation used in **step-(iv)** may be selected from

10 hydrocarbons such as toluene, xylene, n-heptane, cyclohexane, n-hexane; nitriles such as acetonitrile, propionitrile; (C₁ to C₅) alcohols such as methanol, ethanol, isopropanol and the like; ketones such as acetone, methyl ethyl ketones, methyl isobutyl ketones & the like; amides such as N,N-dimethyl acetamides, dimethylformamide N-methyl-2-pyrrolidinone and the likes either independently or suitable mixtures thereof.

15 Thus, the present invention also encompasses a process for the purification of compound of formula (IV). Purification of compound of the Formula (IV) followed by Diafiltration through suitable membrane system removes most of bivalent ions, inorganic salts and unreacted low molecules of solute. So, one of the significance of the present process by using the purification technique is to get the desired molecular

20 weight of pure compound of Formula (I) in a pure form.

The process of the present invention is further described by the following non-limiting examples, which provides the preferred mode of carrying out the process of the present invention. It is to be appreciated that several alterations, modifications, optimizations of the processes described herein are well within the scope of a person

skilled in the art should be construed to be within the scope of the present inventive concept as is disclosed anywhere in the specification.

Example-1

Process for the preparation of Pentosan Polysulfate Sodium (Formula III)

5 Chlorosulfonic acid (350 g) was added slowly in pyridine (870 g) at 25 to 60°C. The solution was maintained for 15 minutes. Xylan (100 g) was added at 25-60 °C. The reaction mixture was heated at 80-85°C. The reaction mixture was stirred for next 2-4 hours at 80-85°C. The reaction mixture was cool down to 55-60 °C. Methanol (1600 mL) was slowly added. The mass was cooled at 25-35°C and stirred for 1-2 hours. The
10 solid mass was filtered and washed with methanol. The wet cake was taken into RO (Reverse Osmosis) water and stirred to get clear solution. Previously prepared sodium chlorite (28 g) and Conc. hydrochloric acid (22 mL) solution was added into above solution in 30 minutes and stirred for 4-6 hours and quenched into methanolic sodium hydroxide solution and was stirred for 1-3 hours at 25-35°C. To the reaction mixture
15 acetic acid was added to get pH 6 to 7 and stirred with 1 hour. The solid mass was filtered and washed with methanol. The wet cake was taken into methanol (500 mL) and stirred for next 1 hour. The solid mass was filtered and washed with methanol. The wet solid was dried at 50-55°C under vacuum to get 180 to 240 g product). GPC average molecular weight. 30000 to 50000D (Yield: 70 to 94 %).

Example-2

Process for the preparation of Pentosan Polysulfate Sodium (Formula IV)

In a 2-lit R. B. Flask water (500 mL) and Pentosan Polysulfate Sodium (Formula III) (200 g) were added. The solution was heated to 95-100°C. The solution of
25 25 to 33% hydrogen peroxide (15.85 g), sulfuric acid (0.9 g) and RO water (100 mL) was added in 30 minutes at 95-100 °C. The reaction mixture was further stirred at 95-100°C next 4 to 7 hours (till one achieves average M.W. 3500 to 6000 D). The reaction mixture was cooled to 15 to 20°C. Activated carbon (5.0 g) and 30% sodium hydroxide solution was added in to reaction mass below 30°C. The reaction mixture was stirred for next 4-6 hours, adjust pH 6 to 7 with dilute acetic acid. The mass was filtered and
30 collected aqueous solution for next step (Diafiltration) without isolation of product. GPC average molecular weight 3500 to 6000 D.

Example-3

Process for the preparation of Pentosan Polysulfate Sodium (Formula V)

In a 50-lit HDPE Tank equipped with mechanical stirrer, RO water (40 L) and Pentosan Polysulfate Sodium (Formula IV) solution obtained in example-2 above, (approx 1200 mL) were charged. The reaction mixture was stirred for 15 minutes. The solution was passed through 2.8 KD membrane and removed free sulfate and lower molecular weight product were collected in permeate HDPE Tank. After removing sulfate salt and lower molecular weight product, solution was passed through RO (Reverse Osmosis) membrane to get concentrated solution by removing the excess of water from the solution. Finally the product in retanate (approx. 7 to 8% solution, 500 to 550 mL) was used for next step without isolation of product. GPC average molecular weight 4000 to 6000 D.

Example-4

Process for the preparation of Pentosan Polysulfate Sodium (Formula I)

In a 2-lit R. B. Flask Pentosan Polysulfate Sodium (Formula V) obtained in example-3 above (550 mL) was added. Water was distilled out below 65°C under vacuum. Finally leaving behind approximately 130 to 150 mL residual product. The reaction mixture was cooled to 25 to 30°C. Methanol (800 mL) was added slowly over 3-4 hours. The solid mass was stirred for next 3 hours. The solid was filtered and washed with methanol. The product was dried at 60 to 65°C for 10 hours to get 60 to 70 g pure product. GPC average molecular weight 4000 to 6000 D. (Yield: 90 to 98 %)

Further aspect of the present invention is to provide an improved process of isolation method for preparation of Pentosan polysulfate Sodium of Formula (I)

Example-5

To a 2-lit R. B. Flask Pentosan Polysulfate Sodium (80 g) and Cyclohexane (800 mL) was charged. The solution was heated at 80°C for 1 hour. Cyclohexane (400 mL) was distilled at 80 to 85°C. Solution was cooled down to 25-35°C and stirred for 30 min. The solid product was filtered and washed with Cyclohexane. The wet solid was dried at 65 to 75°C to get product 72 to 80 g (Yield: 90 to 100 %).

Example-6

To a 50 mL R. B. flask Pentosan Polysulfate Sodium (2 g) was dissolved in RO water under stirring at 25-35°C. Acetonitrile was added dropwise in 1 hour. The reaction mixture was stirred at 25-35°C for next 2 hours. The solid product was filtered and washed with Acetonitrile. The wet solid was dried at 65 to 75°C to get product 1.70 g (Yield: 85 %).

Example – 7

To a 50 mL R. B. flask Pentosan Polysulfate Sodium (2 g) was dissolved in RO water under stirring at 25-35°C. Acetone was added dropwise in 1 hour. The reaction mixture was stirred at 25-35°C for next 2 hours. The solid product was filtered and washed with Acetone. The wet solid was dried at 65 to 75°C to get product 1.78 g. (Yield: 89 %).

Example – 8

To a 50 mL R. B. flask Pentosan Polysulfate Sodium (2 g) was dissolved in RO water under stirring at 25-35°C. N,N-dimethyl acetamide was added dropwise in 1 hour. The reaction mixture was stirred at 25-35°C for next 2 hours. The solid product was filtered and washed with N, N-dimethyl acetamide. The wet solid was dried at 65 to 75°C to get product 1.62 g (Yield: 81 %).

Example – 9

To a 50 mL R. B. Flask Pentosan Polysulfate Sodium (2 g) was dissolved in RO water under stirring at 25-35°C. Ethanol was added dropwise in 1 hour. The reaction mixture was stirred at 25-35°C for next 2 hours. The solid product was filtered and washed with ethanol. The wet solid was dried at 65 to 75°C to get product 1.82 g. (Yield: 91 %).

Example – 10

To a 50 mL R. B. flask Pentosan Polysulfate Sodium (2 g) was dissolved in RO water under stirring at 25-35°C. Isopropanol was added dropwise in 1 hour. The reaction mixture was stirred at 25-35°C for next 2 hours. The solid product was filtered and washed with isopropanol. The wet solid was dried at 65 to 75°C to get product 1.69 g (Yield: 84.5 %).

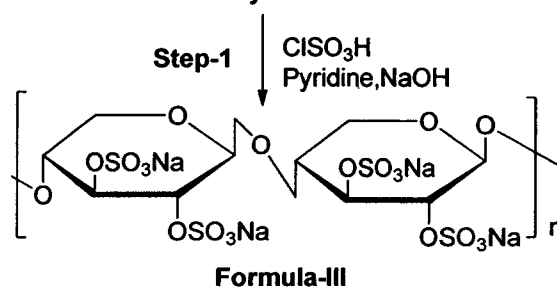
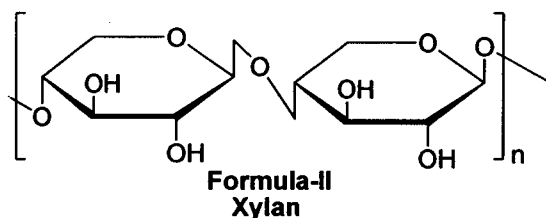
Example – 11

To a 50 mL R. B. flask Pentosan Polysulfate Sodium (2 g) was dissolved in RO water under stirring at 25-35°C. 1-propanol was added dropwise in 1 hour. The reaction mixture was stirred at 25-35°C for next 2 hours. The solid product was filtered and washed with 1-propanol. The wet solid was dried at 65 to 75°C to get product 1.83 g (Yield: 91.5 %).

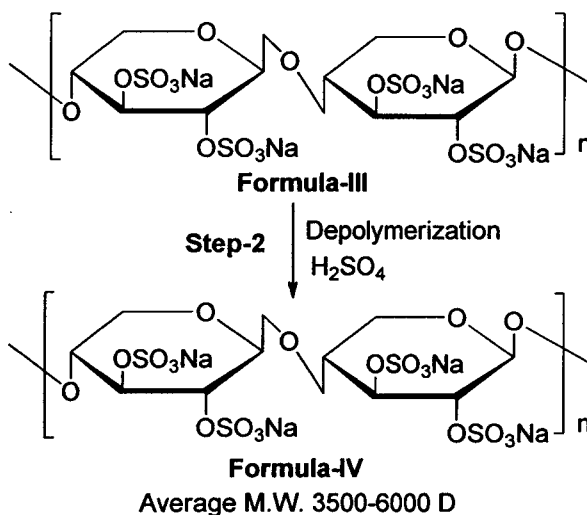
We claim:

1. A process for the preparation of Pentosan Polysulfate Sodium of Formula (I) comprising steps of:

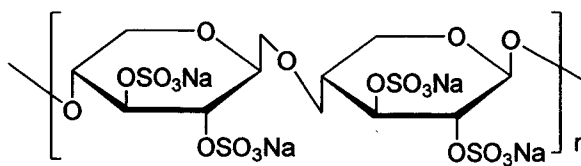
- 5 i) reacting xylan with chlorosulfonic acid in the presence of pyridine followed by addition of suitable alkali in the presence of suitable alcoholic solvent to obtain sodium salt of sulfuric acid ester of xylan Formula (III)



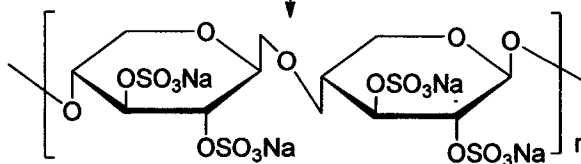
- ii) reacting the compound of Formula (III) with a mixture of suitable oxidizing agents and H_2SO_4 to obtain the depolymerized compound of Formula (IV)



- 10 iii) purifying the depolymerized aqueous solution of Formula (IV) obtained in step (ii) by diluting with excess of water followed by diafiltration through suitable membrane system to obtain compound of Formula (V)

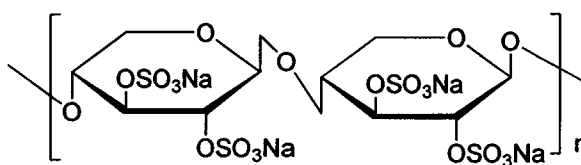
**Formula-IV**

Average M.W. 3500-6000 D

Step-3Diafiltration
2.8 KD, H₂O**Formula-V**

Average M.W. 4000-6000 D

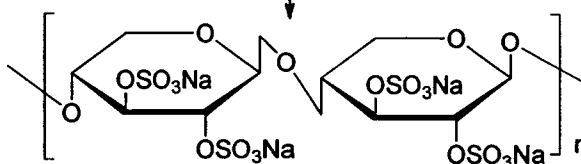
- iv) isolation of the compound of Formula (V) in suitable solvent to obtain compound of Formula (I)

**Formula-V**

Average M.W. 4000-6000 D

Step-4

Isolation

**Formula-I**

Average M.W. 4000-6000 D

- 5 2. The process for the preparation of compound of Formula (I) as claimed in claim 1 step (i), wherein the suitable alkali is selected from alkali metal salt of carbonates, bicarbonates, hydroxide or mixtures thereof.
3. The process for the preparation of compound of Formula (I) as claimed in claim 1 step (i), wherein the suitable solvent selected from alcohols such as methanol, ethanol, propanol, isopropanol, butanol or mixtures thereof.
- 10 4. The process for the preparation of compound of Formula (I) as claimed in claim 1 step (ii), wherein the suitable oxidizing agent selected from peroxides, halogenated oxidizing agents, metallic oxidizing reagents, periodic acids or salts of periodic acids or in suitable mixtures thereof.

5. The process for the preparation of compound of Formula (I) as claimed in claim 1 step (iii), wherein the purification of depolymerized aqueous solution of formula (IV) obtain in step-2 by diluting with excess of water to 0.25 – 2.5 % followed by diafiltration membrane system.
- 5 6. The process for the preparation of compound of Formula (I) as claimed in claim 1 step (iii), wherein the diafiltration membrane is having a filtration capacity of less than 4 KD, preferably 1 KD - 4 KD.
7. The process as claimed in claim 6, wherein the diafiltration membrane having a filtration capacity of preferably 2.8 KD.
- 10 8. The process for the preparation of compound of Formula (I) as claimed in claim 1 step (iv), wherein the suitable solvent for isolation is selected from hydrocarbons, nitriles, (C₁ to C₅) alcohols, ketones, amides and suitable mixtures thereof.
9. The process as claimed in claim 8, wherein the hydrocarbons are selected from toluene, xylene, n-heptane, cyclohexane, n-hexane and suitable mixtures thereof.
- 15 10. The process as claimed in claim 8, wherein the nitriles are selected from acetonitrile, propionitrile and suitable mixtures thereof.
11. The process as claimed in claim 8, wherein the alcohols are selected from methanol, ethanol, isopropanol, butanol and suitable mixtures thereof.
12. The process as claimed in claim 8, wherein the ketones are selected from
20 acetone, methyl ethyl ketones, methyl isobutyl ketones and suitable mixtures thereof.
13. The process as claimed in claim 8, wherein the amides are selected from N,N-dimethyl acetamides, dimethylformamide N-methyl-2-pyrrolidinone and suitable mixtures thereof.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2011/000393

A. CLASSIFICATION OF SUBJECT MATTER
INV. C08B37/00
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 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	WO 2008/107906 A1 (ALEMBIC LTD [IN]; DESHPANDE PANDURANG BALWANT [IN]; LUTHRA PARVEN KUMA) 12 September 2008 (2008-09-12) cited in the application	1-13
Y	page 3, lines 12-16; example 1 -----	1-13
X	WO 2010/000013 A1 (PARNELL LAB AUST PTY LTD [AU]; STAJIC VLADIMIR [AU]; CHEETHAM NORMAN []) 7 January 2010 (2010-01-07) page 26, line 31 - page 27, line 12; claims 60,64 ----- -/-	1-13



Further documents are listed in the continuation of Box C.



See patent family annex.

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"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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Date of the actual completion of the international search

17 October 2011

Date of mailing of the international search report

08/11/2011

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2011/000393

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/087581 A1 (ALEMBIC LTD [IN]; DEO KESHAV [IN]; PRASAD ASHOK [IN]; PATEL HITESH [IN]) 16 July 2009 (2009-07-16) cited in the application	1-13
Y	paragraphs [0016], [0024]; claim 1; example 1	1-13
Y	----- US 5 145 841 A (CULLIS-HILL DAVID [AU] ET AL) 8 September 1992 (1992-09-08) column 13, lines 30-51,63; claim 3	1-13
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