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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: **EXPEDIENTE 05-057-688**

TÍTULO SOLICITADO: **"COMPOSICIONES FARMACÉUTICAS DISPERSABLES"**

SOLICITANTE: **PHARMACIA & UPJOHN COMPANY**

APODERADO: **CARLOS REINALDO OLARTE**

TRÁMITE: **REMISIÓN DE INFORMACIÓN**

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **GENFAR S.A.**, con el propósito de coadyuvar en la decisión que sobre la solicitud de patente en referencia habrá de adoptarse próximamente, por este escrito me permito remitir información fundamentada que demuestra que la solicitud en mención no cumple los requisitos de novedad y nivel inventiva exigidos por la Decisión 486 de 2000, y que por ello, debería su despacho abstenerse de concederle el privilegio solicitado.

Además de la defensa del orden jurídico vigente en materia de propiedad industrial, el presente escrito se fundamenta en la necesidad de evitar que la concesión de la solicitud vulnere la libre competencia, y restrinja el mercado farmacéutico en perjuicio de los consumidores colombianos.

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente **05-057-688** por no cumplir con los requisitos de patentabilidad a que se refieren los artículos

14 y siguientes de la Decisión 486 de la Comunidad Andina de Naciones, y en consecuencia, ordenar el archivo del expediente respectivo.

II. FUNDAMENTOS

2.1. La solicitud colombiana 05-057-688 carece cuando menos de nivel inventivo, a la luz de los siguientes argumentos:

2.1.1. La primera reivindicación de la solicitud colombiana en trámite hace referencia a:

> *"Una composición farmacéutica que comprende un portador que comprende a) un aceite antipático que es dispersable en agua e insoluble en etanol, b) cera microcristalina, y c) un vehículo no acuoso farmacéuticamente aceptable, teniendo dicho vehículo dispersado establemente en él una sustancia antibacteriana en una cantidad eficaz de manera antibacteriana"* (cursiva fuera del texto)

Sin perjuicio de la existencia de reivindicaciones dependientes[1], es necesario concluir que la reivindicación primera en cuestión, en caso de ser concedida cubriría, sin determinarlos, TODOS LOS COMPUESTOS QUE SEAN ANTIBACTERIANOS, EN PRESENCIA DE EXCIPIENTES CON LAS CARACTERÍSTICAS ANTES MENCIONADAS. Es así como además de ser **indeterminada,** la reivindicación primera **carece de claridad** en tanto pretende amparar un número indefinido de compuestos, sin mencionar siquiera sus nombres específicos o incluir sus fórmulas químicas.

Así mismo y con los mismos argumentos tenidos en cuenta anteriormente, es importante llamar la atención del Despacho en cuanto a la redacción de las reivindicaciones 2, 3, 5 y 7 entre otras.

2.1.2. Se pretende obtener patente para una forma de presentación de una(s) sustancia(s) conocida(s).

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[1] Se recuerda que no sólo a la luz del artículo 30 de la Decisión 486 de 2000, sino al tenor del Manual de Examen de la Oficina Europea de Patentes, Parte C, capítulo III, apartado 4-4.1, Art. 84, página 28, (Guidelines for Examination in the European Patent Office – Published by EPO, 1999), el requisito de claridad debe cumplirse tanto en las reivindicaciones individualmente consideradas, como en éstas como un todo. (Según traducción libre del opositor). No resulta de recibo en este caso excusar la indeterminación y falta de claridad de la primera y más importante reivindicación con base en sus dependencias.

Sin perjuicio del argumento anterior, es oportuno recordar que un principio activo conocido – carente, por demás, de protección patentaria en Colombia -no puede ser patentado *a posteriori* por el simple hecho de mostrarlo supuestamente bajo una "forma diversa de presentación", en especial considerando que el solicitante no prueba que dicha forma constituya, desde el punto de vista del efecto terapéutico o aún comercial de la composición, avance alguno frente al arte conocido.

Es oportuno mencionar en este punto lo dicho por Gómez Segade[2], a cuyo tenor "el inventor debe reunir los méritos que le permitan atribuirse una patente, sólo si la invención fruto de su investigación y desarrollo creativo constituye 'un salto cualitativo en la elaboración de la regla técnica', actividad intelectual mínima que le permitirá que su invención no sea evidente (no obvia) del estado de la técnica.

Ahora bien, si se aceptara la discutible tesis según la cual "todo aquello que no haya sido revelado textualmente en una publicación es nuevo", y presumiendo que Ceftiofur y otros activos en las formulaciones expuestas no hubiesen sido reveladas en tales condiciones, es oportuno recordar que la "Novedad" en materia de patentes químicas y farmacéuticas no sólo está dada por la no-comprensión textual en el estado de la técnica, sino que supone evaluar, en forma concomitante, el cumplimiento del requisito de Nivel Inventivo. En efecto, "Si bien en el resto de los sectores técnicos *ésta es la exigencia -la novedad-* que debe cumplir la invención para seguir adelante en el examen de patentabilidad, no ocurre lo mismo en el sector químico farmacéutico. En este sector lo verdaderamente importante es que esa sustancia comprendida o no en el estado de la técnica tenga una utilidad que no esté comprendida en el estado de la técnica (novedad) ni resulte de una manera evidente del estado de la técnica (actividad inventiva)[3]."

Es evidente que la simple presentación de una "Composición distinta" de un objeto conocido no cumple los requisitos "calificados" de Novedad y Nivel Inventivo que

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[2] Citado en la Interpretación Prejudicial 105-IP-2000.

[3] El Nuevo Marco Legal de las Patentes Químicas y Farmacéuticas, Manuel Lobato García-Mijan. Ed. Civitas, Madrid, 1994. Página 116.

deberian aplicarse a las solicitudes de patente sobre fármacos, en especial cuando se tramitan en países en vias de desarrollo.

Es del caso revisar ahora de qué manera la composición farmacéutica en forma de suspensión estable física y químicamente pretendida carece de nivel inventivo. Es necesario anotar que si bien es cierto que una invención puede partir de elementos conocidos, no lo es menos que cuando todos y cada uno de los mismos se conoce con anterioridad, tanto per se como en sus propiedades y efectos, resulta obvio para una persona versada en la materia combinar las enseñanzas de las anterioridades y derivar el objeto pretendido.

Sabe de sobra el Despacho que las sustancias antibacterianas pertenecientes al grupo de cefalosporinas, en particular aquellos conocidos con los nombres genéricos de Ceftiofur, cefalexina, cefadroxilo, cefazolina, entre otros y sus sales farmacéuticamente aceptables, son ampliamente conocidos y han sido profusamente revelados en la literatura y aún empleados en la industria farmacéutica internacional. Es un hecho igualmente notorio que al ser conocidos los principios activos en cuestión – en especial cuando ese conocimiento tiene más de quince años – es obvio conocer las propiedades y características que les son propias, incluyendo aquellas relacionadas, entre otros aspectos, con su solubilidad y estabilidad. No hace falta ser un experto en la materia para saber que en presencia de eventuales problemas de disolución y estabilidad, existen en la ciencia y aún en el mercado farmacéutico mundial soluciones disponibles, que no sólo han sido empleadas sobre los familia de fármacos que se emplea en esta solicitud, sino en formulaciones que contienen fármacos de indicaciones y mecanismos de acción diversos. También es un hecho notorio que antes de la fecha de prioridad se conocen en el estado de la técnica formulaciones de suspensiones que emplean los principios activos en cuestión (Ceftiofur Clorhidrato-entre otros), y que contienen además, aceite de semillas de algodón.

Es así como la patente americana US 4,902,683 titulada "Crystalline cephalosporin hydrohalide salts" y publicada el 20 de febrero de 1990 además de revelar a la sustancia Ceftiofur y sus sales farmacéuticamente aceptables (clorhidrato, sódica, entre otras) –tal como lo hace la reivindicación 4 de la solicitud colombiana en trámite-, permite ver claramente que dicho principio activo o sus sales pueden estar presentes en distintos tipos de composiciones farmacéuticas, veamos:

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Exam-

ples of suitable dosage unit forms in accordance with this invention are tablets, capsules, orally administered liquid preparations in suitable liquid vehicles, sterile preparations in suitable liquid vehicles for intramuscular and intravenous administration, suppositories and sterile dry preparations for the extemporaneous preparation (mixing just prior to administration) of sterile injectable preparations in a suitable liquid vehicle. Suitable solid (...)

trations. Carriers and vehicles include vegetable oils, dimethylacetamide, dimethylformamaide, ethyl lactate, ethyl carbonate, isopropyl myristate, ethanol, polyols, for example, glycerol, propylene glycol, liquid polyethylene glycol, and the like. Any solid preparations for (...)

Lo anterior permite demostrar que, carece al menos de nivel inventivo el pretender proteger una forma o composición farmacéutica que contenga como principio activo a la sustancia Ceftiofur, puesto que como lo observamos, dicho activo puede estar presente en forma de tabletas, cápsulas, liquidos, etc.

También, dicha sustancia antibacteriana puede ser formulada en composiciones como suspensiones ya sea de administración oral o parenteral:

EXAMPLE 5

Oral Suspension

One thousand cc. of an aqueous suspension for oral use, containing in each 5 cc. dose 5 to 300 mg. of crystalline ceftiofur hydrochloride is prepared from the following types of and amounts of ingredients.

Ceftiofur hydrochloride (crystalline): 5 to 300 gms.
Benzoic Acid or Sorbic Acid: 1 gm.
Sucrose: 650 gms.
Sodium Carboxymethylcellulose, Low Viscosity: 1 to 20 gms.
Flavors (e.g., USP cherry, orange) q.s.
Sodium Chloride (0.5 to 10 mg./ml.): 0.5 to 10 gms.
Hydrochloric Acid, Reagent Grade: q.s. adjust pH to approx. 3.0
Deionized Water: q.s. to 1000 cc.

The sodium carboxymethylcellulose, benzoic acid, sucrose, appropriate flavors and sodium chloride are dispersed in sufficient water to make 650 mls. of solution. The ceftiofur hydrochloride is stirred into the syrup until uniformly distributed. The resulting suspension is colloid milled to a uniform consistency. Sufficient water is added to bring volume to 900 cc. If necessary pH is adjusted with hydrochloric acid to about pH3. Sufficient water is added to make 1000 cc.

EXAMPLE 6

Sterile Parenteral Suspension

Sterile Vehicle-Part I

PEG: 5 to 120 gms.
Benzyl Alcohol, or: 9.1 gm.
Benzoic Acid: 1.0 gm.
Povidone: 1 to 10 gms.
Sodium Chloride Fine Crystals, Reagent Grade: 9 gm
Hydrochloric Acid, Reagent Grade q.s. adjust pH to approximately: 3.0
50% Solution Sodium Hydroxide q.s. adjust pH:
Water for Injection q.s. adjust: 1000 cc.

Part II

Ceftiofur hydrochloride, crystalline: 1.0 to 100 gms.
Vehicle Part I q.s. adjust: 1000 cc.

EXAMPLE 11

Extemporaneous Parenteral Suspension (Aqueous)

Sterile Vehicle-Part I

Polyethylene Glycol 3350 NF: 5 to 120 gms.
Polyvinyl Pyrrolidone: 1 to 10 gms.
Quatresin (®) myristyl gamma picolinium chloride: 0.1 to 2.0 gms.
Sodium Chloride, Fine Crystals Reagent Grade: 0.5 to 10 gms.

20% Solution Hydrochloric Acid q.s. adjust pH to approx.. 3.0
50% Solution Sodium Hydroxide q.s. to adjust pH to approx.. 3.0
Water for Injection q.s. adjust to: 1000 cc.

Part II	Amount per Vial
Sterile crystalline ceftiofur hydrochloride (milled or micronized) in a 10 to 100 mL glass vial:	0.01 to 1.5 gms.

Incluso, existen suspensiones parenterales no acuosas de Ceftiofur Clorhidrato micronizado y que entre sus excipientes se encuentra el aceite de semillas de algodón tal como se ve representado en el ejemplo 13 de la US 4,902,683 tantas veces mencionada y, que de cierta manera resultan muy similares o bastante aproximadas a las formulaciones definidas en la parte descriptiva de la solicitud colombiana en trámite desvirtuando una vez más el nivel inventivo de la misma, veamos:

US 4,902,683

EXAMPLE 13

Sterile Nonaqueous Parenteral Suspension

Crystalline ceftiofur hydrochloride (milled or micronized): 1 to 300 gms.
Chlorobutanol Anhydrous: 5.25 gms.
or
Benzyl Alcohol: 9.25 gms.
Corn Oil USP q.s. adjust: 1000 cc.
or
Cottonseed oil q.s. adjust: 1000 cc.

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Example 1

[0145] A suspension to be administered by intramammary infusion for treatment and/or prevention of lactating cow mastitis was prepared having the following composition:

ceftiofur hydrochloride (micronized)	12.5 mg/ml
Labrafil™ M-1944CS	50 mg/ml
microcrystalline wax NF	70 mg/ml
cottonseed oil NF	*q.s.*

Example 6

[0158] A suspension to be administered by intramammary infusion for treatment and/or prevention of dry cow mastitis was prepared having the following composition:

ceftiofur hydrochloride (micronized)	50 mg/ml
Labrafil™ M-1944CS	50 mg/ml
microcrystalline wax NF	70 mg/ml
cottonseed oil NF	*q.s.*

Por su parte, la US 5,736,151 titulada "ANTIBIOTIC OIL SUSPENSIONS" y publicada el 7 de abril de 1998 revela suspensiones oleosas de fármacos activos como Ceftiofur Clorhidrato y que incluyen pequeñas cantidades de agua, lo que hace que estas suspensiones tengan una mejorada resuspendibilidad (ya que se requiere de menos agitación antes de la dosificación), por ende tengan una mejorada estabilidad física.

Más adelante describe en la columna 5 que la composición farmacéutica comprende:

a) un fármaco que puede ser un antibiótico como spectinomicina o una cefalosporina como ceftiofur clorhidrato.
b) un aceite biocompatible como aceite de canola, aceite de maíz, aceite de semillas de algodón, aceite de oliva, aceite de sésamo, aceite de soya, aceite de coco, aceite de girasol, entre otros, preferiblemente aceite de semillas de algodón, y
c) agua presente en cantidades entre 0,25 y 2,20% de la composición, más preferiblemente entre 0,30 y 0,50% de la composición.
d) Además puede contener uno o más excipientes farmacéuticamente aceptables.

Como vemos, estas suspensiones oleosas de Ceftiofur Clorhidrato están acompañadas entre otros excipientes de aceite de semillas de algodón, lo que hace que de cierta manera resulten muy similares o bastante aproximadas a las formulaciones definidas en la parte descriptiva de la solicitud colombiana en trámite desvirtuando nuevamente el nivel inventivo de la misma.

Adicionalmente en la misma columna 5 señala algunos de los distintos fármacos que pueden ser formulados en una suspensión como la descrita hasta el momento y que coinciden con algunos de los activos señalados en la reivindicación 3 de la solicitud colombiana en trámite, veamos:

> Drugs which may be formulated in the suspension of the present invention include the following cephalosporins: First generation (ceftiofur, cefadroxil, cephalexin, cefazolin; Second generation (cefaclor, cefuroxime, cefotetan, cefamandole, cefoxitin, cefonicid, ceftmetazole); and Third generation (ceftizoxime, cefoperazone, cefprozil, ceftazidime, cefotaxime, ceftriaxone, cefixime, cefpodoxime).

Ahora bien, si se tiene en cuenta que según el solicitante la solicitud colombiana en trámite presenta "ventajas sorprendentes" (comillas fuera del texto) con respecto al arte anterior a saber y entre otras: la estabilidad química y física, la eficacia contra una variedad amplia de organismos infecciosos, rápida dispersabilidad, es del caso hacer notar que si bien es cierto que la patente americana US 5,736,151 tantas veces mencionadas no se refiere con exactitud a la misma composición farmacéutica revelada en la solicitud en trámite, si destaca sus ventajas (que coinciden con las propuestas en la solicitud actual) puesto que a lo largo de todo el documento enfatiza en que las suspensiones allí reveladas tienen una mejorada resuspendibilidad (ya que se requiere de menos agitación antes de la dosificación), por ende poseen **una mejorada estabilidad física** y permite que **el producto pueda ser almacenado por más tiempo** (mayor tiempo de vida-media) porque el fármaco en el producto no se asentará y no se compactará.

De igual manera, revela que Ceftiofur Clorhidrato tiene un amplio espectro de empleo contra bacterias gram-positivas y gram-negativas, veamos:

The suspension of the present invention which contains ceftiofur hydrochloride as its active ingredient, is useful as an antibiotic to cure bacterial infections of animals, such as livestock and poultry. Ceftiofur hydrochloride is a broad spectrum cephalosporin antibiotic active against gram-positive and gram-negative bacteria, including beta-lactamase-producing strains. For animals, it is effective in swine against a variety of diseases, such as diarrhea, pneumonia (*Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella choleraesuis* and *Streptococcus suis* type 2), transmissible gastro enteritos; avian pneumonia (*mycoplasma*, *haemophilus*) and Marek's diseases; and is effective in cattle against a variety of diseases, such as bovine diarrhea, pneumonia and mastitis.

Luego, en las columnas 11 y 12 describe detalladamente la estabilidad química y vida-media de las formulaciones allí planteadas, veamos:

B. Chemical Stability and Shelf-life

The stability of suspensions, and ultimately their shelf-life, are based on both chemical and physical stability. The chemical stability is assessed to insure that the product does not become subpotent during use. The chemical stability of the current formulation (ie. non-water-added formulation) has been studied extensively. For example, shown in Table 2 is the stability through 3 years for 3 different batches of the current suspension.

TABLE 2

Chemical Stability of a 50 mg/mL Ceftiofur HCl Suspension with No Additional Water Added when Stored at 25° C.

	Potency in mg/mL ± standard deviation		
Time, months	Lot A	Lot B	Lot C
0	49.8 ± 0.7	51.1 ± 0.5	50.5 ± 0.3
3	48.4 ± 1.3	49.4 ± 1.6	48.4 ± 0.4
6	48.1 ± 0.7	48.8 ± 1.2	48.6 ± 0.7
12	49.1 ± 0.4	50.2 ± 0.3	50.1 ± 0.3
18	46.5 ± 1.4	48.5 ± 0.7	48.5 ± 0.9
24	46.8 ± 4.2	48.8 ± 0.6	49.2 ± 2.7
36	49.1 ± 0.8	49.5 ± 0.4	48.6 ± 0.7

Usually pharmaceutical products are allowed to decrease 10% in potency during their shelf-life. Table 2 shows the current suspension is chemically stable even out to three years when stored at room temperatures.

The chemical stability has not been assessed for as long with the formulation of the present invention containing additional water. Shown in Table 3 is the comparison of two batches that were made identically except for the amount of water added. Similarly, Table 4 shows another comparison of two batches that only varied in water content.

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TABLE 3

Comparison of Chemical Stability of Two Batches with Different Water Contents when Stored at 25° C.

	Potency as a percent of label ± standard deviation	
Time, months	Lot D (0.20% total water)	Lot E (0.39% total water)
0	103.2 ± 0.5	102.2 ± 0.2
2	103.2 ± 0.4	101.6 ± 0.0
4	103.6 ± 0.3	103.3 ± 1.3
6	103.7 ± 0.4	103.0 ± 0.2

TABLE 4

Comparison of Chemical Stability of Two Batches with Different Water Contents when Stored at 25° C.

	Potency as a percent of label ± standard deviation	
Time, months	Lot F (0.14% total water)	Lot G (0.67% total water)
0	104.5 ± 0.3	103.4 ± 0.6
2	104.6 ± 1.7	103.1 ± 0.1
4	105.5 ± 0.7	105.4 ± 0.5
6	103.5 ± 0.5	102.9 ± 0.1

Both Tables 3 and 4 show the suspension to be chemically stable. No difference was observed in chemical stability even with high water content. Thus, contrary to what may be expected, the addition of water did not adversely affect the chemical stability of the suspension. Additional stability data which was obtained at accelerated temperatures shows no difference in stability with higher water content.

En cuanto a la estabilidad física (asociada a la redispersabilidad o resuspendibilidad) tenemos que en la columna 12 se revela:

C: Physical Stability

Physical stability is just as important as chemical stability. If the product does not resuspend adequately when shaken, the dose will be incorrect. With incomplete resuspension when shaken, the initial doses removed will be subpotent. This occurs because drug remains at the bottom of the vial preventing the correct concentration of the suspension when agitated. If part of the product is removed at a concentration significantly less then the labeled concentration, doses removed when the vial contains less product could become superpotent. This happens when further agitation removes drug from the bottom of the container and it is dispersed in the smaller volume of liquid.

It has been found that the addition of water improves the resuspendability characteristics of the suspension. A sensitive method for monitoring resuspendability is to use a 10-second mechanical shake assay. In this test, a vial is shaken for 10 seconds using a mechanical arm. A sample is removed from the suspension 2 cm below the liquid/air interface and assayed for the amount of drug. Shown in Tables 6 and 7 below are batches produced by identical methods except for the amount of water:

TABLE 6

Comparison of Physical Stability of Two Batches with Different Water Contents using a 10-Second Mechanical Shake Test

	Potency as a percent of label ± standard deviation	
Time, months	Lot D (0.20% total water)	Lot E (0.39% total water)
0	82 ± 4	99 ± 2
2	72 ± 40	98 ± 1
4	48 ± 7	97 ± 2
6	49 ± 3	96 ± 1

TABLE 7

Comparison of Physical Stability of Two Batches with Different Water Contents using a 10-Second Mechanical Shake Test

	Potency as a percent of label ± standard deviation	
Time, months	Lot F (0.14% total water)	Lot G (0.67% total water)
0	79 ± 5	104 ± 1
2	37 ± 31	101 ± 2
4	58 ± 16	102 ± 3
6	67 ± 27	95 ± 2

As the data from these tables shows, the increased water content improved resuspendability. The formulations with higher water concentrations were closer to the theoretical 100% of label and had less vial to vial variability (ie. tighter standard deviations).

En consecuencia, siendo las formulaciones del tipo "suspensiones" un tipo de formulación ampliamente utilizado y reconocido en la formulación de cefalosporinas entre ellos Ceftiofur y otros principios activos, y siendo conocidas desde 1998 múltiples ventajas como las descritas anteriormente, queda claro que pretender obtener privilegio sobre la composición planteada en la solicitud colombiana en trámite no representa de ninguna manera avance sorprendente o puede llegar a demostrar al menos nivel inventivo, ya que dicho tipo de formulaciones se encuentran ampliamente reconocidas en el estado del arte, además, resultaría en una simple aplicación de los respectivos ensayos de preformulación y formulación que permitan llegar a obtener una formulación de Ceftiofur con otros excipientes que permita que el fármaco -sensible a la oxidación- sea estable química y físicamente y logre la liberación del mismo de

forma adecuada y en un tiempo adecuado para que ejerza su acción farmacológica.

2.1.3. Obviedad de la combinación de todas las características para derivar el objeto reivindicado.

Basta en este punto con formular una pregunta final: conociendo las características, propiedades y, si se quiere, dificultades intrínsecas de los compuestos y/o formulaciones que se emplean en la solicitud, conociendo las propiedades mejoradas que ofrecen las formulaciones reveladas en la US 5,736,151 (tenidas en cuenta en el numeral anterior), conociendo la existencia y empleo extendido de los excipientes mencionados, conociendo la existencia de composiciones farmacéuticas en forma de suspensiones oleosas química y físicamente estables y que además contienen Ceftiofur Clorhidrato, ¿no resultaría obvio para una persona medianamente versada en la materia derivar una solución como la que se pretende en la solicitud que nos ocupa?

La respuesta puede obtenerse comparando el problema técnico que desea resolverse, el arte más cercano, y la solución propuesta. A nuestro juicio, aún si en gracia de discusión no existiera una revelación textual del objeto reivindicado, lo cierto es que la combinación de las enseñanzas del arte anterior y de los principios generales de química farmacéutica y formulación, permiten, sin duda, derivar el objeto reivindicado, que carece por completo de nivel inventivo.

Por último, considero oportuno traer a colación dos decisiones recientes de la SIC sobre solicitudes de patente relacionadas con formas farmacéuticas, como sigue: En primer lugar, la Resolución 10279 de 22/03/2002, proferida en el trámite del expediente 97-034-775, relacionado con composiciones farmacéuticas orales de Valsartan. En ese caso, la SIC encontró en el examen de fondo que dicho principio activo, al igual que en este caso, ya era conocido en las formas de dosificación allí pretendidas, y negó la solicitud POR FALTA DE NOVEDAD, aún sin existir una revelación anterior idéntica. Dijo entonces la SIC:

> ***"Con estas composiciones (las encontradas en las anterioridades) se demuestra que el compuesto no es nuevo, que las composiciones que contienen Valsartán tampoco son nuevas y que el hecho que la cantidad de principio activo sea superior al 35% también era conocido para la fecha de presentación de la***

solicitud, pues, se reitera, dichas composiciones son ampliamente conocidas en el estado de la técnica a tal punto que se distribuían en concentraciones de 80mg ó 160 mg, lo que indica la total falta de novedad de la presente solicitud." **(Paréntesis explicativo fuera del texto).**

De igual manera, en el examen de fondo practicado a la solicitud 98-57677-A, oficio 15972 de 06/11/2002, dijo la SIC que las formulaciones parenterales de Oxcarbazepina allí pretendidas, en tanto habían sido reveladas por vía general en una publicación anterior a la prioridad carecían de novedad, al paso que en la evaluación de nivel inventivo afirmó:

"(...) para el caso que nos ocupa, conociendo las propiedades de los elementos propuestos para constituir la formulación farmacéutica, (integrada por Oxcarbazepina, un solvente basado en agua y glucosa para administración parenteral) se deriva de manera evidente el ensayo, implementación y final aplicación de estos agentes, puesto que es de esperarse su conveniencia." (Paréntesis explicativo y subrayado fuera del texto).

2.1.5. Las reivindicaciones 13 a 16 revelan un procedimiento de tratamiento o prevención de una infección bacteriana mediante la administración de una composición como la revelada en las reivindicaciones 1 a 10.

Como es bien sabido por ese Despacho, el hecho de pretender la obtención del beneficio patentario sobre usos, riñe con lo dispuesto en el artículo 14 de la Decisión 486 de 2000, que limita el otorgamiento de patente a los PRODUCTOS Y PROCEDIMIENTOS que cumplan, además, con los requisitos de novedad, nivel inventivo y aplicación industrial, de igual manera, el pretender protección sobre métodos terapéuticos, se encuentra expresamente prohibido según lo dispuesto en el artículo 20-d de la Decisión.

Es del caso recordar en este punto que en el proceso de discusión y aprobación de la Decisión mencionada, en el cual tuvo un determinante papel esa entidad, se acordó dar cumplimiento pleno a lo dispuesto en el artículo 27.1 de ADPIC, en el sentido de admitir el privilegio de patente sólo para los PRODUCTOS Y PROCEDIMIENTOS que cumplan las previsiones anotadas. Lo anterior es útil para demostrar que la clara y reiterada posición de la SIC frente a este tema se ha fundamentado en el espíritu y la letra de la Decisión Andina 486 y del Acuerdo

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TRIPS, sin que existan en este caso argumentos para modificar su hasta ahora cumplida aplicación.

Así las cosas, la pretensión del solicitante de obtener privilegio sobre MÉTODOS DE TRATAMIENTO y USO es inaceptable a la luz del ordenamiento subregional andino, no sólo por ser un método terapéutico, sino porque los compuestos allí mencionados, entre ellos Ceftiofur, ya habían sido utilizados con anterioridad a la presentación de la solicitud colombiana en trámite, de acuerdo con la US 4,902,683 y US 5,736,151 –entre otras-, para estados de infección bacteriana manifestada en forma de mastitis. En conclusión, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

III. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- La patente americana US 4,902,683 titulada "Crystalline cephalosporin hydrohalide salts" y publicada el 20 de febrero de 1990.
- La patente americana US 5,736,151 titulada "ANTIBIOTIC OIL SUSPENSIONS" y publicada el 7 de abril de 1998.

IV. NOTIFICACIONES

El suscrito y mi poderdante recibiremos notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad.

Señor Superintendente,

JOSÉ LUIS REYES VILLAMIZAR
C.C. 79'152.473 de Usaquén
T.P.A. 44.655 del C.S.J.

US005736151A

United States Patent [19]

Foster et al.

[11] Patent Number: 5,736,151

[45] Date of Patent: Apr. 7, 1998

[54] ANTIBIOTIC OIL SUSPENSIONS

[75] Inventors: **Todd P. Foster**, Kalamazoo; **David L. Kiefer**, Alanson, both of Mich.

[73] Assignee: **Pharmacia & Upjohn Company**, Kalamazoo, Mich.

[21] Appl. No.: **896,584**

[22] Filed: Dec. 9, 1996

[51] **Int. Cl.**[6] **A61F 2/02**; A61K 31/545

[52] **U.S. Cl.** **424/423**; 514/206

[58] **Field of Search** 424/423; 514/206; 540/227

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,464,367	8/1984	Labeeuw .	
4,877,782	10/1989	Cazers et al.	514/206
4,902,683	2/1990	Amin .	
4,937,330	6/1990	Sacks .	
5,134,137	7/1992	Cazers et al.	514/206
5,223,496	6/1993	Cazers et al.	514/206

OTHER PUBLICATIONS

Amin, M.L., et al., J. Pharm. Sci., vol. 76(11):S255 (1976).

Evans, R.A., et al. "Ceftiofur Hydrochloride, A New Broad-Spectrum Cephalosporin: Effectiveness Against Induced Haemophilus Pleuropneumoniae of Growing Swine." Proceedings of the International Pig Veterinary Society, 10th Congress, Rio de Janeiro, Brazil, p. 94 (1988).

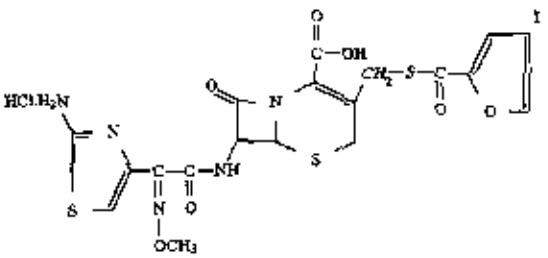
Evans, R.A., et al., "Effectiveness of Ceftiofur Hydrochloride, A New Broad-Spectrum Cephalosporin, in Treatment of Colibacillosis in Neonatal Swine," Proceedings of the International Pig Veterinary Society, 10th Congress, Rio de Janeiro, Brazil, p. 108 (1988).

Primary Examiner—Carlos Azpuru

Attorney, Agent, or Firm—Martha A. Gammill

[57] **ABSTRACT**

The present invention provides for the inclusion of small amounts of water in oil suspensions of active drugs, such as ceftiofur hydrochloride of formula *I*. The resulting suspensions have improved resuspendability. Improved resuspendability results in an improved product because less shaking of the suspension is required before dosing.



23 Claims, 1 Drawing Sheet

ANTIBIOTIC OIL SUSPENSIONS

FIELD OF THE INVENTION

The present invention provides for novel pharmaceutical compositions of active drugs. More particularly, the present invention provides for novel formulations, such as oil suspensions, of the class of drugs known as cephalosporins. Most particularly, the present invention provides for novel oil suspensions of the cephalosporin, ceftiofur hydrochloride, which have improved properties, such as *physical stability* (i.e., *resuspendability*).

BACKGROUND OF THE INVENTION

The following five references: W. I. Higuchi, J. Swarbrick, H. F. H. Ho, A. P. Simonelli and A. Martin, Particle phenomena and coarse dispersions, in *Remington's Pharmaceutical Sciences*, 17th Edition, 1985, Mack Publishing Company, Easton, Pa., pp. 301–329; M. J. Fatkiewicz, Theory of Suspensions, in *Pharmaceutical Dosage Forms: Disperse Systems*, Volume I, Eds. H. A. Liberman, M. M. Rieger and G. S. Banker, 1988, Marcel Dekker, New York, N.Y., pp. 13–48; R. A. Nash, Pharmaceutical Suspensions, in *Pharmaceutical Dosage Forms: Disperse Systems*, Volume 1, Eds. H. A. Lieberman, M. M. Rieger and G. S. Banker, 1988, Marcel Dekker, New York, N.Y., pp. 151–198; N. K. Patel, L. Kennon and R. S. Levinson, *Pharmaceutical Suspensions, in The Theory and Practice of Industrial Pharmacy*, Eds. L. Lachman, H. A. Lieberman and J. L. Kanig, 1986, Lea and Febiger, Philadelphia, Pa., pp. 479–501; and S. E. Tabibi and C. T. Rhodes, Disperse Systems, in *Modern Pharmaceutics*, Third Edition, Revised and Expanded, Eds. G. S. Banker and C. T. Rhodes, 1996, Marcel Dekker, New York, N.Y., pp. 310–319; are general textbook discussions on suspensions and the formulation of physically stable suspensions. Remington's states at page 313 the major challenge with developing a good suspension is obtaining physical stability: "The three major problem areas associated with suspensions are (1) adequate dispersion of the particles in the vehicle, (2) settling of the dispersed particles, and (3) caking of these particles in the sediment so as to resist redispersion."

It is generally recognized in the art that controlled particle-to-particle interaction is a method to produce physically stable suspensions. Coarse Dispersions: Suspensions, Emulsions and Semisolids, in *Physical Pharmacy*, 2nd Edition, Eds. A. N. Martin, J. Swarbrick and A. Cammarata, 1969, Henry Kimpton Publishers, London, England, pp. 522–525; see also E. N. Hiestand, Theory of Coarse Suspension Formulation, *Journal of Pharmaceutical Sciences*, 1964, 53(1): 1–18, especially pages 9–12. Many Investigators refer to this controlled aggregation as "flocculation." The *particle interaction must result in a "loose" particle* aggregation so when the suspension is shaken the particles can separate to some extent and a uniform dose can be obtained. The particle attraction must be "strong" enough so particle aggregation does occur. However, the particle aggregation cannot be so "strong" that the particles will never separate. Proper particle flocculation allows particles to settle with high sedimentation volumes and not to pack or cake drug at the bottom of the container. *Physical Pharmacy* (cited above) at pages 522–525; E. N. Hiestand (cited above) at pages 9–12; and W. I. Higuchi et al. (cited above) at page 315, FIGS. 21–19.

These five general chapters/articles mention several additives which cause suspensions to flocculate. These flocculating agents include electrolytes, surfactants and polymers.

E. N. Hiestand (cited above) at pages 13–15; and *Physical Pharmacy* (cited above) at pages 522–525. Surfactant examples include polyoxyethylene ethers of mixed partial fatty acid esters of sorbitol anhydrides (Tweens), the same compounds without the hydrophilic oxyethylene groups (Spans), higher molecular weight polyethylene glycols (Carbowaxes) and molecular combinations of polyoxyethylene and polyoxypropylene (Pluronics). N. K. Patel et al. (cited above) at page 489. Electrolyte examples include sodium chloride, potassium chloride and calcium salts as well as sulfates, citrates and phosphates. R. A. Nash (cited above) at page 183. Polymers may include gelatin, natural gums like tragacanth and xanthan, and cellulose derivatives like sodium carboxymethylcellulose, hydroxypropylcellulose and hydroxypropylmethylcellulose. R. A. Nash (cited above) at page 184. None of the five review articles discuss the importance of water alone in causing particle-to-particle interaction (or in decreasing particle-to-particle repulsion) when formulating a pharmaceutical suspension.

E. N. Hiestand (cited above) at page 14, discloses that, in the paint industry particularly, oil suspension formulations were prepared using liquids, such as water, as flocculating agents. Also at page 14, Hiestand describes the usefulness of water in pharmaceutical suspensions; however, he does not give any specifics on the drug or the vehicle to be used. Certainly, he does not mention the use of an oil vehicle. He also states that a surface-active material (e.g., surfactant) *should be included in the suspension* to coat the lyophobic drug surface.

The following four references discuss how small amounts of water in hydrophobic vehicles (e.g., organic solvents, oils), especially those used in the paint and printing ink industry, cause flocculation: C. R. Bloomquist and R. S. Shutt, Fine Particle Suspensions in Organic Liquids, *Industrial and Engineering Chemistry*, June, 1940, 32(6): 827–831; F. H. Rhodes and W. J. Jehens, Studies in the Plasticity of Paints, *Journal of Physical Chemistry*, 1930, 35: 383–404; H. R. Kruyt and F. G. Van Selms, The Influence of a Third Phase on the Rheology of Suspensions, *Rec. Trav. Chim.*, 1943, 62: 415–426; and A. C. Zettlemoyer, Modern Techniques for Investigating Interactions with Surfaces, *Chem. Rev.*, 1959, 59: 937–981.

The following more specific prior art references discuss the dispersion of a drug in oil to produce a suspension: J. Heidt, Injectable Suspensions Containing Maleic Acid or a Salt Thereof as a Stabilizing Agent, UK Patent Application 2 105 589 A, published 30 Mar. 1983; A. L. Adjei, S. Borodkin and R. B. Doyle, Anhydrous Oil-Based Liquid Suspension for Delivering a Medicament, International Publication Number WO 91/08734, published 27 Jun. 1991; K. Bauer, K. E. Fetting, R. Gonnert, H. Thomas and H. Voege, New Niclosamide Suspension Formulations, UK Patent 1 527 638, *published 4 Oct. 1978; and K. S. E. Su, J. F. Quey*, K. M. Capanale and J. F. Stucky, Nonaqueous Cephalosporin Suspension for Parenteral Administration: Cefazolin Sodium, *Journal of Pharmaceutical Sciences*, 1984, 73(11): 1602–1606. None of these references mention the addition of water to oil formulations or discuss the importance small amounts of water have on resuspendability.

For example, Heidt claimed a suspension of an active ingredient in a neutral oil that contains maleic acid or a salt thereof to aid in resuspendability. The Adjei et al. patent provides general information on oil suspensions for the administration of drugs which are sensitive to water or which have an unpalatable taste and explains why certain ingredients are added to obtain a good suspension product. In referring to their oil suspension formulation, Adjei et al.

states at page 3: "In a preferred embodiment, the formulation also contains a drying agent to help bind any residual water that would otherwise degrade the active therapeutic agent." Bauer et al. obtained a specific patent for niclosamide (which is an anthelmintic agent) and its salts in an oil-based suspension. The forms of niclosamide which may be used include its anhydrous form, its form which contains water of crystallization, as well as its other salt forms. So et al. studied the suspension characteristics of the cephalosporin compound, cefazolin sodium, dispersed in peanut oil and ethyl oleate (i.e., lipophilic or oleaginous carriers). This article stated that while water is generally the preferred suspending liquid, some physiologically active agents such as the cephalosporin antibiotics are not chemically stable in *water-based parenteral pharmaceutical suspensions.* Therefore, according to the article, to achieve a ready-to-use cephalosporin preparation which can be stored at room temperature, it is desirable to develop a satisfactory suspension utilizing a nonaqueous liquid as the suspending medium.

The following two pharmaceutical articles: D. J. A. Crommelin and C. J. de Blaey, In Vitro Release Studies on Drugs Suspended in Non-Polar Media I. Release of Sodium Chloride from Suspensions in Liquid Paraffin, *International Journal of Pharmaceutics,* 1980, 5:305–316; and D. J. A. Crommelin and C. J. de Blaey, In Vitro Release Studies on Drugs Suspended in Non-Polar Media II. The Release of Paracetamol and Chloramphenicol from Suspensions in Liquid Paraffin, *International Journal of Pharmaceutics,* 1980, 6:29–42; discussed the addition of small amounts of water (0.01 or 0.05% m/m) to liquid paraffin suspensions (ie. mineral oil) which contain sodium chloride, paracetamol or chloramphenicol. Water was added to the oil suspensions to observe the influence of the water on in vitro drug release. The addition of water to the sodium chloride suspension significantly enhanced the release rate. The addition of water to the other two suspensions did not change the release rate. *The enhanced agglomeration* of the particles when water was added to any of the three suspensions was also described.

The Crommelin and de Blaey papers refer to colloidal dispersion research conducted in the 1960's where the influence of water on dispersions in nonpolar media was studied. The following two papers: D. N. L. McGown, G. D. Parfitt and E. Willis, Stability of Non-aqueous Dispersions I. The Relationship between Surface Potential and Stability in Hydrocarbon Media, *Journal of Colloid Science,* 1965, 20:650–664; and A. Kitahara, S. Karasawa and H. Yamada, The Effect of Water on Electrokinetic Potential and Stability of Suspensions in Nonpolar Media, *Journal of Colloid and Interface Science,* 1967, 25:490–495; examined dispersants like alpha-alumina, carbon black, copper phthalocyanine *green pigment or barium sulfate in nonpolar solvents such as* p-xylene, n-heptane, cyclohexane or benzene which contain different amounts of surfactants (e.g. Aerosol TO (sodium di-2-ethylhexyl sulfosuccinate), polyoxyethylene nonylphenol ether). The amounts of water added were small, normally less than 400 ppm. These researchers noticed changes in physical stability, zeta potential and turbidity with different amounts of added water. However, they also stated that adding water may not result in changes for all systems as they noted no effect when adding water to carbon black or barium sulfate in cyclohexane or n-heptane solutions of polyoxyethylene nonylphenol ether. They also observed the formation of unstable colloidal dispersions when water was added to these systems in excess of 400 ppm.

Thus, as documented above, the problem in the art has been to develop *pharmaceutically useful suspensions of* drugs, which are also physically stable (i.e., resuspendable). Attempts to solve this problem have not focused on the addition of water to such suspensions, and in fact, for cephalosporins, have taught away from its use.

INFORMATION DISCLOSURE

EXCENEL® Sterile Suspension (ceftiofur hydrochloride) is currently marketed in the U.S. as a ready-to-use oil suspension product for the treatment/control of swine bacterial respiratory disease. The ingredients of this currently marketed formulation are listed below. No water is added to this formulation, but its ingredients may contain a small amount of water, as will be described further below. This formulation of ceftiofur hydrochloride has several disadvantages, such as poor physical stability (i.e., resuspendability).

Published articles, such as the following, demonstrate the effectiveness of EXCENEL® Sterile Suspension as a veterinary antibiotic: "Ceftiofur Hydrochloride, a New Broad-Spectrum Cephalosporin: Effectiveness Against Induced-Haemophilus pleuropneumonia of Growing Swine," and "Effectiveness of Ceftiofur Hydrochloride, a New Broad-Spectrum Cephalosporin, in Treatment of Colibacillosis in Neonatal Swine," Proceedings of the International Pig Veterinary Society, 10th Congress, Rio de Janeiro, Brazil; pp. 94 and 108, respectively (1988). M. I. Amin et al., "Radiation Sterilization of Suspension Ceftiofur Hydrochloride," J. Pharm. Sci., Vol. 76(11) :S255 (1976), evaluated methods for sterilizing ceftiofur hydrochloride powder and a suspension formulation containing 3% lecithin coated ceftiofur hydrochloride.

NAXCEL/EXCENEL® Sterile Powder (ceftiofur sodium) is also currently marketed throughout the world for the treatment/control of bovine and swine bacterial respiratory diseases. This product must be reconstituted with sterile water before it is injected into the animal.

Amin et al., Crystalline Cephalosporin Hydrohalide Salts, U.S. Pat. No. 4,902,683, 20 Feb. 1990, discloses crystalline hydrochloride and hydrobromide salts of the cephalosporin antibiotic, ceftiofur, processes for their manufacture, and pharmaceutical compositions thereof. None of the compositions disclosed therein teach or suggest the addition of water.

Labeeuw et al., *Cephalosporin Derivatives, Process for* Preparation Thereof and Drugs Containing Said Derivatives Usable as Antibiotics, U.S. Pat. No. 4,464,367, 7 Aug. 1984, discloses the cephalosporin antibiotic, ceftiofur, as well as alkali, alkaline earth and amine salts thereof. This patent discloses as an apparently prophetic example of a pharmaceutical composition, ampoules containing the sodium salt of ceftiofur and water (which would be a solution) for an injectable preparation. However, there is no indication that such a composition would actually work, and in fact, it is believed that any such water solution would not be marketable because of chemical instability.

Dill et al., Conversion of Cephalosporin Hydrohalide Salt to Alkali Metal Salt, U.S. Pat. No. 4,937,330, 26 Jun. 1990, discloses a process for making a alkali metal salt of ceftiofur, such as the sodium salt, by the following steps: a) neutralizing a hydrohalide salt of ceftiofur, such as the hydrochloride salt, in an aqueous organic solvent, by treating it with a basic resin; b) filtering the obtained solution to remove the basic resin; and c) treating the filtrate with a base of an alkali metal.

No where do these references teach or suggest the addition of water to oil suspensions of cephalosporins, such as

ceftiofur hydrochloride. Furthermore, the addition of water, according to the present invention, resulted in unexpected improvements in the physcial properties of the suspension, such as physical stability (i.e., resuspendability) and shelf-life, as will be described further below.

SUMMARY OF THE INVENTION

The present invention particularly provides:

In an oil suspension of ceftiofur hydrochloride in unit dosage form consisting of an effective amount of ceftiofur hydrochloride, a biocompatible oil and one or more pharmaceutically acceptable excipients, the improvement characterized by: an amount of water which is present at about 0.25% to about 20.20% of the suspension; preferably, the water is present at about 0.25% to about 2.20% of the suspension; more preferably, the water is present at about 0.30% to about 0.75% of the suspension; most preferably, the water is present at about 0.30% to about 0.50% of the suspension.

The present invention also provides:

In a pharmaceutical composition containing ceftiofur hydrochloride, the improvement characterized by: the addition of water. The water is added in an amount which is about 0.5 to about 200 mg of water per ml of composition. Preferably, the water is added in an amount which is about 0.5 to about 20 mg of water per ml of composition. More preferably, the water is added in an amount which is about 1 to about 5.5 mg of water per ml of composition. Most preferably, the water is added in an amount which is about 1 to about 3 mg of water per ml of composition.

Finally, the present invention provides:

A pharmaceutical composition in unit dosage form, which comprises:

a) a drug,

b) a biocompatible oil, and

c) water which is present at about 0.25% to about 20.20% of the composition. Preferably, the water is present at about 0.25% to about 2.20% of the composition. More preferably, the water is present at about 0.30% to about 0.75% of the composition. Most preferably, the water is present at about 0.30% to about 0.50% of the composition.

The drug in this composition may be an antibiotic such as spectinomycin. The drug in this composition may also be a cephalosporin such as ceftiofur hydrochloride. The ceftiofur hydrochloride may have a particle size of less than 10 microns and may be present at a concentration of about 50 mg per ml of composition.

The biocompatible oil in this composition may be selected from the group consisting of: canola oil, corn oil, cottonseed oil, olive oil, peanut oil, sesame oil, soybean oil, safflower oil, coconut oil, sunflower oil and palm oil. Cottonseed oil is preferred.

This composition may also contain one or more pharmaceutically acceptable excipients, such as Phospholipon and sorbitan monooleate.

This composition may be an injectable oil suspension.

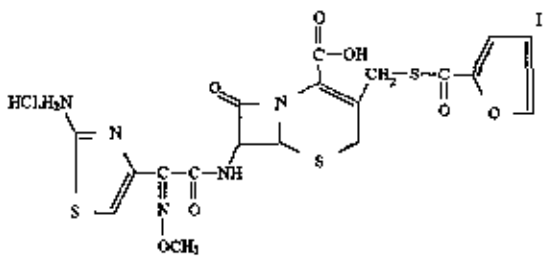
In general, the present invention provides an oil suspension of an active drug which also contains added water.

Drugs which may be formulated in the suspension of the present invention include the following cephalosporins: First generation (ceftiofur, cefadroxil, cephalexin, cefazolin); Second generation (cefaclor, cefuroxime, cefotetan, cefamandole, cefoxitin, cefonicid, ceftmetazole); and Third generation (ceftizoxime, cefoperazone, cefprozil, ceftazidime, cefotaxime, ceftriaxone, cefixime, cefpodoxime).

Other drugs which may also be formulated in the suspension of the present invention include the following: Aids Related Complex Therapeutic Agents (trimethoprim, sulfamethoxazole, zidovudine, dianosine, delavirdine); Analgesics (actaminophen, aspirin, ibuprofen, naproxen); Antacids (aluminum hydroxide, magnesium hydroxide, simethicone); Antibiotics (spectinomycin, gentamicin, erythromycin, penicillins, quinolones, sulfonamides, tetracyclines); Antihistamines (hydroxyzine, diphenhydramine, loratadine); Cardiovascular agents (prazosin, methyldopa, captopril, propranolol, isosorbide dinitrate, verapamil, furosemide); Cough and Cold preparations (pseudoephedrine, dextromethorphan, chlorpheniramine); Dermatologicals (clindamycin, tretinoin, hydrocortisone, ketoconazole, miconazole); Diabetes agents (glyburide, chlorpropamide); Diarrhea medications (loperamide); Hormones (estrogens, growth hormone, methylprednisolone); Hypolipidemics (colestipol, lovastatin); Nausea medications (meclizine, prochlorperazine); Otic preparations (neomycin, polymyxin B sulfates); Parkinsonism drugs (bromocriptine, benztropine); Psycotropics (chlordiazepoxide, diazepam, triazolam, imipramine).

As described above, the present invention provides for a formulation which is an oil suspension containing a cephalosporin with added water. More specifically, the present invention provides for the inclusion of small amounts of water in oil suspensions of the cephalosporin, ceftiofur, particularly ceftiofur hydrochloride. The resulting suspensions have improved resuspendability. Improved resuspendability results in an improved product because less shaking of the suspension is required before dosing and allows the product to be stored longer (i.e., longer shelf-life) because the drug in the product will not settle and compact. The addition of water may also eliminate the need for including other formulation agents, such as viscosity-enhancing suspending agents (e.g., gelling agents).

The structure of ceftiofur hydrochloride is Formula I as follows:



This compound is a crystalline hydrochloride salt of 7-[2-(2-amino-1,3-thiazol-4-yl)-2-methoxyimino) acetamido]-3-[(fur-2-ylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid. This cephalosporin free acid compound is known by the generic name, ceftiofur. Its preparation is described in U.S. Pat. No. 4,902,683, Amin et al., 20 Feb. 1990, which is hereby incorporated by reference.

The amount of water which is to be added to obtain the suspension of the present invention ranges from about 0.5 to about 200 mg of water per ml of formulation; preferably about 0.5 to about 20 mg of water per ml of formulation is added; more preferably about 1 to about 5.5 mg of water per ml of formulation is added; most preferably, about 1 to about 3 mg of water per ml of formulation is added.

As described above, the formulation of the present invention consists of an active drug ingredient, such as the cephalosporin ceftiofur hydrochloride, a biocompatible oil

and water. The biocompatible oil is composed essentially of triglycerides, which are long chain fatty acid esters of glycerol, or mixtures of triglycerides and fatty acids. Trihydroxy, dihydroxy, monohydroxy or even polyhydroxy compounds may be substituted for the glycerol. The oils may be of vegetable, animal or synthetic origin. Preferred oils include canola, corn, cottonseed, olive, peanut, sesame, soybean, safflower, coconut, sunflower, and palm. The especially preferred oil is cottonseed oil.

The concentration of the cephalosporin in the formulation of the present invention may vary between about 1 mg/ml to 500 mg/ml. Preferably, for ceftiofur hydrochloride, the concentration is about 50 mg/ml. In general, the upper limit on the concentration is determined by when the oil composition becomes too viscous to syringe.

The suspension of the present invention may also contain other pharmaceutically acceptable excipients normally included in such suspensions, for example, suspending agents, preservatives, wetting agents or flocculating agents, if desired. Suspending agents, such as gums (e.g., acacia, carrageenan, sodium alginate and tragacanth), cellulosics (e.g., sodium carboxymethylcellulose, microcrystalline cellulose, and hydroxyethylcellulose), and clays (e.g., bentonite and colloidal magnesium aluminum) may be included. Preservatives, such as methyl and propyl paraben, benzyl alcohol, chlorobutanol and thimerosal may be added. Wetting agents such as anionic (e.g., docusate sodium and sodium lauryl sulfate) and nonionic (polysorbates, polyoxamers, octoxynol-9) surfactants may be used. Thickeners, such as gelatin, natural gums and cellulose derivatives (such as those listed above as suspending agents) may be added. Buffers, such as citrate and phosphate buffering agents, may be included, as well as osmotic agents, such as sodium chloride and mannitol. For oral suspensions, additional agents may be used, such as the following: flavoring agents, sweeteners (e.g., mannitol, sucrose, sorbitol and dextrose), colorants and fragrances. Particularly, for the formulations of the present invention, excipients such as sorbitan monooleate (which may be used as a wetting agent) and Phospholipon (which may be used as a dispersant) may be added.

The suspension of the present invention may be prepared by any method known in the art for the preparation of injectable suspensions. All such methods involve the active ingredient being present in a suitable solid form and suspension thereof in a liquid vehicle. However, if the formulation contains Phospholipon, the Phospholipon may be added via a heating and cooling step, which may be considered different from a typical suspension manufacture.

The preparation of a 5 L batch of the ceftiofur hydrochloride suspension of the present invention is shown in EXAMPLE 1 below. Micronized ceftiofur HCl, which consists of particles with a median geometric mean below 10 microns, may be preferably used. However, as one skilled in the art realizes, the particle size may vary above and below the preferred size depending on the cephalosporin, the biocompatible oil and any other ingredients used in the composition. In fact, nonmicronized drug may be used in some embodiments.

A manufacturing facility suitable for producing sterile products must be used if one is making this composition as an injectable for commercial use. Also, all manufacturing equipment and packaging components should be sterilized when making the suspension for administration by injection.

The suspension of the present invention, which contains ceftiofur hydrochloride as its active ingredient, is useful as an antibiotic to cure bacterial infections of animals, such as livestock and poultry. Ceftiofur hydrochloride is a broad spectrum cephalosporin antibiotic active against gram-positive and gram-negative bacteria, including beta-lactamase-producing strains. For animals, it is effective in swine against a variety of diseases, such as diarrhea, pneumonia (*Actinobacillus pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis* and *Streptococcus suis* type 2), transmissible gastro enteritos; avian pneumonia (*mycoplasma, haemophilus*) and Marek's diseases; and is effective in cattle against a variety of diseases, such as bovine diarrhea, pneumonia and mastitis.

The effective amount of this antibiotic to be used will vary depending on the species, age and/or weight of the animal being treated. It could vary between about 0.1 and 100 mg/kg. For example, when treating swine bacterial respiratory disease (swine bacterial pneumonia, SBP), the dose may range between about 3 and 5 mg/kg given once daily for three consecutive days.

Also, the concentration of the oil composition will depend on the species to be treated and the dose of antibiotic required. For example, when treating SBP at a dose of 3 mg/kg, a 50 mg/mL concentration solution is preferred. One injection of 1.0 mL will provide the required composition for each 22–37 pound body weight.

The routes of administration include oral and parenteral, such as subcutaneous and intramuscular. The preferred route of administration in livestock is subcutaneous. However, other parenteral routes of administration, like intramuscular, may be used.

Furthermore, those skilled in the art would know how to formulate the composition of the present invention, using pharmaceutically acceptable excipients, into appropriate unit dosage forms. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for mammalian subjects, each unit containing as the essential active ingredient a predetermined quantity of the drug of this invention with the required pharmaceutical means which adapt said ingredient for systemic administration. Examples of such dosage forms include oral formulations, such as tablets or capsules, or parenteral formulations, such as injectable suspensions.

Additional information on the dosage and mode of administration of the antibiotic ceftiofur hydrochloride is contained in U.S. Pat. No. 4,902,683, which is hereby incorporated by reference herein.

In the present invention, the addition of water to the ceftiofur hydrochloride suspension causes the particles to flocculate and settle in the suspension, resulting in an improved and pharmaceutically useful suspension. This enhanced flocculation (i.e., aggregation) observed when adding small amounts of water to ceftiofur oil suspensions results in a suspension that resuspends more easily. The improved properties of the suspension of the present invention is further detailed in EXAMPLE 2 below.

The currently marketed formulation of ceftiofur hydrochloride, known as EXCENEL® Sterile Suspension, contains the following ingredients per mL:

Ceftiofur HCl micronized	50 mg*
Phospholipon 90-H (lecithin)	0.50 mg
Sorbitan monooleate NF	1.30 mg
Cottonseed oil NF	enough to make 1 mL

*This is the amount of ceftiofur activity.

No water is added to this formulation; however, water may be present in its other ingredients (e.g., bulk ceftiofur hydrochloride and cottonseed oil) and/or due to environ-

mental conditions. As currently manufactured and sold, the total amount of water which has been measured as being present in this formulation ranges from about 0.1% to 0.2% (which is about 1 to 2 mg of water per ml of formulation).

A ceftiofur hydrochloride formulation of the present invention has the following ingredients:

Ceftiofur HCl micronized	50 mg*
Water for Injection, USP	20 mg
Cottonseed oil NF	enough to make 1 mL

*This is the amount of ceftiofur activity.

An important difference between the formulation of the present invention and the formulation that is currently marketed is that water is added to the formulation of the present invention—in addition to that which may already be present, as noted above. Assuming the currently marketed formulation contains about 2.0 mg of water per ml of formulation (which is the upper limit which has been identified, as noted above), the amount of water which is added to obtain the suspension of the present invention ranges from about 0.5 to about 200 mg of water per ml of formulation; preferably about 0.5 to about 20 mg of water per ml of formulation is added; more preferably about 1 to about 5.5 mg of water per ml of formulation is added; most preferably, about 1 to about 3 mg of water per ml of formulation is added.

Thus, the resulting formulation of the present invention will have a total amount of water of about 0.25% to about 20.20% (which is about 2.5 to about 202.0 mg of water per ml of formulation). Preferably, the resulting formulation of the present invention will have a total amount of water of about 0.25% to about 2.20% (which is about 2.5 to about 22.0 mg of water per ml of formulation). More preferably, it will have a total amount of water of about 0.30% to about 0.75% (which is about 3.0 to about 7.5 mg of water per ml of formulation). Most preferably, it will have a total amount of water of about 0.30% to about 0.50% (which is about 3.0 to about 5.0 mg of water per ml of formulation).

Surprisingly and unexpectedly, the addition of this small amount of water results in a ceftiofur hydrochloride formulation with substantially improved properties, as documented below.

A preferred ceftiofur hydrochloride formulation of the present invention has the following ingredients:

Ceftiofur HCl micronized	50 mg*
Phospholipon 90-H (lecithin)	0.50 mg
Sorbitan monooleate NF	1.50 mg
Water for Injection, USP	2.50 mg
Cottonseed oil NF	enough to make 1 mL

*This is the amount of ceftiofur activity.

The unexpected differences in the properties of these two formulations are documented in EXAMPLE 2 below.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

EXAMPLE 1

Ceftiofur Hydrochloride Oil Suspension—Water Added (5 L Batch)

The ingredients listed in Table 1 are secured:

TABLE 1

Amounts Required for a 5 L Batch

Ingredient	Amount	Amount per mL
Ceftiofur HCl micronized	0.258 kg*	50 mg
Phospholipon-90H	0.25 g	0.5 mg
Sorbitan monooleate NF	0.75 g	1.5 mg
Water for Injection, USP	1.25 g	2.5 mg
Cottonseed Oil	q.s. to 5 L	q.s. to 1 mL

*The amount is of active ceftiofur taking into consideration the salt.

Assumes 100% potent ceftiofur HCl with 3.2% w/w of the weight accounting for the HCl. MW of ceftiofur HCl is 560.0.

The required weight or volume of oil is placed into a glass or stainless steel vessel. (See Table 1 for the amounts required for a 5 L batch.) For a 5 L batch, 4.5 L of cottonseed oil is used to begin. The oil is heated to above 100° C. and the required amount of Phospholipon (lecithin) is added and stirred until dissolved. The time required for the Phospholipon (lecithin) to dissolve depends on the temperature, mixing, and size of the batch. It normally dissolves within 1 to 60 minutes. The oil containing the Phospholipon is then cooled. Once cooled the sorbitan monooleate is added and mixed. Next the ceftiofur HCl is added followed by mixing of 1 to 120 minutes. The length of mixing depends on the batch size, size of mixer and speed of mixing. Water is added and the suspension is mixed for 1 to 60 minutes.

The suspension is stored in the original manufacturing vessel as long as mixing continues to keep the drug suspended. It is then filled into vials using standard vial filling equipment. The vials are then closed with a stopper, capped, labeled and boxed.

EXAMPLE 2

Comparison of the Currently Marketed Formulation of Ceftiofur Hydrochloride and Formulations of the Present Invention

A. Resuspendability or Physical Stability

One of the most important differences observed between the formulations was the greater physical stability or resuspendability when water was added to the formulation. Shown in FIG. 1 is a plot of resuspendability compared to the water content of various ceftiofur HCl suspensions.

It is clear from this figure that as the water content increased, the suspension resuspended better. The resuspendability of suspensions with lower water content was poor or, at best, variable. It was not until the water content was increased that consistently more resuspendable suspensions were achieved. More specific physical stability comparisons are shown in the next section.

Several other differences were observed when increasing the water content of the suspension. All these differences help explain why greater physical stability was observed when adding water. First, sedimentation volumes were greater, and the sedimentation rates faster when water was

added. The sedimentation volume is the height of the sediment when compared to the height when the suspension is fully resuspended. Larger sedimentation volumes typically are associated with a suspension that resuspends better. Less packaging of the sediment occurs making it easier to resuspend (i.e., less energy needs to be put into the system via shaking).

Second, the faster settling rate indicates the particles are interacting *to create a flocculated system. A flocculated* suspension typically resuspends better then a nonflocculated suspension. The flocs that form will be larger then the original particles so they settle faster. But, because they interact with themselves and other flocs, they will not settle to such low sedimentation volumes. Thus, they are easier to resuspend. The addition of water to the formulation of the *present invention caused flocculation and faster sedimentation* rates were observed.

Also, flocculation was observed with particle size data. Larger measured particles were observed as the water content of the suspension increased. Furthermore, photomicrographs were taken showing the particles interacting to create larger flocs.

Finally, rheology differences were noted when adding water to the formulation. The rheology, or flow characteristics, changed from Newtonian to non-Newtonian with added water. The plastic systems found with added water indicate a structure was formed in the water-added suspensions. This added structure again indicates a flocculated system which will have improved resuspendability.

In summary, all of the differences found between the suspensions with and without added water indicate that physical stability will be better with the water-added formulation.

B. Chemical Stability and Shelf-life

The stability of suspensions, and ultimately their shelf-life, are based on both chemical and physical stability. The chemical stability is assessed to insure that the product does not become subpotent during use. The chemical stability of the current formulation (ie. non-water-added formulation) has been studied extensively. For example, shown in Table 2 is the stability through 3 years for 3 different batches of the current suspension.

TABLE 2

Chemical Stability of a 50 mg/mL Cefdinir HCl Suspension with No Additional Water Added when Stored at 25° C.

	Potency in mg/mL ± standard deviation		
Time, months	Lot A	Lot B	Lot C
0	49.8 ± 0.7	51.1 ± 0.5	50.5 ± 0.3
3	*48.4 ± 1.3*	*49.4 ± 1.6*	*48.4 ± 0.4*
6	48.1 ± 0.7	48.8 ± 1.2	48.6 ± 0.7
12	49.1 ± 0.4	50.2 ± 0.3	50.1 ± 0.3
18	46.5 ± 1.4	48.5 ± 0.7	48.5 ± 0.9
24	46.8 ± 4.2	48.8 ± 0.6	49.2 ± 2.7
36	49.1 ± 0.8	49.5 ± 0.4	48.6 ± 0.7

Usually pharmaceutical products are allowed to decrease 10% in potency during their shelf-life. Table 2 shows the current suspension is chemically stable even out to three years when stored at room temperatures.

The chemical stability has not been assessed for as long with the formulation of the present invention containing additional water. Shown in Table 3 is the comparison of two batches that were made identically except for the amount of water added. *Similarly, Table 4 shows another comparison* of two batches that only varied in water content.

TABLE 3

Comparison of Chemical Stability of Two Batches with Different Water Contents when Stored at 25° C.

	Potency as a percent of label ± standard deviation	
Time, months	Lot D (0.20% total water)	Lot E (0.39% total water)
0	103.2 ± 0.5	102.2 ± 0.2
2	103.2 ± 0.4	101.6 ± 0.0
4	103.6 ± 0.3	103.3 ± 1.3
6	103.7 ± 0.4	103.0 ± 0.2

TABLE 4

Comparison of Chemical Stability of Two Batches with Different Water Contents when Stored at 25° C.

	Potency as a percent of label ± standard deviation	
Time, months	Lot F (0.14% total water)	Lot G (0.67% total water)
0	104.5 ± 0.3	103.4 ± 0.6
2	*104.6 ± 1.7*	*103.2 ± 0.2*
4	105.5 ± 0.7	105.4 ± 0.5
6	103.5 ± 0.5	102.9 ± 0.1

Both Tables 3 and 4 show the suspension to be chemically stable. No difference was observed in chemical stability even with high water content. Thus, contrary to what may be expected, the addition of water did not adversely affect the chemical stability of the suspension. Additional stability data which was obtained at accelerated temperatures shows no difference in stability with higher water content.

C: Physical Stability

Physical stability is just as important as chemical stability. If the product does not resuspend adequately when shaken, the dose will be incorrect. With incomplete resuspension when shaken, the *initial doses removed will be* subpotent. This occurs because drug remains at the bottom of the vial preventing the correct concentration of the suspension when agitated. If part of the product is removed at a concentration significantly less then the labeled concentration, doses removed when the vial contains less product could become superpotent. This happens when further agitation removes drug from the bottom of *the container and it is dispersed in* the smaller volume of liquid.

The current formulation (ie. no water added) needs to be shaken, sometimes up to 60 seconds, before it becomes fully resuspended as shown in Table 5:

TABLE 5

Physical Stability of a 50 mg/mL Cefdinir HCl Suspension with No Additional Water Added when Stored at 25° C.

	Time Required to Fully Resuspend, Seconds		
Time, months	Lot A	Lot B	Lot C
0	10–20	10	10
3	30–40	10–20	20–30
6	30	10	20
12	50–60	20–30	40–50
18	40–60	20	30
24	50–60	60	40–60
36	60	40–50	60

It has been found that the addition of water improves the *resuspendability characteristics of the suspension. A sensi*tive method for monitoring resuspendability is to use a

10-second mechanical shake assay. In this test, a vial is shaken for 10 seconds using a mechanical arm. A sample is removed from the suspension 2 cm below the liquid/air interface and assayed for the amount of drug. Shown in Tables 6 and 7 below are batches produced by identical methods except for the amount of water:

TABLE 6

Comparison of Physical Stability of Two Batches with Different Water Contents using a 10-Second Mechanical Shake Test

	Potency as a percent of label ± standard deviation	
Time, months	Lot D (0.20% total water)	Lot E (0.39% total water)
0	82 ± 4	99 ± 2
2	72 ± 40	98 ± 1
4	48 ± 7	97 ± 2
6	49 ± 3	96 ± 1

TABLE 7

Comparison of Physical Stability of Two Batches with Different Water Contents using a 10-Second Mechanical Shake Test

	Potency as a percent of label ± standard deviation	
Time, months	Lot F (0.14% total water)	Lot G (0.67% total water)
0	79 ± 5	104 ± 1
2	52 ± 21	101 ± 2
4	58 ± 16	102 ± 3
6	67 ± 27	95 ± 2

As the data from these tables shows, the increased water content improved resuspendability. The formulations with higher water concentrations were closer to the theoretical 100% of label and had less vial-to-vial variability (ie. tighter standard deviations).

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 is a plot of resuspendsbility compared to the water content of various ceftiofur HCl suspensions.

We claim:

1. In an oil suspension of ceftiofur hydrochloride in unit dosage form consisting of an effective amount of ceftiofur hydrochloride, a biocompatible oil and one or more pharmaceutically acceptable excipients, the improvement characterized by:

an amount of water which is present at about 0.25% to about 20.20% of the suspension.

2. The improvement of claim 1 wherein the water is present at about 0.25% to about 2.20% of the suspension.

3. The improvement of claim 2 wherein the water is present at about 0.30% to about 0.75% of the suspension.

4. The improvement of claim 3 wherein the water is present at about 0.30% to about 0.50% of the suspension.

5. In a pharmaceutical composition containing ceftiofur hydrochloride, the improvement characterized by:

the addition of water.

6. The improvement of claim 5 wherein the water is added in an amount which is about 0.5 to about 200 mg of water per ml of composition.

7. The improvement of claim 6 wherein the water is added in an amount which is about 0.5 to about 20 mg of water per ml of composition.

8. The improvement of claim 7 wherein the water is added in an amount which is about 1 to about 5.5 mg of water per ml of composition.

9. The improvement of claim 8 wherein the water is added in an amount which is about 1 to about 3 mg of water per ml of composition.

10. A pharmaceutical composition in unit dosage form, which comprises:

a) a drug,

b) a biocompatible oil, and

c) water which is present at about 0.25% to about 20.20% of the composition.

11. The composition of claim 10 wherein the water is present at about 0.25% to about 2.20% of the composition.

12. The composition of claim 11 wherein the water is present at about 0.30% to about 0.75% of the composition.

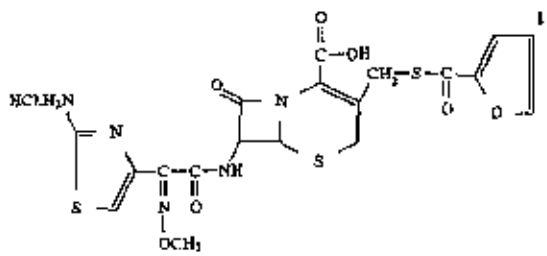
13. The composition of claim 12 wherein the water is present at about 0.30% to about 0.50% of the composition.

14. The composition of claim 10 wherein the drug is an antibiotic.

15. The composition of claim 14 wherein the antibiotic is spectinomycin.

16. The composition of claim 10 where the drug is a cephalosporin.

17. The composition of claim 16 wherein the drug is ceftiofur hydrochloride of formula I



18. The composition of claim 17 wherein the ceftiofur hydrochloride has a particle size of less than 10 microns and is present at a concentration of about 50 mg per ml of composition.

19. The composition of claim 10 wherein the oil is selected from the group consisting of: canola oil, corn oil, cottonseed oil, olive oil, peanut oil, sesame oil, soybean oil, safflower oil, coconut oil, sunflower oil and palm oil.

20. The composition of claim 19 wherein the oil is cottonseed oil.

21. The composition of claim 10 which further comprises one or more pharmaceutically acceptable excipients.

22. The composition of claim 21 wherein the excipients are lecithin and sorbitan monooleate.

23. The composition of claim 10 wherein the composition is an injectable oil suspension.

* * * * *

United States Patent [19]

Amin et al.

[11] **Patent Number: 4,902,683**

[45] **Date of Patent: Feb. 20, 1990**

[54] **CRYSTALLINE CEPHALOSPORIN HYDROHALIDE SALTS**

[75] Inventors: **Mahendra I. Amin**, Kalamazoo; **Jay A. Campbell**, Portage, both of Mich.

[73] Assignee: **The Upjohn Company**, Kalamazoo, Mich.

[21] Appl. No.: **312,401**

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Related U.S. Application Data

[63] Continuation of Ser. No. 898,676, Aug. 21, 1986, abandoned, which is a continuation of Ser. No. 664,651, Oct. 25, 1984, abandoned.

[51] **Int. Cl.**[4] ***C07D 501/36; A61K 31/545***

[52] **U.S. Cl.** **514/206; 540/227**

[58] **Field of Search** 540/227; 514/206

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,464,367 8/1984 Labeeuw et al. 540/227

FOREIGN PATENT DOCUMENTS

2036746A 7/1980 United Kingdom .

Primary Examiner—Nicholas S. Rizzo
Attorney, Agent, or Firm—Martha A. Cox

[57] **ABSTRACT**

Crystalline hydrohalide salts of the cephalosporin antibiotic ceftiofur, processes for their manufacture, and pharmaceutical compositions containing one of these salts are provided.

13 Claims, No Drawings

CRYSTALLINE CEPHALOSPORIN HYDROHALIDE SALTS

This is a continuation of U.S. patent application Ser. No. 898,676 filed Aug. 12, 1986 now abandoned which is a continuation-in-part of U.S. patent application Ser. No. 664,651 filed Oct. 25, 1984, now abandoned.

INTRODUCTION

This invention relates to a new crystalline hydrochloride salt form of a cephalosporin antibiotic and to a process for preparing the crystalline cephalosporin hydrochloride salt substantially free of impurities, and pharmaceutical compositions and methods of use therefor.

BACKGROUND OF THE INVENTION

The cephalosporin antibiotic 7-[2-(2-amino-1,3-thiazol-4-yl)-2-methoxyimino)acetamido]-3-[(fur-2-ylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid (also named 7-[2-(2-amino-4-thiazolyl)-2-methoxyimino)-acetamido]-3-[2-(furanylcarbonylthiomethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-1-carboxylic acid) (2), its alkali metal, alkaline earth metal and amine salts of the carboxylic acid group, and easily hydrolyzable ester groups thereof are described and claimed in Labeeuw et al U.S. Pat. No. 4,464,367. This cephalosporin free acid (2) compound is now known by the generic name ceftiofur, in France.

Those free acid and cationic metal and amine salt and ester forms of this cephalosporin antibiotic are somewhat unstable chemically and are obtained as amorphous compounds which are difficult to purify, and are less desirable to work with in manufacturing pharmaceutical formulations containing them. Those patented salts thus create salt-solid-isolation and salt-solid-handling problems in a pharmaceutical manufacturing plant which those in the pharmaceutical art would prefer to avoid. However, it is not predictable how to make useful crystalline salt forms of any particular active drug cephalosporin compound.

OBJECTS OF THE INVENTION

It is an object of the invention to provide a useful crystalline salt form of the above new cephalosporin compound having advantageous solubility and other physical properties, which make the compound easier to purify and more convenient to work with in preparing pharmaceutical formulation composition dosage forms thereof.

It is another object of this invention to provide a process for purifying and isolating the above cephalosporin compound as its crystalline hydrohalide salt form to obtain the cephalosporin hydrohalide salt in a degree of purification which is not possible when the amorphous solid forms of the cephalosporin are obtained and processed.

It is another object of this invention to provide pharmaceutical compositions containing the new crystalline ceftiofur hydrohalide salt of this invention.

SUMMARY OF THE INVENTION

This invention provides a crystalline hydrohalide salt (1) of 7-(2-amino-1,3-thiazol-4-yl)-2-methoxyimino)acetamido]-3-[(fur-2-ylcarbonyl)thiomethyl]-8-oxo-5-thia-1-azabicyclo[4.2.1]oct-2-ene-1-carboxylic acid (2), ceftiofur, in a form which is easier to isolate, purify and to handle in subsequent pharmaceutical operations, and pharmaceutical composition thereof.

The salt forming and purification process of this invention comprises

(a) treating the N-tritylamino cephalosporin (3) with a solution containing a water-miscible organic solvent such as acetone, tetrahydrofuran, acetonitrile, or methyl ethyl ketone, preferably acetone, water and hydrogen halide which is at least stoichiometrically equivalent to the amount of the N-tritylamino cephalosporin (3),

(b) heating the mixture from step (a) to a temperature and for a time sufficient to effect detritylation,

(c) decreasing the concentration of the water miscible organic solvent in the aqueous phase of the mixture from step (b) to effect formation of the crystalline cephalosporin hydrohalide salt (1), for example, by adding to the mixture a non-polar, water immiscible organic liquid, e.g., toluene or heptane, to extract the water-miscible solvent, e.g., acetone, and to take up the trityl alcohol by-product, or by distillation of the mixture to separate some of the water miscible organic solvent, e.g., acetone, or by other physical or chemical means, and also, optionally by adding water and hydrogen halide to enhance crystal salt formation,

(d) recovering the crystalline cephalosporin hydrohalide salt (1) from the liquid mixture from step (c);

(e) washing the crystalline cephalosporin hydrohalide salt (1) from step (d) with water and water-miscible organic solvent, and

(f) drying the washed crystalline cephalosporin hydrohalide salt from step (e).

This cephalosporin hydrohalide salt (1) can also be prepared from the cephalosporin amino-acid (2) or from other alkali metal, alkaline earth metal or amine salts such as (4) by treating a solution of the cephalosporin compound in an aqueous/organic liquid mixture solution, e.g., an aqueous/acetone mixture, with the hydrogen halide. The crystalline cephalosporin hydrohalide salt (1) is then precipitated by either removing some of the organic liquid, e.g., acetone, or by removing the aqueous phase from the mixture, either of which actions cause the crystalline cephalosporin hydrohalide salt (1) to precipitate, which crystalline precipitate can then be recovered from its liquid mixture by known means.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides a crystalline form of a cephalosporin antibiotic as its hydrohalide salt (see attached STRUCTURE SHEET) of Formula 1 where X is chloride or bromide. As a matter of economics the hydrochloride salt is preferred, although the hydrobromide salt can be made and used in a similar manner. As indicated above the cephalosporin antibiotic can be named by either of two above different nomenclature systems. Some persons prefer the more formal CHEMICAL ABSTRACTS system whereby the compound is named as a derivative of a "bicyclo" ring system. Some prefer the simpler "cephem" ring system nomenclature.

This crystalline hydrochloride salt of structure (1) where X is chloride has the following x-ray powder diffraction pattern when crystallized from water-acetone.

interplanar d-spacings Å	intensity (relative %)
18.4	44.2
12.4	73.1
9.26	50.0
7.82	100.0
7.69	17.9
6.19	48.1
5.86	32.1
5.21	23.1
5.12	40.4
4.74	30.1
4.37	21.8
4.23	13.5
3.98	26.9
3.91	35.9
3.81	17.9
3.30	14.1
3.01	12.8
2.88	14.1

(Peaks with relative intensity equal to or less than 10% are not reported.)

The salt may contain 0.5 to 2.0 equivalents of hydrogen chloride, but most often around one equivalent of HCl.

The crystalline hydrochloride salt can be crystallized in a solvent consisting of a polar organic solvent or water or a mixture of such solvents. A typical crystallization involves slurrying one gram free acid (2) in 20 ml. of 3% V/V water in acetone at 25° C. At least two equivalents of hydrogen chloride are added to dissolve the free acid and crystallize the hydrochloride salt. The crystals can be separated by filtration and washed to remove the remaining mother liquid. The crystals may then be dried under vacuum at elevated temperature. The yields of hydrochloride salt are generally 60% to 95% depending on the solvent and the purity of the free acid (2).

This salt may contain 0.5% to 7% of water or other solvents (usually 1%–3%). Other impurities are usually reduced to 1% or less.

A recrystallization may be performed by either (a) forming and isolating the free acid (2) and then reforming the hydrochloride salt (1) or (b) by dissolving the hydrochloride salt (1) in aqueous organic solvent (usually containing one or more equivalents of HCl) and then removing the organic solvent by distillation, extraction, or other method of separation.

The free acid (2) or other pharmaceutically acceptable salts (such as (4)) can be made from the purified hydrochloride salt.

Other crystallization solvents include acetonitrile, tetrahydrofuran, methyl ethyl ketone and water. The hydrobromide salt can be made by a similar procedure.

The hydrochloride salt can also be made directly from the tritylprotected cephalosporin. For example, the crude trityl cephalosporin is slurried in 37% V/V water in acetone. Three equivalents of hydrogen chloride are added and the solution is refluxed until detritylation is complete. Toluene or equivalent non-polar water immiscible organic liquid solvent is added while stirring. The mixture is allowed to separate and the aqueous phase is removed and cooled to crystallize the hydrochloride salt. See Example 4 hereinbelow.

In aqueous buffer solutions the sodium salt (Formula 4) is more stable as the pH decreases. In hydrochloric acid at pH values equal to or lower than 2.8 the sodium salt (4) is converted to the hydrochloride salt (1) which exhibits better shelf stability when it is separated, washed and dried.

The new hydrochloride salt (1) has lower aqueous solubility than the sodium salt (4) and the free acid (2), and is better adapted for making controlled release pharmaceutical dosage formulations such as oral and parenteral suspensions, suppository and tablet dosage forms.

The new hydrochloride salt (1) produces acceptable pharmaceutical dispersions in water for injection and in pharmaceutical vegetable oils. Due to this property, the hydrochloride salt (1) can be formulated into extemporaneous (liquid and drug powder mixed just prior to administration) liquid suspensions by the addition of an aqueous or an oily vehicle to the hydrochloride salt (1) powder, just prior to dosing the patient. Oral and subcutaneous studies in mice with aqueous and oil dispersions of both the hydrochloride (1) and the sodium salt (4) indicate that the hydrochloride (1) is bioequivalent to the sodium salt (4). However, we have found that the crystalline hydrochloride salt (1) can be made in more pure form, is easier and is less expensive to manufacture than the sodium salt (4). Further, since the hydrochloride (1) has more limited solubility in water various controlled release pharmaceutical dosage formulations can be made with it (1) that are not readily adaptable to the sodium salt (4).

Due to the lower solubility of the ceftiofur hydrochloride, its rate of dissolution is slower. As a result absorption is less, and thus various controlled release formulation(s) can be formulated.

The controlled release parenteral suspension (see Examples 12 and 14 below) can be given once every 2 to 5 days as opposed to being given daily with other formulations.

The invention, how to make it and how to use it are further exemplified by the following detailed examples which are not intended to be limiting. In these examples, "povidone" is a known form of polyvinylpyrrolidone, used in pharmacy. "Quatresin" is a brand name for myristyl gamma-picolinium chloride. The corn oil glycerol monostearate gel and cottonseed oil glycerol monostearate gel materials are described in U.S. Pat. No. 4,034,099. "Suppocire" refers to a brand name of a series of mixtures of saturated glycerides of C_{10} to C_{18} fatty acids which are known in pharmacy as excipients for use in various suppository and other pharmaceutical formulations and are described in product bulletins of Gatte fosse Establissment SA., Paris, France, 39 Avenue Edouard-Vaillant: "Suppocire AM" is said to have a melting point of 35° C. to 36.5° C. PEG-400 and PEG-8000 are well known pharmaceutical excipient forms based upon polyethylene glycol. Carnauba wax is the pharmaceutical form thereof defined in the National Formulary (NF).

The improved hydrohalide salt forming and purification process of this invention is adaptable to and can be used with a proposed large scale process for making the cephalosporin compound itself.

The N-trityl cephalosporin derivative (3) which is the preferred starting material is prepared by acylation of the corresponding 7-amino precursor 3-cepham-4-carboxylic acid nucleus compound with the N-trityl-2-amino-1,3-thiazol-4-yl-2-methoxyimino acetic acid by acylation methods well known to those skilled in the cephalosporin production art. For example, the procedure described in U.S. Pat. No. 4,464,367 for the preparation of (3) with N-hydroxybenzotriazole and N,N-

dicyclohexylcarbodiimide can be used. Alternately, the corresponding acid chloride can be prepared and used as described in the *Journal of Antibiotics*, 36, 180 (1983).

According to the process of this invention in step (a) the N-trityl-cephalosporin (3) (see STRUCTURE SHEET) is treated with a solution mixture of a polar solvent (e.g., acetone) and water (in proportions ranging from about 200 to 100 parts V/V of polar solvent per 100 parts of water) in an amount to obtain a workable slurry. Sufficient hydrogen halide (e.g., hydrogen chloride) is then added. The hydrogen halide can be added in an amount which is at least stoichiometrically equivalent to the trityl-amino compound (3). For efficiency reasons, we prefer to add about three equivalents of hydrogen halide per equivalent of the trityl-protected cephalosporin (3). The hydrogen halide can be added as a gas, below the liquid surface, or as a hydrohalic acid solution in water.

In step (b), the acidified mixture from step (a) is heated to a temperature, generally above 45° C., and for a time sufficient to effect detritylation of the cephalosporin (3) and to form the cephalosporin hydrohalide salt (1). We have found that reflux of the mixture, which occurs in our mixtures at about 56° C., for about one hour is sufficient to effect the detritylation, without destruction of the cephalosporin.

In step (c) of the process the detritylated cephalosporin hydrohalide mixture is washed with a non-polar non-water miscible organic liquid which liquid takes up the trityl alcohol by-product and some of the acetone in the mixture. Examples of useful liquids for this purpose include liquid aromatic hydrocarbons such as benzene, toluene, xylene, chlorinated aromatic hydrocarbons such as chlorinated benzene, toluene and xylene, and chlorinated alkanes such as methylene chloride, dichloroethane, chloroform, carbon tetrachloride, as well as C_2 to C_3-alkyl acetate and propionate esters such as ethyl acetate, propyl acetate and liquid C_6 to C_{10}-alkanes such as hexanes, heptane, octane, nonane and decane, and liquid C_5 to C_7-cycloalkanes such as cyclopentane, cyclohexane, cycloheptane, and mixtures, including commercial mixtures of such liquids. Toluene and/or heptane are preferred. Optionally, extra water and acid may also be added at this point. The hydrohalic acid addition is optional because it depends upon the amount of hydrogen halide already present in the mixture. The added hydrogen halide at this stage gives shorter cyrstallization times.

In step (d) the crystalline cephalosporin hydrohalide salt (1) is separated from the liquid phase by known means such as by filtration or centrifugation procedures, and in step (e) the separated crystalline cephalosporin hydrohalide salt (1) is washed one or more times with water and water-miscible organic solvent, e.g., acetone, or mixtures thereof, and then dried (step f), for example, by spreading the crystalline salt in trays, and drying the salt in a vacuum oven at 40°-60° C. for a time sufficient to remove any adhering volatile liquids therefrom.

The compounds of Formula 1 herein are useful as the active antibiotic drug compound in pharmaceutical dosage forms for treating valuable mammalian animals and humans to treat bacterial infections in that valuable animal or human. Presently it is contemplated that this compound will be especially useful as a veterinary antibiotic drug to treat valuable animals such as cattle, horses, goats, dogs and cats to fight the effects of bacterial infections caused by organisms such as *Pasturella hemolitica, Salmonella typhimurium, E. coli, Staphylococcus, aureus*, and the like, some of which are commonly associated with 'shipping fever' in animals.

The term "dosage unit form" as used in this specification and in the claims refers to physically discrete units suitable as unitary dosages for mammalian subjects, each unit containing as the essential active ingredient a predetermined quantity of a compound of this invention with the required pharmaceutical means which adapt said ingredient for systemic administration. The specification for the novel dosage unit forms of this invention are dictated by and directly dependent on the physical characteristics of the essential active ingredient and the particular effect to be achieved in view of the limitations inherent in the art of compounding such an essential active material for beneficial effects in humans and animals as disclosed in detail in this specification. Examples of suitable dosage unit forms in accordance with this invention are tablets, capsules, orally administered liquid preparations in suitable liquid vehicles, sterile preparations in suitable liquid vehicles for intramuscular and intravenous administration, suppositories and sterile dry preparations for the extemporaneous preparation (mixing just prior to administration) of sterile injectable preparations in a suitable liquid vehicle. Suitable solid diluents or carriers for the solid oral pharmaceutical dosage unit forms are selected from the group consisting of lipids, carbohydrates, proteins and mineral solids, for example, starch, sucrose, lactose, kaolin, dicalcium phosphate, gelatin, acacia, corn syrup, corn starch, talc and the like. Capsules, both hard and soft, are filled with compositions of this antibiotic active ingredient in combination with suitable diluents and excipients, for example, edible oils, talc, calcium carbonate and the like and also calcium stearate. Liquid preparations for oral administration are prepared in water or aqueous vehicles which advantageously contain suspending agents, for example, methylcellulose, alginates, tragacanth, pectin, kelgin, carragenan, acacia, polyvinylpyrrolidone, polyvinyl alcohol, and the like, to increase the viscosity of the composition. In the case of injectable forms, the injectable formulation must be sterile and must be fluid to the extent that easy syringeability exists. Such preparations must be stable under the conditions of manufacture and storage, and ordinarily contain in addition to the principal solvent or suspending liquid, preservatives in the nature of bacteriostatic and fungistatic agents, for example, parabens, chlorobutanol, benzyl alcohol, benzoic acid, phenol, thimerosal, and the like to preserve the composition against microorganisms. In many cases, it is preferable to include osmotically active agents, for example, sugars or sodium chloride in isotonic concentrations. Carriers and vehicles include vegetable oils, dimethylacetamide, dimethylformamaide, ethyl lactate, ethyl carbonate, isopropyl myristate, ethanol, polyols, for example, glycerol, propylene glycol, liquid polyethylene glycol, and the like. Any solid preparations for subsequent extemporaneous preparation of sterile injectable preparations are sterilized, by exposure to steam, cobalt 60 irradiation, or by exposure to a sterilizing gas, for example, ethylene oxide. The aforesaid carriers, vehicles, diluents, surfactants, excipients, preservatives, isotonic agents and the like constitute the pharmaceutical means which adapt the preparations for systemic administration.

In these pharmaceutical compositions it may be desirable to include a viscosity increasing agent such as sodium carboxymethylcellulose (sodium CMC). Other

suitable viscosity increasing agents can be substituted for sodium CMC.

The pharmaceutical dosage unit forms of the compounds of this invention are prepared in accordance with the preceding general description to provide from about 1 mg. to about 500 mg. of the essential active ingredient per dosage unit form, which as aforesaid may be in the form of a semi-solid or solid, topical, oral or rectal preparation, a liquid oral preparation, an injectable preparation including liquid preparations and solid dry preparations for extemporaneous reconstitution to a liquid injectable preparation. The amount of the essential active ingredient provided in the pharmaceutical dosage unit forms is that amount sufficient to obtain antibiotic effects within the aforesaid effective non-toxic range. Expressed otherwise, when used systemically, an amount of the essential active ingredient is provided to a recipient within a range from about 0.2 mg./kg. to about 10 mg./kg. of body weight of the recipient.

Preferred dosages for most applications are 0.2 mg./kg. to 5.0 mg./kg. of body weight. In a topical semi-solid ointment formulation the concentration of the active ingredient may be 1%–20%, preferably 5%–10% in a carrier, such as a pharmaceutical cream base.

The useful pharmaceutical dosage unit forms of these compounds in pharmaceutical formulations are preferably adapted for systemic administration to obtain antibiotic effects comprising an effective, non-toxic amount of the Formula 1 salt.

Further, the invention relates to methods of obtaining antibiotic effects in mammals, for example, humans and valuable warm-blooded animals such as dogs, cats, horses, and other commercially valuable animals, by administering systemically to the mammals the aforesaid pharmaceutical dosage units forms supplying an effective, non-toxic amount for antibiotic effects.

The invention is further illustrated by the following detailed examples.

EXAMPLE 1

A slurry of 0.7 g. of ceftiofur as its free acid in 7 ml. of acetone and 0.35 ml. of water is made up. To this slurry is added 0.24 ml. of 37.7% hydrochloric acid solution. The resulting acidified slurry becomes a solution within a minute, and then crystallization of the ceftiofur hydrochloride salt begins within 2 or 3 minutes. An additional 7 ml. of acetone are added to thin the slurry. The slurry mixture is stirred for 10 minutes at 20° C. and then filtered and the filtered hydrochloride salt crystals are washed with acetone. The ceftiofur hydrochloride salt crystals are then dried for 16 hours in a vacuum oven. The yield of the ceftiofur hydrochloride salt crystals is 0.63 g., for an 84% chemical yield.

EXAMPLE 2

A slurry of 0.7 g. of ceftiofur free acid in 11.8 ml. of acetone and 6.9 ml. of water is made up. To this slurry there is added 0.27 ml. of 37.7% hydrochloric acid solution, and the mixture is warmed to 55° C. The ceftiofur free acid is in solution. To this warmed solution a 55° C. temperature mixture of 13.2 ml. of toluene and 3.2 ml. of water is added while stirring. The liquid phases are allowed to separate, and the upper organic layer is discarded. The lower aqueous layer is cooled to 15° C. after seeding with previous crystalline ceftiofur hydrochloride, and allowed to stand for two hours. After standing, the mixture is filtered to separate the crystalline ceftiofur hydrochloride salt from the liquid mother liquor. The filtered salt crystals are washed with 4 ml. of 20% acetone in water V/V mixture. Then the salt crystals are washed with 10 ml. of water. The washed ceftiofur hydrochloride salt crystals are dried for 16 hours in a vacuum oven at 40° C. The yield of ceftiofur hydrochloride salt crystals is 0.50 g. for a 67% chemical yield.

EXAMPLE 3

Detritylation of N-trityl-ceftiofur and Crystallization of Ceftiofur Hydrochloride Salt Using Toluene Extraction of Acetone

To a three-necked, round-bottom 250 ml. flask is charged 14.8 g. of N-tritylated ceftiofur free acid (3), 91 ml. of acetone, 2.4 ml. of concentrated hydrochloric acid and 91 ml. of water. This resulting mixture is heated to reflux. Then 10 ml. more of acetone is added to dissolve a precipitate, presumably trityl alcohol.

While the mixture is still hot (55° C.), 60 ml. of toluene is added to remove trityl alcohol and to decrease the concentration of acetone in the aqueous phase. The resulting mixture is transferred to a separatory funnel and the liquid layers are separated. The organic liquid phase is washed with a mixture of 25 ml. of water and 10 ml. of acetone. The organic layer is 120 ml. total volume. The separated aqueous layer is washed with 30 ml. of toluene, and then the toluene and aqueous phases are separated to give a 45 ml. total volume toluene plus inter-phase. The aqueous layer (about 140 to 150 ml.) is stirred with a magnetic stir bar for three hours, and then cooled to −5° C. and filtered to separate the ceftiofur hydrochloride salt crystals which form. This crystalline filtered salt product is washed with 15 ml. of a mixture consisting of 10 ml. of water and 5 ml. of acetone. The washed ceftiofur hydrochloride crystalline product, 4.63 g., is dried at 50° C.

A second crop can be obtained by filtering mother liquor filtrate. The resulting ceftiofur hydrochloride crystalline product, 1.46 g., is washed with water. The total yield is 88.1%.

EXAMPLE 4

A mixture of 96 ml. acetone, 55 ml. water and 2.93 ml. 37.7% HCl in water solution are added to about 10.0 gm. trityl cephalosporin (3) and refluxed (about 58° C.) for one hour to affect detritylation.

A mixture of 18 ml. heptane and 4.5 ml. acetone is added to the above solution. The combined liquids are transferred to a separatory funnel and allowed to separate. The lower layer (aqueous) is transferred to another separatory funnel and 18 ml. of heptane and 4.5 ml. of acetone are added to the aqueous phase in the second separatory funnel. The combined liquids are contacted and allowed to separate as before. The lower phase (aqueous) is distilled atmospherically to a temperature of 67° C. which reduces the concentration of acetone to about 15%. Before cooling to 15° C., 2.93 ml. of 37.7% HCl solution are added. The cephalosporin HCl salt (1) begins crystallizing between 50° C. and 60° C.

The crystals are filtered and washed with 20 ml. of 10% acetone in water to remove any adhering filtrate. The resulting washed, filtered solids are then washed with water and dried in a vacuum oven at 65° C. to give 6.87 g. of product.

EXAMPLE 5

Oral Suspension

One thousand cc. of an aqueous suspension for oral use, containing in each 5 cc. dose 5 to 300 mg. of crystalline ceftiofur hydrochloride is prepared from the following types of and amounts of ingredients.

Ceftiofur hydrochloride (crystalline): 5 to 300 gms.
Benzoic Acid or Sorbic Acid: 1 gm.
Sucrose: 650 gms.
Sodium Carboxymethylcellulose, Low Viscosity: 1 to 20 gms.
Flavors (e.g., USP cherry, orange) q.s.
Sodium Chloride (0.5 to 10 mg./ml.): 0.5 to 10 gms.
Hydrochloric Acid, Reagent Grade: q.s. adjust pH to approx. 3.0
Deionized Water: q.s. to 1000 cc.

The sodium carboxymethylcellulose, benzoic acid, sucrose, appropriate flavors and sodium chloride are dispersed in sufficient water to make 650 mls. of solution. *The ceftiofur hydrochloride is stirred into the* syrup until uniformly distributed. The resulting suspension is colloid milled to a uniform consistency. Sufficient water is added to bring volume to 900 cc. If necessary pH is adjusted with hydrochloric acid to about pH3. Sufficient water is added to make 1000 cc.

EXAMPLE 6

Sterile Parenteral Suspension

Sterile Vehicle-Part I

PEG: 5 to 120 gms.
Benzyl Alcohol, or: 9.1 gm.
Benzoic Acid: 1.0 gm.
Povidone: 1 to 10 gms.
Sodium Chloride Fine Crystals, Reagent Grade: 9 gms.
Hydrochloric Acid, Reagent Grade q.s. adjust pH to approximately: 3.0
50% Solution Sodium Hydroxide q.s. adjust pH:
Water for Injection q.s. adjust: 1000 cc.

Part II

Ceftiofur hydrochloride, crystalline: 1.0 to 100 gms.
Vehicle Part I q.s. adjust: 1000 cc.

DIRECTIONS

Part I

All of the ingredients are dissolved in water and pH adjusted to about 2.6 to 3.2, preferably about 3.0. The vehicle sterilized by filtration and used in Part II.

Part II

Aseptically add sterile crystalline ceftiofur hydrochloride in sufficient vehicle from Part I to make 900 mls. Stir the suspension and colloid mill the suspension to a uniform consistency. Add sufficient vehicle to make 1000 mls.

EXAMPLE 7

Sterile Parenteral Suspension

Sterile Vehicle-Part I

Polysorbate 80, N.F.: 0.1 to 10 gms.
Sodium Carboxymethylcellulose low viscosity: 2 to 20 gms.
Benzyl Alcohol: 9.1 gms.
Benzoic Acid: 0.2 to 2.0 gms.
Povidone: 1 to 10 gms.
Sodium Chloride, Fine Crystals Reagent if needed: 9 gms.
Hydrochloric Acid, Reagent Grade q.s. adjust pH to approx.: 3.0
50% Solution Sodium Hydroxide q.s. adjust pH:
Water for Injection q.s. adjust: 1000 cc.

Part II

Ceftiofur hydrochloride, crystalline: 1.0 to 100 gms.
Vehicle Part I q.s. adjust: 1000 cc.

DIRECTIONS

Part I

All of the ingredients are dissolved in water and the vehicle sterilized by filtration.

Part II

Aseptically add sterile crystalline ceftiofur in sufficient vehicle to make 900 mls. Stir the suspension and pass through *colloid mill to a uniform consistency. Add* sufficient vehicle to make 1000 mls.

EXAMPLE 8

Sterile Parenteral Suspension

Sterile Vehicle-Part I

PEG 3350 NF: 5 to 120 gms.
Benzyl Alcohol: 9.1 gms.
Benzoic Acid: 0.2 to 2.0 gms.
Polysorbate 80 NF Food Grade: 1 to 5 gms.
Sodium Chloride Fine Crystals Reagent: 0.5 to 10 gms.
Hydrochloric Acid, Reagent Grade q.s. adjust pH to approx.: 3.0
50% Solution Sodium Hydroxide q.s. adjust pH:
Water for Injection q.s. adjust: 1000 cc.

Part II

Ceftiofur hydrochloride, crystalline: 1 to 100 gms.
Vehicle Part I q.s. adjust: 1000 cc.

DIRECTIONS

Part I

All of the ingredients are dissolved in water and pH adjusted to approximately 3.0, and the vehicle sterilized by filtration.

Part II

Aseptically add sterile crystalline ceftiofur hydrochloride in sufficient vehicle from Part I to make 900 mls. Stir the suspension and pass through a colloid mill to a uniform consistency. Add sufficient vehicle to make 1000 mls.

EXAMPLE 9

Sterile Extemporaneous Parenteral Suspension (Aqueous)

Sterile Vehicle-Part I

Benzyl Alcohol or: 9.1 gms. or
Benzoic Acid: 0.2 to 2.0 gms.
Carboxymethylcellulose Sodium USP: 1.0 to 20.0 gms. low viscosity or any other viscosity:
inducing agent:
Sodium Chloride Fine Crystals, Reagent Grade: 0.5 to 10 gms.

Hydrochloric Acid, Reagent Grade q.s. adjust pH to approx.: 3.0
Water for Injection

Part II	Amount per Vial
Sterile Crystalline ceftiofur, hydrochloride in a 10 to 100 mL glass vial	0.01 to 1.5 gm.

DIRECTIONS

Part I

All of the ingredients are dissolved in water, and pH adjusted to approximately 2.6 to 3.2, preferably about 3.0. Vehicle sterilized by filtration and packaged in appropriate glass vials.

Part II

Sterile crystalline ceftiofur hydrochloride is packaged aseptically in sterile vials or crystalline ceftiofur hydrochloride is first packaged and the final container(s) sterilized by Cobalt 60 irradiation.

EXAMPLE 10

Sterile Extemporaneous Parenteral Suspension

Sterile Vehicle Part I

Methylparaben: 1.0 to 2.7 gms.
Propylparaben: 0.1 to 0.5 gm.
Povidone: 1 to 10 gms.
Sodium Chloride Fine Crystals Reagent Grade: 0.5 to 10 gms.
20% Solution Hydrochloric acid q.s. adjust pH to approx.: 3.0
50% Solution Sodium Hydroxide q.s. adjust pH
Water for Injection q.s. adjust: 1000 cos.

Part II	Amount per Vial
Sterile crystalline ceftiofur hydrochloride in a 10 to 100 mL glass vial	0.01 to 1.5 gm.

DIRECTIONS

Part I

Methylparaben and propylparaben are dissolved in boiling water. Then all of the ingredients dissolved in water, and pH adjusted to approximately 2.6 to 3.2, preferably about 3.0. Vehicle sterilized by filtration and packaged in appropriate glass vials.

Part II

Sterile crystalline ceftiofur hydrochloride is packaged aseptically in sterile vials or crystalline ceftiofur hydrochloride is first packaged and the final container(s) shall be sterilized by Cobalt 60 irradiation.

EXAMPLE 11

Extemporaneous Parenteral Suspension (Aqueous)

Sterile Vehicle-Part I

Polyethylene Glycol 3350 NF: 5 to 120 gms.
Polyvinyl Pyrrolidone: 1 to 10 gms.
Quatresin ® myristyl gamma picolinium chlorice: 0.1 to 2.0 gms.
Sodium Chloride, Fine Crystals Reagent Grade: 0.5 to 10 gms.
20% Solution Hydrochloric Acid q.s. adjust pH to approx.: 3.0
50% Solution Sodium Hydroxide q.s. to adjust pH to approx.: 3.0
Water for Injection q.s. adjust to: 1000 cc.

Part II	Amount per Vial
Sterile crystalline ceftiofur hydrochloride (milled or micronized) in a 10 to 100 mL glass vial	0.01 to 1.5 gms.

DIRECTIONS

Part I

All of the ingredients are dissolved in water, and pH adjusted to approximately 2.6 to 3.2, preferably about 3.0. Vehicle sterilized by filtration and packaged in appropriate glass vials.

Part II

Sterile crystalline ceftiofur hydrochloride is packaged aseptically in sterile vials or crystalline ceftiofur hydrochloride is first packaged and the final container(s) are sterilized by Cobalt 60 irradiation.

EXAMPLE 12

Sterile Nonaqueous Parenteral Suspension

Crystalline ceftiofur hydrochloride (milled or micronized): 1 to 100 gms.
Chlorobutanol Anhydrous-preservative: 5.25 gms.
or:
Benzyl Alcohol: 9.25 gms.
Corn Oil Glyceryl Monostearate Gel
or
Cottonseed Oil Glyceryl Monostearate Gel: q.s. adjust

DIRECTIONS

Preservative is dissolved in sufficient oily gel to make 800 cc. Crystalline ceftiofur hydrochloride is added, and the suspension is colloid milled to a uniform consistency. Add sufficient gel to make 1000 mls. After packaging into glass vials, the suspension is sterilized by Cobalt 60 irradiation or by any other suitable method.

EXAMPLE 13

Sterile Nonaqueous Parenteral Suspension

Crystalline ceftiofur hydrochloride (milled or micronized): 1 to 100 gms.
Chlorobutanol Anhydrous: 5.25 gms.
or
Benzyl Alcohol: 9.25 gms.
Corn Oil USP q.s. adjust: 1000 cc.
or
Cottonseed oil q.s. adjust: 1000 cc.

DIRECTIONS

Preservative is dissolved in sufficient oil to make 800 cc. Crystalline ceftiofur hydrochloride is added, and the suspension is colloid milled to a uniform consistency to break the aggregates. Add sufficient amount of oil to make 1000 mls. Stir and package into glass vials. The suspension can be sterilized by Cobalt 60 irradiation or sterile crystalline ceftiofur hydrochloride can be added to sterile vehicle and manufactured following aseptic procedure(s).

EXAMPLE 14

Sterile Extemporaneous Parenteral Suspension (Nonaqueous Gel)-Controlled Release Formulation

Sterile Vehicle Part I	1000
Benzyl Alcohol - preservative	9.0 to 9.25 gms.
or	
Chlorobutanol	5.0 to 5.25 gms.
Corn Oil Glyceryl Monostearate Gel	1000 cc.
or	
Cottonseed Oil Glyceryl Monostearate Gel	1000 cc.
Part II	100 Vials
Crystalline ceftiofur hydrochloride (milled or micronized)	1 to 100 gms.

DIRECTIONS

Part I

Preservative is dissolved in sufficient gel, and the gel is filled into vials asceptically and the vials sealed. These vials will be packaged with the vials of Part II as companion package.

Part II

0.01 to 1.0 gm. of crystalline ceftiofur hydrochloride or sterilized crystalline ceftiofur hydrochloride is packaged in a sterile glass vial and the vials sealed. If the crystalline ceftiofur hydrochloride is non-sterile, then the packaged vials will be sterilized by Cobalt 60 irradiation.

Prior to dosing appropriate amounts of Part I diluent will be added to Part II sterile powder and shaken until homogeneous.

EXAMPLE 15

Sterile Extemporaneous Parenteral Suspension (Nonaqueous)

Sterile Vehicle Part I	1000
Benzyl Alcohol - preservative	9.0 to 9.25 gms.
or	
Chlorobutanol	5.0 to 5.25 gms.
Corn Oil, USP q.s. ad.	1000 cc.
or	
Cottonseed Oil, USP q.s. ad.	1000 cc.
Part II	100 Vials
Crystalline ceftiofur hydrochloride, (milled and micronized)	50 to 100 gms.

Part I

Preservative is dissolved in the oil, and the solution sterilized by filtration. The sterile solution is filled into vials and the vials sealed. These vials will be packaged with the vials of Part II as companion package.

Part II

0.5 to 1.0 gm. of crystalline ceftiofur hydrochloride or sterilized crystalline ceftiofur hydrochloride is packaged in a sterile glass vial and the vials sealed. If the crystalline ceftiofur hydrochloride is non-sterile, then the packaged vials will be sterilized by Cobalt 60 irradiation.

Prior to dosing appropriate amounts of Part I diluent will be added to Part II sterile powder and shaken until uniformly mixed.

EXAMPLE 16

Suppositories

Formulation for a 2 gm. suppository containing 62.5 mg. of crystalline ceftiofur hydrochloride is given. However, any size suppository can be manufactured using any amount of ceftiofur hydrochloride and appropriate amounts of excipients at the same ratio as indicated below.

	Lot Size 12
Crystalline ceftiofur hydrochloride (milled or micronized)	0.750 gm.
PEG-400	14.4 ml.
PEG-8000	9.6 gm.

DIRECTIONS

Measure out 14.4 ml. of PEG-400 and place in a container suitable for heating. Add 9.6 gms. of PEG-8000 (melting point 140° F.) to the PEG-400 solution and melt over a hot water bath approximately two minutes or until there is a clear solution.

Add crystalline ceftiofur hydrochloride and stir until dispersed. Pour the mix into the mold and let set. Chill the mold. Remove suppositories after they set up 15–30 minutes at room temperature. Sterile suppositories can be manufactured with sterile raw materials and observing aseptic conditions during manufacturing, or can be sterilized by Cobalt 60 irradiation.

EXAMPLE 17

Suppositories

Suppositories can also be manufactured from excipients such as cocoa butter, Suppocire TM AM, Suppocire AS_2, and Suppocire AT, Suppocire BT or Suppocire CT brand of C_8 to C_{10}-saturated fatty acid glycerides.

Formula for a 2 gm. suppository containing 62.5 mg. of crystalline ceftiofur hydrochloride is given; however, any size suppository can be manufactured using any desired amount of crystalline ceftiofur hydrochloride, and appropriate amount of excipient.

	Lot Size 12
Crystalline ceftiofur hydrochloride (milled or micronized) Sterile	0.750 gm.
Suppocire AM or AS_2, or AT, or BT or CT	23.25 gm.

DIRECTIONS

Weigh the Suppocire TM diluent in a container suitable for heating. Melt (45° C. temperature) over a hot water bath for approximately two minutes or until there is a clear solution (microwave oven can also be used instead of the water bath). Sterilize by filtration. Add sterile crystalline ceftiofur hydrochloride and stir until dispersed. Pour the mix into the cold mold. After two to four minutes, the surplus of the casting is eliminated by scraping. The temperature and time of cooling must be governed according to the type of formula. The circulating cold air should come in contact with all faces of the mold. Release from the mold must be gentle. Sterile suppositories can be manufactured with sterile raw

materials and observing aseptic conditions during manufacturing, or can be sterilized by Cobalt 60 irradiation.

EXAMPLE 18

Capsules

One thousand two-piece hard gelatin capsules for oral use, each containing 50 mgs. of activity of crystalline ceftiofur hydrochloride, are prepared from the following types and amounts of materials:

	1000
Crystalline ceftiofur hydrochloride	(50 gms.)
or	
*Coated with Carnauba Wax ®	
or	
*White Wax	
Talc and/or	75 gms.
Magnesium Stearate	25 gms.

( ) = Activity of ceftiofur hydrochloride

*Coated crystalline ceftiofur hydrochloride will have controlled release properties. The materials are thoroughly mixed and then encapsulated in the usual manner. Different strength capsules can be prepared by changing the amounts of crystalline ceftiofur hydrochloride.

EXAMPLE 19

Tablets

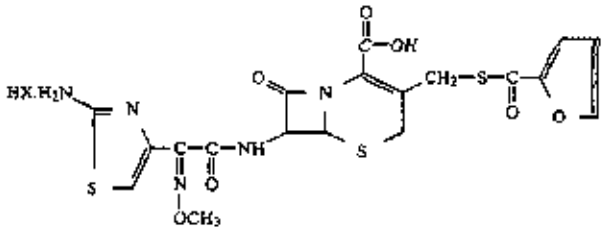
One thousand compressed tablets for oral use, each containing an amount equivalent to 50 mgs. crystalline ceftiofur hydrochloride can be prepared using the following:

Ceftiofur hydrochloride crystalline: 50 gms.
Lactose: 375 gms.
Corn Starch: 65 gms.
Magnesium Stearate: 10 gms.

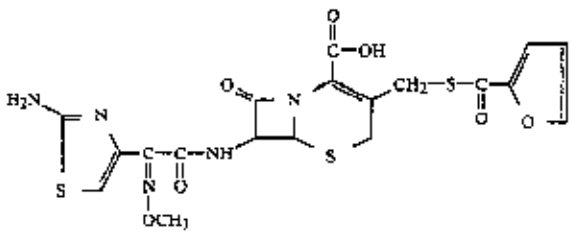
The ingredients are thoroughly mixed and slugged. The slugs are broken down by forcing through a screen. The resulting mixture is then compressed into tablets. Different strength tablets can be prepared by appropriate changes in the amounts of ceftiofur hydrochloride and the excipients.

STRUCTURE SHEET

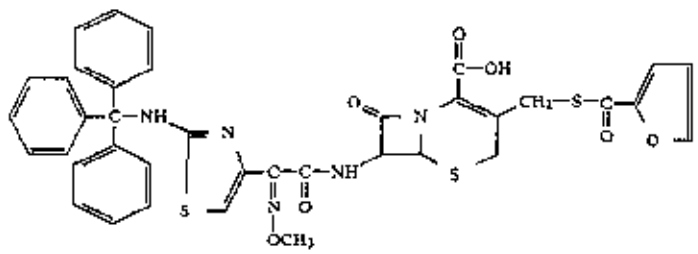
Formula (1)



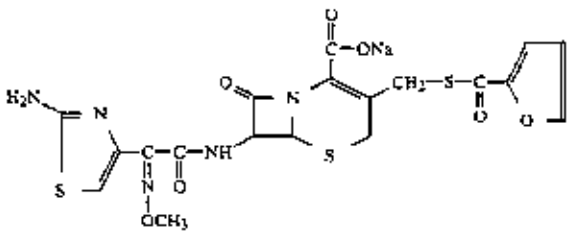
Formula (2)



Formula (3)

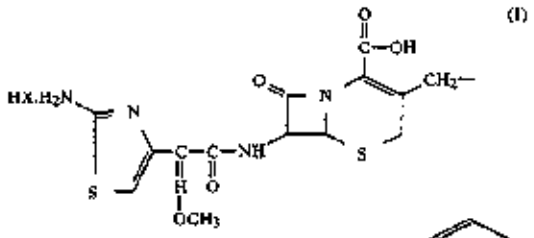


Formula (4)



We claim:

1. A cephalosporin hydrohalide compound of the formula



(I)

where X is chloride or bromide.

2. A compound according to claim 1 where X is chloride.

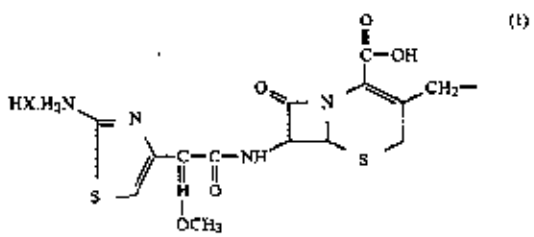
3. A crystalline compound according to claim 1.

4. A crystalline compound according to claim 2.

5. A compound according to claim 4 which has the following x-ray powder diffraction pattern when crystallized from an acetone/water mixture.

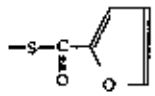
interplanar d-spacings	intensity (relative %)
18.4	44.2
12.4	73.1
8.26	50.0
7.82	100.0
7.69	17.9
6.19	48.2
5.86	32.1
5.21	23.1
5.12	40.4
4.74	20.1
4.37	21.8
4.23	13.5
3.98	26.9
3.91	25.9
3.81	17.9
3.30	14.1
3.01	12.8
2.88	14.1

6. A process for preparing a crystalline cephalosporin hydrohalide salt of the formula



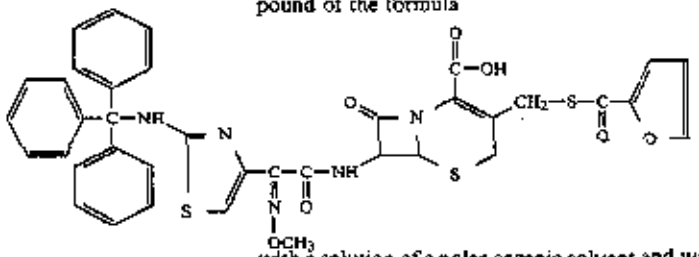
(I)

-continued



where X is chloride or bromide, which comprises the steps of

(a) treating the N-tritylamino cephalosporin compound of the formula



(3)

with a solution of a polar organic solvent and water and hydrogen halide, where halide is chloride or bromide, in an amount which is at least stoichiometrically equivalent to the amount of the N-trityl compound (3) in the mixture,

(b) heating the mixture from step (a) to a temperature of at least 45° C. and for a time sufficient to effect detritylation,

(c) decreasing the concentration of the polar organic solvent in the aqueous phase of mixture from step (b) to effect formation of crystalline cephalosporin hydrohalide salt (1),

(d) separating the crystalline cephalosporin hydrohalide salt from the slurry mixture from step (c),

(e) washing the separated crystalline cephalosporin hydrohalide salt from step (d) with water and polar organic solvent, and drying the washed crystalline cephalosporin hydrohalide salt from step (c).

7. A process according to claim 6 wherein the crystalline cephalosporin hydrohalide salt of Formula I being prepared is the hydrochloride salt.

8. A process according to claim 7 wherein in step (c) of the process, toluene is used as the non-polar, water immiscible organic liquid to separate by-product trityl alcohol and to decrease the quantity of the polar organic liquid in the aqueous phase of the mixture.

9. A process according to claim 7 wherein step (c) of the process heptane is used as the non-polar, water immiscible organic liquid to separate trityl alcohol by-product and the mixture is distilled to remove polar organic liquid therefrom to enhance formation of the crystalline cephalosporin hydrochloride.

10. A pharmaceutical composition useful in pharmaceutically effective dosage unit form for alleviating the effects of undesired bacterial infections in warm-blooded mammals which comprises a compound according to claim 1 in combination with a pharmaceutically acceptable carrier.

11. A composition according to claim 10 wherein the compound is ceftiofur hydrochloride.

12. A method for alleviating the effects of undesired bacterial infections in a warm-blooded animal which comprises administering to an animal suffering such a bacterial infection an effective amount of a compound of claim 1 in a pharmaceutically acceptable dosage unit form.

13. A method according to claim 12 wherein the active compound is ceftiofur hydrochloride.

* * * * *

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APC
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Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E. S. D.

Ref. PODER ESPECIAL
EXPEDIENTE 05-057-688
Título: "COMPOSICIONES FARMACÉUTICAS DISPERSABLES".
GACETA No. 557 N.P. 653
SOLICITANTE: PHARMACIA & UPJOHN COMPANY
APODERADO: CARLOS REINALDO OLARTE GARCIA
TRÁMITE: REMISIÓN DE INFORMACIÓN

MARIO MOLANO MORALES, mayor de edad, identificado como aparece al pie de la firma, obrando en nombre y representación legal de **GENFAR S.A.**, sociedad comercial organizada y existente conforme a las leyes colombianas, con domicilio y sede principal en Bogotá, D.C., hechos que constan en el certificado de existencia y representación legal que se anexa a este documento, por este escrito confiero poder especial, amplio y *suficiente a los Doctores* ***JOSÉ LUIS REYES VILLAMIZAR y/o JUAN PABLO REYES*** **VILLAMIZAR**, mayores de edad, y vecinos de Bogotá, identificados como aparece al pie de sus firmas, abogados en ejercicio, para que en nombre y representación de esta sociedad presenten ante esa entidad peticiones, escritos de remisión de información y en general adelanten las gestiones que estimen necesarias para evitar la concesión de la solicitud de patente indicada en la referencia.

Los apoderados quedan facultados para ejercer las facultades conferidas por el artículo 70 del C.P.C., en especial para desistir, conciliar, transigir, sustituir, reasumir, presentar recursos, así como para realizar todas las demás gestiones inherentes al presente mandato.

Señor Superintendente,

MARIO MOLANO MORALES
C.C. No 19.086.654 de Bogotá

Aceptamos,

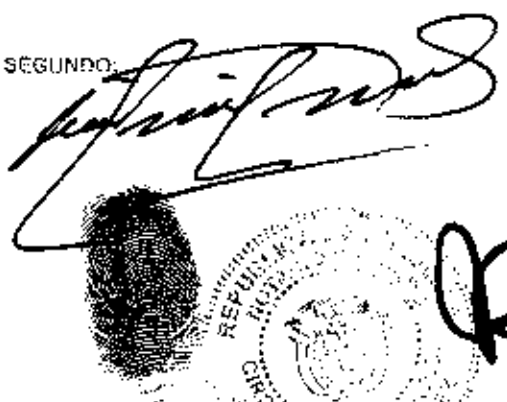
JOSE LUIS REYES VILLAMIZAR
C.C. No. 79'152.473 de Usaquén
T.P.A. No. 44655 del C. S. J.

JUAN PABLO REYES VILLAMIZAR
C.C. 80.419.709 de Usaquén
T.P.A. No. 92.159 del C.S.J.

El anterior memorial fue presentado personalmente por
Mario Molano Morales quien se
identificó con la C. de C. No. 19086254 de Bogotá
Tarjeta Profesional No. _____ y
quien en constancia firma:

Bogotá, D.E.

EL NOTARIO SEGUNDO:



08 JUL. 2008

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CAMARA DE COMERCIO DEL CAUCA

SEDE PRINCIPAL

Fecha : 20080609 Hora Certificado : 09:44:27

Operacion: 01C04060901708C04060 PAGINA No. 1

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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O INSCRIPCION DE DOCUMENTOS.
LA CAMARA DE COMERCIO DEL CAUCA , CON FUNDAMENTO EN LAS MATRICULAS E INSCRIPCIONES DEL REGISTRO MERCANTIL,

CERTIFICA :

NOMBRE : GENFAR S.A.
SOCIEDAD VIGILADA POR SUPERINTENDENCIA DE SOCIEDADES SEGUN OFICIO 6201604 DE ABRIL 30 DE 1998
N.I.T.:0817001644-1
DIRECCION COMERCIAL: PARQUE INDUSTRIAL CAUCADESA KM 43 VIA PANAMERICANA
DOMICILIO : VILLA RICA
TELEFONO COMERCIAL: 3905400
DIRECCION DE NOTIFICACION JUDICIAL : PARQUE INDUSTRIAL CAUCADESA KM 43 VIA PANAMERICANA
MUNICIPIO JUDICIAL: VILLA RICA
E-MAIL: jmoreno@genfar.com
TELEFONO NOTIFICACION JUDICIAL: 3905400

CERTIFICA :

MATRICULA NO. 00049488
FECHA DE MATRICULA EN ESTA CAMARA: 19 DE DICIEMBRE DE 1997
RENOVO EL AÑO 2008 , EL 28 DE MARZO DE 2008

CERTIFICA :

CONSTITUCION : QUE POR ESCRITURA PUBLICA NO. 0007839 DE NOTARIA SEXTA DE BOGOTA DEL 17 DE DICIEMBRE DE 1997 , INSCRITA EL 19 DE DICIEMBRE DE 1997 BAJO EL NUMERO 00011974 DEL LIBRO IX, SE CONSTITUYO LA PERSONA JURIDICA: GENFAR S.A.
QUE POR ESCRITURA PUBLICA NO. 0002326 DE NOTARIA SEXTA DE BOGOTA D.C. DEL 26 DE MARZO DE 2007 , INSCRITA EL 13 DE ABRIL DE 2007 BAJO EL NUMERO 00022695 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE : GENFAR S.A. POR EL DE : C.I. GENFAR S.A.
QUE POR ESCRITURA PUBLICA NO. 0003471 DE NOTARIA SEXTA DE BOGOTA D.C. DEL 7 DE MAYO DE 2007 , INSCRITA EL 14 DE MAYO DE 2007 BAJO EL NUMERO 00022834 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE : C.I. GENFAR S.A. POR EL DE : GENFAR S.A.

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GENFAR S.A.

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL PAGINA No. 2
Fecha : 20080609 Hora : 09:44:27 Operacion: 01C04060901708C04060

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CERTIFICA :

QUE POR ESCRITURA PUBLICA NO. 0001019 DE NOTARIA SEXTA DE BOGOTA DEL 23 DE FEBRERO DE 1999 , INSCRITA EL 2 DE MARZO DE 1999 BAJO EL NUMERO 00013641 DEL LIBRO IX, LA PERSONA JURIDICA REPORTO : CAMBIO DE DOMICILIO DE LA CIUDAD DE SANTANDER DE QUILICHAO A VILLA RICA

CERTIFICA :

QUE POR ESCRITURA PUBLICA NO. 0001019 DE NOTARIA SEXTA DE BOGOTA DEL 23 DE FEBRERO DE 1999 , INSCRITA EL 2 DE MARZO DE 1999 BAJO EL NUMERO 00013641 DEL LIBRO IX, LA PERSONA JURIDICA REPORTO : CAMBIO DE DOMICILIO DE LA CIUDAD DE SANTANDER DE QUILICHAO A VILLA RICA

CERTIFICA :

QUE POR ESCRITURA PUBLICA NO. 0001019 DE NOTARIA SEXTA DE BOGOTA DEL 23 DE FEBRERO DE 1999 , INSCRITA EL 02 DE MARZO DE 1999 BAJO EL NUMERO 00013641 DEL LIBRO IX, LA PERSONA JURIDICA REPORTO : CAMBIO DE DOMICILIO DE LA CIUDAD DE SANTANDER DE QUILICHAO A VILLA RICA

CERTIFICA :

QUE POR ESCRITURA PUBLICA NO. 0000004 DE NOTARIA 73 DE BOGOTA D.C. DEL 3 DE ENERO DE 2008 , INSCRITA EL 23 DE ENERO DE 2008 BAJO EL NUMERO 00023751 DEL LIBRO IX, LA PERSONA JURIDICA REGISTRO FUSION EN EL CUAL INFORMA : FUSION POR ABSORCION. ABSORBENTE: GENFAR S.A. ABSORBIDA: LABORATORIOS GENERICOS FARMACEUTICOS S.A.

CERTIFICA :

REFORMAS:

DOCUMENTO	FECHA	ORIGEN	CIUDAD	INSCRIPCION	FECHA
0001019	1999/02/23	NOTARIA SEXTA DE	BOGOTA	00013641	1999/03/02
0000004	2008/01/03	NOTARIA 73	BOG	00023751	2008/01/23
0003338	1998/05/26	NOTARIA SEXTA DE	BOGOTA	00012675	1998/06/18
0005827	1998/08/27	NOTARIA SEXTA DE	BOGOTA	00012899	1998/09/11
0002198	1999/04/21	NOTARIA SEXTA DE	BOGOTA	00013824	1999/04/29
0003616	2002/08/08	NOTARIA SEXTA DE	BOGOTA	00017568	2002/08/28
0005979	2002/12/05	NOTARIA SEXTA	BOG	00017864	2002/12/30

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0003401	2003/07/31	NOTARIA SEGUNDA	BOG	00018528	2003/08/12
0002326	2007/03/26	NOTARIA SEXTA	BOG	00022695	2007/04/13
0003471	2007/05/07	NOTARIA SEXTA	BOG	00022834	2007/05/14
0006090	2007/08/08	NOTARIA SEXTA	BOG	00023175	2007/08/13
00C0104	2008/02/14	REPRESENTACION LEGALVIL		00023950	2008/03/12
0008400	1998/12/07	NOTARIA SEXTA DE BOGOTA		00013204	1998/12/16
0005618	1999/09/15	NOTARIA SEXTA DE BOGOTA		00014632	1999/09/21
0007103	1999/11/23	NOTARIA SEXTA DE BOGOTA		00014817	1999/12/02
0007927	1999/12/29	NOTARIA SEXTA DE BOGOTA		00014972	2000/01/04
0005722	2000/11/10	NOTARIA SEXTA DE BOGOTA		00015960	2000/11/27

CERTIFICA

VIGENCIA: QUE LA PERSONA JURIDICA NO SE HALLA DISUELTA. DURACION HASTA EL 16 DE DICIEMBRE DE 2047 .

CERTIFICA :

OBJETO SOCIAL: 1. LA ELABORACION, PRODUCCION, TRANSFORMACION, COMPRA, VENTA, ENAJENACION, IMPORTACION, EXPORTACION, DISTRIBUCION Y EN GENERAL COMERCIALIZACION DE INSUMOS Y MATERIAS QUIMICAS NECESARIAS PARA LA ELABORACION DE PRODUCTOS FARMACEUTICOS Y FARMOQUIMICOS, DROGAS DE USO HUMANO, Y VETERINARIO, EN GENERAL SUS DERIVADOS Y COSMETICOS. 2- LA ELABORACION, PRODUCCION, TRANSFORMACION, COMPRAVENTA, ENAJENACION, IMPORTACION, EXPORTACION, DISTRIBUCION Y EN GENERAL COMERCIALIZACION DE LOS PRODUCTOS EN EL PUNTO PRIMERO DESCRITOS, Y DE AQUELLOS APROPIADOS PARA ENVASARLOS, ENVOLVERLOS, Y/O EMPACARLOS. 3- LA REPRESENTACION Y AGENCIAMIENTO DE CASAS NACIONALES O EXTRANJERAS QUE SE DEDIQUEN A ACTIVIDADES IGUALES O COMPLEMENTARIAS A LAS DESCRITAS EN LOS PUNTOS PRIMERO Y SEGUNDO ANTERIORES. 4- LA INVERSION A CUALQUIER TITULO EN ACCIONES, CUOTAS, PARTES DE INTERES Y DERECHOS EN OTRAS SOCIEDADES O EMPRESAS CUALQUIERA QUE SEA SU NATURALEZA, FORMA U OBJETO SOCIAL, BIEN CON EL ANIMO DE REVENDERLAS O PERCIBIR LAS UTILIDADES O VALORIZACIONES DE LA EMPRESA A LA CUAL SE ADQUIERAN; ACTIVIDADES ESTAS QUE EN NINGUN EVENTO CONSTITUIRAN O IMPLICARAN OPERACIONES DE INTERMEDIACION BURSATIL. 5- LA EXPLOTACION AGROPECUARIA O FORESTAL, PUDIENDO ADQUIRIR O VENDER SEMOVIENTES O EQUIPOS AGRICOLAS Y EN FIN TODO LO RELACIONADO CON LA AGRICULTURA Y LA GANADERIA. EN DESARROLLO DEL OBJETO SOCIAL ANTES ENUNCIADO, LA SOCIEDAD PODRA PROMOVER Y FUNDAR ESTABLECIMIENTOS, ALMACENES, FABRICAS, DEPOSITOS O AGENCIAS; PODRA ADEMAS ADQUIRIR CUALQUIER TITULO TODA CLASE DE BIENES MUEBLES O INMUEBLES, ARRENDARLOS, ENAJENARLOS O GRAVARLOS Y

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DARLOS EN GARANTIA DE SUS PROPIAS OBLIGACIONES; EXPLOTAR MARCAS, NOMBRES COMERCIALES, PATENTES, INVENCIONES O CUALQUIER OTRO BIEN INCORPORAL, SIEMPRE QUE SEAN AFINES AL OBJETO PRINCIPAL. GIRAR, ACEPTAR, ENDOSAR, COBRAR Y PAGAR TODA CLASE DE TITULOS VALORES, PARTICIPAR EN LICITACIONES PUBLICAS, PRIVADAS Y TAMBIEN CONTRATAR DIRECTAMENTE; PODRA CELEBRAR EL CONTRATO DE MUTUO, SEGURO, TRANSPORTE, CUENTAS EN PARTICIPACION, CONTRATOS DE CUALQUIER INDOLES CON ENTIDADES BANCARIAS Y FINANCIERAS, REALIZAR TODA CLASE DE OPERACIONES CON TITULOS VALORES, PRESTAR ASESORIAS EN GENERAL Y CELEBRAR TODO ACTO O CONTRATO QUE SE RELACIONE CON EL OBJETO SOCIAL PRINCIPAL. PARAGRAFO: ES CONTRARIO AL OBJETO SOCIAL, GARANTIZAR, RESPALDAR, FIAR O AVALAR DEUDAS Y / O OBLIGACIONES DE PERSONAS NATURALES O JURIDICAS DISTINTAS DE AQUELLAS PERSONAS CON QUIEN COMERCIALIZA GENFAR S.A. , TENGA LA CALIDAD DE MATRIZ, FILIAL, SUBSIDIARIA O VINCULADA ECONOMICAMENTE, O SEA PROPIETARIA DE ACCIONES O CUOTAS. LA SOCIEDAD COMO CONFORMANTE DEL GRUPO EMPRESARIAL GENFAR PODRA DAR Y RECIBIR PRESTAMOS DE LAS DEMAS COMPAÑIAS QUE HACEN PARTE DEL GRUPO, ASIMISMO, PODRA OTORGAR LAS GARANTIAS Y CONTRAGARANTIAS QUE SEAN NECESARIAS, BIEN SEA PARA RESPALDAR A LA MISMA SOCIEDAD O PARA LAS OTRAS.----------

CERTIFICA :

CAPITAL:

** CAPITAL AUTORIZADO **

VALOR :$12,001,000,000.00
NO. DE ACCIONES:12,001,000.00
VALOR NOMINAL :$1,000.00

** CAPITAL SUSCRITO **

VALOR :$8,418,090,000.00
NO. DE ACCIONES:8,418,090.00
VALOR NOMINAL :$1,000.00

** CAPITAL PAGADO **

VALOR :$8,418,090,000.00
NO. DE ACCIONES:8,418,090.00
VALOR NOMINAL :$1,000.00

CERTIFICA :

QUE POR DOCUMENTO PRIVADO DEL 22 DE FEBRERO DE 2001 , INSCRITA EL 6 DE MARZO DE 2001 BAJO EL NUMERO 00075935 DEL LIBRO 11, SE INSCRIBIO :
CONSTITUCION PRENDA

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GENFAR S.A.

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL PAGINA No. 5
Fecha : 20080609 Hora : 09:44:27 Operacion: 01C040609017O8C04060

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CERTIFICA :

** JUNTA DIRECTIVA: PRINCIPAL(ES) **

QUE POR ACTA NO. 0000047 DE ASAMBLEA DE ACCIONISTAS DEL 18 DE MARZO DE 2005 , INSCRITA EL 29 DE ABRIL DE 2005 BAJO EL NUMERO 00020220 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

NOMBRE	IDENTIFICACION
MIEMBRO DE JUNTA DIRECTIVA TITULAR	
GARCIA BORRERO JUAN MANUEL	C.C.00079152415
MIEMBRO DE JUNTA DIRECTIVA TITULAR	
CARO RODRIGUEZ JOSE VICENTE	C.C.00019084476
MIEMBRO DE JUNTA DIRECTIVA TITULAR	
CARO PAZOS JOSE VICENTE	C.C.00079949522
MIEMBRO JUNTA DIRECTIVA TITULAR	
CRUZ AGUIRRE JOSE MANUEL	C.C.00017063784

** JUNTA DIRECTIVA: SUPLENTE(S) **

QUE POR ACTA NO. 0000047 DE ASAMBLEA DE ACCIONISTAS DEL 18 DE MARZO DE 2005 , INSCRITA EL 29 DE ABRIL DE 2005 BAJO EL NUMERO 00020220 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

NOMBRE	IDENTIFICACION
SUPLENTE DE MIEMBRO DE JUNTA DIRECTIVA	
CRUZ GRACA RONALD JOSE	C.C.00080091075
SUPLENTE DE MIEMBRO DE JUNTA DIRECTIVA	
PAZOS MERA GLORIA AMANDA	C.C.00041604009
SUPLENTE DE MIEMBRO DE JUNTA DIRECTIVA	
CARO PAZOS SONIA ALEXANDRA	C.C.00052250181
SUPLENTE DE MIEMBRO DE JUNTA DIRECTIVA	
CRUZ GRACA GEISSLER MANUEL	C.C.00079942132

CERTIFICA :

** NOMBRAMIENTOS : **

QUE POR ESCRITURA PUBLICA NO. 0007839 DE NOTARIA SEXTA DE BOGOTA DEL 17 DE DICIEMBRE DE 1997 , INSCRITA EL 19 DE DICIEMBRE DE 1997 BAJO EL NUMERO 00011974 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

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NOMBRE	IDENTIFICACION

PRESIDENTE
MARIO MOLANO MORALES C.C.00019086654
QUE POR ACTA NO. 0000132 DE JUNTA DIRECTIVA DEL 22 DE SEPTIEMBRE DE 2004 , INSCRITA EL 1 DE DICIEMBRE DE 2004 BAJO EL NUMERO 00019849 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

NOMBRE	IDENTIFICACION

PRIMER SUPLENTE DEL PRESIDENTE
HECTOR MACIAS CHAUX C.C.00017193071
SEGUNDO SUPLENTE DEL PRESIDENTE
CARO RODRIGUEZ JOSE VICENTE C.C.00019084476
TERCER SUPLENTE DEL PRESIDENTE
CARLOS MARIO HERNANDEZ MUÑOZ C.C.00019266964

CERTIFICA :

ORGANOS DIRECTIVOS: ASAMBLEA GENERAL, JUNTA DIRECTIVA, PRESIDENTE .----------
FUNCIONES DE LA ASAMBLEA: SON FUNCIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS: 1- ESTUDIAR Y APROBAR LAS REFORMAS DE LOS ESTATUTOS. 2- CONSIDERAR LOS INFORMES DE LOS ADMINISTRADORES Y DEL PRESIDENTE SOBRE EL ESTADO DE LOS NEGOCIOS SOCIALES Y EL INFORME DEL REVISOR FISCAL. 3- EXAMINAR Y APROBAR O IMPROBAR LOS BALANCES DE FIN DE EJERCICIO Y LAS CUENTAS QUE DEBEN RENDIR LOS ADMINISTRADORES. 4- DISPONER DE LAS UTILIDADES SOCIALES CONFORME A LOS ESTATUTOS Y A LAS LEYES. 5- CONSTITUIR E INCREMENTAR LAS RESERVAS A QUE HAYA LUGAR. 6- FIJAR EL MONTO DEL DIVIDENDOS ASI COMO LA FORMA Y PLAZOS EN QUE SE PAGARA. 7 - NOMBRAR Y REMOVER A LOS MIEMBROS DE LA JUNTA DIRECTIVA Y EL REVISOR FISCAL CON SUS RESPECTIVOS SUPLENTES Y FIJARLES SUS ASIGNACIONES. 8- NOMBRAR AL LIQUIDADOR DE LA SOCIEDAD. 9 - ORDENAR LAS ACCIONES QUE CORRESPONDAN CONTRA LOS ADMINISTRADORES, FUNCIONARIOS, DIRECTIVOS Y EL REVISOR FISCAL. 10- DECRETAR LA EMISION DE BONOS Y TITULOS REPRESENTATIVOS DE OBLIGACIONES. 11- DELEGAR EN LA JUNTA DIRECTIVA O EN LA PRESIDENCIA AQUELLAS FUNCIONES CUYA DELEGACION NO ESTE PROHIBIDA POR LA LEY. 12- ADOPTAR LAS MEDIDAS QUE RECLAME EL CUMPLIMIENTO DE LOS ESTATUTOS Y EL INTERES COMUN DE LOS ASOCIADOS.----------
FUNCIONES DE LA JUNTA: SON FUNCIONES DE LA JUNTA: 1- DAR SU PROPIO REGLAMENTO Y HACER LOS REGLAMENTOS INTERNOS DE LA

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SOCIEDAD. 2- COOPERAR CON EL PRESIDENTE EN LA ADMINISTRACION Y DIRECCION DE LOS NEGOCIOS SOCIALES. 3- ELEGIR CADA ANO AL PRESIDENTE DE LA SOCIEDAD Y FIJARLE LA REMUNERACION RESPECTIVA. 4- DISPONER CUANDO LO CONSIDERE OPORTUNO, LA FORMACION DE COMITES CONSULTIVOS O TECNICOS, INTEGRADOS POR EL NUMERO DE MIEMBROS QUE DETERMINE, PARA QUE ASESOREN AL PRESIDENTE EN DETERMINADOS ASUNTOS. 5- PROPONER A LA ASAMBLEA GENERAL DE ACCIONISTAS LAS REFORMAS QUE JUZGUE CONVENIENTE INTRODUCIR A LOS ESTATUTOS. 6- AUTORIZAR AL PRESIDENTE DE LA COMPAÑIA PARA LA CELEBRACION DE TODO ACTO O CONTRATO CUYA CUANTIA EXCEDA DE CUATRO MIL (4.000) SALARIOS MINIMOS MENSUALES VIGENTES. 7 - ASESORAR AL PRESIDENTE EN RELACION CON LAS ACCIONES JUDICIALES QUE DEBAN INICIARSE O PROSEGUIRSE. 8 - CONVOCAR A LA ASAMBLEA GENERAL DE ACCIONISTAS A SESIONES EXTRAORDINARIAS, SIEMPRE QUE LO CREA CONVENIENTE Y CUANDO LO SOLICITE UN NUMERO DE ACCIONISTAS QUE REPRESENTE LA CUARTA PARTE DE LAS ACCIONES SUSCRITAS. 9- DAR SU VOTO CONSULTIVO CUANDO LA ASAMBLEA LO PIDA O CUANDO LO DETERMINEN LOS ESTATUTOS. 10 - DECIDIR SOBRE LAS EXCUSAS O LICENCIAS DE LOS EMPLEADOS NOMBRADOS POR LA ASAMBLEA GENERAL Y LLAMAR A LOS SUPLENTES RESPECTIVOS. 11 - EXAMINAR CUANDO LO TENGA A BIEN, DIRECTAMENTE, O POR MEDIO DE UNA COMISION, LOS LIBROS, CUENTAS, DOCUMENTOS Y CAJA DE LA SOCIEDAD. 12 - APROBAR LA ADQUISICION DE OTRAS EMPRESAS O PROPONER A LA ASAMBLEA SU INCORPORACION O FUSION A OTRA SOCIEDAD. 13 - ESTABLECER SUCURSALES O AGENCIAS DENTRO O FUERA DEL PAIS. 14 - REGLAMENTAR LA COLOCACION DE ACCIONES ORDINARIAS QUE LA SOCIEDAD TENGA EN RESERVA. 15- INTERPRETAR LAS DISPOSICIONES DE LOS ESTATUTOS QUE DIEREN LUGAR A DUDAS Y FIJAR SU SENTIDO MIENTRAS SE REUNE LA PROXIMA ASAMBLEA PARA SOMETERLE LA CUESTION. 16 - CREAR LOS CARGOS QUE SEAN NECESARIOS PARA LA MARCHA DE LA EMPRESA Y FIJAR SUS RESPECTIVAS ASIGNACIONES. Y 17- CUIDAR DEL ESTRICTO CUMPLIMIENTO DE TODAS LAS DISPOSICIONES CONSIGNADAS EN ESTOS ESTATUTOS Y DE LAS QUE SE DICTEN PARA EL BUEN FUNCIONAMIENTO DE LA EMPRESA.----------

REPRESENTACION LEGAL: LA REPRESENTACION LEGAL ESTARA EN CABEZA DEL PRESIDENTE, QUIEN TENDRA A SU CARGO LA ADMINISTRACION Y

GESTION DE LOS NEGOCIOS SOCIALES CON SUJECION A LA LEY Y A ESTOS ESTATUTOS Y LOS REGLAMENTOS Y RESOLUCIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS Y LA JUNTA DIRECTIVA.----------

FACULTADES DEL PRESIDENTE Y SUS SUPLENTES: EL PRESIDENTE EJERCERA LAS FUNCIONES PROPIAS DE SU CARGO Y EN ESPECIAL LAS SIGUIENTES: 1- REPRESENTAR A LA SOCIEDAD JUDICIAL Y

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EXTRAJUDICIALMENTE, ANTE LOS ASOCIADOS, ANTE TERCEROS Y ANTE TODA CLASE DE AUTORIDADES JUDICIALES Y ADMINISTRATIVOS. 2 - EJECUTAR LOS ACUERDOS Y RESOLUCIONES DE LA ASAMBLEA GENERAL Y DE LA JUNTA DIRECTIVA. 3- REALIZAR O CELEBRAR CONTRATOS O ACTOS QUE TIENDAN A LLENAR LOS FINES DE LA SOCIEDAD CON LAS LIMITACIONES PREVISTAS EN ESTOS ESTATUTOS, Y SIEMPRE QUE SU CUANTIA NO EXCEDA DE CUATRO MIL (4.000) SALARIOS MINIMOS LEGALES MENSUALES, LIQUIDADOS AL DIA EN QUE SE REALICE LA OperaciÑn Y CUANDO EXCEDA DE DICHA SUMA SE REQUERIRA AUTORIZACION PREVIA DE LA JUNTA DIRECTIVA. PARAGRAFO PRIMERO. CUANDO SE TRATE DE EMPRESTITOS QUE NO SOBREPASEN LA CUANTIA ANTES SEÑALADA, EL PRESIDENTE DE LA COMPANIA PODRA OTORGAR LAS GARANTIAS QUE SEAN NECESARIAS. PARAGRAFO SEGUNDO. EL PRESIDENTE DE LA SOCIEDAD, ESTA FACULTADO PARA VENDER Y EXPORTAR LOS PRODUCTOS QUE CONSTITUYAN EL OBJETO DE LA SOCIEDAD; ASI COMO PARA PARTICIPAR EN OFERTAS Y LICITACIONES SIN LIMITACION LAGUNA, EN RELACION A LA CUANTIA DEL ACTO O CONTRATO .4 - PRESENTAR CONJUNTAMENTE CON LA JUNTA DIRECTIVA, SI FUERE EL CASO, LOS INFORMES Y DOCUMENTOS DE QUE TRATA EL ARTICULO CUATROCIENTOS CUARENTA Y SEIS (446) DEL CODIGO DEL COMERCIO. 5- NOMBRAR Y REMOVER LOS EMPLEADOS DE LA SOCIEDAD, CUYA DESIGNACION O REMOCION NO CORRESPONDA A LA ASAMBLEA Y SOLICITAR A LA JUNTA LA FIJACION DE LAS RESPECTIVAS ASIGNACIONES. 6 - DELEGAR DETERMINADAS FUNCIONES PROPIAS DE SU CARGO Y DENTRO DE LOS LIMITES SENALADOS EN LOS ESTATUTOS. 7- CONSTITUIR LOS APODERADOS JUDICIALES Y EXTRAJUDICIALES QUE OBRANDO A SUS ORDENES JUZGUE NECESARIOS Y DELEGARLES LAS ATRIBUCIONES QUE CONSIDERE PERTINENTES, SIEMPRE QUE TALES FACULTADES SEAN COMPATIBLES CON LA NATURALEZA DE SU CARGO Y LAS LIMITACIONES DE SUS PROPIAS ATRIBUCIONES. 8- CONVOCAR A LA JUNTA DIRECTIVA Y LA ASAMBLEA GENERAL DE ACCIONISTAS. 9 - CUIDAR DE LA RECAUDACION E INVERSION DE LOS FONDOS DE LA EMPRESA. 10 - VELAR PORQUE TODOS LOS EMPLEADOS DE LA SOCIEDAD CUMPLAN ESTRICTAMENTE CON SUS DEBERES. Y 11 - EJERCER LAS DEMAS FUNCIONES QUE DELEGUE LA ASAMBLEA GENERAL Y LA JUNTA DIRECTIVA.

CERTIFICA :

QUE EL DIA 27 DE OCTUBRE DE 2004, BAJO INSCRIPCION NO. 659 DEL LIBRO V, SE INSCRIBIO EN LA CAMARA DE COMERCIO LA ESCRITURA NRO. 5682 DE FECHA OCTUBRE 7 DE 2004, DE LA NOTARIA SEXTA (6a) DEL CIRCULO DE BOGOTA D.C., Y COMPARECIO CON MINUTA (E-MAIL) EL SEÑOR MARIO MOLANO MORALES, IDENTIFICADO CON CEDULA DE CIUDADANIA NO. 19.086.654 DE BOGOTA, QUIEN MANIFESTO: PRIMERO.

*** CONTINUA ***

GENFAR S.A.

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL PAGINA No. 9
Fecha : 20080609 Hora : 09:44:27 Operacion: 01C04060901708C04060

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QUE OBRA EN ESTE INSTRUMENTO, EN SU CONDICION DE REPRESENTANTE LEGAL DE LA SOCIEDAD GENFAR S. A. SOCIEDAD COLOMBIANA IDENTIFICADA CON NIT, 817. 001. 64 4- 1, CON MATRICULA NO. 49488, CONSTITUIDA MEDIANTE ESCRITURA PUBLICA NUMERO 7839 DE LA NOTARIA SEXTA (6 ¬) DEL CIRCULO DE BOGOTA D.C. DEL 17 DE DICIEMBRE DE 1.997, CALIDAD QUE ACREDITA MEDIANTE EL CERTIFICADO DE CONSTITUCION Y GERENCIA EXPEDIDO POR LA CAMARA DE COMERCIO DEL CAUCA, QUE SE PROTOCOLIZA. SEGUNDO QUE COMO REPRESENTANTE LEGAL DE LA SOCIEDAD, MEDIANTE EL PRESENTE ACTO VIENE A OTORGAR PODER GENERAL AL DOCTOR JESUS ENRIQUE CABRERA ROJAS, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NO. 19.111.955 DE BOGOTA D.C., PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO NO. 16.742 DEL CONSEJO SUPERIOR DE LA JUDICATURA, PARA QUE A NOMBRE DE LA SOCIEDAD REALICE LOS SIGUIENTES ACTOS: 3 - FIRMAR TODAS LAS DECLARACIONES DE IMPUESTOS, BIEN SEA LA DE IMPUESTO DE RENTA, IMPUESTO AL VALOR AGREGADO I.V.A, RETENCIONES EN LA FUENTE O DE IMPUESTO DE INDUSTRIA COMERCIO AVISOS Y TABLEROS. 4- REPRESENTAR A LA SOCIEDAD ANTE CUALQUIER AUTORIDAD DE ORDEN NACIONAL, DEPARTAMENTAL O MUNICIPAL, RESPECTO DE LOS IMPUESTOS QUE SEAN DE CARGO O RESPONSABILIDAD DE LA SOCIEDAD, YA SEA PARA EJECUTAR TRAMITES, INTERPONER RECURSOS, NOTIFICARSE DE ACTOS ADMINISTRATIVOS, ETC, Y EN GENERAL, PARA EJECUTAR TODA CLASE DE ACTUACIONES NECESARIAS PARA LA SOCIEDAD SIEMPRE ESTE ADECUADAMENTE REPRESENTADA EN TODO LO RELACIONADO CON IMPUESTOS NACIONALES, DEPARTAMENTALES O MUNICIPALES QUE DE CUALQUIER FORMA SE ENCUENTREN A CARGO DE O DE RESPONSABILIDAD DE LA MISMA.-------

CERTIFICA :

** REVISOR FISCAL: **

QUE POR ACTA NO. 0000047 DE ASAMBLEA DE ACCIONISTAS DEL 18 DE MARZO DE 2005 , INSCRITA EL 29 DE ABRIL DE 2005 BAJO EL NUMERO 00020221 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL	
CABRERA DELGADO Y PARDO LTDA CABADELPA LTDA	N.I.T.00830050795

QUE POR DOCUMENTO PRIVADO NO. 0000000 DE REVISOR FISCAL DEL 1 DE FEBRERO DE 2001 , INSCRITA EL 22 DE FEBRERO DE 2001 BAJO EL NUMERO 00016208 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

NOMBRE	IDENTIFICACION

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REVISOR FISCAL PRINCIPAL
REINA VIRGINIA PARDO DE D. C.C.00051671496
QUE POR DOCUMENTO PRIVADO NO. 0000001 DE REPRESENTACION LEGAL DEL 18 DE JUNIO DE 2003 , INSCRITA EL 2 DE JULIO DE 2003 BAJO EL NUMERO 00018395 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

NOMBRE IDENTIFICACION

REVISOR FISCAL SUPLENTE
NANCY PIDIACHE ALFONSO C.C.00052173939

CERTIFICA :

QUE EL 12 DE MARZO DE 2008 BAJO EL NRO. 23950 DEL LIBRO IX-, SE INSCRIBIO EN LA CAMARA DE COMERCIO UN DOCUMENTO PRIVADO DE FECHA 14 DE FEBRERO DE 2008, RELATIVO A LA MODIFICACION SITUACION DE CONTROL CAMBIO DE MATRIZ Y SUBORDINADAS.----------
QUE EL 12 DE FEBRERO DE 2001 BAJO EL NRO. 16164 DEL LIBRO IX-, SE INSCRIBIO EN LA CAMARA DE COMERCIO UN DOCUMENTO PRIVADO DE FECHA 23 DE ENERO DE 2001, RELATIVO A LA MODIFICACION AL PRESUPUESTO DE CONTROL EJERCIDO POR LABORATORIOS GENERICOS FARMACEUTICOS S.A.----------
-QUE EL 25 DE MARZO DE 1998, BAJO EL NRO: 12436 DEL LIBRO IX -, SE INSCRIBIO EN LA CAMARA DE COMERCIO UN DOCUMENTO PRIVADO DE FECHA 13 DE MARZO DE 1998, RELATIVO A LA DECLARACION DE UNA SITUACION DE CONTROL EN EL CUAL CONSTA:-----
MATRIZ: GENFAR S.A.----------
DOMICILIO:VILLA RICA----------
NACIONALIDAD:COLOMBIANA.----------
SUBORDINADA: GENFAR PERU S.A.----------
-DOMICILIO: LIMA PERU.----------
-NACIONALIDAD PERUANA .----------
-INSCRITA EN LA FICHA NO. 97996 CON PARTIDA ELECTRONICA NO. 00405752 DEL REGISTRO DE PERSONAS JURIDICAS DE LA OFICINA REGISTRAL DE LIMA Y CALLO, CON FECHA 16 DE ABRIL DE 1993.
-OBJETO SOCIAL: DEDICARSE A LA FABRICACION, IMPORTACION, EXPORTACION, DISTRIBUCION Y COMERCIALIZACION DE TODA CLASE DE PRODUCTOS FARMACEUTICOS Y QUIMICOS, ASI MISMO PODRA DEDICARSE A LA EXPORTACION, REPRESENTACION, DISTRIBUCION Y COMERCIALIZACION AL POR MAYOR O MENOR DE MATERIAL MEDICO QUIRURGICO, TAMBIEN PODRA REALIZAR TODAS LAS ACTIVIDADES CONEXAS A LOS OBJETOS NOMBRADOS.----------
-SUBORDINADA: LABORATORIOS GENERICOS ECUATORIANOS S.A.--------
-GENFAR ECUADOR .----------

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GENFAR S.A.

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL PAGINA No. 11
Fecha : 20080609 Hora : 09:44:27 Operacion: 01C04060901708C04060

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-DOMICILIO: GUAYAQUIL .----------

-NACIONALIDAD: ECUATORIANA .----------

-- REGISTRO MERCANTIL: INSCRITO EN EL REGISTRO MERCANTIL DEL CANTON GUAYAQUIL CON EL NO. 17908 EL 8 DE SEPTIEMBRE DE 1998 .----------

OBJETO SOCIAL: LA IMPORTACION, DISTRIBUCION Y VENTA DE MEDICAMENTOS PARA USO HUMANO Y VETERINARIO, MAQUINARIA, EQUIPOS Y PRODUCTOS MEDICOS, HOSPITALARIOS DE LABORATORIOS Y TODO LO AFIN PARA ESTA ACTIVIDAD .----

-PRESUPUESTO: LA SOCIEDAD MATRIZ O CONTROLANTE ES GENFAR S.A. Y LA RAZON QUE DA LUGAR A LA SITUACION DE CONTROL ES EL HECHO DE QUE EN LAS SOCIEDADES GENFAR PERU S. A. COMO EN LABORATORIOS GENERICOS FARMACEUTICOS ECUATORIANOS S. A. GENFAR ECUADOR SE TIENE UNA PARTICIPACION DEL 90 % Y DEL 10 0 % RESPECTIVAMENTE.----------

CERTIFICA :

CERTIFICA:
SUCURSAL (ES) O AGENCIA (S) MATRICULADAS ANTE ESTA JURISDICCION: NOMBRE DE LA AGENCIA:
GENFAR S.A.
MATRICULA: 389872.
DIRECCION: M/PARQUE C/VALAR BD 2 Y 3.
TELEFONO: 3289359.
DOMICILIO: BARRANQUILLA.

CERTIFICA :

QUE LA PERSONA JURIDICA TIENE MATRICULADOS LOS SIGUIENTES ESTABLECIMIENTOS :

NOMBRE : GENFAR
MATRICULA NO. 00049489
RENOVACION DE LA MATRICULA : EL 28 DE MARZO DE 2008
ULTIMO AÑO RENOVADO : 2008

CERTIFICA :

QUE NO FIGURAN INSCRIPCIONES ANTERIORES A LA FECHA DEL PRESENTE CERTIFICADO, QUE MODIFIQUEN TOTAL O PARCIALMENTE SU CONTENIDO.

!!! NOTIFICACION !!!

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LOS DOCUMENTOS DE REGISTRO AQUI CERTIFICADOS QUEDAN EN FIRME CINCO DIAS HABILES DESPUES DE SU INSCRIPCION EN EL LIBRO RESPECTIVO, SIEMPRE Y CUANDO NO SE PRESENTE NINGUN RECURSO POR LA VIA GUBERNATIVA.
LA INFORMACION SOBRE EMBARGOS DE ESTABLECIMIENTOS Y/O CONTRATOS SUJETOS A REGISTRO, SE SUMINISTRA EN "CERTIFICADOS DE MATRICULA" O "CERTIFICADOS ESPECIALES", RESPECTIVAMENTE.

VALOR DEL CERTIFICADO : $ 3200.00

DE CONFORMIDAD CON EL ARTICULO 12 DEL DECRETO 2150 DE 1995 LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.

EL SECRETARIO DE LA CAMARA DE COMERCIO,

MARIA HELENA CASTRO B.
Jefe de Registros Públicos

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Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 05-57688

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **557** DE

FECHA **31 DE OCTUBRE DE 2005** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **27 DE ENERO DE 2006**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO ____X____

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United States Patent [19]

Amin et al.

[11] Patent Number: 4,902,683

[45] Date of Patent: Feb. 20, 1990

[54] **CRYSTALLINE CEPHALOSPORIN HYDROHALIDE SALTS**

[75] Inventors: **Mahendra I. Amin**, Kalamazoo; **Jay A. Campbell**, Portage, both of Mich.

[73] Assignee: **The Upjohn Company**, Kalamazoo, Mich.

[21] Appl. No.: **312,401**

[22] Filed: **Feb. 17, 1989**

Related U.S. Application Data

[63] Continuation of Ser. No. 898,676, Aug. 21, 1986, abandoned, which is a continuation of Ser. No. 664,651, Oct. 25, 1984, abandoned.

[51] Int. Cl.[4] C07D 501/36; A61K 31/545

[52] U.S. Cl. 514/206; 540/227

[58] Field of Search 540/227; 514/206

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,464,367 8/1984 Labeeuw et al. 540/227

FOREIGN PATENT DOCUMENTS

2036746A 7/1980 United Kingdom .

Primary Examiner—Nicholas S. Rizzo

Attorney, Agent, or Firm—Martha A. Cox

[57] **ABSTRACT**

Crystalline hydrohalide salts of the cephalosporin antibiotic ceftiofur, processes for their manufacture, and pharmaceutical compositions containing one of these salts are provided.

13 Claims, No Drawings

Hydrochloric Acid, Reagent Grade q.s. adjust pH to approx.: 3.0
Water for Injection

Part II	Amount per Vial
Sterile Crystalline ceftiofur, hydrochloride in a 10 to 100 ml. glass vial	0.01 to 1.5 gm.

DIRECTIONS

Part I

All of the ingredients are dissolved in water, and pH adjusted to approximately 2.6 to 3.2, preferably about 3.0. Vehicle sterilized by filtration and packaged in appropriate glass vials.

Part II

Sterile crystalline ceftiofur hydrochloride is packaged aseptically in sterile vials or crystalline ceftiofur hydrochloride is first packaged and the final container(s) sterilized by Cobalt 60 irradiation.

EXAMPLE 10

Sterile Extemporaneous Parenteral Suspension

Sterile Vehicle Part I

Methylparaben: 1.0 to 2.7 gms.
Propylparaben: 0.1 to 0.5 gm.
Povidone: 1 to 10 gms.
Sodium Chloride Fine Crystals Reagent Grade: 0.5 to 10 gms.
20% Solution Hydrochloric acid q.s. adjust pH to approx.: 3.0
50% Solution Sodium Hydroxide q.s. adjust pH
Water for Injection q.s. adjust: 1000 ccs.

Part II	Amount per Vial
Sterile crystalline ceftiofur hydrochloride in a 10 to 100 ml. glass vial	0.01 to 1.5 gm.

DIRECTIONS

Part I

Methylparaben and propylparaben are dissolved in boiling water. Then all of the ingredients dissolved in water, and pH adjusted to approximately 2.6 to 3.2, preferably about 3.0. Vehicle sterilized by filtration and packaged in appropriate glass vials.

Part II

Sterile crystalline ceftiofur hydrochloride is packaged aseptically in sterile vials or crystalline ceftiofur hydrochloride is first packaged and the final container(s) shall be sterilized by Cobalt 60 irradiation.

EXAMPLE 11

Extemporaneous Parenteral Suspension (Aqueous)

Sterile Vehicle-Part I

Polyethylene Glycol 3350 NF: 5 to 120 gms.
Polyvinyl Pyrrolidone: 1 to 10 gms.
Quatresin ® myristyl gamma picolinium chloride: 0.1 to 2.0 gms.
Sodium Chloride, Fine Crystals Reagent Grade: 0.5 to 10 gms.
20% Solution Hydrochloric Acid q.s. adjust pH to approx.: 3.0
50% Solution Sodium Hydroxide q.s. to adjust pH to approx.: 3.0
Water for Injection q.s. adjust to: 1000 cc.

Part II	Amount per Vial
Sterile crystalline ceftiofur hydrochloride (milled or micronized) in a 10 to 100 ml. glass vial	0.01 to 1.5 gms.

DIRECTIONS

Part I

All of the ingredients are dissolved in water, and pH adjusted to approximately 2.6 to 3.2, preferably about 3.0. Vehicle sterilized by filtration and packaged in appropriate glass vials.

Part II

Sterile crystalline ceftiofur hydrochloride is packaged aseptically in sterile vials or crystalline ceftiofur hydrochloride is first packaged and the final container(s) are sterilized by Cobalt 60 irradiation.

EXAMPLE 12

Sterile Nonaqueous Parenteral Suspension

Crystalline ceftiofur hydrochloride (milled or micronized): 1 to 100 gms.
Chlorobutanol Anhydrous-preservative: 5.25 gms.
or:
Benzyl Alcohol: 9.25 gms.
Corn Oil Glyceryl Monostearate Gel
or
Cottonseed Oil Glyceryl Monostearate Gel: q.s. adjust

DIRECTIONS

Preservative is dissolved in sufficient oily gel to make 800 cc. Crystalline ceftiofur hydrochloride is added, and the suspension is colloid milled to a uniform consistency. Add sufficient gel to make 1000 mls. After packaging into glass vials, the suspension is sterilized by Cobalt 60 irradiation or by any other suitable method.

EXAMPLE 13

Sterile Nonaqueous Parenteral Suspension

Crystalline ceftiofur hydrochloride (milled or micronized): 1 to 100 gms.
Chlorobutanol Anhydrous: 5.25 gms.
or
Benzyl Alcohol: 9.25 gms.
Corn Oil USP q.s. adjust: 1000 cc.
or
Cottonseed oil q.s. adjust: 1000 cc.

DIRECTIONS

Preservative is dissolved in sufficient oil to make 800 cc. Crystalline ceftiofur hydrochloride is added, and the suspension is colloid milled to a uniform consistency to break the aggregates. Add sufficient amount of oil to make 1000 mls. Stir and package into glass vials. The suspension can be sterilized by Cobalt 60 irradiation or sterile crystalline ceftiofur hydrochloride can be added to sterile vehicle and manufactured following aseptic procedure(s).

EXAMPLE 14

Sterile Extemporaneous Parenteral Suspension (Nonaqueous Gel)-Controlled Release Formulation

Sterile Vehicle Part I	1000
Benzyl Alcohol - preservative	9.0 to 9.25 gms.
or	
Chlorobutanol	5.0 to 5.25 gms.
Corn Oil Glyceryl Monostearate Gel	1000 cc.
or	
Cottonseed Oil Glyceryl Monostearate Gel	1000 cc.
Part II	100 Vials
Crystalline ceftiofur hydrochloride (milled or micronized)	1 to 100 gms.

DIRECTIONS

Part I

Preservative is dissolved in sufficient gel, and the gel is filled into vials asceptically and the vials sealed. These vials will be packaged with the vials of Part II as companion package.

Part II

0.01 to 1.0 gm. of crystalline ceftiofur hydrochloride or sterilized crystalline ceftiofur hydrochloride is packaged in a sterile glass vial and the vials sealed. If the crystalline ceftiofur hydrochloride is non-sterile, then the packaged vials will be sterilized by Cobalt 60 irradiation.

Prior to dosing appropriate amounts of Part I diluent will be added to Part II sterile powder and shaken until homogeneous.

EXAMPLE 15

Sterile Extemporaneous Parenteral Suspension (Nonaqueous)

Sterile Vehicle Part I	1000
Benzyl Alcohol - preservative	9.0 to 9.25 gms.
or	
Chlorobutanol	5.0 to 5.25 gms.
Corn Oil, USP q.s. ad.	1000 cc.
or	
Cottonseed Oil, USP q.s. ad.	1000 cc.
Part II	100 Vials
Crystalline ceftiofur hydrochloride, (milled and micronized)	50 to 100 gms.

Part I

Preservative is dissolved in the oil, and the solution sterilized by filtration. The sterile solution is filled into vials and the vials sealed. These vials will be packaged with the vials of Part II as companion package.

Part II

0.5 to 1.0 gm. of crystalline ceftiofur hydrochloride or sterilized crystalline ceftiofur hydrochloride is packaged in a sterile glass vial and the vials sealed. If the crystalline ceftiofur hydrochloride is non-sterile, then the packaged vials will be sterilized by Cobalt 60 irradiation.

Prior to dosing appropriate amounts of Part I diluent will be added to Part II sterile powder and shaken until uniformly mixed.

EXAMPLE 16

Suppositories

Formulation for a 2 gm. suppository containing 62.5 mg. of crystalline ceftiofur hydrochloride is given. However, any size suppository can be manufactured using any amount of ceftiofur hydrochloride and appropriate amounts of excipients at the same ratio as indicated below.

	Lot Size 12
Crystalline ceftiofur hydrochloride (milled or micronized)	0.750 gm.
PEG-400	14.4 ml.
PEG-8000	9.6 gm.

DIRECTIONS

Measure out 14.4 ml. of PEG-400 and place in a container suitable for heating. Add 9.6 gms. of PEG-8000 (melting point 140° F.) to the PEG-400 solution and melt over a hot water bath approximately two minutes or until there is a clear solution.

Add crystalline ceftiofur hydrochloride and stir until dispersed. Pour the mix into the mold and let set. Chill the mold. Remove suppositories after they set up 15-30 minutes at room temperature. Sterile suppositories can be manufactured with sterile raw materials and observing aseptic conditions during manufacturing, or can be sterilized by Cobalt 60 irradiation.

EXAMPLE 17

Suppositories

Suppositories can also be manufactured from excipients such as cocoa butter, Suppocire TM AM, Suppocire AS_2, and Suppocire AT, Suppocire BT or Suppocire CT brand of C_8 to C_{10}-saturated fatty acid glycerides.

Formula for a 2 gm. suppository containing 62.5 mg. of crystalline ceftiofur hydrochloride is given; however, any size suppository can be manufactured using any desired amount of crystalline ceftiofur hydrochloride, and appropriate amount of excipient.

	Lot Size 12
Crystalline ceftiofur hydrochloride (milled or micronized) Sterile	0.750 gm.
Suppocire AM or AS_2, or AT, or BT or CT	23.25 gm.

DIRECTIONS

Weigh the Suppocire TM diluent in a container suitable for heating. Melt (45° C. temperature) over a hot water bath for approximately two minutes or until there is a clear solution (microwave oven can also be used instead of the water bath). Sterilize by filtration. Add sterile crystalline ceftiofur hydrochloride and stir until dispersed. Pour the mix into the cold mold. After two to four minutes, the surplus of the casting is eliminated by scraping. The temperature and time of cooling must be governed according to the type of formula. The circulating cold air should come in contact with all faces of the mold. Release from the mold must be gentle. Sterile suppositories can be manufactured with sterile raw

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United States Patent [19]

Patil et al.

[11] 4,299,501

[45] Nov. 10, 1981

[54] CONTINUOUS PROCESS FOR THE PREPARATION OF SEMISOLID DISPERSIONS

[75] Inventors: Deepak R. Patil, Livingston; Glenn A. VanBuskirk, Bernardsville, both of N.J.

[73] Assignee: Ortho Pharmaceutical Corporation, Raritan, N.J.

[21] Appl. No.: 65,665

[22] Filed: Aug. 10, 1979

[51] Int. Cl.³ B01F 13/00; B01F 15/02; B01F 15/06

[52] U.S. Cl. 366/349; 366/136; 366/144; 366/159

[58] Field of Search 366/349, 341, 22, 23, 366/24, 76, 91, 96, 136, 159, 144, 145, 149, 336

[56] References Cited

U.S. PATENT DOCUMENTS

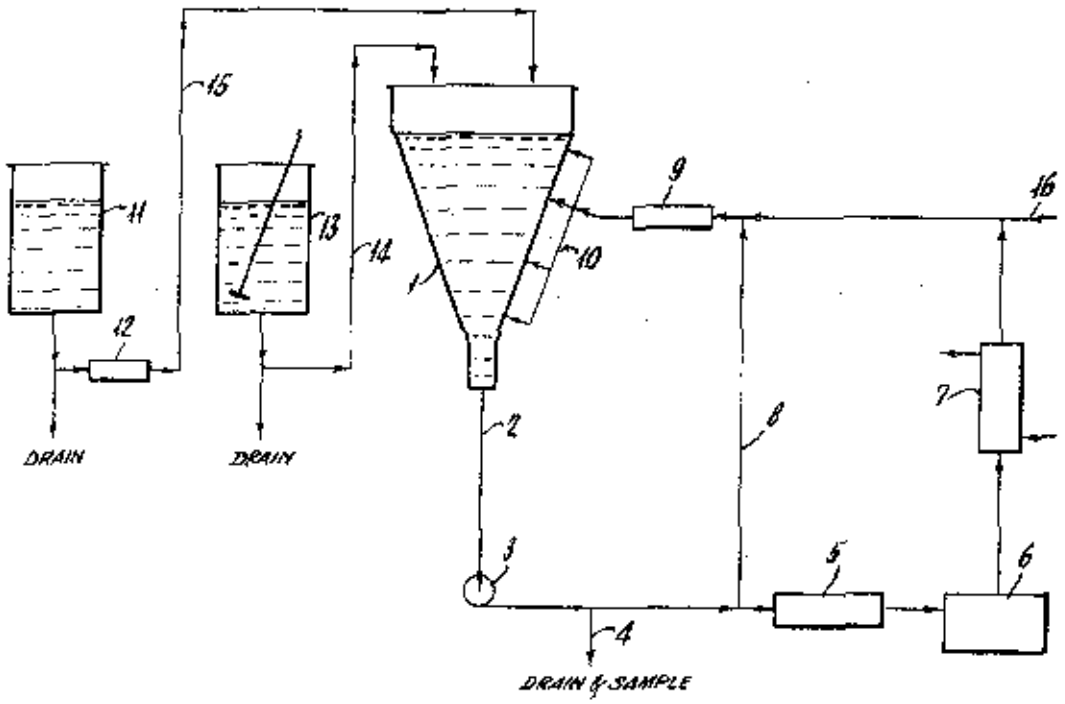
1,792,067	2/1931	Brown	366/76
2,389,012	11/1945	Trist	366/136
3,572,649	3/1971	Joel	366/136
3,784,169	1/1974	Bockmann	366/159

Primary Examiner—Edward J. McCarthy
Attorney, Agent, or Firm—Benjamin F. Lambert

[57] ABSTRACT

A semicontinuous or continuous process for preparing semisolid dispersions is provided wherein oil and water phases are circulated from a single vessel through a system of mixers and homogenizers until a dispersion is obtained.

6 Claims, 3 Drawing Figures



of the ingredients are not soluble in either phase, they can be suspended in the finished emulsion.

The aqueous phase generally includes about 70 to about 90% by weight of water and from about 10 to about 30% by weight of emulsifiers, emollients and/or preservatives. Other ingredients which can be present in the aqueous phase include antifoam agents, pharmaceutical materials, perfumes and dyes, for example.

An emulsifier can be included in the aqueous phase and/or the oil phase separately or mixed with the two phases. Emulsifiers suitable for use in the present process include those of the anionic, cationic and nonionic types, all of which are well known to those skilled in the art.

Other ingredients which can be included in either or both phases separately or mixed with the two phases include film-forming agents, astringents, deodorants, dyes, perfume, opacifiers, antifoam agents and solvents.

The advantages of the present invention over the prior art inventions include the elimination of extraneous tanks and agitation systems, elimination of transfer time required for mixing the oil and water phases, increased process control and greater process latitude. The latter two advantages are obtainable through subdivision of a complex manufacturing process into a series of unit operations which can be easily defined and controlled. The process described above is essentially a semicontinuous process, however, the process can be made continuous by adding to the main vessel an amount of the mixture of aqueous and oil phases equal to the amount of product withdrawn.

The following examples illustrate how the invention is carried into effect but is not meant to be limiting on the invention since it will be obvious to those skilled in the art how various changes can be made.

EXAMPLE 1

	% (w/w)
Aqueous Phase	
Purified Water	73.8
Benzoic Acid	0.2
Oil Phase	
Pegoxyl 7 Stearate	20.0
Peglicol 5 Oleate	3.0
Heavy Mineral Oil	3.0

Procedure

The pegoxyl 7 stearate, peglicol 5 oleate and heavy mineral oil are mixed while being melted and heated to 140° F. Hot purified water (120° F.) is transferred to the main vessel and circulated through the homogenizer. The benzoic acid is added to the water and the mixture is circulated until the benzoic acid is completely dissolved. The temperature of the solution stays at 120° F. The oil phase is added to the water phase and the temperature in the main vessel upon completion of the addition rises to 123° F. The two phases are circulated through the homogenizer until an emulsion is formed. The emulsion is withdrawn from the circulation system through a heat exchanger at a temperature of 90° F. Samples of the product are taken periodically from the batch as it passes through the heat exchanger.

EXAMPLE 2

Lubricating Jelly Ingredients	% (w/w)
CMC Type 7HF	1.35
Kelgin LV	1.08
Methylparaben	0.15
Propylene Glycol	3.75
Glycerin	11.25
Potassium Hydroxide	0.03
Boric Acid	3.00
Water	78.89

Procedure

The water (at 75° C.) and the boric acid are added into the main vessel. The mixture is circulated through the bypass loop until a solution is formed. To this solution, Kelgin LV is added and the mixture is circulated again until the Kelgin is completely dissolved.

In the slurry tank, a slurry of propylene glycol, glycerin, CMC and methylparaben is prepared. While the mixture is circulated through the homogenizer, the slurry is transferred to the main vessel and the circulation is maintained until a solution is formed. During this circulation period, the temperature of the jelly is maintained at 70° to 75° C. until all the solids are in solution.

This solution, with the aid of the heat exchanger, is cooled to 30° to 35° C. to form the lubricating jelly.

EXAMPLE 3

	% (w/w)
Aqueous Phase	
Purified Water	73.8
Benzoic Acid	0.2
Oil Phase	
Pegoxyl 7 Stearate	20.0
Peglicol 5 Oleate	3.0
Heavy Mineral Oil	3.0

Procedure

The pegoxyl 7 stearate, peglicol 5 oleate and heavy mineral oil are mixed while being melted and heated to 180° F. Hot purified water (180° F.) is transferred to the main vessel and circulated through the homogenizer. The benzoic acid is added to the water and the mixture is circulated until the benzoic acid is completely dissolved. The temperature of the solution drops to 165° F. The oil phase is added to the water phase and the temperature in the main vessel upon completion of the addition rises to 167° F. The two phases are circulated through the homogenizer until an emulsion is formed. The emulsion is withdrawn from the circulation system through a heat exchanger at a temperature of 110° F. Samples of the product are taken periodically from the batch as it passes through the heat exchanger.

EXAMPLE 4

A.	% (w/w)
Oil Phase	
Mineral Oil	25.0
Microcrystalline Wax	10.0
Ceryl Alcohol	5.0
Mixed Lanolin Alcohols	10.0
Sorbitan Sesquioleate	3.0

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
CARLOS R. OLARTE

ASUNTO		
	Radicación	05-057688
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	11633
	Folios	9

Patente de Invención	X	Patente de Modelo de Utilidad			
Vía Nacional					
Vía PCT (fase nacional)		Cap. I		Cap. II	X

No. Sol. Internacional PCT/US2003/039508
Fecha de Presentación Internal. Diciembre 11 de 2003

Como resultado del examen de fondo, realizado con fundamento en el articulo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1.	Descripciòn:	Folios: 50 a 87	como se radicó inicialmente
1.2.	Reivindicaciones:	Folios: 88 a 92	como se radicó inicialmente
1.3.	Prioridad:	US 60/434,985 del 19 de Diciembre de 2002 US 10/687,986 del 17 de Octubre de 2003	

2. Objeto de la invención

- Titulo: "COMPOSICIONES FARMACEUTICAS DISPERSABLES".

El objeto de la solicitud de la presente invención consiste en:

- Reivindicaciones 1 a 10: Composiciòn farmacéutica
- Reivindicaciones 11 a 12: Articulo de fabricación
- Reivindicaciones 13 a 16: Método de tratamiento

El problema planteado en esta solicitud es la necesidad de desarrollar composiciones farmacéuticas novedosas para ser usadas en el tratamiento de la mastitis; las cuales muestran estabilidad química y/o física prolongada.

Para resolver este problema técnico, la solicitud en estudio proporciona una composición farmacéutica y un artículo de fabricación.

- El objeto de la invención definido anteriormente se clasifico de acuerdo con la IPC: A61K 9/00

3. De la solicitud de Patente

3.1 Reivindicaciones (artículo 30 D 486)

- La Reivindicación 1; no es clara ni concisa, porque se relaciona con grupos de sustancias y no con un componente específico. Tener en cuenta que una composición se debe caracterizar por cada uno de sus componentes.

- Las Reivindicaciones 2, 3 5 y 7; las cuales son dependientes de la reivindicación 1, adolecen de la falta de claridad y concisión de la misma.

- Las Reivindicaciones 2 y 3; no están soportadas; porque la única sustancia antibacteriana mencionada en el capitulo descriptivo es el Ceftiofur (cefalosporina de tercera generación).

- La Reivindicación 1: la palabra y/o expresión: "sustancia antibacteriana", "aceite anfipático", "vehículo no acuoso"; no son precisas, por tanto no permiten delimitar la materia a proteger.

Por lo anteriormente expuesto, es preciso requerir al interesado para que señale el alcance de su invención.

4. Unidad de invención (artículo 25 D 486)

En las reivindicaciones 11 a 12, se considera que las partes que conforman el Artículo de fabricación que comprende un recipiente o dispositivo de distribución que tiene una pared permeable al oxigeno, y que contiene en su interior la composición no poseen una relación técnica entre sí, que las haga dependientes. Y que una parte necesite de la otra para poder coexistir y ser consideradas como un solo concepto inventivo. Ya que el Artículo de fabricación tienen varios grupos inventivos (folio 66 del capitulo descriptivo) como recipientes y dispositivos (jeringas), boquilla de cánula, el envase, el empaque, las instrucciones, los medios de dosificación, etc. Por tal razón se considera que el Artículo de fabricación no tiene unidad de invención.

En consecuencia esta Oficina recomienda que las reivindicaciones que no guardan unidad de invención en si mismas sean eliminadas del alcance de la invención.

5. Excepción a la patentabilidad (artículo 20 D486 literal d)

Las Reivindicaciones 13 a 16, reclaman método de tratamiento, y de acuerdo con la legislación Colombiana, éstos no se consideran para protección por patente.

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6. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

- Fecha de presentación de la solicitud prioritaria: Diciembre 19 de 2002

Teniendo en cuenta la fecha indicada se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud; aclarando, que esta búsqueda se realizo únicamente para aquellas partes que parecen ser claras y/o concisas:

Nº	Documento	Titulo	Fecha de publicación
D1	US 4,902,683	CRYSTALLINE CEPHALOSPORIN HYDROHALIDE SALTS	Febrero 20 de 1990
D2	US 4,299,501	CONTINUOS PROCESS FOR THE PREPARATION OF SEMISOLID DISPERSIONS	Noviembre 10 de 1981

7. Análisis de patentabilidad (artículo 14 D486)

7. 1 Nivel inventivo (artículo18 D486)

- Reivindicación 1: Composición farmacéutica

CARACTERISTICAS ESENCIALES DE LA SOLICITUD COLOMBIANA No. 05-057688	D1 = US 4,902,683	D2 = US 4,299,501
Composición farmacéutica, que comprende:	Composición farmacéutica, que comprende:	Composición farmacéutica, (dispersión semisòlida)que comprende:
a. Aceite anfipático	a. Aceite anfipático: (aceite de mono estearato de glicerilo)	a. Aceite anfipático (5 oleato de peglicol)
b. Cera microcristalina		b. Cera microcristalina
c. Vehiculo no acuoso	c. Vehículo no acuoso (Aceite de semilla de algodón)	
d. Sustancia antibacteriana	d. Sustancia antibacteriana (Ceftiofur)	
	Columnas 12 y 13 del Documento.	Columnas 3 y 4 del Documento.

Composición Farmacéutica:

El estado de la técnica más cercano es D1, ya que divulga una composición farmacéutica estable, para aplicación vía parenteral entre otras; y la cual se utiliza como antibiótico para tratar infecciones bacterianas en animales.

La solicitud se diferencia de D1, en que ésta, contiene cera microcristalina; mientras que la anterioridad no.

No hay evidencia de una ventaja técnica, por la presencia de la cera microcristalina; ni tampoco hay evidencia, que la composición farmacéutica reclamada sea más estable física y químicamente.

El Problema Técnico Objetivo de esta solicitud es desarrollar composiciones farmacéuticas alternativas para ser usadas en el tratamiento de la mastitis.

D2 divulga preparaciones de dispersiones semisólidas, las cuales contienen ingredientes como lo es la cera microcristalina.

Por tal razón, la solicitud como esta reivindicada se considera obvia, porque para un experto en la materia que tenga que desarrollar composiciones farmacéuticas alternativas y conozca las composiciones divulgadas en D1, incluiría la cera microcristalina de D2, para obtener la composición de la invención.

Por tanto, la composición farmacéutica reclamada en las reivindicaciones 1 a 10, no tiene Nivel Inventivo.

8. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	US 4,902,683	1 a 10	Nivel Inventivo
D2	US 4,299,501	1 a 10	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiendo que contra él no procede recurso alguno en la vía gubernativa.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 16 OCT. 2009

CONCEPTO TÉCNICO No. 2125	EXAMINADOR TÉCNICO Código No. 202080

090610

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Industria y Comercio
SUPERINTENDENCIA

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 009182

Por la cual se niega una patente de invención

Rad. PCT/05-57688

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
En ejercicio de sus facultades legales, en especial de las que se confirieron en el artículo 3, numeral 30 del decreto 3523 de 2009, y

CONSIDERANDO:

PRIMERO: Que la solicitud de patente de invención titulada "COMPOSICIONES FARMACEUTICAS DISPERSABLES", que corresponde a la solicitud internacional PCT/US2003/039508 de fecha 11 de diciembre del 2003, fue radicada en esta Superintendencia el 15 de junio del 2005 bajo el número 05-057688 -00000-0000, para que se iniciara la fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

SEGUNDO: Que efectuado el examen de forma en cuanto a los requisitos que debe llenar la solicitud y cumplidas las exigencias legales, se ordenó publicar el extracto sin que se hubieran presentado oposiciones por parte de terceros.

TERCERO: Que el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: *"Si la oficina nacional competente encontrara que la invención no es patentable* o que no cumple con alguno de los requisitos establecidos en esta Decisión para *la concesión de la patente, lo notificará al solicitante. Este deberá responder a la notificación dentro del plazo de sesenta días contados a partir de la fecha de la notificación. Este plazo podrá ser prorrogado por una sola vez por un período de treinta días adicionales.(...) Si el solicitante no respondiera a la notificación dentro del plazo señalado, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, la oficina nacional competente denegará la patente".*

CUARTO: Que realizado el examen de fondo, se requirió al solicitante en los términos del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, para que presentara respuesta a las observaciones de carácter técnico visibles a folios 150 a 156 del cuaderno administrativo, relacionadas con la patentabilidad o cumplimiento de los requisitos establecidos por esta Decisión para la concesión de la patente. Frente a dicho requerimiento no hubo pronunciamiento alguno por parte del solicitante, por lo cual es procedente negar el privilegio de patente solicitado con fundamento en lo dispuesto en el artículo 45 de la Decisión 486.

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Industria y Comercio
SUPERINTENDENCIA

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 009182

Por la cual se niega una patente de invención

Rad. PCT/05-57688

RESUELVE:

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "COMPOSICIONES FARMACEUTICAS DISPERSABLES", que entró en fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente al doctor Carlos Reinaldo Olarte García, en su calidad de apoderado de PHARMACIA & UPJOHN COMPANY, o a quien haga sus veces, entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los 19 FEB. 2010

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO (E),

GIANCARLO MARCENARO JIMENEZ

Doctor
CARLOS REINALDO OLARTE GARCIA
Diagonal 34 No. 5-28
Bogotá D.C.