

Industria y Comercio
SUPERINTENDENCIA

99
Radicación : 03046045 00000006
Fecha (AMB): 2004-12-21 15:50:48
Trámite : 011 PCT-PATENT 379 FASE NACI 400 OPOSICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A :

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

SOLICITUD
PUBLICADA

Número del expediente: 03-046045
Solicitante: NICOLAS PIRAMAL INDIA LIMITED.
Apoderado: MARGARITA CASTELLANOS ABONDANO
Título de la nueva creación o denominación del signo: "SALES DE METAL CRISTALINA DE SULFATO DE GLUCOSAMINA Y PROCEDIMIENTO PARA SU PREPARACIÓN".
Gaceta: 545

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: PROCAPS S.A.	IDENTIFICACIÓN	
	Dirección: CALLE 80 No. 78b-201 Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BARRANQUILLA Teléfono: 371 99 00 Fax: 373 0815 E-mail:	C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Número 890.106.527-5	
REPRESENTANTE O APODERADO	Nombre: LUIS FERNANDO RINCÓN	IDENTIFICACIÓN	
	Dirección: CALLE 119ª No. 53.99 Teléfono: 613 34 18 Fax: 24 47 87 E-mail: negocios@optimum-co.com	C.C. ☒ NT ☐ C.E. ☐ Otro ☐ Cual _____ Número 79.532.186 Tp 113438	

④ FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causa: No cumple con los requisitos de patentabilidad.

Signo opositor: _____

Justificación: _____

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

100
⑤ Comprobante de pago No. _____ Fecha _____

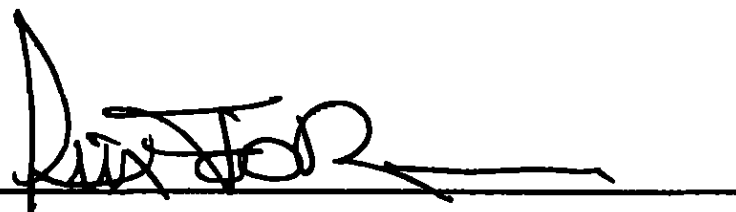
⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

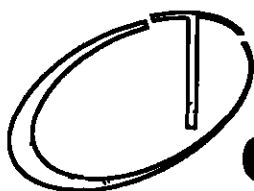
NOMBRE: LUÍS FERNANDO RINCÓN CUELLAR

FIRMA:



C.C. 79.532.186

TP. 113438



Optimum

101
Derech de la Competencia, Propiedad
Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 03-046045

**Asunto : Oposición a la solicitud de patente de Invención titulada
"SALES DE METAL CRISTALINA DE DE
SULFATO DE GLUCOSAMINA Y
PROCEDIMIENTO PARA SU PREPARACIÓN".**

Solicitante :NICOLAS PIRAMAL INDIA LIMITED.

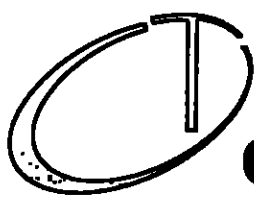
Opositora :PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 545 del 29 de Octubre de 2004

**Yo, Luís Fernando Rincón Cuellar, abogado con tarjeta profesional
N° 113438 del consejo superior de la judicatura, en mi condición de
apoderado de la sociedad PROCAPS S.A. conformada bajo las leyes de la
República de Colombia y domiciliada en la ciudad de Barranquilla,
Colombia, atentamente manifiesto que estando dentro del término de ley
y por orden expresa de mi representada, presento oposición a la concesión
del registro de la patente de Invención titulada "SALES DE METAL
CRISTALINA DE DE SULFATO DE GLUCOSAMINA Y
PROCEDIMIENTO PARA SU PREPARACIÓN", solicitada por
NICOLAS PIRAMAL INDIA LIMITED, y pido a Usted declarar**

**Calle 119 A N° 53-99. Tel. (571) 6 13 34 18 – 6 13 33 74 – Fax. (571) 6 24 47 87
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia**



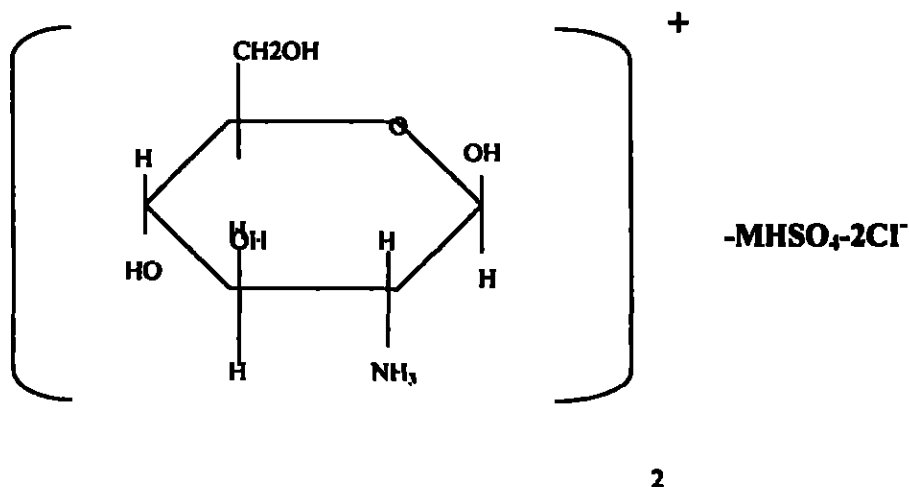
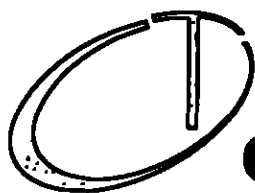
fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada debido a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida atentaría directamente a la comercialización que mi representada pretende con la presentación farmacéutica elaborada con base en Glucosamina Sulfato Sódica. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

- 2.1. La solicitud objeto de la presente oposición fue presentada en Colombia el 30 de mayo de 2003, reivindicando prioridad bajo IN/MUM1087 del 01-12-2000, con publicación internacional N° WO 02/43653 del 6 de Junio de 2002 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 545, del 29 de Octubre de 2004, bajo el N° de publicación NP. 542 (página 399).
- 2.2. La solicitud colombiana N° 03-046045 objeto de la presente oposición, comprende según sus cláusulas, nuevas sales metálicas cristalinas de sulfato de glucosamina con bajo contenido de metal, representadas por la fórmula:



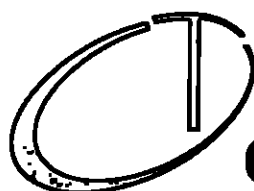
I

en donde M representa un metal seleccionado entre Na o K; donde el compuesto de fórmula I, M es Na (sodio); o, donde el compuesto de fórmula I, M es K (potasio). También el documento se refiere a su proceso de preparación.

2.3. Por su parte el artículo 14 de la Decisión 486 de la CAN, se refiere a que las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la patentabilidad de la presente solicitud:

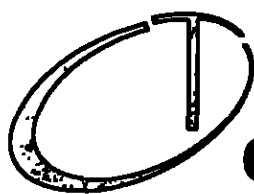
- D1: "THE MERCK INDEX". THIRTEENTH EDITION. ITEM 4471. Pág. 793.
- D2: US4642340
- D3: US5847107
- D4: EP0214642

Calle 119 A N° 53-99. Tel. (571) 6 13 34 18 – 6 13 33 74 – Fax. (571) 6 24 47 87
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia



- D5: US5843923

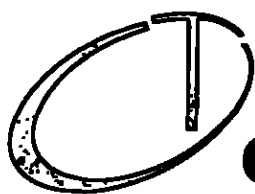
2.4. Ahora bien, remontándonos a los antecedentes de la molécula de la glucosamina, según D1, ítem 4471, la glucosamina tiene sus primeros antecedentes de síntesis en 1902, formas de separación alfa y beta desde 1942. Así las cosas, obviamente la molécula como tal no es patentable, pues hace parte del estado de la técnica desde hace muchos años atrás. Por su parte, el documento D2, se revela una mezcla de sales de sulfato de glucosalina y cloruro de sodio, el proceso para preparar dicha sal y el uso en varias presentaciones farmacéuticas. Como tal este documento D2 se dirige a definir sales metálicas cristalinas de sulfato de glucosalina. Este documento se refiere, particularmente a partir de los ejemplos 1 a 5, a métodos de preparación de glucosamina usando acetona, etanol, acetonitrilo, tetrahydrofuran y dioxan como agente de precipitación. Ahora bien, el documento D3 por su parte se refiere a métodos similares en los ejemplos 1 a 5 a los ejemplos 1 a 5 del D2, pero en los ejemplos 6 a 8 se refiere, respectivamente a la preparación de mezclas de sales comenzando con glucosalina hidróclorida y sulfato de potasio; sulfato de calcio dihidratado; o, sulfato de magnesio heptahidratado. En los ejemplos de estos documentos se hace reaccionar la glucosalina hidróclorida con sulfatos de metal hidrogenados, igual a lo reivindicado en la presente solicitud objeto de oposición. Así las cosas, con base en lo que dictan estos ejemplos de los documentos D2 y D3, Cualquier persona versada en la materia, puede llegar de manera obvia a una sales metálicas cristalinas de sulfato de glucosamina con bajo contenido de metal, representadas por la formula de la cláusula 1. Por lo tanto, la combinación del conocimiento revelado, afecta de manera directa el requisito de ALTURA INVENTIVA de la solicitud colombiana que se pretenden proteger.



2.5. Ahora bien, el documento D4 revela sales mixtas de sulfato de glucosamina y ciertos alcalinos como por ejemplo, cloruro de potasio y a un proceso para la preparación del mismo. Particularmente en la columna 5, líneas 5 a 63 se refiere a una preparación de glucosamina libre que se convierte a una sal mixta de sulfato del glucosamina y cloruro de potasio que se producen disolviendo glucosamina basada en el agua, agregando una cantidad de ácido sulfúrico concentrado para llegar al sulfato de glucosamina. La precipitación se causa agregando un solvente orgánico como, por ejemplo, isopropanol. Según el documento D5, se revela un procedimiento para la preparación de sulfato glucosamina y cloruro de potasio con un porcentaje de pureza de al menos un 97%. Según lo expuesto en estos documentos se muestra la forma de preparar sales metálicas cristalinas de sulfato de glucosamina, igual a lo reivindicado en la presente solicitud objeto de oposición. Así las cosas, con base en lo que dictan los documentos D4 y D5, cualquier persona versada en la materia, puede llegar de manera obvia a una sales metálicas cristalinas de sulfato de glucosamina con bajo contenido de metal, representadas por la formula de la cláusula 1. Por lo tanto, la combinación del conocimiento revelado en los documentos D4 y D5, afecta de manera directa el requisito de ALTURA INVENTIVA de la solicitud colombiana que se pretenden proteger.

2.6. Así las cosas, es posible deducir que el hecho de preparar sales metálicas cristalinas de sulfato de glucosamina conforme a lo plasmado en las cláusulas, se deriva obviamente del arte anterior, específicamente de los documentos D2 a D5.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana **03-046045** no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los requisitos necesarios para su protección.



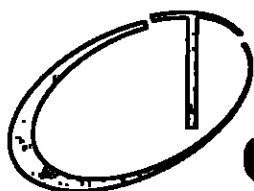
2.8. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.8.1. **CARENCIA DE ALTURA INVENTIVA**. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”*. A la fecha de prioridad, 1º de diciembre de 2000, los documentos D2 a D5 en combinación, puede derivar de manera evidente hecho de preparar sales metálicas cristalinas de sulfato de glucosalina conforme a lo plasmado en las cláusulas de la presente solicitud objeto de oposición.

2.9. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.”*. La solicitud pretendida no cumple con los requisitos de patentabilidad.

2.10. Por consiguiente, si se concede el registro solicitado se induciría al monopolio de un producto que no cumple con los requisitos primordiales exigidos por la mencionada Decisión 486.

2.11. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **“SALES DE METAL CRISTALINA DE DE SULFATO**



DE GLUCOSAMINA Y PROCEDIMIENTO PARA SU PREPARACIÓN", solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 545 del 29 de octubre de 2004, en la página 399, bajo el NP 542.

3. PRUEBAS

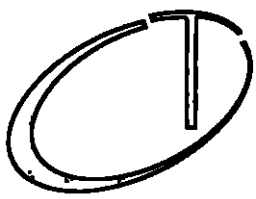
De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1: "THE MERCK INDEX". THIRTEENTH EDITION. ITEM 4471. Pág. 793.
- D2: US4642340
- D3: US5847107
- D4: EP0214642
- D5: US5843923

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.



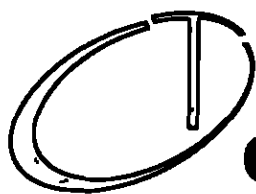
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Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

5. ANEXOS

Para los efectos correspondientes anexo al presente, aquellas referenciadas en el capítulo de pruebas así como los siguientes documentos:

- 5.1. Recibo de pago expedido por el Fondo Especial de esa Superintendencia, en el cual consta que se ha pagado el valor correspondiente a la tasa por tramitación de esta oposición.**
- 5.2. Copia de la oposición para el traslado al solicitante.**
- 5.3. Poder para actuar a nombre de mi representada.**

**6. NOTIFICACIONES**

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas de abogado situadas en la calle 119ª N° 53-99 de esta ciudad de Bogotá.

Señora Jefe,

LUIS FERNANDO RINCÓN CUELLAR

C.C. 79'532.186 de Bogotá

T.P.A. 113.438 del C.S. de la J.



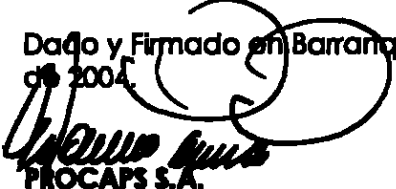
PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a **LUIS FERNANDO RINCON CUELLAR**, abogado titulado, identificado como aparece al pie de su firma, con tarjeta profesional No. 113438 expedida por el Consejo Superior de la Judicatura, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **03-046045**, de título: **"SALES DE METAL CRISTALINAS DE SULFATO DE GLUCOSAMINAY PROCEDIMIENTOS PARA SU PREPARACIÓN"**, publicada en la Gaceta de la Propiedad Industrial N° 545, del 29 de octubre de 2004, bajo el N° de publicación NP. 542, y cuyo solicitante es la sociedad **NICHOLAS PIRAMAL INDIA LIMITED**.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistirse, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 13 días del mes de diciembre de 2004.


PROCAPS S.A.
WALTER TANAKA TATEKAWA
C.C. N° 14.251.923 de Palmira
Representante Legal

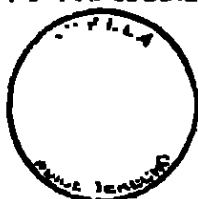
Acepto,

LUIS FERNANDO RINCÓN CUÉLLAR
C.C. No. 79.532.186
T.P. 113438

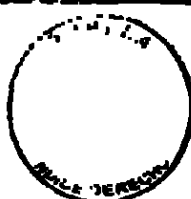
DILIGENCIA DE PRESENTACION PERSONAL
DECRETO 980 DE 1970 - ART. 68
MARIA DEL S. ROMAN DE ARTETA - NOTARIA SEGUNDA DE BARRANQUILLA
CERTIFICA

En Barranquilla a los 16 días del mes de Diciembre de 2004. Firmaron esta diligencia en su presencia: Walter Paula Jotekaua -

Portadores de las cédulas 16 201.923



Expedidas en Barranquilla
y dieron fe de su contenido del documento
que antecede y esta autorización con sus firmas



Comparecientes [Firmas]

REPUBLICA DE COLOMBIA
NOTARIA SEGUNDA DEL CIRCULO DE BARRANQUILLA
DILIGENCIA DE RECONOCIMIENTO
Y PRESENTACION PERSONAL

Ante el Notario Once del Circulo de Santa Fe de Bogotá, compareció [Firma]

Quien exhibió la C.C. No. 16 201.923

expedida en Barranquilla T.P. 11 2438

y declaró que la firma y huella que aparecen en el presente memorial son auyas y que el contenido del mismo es cierto.

Memorial dirigido a

Santa Fe de Bogotá, D.C.

21 DIC 2004

[Firma]
Firma del Declarante



Autorizó la anterior Diligencia

NOTARIO ONCE DEL CIRCULO DE SANTA FE DE BOGOTA

REPUBLICA DE COLOMBIA
NOTARIA 1 DEL CIRCULO DE
SANTA FE DE BOGOTA, D.C.

ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE

*****No. 8573851

CAMARA DE COMERCIO

DE BARRANQUILLA



CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
DE INSCRIPCION DE DOCUMENTOS.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

Que por Escritura Publica Nro. 1190 del 22 de Julio de 1,976,
otorgada en la Notaria Tercera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 28 de Julio de 1,976 bajo
el No. 6,070 del libro respectivo, fue constituida la sociedad
limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA
"PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Publica Nro. 1307 del 28 de Junio de 1,979,
otorgada en la Notaria Tercera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 23 de Julio de 1,979 bajo
el No. 10,039 del libro respectivo, la sociedad antes mencionada
se transformo en sociedad anonima bajo la denominacion social de
"PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A."-----

C E R T I F I C A

Que por Escritura Publica Nro. 3810 del 31 de Dic/bre de 1,980,
otorgada en la Notaria Primera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 30 de Enero de 1,981 bajo
el No. 12,705 del libro respectivo, la sociedad antes mencionada
se transformo en sociedad de responsabilidad limitada bajo al razon
social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI -
MITADA".-----

C E R T I F I C A

Que por Escritura Publica Nro. 3755 del 10 de Nov/bre de 1,983,
otorgada en la Notaria Unica de Soledad, -----
inscrita en esta Camara de Comercio, el 22 de Nov/bre de 1,983 bajo
el No. 17,922 del libro respectivo, la sociedad antes mencionada
se transformo en sociedad anonima bajo la denominacion social de
"PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A."-----

C E R T I F I C A

Que por Escritura Publica Nro. 3615 del 6 de Dic/bre de 1,996,
otorgada en la Notaria 2a. de Barranquilla -----
inscrita en esta Camara de Comercio, el 20 de Dic/bre de 1,996 bajo

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----

~~el No. 67,218 del libro respectivo, la sociedad antes mencionada~~
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A

C E R T I F I C A

Que por Escritura Publica Nro. 3775 del 18 de Dic/bre de 1,996,
otorgada en la Notaria 2a. de Barranquilla -----
inscrita en esta Camara de Comercio, el 23 de Enero de 1,997 bajo
el No. 67,704 del libro respectivo, la sociedad antes mencionada
cambio de razon social, por la denominacion PROCAPS S.A. -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras
y/o documentos privados:

Numero	mm/dd/aaaa	Notaria	No.Ins o Reg	mm/dd/aaaa
39	1/18/1979	Notaria 3a. de Barranquilla	9,452	1/24/1979
992	4/30/1981	Notaria 1a. de Barranquilla	13,112	5/ 6/1981
1,464	8/27/1982	Notaria Unica de Soledad	15,533	9/ 8/1982
2,744	8/18/1983	Notaria Unica de Soledad	17,416	8/26/1983
3,826	7/16/1984	Notaria Unica de Soledad	19,554	7/27/1984
3,835	8/26/1985	Notaria Unica de Soledad	22,230	9/ 4/1985
2,260	9/10/1986	Notaria Unica de Soledad.	24,995	9/15/1986
1,849	7/11/1989	Notaria 2a. de Barranquilla	33,909	7/13/1989
444	2/21/1990	Notaria 2a. de Barranquilla	36,101	3/16/1990
3,090	12/17/1991	Notaria 2a. de Barranquilla	43,993	1/28/1992
269	2/ 1/1993	Notaria 2a. de Barranquilla	48,428	2/16/1993
2,342	7/28/1993	Notaria 2a. de Barranquilla	50,582	8/10/1993
3,652	11/ 9/1993	Notaria 2a. de Barranquilla	51,798	11/22/1993
3,615	12/ 6/1996	Notaria 2a. de Barranquilla	67,218	12/20/1996
89	1/16/1997	Notaria 2a. de Barranquilla	67,704	1/23/1997
2,070	7/17/1997	Notaria 2a. de Barranquilla	70,627	7/31/1997
2,281	8/ 4/1997	Notaria 2a. de Barranquilla	70,813	8/14/1997
765	4/22/1999	Notaria 3a. de Barranquilla	80,628	4/23/1999
459	2/21/2001	Notaria 2a. de Barranquilla	91,502	2/23/2001
2,608	10/ 5/2001	Notaria 2a. de Barranquilla	95,771	11/ 8/2001
1,730	7/29/2004	Notaria 2. de Barranquilla	112,999	8/26/2004

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad
se rige por las siguientes disposiciones: -----

DENOMINACION O RAZON SOCIAL: -----

PROCAPS S.A. -----

Sigla: PROCAPS -----

DOMICILIO PRINCIPAL: BARRANQUILLA -----

Nit No. 890,106,527-5-----

MATRICULA MERCANTIL: 24,802 -----

***** C O N T I N U A *****

*****No. 8573852*****

CAMARA DE COMERCIO

DE BARRANQUILLA



CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

C E R T I F I C A

Direccion para notificaciones judiciales
CL 80 # 78B -201
de la ciudad de BARRANQUILLA

C E R T I F I C A

DURACION: El termino de duracion de la sociedad se fijo hasta el
18 de Agosto del ano 2,073. -----

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-La fabricaci n de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas,alimentos y cosmeticas, asi como la comercializacion interna y externa de los productos terminados, d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos, y hospitalarios para la salud humana y animal. e)La compra,venta,exportacion y distribucion de dulces, confites, galletas y todo tipo de g losinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c). d) y e) antes descritos; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titul , empresa o establecimientos dedicados a la investigacion, de-

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----

desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.-----

C E R T I F I C A

CAPITAL:	Nro.Acciones	Valor Accion
AUTORIZADO:		
\$*****2,000,000,000.00	2,000,000.00	1,000.00
SUSCRITO:		
\$*****1,212,449,000.00	1,212,449.00	1,000.00
PAGADO:		
\$*****1,212,449,000.00	1,212,449.00	1,000.00

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponde a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con

***** C O N T I N U A *****

*****No. 8572853

CAMARA DE COMERCIO
DE BARRANQUILLA



CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fij de la sociedad, inclusive de naturaleza muebles, acciones, cu tas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para

***** C O N T I N U A *****

113

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----

~~ello acreditar la ausencia del principal. La sociedad tendra un~~
gerente general con su respectivo suplente, quienes tambien ejerceran la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el presidente y el vicepresidente. El gerente general, tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o superior al equivalente en pesos colombianos cincuenta mil dolares de los estados unidos de America (US\$50.000) liquidados a la tasa de cambio representativa del mercado vigente el dia en que surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del presidente. Las demas funciones que les correspondan como representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El gerente lo reemplazara conjunta o separadamente en sus faltas temporales, ausencias o meramente accidentales, con identicas facultades.-----

C E R T I F I C A

Que segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----

PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo, y por Acta No. 127 del 22 de Marzo de 2,000, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----

PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 29 de Mayo de 2,000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos: -----

J U N T A D I R E C T I V A

Principales

1. Minski Gontovnik Ruben
2. Minski Gontovnik Meyer
3. Minski Gontovnik Jose

Suplentes

- Minski Zilberblum Elliot
Minski Deitel Daniel
Minski Sharon

C E R T I F I C A

Que segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----

PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo

Nombre

Identificacion

***** C O N T I N U A *****

*****No. 8573854

CAMARA DE COMERCIO
DE BARRANQUILLA



CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
DE INSCRIPCION DE DOCUMENTOS.

Presidente.	Minski Gontovnik Ruben	C.*****7,463,982=
Suplente del Presidente	Minski Minski Abraham	C.*****802,575=
Vicepresidente	Minski Gontovnik Meyer	C.*****7,461,324=
Suplente del vicepresidente	Minski Gontovnik Jose	C.*****8,671,834=

C E R T I F I C A

Que segun Acta No. 124 del 29 de Marzo de 1,999, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 4 de Agosto de 1,999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Revisor Fiscal Ppal.	Vargas Pertuz Ana Isabel	C.****32,696,645=

C E R T I F I C A

Que segun Acta No. 127 del 22 de Marzo de 2,000, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 29 de Mayo de 2,000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Suplente del Revisor Fiscal.	Lozada Villareal Milena	C.****32,748,111=

C E R T I F I C A

Que segun Acta No. 11 del 1 de Febrero de 2,001, correspondiente a la Junta Directiva en Barranquilla de la sociedad: -----
PROCAPS S.A. -----
cuya parte pertinente se inscribio en esta Camara de Comercio, el 12 de Febrero de 2,001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Gerente General.	Uribe Ochoa Guillermo Luis	C.****70,073,754=

C E R T I F I C A

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----

Que segun Acta No. 406 del 2 de Sep/bre de 2,004, correspondiente a la Junta Directiva en Barranquilla de la sociedad: -----

PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 9 de Sep/bre de 2,004 bajo el No.113,263 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Suplente del Gerente.	Tanaka Walter	C.****16,251,923=

C E R T I F I C A

Que por escritura publica No. 2.608 del 5 de Octubre del 2.001, otorgada en la Notaria 2a. de Barranquilla, inscrita en esta Camara de Comercio el 8 de Noviembre del 2.001, bajo los Nos. 95.771, 2.056, 2.057, 2.058, 2.059, 2.060, 2.061, 2.062 y 2.064 del libro respectivo, se reforma totalmente el articulo 65, contenido en la escritura publica No. 3.705 de Noviembre 6 de 1.998, de la Notaria Segunda del Circuito de Barranquilla, y se constituyen los siguientes Apoderados Generales, quienes tendran las funciones que a continuacion se indican en razon de su cargo en la sociedad: 1.-Se confiere Poder Especial, Amplio y Suficiente a los senores: WALTER TANAKA TATEKAWA, C.C. No. 16.251.923; WILLIAM ALBERTO BARROS CERRA, C.C. No. 8.715.941, para que cada uno en forma independiente en nombre y representacion de PROCAPS S.A., suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad, asi como para que responda todo tipo de requerimiento o solicitudes de informacion de las autoridades tributarias, aduaneras o cambiarias, en los ordenes Distrital, Departamental y Nacional. 2.-Se confiere Poder Especial, amplio y suficiente, a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancias y servicios con entidades oficiales, hasta por la suma de US\$800.000.00 (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. GUPO A: GUILLERMO LUIS URIBE OCHO C.C. No. 70.073.754, LINO LAZALA SILVA VARGAS C.C. No. 19.260.410, JAIRO MOLINA MEJIA C.C. No. 8.706.380, CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.293. BRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, HENRY CARO DIAZ C.C. No. 19.395.298, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZGRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requerira por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C.C. No. 33.138.497, a la Doctora MARCELA CARVAJALINO PAGANO C.C. No. 22.579.748, y al Doctor DANIEL MORENO VILLALBA, C.C. No. 19.113.210; para que cada uno representen a PROCAPS S.A., ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como: Contestar e interponer demandas y requerimientos, com-

***** C O N T I N U A *****

*****No. 8573855

CAMARA DE COMERCIO

DE BARRANQUILLA



CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
DE INSCRIPCION DE DOCUMENTOS.

parecer en juicios, pedir la practica de pruebas, recibir notificaciones, interponer recursos y ejercer acciones contencioso administrativas y de tutela, transigir, conciliar, recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato. Para la celebracion de cualquier acuerdo conciliatorio o transaccional, judicial o extrajudicial, cualquiera que sea su cuantia, los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la sociedad. Los Apoderados podran presentar solicitudes de devolucion y/o compensacion de impuestos y recibir los pagos por devoluciones de impuestos, firmar, notificarse y realizar todo acto necesario para cumplir con el mandato encomendado.

C E R T I F I C A

Que segun documento privado de fecha 7 de junio de 2000, inscrito en esta Camara de Comercio el 8 de junio de 2000, bajo el No.1.786 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a KAREN FIGUEROA GARCIA, C.C.No.32.732.070 de Barranquilla, para que en su nombre y representacion de la sociedad suscriba todas declaraciones cambiarias a que este obligada PROCAPS S.A, en el giro normal de sus negocios y operaciones sociales.--

C E R T I F I C A

Que segun Documento Privado del 13 de diciembre del 2.002, inscrito en esta Camara de Comercio el 15 de enero del 2.003 bajo el No.2.290 del libro respectivo, el senor RUBEN MINSKI GONTOVNIK, C.C.No.7.463.982, en calidad de REPRESENTANTE LEGAL, y en condicion de PRESIDENTE de PROCAPS S.A., mediante el presente documento otorgo PODER ESPECIAL al Sr. MARLON TATIS PAREDES, C.C.No.72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces. En consecuencia, el Sr. MARLON TATIS PAREDES, podra suscribir en representacion de PROCAPS S.A. declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces.

C E R T I F I C A

Que en esta Camara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolucion, liquidacion o nombramientos de representantes legales de la expresada sociedad.

***** C O N T I N U A *****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----

C E R T I F I C A

Que su ultima Renovacion fue el: 31 de Marzo de 2,004. -----

La informacion sobre embargos de establecimientos se suministra en
Certificados de Matricula, la de contratos sujetos a registro, en
Certificados Especiales.

NO CAUSA IMPUESTO DE TIMBRE


EL SECRETARIO
MARIBEL REYES OVIEDO

ANEXO 1

THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

THIRTEENTH EDITION

Editorial Staff

Maryadele J. O'Neil, *Senior Editor*

Ann Smith, *Senior Associate Editor*

Patricia E. Heckelman, *Associate Editor*

John R. Obenchain Jr., *Editorial Assistant*

Jo Ann R. Gallipeau, *Technical Assistant*

Mary Ann D'Arecca, *Administrative Associate*

Susan Budavari, *Editor Emeritus*

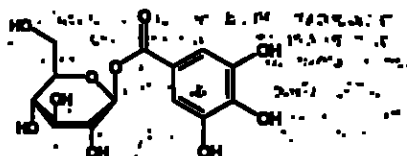
Published by
Merck Research Laboratories
Division of

MERCK & CO., INC.
Whitehouse Station, NJ

2001

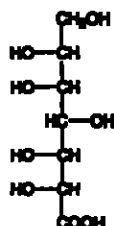
at 70° under
as hydrate);
-37.8° (c =
with
sol

u-N; kgalak.
O 38.72%,
frangula L.,
=, Bull. Soc.
14, 316
1159a (1964).
Inocfrangula
at the 3 po-
Chin. Acta
310 (1964);
ner, Hôrhun-
urey, Gluco-
forma 24,



Bipar microscopic prisms from water, methanol or 80% ethanol, mp 207°. $[\alpha]_D^{25} -24.5^\circ$ (c = 1.75 in water). Freely sol in hot water. Sparingly sol in cold water, methanol, ethanol, acetone, ethyl acetate. Practically insol in ether, benzene, chloroform, petr ether.

4468. Glucoheptonic Acid. [87-74-1] D-glycero-D-gulo-heptonic acid; α -glucoheptonic acid; glucoheptanecarboxylic acid; glucoheptanecarboxylic acid. $C_7H_{12}O_8$; mol wt 226.18. C 37.17%, H 6.24%, O 56.59%. Obtained by treating glucose with HCN yielding a cyanohydrin which is saponified to glucoheptonic acid. Killard, *Rev.* 19, 769 (1986); Fischer, *Ann.* 278, 71 (1892); Armstrong, *CA* 45, 2865 (1951). Process starting with calcium cyanide and glucose: Cleveland, US 2739866 (1956 to Lab. Cleveland). Diagnostic use of ^{99m}Tc complexes in renal scintigraphy: R. E. Boyd *et al.*, *Brit. J. Radiol.* 46, 604 (1973); in brain scanning: J. Léveillé *et al.*, *J. Nucl. Med.* 18, 957 (1977); T. W. Ryerson *et al.*, *Radiology* 127, 429 (1978). Subacute toxicity study: L. Belbeck *et al.*, *Can. J. Comp. Med.* 45, 299 (1981).



Lactonizes upon evapn. The lactone forms large sweetish crystals, mp 145-148°. $[\alpha]_D^{25} -56.0^\circ$ (shows mutarotation). Sol in water.

Sodium salt. [13007-85-7] Glucoheptate sodium; sodium glucoheptanate. $C_7H_{11}NaO_8$. Prepn from corn syrup: Behnke, US 3223343 (1962 to Pharnitshi Labs). Crystals (α -form), dec 161°. $[\alpha]_D^{25} +6.06^\circ$ (c = 10 in H_2O). Freely sol in water.

Calcium salt. Glucoheptate calcium; calcium glucoheptanate; calcium glucoheptanecarboxylate; calcium glucoheptanecarboxylate; Calciforce; Calheptone. $C_{14}H_{26}CaO_{16}$; mol wt 490.42. Prepn from Na salt: Holstein, US 3033900 (1962 to Pharnitshi Labs). Hygroscopic crystals, somewhat acid taste, dec 200°. Sol in water.

Magnesium salt. Magnesium glucoheptanate; magnesium glucoheptanecarboxylate; magnesium glucoheptanecarboxylate; Na-salt. $C_{12}H_{22}MgO_{14}$; mol wt 474.65. Prepn: Cipelli, US 3043896 (1962 to Merck & Co.). Water-sol crystals, pleasant taste.

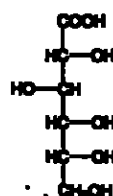
Complex with ^{99m}Tc . ^{99m}Tc glucoheptate; ^{99m}Tc gluheptanate; GlucoScan; TechnaScan glucoheptate.

USE: Pharmacologic aid.

THERAP CAT: ^{99m}Tc complex as diagnostic aid (radioactive imaging agent).

4469. Gluconic Acid. [326-93-4] D-Gluconic acid; dextroic acid; mabonic acid; glyconic acid; glyconic acid; pentahydroxypropionic acid. $C_6H_{12}O_7$; mol wt 196.15. C 36.74%, H 6.17%, O 57.10%. Prepd by oxidation of glucose: H. Hinselwood, J. Habermann, *Ann.* 155, 120 (1870); J. Habermann, *Ibid.* 168, 297 (1872). Fermentative prepn using *Aspergillus niger*: E. Bornhauser, L. Schulof, US 1849853 (1932 to Pfizer); A. J. Meyer *et al.*, *Ind. Eng. Chem.* 32, 1379 (1940). Review of prepn and uses: F. J. Prescott *et al.*, *Ibid.* 48, 338 (1953); M. Ruder *et al.* in *Biochemistry*, Vol. 6, H. Rahm, G. Reed, Eds.

(VCH, Weinheim, 2nd ed, 1996) pp 347-362. See also Gluco-nolactone.



Crystals, mp 131°. Mild acid taste. $[\alpha]_D^{25} -6.7^\circ$ (c = 1). pK (25°) 3.60. Freely sol in water, slightly sol in alcohol. Insol in ether and most other organic solvents. In aq solns the acid is partially transformed into an equilibrium mixt with gamma and delta gluconolactones.

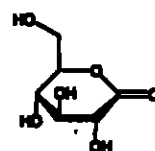
Magnesium salt. [3632-91-5] Magnesium gluconate; Al-mora; Ultra-Mg. $C_{12}H_{22}MgO_{14}$; mol wt 414.60. Clinical pharmacokinetics and use as magnesium supplement: J. White *et al.*, *Clin. Ther.* 14, 678 (1992). Also occurs as the dihydrate. Sol in water, slightly sol in alcohol. Insol in ether.

Zinc complex. [4468-02-4] (7-6)-Bis-(D-gluconato- αO^1 , αO^2)zinc; zinc gluconate; Rubozinc. $C_{12}H_{22}O_{14}Zn$; mol wt 455.73. Review of clinical use in treatment of colds: M. L. Garland, K. O. Hagmeyer, *Ann. Pharmacother.* 32, 63-69 (1998). Clinical trial in inflammatory acne: J. Maynard, *Eur. J. Dermatol.* 10, 269 (2000).

USE: Chelating agent. In high alkalinity bottle washes and other cleansers; in finish removers; in the tanning and textile industry.

THERAP CAT: Magnesium salt as magnesium replenisher; zinc complex as zinc supplement.

4470. Glucoconactone. [90-80-2] D-Gluconic acid δ -lactone; glucono delta lactone; delta gluconolactone; Füllglimm. $C_6H_{10}O_6$; mol wt 178.14. C 40.43%, H 5.66%, O 53.89%. Prepn by oxidation of glucose with bromine water: Labell, Pignani, *J. Res. Nat. Bur. Stand.* 10, 337 (1933); by oxidation of glucose in *Acetobacter suboxydans*: King, Chalklin, *Biochem. J.* 68, 31P (1958). Structure: J. Smolík *et al.*, *The Monosaccharides* (Academic Press, New York, 1963) p 271.

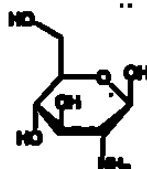


Crystals, dec 153°. Sweet taste (different from gluconic acid). $[\alpha]_D^{25} +61.7^\circ$ (c = 1). Soly in water 59 g/100 ml; in alc about 1 g/100 g. Insol in ether. Hydrolyzed to gluconic acid by water. A freshly prepd 1% aq soln has a pH of 3.6 changing to pH 2.5 within 2 hrs.

USE: Component of many cleaning cmpds because of the sequestering ability of the gluconate radical which remains active in alk solns; in the dairy industry to prevent milkstone; in breweries to prevent beerstone; as latent acid catalyst for acid colloid resins, particularly in textile printing; as a coagulant for tofu.

4471. Glucosamine. [3416-24-8] 2-Amino-2-deoxy-D-glucose; chitosamine. $C_6H_{13}NO_5$; mol wt 179.17. C 40.22%, H 7.31%, N 7.82%, O 44.65%. Found in chitin, in mucopolysaccharides, and in mucopolysaccharides. Isola from chitin: Ladderhous, *Z. Physiol. Chem.* 2, 213 (1878); Hackman, *Aust. J. Biol. Sci.* 7, 168 (1954). Synthesis: Fischer, Leuchs, *Ber.* 35, 3787 (1902); 36, 24 (1903). Separation of α - and β -forms: Westphal, Holzmair, *Ibid.* 758, 1274 (1942). Structure: Haworth *et al.*, *J. Chem. Soc.* 1938, 271; Cotter, *Proc. R. Soc. Lond.* 182, 384 (1939). Pharmacokinetics in dog and man: L.

Schulze *et al.*, *Arzneimittel-Forsch.* 36, 729 (1986). Clinical trials in arthritis: Y. Vajradal, *Clin. Ther.* 3, 336 (1981); M. J. Tapadinas *et al.*, *Pharmatherapeutics* 3, 157 (1982). Review: Foster, Stacey, "The Chemistry of the 2-Amino Sugars" in C. S. Hudson *et al.*, *Advan. Carbohydr. Chem.* vol. 7 (Academic Press, New York, 1952) pp 247-288.



α -Form. [28903-11-5] Crystals, mp 85°. $[\alpha]_D^{25} +100^\circ$ changing to $+47.5^\circ$ after 30 min (water).

β -Form. [28903-10-4] Needles from methanol, dec 110°. $[\alpha]_D^{25} +28^\circ$ changing to $+47.5^\circ$ after 30 min (water). Very sol in water, sol in about 35 parts boiling methanol; sparingly sol in cold methanol or ethanol. Practically insol in ether, chloroform.

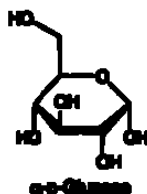
N-Acetylglucosamine. [7512-17-6] $C_8H_{15}NO_5$. Needles from methanol + ether, mp 203°. $[\alpha]_D^{25} +64^\circ$ changing to $+40.9^\circ$ (in water).

Sulfate salt. [29031-19-4] Dext. $C_8H_{15}NO_5 \cdot xH_2SO_4$.

USE: Pharmaceutical aid.

THERAP CAT: Antidiabetic.

4472. Glucose. [50-99-7] D-Glucose; dextrose; blood sugar; grape sugar; corn sugar; Dextropur; Dextrosol; Glucosin. $C_6H_{12}O_6$; mol wt 180.16. C 40.00%, H 6.71%, O 53.28%. A main source of energy for living organisms. Occurs naturally and in the free state in fruits and other parts of plants. Combined in glucosides, in di- and oligosaccharides, in the polysaccharides cellulose and starch, and in glycogen. Normal human blood contains 0.08-0.1%. Mannf on a large scale from starch: Dean, Gottfried, *Advan. Carbohydr. Chem.* 5, 127 (1950). Below 50°, α -D-glucose hydrate is the stable cryst form, above 50° the anhyd form is obtained and at still higher temps β -D-glucose is formed: W. Pigman, *The Carbohydrates* (Academic Press, New York, 1957) p 92. Structure: Kjaer, Lindberg, *Acta Chem. Scand.* 13, 1713 (1959). Conformation: E. Percival, *Structural Carbohydrate Chemistry* (J. Garnet Miller, London, 1962) pp 51-57. Comprehensive monograph: H. Bertelheimer *et al.*, *D-Glucose und verwandte Verbindungen in Medizin und Biologie* (Bake, Stuttgart, 1966) 1126 pp.



α -Form monohydrate. Crystals from water, mp 83°. $[\alpha]_D^{25} +102.0^\circ \rightarrow +47.5^\circ$ (water). 0.74 times as sweet as sucrose. One gram dissolves in about 1 ml water and in about 60 ml alcohol.

α -Form anhydr. Crystals from hot ethanol or water, mp 146°. $[\alpha]_D^{25} +112.2^\circ \rightarrow +52.7^\circ$ ($c = 10$ in water). The final value is obtained instantly in the presence of hydroxyl ions. Formula for varying concn: $[\alpha]_D^{25} +52.5^\circ + 0.0188p$ ($p = g/100$ ml). pH of 0.5 molar aq soln 5.9. d_{4}^{25} of water soln: 5% = 1.019; 10% = 1.038; 20% = 1.076; 30% = 1.113; 40% = 1.149. n_D^{20} 10% soln 1.3479. One gram dissolves in 1.1 ml water at 25°; in 0.8 ml at 30°; in 0.41 ml at 50°; in 0.28 ml at 70°; in 0.18 ml at 90°; in 120 ml methanol at 20°. Very sparingly sol in abs alcohol, ether, acetone; sol in hot glacial acetic acid, pyridine, miline.

β -Form. Crystals from hot water + ethanol, from dil acetic acid, or from pyridine, mp 148-155°. $[\alpha]_D^{25} +18.7^\circ \rightarrow +52.7^\circ$ ($c = 10$ in water).

THERAP CAT: Fluid and nutrient replacer.

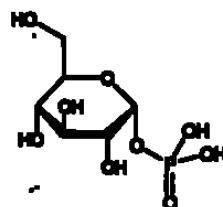
THERAP CAT (VET): Nutrition (usually parenterally), hypoglycemia, ketosis, to counteract hepatotoxicity.

4473. Glucose Oxidase. [9001-37-0] β -D-Glucopyranose aerodehydrogenase; P-FAD; corylophyllin; microcide; milne; ald; notata. An enzyme obtained from mycelia of fungi, such as *Aspergilli* and *Penicillia*; a typical aerobic dehydrogenase which catalyzes the oxidation of glucose to gluconic acid (molecular oxygen is reduced to hydrogen peroxide). It is a flavoprotein, the prosthetic group being flavine-adenine dinucleotide (FAD). Commercial preps frequently contain appreciable amounts of another enzyme, catalase, which is desirable for certain uses since it removes hydrogen peroxide aerobically generated by glucose oxidase. Names of some commercial preps are: *DesO*, *Formocytase*, *OxyBas*, *Oxycase*. Isola from *Penicillia* cultures: Coulhard *et al.*, *Biochem. J.* 39, 24 (1945). Commercial production from *Aspergilli* and *Penicillia*: Goldsmith *et al.*, US 2926122 (1960); from *Aspergillus niger*: Faccetti *et al.*, US 3182881 (1963 to Miles Lab.). Removal of proteolytic enzymes from glucose oxidase (contg catalase) obtained from *Aspergilli* or *Penicillia* cultures: Ohlmeyer, US 2948984 (1960 to Ben L. Saron). Separation from catalase: Patur *et al.*, *Biochem. Biophys. Acta* 65, 369 (1962). Properties: Muller, *Enzymologia* 10, 40 (1941); Kellin, Hartree, *Biochem. J.* 42, 221 (1948), 30, 331 (1952). Review: L. A. Underkofler "Glucose Oxidase: Production, Properties, Present and Potential Applications" in *Soc. Chem. Ind. (London) Monograph* no. 11, 72-86 (1961); R. Bentley, "Glucose Oxidase" in *The Enzymes* vol. 7, P. D. Boyer *et al.*, Eds. (Academic Press, New York, 1963) pp 367-386. Review of use as analytical reagent: J. Kohn, H. A. Motzola, *Crit. Rev. Anal. Chem.* 25, 1-42 (1995).

Amorphous powder or crystals. Abs max between 270-280, 373-380, and 450-460 nm (aq soln). Freely sol in water giving yellowish-green soln. Most active at pH 5.5-6.0 and 30-35°. Stable between pH 4.5 and 7.0. Stable to pepsin and trypsin. A glucose oxidase unit is defined as that quantity of enzyme which will cause the uptake of 10 mm³ oxygen per min in a Warburg manometer at 30° in the presence of excess air and excess catalase with a substrate contg 3.3% glucose monohydrate and 0.1M phosphate buffer, pH 5.9 with 0.4% sodium dehydroascorbate: Scott, *J. Agr. Food Chem.* 1, 727 (1953).

USE: Analytical reagent for the selective detern of glucose. Food additive for the removal of glucose during the prep of dried egg products. Antioxidant in food and food wrappers. Stabilizer for ascorbic acid and vitamin B₁₂.

4474. α -Glucose-1-phosphate. [59-56-3] α -D-Glucopyranose 1-dihydrogenphosphate; α -glucose-1-phosphoric acid; α -D-glucopyranose-1-phosphate; Cori ester. $C_6H_{11}O_6P$; mol wt 260.14. C 27.70%, H 5.04%, O 55.35%, P 11.91%. Found widely in both plants and animals. In plants it is the immediate precursor of starch, and in animals of glycogen, being also the first product in the breakdown and utilization of these substances. Isola from muscle and synthesis using triethyl phosphate: Cori *et al.*, *J. Biol. Chem.* 121, 465 (1937); Kahl, Cori, *Biochem. Biophys. Res.* 1, 33 (1949). Prep from α -acetobromoglucose + silver diphenyl phosphate: Posternak, *J. Am. Chem. Soc.* 72, 4824 (1950); by phosphorylation of starch using phosphorylase and orthophosphate: McCready, Hasid, *Biochem. Biophys. Res.* 4, 63 (1955). Structure: Wolfson, Fletcher, *J. Am. Chem. Soc.* 63, 1050 (1941). Configuration: Wolfson *et al.*, *Ibid.* 64, 23 (1942); Harmon, *Dis. Abstr.* 24, 4400 (1964); Boovera, Macosochla, *Acta Cryst.* 18, 232 (1965).



Free acid. $[\alpha]_D^{25} +120^\circ$. $pK_1 = 1.11$; $pK_2 = 6.13$. Stronger acid than H_2PO_4 . Extremely sol in water.

ANEXO 2

United States Patent [19]

Senta et al.

[11] Patent Number: 4,642,340

[45] Date of Patent: Feb. 10, 1987

[54] STABLE COMPOUNDS OF GLUCOSAMINE SULPHATE

[75] Inventors: Paolo Senta; Francesco Makovec, both of Monza; Luigi Rovati, San Prassisco di Monza, all of Italy

[73] Assignee: Botta Research Laboratories S.p.A., Milan, Italy

[21] Appl. No.: 373,543

[22] Filed: Apr. 30, 1982

[30] Foreign Application Priority Data

Apr. 30, 1981 [IT] Italy 67596 A/81

[51] Int. Cl.⁴ C07H 5/06

[52] U.S. Cl. 536/55.2

[58] Field of Search 536/55.2, 52; 424/180; 514/53

[56] References Cited

U.S. PATENT DOCUMENTS

3,232,836 1/1966 Cariozzi et al. 424/180
3,683,076 8/1972 Rovati 424/180

FOREIGN PATENT DOCUMENTS

1036331 1/1967 United Kingdom 536/111

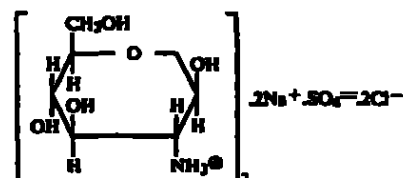
Primary Examiner—Albert T. Meyers

Assistant Examiner—C. Joseph Paraci

Attorney, Agent, or Firm—Sughrue, Mion, Zinn, Macpeak, and Seas

[57] ABSTRACT

The compound consists of a mixed salt of glucosamine sulphate and sodium chloride corresponding to the formula:



and is in the form of a crystalline powder with a melting point above 300° C. The salt is stable at ambient temperatures and humidities and has pharmacological properties practically identical to those of glucosamine sulphate.

5 Claims, No Drawings

STABLE COMPOUNDS OF GLUCOSAMINE SULPHATE

The subject of the present invention is a mixed salt of glucosamine sulphate and sodium chloride, a process for preparing this salt and the use of the said salt in the preparation of pharmaceutical forms otherwise unobtainable, or difficult to obtain, from glucosamine sulphate.

Glucosamine sulphate is a well known and extremely important substance in the treatment of rheumatic fever, arthritic and arthrosic complaints, both in the acute and chronic forms, and, generally, of all pathological conditions originating from metabolic disorders of the osteo-articular tissue.

The synthesis of glucosamine sulphate was described by Breuer in 1898 (Chem. Ber. 31, 2197) and an industrial method is the subject of U.K. Pat. No. 1056331, U.S. Pat. No. 3,683,076 and Swiss Pat. No. 525,861, all owned by our Company.

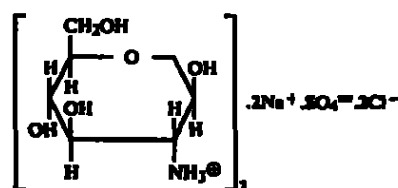
However, until now, it has not been possible to eliminate several unfavourable properties of this compound, specifically, its highly hygroscopic nature and the facility with which its amino group oxidises if not completely saltified.

These unfavourable properties give rise to difficulties and limitations in the practical use of glucosamine sulphate. For example, oral forms, such as tablets or capsules, require anti-oxidants, such as sodium hyposulphite, to be present in their formulations, which substances, although blocking the oxidation of the amino group, leave the problem of the hygroscopic nature of the sulphate unsolved; this necessitates the preparation of these forms in environments with a relative humidity not greater than 30%, with results which are even then unsatisfactory and with a stability lifetime which is practically insufficient for their use. Similar comments apply to rectal forms (suppositories) which, even if kept under dry, refrigerated conditions, degrade with considerable rapidity.

There remain the injectable forms, which are rather delicate to prepare but which are sufficiently stable for practical purposes. It is not possible to make freeze-dried preparations since, invariably, products having the appearance and consistency of viscous oils are obtained, which are thus practically unusable.

It has now been found that it is possible to stabilise glucosamine sulphate by the formation of a mixed salt thereof with sodium chloride. This result is certainly surprising in that it was not predictable that a hygroscopic salt, such as glucosamine sulphate, might be stabilised by sodium chloride, which is another hygroscopic salt.

The mixed salt which is the subject of the present invention and which will be called "glucosamine-SP" for brevity, is constituted by an ionic lattice in which the cations are constituted by protonated glucosamine and Na^+ , and the anions are Cl^- and SO_4^{2-} , these cations and anions being distributed in a fashion such that the simplest formula is $2 (\text{C}_6\text{H}_{14}\text{NO}_5)^+ \cdot \text{Na}^+ \cdot \text{SO}_4^{2-} \cdot 2\text{Cl}^-$ and the structural formula is:



Its melting point is above 300° C. and its sensitivity to ambient relative humidity, even at high temperatures (as will be seen below) is practically negligible.

The method of preparation of glucosamine-SP comprises essentially the steps of: dissolving dry particular sodium chloride under agitation in a quantity of distilled water which may vary between 5.5 and 7.5 (preferably 6.5) times the weight of the sodium chloride itself, at a temperature of from 50° C. to 70° C. (preferably 60° C.); dissolving in the obtained solution the stoichiometric quantity of glucosamine sulphate at a solution temperature of from 35° C. to 45° C. (preferably 40° C.), under agitation; precipitating glucosamine-SP by the addition of a liquid precipitant which is miscible with water and in which glucosamine-SP has a solubility not greater than 0.1% (weight/volume), while operating under agitation at a temperature of from 40° C. to 50° C. (preferably 45° C.); completing the precipitation at a lowered temperature; and recovering the precipitated glucosamine-SP.

The liquid precipitants which may be used are, for example, acetone, ethanol, acetonitrile, tetrahydrofuran and dioxan, and are preferably added in volumes of 5 to 7 (preferably 6) times the volume of the distilled water used for dissolving the starting salts. To advantage, the addition of the liquid precipitant is carried out over a period of 2.5 to 3.5 (preferably 3) hours, whereupon the resulting suspension of glucosamine-SP is maintained for a further period, variable between 12 and 24 (preferably 18) hours, under slow agitation, and at a temperature of from 25° C. to 35° C. (preferably 30° C.) in order to allow both the complete precipitation and the correct growth of the crystals. Once the necessary time has elapsed, the reaction mass is further cooled to a temperature of from 0° C. to 10° C. (preferably 5° C.) and the glucosamine-SP crystals are filtered off and dried in an oven with air circulation, for example at a temperature of from 45° C. to 65° C. (preferably 55° C.) for a period of time which may vary from 12 to 24 (preferably 18) hours.

The glucosamine sulphate which is used with the sodium chloride in the synthesis may be prepared substantially as described in Swiss Pat. No. 525,861, by liberation of the glucosamine from its hydrochloride in an aqueous-alcoholic medium, in the presence of triethylamine, and subsequent treatment of the obtained base in an acetone medium with the stoichiometric quantity of concentrated sulphuric acid to give the glucosamine sulphate. In the patent cited above ethyl ether is used but, in industrial preparations on a large scale, it is preferred to use acetone which is much less dangerous and, moreover, yields a product with the same characteristics as those described in said patent.

EXAMPLE 1

Preparation of glucosamine-SP using acetone as the precipitating agent

75 ml distilled water are loaded into a four-necked flask of a useful volume of 750 ml, provided with a paddle stirrer, a thermometer and a condenser and the flask is heated to a temperature of 60° C. in an electrically-heated bath. 11.68 g (0.2 mol.—M.W. 58.4) of sodium chloride, previously dried to constant weight in an oven at 70° C., are added with moderate stirring (170±10 revolutions per minute) and the mass is maintained under agitation at 60° C. until the solid has completely dissolved, which takes about 20 minutes. As a general rule, the stirring should be carried out so as to avoid both the deposition of particles on the bottom of the flask and their projection against the walls, since, in either case, the dissolution would become more difficult.

Once the solid has completely dissolved, the temperature is lowered to 40° C. and 45.64 g (0.1 moles—M.W. 456.4) of glucosamine sulphate (previously prepared and maintained in an environment with a relative humidity not greater than 30% and a temperature not above 15° C.) is added, the temperature and the stirring at 170±10 revolutions per minute being maintained for the reasons specified above. During this stage a temperature above 45° C. could result in the product turning yellow while at a temperature below 35° C. The glucosamine sulphate would dissolve too slowly for practical purposes.

Under the recommended conditions, the sulphate dissolves completely in about 45 minutes, whereupon the temperature is brought to 45° C. and the precipitation is effected. At temperatures below 45° C. precipitation occurs too quickly, with formation of crystalline agglomerates which may encapsulate some solvent and impurities, while above 50° C. an undesirable yellowing of the suspension may occur. The precipitation is carried out by using 450 ml of acetone, which is added dropwise over a period of 3 hours. In less than 2.5 hours the precipitation occurs too rapidly, while a time of more than 3.5 hours offers no practical advantages. Stirring at 140±10 revolutions per minute is effected during precipitation, ensuring a correct balance between homogenisation of the phases and formation of the optimum quantity of nuclei for crystallisation.

Once the addition of the precipitating agent is terminated, the precipitation is completed and the precipitate is conditioned by lowering the temperature to 30° C. and reducing the stirring rate to 100±10 revolutions per minute for a period of 18 hours. Under these conditions a product with a high purity is obtained since the temperature of 30° C. in the conditioning stage favours the expulsion of any impurities and the reorganisation of the crystals, with absorption of any ions remaining in solution, while the mild agitation allows the whole precipitated mass to be maintained constantly in contact with the solution without altering the uniformity of the crystalline mass. The time indicated above is that necessary to allow the completion of the processes described above. After 18 hours, the temperature is lowered to 5° C. with the aid of an ice-water bath and the crystalline mass obtained is filtered through a Buchner funnel.

After the mass has been well squeezed in order to remove the greatest possible quantity of mother-liquid,

it is transferred to an oven with air circulation and dried at 55° C. for 18 hours.

50.5 g (yield 88.1%) of creamy white crystals with a bitter taste are obtained.

The glucosamine-SP thus prepared has the following characteristics:

Microanalysis for C ₁₂ H ₂₂ O ₁₁ N ₂ Na ₂ SO ₄		
	theoretical %	% found
carbon	23.14	23.02
hydrogen	4.92	4.70
nitrogen	4.88	4.85
Glucosamine titre	97.5–102.5% (according to Elson L. A.-Morgan W. T. J.: <i>Biochem. J.</i> , 27, 1824, (1933)).	
Sulphate titre	97.5–102.5% (by precipitation with BaCl ₂ and titration with EDTA in a medium made basic with NH ₃ , in the presence of the indicator eriochrome black T - sodium rhodanate 2:1).	
Chloride titre	97.5–102.5% (argentometric method).	
Sodium titre	97.5–102.5% (flame photometry).	

Appearance, Colour, Smell: Crystalline powder, bright cream colour, no smell and with a very bitter taste.

Solubility (at 25° C.—w/v).

This test was carried out by preparing saturated solutions of glucosamine-SP in various solvents and determining the concentration of the glucosamine by the Elson-Morgan colorimetric method mentioned above.

Water: very soluble (~40%)
Methanol: slightly soluble (~1%)
Ethanol: very slightly soluble (~0.03%)
Acetone, acetonitrile, tetrahydrofuran, dioxan: practically insoluble (<0.01%).
Benzene, chloroform, carbon tetrachloride, methylene chloride, ligroin, ethyl ether: insoluble.

pH-value:

The pH of an aqueous saturated solution of glucosamine-SP at 20° C. is 3.0±0.2.

Partition Coefficient (K): The partition coefficient K of glucosamine-SP determined at 25° C. in a mixture of phosphate buffer (pH 6.8) with n-octanol has a value which tends to infinity.

Melting point: >300° C. (with partial decomposition above 200° C.).

Specific rotation: [α]_D²⁰=+52±0.1° (at equilibrium in 10% aqueous solution).

Weight loss in drying: ≤0.5% (at 40° C./16–18 Torr for 8 hours in the presence of sulphur trioxide).

EXAMPLE 2

Preparation of glucosamine-SP using ethanol as the precipitating agent

The procedure is as described in Example 1, with the use of absolute ethanol instead of acetone. 48.9 g (yield 85.3%) of glucosamine-SP are obtained with the same characteristics as those described in Example 1.

EXAMPLE 3

Preparation of glucosamine-SP using acetonitrile as the precipitating agent

The procedure is as described in Example 1, with the use of acetonitrile instead of acetone. 51.2 g (yield 89.3%) of glucosamine-SP are obtained having the characteristics described in Example 1.

Example 4

Preparation of glucosamine-SP using tetra hydrofuran as the precipitating agent

The procedure is as described in Example 1, with the use of tetrahydrofuran instead of acetone. 48.1 g (yield 83.9%) of glucosamine-SP are obtained having the characteristics described in Example 1.

EXAMPLE 5

Preparation of glucosamine-SP using dioxan as the precipitating agent

The procedure is as described in Example 1, with the use of dioxan instead of acetone. 47.6 g (yield 83.04%) of glucosamine-SP are obtained having the characteristics described in Example 1.

In order to make clear the difference in stability between the glucosamine-SP prepared by the method described above and glucosamine sulphate (prepared as described in the previously cited Switt Pat. No. 325,861), comparative stability tests were carried out under various conditions of temperature and relative humidity.

Two parameters were taken into consideration for the evaluation, that is, the external appearance of the tested substances and the percent titre of glucosamine determined by the previously cited Elson-Morgan colorimetric method.

The external appearance of the glucosamine sulphate was evaluated according to a scale of from 1 to 6, the significance of which is as follows:

- 1: Microcrystalline powder of white-cream colour
- 2: Slight yellowing with formation of some lumps
- 3: Marked yellowing with numerous darker lumps
- 4: Bright brown colouring and pasty consistency
- 5: Brown-coloured viscous paste
- 6: Dark brown liquid.

Such a scale resulted not necessary for the glucosamine-SP since its appearance remained the same in all the tests and accordingly the scale value assigned was always 1.

The results obtained are given in Tables 1 to 6.

TABLE 1

Stability of Glucosamine-SP and of Glucosamine sulphate at 15° C. and 30% R.H.				
Time (days)	Glucosamine sulphate		Glucosamine-SP	
	Appearance	Titre	Appearance	Titre
0	1	98.7%	1	101.2%
7	1	99.3%	1	100.7%
15	1	98.4%	1	101.5%
30	1	99.3%	1	101.1%
60	1	98.1%	1	100.4%
120	2	97.2%	1	101.9%
360	2-3	84.1%	1	100.7%

TABLE 2

Stability of Glucosamine-SP and of Glucosamine sulphate at 15° C. and 45% R.H.				
Time (days)	Glucosamine sulphate		Glucosamine-SP	
	Appearance	Titre	Appearance	Titre
0	1	99.5%	1	100.7%
7	1	98.3%	1	99.1%
15	1	100.2%	1	99.8%
30	1	99.4%	1	100.4%
60	2	86.2%	1	98.6%
120	4	42.9%	1	99.1%
360	6	not deter.	1	98.4%

TABLE 3

Stability of Glucosamine-SP and of Glucosamine sulphate at 15° C. and 60% R.H.				
Time (days)	Glucosamine sulphate		Glucosamine-SP	
	Appearance	Titre	Appearance	Titre
0	1	99.5%	1	101.2%
3	1	98.4%	1	101.8%
6	1	76.2%	1	100.9%
12	5	31.4%	1	99.8%
24	6	not deter.	1	99.9%
36	6	"	1	101.3%
48	6	"	1	100.7%

TABLE 4

Stability of Glucosamine-SP and of Glucosamine sulphate at 25° C. and 30% R.H.				
Time (days)	Glucosamine sulphate		Glucosamine-SP	
	Appearance	Titre	Appearance	Titre
0	1	99.6%	1	99.1%
7	1	99.1%	1	99.7%
15	1	98.3%	1	98.9%
30	1	99.5%	1	99.9%
60	2	87.8%	1	100.4%
120	3	73.2%	1	98.2%
360	4	40.4%	1	98.8%

TABLE 5

Stability of Glucosamine-SP and of Glucosamine sulphate at 25° C. and 45% R.H.				
Time (days)	Glucosamine sulphate		Glucosamine-SP	
	Appearance	Titre	Appearance	Titre
0	1	100.5%	1	98.9%
3	1	100.3%	1	99.5%
6	1	99.8%	1	98.6%
12	2	80.3%	1	97.7%
24	3	74.5%	1	98.1%
36	5	29.6%	1	97.7%
48	6	not deter.	1	98.4%

TABLE 6

Stability of Glucosamine-SP and of Glucosamine sulphate at 25° C. and 60% R.H.				
Time (hours)	Glucosamine sulphate		Glucosamine-SP	
	Appearance	Titre	Appearance	Titre
0	1	99.3%	1	100.7%
2	1	not deter.	1	not deter.
4	1	"	1	"
8	2	95.8%	1	101.2%
16	3	73.8%	1	not deter.
24	4	44.6%	1	99.2%
36	6	not deter.	1	100.4%

From the results given in Tables 1 to 6 it is clear that glucosamine sulphate is a particularly unstable substance since it is readily oxidised and strongly hygroscopic. The conditions under which it is kept are clearly very important (particularly the ambient relative humidity) and must be rigorously controlled. Only at temperatures less than 15° C., with a relative humidity not greater than 30%, can a stability of about 4 to 5 months be obtained while at 25° C., under the same conditions of relative humidity, signs of degradation are shown even after about 60 days. Further, if the conditions of temperature and humidity are such as to be considered normal 25° C. and 60% R.H.) the first signs of degradation appear even after 4 hours and the glucosamine sulphate is completely decomposed after barely 36 hours.

Glucosamine-SP, on the contrary, shows to be particularly stable to temperature and humidity and hence is easy to preserve and perfectly usable in pharmaceutical techniques. From the tests described above it is seen that, after one year at 25° C. and a relative humidity of 60%, it is perfectly preserved and further tests have shown that, only by operating under extremely drastic conditions, that is at 40° C. and 85% relative humidity, is it possible to observe a slight darkening of the colour and a slight lowering of the glucosamine titre (about 3 to 4%) after about 12 months and this then remains constant under the same conditions of preservation for the subsequent 12 months.

PHARMACOTOXICOLOGICAL SECTION

Although there are marked differences in the physico-chemical characteristics, the stability and the conditions of preservation of glucosamine sulphate and glucosamine-SP, their pharmacotoxicological properties are practically identical.

In confirmation of this, methods and results of testing the two substances contemporaneously "in vitro" and "in vivo" for their pharmacobiological activities, in addition to results of acute toxicity tests carried out on two animal species by different methods of administration are given below.

BIOLOGICAL ACTIVITY "IN VITRO"

Stimulation of the synthesis of glucosaminoglycans (GAG) in mice-embryo fibroblast cultures—evaluation carried out by uptake of ³⁵S

Fibroblast are embryonic cells which, by successive differentiations, give rise to different types of the con-

nective tissue and, consequently, of the osteo-cartilaginous tissue.

Such cells thus provide a very useful experimental model for the evaluation of any pharmacobiological effects (both positive and negative) induced by substances under examination on tissues resulting from this cellular substrate, and particularly on articular tissue.

Methods and results of a test relating to the uptake of ³⁵S by sulphated mucopolysaccharides (GAG), mainly chondroitin-sulphate, both on the cellular and the extracellular level, wherein the uptake of ³⁵S is, consequently, proportional to the rate at which the GAG are synthesised by the fibroblasts, will now be given. For this purpose, primary cultures of mice-embryo fibroblasts (strain C57 BL/6 atCrI) were prepared by mechanical and enzymatic dissociation (in Trypsin Versene mixture-Microbiological Associates) of the embryos taken from the mother on the 18th day of pregnancy. The culture medium is the Eagle medium modified by Dulbecco and supplemented with 15% of calf foetus serum. The incubation atmosphere consists of 5% of carbon dioxide in air at 37° C. 24 hours after inoculation, the medium is replaced by a new medium containing the drug under examination and the radioactive precursor (Na₂³⁵SO₄) for the measurement of the synthesis both of soluble and tissue-bound GAG; the culture is left to incubate for a further 24 hours and then the culture medium (containing the soluble GAG) and fibroblasts (containing the tissue-bound GAG) are separated.

The soluble GAG are isolated from the culture medium by precipitation with a solution of 5% trichloroacetic acid in ice-water while the fibroblast residues, containing the tissue-bound GAG, after repeated washings with physiological solutions, are dissolved in DIMILUME or VERSENE.

The quantity of ³⁵S incorporated both in the soluble GAG and in the tissue-bound GAG are evaluated by the usual scintillation methods and expressed in cpm (counts per minute).

The tests were carried out five times for each sample in order to allow the results to be evaluated statistically.

The results obtained are given in Tables 7 and 8.

TABLE 7

Stimulation of the production of soluble GAG in mice-embryo fibroblast cultures. Evaluation by uptake of ³⁵ S							
SUBSTANCE	Conc. (γ/ml)	Soluble GAG synthesis (in cpm)				Δ % over a.1 ct.	
		Average ± s.e.	t ₁ ⁽¹⁾	p ₁ ⁽¹⁾	t ₂ ⁽²⁾	p ₂ ⁽²⁾	
Untreated controls	—	5630 ± 654	—	—	—	—	±0
Glucosamine sulphate	10	7250 ± 905	1.27	N.S.	—	—	+24.3
Glucosamine sulphate	50	11430 ± 1108	4.35	<0.01	—	—	+96.0
Glucosamine sulphate	100	9980 ± 1271	2.90	<0.02	—	—	+71.2
Glucosamine-SP	12.5 ⁽³⁾	6750 ± 718	0.95	N.S.	0.43	N.S.	+15.8
Glucosamine-SP	62.5 ⁽²⁾	12730 ± 1201	5.04	<0.01	0.80	N.S.	+118.3
Glucosamine-SP	125 ⁽²⁾	12440 ± 1473	4.10	<0.01	1.26	N.S.	+113.3

TABLE 8

Stimulation of the production of tissue-bound GAG in mice-embryo fibroblast cultures. Evaluation by uptake of ³⁵ S							
SUBSTANCES	Conc. (γ/ml)	Soluble GAG Synthesis (in cpm)				Δ % over n.t. ct.	
		Average ± s.e.	t ₁ ⁽¹⁾	p ₁ ⁽¹⁾	t ₂ ⁽²⁾	p ₂ ⁽²⁾	
Untreated controls	—	4680 ± 664	—	—	—	—	±0
Glucosamine sulphate	10	6210 ± 779	1.49	N.S.	—	—	+32.7
Glucosamine sulphate	50	8220 ± 1033	2.94	<0.02	—	—	+75.6
Glucosamine sulphate	100	9110 ± 879	4.02	<0.01	—	—	+94.7
Glucosamine-SP	12.5 ⁽³⁾	5490 ± 604	0.90	N.S.	0.73	N.S.	+17.3
Glucosamine-SP	62.5 ⁽³⁾	7780 ± 612	3.38	<0.01	0.37	N.S.	+66.2
Glucosamine-SP	125 ⁽³⁾	8320 ± 1295	2.50	<0.05	0.50	N.S.	+77.8

Notes to Tables 7 and 8:
The statistical significance was evaluated by the Student "t" test.
Thus, the Student "t" values relating to the comparison between groups of values under consideration are given in the columns headed t₁ and t₂ while columns headed p₁ and p₂ report statistical probabilities that the compared groups of values belong to the same population.
Hence the notation N.S. indicates that the groups of values compared are not, from a statistical point of view, significantly different.
It is assumed, however, that two groups of values compared are statistically different when p, in dependence on the value "t" and the degrees of freedom, is 0.05.
(1): t₁ and p₁ relate to the comparison between treated groups and non-treated controls.
(2): t₂ and p₂ relate to the comparison between groups

40 female albino rats of the Sprague Dawley strain, having a weight of about 130 g, subdivided at random into 5 groups of 8 animals, were used.
One group of animals was used as a control. The other 4 groups were treated orally with 300 and 600 mg/kg doses of glucosamine sulphate and 375 and 750 mg/kg doses of glucosamine-SP (corresponding respectively to 300 and 600 mg/kg of glucosamine sulphate).
After the subcutaneous implant of 2 cotton pellets each having a weight of 20 mg into the dorsal region, the animals were administered daily, for 4 consecutive days, with the substances under examination in the doses given above.
At the end of the treatment, the granuloma were taken from the animals, which had been killed by prolonged anaesthesia with ether, and were dried in an oven at a temperature of 60° C. for 24 hours and were then weighed.
The results obtained are given in Table 9.

TABLE 9

Anti-inflammatory activity of glucosamine sulphate and glucosamine-SP in the test for granuloma from cotton pellets in rats						
TREATMENT	Dose (mg/kg/os)	Average dry weight of the granuloma (average ± s.e.)	t ₁ ⁽¹⁾ p ₁ ⁽¹⁾ t ₂ ⁽²⁾ p ₂ ⁽²⁾			
			Inhibition			
Untreated controls	—	154.2 ± 11.9	—	—	—	±0
Glucosamine sulphate	300	91.2 ± 10.8	3.92	<0.01	—	40.9
Glucosamine sulphate	600	70.7 ± 7.9	5.84	<0.01	—	54.1
Glucosamine-SP	375 ⁽³⁾	94.6 ± 10.7	3.73	<0.01	0.22	38.7
Glucosamine-SP	750 ⁽³⁾	64.8 ± 7.0	6.47	<0.01	0.56	58.0

Note to table 9:
The meanings of t₁ p₁ t₂ p₂ (1) (2) are the same as those given for Tables 7 and 8.
⁽³⁾ 375 and 750 mg/kg of glucosamine-SP correspond to 300 and 600 mg/kg of glucosamine sulphate, respectively.

treated with equal doses, that is:
Glucosamine sulphate 10 γ/ml, glucosamine-SP 12.5 γ/ml, and so on.
(3): 12.5, 62.5 and 125 γ/ml of glucosamine sulphate.
Abbreviation meanings for Tables 7 and 8:
cpm: counts per minute
s.e.: standard error
n.t. ct: non-treated controls.
From the results given in Tables 7 and 8 it can be seen that glucosamine sulphate and glucosamine-SP, at the same concentrations, have the same activity in stimulating the synthesis of both soluble and tissue-bound GAG by mice-embryo fibroblasts.

PHARMOCOLOGICAL ACTIVITY "IN VIVO"
Anti-inflammatory activity in tests on granuloma induced by cotton-pellets

The test consists of evaluating the capacity of the substances under examination to inhibit the formation of granuloma following the subcutaneous implantation of extraneous bodies (in this case, cotton pellets).

Not to Table 9:
The meanings of t₁p₁t₂p₂ (1) (2) are the same as those given for Tables 7 and 8.
(3): 375 and 750 mg/kg of glucosamine-SP correspond to 300 and 600 mg/kg of glucosamine sulphate, respectively.
From the results given in Table 9 it can be seen that glucosamine sulphate and glucosamine-SP also have the same pharmacological activity "in vivo".
More precisely, for the same dosage, the two substances are equivalent from a pharmacological point of view.

ACUTE TOXICITY

A. In mice:
Swiss NMRI mice having an average weight of 20±2 g, subdivided in groups of 10 animals (5 females and 5 males) were used for each dose and for each method of administration.

The methods of administration were: oral by means of gastric probe, intramuscular and endovenous into the caudal vein.

The observation time after administration was 10 days.

The doses used and results obtained are given in Table 10.

TABLE 10

Acute toxicity of glucosamine sulphate and glucosamine-SP in mice with various methods of administration.				
SUBSTANCE	Method of Administration	Max. dose administered (mg/kg)	% mortality	DL ₅₀ (mg/kg)
Glucosamine sulphate	Oral	3000	0	>3000
Glucosamine sulphate	Intra-muscular	3000	0	>3000
Glucosamine sulphate	Endo-venous	1500	0	>1500
Glucosamine-SP	Oral	6250 ⁽¹⁾	0	>6250
Glucosamine-SP	Intra-muscular	3750 ⁽¹⁾	0	>3750
Glucosamine-SP	Endo-venous	1875 ⁽¹⁾	0	>1875

⁽¹⁾1875, 3750 and 6250 mg/kg of glucosamine-SP correspond to 1500, 3000 and 5000 mg/kg of glucosamine sulphate, respectively.

B. In rats

Sprague Dawley albino rats having an average weight of about 150 g. subdivided into groups of 10 animals (5 males and 5 females) were used for each dose and for each method of administration.

The methods of administration were: oral by means of a gastric probe, intramuscular and endovenous into the caudal vein.

The observation time after administration was 10 days.

The doses used and the results obtained are given in Table 11.

TABLE 11

Acute toxicity of glucosamine sulphate and glucosamine-SP in rats with different methods of administration.				
SUBSTANCE	Method of administration	Max. dose administered (mg/kg)	% mortality	DL ₅₀ (mg/kg)
Glucosamine sulphate	Oral	3000	0	>3000
Glucosamine sulphate	Intra-muscular	3000	0	>3000
Glucosamine sulphate	Endo-venous	1500	0	>1500
Glucosamine-SP	Oral	6250 ⁽¹⁾	0	>6250
Glucosamine-SP	Intra-muscular	3750 ⁽¹⁾	0	>3750
Glucosamine-SP	Endo-venous	1875 ⁽¹⁾	0	>1875

⁽¹⁾1875, 3750 e 6250 mg/kg of glucosamine-SP correspond to 1500, 3000 and 5000 mg/kg of glucosamine sulphate, respectively.

As may be seen from Tables 10 and 11, even at levels of acute toxicity, no differences are found between glucosamine sulphate and glucosamine-SP. For all the methods of administration and all the species of animals tested, both have such a low toxicity that there is no mortality even with very high doses, so that it is difficult to establish exactly a precise DL₅₀.

The fact that glucosamine-SP has the same pharmacotoxicological and pharmacokinetic characteristics as glucosamine sulphate, it is clear that the former, thanks to its properties of stability and ease of preparation, represents a clear progress in the state of the art. Accordingly, a number of examples of formulations of

pharmaceutical preparations containing glucosamine-SP will be given below. It should be noted that they differ from the formulations described in U.S. Pat. No. 3,863,076 for pharmaceutical forms containing glucosamine sulphate in that they do not include stabilising or preserving ingredients or anti-oxidants since they present no problems with regard to their preparation, preservation or stability.

PREPARATIONS OF PHARMACEUTICAL FORMS FOR ORAL ADMINISTRATION

1. Capsules:

Glucosamine-SP	314 mg
Molbe starch	40 mg
Lactose	28.5 mg
Magnesium stearate	5 mg
Talc	2.5 mg

The components are mixed until a homogeneous mixture is obtained, sieved through a 30-mesh sieve and filled into a capsule of gelatine.

Each capsule contains 410 mg of powder, corresponding to 314 mg of glucosamine-SP.

2. Tablets:

Glucosamine-SP	314 mg
Lactose	42 mg
Polyvinyl pyrrolidone	20 mg
Carboxymethyl cellulose sodium salt	10 mg
Silicon dioxide	5 mg
Magnesium stearate	5 mg
Talc	4 mg

The glucosamine-SP, the polyvinyl pyrrolidone and the lactose are formed into a paste with 95% ethanol, the paste is dried at 45° C., granulated and sieved through a 20-mesh sieve. The other ingredients are added to the obtained granulate and mixed until the mixture is homogeneous.

The mixture is then compression-moulded to form tablets having a weight of 400 mg and containing 314 mg of glucosamine-SP.

3. Dragées:

Glucosamine-SP	314 mg
Molbe starch	30.4 mg
Polyvinyl pyrrolidone	6.4 mg
Glyceryl monostearate	12.8 mg
Methyl-cellulose	3.6 mg
Stearic acid	4 mg
Silicon dioxide	0.8 mg
Succharose	66.3 mg
Talc	90.9 mg
Calcium carbonate	25 mg
Gum arabic	4.3 mg
Magnesium stearate	5.6 mg
Shellac	16.7 mg
Caster oil	0.35 mg
Titanium dioxide	1.8 mg
White beeswax	0.05 mg

The glucosamine-SP, starch, polyvinyl pyrrolidone, glyceryl monostearate, methyl-cellulose, stearic acid and titanium dioxide are mixed until homogeneous, sieved through a 30-mesh sieve and compression-moulded to form cores of 392 mg. The prepared cores are coated, in an enrober, with a suspension of talc,

magnesium stearate, shellac and castor oil in 95% ethanol and subsequently dried for 12 hours at 35° C.

Primary dragées of 415.7 mg are obtained which are further coated with a previously-prepared aqueous suspension containing the saccharose, talc, calcium carbonate, gum arabic and titanium dioxide. After drying at 30° to 35° C. for 12 hours, dragées of 603.95 mg are obtained which are finally polished with the beeswax.

The final weight of the dragées is 604 mg and the glucosamine-SP content is 314 mg.

PREPARATION OF PHARMACEUTICAL FORMS FOR RECTAL ADMINISTRATION

Glucosamine-SP	314 mg
Semi-synthetic glycerides	1586 mg
Polysorbitan monostearate	80 mg
Distilled H ₂ O	20 mg

The semi-synthetic glycerides are melted at 45° C. under constant agitation; still under agitation, a previously-prepared mixture of water and polysorbitan monostearate is added and finally the glucosamine-SP, which has previously been micronized to a grain size of from 5 to 20 microns, is added.

The mixture is left under agitation for 30 minutes, that is until complete dispersion is achieved, then it is injected into polyvinylchloride shells which, after cooling, are sealed.

Suppositories weighing 2000 mg, containing 314 mg of glucosamine-SP are obtained.

PREPARATIONS OF PHARMACEUTICAL FORMS WHICH CAN BE USED FOR INTRAMUSCULAR, INTRAVENOUS, INTRA-ARTICULAR INJECTIONS

1. Phials:

<u>Phial A:</u>	
Glucosamine-SP	302.5 mg
Lidocaine hydrochloride	10 mg
H ₂ O for injection to make	2 ml
<u>Phial B:</u>	
Diethanolamine	24 mg
H ₂ O for injection to make	1 ml

PREPARATION OF PHIAL A

The glucosamine-SP and the lidocaine hydrochloride are dissolved in water in the proportions indicated, under agitation, filtered under inert gas blanket through a membrane filter with a porosity of 0.45, and introduced into 3 ml phials which are finally sterilised at 115° to 120° C. for 30 minutes in an autoclave with a steam current.

PREPARATION OF PHIAL B

The diethanolamine is dissolved in water under agitation in the proportion indicated, filtered under inert gas blanket through a membrane filter with a porosity of 0.45, introduced into 1 ml phials which are finally sterilised at 115° to 120° C. for 30 minutes in an autoclave with a steam current.

Pairs of 3 ml and 1 ml phials are obtained, the contents of which are mixed immediately before use. This recourse is due to the fact that the natural pH of

glucosamine-SP, at the concentrations used, is about 3 and therefore is physiologically unacceptable.

In order to achieve a physiologically tolerable pH it is necessary to add a base (such as diethanolamine) with consequent liberation of the amino group of the glucosamine which, as stated above, is readily decomposable. Thus, for reasons of stability, use is made of pairs of phials, the contents of which are mixed immediately before use, with the double advantage of having a product which is stable with time (phial A), and which, by the addition of the base (phial B), achieves a physiological, and thus tolerable, pH.

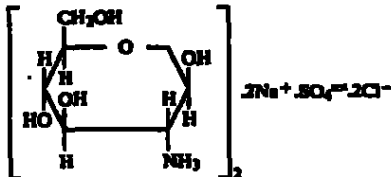
2. Freeze-dried preparation

Glucosamine-SP	302.5 mg
Lidocaine hydrochloride	10 mg
Diethanolamine	20 mg

The components are dissolved in the desired volume of sterile water for injections, filtered under an inert gas blanket through a membrane filter with a porosity of 0.45µ and freeze-dried in small flasks. A white solid residue is obtained which, in use, is dissolved in 2 ml of sterile water for injections within a time of not more than 30 seconds (pH 6.8).

We claim:

1. Mixed salt of glucosamine sulphate and sodium chloride corresponding to the formula:



said mixed salt being in the form of a crystalline powder having a melting point above 300° C.

2. Process for the preparation of the mixed salt of glucosamine sulphate and sodium chloride according to claim 1, characterised by the steps of:

- (a) dissolving dry sodium chloride in 5.5 to 7.5 parts by weight of distilled water for every part of sodium chloride at a temperature of from 50° to 70° C. under agitation;
- (b) dissolving in the solution obtained in step (a) the stoichiometric quantity of glucosamine sulphate at a temperature of from 35° to 45° C., under agitation;
- (c) precipitating the mixed salt by the addition of a liquid precipitant which is miscible with water and in which the said mixed salt has a solubility not greater than 0.1% (w/v) while operating under agitation at a temperature of from 40° C. to 50° C.;
- (d) completing the precipitation by lowering the temperature of the mixture; and
- (e) recovering the precipitated mixed salt.

3. The process of claim 2, wherein the liquid precipitant is acetone, ethanol, acetonitrile, tetrahydrofuran or dioxan.

4. The process of claim 2 or 3, wherein the liquid precipitant is added in a proportion of 5 to 7 parts by volume with respect to the water used in step (a) over a period of from 2.5 to 3.5 hours.

5. The process of claim 2 or 3, wherein the recovered mixed salt is dried in air-circulation oven at 45°-65° C.

* * * * *

ANEXO 3



US005847107A

130

United States Patent [19]

[11] Patent Number: 5,847,107

De Wan et al.

[45] Date of Patent: Dec. 8, 1998

[54] METHOD OF PREPARING MIXED GLUCOSAMINE SALTS

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[73] Assignee: Rotta Research B.V. Amsterdam (Swiss Branch), Lugano, Switzerland

[21] Appl. No.: 910,749

[22] Filed: Aug. 13, 1997

[30] Foreign Application Priority Data

Aug. 19, 1996 [CH] Switzerland 2024/96

[51] Int. Cl.⁶ C07H 5/06; C07H 1/00

[52] U.S. CL 536/55.3; 514/62; 536/55.2

[58] Field of Search 514/62; 536/17.2, 536/17.9, 29.1, 55.2, 55.3

[56] References Cited

U.S. PATENT DOCUMENTS

4,642,340 2/1987 Senin et al. 536/55.2

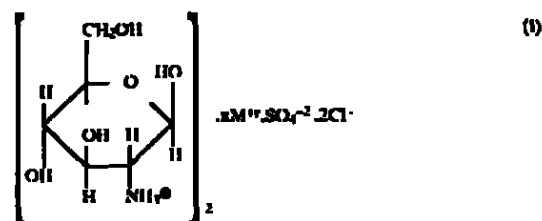
FOREIGN PATENT DOCUMENTS

893010 8/1982 Belgium .
444000 8/1991 European Pat. Off. .
3532081 A1 3/1987 Germany .
89-05646 6/1989 WIPO .

Primary Examiner—Marian C. Knude
Assistant Examiner—Howard C. Lee
Attorney, Agent, or Firm—Sughrue, Mion, Zinn, Macpeak & Seas, PLLC

[57] ABSTRACT

A method of preparing a therapeutically active crystalline form of glucosamine sulphate which is stable at ambient temperature and humidity and corresponds to the empirical formula:



in which M represents a metal selected from the group consisting of Na, K, Ca, Mg,

x=1 if y=2, and

x=2 if y=1,

wherein glucosamine hydrochloride and a sulphate of a metal selected from Na, K, Ca, Mg are reacted in the stoichiometric ratio defined by formula (I), in an aqueous solvent, and the stable crystalline form is precipitated by the addition of a liquid precipitating agent miscible with water.

5 Claims, No Drawings

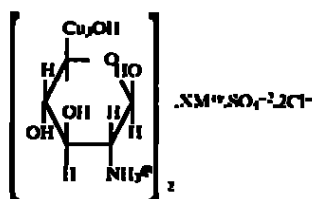
METHOD OF PREPARING MIXED GLUCOSAMINE SALTS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a novel and advantageous method of synthesizing mixed glucosamine salts, including in their formula, protonated glucosamine and an alkali-metal or alkaline-earth ion such as sodium, potassium, calcium or magnesium as cations and chlorides and sulphates as negative ions.

The minimum empirical formula of the above mentioned salts may be represented as follows:



wherein

M represents Na, K, Ca, or Mg and

x=1 if y=2

x=2 if y=1

These mixed salts are in crystalline form with melting points above 300° C. and are stable at ambient temperature and humidity.

2. Background Information

Glucosamine sulphate is a well known substance which is extremely important in the treatment of both acute and chronic rheumatic and arthritic diseases and arthritis and, in fact, in all pathological conditions originating from metabolic dysfunctions affecting bone and joint tissue.

The synthesis of glucosamine sulphate was described by Breuer in 1898 (Chem. Ber. 31, 2197) and an industrial method forms the subject of GB 1,056,331, of U.S. Pat. No. 3,683,076, and of Swiss patent 525, 861.

However, this substance has some disadvantages, such as the fact that it is highly hygroscopic, and the case with which the amine group is oxidized when it is not completely salified, which render it practically impossible to use in the preparation of pharmaceutical forms for use in human therapy.

Oral forms such as tablets, capsules and powders therefore require the presence of antioxidants in their formulations, but these do not solve the problem of hygroscopicity; it is then necessary to prepare these forms in environments with a relative humidity no greater than 30%, with still unsatisfactory results, the instability of these forms over time rendering them practically impossible to use.

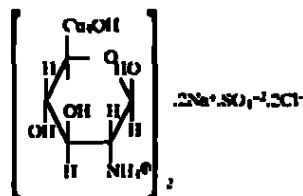
Similar remarks apply to rectal forms (suppositories) which degrade very quickly, even if kept in dry and refrigerated environments.

Injectable forms are sufficiently stable for practical purposes, however difficulties apply to their preparation. It is not possible to prepare lyophilized forms because, invariably, one obtains products which have the appearance and consistency of viscous oils and, as such, are practically unusable.

The problems of glucosamine sulphate, which are such as to preclude its practical use for treatment in man, were overcome by the invention of glucosamine-SP and of the method of preparation thereof described in U.S. Pat. No. 4,642,340.

2

Glucosamine-SP is a mixed salt in the formula of which protonated glucosamine and the Na⁺ ion appear as cations and the chloride and the sulphate ions as anions, according to the following empirical formula:



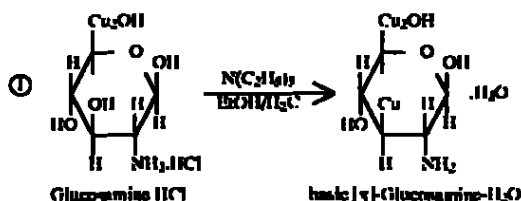
This is a non-hygroscopic, crystalline substance with a melting point above 300° C., which is stable in normal conditions of temperature and relative humidity. It also has pharmacological properties practically identical to those of glucosamine sulphate with the advantage of being easily usable in the preparation of oral and parenteral pharmaceutical forms for use in human therapy.

The method of preparation of glucosamine-SP described in U.S. Pat. No. 4,642,340 consists essentially of dissolving glucosamine sulphate and sodium chloride in distilled water and separating the glucosamine-SP by the addition of water-soluble liquid precipitating agents in which glucosamine sulphate has a solubility no greater than 0.1% (w/v). Acetone, ethanol, acetonitrile, tetrahydrofuran and dioxane are mentioned as precipitating agents in the examples. Moreover, in the patent, the volumetric ratios between the solvent and precipitating agents, as well as the other reaction parameters such as temperatures, contact times and stirring speeds, are strictly fixed.

The glucosamine sulphate which is used as the starting product in the synthesis of glucosamine-SP is in turn produced from glucosamine hydrochloride, according to Swiss patent 525, 861, by a synthesis which consists essentially of two steps which can be summarized as follows:

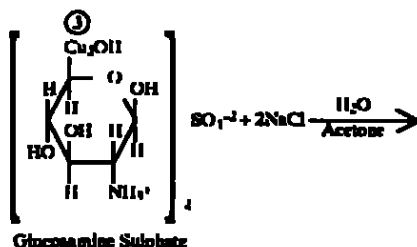
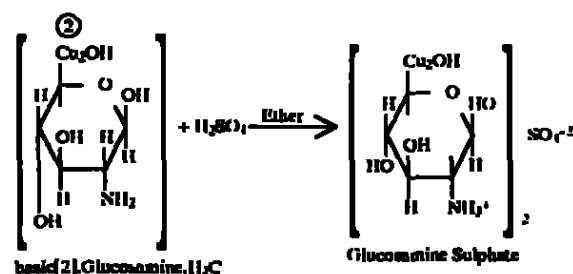
1. Liberation of the alpha form of glucosamine from its salt with hydrochloric acid in an aqueous-alcoholic medium, in the presence of triethylamine.
2. Salification of the alpha form of glucosamine with the stoichiometric quantity of sulphuric acid in an ethyl ether medium to produce glucosamine sulphate.

The entire process which leads to the synthesis of glucosamine-SP, described in the patent U.S. Pat. No. 4,642, 340 from glucosamine hydrochloride can therefore be represented schematically by the following 3 steps:



3

-continued



SUMMARY OF THE INVENTION

The present patent application describes a novel method of synthesising mixed glucosamine salts, amongst which glucosamine-SP is also included. It has the advantage of producing this substance and its analogues, in the molecular formula of which not only sodium but other alkali-metal and alkaline-earth elements such as K, Ca and Mg may appear alternatively as cations, in a single step from glucosamine hydrochloride.

This method avoids the steps of liberating the basic glucosamine from its hydrochloride and subsequent salification with sulphuric acid, rendering unnecessary the laborious method of preparing glucosamine sulphate which is used as the starting product in the synthesis of glucosamine-SP.

In the method of the present invention, as defined by the appended claims, in place of glucosamine sulphate and sodium chloride, the starting products are glucosamine hydrochloride and the sulphate of the metal to be inserted in the composition of the mixed salt.

When reacted in the correct stoichiometric ratios and in reaction conditions similar to those described in the U.S. Pat. No. 4,642,340, these give rise directly to a product which corresponds exactly to glucosamine-SP, in the case of a combination of glucosamine hydrochloride and sodium sulphate, or to an analogue thereof in the case of a combination of glucosamine hydrochloride and the sulphate of another of the alkali-metals or alkaline-earths already mentioned. The technological progress associated with the method of the present invention is very clear in consideration of the advantages which it offers in comparison with the current state of the art.

4

These advantages may be summarised as follows:

1. Unlike glucosamine sulphate, glucosamine hydrochloride is a stable substance and does not therefore require particular precautions as far as its storage is concerned, in terms either of time or of temperature and humidity.
2. Costs are lower in terms of solvents and reagents (the synthesis starts directly from glucosamine hydrochloride without the need to synthesise glucosamine sulphate from glucosamine hydrochloride, in a vicious circle).
3. Energy costs are lower (again for the reasons given in point No. 2).
4. There is less wear of the equipment (again for the reasons given in point No. 2).
5. Less labour is used (the process takes place in a single step rather than in three steps).
6. A practically quantitative yield is obtained.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The preferred method of preparation according to the present invention comprises essentially the steps of dissolving the preselected sulphate, with stirring, in a quantity of distilled water variable between 4.5 and 6.5 (preferably 5) times the weight of the sulphate, at a temperature no higher than the boiling point of water, then reducing the temperature so that it does not exceed 60° C. (preferably 50° C.), adding the stoichiometric quantity of glucosamine hydrochloride, again with stirring, keeping the temperature constant until it is fully dissolved and, again with stirring and with the temperature being kept constant, precipitating the mixed glucosamine salt by the addition of a liquid precipitating agent which is miscible with water and in which the mixed glucosamine salt has a solubility no greater than 0.1% (w/v).

For example, acetone, ethanol, acetonitrile, tetrahydrofuran and dioxane may be used as precipitating agents added in volumes 5-7 (preferably 6) times greater than the volume of distilled water used to dissolve the starting salts. The precipitating agent is advantageously added over a period of 2.5 to 3.5 (preferably 3) hours, after which the resulting suspension of the mixed salt is kept, with slow stirring, for a further period ranging between 12 and 24 (preferably 18) hours at a temperature of between 25° and 35° C. (preferably 30° C.) to permit both complete precipitation and the correct crystal growth.

When the necessary period has elapsed, the reaction mass is cooled to a temperature of between 0° and 10° C. (preferably 5° C.) and the mixed salt thus obtained is filtered out and then dried in a forced-air oven at a temperature of between 45° and 65° C. (preferably 55° C.) for a period variable between 12 and 24 (preferably 18) hours.

EXAMPLE 1

Preparation of glucosamine-SP with the use of acetone as the precipitating agent

75 ml of distilled water were loaded into a four-necked flask with a usable capacity of 750 ml, with a paddle stirrer, thermometer and condenser and the temperature was brought to 70° C. by means of an electric heating bath. 14.21 g (0.1 moles - M.W. 142.06) of sodium sulphate previously dried to constant weight in an oven at 70° C. was added with moderate stirring (170 +/- 10 revolutions per minute) and the mass was kept at 70° C. with stirring until dissolving was complete, which was achieved in about 20 minutes.

5

Upon completion of the dissolving, the temperature was reduced to 50° C. and 43.13 g (0.2 moles - M.W. 215.64) of glucosamine hydrochloride was added, the temperature being kept constant and stirring being maintained at 170 +/-10 revolutions per minute.

At this stage, a temperature greater than 60° C. could lead to yellowing of the reaction mass with a reduction both in the yield and in the purity of the final mixed salt.

In the conditions recommended, complete dissolving was achieved in about 45 minutes, after which the temperature was brought to 55° C. and precipitation was then carried out.

At temperatures below 50° C. too rapid a precipitation is brought about with the formation of crystalline agglomerations which may incorporate solvent and impurities, whereas above 60° C. undesirable yellowing of the suspension may occur. The precipitation was effected with the use of 450 cc of acetone which was dropped in over a period of 3 hours (with less than 2.5 hours the precipitation is too rapid and with more than 3.5 hours there are no practical advantages) and with stirring at 140 +/-10 revolutions per minute, which ensured the correct equilibrium between homogenisation of the phases and formation of the optimal quantity of crystallisation seeds.

Upon completion of the addition of the precipitating agent, the separation was complete and the precipitate was conditioned by reducing the temperature to 30° C. and by reducing the stirring speed to 100 +/-10 revolutions per minute, for a period of 18 hours.

In these conditions, a product of high purity was produced since the temperature of 30° C. favours the expulsion of any impurities and the reorganisation of crystals in the conditioning stage with absorption of any ions remaining in solution, whilst the gentle stirring enabled the entire precipitated mass to be kept constantly in contact with the solution without alteration of the uniformity of the crystalline mass.

The time indicated above is that required to allow the processes described above to be completed.

After 18 hours, the temperature was reduced to 5° C. by means of a water-ice bath and the crystalline mass obtained was filtered out with a Buchner filter.

After the moist filter cake had been well pressed in order to eliminate as much solvent as possible it was transferred into a forced-air oven and dried at 55° C. for 18 hours.

55.1 g (yield 96.1%) of creamy-white crystals with a bitter flavour were obtained.

The chemical and physical analytical characteristics of the glucosamine-SP obtained as described in Example 1 can be superimposed perfectly on those described in U.S. Pat. No. 4,642,340.

These characteristics are: Microanalysis for $C_{12}H_{24}Cl_2N_2Na_2SO_{14}$:

	% theoretical	% found
Carbon	25.14	25.23
Hydrogen	4.92	4.86
Nitrogen	4.88	4.97

Titre of glucosamine: 97.5-102.5% (potentiometric titre with NaOH in an aqueous medium).

Titre of sulphates: 97.5-102.5% (complexometric titre with EDTA in an NH_3 basic medium after precipitation with $BaCl_2$).

Titre of chlorides: 97.5-102.5% (argentometric titre).

6

Titre of sodium: 97.5-102.5% (in atomic absorption)

Appearance, colour, odour: Crystalline powder of pale cream colour, odourless and with a strongly bitter flavour.

Solubility (25° C. - w/v): Very soluble (about 40%); Water

Slightly soluble (about 1%); Methanol Very slightly soluble

(about 0.03%); Ethanol Practically insoluble (<0.01%);

Acetone, acetonitrile, tetrahydrofuran, dioxane

Insoluble: Benzene chloroform, carbon tetrachloride, methylene chloride, ligroin, ethyl ether.

pH: The pH of a saturated aqueous solution of glucosamine-SP at 20° C. is 3 +/-0.2.

Partition coefficient: The partition coefficient of Glucosamine-SP determined at 25° C. in phosphate buffer (pH 6.8)/n-octanol has a practically infinite value.

Melting point: >300° C. (with partial decomposition above 200° C.).

Specific Rotation: 52 +/-0.2° (in equilibrium in 10% aqueous solution).

Röntgenographic investigation carried out both on samples of glucosamine-SP prepared according to the method described in the present patent application and on samples prepared according to the U.S. Pat. No. 4,642,340 showed that there was no difference between the two substances from a crystallographic point of view.

In fact, upon examination, the angular values and the intensity sequences of the diffraction patterns (Debye) of powders of the samples of the two types could be superimposed perfectly and were therefore indistinguishable.

EXAMPLE 2

Preparation of glucosamine-SP with the use of ethanol as the precipitating agent

The method described in Example 1 was followed with the use of absolute ethanol instead of acetone. 54.3 g (94.7%) of glucosamine-SP having the same characteristics as described in Example 1 were obtained.

EXAMPLE 3

Preparation of glucosamine-SP with the use of acetonitrile as the precipitating agent

The method described in Example 1 was followed, with the use of acetonitrile instead of acetone. 55.3 g (96.5%) of glucosamine-SP having the same characteristics as described in Example 1 were obtained.

EXAMPLE 4

Preparation of glucosamine-SP with the use of tetrahydrofuran as the precipitating agent

The method described in Example 1 was followed, with the use of tetrahydrofuran instead of acetone. 53.7 g (93.7%) of glucosamine-SP having the same characteristics as described in Example 1 were obtained.

EXAMPLE 5

Preparation of glucosamine-SP with the use of dioxane as the precipitating agent

The method described in Example 1 was followed, with the use of dioxane instead of acetone. 53.4 g (93.1%) of glucosamine-SP having the same characteristics as described in Example 1 were obtained.

EXAMPLE 6

Preparation of the mixed salt starting with glucosamine hydrochloride and potassium sulphate

Exactly the same method as described in Example 1 was followed, the sodium sulphate being replaced by 17.43 g (0.1 moles - M.W. 174.3) of potassium sulphate.

7

58.9 g (yield 97.3%) of creamy-white crystals with a bitter flavour and having the following chemical and physical analytical characteristics were obtained: Microanalysis for $C_{12}H_{20}Cl_2N_2K_2SO_{14}$:

	% theoretical	% found
Carbon	23.80	23.94
Hydrogen	4.66	4.60
Nitrogen	4.63	4.67

Titre of glucosamine: 97.5–102.5% (potentiometric titre with NaOH in an aqueous medium).

Titre of sulphates: 97.5–102.5% (complexometric titre with EDTA in an NH_3 basic medium after precipitation with $BaCl_2$).

Titre of chlorides: 97.5–102.5% (argentometric titre).

Titre of potassium: 97.5–102.5% (in atomic absorption)

Appearance, colour, odour: Crystalline powder of pale cream colour, odourless and with a strongly bitter flavour.

Solubility (25° C. - w/v):

Very soluble (about 40%): water

Slightly soluble (about 1%): Methanol

Very slightly soluble (about 0.03%): Ethanol

Practically insoluble (<0.01%): Acetone, acetonitrile, tetrahydrofuran, dioxane

Insoluble: Benzene, chloroform, carbon tetrachloride, methylene chloride, ligroin, ethyl ether.

pH: The pH of a saturated aqueous solution of the mixed salt at 20° C. is 3 ± 0.2.

Partition coefficient: The partition coefficient of the mixed salt determined at 25° C. in phosphate buffer (pH 6.8)/n-octanol has a practically infinite value.

Melting point: >300° C. (with partial decomposition above 200° C.).

Specific Rotation: 49 ± 0.2° (in equilibrium in 10% aqueous solution).

EXAMPLE 7

Preparation of the mixed salt from glucosamine hydrochloride and calcium sulphate dihydrate.

Exactly the same method as described in Example 1 was followed, the sodium sulphate being replaced by 15.42 g of calcium sulphate dihydrate (0.1 moles - M.W. 154.16).

55.6 g (yield 98%) of creamy-white crystals having the following chemical and physical analytical characteristics were obtained: Microanalysis for $C_{12}H_{20}Cl_2N_2CaSO_{14}$:

	% theoretical	% found
Carbon	25.40	25.20
Hydrogen	4.97	5.07
Nitrogen	4.94	4.87

Titre of glucosamine: 97.5–102.5% (potentiometric titre with NaOH in an aqueous medium).

Titre of sulphates: 97.5–102.5% (complexometric titre with EDTA in an NH_3 basic medium after precipitation with $BaCl_2$).

Titre of chlorides: 97.5–102.5% (argentometric titre).

Titre of calcium: 97.5–102.5% (in atomic absorption)

Appearance, colour, odour: Crystalline powder of pale cream colour, odourless and with a strongly bitter flavour.

Solubility (25° C. - w/v):

Very soluble (about 40%): water

8

Slightly soluble (about 1%): Methanol

Very slightly soluble (about 0.03%): Ethanol

Practically insoluble (<0.01%): Acetone, acetonitrile, tetrahydrofuran, dioxane

Insoluble: Benzene, chloroform, carbon tetrachloride, methylene chloride, ligroin, ethyl ether.

pH: The pH of a saturated aqueous solution of the mixed salt at 20° C. is 3 ± 0.2.

Partition coefficient: The partition coefficient of the mixed salt determined at 25° C. in phosphate buffer (pH 6.8)/n-octanol has a practically infinite value.

Melting point: >300° C. (with partial decomposition above 200° C.).

Specific Rotation: 52.5 ± 0.2° (in equilibrium in 10% aqueous solution).

EXAMPLE 8

Preparation of the mixed salt from glucosamine hydrochloride and magnesium sulphate heptahydrate.

Exactly the same method as described in Example 1 was followed, the sodium sulphate being replaced by 24.65 g (0.1 moles - M.W. 246.49) of magnesium sulphate heptahydrate.

52.2 g (94.6%) of creamy-white crystals of bitter flavour and having the following chemical and physical characteristics were obtained:

Microanalysis for $C_{12}H_{20}Cl_2N_2MgSO_{14}$:

	% theoretical	% found
Carbon	26.12	26.27
Hydrogen	5.11	5.01
Nitrogen	5.08	5.14

Titre of glucosamine: 97.5–102.5% (potentiometric titre with NaOH in an aqueous medium).

Titre of sulphates: 97.5–102.5% (complexometric titre with EDTA in an NH_3 basic medium after precipitation with $BaCl_2$).

Titre of chlorides: 97.5–102.5% (argentometric titre).

Titre of magnesium: 97.5–102.5% (in atomic absorption)

Appearance, colour, odour: Crystalline powder of pale cream colour, odourless and with a strongly bitter flavour.

Solubility (25° C. - w/v):

Very soluble (about 40%): water

Slightly soluble (about 1%): Methanol

Very slightly soluble (about 0.03%): Ethanol

Practically insoluble (<0.01%): Acetone, acetonitrile, tetrahydrofuran, dioxane

Insoluble: Benzene, chloroform, carbon tetrachloride, methylene chloride, ligroin, ethyl ether.

pH: The pH of a saturated aqueous solution of the mixed salt at 20° C. is 3 ± 0.2.

Partition coefficient: The partition coefficient of the mixed salt determined at 25° C. in phosphate buffer (pH 6.8)/n-octanol has a practically infinite value.

Melting point: >300° C. (with partial decomposition above 200° C.).

Specific Rotation: 54 ± 0.2° (in equilibrium in 10% aqueous solution).

From the stability point of view, the mixed salts of the present invention, like the glucosamine-SP described in the U.S. Pat. No. 4,642,340, were also found to be temperature- and moisture-resistant and thus easy to keep and perfectly usable in pharmaceutical techniques.

In fact, after 12 months at 25° C., and 60% relative humidity, preservation was perfect (see Tables 1 and 2) and further tests showed that only under extremely severe conditions, that is, 40° C. and 85% relative humidity was it possible, after 12 months, to observe a slight darkening of the colour and a slight reduction of the glucosamine titre (about 3-4%) which then remained constant under the same conditions of preservation for the next 12 months (see Tables 3 and 4).

TABLE 1

Comparison of the stability of Glucosamine-SP prepared according to the invention and prepared according to U.S. Pat. No. 4,642,340 at 25° C. and 60% R.H.				
Glucosamine-SP (invention)		Glucosamine-SP U.S. Pat. No. 4,642,340		
Time (months)	Appearance	Titre (%)	Appearance	Titre (%)
0	conforms (*)	99.6	conforms (*)	100.3
3	unchanged	100.2	unchanged	100.4
6	unchanged	100.0	unchanged	99.7
9	unchanged	99.6	unchanged	99.9
12	unchanged	100.4	unchanged	100.3

TABLE 2

Stability of the other mixed glucosamine salts at 25° C. and 60% R.H.						
Mixed salt of glucosamine hydrochloride with						
Potassium sulphate		Calcium sulphate		Magnesium sulphate		
Time (months)	Appearance	Titre (%)	Appearance	Titre (%)	Appearance	Titre (%)
0	conforms (*)	100.1	conforms (*)	99.6	conforms (*)	100.5
3	unchanged	100.3	unchanged	99.8	unchanged	100.1
6	unchanged	99.8	unchanged	100.1	unchanged	99.8
9	unchanged	99.6	unchanged	99.7	unchanged	100.3
12	unchanged	100.3	unchanged	100.0	unchanged	100.6

TABLE 3

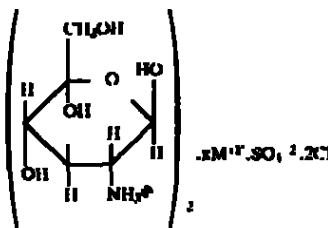
Comparison of the stability of Glucosamine-SP prepared according to the invention and prepared according to U.S. Pat. No. 4,642,340 at 40° C. and 85% R.H.				
Glucosamine-SP (invention)		Glucosamine-SP U.S. Pat. No. 4,642,340		
Time (months)	Appearance	Titre (%)	Appearance	Titre (%)
0	conforms (*)	99.6	conforms (*)	100.3
3	unchanged	99.8	unchanged	99.7
6	unchanged	100.3	unchanged	99.9
9	unchanged	100.2	unchanged	100.1
12	sl. yellowing	96.8	sl. yellowing	96.4
18	unchanged	97.1	unchanged	96.3
24	unchanged	96.6	unchanged	96.9

TABLE 4

Stability of the other mixed glucosamine salts at 40° C. and 85% R.H.					
Mixed salt of glucosamine hydrochloride with					
Potassium sulphate		Calcium sulphate		Magnesium sulphate	
Time (months)	Appearance	Titre (%)	Appearance	Titre (%)	Appearance
0	conforms (*)	100.1	conforms (*)	99.6	conforms (*)
3	unchanged	100.3	unchanged	99.8	unchanged
6	unchanged	99.8	unchanged	100.0	unchanged
9	unchanged	100.0	unchanged	99.6	unchanged
12	sl. yellowing	95.7	sl. yellowing	94.9	sl. yellowing
18	unchanged	96.2	unchanged	94.7	unchanged
24	unchanged	95.5	unchanged	94.8	unchanged

(*) Crystalline powder of pale cream colour.

What is claimed is:
1. A method of preparing a therapeutically active crystalline form of glucosamine sulphate which is stable at ambient temperature and humidity and corresponds to the empirical formula:



in which M represents a metal selected from the group consisting of Na, K, Ca, and Mg,
x=1 if y=2, and
x=2 if y=1,
wherein glucosamine hydrochloride and a sulphate of a metal selected from the group consisting of Na, K, Ca, and Mg are used as the starting materials, the method comprising directly reacting said glucosamine hydrochloride and said sulphate in the stoichiometric ratio defined by formula (I), in an aqueous solvent, and precipitating said stable crystalline form of glucosamine sulphate by addition of a liquid precipitating agent miscible with water.
2. A method according to claim 1, comprising the steps of:
a) dissolving the sulphate defined above, with stirring, in a quantity of from 4.5 to 6.5 parts by weight of distilled water per part by weight of sulphate,
b) dissolving the stoichiometric quantity of glucosamine hydrochloride in the solution thus obtained, at a temperature no greater than 60° C., with stirring,
c) precipitating the stable crystalline form by the addition of a liquid precipitating agent which is miscible with water and in which the crystalline form has a solubility no greater than 0.1% (w/v), with stirring,
d) completing the precipitation by reducing the temperature of the mixture, and

11

e) recovering the precipitated crystalline form.

3. A method according to claim 1 in which the liquid precipitating agent is selected from the group consisting of acetone, ethanol, acetonitrile, tetrahydrofuran and dioxane.

4. A method according to claim 1, in which the liquid precipitating agent is added in a proportion of from 5 to 7

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parts by volume relative to the volume of aqueous solvent, over a period of from 2.5 to 3.5 hours.

5. A method according to claim 1, in which the stable crystalline form recovered is dried at a temperature of from 45° to 65° C.

* * * * *

ANEXO 4

②

EUROPEAN PATENT APPLICATION

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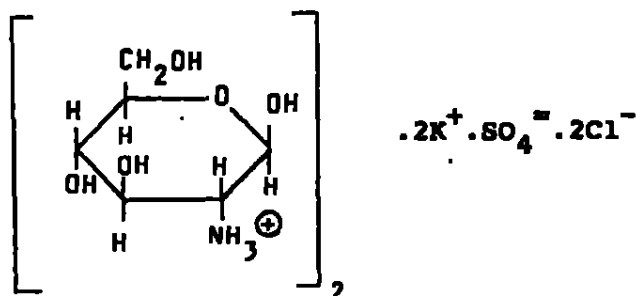
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⑮ Mixed salts of glucosamine sulphate and a process for the preparation of the same.

⑯ The present invention relates to mixed salts of glucosamine sulphate and to a process for the preparation of the same. The compounds according to the invention consist of a mixed salt of glucosamine

sulphate and alkaline or earth alkaline metal halides e.g. potassium chloride corresponding to the formula:

EP 0 214 642 A2



MIXED SALTS OF GLUCOSAMINE SULPHATE AND A PROCESS FOR THE PREPARATION OF THE SAME

This invention relates to mixed salts of glucosamine sulphate and certain alkaline or earth alkaline metal halides such as, for example, potassium chloride, and to a process for the preparation of the same.

Glucosamine sulphate is a well-known substance in the treatment of, for example, rheumatic fever, pains resulting from arthrosis or arthritis and osteo-articular diseases.

The synthesis of glucosamine sulphate was described by Brauer in 1898 (Chem. Ber. 31, 2187) and, industrially, in GB-A-1 058 331, US-A-3 883 076 and CH-A-625 881.

The use of glucosamine sulphate in the preparation of pharmaceutical formulations is difficult owing to its instability since it is readily oxidized and strongly hygroscopic. Oral forms, thus, often contain antioxidants such as, for example, sodium

hyposulphite to prevent oxidation of the amino group. According to GB-A-2 101 585 the hygroscopic nature of glucosamine sulphate can be considerably reduced by forming a mixed salt with sodium chloride.

It has now been found that glucosamine sulphate also forms mixed crystalline salts with potassium chloride, magnesium chloride, sodium bromide and potassium bromide. Iodides and all the lithium halides are too soluble in organic water-miscible solvents and calcium halides are too reactive to form homogeneous crystalline mixed salts with glucosamine sulphate in the present reaction conditions. In particular, the mixed salt of glucosamine sulphate and potassium chloride is very stable at ambient temperature and humidity.

The mixed salts according to the invention correspond to the formulae (I), (II) or (III):

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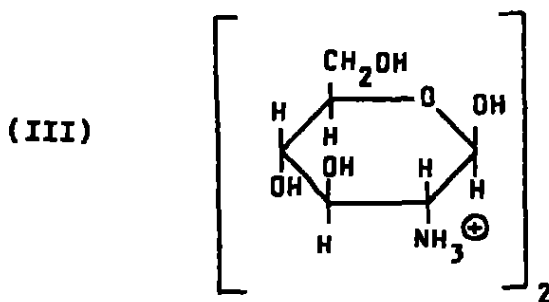
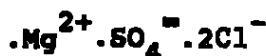
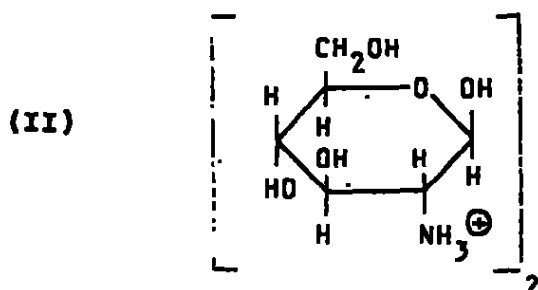
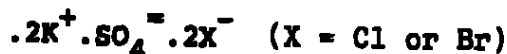
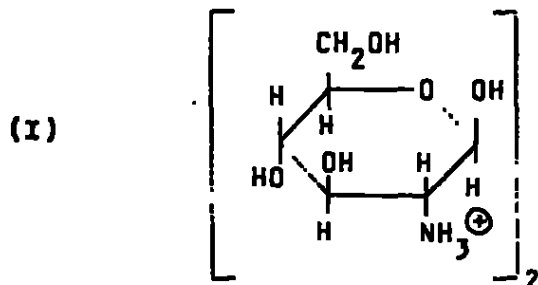
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Glucosamine sulphate has been used as a sulphate itself or as a mixed salt of sulphate and sodium chloride. Glucosamine sulphate has several unfavourable properties, e.g. it has a highly hygroscopic nature and its amino group oxidises easily. The mixed salt of glucosamine sulphate and sodium chloride is stable, but its disadvantage lies in the use of sodium chloride.

The normal daily diet of an adult contains sufficient sodium chloride (1 to 5 g per day) to maintain the osmotic pressure of the blood and tissues. Often the daily intake with a normal diet is much higher though which is unfavourable for patients with hypertonus arterialis. The result is an increase in extracellular fluid and, to prevent this phenomenon from occurring, it is recommended that a part of the sodium chloride contained in the normal daily diet be replaced with other salts such as, for example, potassium chloride in table salt. Dosage ranges for the treatment with glucosamine sulphate

are wide and it is possible that, during therapy, daily levels of 0.4 g of sodium chloride, which is from 8 to 40% of the normal daily diet, are reached.

A reported disadvantage with mixed salts of glucosamine sulphate and sodium chloride is an accumulation of sodium and water in the tissue, which is detrimental to patients suffering from cardiovascular diseases.

In rheumatic diseases, corticosteroids are often also administered during the glucosamine treatment and it is known that the treatment with corticosteroids often results in a lack of potassium which then has to be compensated with potassium chloride tablets.

It has now been found that it is possible to simplify the production of mixed salts of glucosamine sulphate and alkali or earth alkali metal halide compared with previous patents (such as GB-A-2 101 585). In this process, the glucosamine

base is converted to glucosamine sulphate and this intermediate is then converted without isolation to form a mixed salt of glucosamine sulphate and alkali or earth alkali metal halide.

The mixed salts are produced by dissolving the glucosamine base in water, adding a stoichiometric quantity of concentrated sulphuric acid to arrive at glucosamine sulphate and dissolving the stoichiometric quantity of alkaline or earth alkaline metal halide in the solution thus obtained. Precipitation is caused by adding a water-miscible organic solvent such as, for example, isopropanol. After addition of the liquid precipitant, the mixture is stirred at room temperature for about 14 hours to complete precipitation, cooled to 0°C and filtered.

The free glucosamine may be prepared according to Westphal and Holzmann (Chem. Ber. 75, 1274) by treating glucosamine hydrochloride with an ethanolic solution of a tertiary base such as triethylamine.

Example 1

Mixed salt of glucosamine sulphate and potassium chloride.

12,7 g (0,071 mol) of glucosamine was dissolved in 40 ml of water, cooled to 0°C and the mixture was adjusted to pH 4-5 by the slow addition of 3,5 g of 88 % H_2SO_4 . The temperature was then raised to 20°C and 5,3 g (0,071 mol) of potassium chloride was added. Once the salt had dissolved the precipitation was carried out by using 240 ml of isopropanol, which was added over a period of 3 hours. To complete the precipitation the mixture was stirred for 14 hours at 20°C. After that the temperature was lowered to 0°C, the precipitate was isolated by filtration and dried at 50°C in reduced pressure. The yield was 19,7 g - (81,5 % of the theoretical) of $2(C_6H_{12}NO_6) \cdot 2K^+ \cdot SO_4^{2-} \cdot 2Cl^-$, mp 210°C (dec.).

Example 2

Mixed salt of glucosamine sulphate and magnesium chloride.

The same procedure as that described in Example 1 was employed, using of 7,2 g (0,035 mol) of $MgCl_2 \cdot 6H_2O$ instead of KCl. The yield was 17,9 g (82,9 %) of $2(C_6H_{12}NO_6) \cdot Mg^{2+} \cdot SO_4^{2-} \cdot 2Cl^-$, mp 210°C (dec.).

Example 3.

Mixed salt of glucosamine sulphate and sodium bromide.

The procedure was as described in Example 1 with the use of 7,3 g (0,071 mol) NaBr instead of KCl. The yield was 19,5 g (82,7 %) of $2(C_6H_{12}NO_6) \cdot 2Na^+ \cdot SO_4^{2-} \cdot 2Br^-$, mp 200 °C (dec.).

Example 4

Mixed salt of glucosamine sulphate and potassium bromide.

The procedure was as described in Example 1 with the use of 8,4 g (0,071 mol) KBr instead of KCl. The yield was 20,7 g (84,9 %) of $2(C_6H_{12}NO_6) \cdot 2K^+ \cdot SO_4^{2-} \cdot 2Br^-$, mp 200 °C (dec.).

Example 5

The procedure was as described in Example 1 with the use of ethanol instead of isopropanol. The yield was 18,8 g (87,5 %) of $2(C_6H_{12}NO_6) \cdot 2K^+ \cdot SO_4^{2-} \cdot 2Cl^-$.

Example 6

The procedure was as described in Example 1 with the use of acetone instead of isopropanol. The yield was 20,3 g (84,5 %) of $2(C_6H_{12}NO_6) \cdot 2K^+ \cdot SO_4^{2-} \cdot 2Cl^-$.

Stability test

To determine the stability of mixed salt of glucosamine sulphate and potassium chloride a sample was stored for 30 days at 20 °C and 75 % relative humidity. The results obtained are given in Table 1.

Table 1

Stability of mixed salt of glucosamine sulphate and potassium chloride at 20 °C and 75 % R.H.

Time (days)	Assay
0	99,4 %
1	99,3 %
2	98,7 %
4	98,8 %
8	98,7 %
16	98,9 %
30	98,7 %

According to the results no remarkable degradation could be detected in mixed salt of glucosamine sulphate and potassium chloride during 30 days storage. On the other hand pure glucosamine sulphate decomposes completely at 20°C and 75 % R.H. in a few days.

Claims

1. A mixed salt of glucosamine sulphate and potassium chloride, magnesium chloride, sodium bromide or potassium bromide.

2. A mixed salt of glucosamine sulphate and potassium chloride.

3. A process for the preparation of a mixed salt of glucosamine sulphate and potassium chloride, magnesium chloride, sodium bromide or potassium

bromide, characterized by first forming glucosamine sulphate from glucosamine and sulphuric acid and then forming the mixed salt by adding an approximately stoichiometric amount of the corresponding alkaline or earth alkaline metal halide and by precipitating the mixed salt by adding a water-soluble solvent.

4. A process in accordance with claim 3, characterized in that the formation of the mixed salt takes place at temperatures of from 0 to 40°C.

5. A process in accordance with claim 3 or 4, characterized in that the mixed salt is precipitated by adding isopropanol, mixing and cooling the mixture to a temperature of 0°C and filtering the precipitated product.

6. A process in accordance with any one of claims 3 to 5, characterized in that the precipitating solvent is ethanol, acetone or acetonitrile.

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ANEXO 5



144

US005843923A

United States Patent [19]
Schleck et al.

[11] **Patent Number:** **5,843,923**
[45] **Date of Patent:** **Dec. 1, 1998**

[54] **GLUCOSAMINE SULFATE POTASSIUM
CHLORIDE AND PROCESS OF
PREPARATION THEREOF**

5,463,415 9/1997 Chopdekar et al. .

FOREIGN PATENT DOCUMENTS

0214642 3/1987 European Pat. Off. .

[75] **Inventors:** James R. Schleck, Somerset;
Christopher M. Burger, Toms River;
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Primary Examiner—James O. Wilson
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Attorney, Agent, or Firm—Jack Matalon

[73] **Assignee:** Jame Fine Chemicals, Inc., Bound
Brook, N.J.

[57] **ABSTRACT**

[21] **Appl. No.:** 83,173

A composition comprising the compound glucosamine sul-
fate potassium chloride having a purity level of at least about
97% and water present in a maximum amount of about 10
wt. %, based on the weight of the composition. The com-
pound is prepared by contacting glucosamine hydrochloride
with potassium sulfate in the presence of water to form an
aqueous solution of glucosamine sulfate potassium chloride
and thereafter freeze-drying the solution at a temperature
and at a reduced pressure for such period of time that at least
about 90 wt. % of the water is removed and decomposition
of the compound glucosamine sulfate potassium chloride is
limited to a maximum of about 3%.

[22] **Filed:** May 22, 1998

[51] **Int. Cl.⁶** C07H 5/06; A01N 43/04

[52] **U.S. Cl.** 514/62

[58] **Field of Search** 536/18.7, 55.2;
514/23, 62

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,683,076 8/1972 Rovati .

4,642,340 2/1987 Senin et al. .

12 Claims, No Drawings

1

GLUCOSAMINE SULFATE POTASSIUM CHLORIDE AND PROCESS OF PREPARATION THEREOF

FIELD OF INVENTION

The invention relates to a composition comprising glucosamine sulfate potassium chloride and a process for preparing same. The glucosamine sulfate potassium chloride is a pure compound having a purity level of at least about 97%.

BACKGROUND OF THE INVENTION

Glucosamine sulfate is a well known and widely used substance for the treatment of rheumatic fever, arthritic and arthritic complaints, in the acute as well as chronic forms, as well as in the treatment of pathological conditions originating from metabolic disorders of the osteo-articular tissue.

Mixed salts of glucosamine sulfate and alkaline or earth alkaline metal halides such as potassium chloride, and sodium chloride are well known. Such mixed salts are used rather than glucosamine sulfate alone since the latter is unstable in view of its highly hygroscopic nature and the facility with which its amino group oxidizes if not completely saltified, see e.g. U.S. Pat. No. 4,642,340, U.S. Pat. No. 3,683,076 discloses a mixture of glucosamine sulfate and glucosamine hydrochloride for the treatment of osteoarthritis and rheumatoid arthritis.

Free glucosamine base may be prepared by the method recited in *Chem. Ber.*, volume 75, page 1274. Such method involves the treatment of glucosamine hydrochloride with an ethanolic solution of a tertiary base such as triethylamine. Triethylamine hydrochloride is filtered off and the free glucosamine is then recovered from the reaction mixture. However, triethylamine is a toxic material even in small quantities and the yield of the free glucosamine base is quite low.

In EP 0 214 642, free glucosamine base is converted to a mixed salt of glucosamine sulfate and potassium chloride by dissolving the glucosamine base in water, adding a stoichiometric quantity of concentrated sulfuric acid to form a solution of glucosamine sulfate in water and dissolving a stoichiometric amount of potassium chloride in the solution. The mixed salt is precipitated from the solution by addition of a precipitant such as isopropanol, stirring the mixture for about 14 hours to complete the precipitation, cooling the reaction mass to 1° C. and recovering the precipitated salt by filtration. This process results in low yields.

SUMMARY OF THE INVENTION

It has now been found possible to prepare a composition comprising a pure compound, and not a salt mixture, of glucosamine sulfate potassium chloride. The compound will have a purity level of about 97%, preferably at least 99%. Moreover, the process of the invention avoids the use of toxic reagents such as triethylamine and also avoids the use of precipitants such as isopropanol, thereby permitting substantially quantitative yields with little or no impurities present other than very minor quantities of water.

DETAILS OF THE INVENTION

The invention pertains to a novel composition and a process for preparing same. The composition comprises:

- (a) the compound glucosamine sulfate potassium chloride having a purity level of at least about 97%; and
- (b) water, present in a maximum amount of about 10 wt. %, based on the weight of the composition.

2

Preferably, the compound will have a purity level of at least 99%. Indeed, the process of the invention typically results in a compound having a purity level in excess of 99%. The principal impurity will be water which is preferably present in a maximum amount of 5 wt. %, based on the weight of the composition. Typically, the process of the invention will produce a composition with a water content of not greater than 3 wt. %.

Any water present in the composition of the invention is not to be regarded as an "impurity" in the classical sense. The composition of the invention is intended to be ingested and minor adjustments in the dosage to be ingested can be readily made to account for such water.

Commercially available compositions of glucosamine sulfate and potassium chloride will have a density in excess of 1.10 g/cc and, as discussed below, appear to be a mixture of glucosamine hydrochloride and potassium sulfate rather than the compound glucosamine sulfate potassium chloride. Glucosamine sulfate potassium chloride prepared using isopropanol or acetone as a precipitant exhibited unacceptable glucosamine hydrochloride assay values of about 93% and densities of 0.55-0.65, indicating that some potassium chloride is abstracted from the composition and remains in the aqueous precipitant layer.

The compound glucosamine sulfate potassium chloride of the invention has a density of less than about 1.10 g/cc, preferably in the range of 0.90 to 1.00 g/cc. As discussed below in respect to Table I, the glucosamine hydrochloride assay value of the compound of the invention remains about 100 wt. %, prior to and subsequent to nitrogen sparging, which indicates that a true compound, rather than a mixture of salts or a mixture of reacted components plus unreacted components has been prepared by the process of the invention.

The process for preparing the novel composition of the invention is quite simple and straightforward and typically results in quantitative yields. The process involves the following steps:

- (a) contacting glucosamine hydrochloride with potassium sulfate in the presence of water to form an aqueous solution of glucosamine sulfate potassium chloride; and
- (b) recovering the compound by freeze-drying the solution from step (a) at a temperature and at a reduced pressure for such period of time that: (i) at least about 90 wt. % of the water is removed and (ii) decomposition of the compound glucosamine sulfate potassium chloride is limited to a maximum of about 3 wt. %.

Typically, the glucosamine hydrochloride and potassium sulfate are contacted in stoichiometric quantities in the presence of sufficient water to form a concentration of solids of about 15 to 40 wt. %, preferably 20 to 30 wt. %, and the contacting takes place for a period of about 15 minutes to 2 hours. Step (a) takes place at temperatures, e.g. 20° to 50° C.

The freeze-drying in step (b) is typically carried out at a pressure of not greater than about 800 milliTorr, preferably 300 to 500 milliTorr, and at a temperature in the range of about -60° C. to 0° C., preferably -40° to -5° C.

The process of the invention avoids the use of precipitants such as isopropanol, acetone, dioxane, etc. in order to recover the glucosamine sulfate potassium chloride from the aqueous reaction mixture.

It has also been found that if distillation instead of freeze-drying is used to recover the glucosamine sulfate potassium chloride, some decomposition of the product occurs, even if the distillation is carried out at moderate

3

temperatures of about 65° C. and under vacuum at a pressure of about 20 mm Hg. Decomposition of the product is evidenced by a yellowing of the product and a shift in taste from sweetish and slightly salty to a bitter taste. When the water was attempted to be removed under vacuum at a pressure of about 20 mm Hg at ambient temperatures, significant foaming of the reaction mass occurred which prevented the water from being distilled off without also causing the product to flow out of the flask containing the aqueous solution.

The following non-limiting examples shall serve to illustrate the various embodiments of this invention. Unless otherwise indicated to the contrary, all parts and percentages are on a weight basis.

EXAMPLE 1

The purpose of this example was to prepare an aqueous solution of glucosamine sulfate potassium chloride and isolate the product by removing the water by vacuum distillation.

A one-liter, three-necked flask equipped with a thermometer, stirrer, heating mantle and condenser was charged with 352.7 g of purified water, 107.8 g (0.5 mole) of glucosamine hydrochloride. The glucosamine hydrochloride promptly went into solution, with stirring (the dissolution of the glucosamine hydrochloride was endothermic in nature). After stirring for a few minutes, 43.5 g (0.25 mole) of potassium sulfate was added to the solution and stirring was continued for about one hour at 35°-40° C. to complete the reaction.

The clear solution was transferred to a one-liter single-neck flask and water was stripped off at 60°-65° C. under a vacuum of approximately 20 mm Hg. It was noticed that the product turned progressively yellow in color as the water was being stripped off. The product was dried under vacuum at 70° C. for 8 hours. The product assay, by titration, was 98.5%. The yield of product was 147.5 g (97.5% of theory). However, the product had a yellow-orange color and was therefore not deemed to be acceptable, notwithstanding that the assay and yield were good.

EXAMPLE 2

The equipment described in Example 1 was employed in this example. 56 g (0.26 mole) of glucosamine hydrochloride and 200 ml of isopropanol were charged to the flask, resulting in a slurry. 25.2 g (0.25 mole) of triethylamine were added over a 1-hour period and stirring continued for 24 hours at 25° C. and thereafter filtered. Gas chromatographic analysis of the filtrate indicated the presence of free triethylamine which is a toxic material.

EXAMPLE 3

This example was carried out to demonstrate the process of the invention. Example 1 was repeated up to the point of obtaining the clear solution of glucosamine sulfate potassium chloride. The water was then stripped off from the clear solution by freeze-drying under the following conditions:

The freeze temperature was set at -40° C., the condenser set point was -45° C., the vacuum set point was 200.0 milliTorr and the vacuum safety was set at 800 milliTorr. The solution was then subjected to the following freeze-drying steps:

4

Step	Temp. °C.	Time, minutes
1	-30	120
2	-15	300
3	-5	540
4	0	540
5	10	300
6	20	240
Post Heat	25	60

A white powder was obtained in a yield of 98.5% of theoretical; the assay of the product was 100.3%.

EXAMPLE 4

This example was carried out to prepare glucosamine sulfate potassium chloride by the prior art method of precipitation using isopropanol.

The same equipment as employed in Example 1 was used for this Example. 25.9 g (0.12 m) of glucosamine hydrochloride was added to 84 g of purified water in the flask and the mixture was stirred to obtain a clear solution. 10.6 g of potassium sulfate was added to the solution and stirring was continued for 1 hour at 25°-30° C. Thereafter, 336 g of isopropanol were added to precipitate the glucosamine sulfate potassium chloride. The reaction mixture was maintained at 20° C. for 4 hours and the product was recovered by filtration. The product was washed with 100 g of isopropanol and dried under vacuum. The yield was 31 g (85.4% of theory). The product was then assayed by titration and the assay result was 93%, which was not deemed to be acceptable.

The results of this example indicate that precipitation of glucosamine sulfate potassium chloride is undesirable in several respects: low yield, poor volume efficiency, high solvent disposal cost, low product assay and the possibility of contamination of the final product with residual isopropanol.

EXAMPLE 5

This example was carried out to prepare glucosamine sulfate potassium chloride by the prior art method of precipitation using acetone.

Example 4 was repeated using 336 g of acetone to precipitate the product. The product yield was 32.6 g (90% of theory). The product was assayed by titration and the assay result was 93.4% which was deemed to be unacceptable.

EXAMPLE 6

The purpose of this example was to compare glucosamine sulfate potassium chloride obtained (a) by preparing a synthetic mixture of solid glucosamine hydrochloride and potassium sulfate, (b) from various commercial sources and (c) from Examples 4 and 5 with that prepared by the freeze-dried process of the invention exemplified by Example 3.

The synthetic mixture was prepared by thoroughly mixing (but not milling) 400 g of glucosamine hydrochloride with 160 g of potassium sulfate. The particular method by which the various commercial-sourced glucosamine sulfate potassium chloride samples were prepared was not known. However, based on the results set forth in Table I below, it appears that the commercial-sourced glucosamine sulfate potassium chloride was prepared by thoroughly mixing

142

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radicacion : 03046045 00000006 Folios: 48
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Tramite : 011 PCT-PATENT 379 FASE MARCI 400 04-081C10
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 98,364
FECHA : DICIEMBRE 21 DE 2004

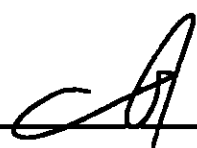
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	33942366	02/12/2004	896,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
12		MARCAS Y LEMAS COMERCIALES	224,000.
		TOTAL :	\$ 224,000.00

SOM: DOSCIENTOS VEINTICUATRO MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

2020
Bogotá, D.C.,

Doctora:
Margarita Castellanos Abondano
Apoderada

Oficio N°: 12.12

ASUNTO:	Radicación PCT N°	03-46045
	Trámite	011
	Evento	379
	Actuación	440
	Folios	010

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor Luis Fernando Rincón Cuellar, en su calidad de apoderado de Procaps S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 11 FEB. 2005.

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