CRYSTALLINE GLUCOSAMINE SULPHATE METAL SALTS AND PROCESSES FOR PREPARING THE SAME
KRISTALLINE GLUKOSAMINSULFATMETALLSALZE UND VERFAHREN ZU DEREN HERSTELLUNG
SELS METALLIQUES DE SULFATE DE GLUCOSAMINE CRISTALLIN ET PROCESSUS DE PREPARATION DE CES SELS

Described herein is a crystalline glucosamine sulphate metal salt which is a rare earth metal salt, in particular a rare earth metal salt containing a metal of the lanthanide group.

The invention also relates to a process for preparing said salt.

This preparation is carried out via a process which involves the crystallisation of a solution containing a glucosamine salt and a metal salt.

The metal salts of the lanthanide group are particularly preferred for the preparation of the salt of the invention.

The invention also relates to the use of said salt in the treatment of at least one disease or disorder which is the result of a reduced concentration in the organism of a glucosamine salt.

Mukhopadhyay, Triptikumar
Bhat, Ravi Gajanan
Sreekumar, E. S.

Representative: Oxley, Rachel Louise
Mewburn Ellis,
York House,
23 Kingsway
London WC2B 6HP (GB)

References cited:
EP-A2- 0 214 642
Description

Field of the invention:

[0001] The present invention relates to novel crystalline glucosamine sulphate metal salts for use in the treatment of acute and chronic forms of rheumatic and arthritic diseases and of all the pathological conditions originating from metabolic disorders of the osteo-articular tissues. More particularly, the present invention relates to novel crystalline glucosamine sulphate metal salts having low metal content wherein the metal may be either sodium or potassium. The present invention further relates to a solution-based and a solvent-free process for the preparation of the novel crystalline glucosamine sulphate metal salts having low metal content and to pharmaceutical compositions comprising the novel crystalline glucosamine sulphate metal salts having low metal content.

Background of the invention:

[0002] Both acute and chronic forms of rheumatic and arthritic diseases are associated with joint pain and inflammation and hence cause a lot of distress to patients suffering from such a disease. Osteoarthritis, a degenerative joint disease, is the most common form of arthritis. This disease is mostly prevalent in older people. The standard therapy for the treatment of osteoarthritis mostly includes the use of aspirin, corticosteroids, non-steroidal anti-inflammatory drugs (NSAID’s) e.g. ibuprofen, naproksen etc. and the most recent COX-2 inhibitors e.g. rofecoxib, celecoxib. However, all these drugs are associated with one or more side effects which may also be long term in some cases. An ideal treatment of osteoarthritis must effectively control pain as well as slow down or reverse the degeneration of joints and also cause fewer side effects. In the early 1970’s it was discovered that a naturally occurring substance namely glucosamine can slow down the progression of osteoarthritis and also alleviate the pain associated with this disease [Kurtz J. F. et. al.: Z. Allgemeinmed 46(21): 1090-1095 (1970); Vinel P. et. al.: Therapeutique, 47(10): 839-843 (1971)].


[0004] Although highly effective, glucosamine sulphate is unstable in its free form due to its highly hygroscopic nature and also the amino group gets oxidised readily. Hence, oral formulations such as capsules, tablets of this drug contain anti-oxidants. However, this does not solve the problem of its hygroscopic nature. To overcome this problem glucosamine sulphate is usually combined with metal salts preferably sodium or potassium salts. Mixed salts of glucosamine hydrochloride with alkali metals or alkaline earth metal sulphates such as sodium or potassium sulphates are well known in the literature. Usually glucosamine sulphate metal salts are prepared starting from either glucosamine hydrochloride or the glucosamine free base.


[0006] Preparation of mixed salt of glucosamine sulphate and sodium chloride is described in U.S. Patent No. 4642340 wherein previously prepared glucosamine sulphate is treated with sodium chloride solution followed by addition of liquid precipitant to precipitate the mixed salt. This process involves direct use of glucosamine sulphate which has to be strictly maintained in an environment with a relative humidity not greater than 30 % and a temperature not more than 15°C, thus one has to take proper precautions in this case.

[0007] EP 214642 describes a process for the preparation of mixed salt of glucosamine sulphate and potassium chloride starting from glucosamine free base wherein solution of the glucosamine free base in water is treated with concentrated sulphuric acid and to the resulting solution potassium chloride is added. The metal salt is precipitated out from the solution by adding liquid precipitant. This is a lengthy process since it first involves liberation of free glucosamine base from glucosamine hydrochloride followed by the subsequent reaction steps. Also this process results in low yield.

[0008] U.S. Patent No. 5847107 teaches a process for preparing crystalline form of mixed glucosamine sulphate salt wherein glucosamine hydrochloride is treated with a metal sulphate e.g. sodium sulphate in an aqueous solvent and the stable crystalline form of glucosamine sulphate is precipitated from the solution by adding a liquid precipitant.

[0009] U.S. Patent Nos. 5843923 and 5902801 follow the same method for the preparation of glucosamine sulphate metal salts, however, in these cases the process avoids addition of liquid precipitating agent but involves freeze drying of the solution resulted from the reaction of glucosamine hydrochloride and metal sulphate.

[0010] Although, the mixed glucosamine sulphate metal salts, the products described in U.S. Patent Nos. 5847107 and 5902801, are suitable for treatment of rheumatic and arthritic diseases, they have proportion-
ately high metal content e.g. sodium or potassium. Rheumatic and arthritic diseases are mostly prevalent in older people who are also at higher risk of other diseases such as hypertension and cardiovascular diseases. Hyperkalemia (high potassium level) is also a serious electrolyte disorder which appears to develop more commonly in the aged patients. In such cases the patients are advised a restricted sodium or potassium intake depending on the case history. Also people suffering from renal dysfunction require low sodium intake. Therefore, administration of glucosamine sulphate mixed salts having proportionately high sodium or potassium content may not be advisable to those rheumatic or arthritic patients who are also having history of hypertension, cardiovascular diseases, renal dysfunction, hyperkalemia and other diseases which require restricted sodium or potassium intake. Taking into account the proven safety and efficacy of glucosamine sulphate over other conventional drugs for arthritic diseases, there is a need to develop a specific form of glucosamine sulphate which can also be safely administered to sodium or potassium sensitive patients.

Objects of the invention:

- The primary object of the invention aims at providing novel crystalline glucosamine sulphate metal salts having low metal content, useful in the treatment of acute and chronic forms of rheumatic and arthritic diseases and of all the pathological conditions originating from metabolic disorders of the osteo-articular tissues.
- Another object of the present invention is to provide novel crystalline glucosamine sulphate metal salts having low metal content, wherein the metal may be either sodium or potassium, as efficacious and safer remedy to sodium or potassium sensitive arthritic patients.
- Yet another object of the invention is to provide a solution-based process and a solvent-free process for the preparation of the crystalline glucosamine sulphate metal salts having low metal content.
- A further object of the invention is to provide a pharmaceutical composition containing the novel crystalline glucosamine sulphate metal salts having low metal content.

Summary Of The Invention:

Thus in accordance with the present invention there is provided novel crystalline glucosamine sulphate metal salts having low metal content, which are represented by the following formula I:

\[
\text{CH}_3\text{OH} \quad + \quad \text{CH}_2\text{OH} \quad + \quad \text{H}_2\text{O} \\
\text{MHSO}_4 \cdot \text{2Cl}^- \\
\text{I} \\
\begin{align*}
\text{M} &\text{ represents Na or K (hereinafter referred to as compound I).} \\
\text{In compound I (M=Na), the amount of sodium content is only 4.22 % as against 8 % of sodium that is present in the mixed glucosamine sulphate sodium salt, the product described in the prior art (U. S. Patent Nos. 5 847 107 and 5 902 801). Also the potassium content in compound I (M=K) is only 7.16 % as against 12.9 % of potassium that is present in the product described in U. S. Patent Nos. 5 847 107 and 5 902 801.} \\
\text{Thus, the compounds of formula I of the present invention are significantly advantageous over those reported in the prior art with respect to their usefulness specifically in the treatment of arthritic patients who are sodium and potassium sensitive.} \\
\text{According to a further aspect of the present invention there is provided a solution-based process for the preparation of compounds of formula I, which comprises the steps of:} \\
i. reacting glucosamine hydrochloride and a metal hydrogen sulphate selected from sodium hydrogen sulphate and potassium hydrogen sulphate in stoichiometric ratio in a solvent; 
ii. precipitating the resulting glucosamine sulphate metal salt in the presence of a water miscible organic solvent; 
iii. filtering the reaction mass to obtain the compound of formula I.
\text{In the above process the solvent used in the reaction step (i) can be water. Also, the said steps of precipitating the resulting glucosamine sulphate metal salt can comprise either adding the resulting solution of step (i) to a water-miscible organic solvent or the water-miscible organic solvent to the resulting solution of step (i), followed by stirring the resulting solution obtained for a predetermined period of time. This well stirred reaction mass is then filtered to obtain the desired compound of}
According to another aspect of this invention, prior to the step of filtering the reaction mass in step (iii) the reaction mass is allowed to cool for a predetermined period of time and then filtered to obtain the desired compound of formula I.

The term stoichiometric ratio in the solution-based process refers to 2:1 ratio of glucosamine hydrochloride to the metal hydrogen sulphate.

The water-miscible organic solvent may be selected from ethanol, propanol, isopropanol, acetone, acetonitrile, tetrahydrofuran, dioxane, dimethylformamide and the like. The most preferred solvent is isopropanol.

The water-miscible organic solvent is taken in a proportion of four to ten parts by volume with respect to solution of step (i). Preferably solution of step (i) is added to six times its volume of the water-miscible solvent.

The time period required for the addition might vary from five minutes to four hours, preferably one hour.

The addition of the resulting solution of step (i) to the water-miscible organic solvent or the addition of the water-miscible organic solvent to the resulting solution of step (i) is carried out room temperature ranging from 17°C to 35°C preferably 20 to 25°C.

The resultant mixture containing the precipitate is stirred for a period of about 2 to 6 hours preferably 4 hours at room temperature ranging from 17°C to 35°C preferably 20 to 25°C. This well stirred reaction mass is then filtered under vacuum. The product is washed to obtain glucosamine sulphate salt as white solid and is further dried at 25°C under vacuum.

According to another aspect of this invention, this well stirred mass may be cooled to 0-20°C, preferably 0-10°C, more preferably 0-5°C, and maintained at this temperature for about 1-24 hours preferably 1-20 hours more preferably 1-16 hours. The reaction mass is then filtered under vacuum. The product is washed to obtain glucosamine sulphate salt as white solid and is further dried at 25°C under vacuum.

According to another aspect of this invention, there is provided a solvent-free process for the preparation of compounds of formula I, which comprises pulverizing a mixture of glucosamine hydrochloride and a metal hydrogen sulphate in a stoichiometric ratio at ambient temperature over a predetermined period of time.

The term stoichiometric ratio in the solvent-free process refers to 2:1 ratio of glucosamine hydrochloride to a metal hydrogen sulphate.

The term ambient temperature in the solvent-free process refers to room temperature ranging from 17°C to 35°C, preferably 20 to 25°C.

The pulverization of the mixture is carried out by using an appropriate device such as a ball mill, a multi mill, a hammer mill and the like; or a mortar and pestle. Preferably mortar and pestle is used for the pulverization.

The pulverization is carried out over a period ranging from 0.2 hours to 2 hours, preferably 0.5 hours to 1 hour.

Compounds I according to present invention are stable at ambient temperature and humidity. The yield of the product is between 75% to 85%, when the solution-based process is employed. The yield of the product is between 97% to 99.5%, when the solvent-free process is employed.

The compounds of formula I of the present invention are suitable for use in the treatment of both acute and chronic forms of rheumatic and arthritic diseases, in particular osteoarthritis and generally, of all pathological conditions originating from metabolic disorders of the osteo-articular tissues.

The compounds of the present invention may be administered preferably in the form of oral formulations such as tablets or capsules or in injectable form. Other forms of formulations containing the compounds of the present invention are also included within the scope of this invention.

Thus, in a further aspect of the present invention there is provided a pharmaceutical composition comprising compound I of the present invention. The pharmaceutical composition according to the present invention may be prepared by standard techniques by mixing the compound I with one or more pharmaceutically acceptable excipients and/or auxiliaries such as fillers, emulsifiers, lubricants, masking flavour colorants or buffer substances, and converting the mixture into a suitable pharmaceutical form such as tablets, coated tablets, capsules or a suspension or solution suitable for parenteral administration.

The scope and objects of the present invention may further be illustrated by the following examples, which may not be considered to be limiting the invention in any manner.

**Example 1:**

Preparation of glucosamine sulphate sodium salt (low sodium content)

Glucosamine hydrochloride (6.45 g, 0.03mol) and sodium hydrogen sulphate (1.8 g, 0.015mol) were taken in a flask and dissolved in water (25 ml). The resulting solution was added dropwise to vigorously stirred isopropanol (150 ml) at room temperature over a period of one hour. The contents in the flask were further stirred for 4 hrs and then kept at 0°C-5°C for 16 hrs. The precipitate was filtered under vacuum (150 mm Hg). The product was washed twice (each time with 25 ml of isopropanol). Glucosamine sulphate salt was obtained as white solid and was further dried at 25°C under vacuum (2mm Hg).

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<td>Melting Point</td>
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Example 2:
Preparation of glucosamine sulphate potassium salt (low potassium content)

Glucosamine hydrochloride (6.45 g, 0.03 mol) and potassium hydrogen sulphate (2.040 g, 0.015 mol) were taken in a flask and dissolved in water (25 ml). The resulting solution was added dropwise to vigorously stirred isopropanol (150 ml) at room temperature over a period of one hour. The contents in the flask were further stirred for 4 hrs and then kept at 0°C-5°C for 16 hrs. The precipitate was filtered under vacuum (150 mm Hg). The product was washed twice (each time with 25 ml of isopropanol). Glucosamine sulphate salt was obtained as white solid and was further dried at 25°C under vacuum (2mm Hg).

Example 3:
Preparation of glucosamine sulphate sodium salt (low sodium content)

Glucosamine hydrochloride (6.45 g, 0.03 mol) and sodium hydrogen sulphate (1.8 g, 0.015 mol) were taken in a flask and dissolved in water (25 ml). The resulting solution was added dropwise to vigorously stirred isopropanol (150 ml) at room temperature over a period of one hour. The contents in the flask were further stirred for 4 hrs and then kept at 0°C-5°C for 16 hrs. The precipitate was filtered under vacuum (150 mm Hg). The product was washed twice (each time with 25 ml of isopropanol). Glucosamine sulphate salt was obtained as white solid and was further dried at 25°C under vacuum (2mm Hg).

Example 4:
Preparation of glucosamine sulphate sodium salt (low sodium content)

Glucosamine hydrochloride (6.45 g, 0.03 mol) and sodium hydrogen sulphate (1.8 g, 0.015 mol) were taken in a flask and dissolved in water (25 ml). The resulting solution was added dropwise to vigorously stirred isopropanol (150 ml) at room temperature over a period of one hour. The contents in the flask were further stirred for 4 hrs and then kept at 0°C-5°C for 4 hrs. The precipitate was filtered under vacuum (150 mm Hg). The product was washed twice (each time with 25 ml of isopropanol). Glucosamine sulphate salt was obtained as white solid and was further dried at 25°C under vacuum (2mm Hg).

Example 5:
Preparation of glucosamine sulphate sodium salt (low sodium content)

Glucosamine hydrochloride (6.45 g, 0.03 mol) and sodium hydrogen sulphate (1.8 g, 0.015 mol) were taken in a flask and dissolved in water (25 ml). The resulting solution was added dropwise to vigorously stirred isopropanol (150 ml) at room temperature over a period of one hour. The contents in the flask were further stirred for 4 hrs and then kept at 0°C-5°C for 2 hrs. The precipitate was filtered under vacuum (150 mm Hg). The product was washed twice (each time with 25 ml of isopropanol). Glucosamine sulphate salt was obtained as white solid and was further dried at 25°C under vacuum (2mm Hg).

Example 6:
Preparation of glucosamine sulphate sodium salt (low sodium content)

Glucosamine hydrochloride (6.45 g, 0.03 mol) and sodium hydrogen sulphate (1.8 g, 0.015 mol) were taken in a flask and dissolved in water (25 ml). The resulting solution was added dropwise to vigorously stirred isopropanol (150 ml) at room temperature over a period of one hour. The contents in the flask were further stirred for 4 hrs and then kept at 0°C-5°C for 4 hrs. The precipitate was filtered under vacuum (150 mm Hg). The product was washed twice (each time with 25 ml of isopropanol). Glucosamine sulphate salt was obtained as white solid and was further dried at 25°C under vacuum (2mm Hg).
Example 7

Preparation of glucosamine sulphate sodium salt (low sodium content)

[0045] Glucosamine hydrochloride (6.45 g, 0.03 mol) and sodium hydrogen sulphate (1.8 g, 0.015 mol) were taken in a flask and dissolved in water (25 ml). The resulting solution was added to vigorously stirred isopropanol (150 ml) at room temperature over a period of five minutes.

[0046] The contents in the flask were further stirred for 4 hrs and then kept at 0°C-5°C for 16 hrs. The precipitate was filtered under vacuum (150 mm Hg). The product was washed twice (each time with 25 ml of isopropanol). Glucosamine sulphate salt was obtained as white solid and was further dried at 25°C under vacuum (2 mm Hg).

Example 8:

[0047] Glucosamine hydrochloride (12.9 g, 0.06 mol) was added to sodium hydrogen sulphate (3.6 g, 0.03 mol) and the mixture was pulverised by using a mortar and pestle to obtain the Glucosamine sulphate salt.

Estimation of metal content in the mixed glucosamine sulphate metal salt:

[0048] The sodium content in the mixed glucosamine sulphate sodium salt or the potassium content in the mixed glucosamine sulphate potassium salt respectively is estimated using Inductively Coupled Plasma Method. The sodium content was measured at 589.592 nm and the potassium content was measured at 766.491 nm.

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<td>[α]D25⁰</td>
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<tr>
<td>[α]D25⁰</td>
<td>+51° (c 2, water)</td>
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Claims

1. A crystalline glucosamine sulphate metal salt having low metal content, which is represented by the following formula I:

\[
\text{MHSO}_4 \cdot 2\text{Cl}^-
\]

wherein M represents a metal selected from either sodium or potassium.

2. A compound of formula I as claimed in claim 1 wherein M is sodium.

3. A compound of formula I as claimed in claim 1 wherein M is potassium.

4. A method for the preparation of compound of formula I as defined in claim 1 comprising the steps of:
   (i) reacting glucosamine hydrochloride and a metal hydrogen sulphate of formula
   \[\text{MHSO}_4\]
   wherein M is as defined in respect of formula I above; in a stoichiometric ratio in an aqueous solvent to obtain glucosamine sulphate metal salt;
   (ii) precipitating the resulting glucosamine sulphate metal salt contained in the resulting solution of step (i) using a water miscible organic solvent;
   (iii) filtering the reaction mass as obtained in step (ii) to yield the glucosamine sulphate metal salt of formula I.

5. A method as claimed in claim 4 wherein said aqueous solvent used in step (i) is water.

6. A method as claimed in claim 4 wherein said step of precipitating the resulting glucosamine sulphate metal salt comprises either adding the resulting so-
olution of step (i) to the water-miscible organic solvent or adding the water-miscible organic solvent to the resulting solution of step (i) at an appropriate temperature for a predetermined period of time; followed by stirring the resulting reaction mixture.

7. A method as claimed in claim 6 wherein the addition is carried out at temperature ranging from 17°C to 35°C.

8. A method as claimed in claim 6 wherein the addition is carried out over a period of five minutes to four hours.

9. A method as claimed in claim 4 or 6 wherein the ratio of the resulting solution of step (i) to the water-miscible organic solvent ranges from 1:4 to 1:10.

10. A method as claimed in claim 4 or 6 wherein the said watermiscible organic solvent is selected from ethanol, propanol, isopropanol, acetone, acetonitrile, tetrahydrofuran, dioxane, and dimethylformamide.

11. A method as claimed in claim 6 wherein stirring of the resulting reaction mixture is carried out at an appropriate temperature for a predetermined period of time.

12. A method as claimed in claim 11 wherein stirring of the resulting reaction mixture is carried out for a period of 2 to 6 hours.

13. A method as claimed in claim 11 wherein stirring of the reaction mixture is carried out at a temperature ranging from 17°C to 35°C.

14. A method as claimed in claim 4 wherein said step (iii) of filtering the reaction mass is preceded by cooling of the reaction mass to an appropriate temperature and maintaining it at the said temperature for a predetermined period of time.

15. A method as claimed in claim 14 wherein said reaction mass is cooled to 0-20°C.

16. A method as claimed in claim 14 wherein said reaction mass is maintained at the said temperature for a period of 1-24 hours.

17. A method for the preparation of compound of formula I as defined in claim 1 which comprises pulverising using an appropriate device, a mixture of glucosamine hydrochloride and a metal hydrogen sulphate of formula, wherein M represents a metal selected from Na or K; in a stoichiometric ratio at an ambient temperature over a predetermined period of time.

18. A method as claimed in claim 17 wherein the pulverization is carried out over a period ranging from 0.2 hours to 2.0 hours.

19. A pharmaceutical composition comprising an effective amount of compound of formula I as defined in claim 1.

20. A compound as defined in claim 1 for use in a method of treatment of the human or animal body.

21. A compound according to claim 20 wherein said treatment is treatment of both acute and chronic forms of rheumatic and arthritic diseases and all of the pathological conditions originating from metabolic disorders of the osteo-articular tissues.

22. Use of a compound as defined in claim 1 in the manufacture of a medicament for the treatment of both acute and chronic forms of rheumatic and arthritic diseases and all of the pathological conditions originating from metabolic disorders of the osteo-articular tissues.

Patentansprüche

1. Kristallines Glucosaminsulfatmetallsalz mit gerin
gem Metallgehalt, dargestellt durch die folgende Formel I:

   \[
   \text{MHSO}_4 \cdot 2\text{Cl}^{-}
   \]

   worin M für ein Metall steht, das aus Natrium oder Kalium ausgewählt ist.

2. Verbindung der Formel I nach Anspruch 1, worin M Natrium ist.

3. Verbindung der Formel I nach Anspruch 1, worin M
Kalium ist.

4. Verfahren zur Herstellung einer Verbindung der Formel I nach Anspruch 1, folgende Schritte umfassend:
   (i) Umsetzen von Glucosaminhydrochlorid mit einem Metallhydrogensulfat der Formel \( \text{MHSO}_4 \)
   worin M wie oben in Formel I definiert ist; und zwar in einem stöchiometrischen Verhältnis in einem wässrigen Lösungsmittel, um Glucosaminsulfatmetallosalz zu erhalten;
   (ii) Ausfällen des resultierenden Glucosaminsulfatmetallosalzes, das in der in Schritt (i) erhaltenen Lösung enthalten ist, wobei ein wassermischbares organisches Lösungsmittel verwendet wird;
   (iii) Filtrieren der Reaktionsmasse, die in Schritt (ii) erhalten wird, um das Glucosaminsulfatmetallosalz der Formel I zu erhalten.

5. Verfahren nach Anspruch 4, worin das in Schritt (i) verwendete wässrige Lösungsmittel Wasser ist.


7. Verfahren nach Anspruch 6, worin der Zusatz bei einer Temperatur von 17 °C bis 35 °C durchgeführt wird.

8. Verfahren nach Anspruch 6, worin der Zusatz über einen Zeitraum von 5 Minuten bis 4 Stunden durchgeführt wird.

9. Verfahren nach Anspruch 4 oder 6, worin das Verhältnis zwischen der Lösung von Schritt (i) und dem wassermischbaren organischen Lösungsmittel 1:4 bis 1:10 beträgt.


14. Verfahren nach Anspruch 4, worin die Reaktionsmasse vor Schritt (iii) des Filtrierens der Reaktionsmasse auf eine geeignete Temperatur abgekühlt und über einen vorgegebenen Zeitraum auf dieser Temperatur gehalten wird.

15. Verfahren nach Anspruch 14, worin die Reaktionsmasse auf 0-20 °C abgekühlt wird.

16. Verfahren nach Anspruch 14, worin die Reaktionsmasse 1-24 Stunden lang auf dieser Temperatur gehalten wird.

17. Verfahren zur Herstellung einer Verbindung der Formel I nach Anspruch 1, umfassend das Pulverisieren eines Gemischs aus Glucosaminhydrochlorid und einem Metallhydrogensulfat der Formel \( \text{MHSO}_4 \)
   worin M für ein aus Na oder K ausgewähltes Metall steht; in einem stöchiometrischen Verhältnis bei Umgebungstemperatur über einen vorgegebenen Zeitraum unter Verwendung einer geeigneten Vorrichtung.

18. Verfahren nach Anspruch 17, worin das Pulverisieren über einen Zeitraum von 0,2 Stunden bis 2,0 Stunden durchgeführt wird.


20. Verbindung nach Anspruch 1 zur Verwendung bei einem Verfahren zur Behandlung des Körpers eines Menschen oder Tiers.


Revendications

1. Sel métallique de sulfate de glucosamine cristallin ayant une faible teneur en métal qui est représenté par la formule I qui suit:

![Diagramme de la formule I](image)

où M représente un métal sélectionné parmi sodium ou potassium.

2. Composé de la formule I selon la revendication 1 où M est sodium.

3. Composé de la revendication 1 selon la revendication 1 où M est potassium.

4. Méthode de préparation d'un composé de formule I tel que défini à la revendication 1 comprenant les étapes de:

(i) faire réagir du chlorhydrate de glucosamine et un hydrogénosulfate de métal de la formule

\[ \text{MHSO}_4 \]

où M est tel que défini par rapport à la formule I ci-dessus; à un rapport stoechiométrique dans un solvant aqueux pour obtenir un sel métallique de sulfate de glucosamine;

(ii) précipiter le sel métallique de sulfate de glucosamine résultant contenu dans la solution résultant de l'étape (i) en utilisant un solvant organique miscible dans l'eau;

(iii) filtrer la masse réactionnelle telle qu'obtenue à l'étape (ii) pour donner le sel métallique de sulfate de glucosamine de la formule I.

5. Méthode selon la revendication 4 où ledit solvant aqueux utilisé à l'étape (i) est de l'eau.

6. Méthode selon la revendication 4 où ladite étape de précipiter le sel métallique de sulfate de glucosamine résultant comprend soit l'addition de la solution résultant de l'étape (ii) au solvant organique miscible dans l'eau ou l'addition du solvant organique miscible dans l'eau à la solution résultant de l'étape (i) à une température appropriée pendant une période prédéterminée de temps; avec ensuite agitation du mélange réactionnel résultant.

7. Méthode selon la revendication 6 où l'addition est effectuée à une température allant de 17°C à 35°C.

8. Méthode selon la revendication 6 où l'addition est effectuée sur une période de cinq minutes à quatre heures.

9. Méthode selon la revendication 4 ou 6 où le rapport de la solution résultant de l'étape (i) au solvant organique miscible dans l'eau est compris entre 1:4 et 1:10.

10. Méthode selon la revendication 4 ou 6 où ledit solvant organique miscible dans l'eau est sélectionné parmi éthanol, propanol, isopropanol, acétone, acétonitrile, tétrahydrofuranne, dioxane, et diméthylformamide.

11. Méthode selon la revendication 6 où l'agitation du mélange réactionnel résultant est effectuée à une température appropriée pendant une période prédéterminée de temps.

12. Méthode selon la revendication 11 où l'agitation du mélange réactionnel résultant est effectuée pendant une période de 2 à 6 heures.

13. Méthode selon la revendication 11 où l'agitation du mélange réactionnel est effectuée à une température allant de 17°C à 35°C.

14. Méthode selon la revendication 4 où l'étape (iii) de filtration de la masse réactionnelle est précédée du refroidissement de la masse réactionnelle à une température appropriée et son maintien à ladite température pendant une période prédéterminée de temps.

15. Méthode selon la revendication 14 où ladite masse réactionnelle est refroidie à 0-20°C.
16. Méthode selon la revendication 14 où ladite masse réactionnelle est maintenue à ladite température pendant une période de 1-24 heures.

17. Méthode pour la préparation d'un composé de formule I telle que définie à la revendication 1 qui comprend la pulvérisation en utilisant un dispositif approprié, d'un mélange de chlorhydrate de glucosamine et d'un hydrogéno-sulfate de métal de la formule,

\[ \text{MHSO}_4 \]

où M représente un métal sélectionné parmi Na ou K; à un rapport stoechiométrique à une température ambiante sur une période prédéterminée de temps.

18. Méthode selon la revendication 17 où la pulvérisation est effectuée sur une période allant de 0,2 heure à 2,0 heures.

19. Composition pharmaceutique comprenant une quantité efficace du composé de formule I telle que définie à la revendication 1.

20. Composé tel que défini à la revendication 1 à utiliser dans une méthode de traitement du corps humain ou animal.

21. Composé selon la revendication 20 où ledit traitement est un traitement de formes aigües et chroniques de maladies rhumatismales et arthritiques et toutes les conditions pathologiques provenant des troubles métaboliques des tissus ostéo-articulaires.

22. Utilisation d'un composé tel que défini à la revendication 1 dans la fabrication d'un médicament pour le traitement des formes aigües et chroniques des maladies rhumatismales et arthritiques et toutes les conditions pathologiques provenant de troubles métaboliques des tissus ostéo-articulaires.