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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: Expediente No. 06.073.023

Solicitud de patente de invención titulada:

"CONSERVANTES ANTIMICROBIANOS PARA LOGRAR UNA FORMULACION DE DOSIS MULTIPLES USANDO CICLODEXTRINAS B PARA FORMAS DE DOSIFICACION LIQUIDAS".

Solicitante: PFIZER PRODUCTS INC.

N. Ref.: P2006/000126

RESPUESTA AL OFICIO No. 211 NOTIFICADO POR FIJACIÓN EN LISTA No. 07,
DE FECHA 8 DE ENERO DE 2010
(PRIMER EXAMEN DE FONDO)

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 45 de la Decisión 486, en los siguientes términos:

1. En primer lugar, y con el ánimo de brindar mayor claridad a la materia reivindicada, me permito presentar un **Capítulo Reivindicatorio Modificado**, que reemplaza en su totalidad al Capítulo Reivindicatorio presentado al momento de radicar esta solicitud.

Así, del Capítulo Reivindicatorio Modificado se eliminaron las Reivindicaciones 8 a 10 y la nueva Reivindicación 1 ahora incluye la limitación de la antigua Reivindicación 4.

Valga anotar que las modificaciones efectuadas al Capítulo Reivindicatorio cumplen a cabalidad con lo estipulado en el Artículo 34 de la Decisión 486, ya que éstas de ninguna manera implican una ampliación de la protección correspondiente a la divulgación contenida en la solicitud inicial.

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2. a- El Examinador argumenta que las Reivindicaciones 8 a 10 no son patentables porque reclaman usos y métodos de tratamiento.

b- Considero superada la anterior objeción en tanto que las Reivindicaciones 8 a 10 han sido eliminadas del Capítulo Reivindicatorio Modificado.

3. a- El Examinador señala que la patente US2003/0139443 (D1) afecta la novedad y el nivel inventivo de la presente invención.

El Examinador argumenta que D1 revela composiciones líquidas que comprenden un antagonista del receptor NK-1 (o sus sales), un preservativo (PEG), un vehículo (glicerina) y una β -ciclodextrina (sulfobutileter ciclodextrina). Por lo anterior, el Examinador concluye que la materia reivindicada no es nueva.

El Examinador también anota que las Reivindicaciones 5 a 7, que reclaman cantidades específicas de ingredientes en las composiciones de la invención no son inventivas, porque una persona medianamente versada en la materia podría formular composiciones con diferentes cantidades de ingredientes.

b- i) En primer lugar, deseo llamar la atención al hecho que el Capítulo Reivindicatorio Modificado reclama composiciones farmacéuticas que específicamente contienen: (i) una cantidad terapéuticamente efectiva de un ingrediente farmacéutico, (ii) una ciclodextrina farmacéuticamente aceptable y (iii) un preservativo farmacéuticamente aceptable seleccionado entre timerosal, propilenglicol, fenol o meta-cresol o una combinación de éstos. El ingrediente activo preferido es un compuesto de Fórmula I (Reivindicación 2) y la β ciclodextrina preferida es 2-hidroxipropil o sulfobutileter- β ciclodextrina (Reivindicación 3).

Las formulaciones de la presente invención que contienen ciclodextrina proporcionan una solubilidad ~~del~~ aumentada del compuesto activo y una tolerancia mejorada en el sitio de inyección, manteniendo al mismo ^{tiempo} inalterada la actividad de los preservativos.

ii) Ahora bien, en cuanto a D1, este documento no revela composiciones que, además del compuesto activo y de la ciclodextrina, comprendan los preservativos de las composiciones reclamadas en la nueva Reivindicación 1.

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En este punto, es importante recordar que para fundamentar una afectación válida contra la novedad de una invención, el arte previo debe divulgar explícitamente todas y cada una de las características de la invención.¹ Es más, el Tribunal Andino de Justicia ha determinado que para establecer una objeción de novedad válida, la divulgación del arte previa debe ser lo suficientemente completa para que una persona versada en la materia pueda usar dicha información para reproducir y explotar la invención.² En el presente caso, D1, al no divulgar todos y cada uno de los componentes de las composiciones reivindicadas, no puede afectar su novedad.

iii) En cuanto al nivel inventivo de la presente invención, debo señalar que D1 no sugiere el empleo de preservativos en formulaciones que comprenden compuestos de Formula I y ciclodextrinas. Por lo tanto, una persona medianamente versada en la materia con la tarea de desarrollar formulaciones de un antagonista del receptor de NK-1 de Formula I que incluyan ciclodextrinas, con el ánimo específico de mejorar la solubilidad, no hubiera encontrado en D1 ninguna sugerencia sobre cómo evitar la complejación entre los preservativos y las β -ciclodextrinas y así evitar los problemas asociados a la ineffectividad de los antimicrobianos.

Así entonces, nada en D1 proporciona enseñanzas que hubiesen conducido a la persona medianamente versada en la materia a determinar el balance óptimo entre una concentración suficiente de ciclodextrina (ej. SBE-CD que presente una reacción tolerable en el sitio de inyección) y el preservativo antimicrobiano (ej. meta-cresol). De hecho, es bien conocido en el campo de las formulaciones farmacéuticas que la ciclodextrina se compleja tanto con ingredientes activos como con preservantes antimicrobianos, afectando así la estabilidad, la eficacia y la efectividad de los preservativos. Otros documentos del arte previo, no citados por el Examinador, enseñan que los preservativos a base de fenol halogenado no causan precipitación del complejo de inclusión *farmaco/ciclodextrina/preservante* (EP0119737). Adicionalmente, el documento WO00/12137 revela que los preservantes típicos se complejan con ciclodextrinas y por lo tanto sugiere emplear dióxido de cloro (chlorine dioxide), ácido sórbico, sorbatos de metales alcalinos, a concentraciones cercanas al 1% (p/v) como preservantes, los cuales no forman complejos con el componente de ciclodextrina.

Por lo tanto, una persona versada en la materia con la información disponible en el estado del arte a la fecha de presentación de la invención se vería motivada a excluir de formulaciones que contienen ciclodextrina, aquellos preservantes diferentes a fenoles halogenados y a incluir

¹ Manual Andino de Patentes, OMPI 2004. ISBN9978-43-855-6. Sección 9.4.

² Proceso 06-IP-89 ([http://intranet.comunidadandina.org/Documentos/Procesos/209-\(P-2005.doc\)](http://intranet.comunidadandina.org/Documentos/Procesos/209-(P-2005.doc)));

y Proceso 36-IP-2004 (<http://www.notinet.com.co/serverfiles/servicios/archivos/30jul04/ca36-04.htm>)

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aquellos sugeridos en el documento WO00/12137. Nada en D1 o en el estado del arte sugiere el empleo de preservativos típicos como el metacresol en una composición que comprende β -ciclodextrinas y un compuesto antagonista NK1 de Fórmula I.

Para hacer esto más claro llamo la atención del Examinador a la Descripción en donde se ilustran los estudios de unión, solubilidad, selección de preservantes que debieron realizarse para llegar a las composiciones de la presente invención.

4. Por último, me permito señalar que la materia reclamada en la presente solicitud ha sido concedida en Sudáfrica (2006/05148); Australia (2005216709), Canadá (2554346), Korea del Sur (834232), Rusia (2332997), Singapur (P-124084).

Si bien es cierto que las concesiones de patentes en oficinas de otros países no son vinculantes en el sentido que obliguen a la SIC a tomar una decisión en el mismo sentido, considero que dichas concesiones sugieren el cumplimiento de los requisitos de patentabilidad de la materia reivindicada, ya que los criterios de evaluación y estudio aplicados para concluir la aceptación de dichas patentes resultan equivalentes a los que la SIC debe emplear.

5. Por todo lo anterior, considero que las objeciones presentadas por el Examinador en su examen de fondo No. 4209 han sido resueltas y por consiguiente, solicito respetuosamente se e tengan por cumplidos los requisitos de patentabilidad en tanto no se desvirtuó ninguno de ellos por parte del Despacho, y se proceda con la concesión de la patente.

Atentamente,



CARLOS R. OLARTE

C.C. No. 79.782.747 de Bogotá

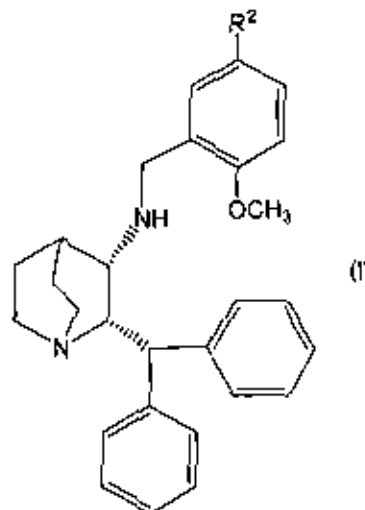
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Anexos:

- Capítulo Reivindicatorio Modificado

CAPITULO REIVINDICATORIO MODIFICADO
(Primer Examen de Fondo)

1. Una composición farmacéutica parenteral, que comprende:
una cantidad terapéuticamente efectiva de un compuesto de Formula (I)



donde R^2 es tert-butyl; o una sal farmacéuticamente aceptable del mismo;

una β -cyclodextrina;

un preservante farmacéuticamente aceptable que es metacresol; y

un vehiculo farmacéuticamente aceptable;

de manera que dicha composición no genera reacción en el sitio de inyección y proporciona efectividad preservante farmacéuticamente aceptable.

2. La composición farmacéutica de acuerdo con las Reivindicación 1 donde la sal es una sal de citrato monohidrato.

3. La composición farmacéutica de acuerdo con las Reivindicación 2 donde la β -cyclodextrina es sulfobutileter- β -cyclodextrina.

4. La composición farmacéutica de acuerdo con las Reivindicación 3 en la que entre 1 mg/mL y 5 mg/mL del preservante no se encuentra secuestrado en la ciclodextrina.

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5. La composición farmacéutica de acuerdo con las Reivindicación 4 en la que el preservante presenta un valor de unión a la ciclodextrina que es menor que el valor de unión del compuesto a la ciclodextrina.

6. La composición farmacéutica de acuerdo con las Reivindicación 5 en la que el valor de unión del compuesto a la ciclodextrina es entre 500M^{-1} y 10.000M^{-1} .

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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: USE OF SULFOALKYL ETHER CYCLODEXTRIN AS A PRESERVATIVE

(57) Abstract: A method of preserving formulations is provided. The method includes the step of including a derivatized cyclodextrin in a formulation capable of sustaining microbial growth. One embodiment of the formulation employs a sulfoalkyl ether cyclodextrin as a preservative and optionally as a solubilizing and complexing agent. A suitable cyclodextrin is the CAPTISOL® brand cyclodextrin (sulfobutyl ether β-cyclodextrin). Whether or not the formulation includes a conventional preservative, the formulation will remain preserved for at least a minimum predetermined period. Specific embodiments of the invention include a carrier, a derivatized cyclodextrin and optionally one or more active agents, one or more water activity-reducing agents, and/or one or more complexation-enhancing agents. The derivatized cyclodextrin reduces the water activity of the formulation. A liquid formulation can be lyophilized or otherwise dried to yield a solid formulation that is optionally reconstitutable.

WO 03/080079 A1

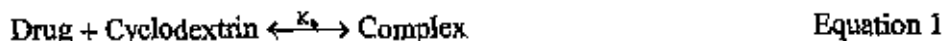
- 2 -

based and lipid-based formulations are particularly prone to contamination by microbes and always require a conventional preservative in order to maintain an acceptable shelf life.

Lipid-based emulsion formulations are typically problematic with regard to microbial growth, not only because the lipid components can readily support the growth, but because 0.22 μm or smaller "sterilizing" filters cannot be used. A filter pore size of ≥ 5 μm is generally recommended for emulsion formulations.

Cyclodextrins are cyclic carbohydrates derived from starch. The unmodified cyclodextrins differ by the number of glucopyranose units joined together in the cylindrical structure. The parent cyclodextrins contain 6, 7, or 8 glucopyranose units and are referred to as α -, β -, and γ -cyclodextrin respectively. Each cyclodextrin subunit has secondary hydroxyl groups at the 2 and 3 positions and a primary hydroxyl group at the 6-position. The cyclodextrins may be pictured as hollow truncated cones with hydrophilic exterior surfaces and hydrophobic interior cavities. In aqueous solutions, these hydrophobic cavities provide a haven for hydrophobic organic compounds that can fit all or part of their structure into these cavities. This process, known as inclusion complexation, may result in increased apparent aqueous solubility and stability for the complexed drug. The complex is stabilized by hydrophobic interactions and does not involve the formation of any covalent bonds.

This dynamic and reversible equilibrium process can be described by Equations 1 and 2, where the amount in the complexed form is a function of the concentrations of the drug and cyclodextrin, and the equilibrium or binding constant, K_b . When cyclodextrin formulations are administered by injection into the blood stream, the complex rapidly dissociates due to the effects of dilution and non-specific binding of the drug to blood and tissue components.



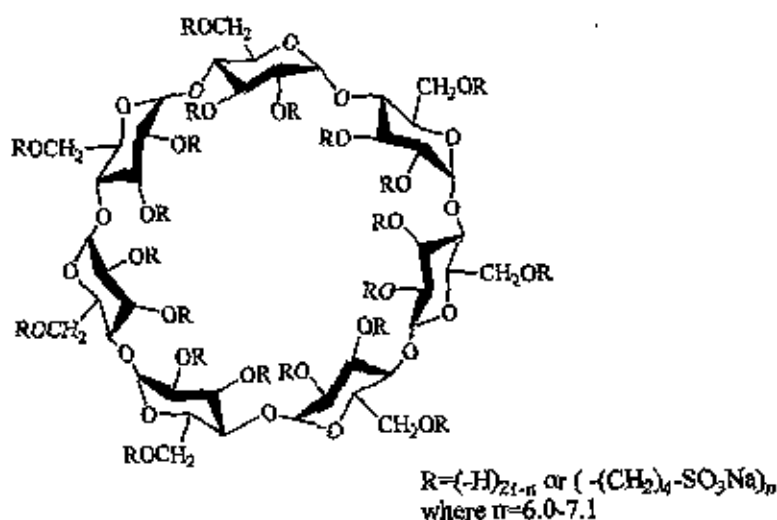
$$K_b = \frac{[\text{Complex}]}{[\text{Drug}][\text{Cyclodextrin}]} \quad \text{Equation 2}$$

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Binding constants of cyclodextrin and an active agent can be determined by the equilibrium solubility technique (T. Higuchi et al. in "Advances in Analytical Chemistry

and Instrumentation Vol. 4"; C.N. Reilly ed.; John Wiley & Sons, Inc, 1965, pp. 117-212). Generally, the higher the concentration of cyclodextrin, the more the equilibrium process of Equations 1 and 2 is shifted to the formation of more complex, meaning that the concentration of free drug is generally decreased by increasing the concentration of cyclodextrin in solution.

The underivatized parent cyclodextrins are known to interact with human tissues and extract cholesterol and other membrane components, particularly upon accumulation in the kidney tubule cells, leading to toxic and sometimes fatal renal effects. Chemical modification of the parent cyclodextrins (usually at the hydroxyls) has resulted in derivatives with improved safety while retaining or improving the complexation ability. Of the numerous derivatized cyclodextrins prepared to date, only two appear to be commercially viable: the 2-hydroxypropyl derivatives (HP-CD; neutral cyclodextrins being commercially developed by Janssen and others), and the sulfoalkyl ether derivatives, such as *sulfobutyl ether*, (SBE-CD; anionic cyclodextrins being developed by CyDex, Inc.) However, the HP- β -CD still possesses toxicity that the SBE-CD does not.



Sulfobutyl Ether- β -Cyclodextrin (Captisol[®])

A sulfobutyl ether derivative of beta cyclodextrin (SBE- β -CD), in particular the derivative with an average of about 7 substituents per cyclodextrin molecule, is being commercialized by CyDex, Inc. as CAPTISOL[®]. The anionic sulfobutyl ether substituent dramatically improves the aqueous solubility of the parent cyclodextrin. In addition, the

presence of the charges decreases the ability of the molecule to complex with cholesterol as compared to the hydroxypropyl derivative. Reversible, non-covalent, complexation of drugs with CAPTISOL[®] cyclodextrin generally allows for increased solubility and stability of drugs in aqueous solutions. While CAPTISOL[®] cyclodextrin is a relatively new but known cyclodextrin, its use as a preservative has not previously been evaluated.

Hemolytic assays are generally used in the field of parenteral formulations to predict whether or not a particular formulation is likely to be unsuitable for injection into the bloodstream of a subject. If the formulation being tested induces a significant amount of hemolysis, that formulation will generally be considered unsuitable for administration to a subject. It is generally expected that a higher osmolality is associated with a higher hemolytic potential. As depicted in FIG. 1 (Thompson, D.O., *Critical Reviews in Therapeutic Drug Carrier Systems*, (1997), 14(1), 1-104), the hemolytic behavior of the CAPTISOL[®] cyclodextrin is compared to the same for the parent β -cyclodextrin, the commercially available hydroxypropyl derivatives, ENCAPSIN[™] cyclodextrin (degree of substitution~3-4) and MOLECUSOL[®] cyclodextrin (degree of substitution~7-8), and two other sulfobutyl ether derivatives, SBE1- β -CD and SBE4- β -CD. Unlike the other cyclodextrin derivatives, sulfoalkyl ether (SAE-CD) derivatives, in particular those such as the CAPTISOL[®] cyclodextrin (degree of substitution~7) and SBE4- β -CD (degree of substitution~4), show essentially no hemolytic behavior and exhibit substantially lower membrane damaging potential than the commercially available hydroxypropyl derivatives at concentrations typically used to solubilize pharmaceutical formulations. The range of concentrations depicted in the figure includes the concentrations typically used to solubilize pharmaceutical formulations and provide preserving activity when initially diluted in the blood stream after injection.

The osmolality of a formulation is generally associated with its hemolytic potential: the higher the osmolality (or the more hypertonic), the greater the hemolytic potential. Zannou et al. ("Osmotic properties of sulfobutyl ether and hydroxypropyl cyclodextrins", *Pharma. Res.* (2001), 18(8), 1226-1231) compared the osmolality of solutions containing SBE-CD and HP-CD. As depicted in FIG. 2, the SBE-CD containing solutions have a greater osmolality than HP-CD containing solutions comprising similar concentrations of cyclodextrin derivative. Thus, it is surprising that SAE-CD exhibits lower hemolysis than does HP-CD at equivalent concentrations, even though HP-CD has a lower osmolality.

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Methylated cyclodextrins have been prepared and their hemolytic effect on human erythrocytes has been evaluated. These cyclodextrins were found to cause moderate to severe hemolysis (Jodal et al., *Proc. 4th Int. Symp. Cyclodextrins*, (1988), 421-425; Yoshida et al., *Int. J. Pharm.*, (1988), 46(3), 217-222).

5 Cyclodextrins have been used widely in all different types of cosmetic, food and pharmaceutical formulations. The underivatized α -cyclodextrin and β -cyclodextrin are the most widely used cyclodextrins. Cyclodextrins, however, are not generally known for their ability to preserve formulations. For this reason, preservatives are typically added to cyclodextrin containing formulations. Most preservatives complex to some degree with
10 cyclodextrins, and in some cases, only the uncomplexed fraction is available to act as a preservative. However, since many of the preservatives are poorly soluble in aqueous systems, the complexation can assist in providing constant levels of the preservative in the formulation.

Japanese Patent Application JP 2001029054 discloses a food formulation
15 comprising a complex of cyclodextrin and a volatile preservative. Japanese Patent Application JP 2002029901 discloses a film used for food packaging, wherein the film comprises a known preservative complexed with a cyclodextrin. Japanese Patent Application JP 2002281894 discloses a preservative comprising an inclusion complex of hinokitiol and cyclodextrin for use in lining packages of fruits and vegetables. Japanese
20 Patent Applications JP 2000004854, JP 11089548, JP 11130608, JP 10147380, and JP 09299458 disclose a preservative comprising an inclusion complex of isothiocyanate and cyclodextrin for use in lining packages of food. Japanese Patent Application JP 2000302601 discloses a preservative comprising an inclusion complex of 2-octyl-4-isothiazolin-3-one and cyclodextrin for use in a sprayable paint. European Patent
25 Application EP 895718 to Wimmer et al. discloses a microbicidal formulation comprising an isothiazolinone and β -cyclodextrin complex. Japanese Patent Application JP 11279139 discloses a complex comprising diiodomethyl p-tolyl sulfone with methyl- β -cyclodextrin as a microbicidal agent. Japanese Patent Application JP 11276135 discloses a film for preserving, wherein the film includes a complex comprising thiamine lauryl sulfate and maltosyl cyclodextrin. Japanese Patent Application JP 11228302 discloses a complex
30 comprising 2-(4-thiazolyl)benzimidazole (a preservative) and a cyclodextrin for preserving food. Japanese Patent Application JP 11151288 discloses a complex comprising a silver-protein complex complexed with hydroxypropyl cyclodextrin for use

biocides to inactive their antimicrobial activity. Loftsson et al. (*Drug Development Indust. Pharm.* (1992), 18(13), 1477-84) and Lehner et al. (*International J. Pharmaceutics* (1993), 93(1-3), 201-208) disclose that hydroxypropyl cyclodextrin reduces the antimicrobial activity of a range of preservatives, and the preservatives displace a drug that is complexed with the cyclodextrin thereby reducing the solubilizing effect of the cyclodextrin.

Since cyclodextrins are carbohydrate-based, they too might serve as a food source for microbes. Indeed, Japanese Patent Application JP 2001112465 discloses a method of promoting the growth of microorganisms by including a natural or derivatized cyclodextrin and another polysaccharide in the medium.

Sikorski et al. (U.S. Pregrant Patent Application Publication No. 2002/0187960) discloses a method of inhibiting microbial growth in liquid formulations containing cyclodextrin. Sikorski et al. require that the formulations, which may contain HPCD, possess an alkaline pH or an added antimicrobial agent.

Water availability is one of the most important factors affecting the growth of microorganisms and is generally expressed in physical terms as water activity. Water activity, abbreviated a_w , is a ratio of the water vapor pressure of the air over the substance or solution divided by the vapor pressure of pure water at the same temperature ($a_w = P_{\text{product}} / P_{\text{water}}$). Thus the value of a_w varies between 0 and 1. Bacteria, yeasts, and molds require a certain amount of available water to support growth. Therefore, by lowering the water activity the proliferation of these microorganisms can be controlled. Growth of most bacteria can be stopped by lowering the water activity to 0.80. Yeasts and molds tend to be more resistant to water activity and therefore it is generally necessary to lower the water activity to 0.70-0.75 to prevent growth. More specifically, the water activity range generally recognized as the lower limit necessary to prevent the growth of the microorganisms commonly used for challenging pharmaceutical products during preservative effectiveness testing are listed in the table below.

Microorganism	a_w range
<i>Pseudomonas aeruginosa</i>	0.97-0.95
<i>Escherichia coli</i>	0.96-0.95
<i>Staphylococcus aureus</i>	0.86-0.80
<i>Candida albicans</i>	0.87
<i>Aspergillus niger</i>	0.80-0.77

The minimum a_w for growth of the microorganisms is generally determined by the addition of salt. It is recognized that the minimum a_w values for growth prevention with other solutes may be different.

Lowering the a_w of a product can be thought of as "binding-up" moisture. In other words, water is still present, however, it is just not readily available to be used for biological processes. Thus, substantial moisture can stay in the product, as long as it is bound-up somehow. Binding of the free water can be achieved by the addition of solutes such as glycerin, alcohol, sugar, sugar-alcohol, salt or sugar-salt combinations.

When a bacterial cell is placed in a solution with low water activity, the cell dehydrates and bacterial growth is inhibited. It is generally recognized, according to the principles of thermodynamics, that water activity is the driving force behind dehydration. Donald Orth, Ph.D., in the book Preservative-Free and Self-Preserving Cosmetics and Drugs (1997, Marcel Dekker, New York), discusses various different conventional preservatives and a "preservative system." Lehner et al. (*Pharm. Ind.* (1994), 56(10), 911-914) disclose the biostatic/biocidal activity of HPCD.

Humectants and other water activity-reducing agents are often added to food, drug or cosmetic formulations in order to reduce the water activity of and preserve the formulations. A number of scientific publications discuss the effect that poly(ethylene glycol) has upon the water activity of aqueous compositions. Ambrose et al. (*Antimicrobial Agents and Chemotherapy* (1991), 35(9), 1799-1803) disclose a composition comprising sucrose or xylose and PEG 400 and H_2O_2 . An antibacterial effect against *Staphylococcus aureus* was observed in the presence and absence of H_2O_2 . Eliassi et al. (*Journal of Chemical and Engineering Data* (1999), 44(1), 52-55; *European Polymer Journal* (2001), 37(7), 1487-1492) and Ninni et al. (*Thermochimica Acta*, (22 MAR 1999), 328(1-2), 169-176) disclose the results of studies on the water activity of solutions containing differing amounts of PEG. Vaamonde et al. (*J. Food Sci.* (1982) 47(4), 1259-1262; *J. Food Sci.* (1984), 49(1), 296-297) disclose the results of studies on the effect that solutes such as L-proline, L-lysine, β -alanine, sorbitol, KCl, sodium lactate and PEG have on the growth of *S. aureus*. No growth was observed in any case when the water activity was at or slightly below a_w 0.86. Chirife et al. (*Antimicrobial Agents and Chemotherapy*, (1983 Sep) 24(3), 409-412) disclose that concentrated polyethylene glycol 400 solutions have significant antibacterial activity against various pathogenic bacteria including *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, and

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Staphylococcus aureus. Voilley et al. (*Lebensmittel-Wissenschaft und -Technologie* (1989), 22(1), 32-38) disclose the results on the reduction of water activity in aqueous solutions of sugars (glucose, maltose, maltotriose) or PEG 35,000.

Although artisans have recognized that poly(vinylpyrrolidone) (PVP) and poly (ethylene glycols) can have an impact on the water activity of aqueous solutions, no work has been done to evaluate their water activity in combination with cyclodextrins, or their potential use as a preservative. Jellinek et al. (*Kolloid Z. Z. Polym.* (1967), 220(2), 122-133) disclose the results of studies on the effect that PVP has upon freezing of water.

Given the fact that many conventional preservatives complex with cyclodextrins, it would be extremely beneficial to identify a cyclodextrin derivative that possesses biostatic, (inhibiting the growth of microorganisms), or biocidal, (destroying microorganisms,) properties on its own, i.e., in the absence of a conventional preservative. As noted above, in the field of preservatives for cosmetic, food or pharmaceutical use, there has not been identified any particular cyclodextrin derivative that possesses antimicrobial activity in aqueous solutions in the absence of an additional added conventional preservative. A need remains in the art for simplified aqueous formulations that remain preserved in the absence of a conventional preservative. A need also remains for a preserved pharmaceutical formulation containing a cyclodextrin complexed with a drug, wherein the formulation excludes a conventional pharmaceutical preservative. A need also remains for a formulation comprising an active agent, a cyclodextrin and a conventional preservative, wherein the cyclodextrin does not reduce the activity of the preservative or wherein the antimicrobial activity of the formulation is not reduced.

SUMMARY OF THE INVENTION

The present invention seeks to overcome the disadvantages present in known formulations. As such, a derivatized cyclodextrin-based, e.g., sulfoalkyl ether cyclodextrin (SAE-CD)-based, preserved formulation is provided. The present formulation can include any known active agent. The formulation is preserved in terms of its ability to resist microbial contamination, i.e., it has a reduced potential for sustaining bacterial growth as compared to a similar formulation that excludes the SAE-CD and a conventional preservative. The present formulation may provide enhanced solubility and/or enhanced chemical, thermochemical, hydrolytic and/or photochemical stability of

the active agent or other ingredients in the formulation. Moreover, the present formulation possesses other physicochemical advantages over other formulations.

The formulation of the invention includes underivatized cyclodextrin and/or derivatized cyclodextrin in an amount sufficient to reduce the water activity of the formulation to a value below which a target microbe will not be able to grow and/or will be killed. In the absence of a conventional preservative or other agent(s) that enhance(s) or improve(s) the biostatic or biocidal activity of the cyclodextrin, a formulation of the invention will have a water activity (a_w) less than about 0.97 ± 0.025 . Another biostatic, biocidal, or water activity reducing-agent can be included in the formulation to provide further improved preserving capacity.

An SAE-CD-containing formulation can be prepared with sufficient active agent solubility and stability for a commercial product. If needed, the SAE-CD-containing formulation can be prepared as a clear aqueous solution that can be sterile filtered through a filter having a pore size of $0.45 \mu\text{m}$ or less and that is stable and preserved under a variety of storage conditions. An SAE-CD-containing liquid formulation can also be converted to a solid or powder for reconstitution.

One aspect of the invention provides a liquid formulation comprising an effective amount of an active agent and an SAE-CD, wherein the SAE-CD is present in an amount sufficient to preserve the formulation during storage. The SAE-CD can be present in less than stoichiometric, stoichiometric or greater than stoichiometric amounts with respect to the amount of active agent present in the formulation. The SAE-CD need not complex with the active agent. The SAE-CD need not form ionic associations with the active agent. The formulation can comprise more than one active agent.

Specific embodiments of the invention include those wherein: 1) the active agent to SAE-CD molar ratio is less than one, about one or greater than one; 2) the SAE-CD is sulfobutyl ether 4- β -CD or sulfobutyl ether 7- β -CD; 3) the SAE-CD is a compound of the formula 1 or a mixture thereof; 4) the formulation further comprises a conventional preservative, an antioxidant, a buffering agent, an acidifying agent, a solubilizing agent, a complexation enhancing agent, saline, an electrolyte, another therapeutic agent, an alkalizing agent, a humectant or a combination thereof; 5) the SAE-CD is present in an amount sufficient to provide a clear solution; 6) the liquid formulation is lyophilized or otherwise dried to form a solid formulation for reconstitution; 7) the formulation comprises at least $4.8 \pm 0.5\%$ wt./vol of SAE-CD to provide biostasis; 8) the formulation

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comprises more than one active agent, wherein each active agent may or may not complex with the SAE-CD; 8) the formulation comprises an excess, on a molar basis, of SAE-CD; 9) the formulation comprises an excess, on a molar basis, of active agent; 10) the formulation has been purged with an inert gas to remove substantially all of the oxygen contained in the formulation; 11) the formulation further comprises one or more conventional preservatives; 12) at least one active agent present in the formulation has a greater binding with the SAE-CD than does a conventional preservative in the formulation; 13) the water activity of the formulation is less than about 0.97 ± 0.025 as measured according to the procedures detailed herein; 14) the formulation further comprises a liquid carrier other than water; 15) the formulation is a liquid; 16) the formulation is a semi-solid; 17) the formulation is a solid; 18) the formulation has been prepared at a temperature at or above 5°C , at or above 25°C , at or above 35°C , at or above 45°C or at or above 50°C ; 19) the formulation has been prepared at a temperature approximating ambient temperature; 20) the SAE-CD, or derivatized cyclodextrin, reduces the water activity of the formulation; 21) the formulation comprises at least $25.6 \pm 2.5\%$ wt./vol of SAE-CD to provide biocidal properties; 22) the SAE-CD is present in an amount sufficient to unmask the biocidal or biostatic properties of an active agent, which properties are masked when the active agent is present in another formulation.

The water activity of the formulation is generally reduced to less than about 0.98 ± 0.019 , less than 0.97 ± 0.025 , less than 0.96 ± 0.025 , less than 0.95 ± 0.01 , less than 0.925 , less than 0.90 or less than 0.80 . The preferred water activity value may vary according to the components present in the formulation. The observed water activity value can also vary according to the instrument used to measure it as well as the calibration of the instrument and reproducibility of measurements (as expressed by standard deviation) taken by the instrument.

The invention also provides a liquid formulation that can be sterile filtered, wherein the formulation comprises a liquid carrier, an SAE-CD and one or more active agents.

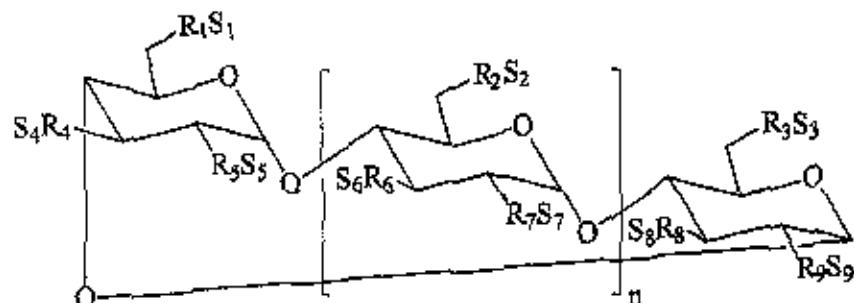
The invention also provides methods of preparing a liquid formulation. A first method comprises the steps of: forming a first aqueous solution comprising a cyclodextrin derivative; forming a second solution comprising active agent; and mixing the first and second solutions to form the liquid formulation. A second method is similar to the first step except that the active agent is added directly to the first solution without formation of

derivatized cyclodextrin serves to preserve the formulation from microbial contamination and/or proliferation.

_____ The preserved formulation can be a liquid, solid, suspension, powder, gel, cream, ointment, paste, stick, tablet, capsule, osmotic device, dispersion, emulsion, patch or any other type of formulation requiring preservation.

The formulation of the invention can employ different means of stopping or inhibiting an increase in bioburden. In other words, it can employ a derivatized cyclodextrin and one or more preservatives in order to form a preserved formulation. One reason for doing so is that though a microorganism might survive a single preservative challenge relatively well, the energy expenditure required to meet the first challenge leaves it exposed and vulnerable to attack from another preservative. For example, under ideal conditions, 10% sodium chloride is required to inhibit *Clostridium botulinum* via reduction in water activity. However, at pH 5.4-5.8 in the presence of only 100ppm nitrate, only 3.5% sodium chloride is required to preserve the system. Another reason is that some microorganisms may develop resistance to a particular approach of preservation. Thus a combination of preservative approaches might be required to preserve a preparation from contamination by several microbes.

The present invention provides SAE-CD based formulations, wherein the SAE-CD is a compound of the Formula 1:



Formula 1

wherein:

n is 4, 5 or 6;

$R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8$ and R_9 are each, independently, -O- or α -O-(C₂ - C₆ alkylene)-SO₃⁻ group, wherein at least one of R_1 and R_2 is independently a -O-(C₂ - C₆ alkylene)-SO₃⁻ group, preferably a -O-(CH₂)_mSO₃⁻ group, wherein m is 2 to 6, preferably 2 to 4, (e.g. -OCH₂CH₂CH₂SO₃⁻ or -OCH₂CH₂CH₂CH₂SO₃⁻); and

charged compound is complexed with the cyclodextrin either by inclusion in the cavity or formation of a salt bridge. The preservative property of SAE-CD does not require inclusion complexation or salt formation with an active agent.

The amount of derivatized cyclodextrin required to provide the desired level of preservation will vary according to the materials comprising the formulation. The more prone a formulation is to microbial contamination, the higher the amount of derivatized cyclodextrin that may be required. The less prone a formulation is to microbial contamination, the lower the amount of derivatized cyclodextrin that may be required. In the absence of other preservative, the formulation comprises greater than about 25 % w/v of derivatized cyclodextrin for biocidal effect or greater than about 4.8%±0.5% for biostasis.

The parent cyclodextrins have limited water solubility as compared to SAE-CD and HPCD. Underivatized α -CD has a water solubility of about 14.5% w/v at saturation. Underivatized β -CD has a water solubility of about 1.85% w/v at saturation. Underivatized γ -CD has a water solubility of about 23.2% w/v at saturation. At these concentrations, these parent cyclodextrins are unable to, on their own, preserve formulations containing them. Dimethyl-beta-cyclodextrin (DMCD) forms a 43% w/w aqueous solution at saturation. At this concentration, DMCD is unable to preserve a formulation containing it.

However, the present inventors have discovered that SAE-CD in addition to other cyclodextrin derivatives possesses the ability to reduce water activity in the formulations of the invention. It is believed that the formulation-preserving activity of the derivatized cyclodextrins is at least in part due to their ability to reduce water activity. Generally, the greater the water activity-reducing power of a derivatized cyclodextrin, the lower the amount of cyclodextrin required to preserve a solution. It is also possible that an ionized derivatized cyclodextrin possesses preservative activity when present as a salt. The preservative activity of a derivatized cyclodextrin might also be the result of its osmolality.

Other water soluble cyclodextrin derivatives that decrease water activity can be used according to the invention. Exemplary derivatives include the hydroxyethyl, hydroxypropyl (including 2- and 3-hydroxypropyl) and dihydroxypropyl ethers, their corresponding mixed ethers and further mixed ethers with methyl or ethyl groups, such as methylhydroxyethyl, ethyl-hydroxyethyl and ethyl-hydroxypropyl ethers of alpha-, beta-

improved, additive or synergistic enhancement over the water activity-reducing effect of either material alone.

One or more water activity-reducing agents can be used in combination with one or more derivatized or non-derivatized cyclodextrins in the formulation.

5 Accordingly, the invention provides an alternate method of increasing the shelf-life of (such as by preserving) a formulation that sustains microbial growth. The formulation of the alternate method would comprise an aqueous carrier, and a first water activity-reducing agent present in an amount insufficient to, on its own, preserve the formulation. The method would comprise the step of including a derivatized or non-derivatized
10 cyclodextrin in the formulation. By so doing, the first water activity-reducing agent and the cyclodextrin cooperate to improve the shelf-life of the formulation. This can be done even when the cyclodextrin is present in an amount insufficient to, on its own, preserve the formulation.

A formulation according to the invention will have a storage shelf life of no less
15 than three days, one week, three weeks, one month, three months, six months, or one year. In this case, shelf life is determined only as regards the increase in bioburden in the formulation. For example, for a formulation having a shelf life of at least six months, the formulation will not demonstrate an unacceptable and substantial increase in bioburden during the storage period of at least six months. The criteria for acceptable shelf-life are
20 set as needed according to a given product and its storage stability requirements. In other words, the bioburden of a formulation having an acceptable shelf-life will not increase beyond a predetermined value during the intended period of storage. On the other hand, the bioburden of a formulation having an unacceptable shelf-life will increase beyond the predetermined value during the intended period of storage. It should be noted that a shelf-
25 life of as little as one week is suitable for products that are compounded by a pharmacist and sold to customers of a pharmacy. At a minimum, a preserved formulation will have an acceptable shelf-life of at least 24-hours after initial contamination. This is particularly true to for multi-dose parenteral formulations. In other embodiments, a preserved formulation will have a shelf-life of at least 28 days as per USP guidelines. In another
30 embodiment, a preserved formulation will have a shelf-life of at least two years.

Osmolality is related to water activity and thus can also be an indicator of formulation preserving activity. Increases in osmolality correspond to decreases in water activity. Figure 3 depicts the relationship between osmolality and concentration of

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SBE-CD in an unbuffered aqueous solution at room temperature. At concentrations up to about 20% to 30% w/v, the relationship is linear. At SBE-CD concentrations below about 11-13% w/v, the solutions are hypotonic or hypoosmotic with respect to blood and at SBE-CD concentrations above about 11-13% w/v the SBE-CD containing solutions are hypertonic or hyperosmotic with respect to blood. When red blood cells are exposed to solutions that are hypo- or hypertonic, they can shrink or swell in size which can lead to hemolysis. As noted above and in Figure 1, SBE-CD is less prone to induce hemolysis than other derivatized cyclodextrins.

A formulation containing the active agent propofol at 1% w/v and 22% w/v CAPTISOL is hypertonic and has an osmolality of 687 mOsmoles/kg. A lipid emulsion formulation of 1% propofol (the marketed product Diprivan) has a measure osmolality of 303 mOsmoles/kg and is isoosmotic with blood. The hemolytic potential of each formulation was evaluated according to Vasque et al. ("In Vitro Evaluation Of Biocompatibility Of A Dose Formulation" presented at the 40th Annual Meeting of the Society of Toxicology, San Francisco, CA, (Mar 25-29, 2001)). The data indicated there was no measured evidence for hemolysis caused by the Captisol formulation at any of the formulation:blood ratios. The Diprivan formulation induced moderate hemolysis at formulation:blood ratios of 1:1 and slight hemolysis at ratios of 0.5:1, 0.25:1 and 0.1:1.

Accordingly, the invention also provides a liquid formulation of an active agent and an SAE-CD, wherein the formulation has a reduced hemolytic potential as compared to other cyclodextrin-based formulations.

The formulation can include one or more of any known active agents. The active agent included in the present invention can possess a wide range of values for water solubility, bioavailability and hydrophilicity. Active agents to which the present invention is particularly suitable include water insoluble, poorly water soluble, slightly water soluble, moderately water soluble, water soluble, very water soluble, hydrophobic, or hydrophilic therapeutic agents. It will be understood by the artisan of ordinary skill that an active agent used in the formulation of the present invention is independently selected at each occurrence from any known active agent and from those disclosed herein. It is not necessary that the active agent complex with the derivatized cyclodextrin or form an ionic association with the derivatized cyclodextrin.

Active agents generally include physiologically or pharmacologically active substances that produce a systemic or localized effect or effects on animals and human

benzoate and sodium phenylacetate, bromocriptine mesylate, cabergoline, agents for gout, and antidotes.

Exemplary cardiovascular agents include nootropic agents, antiarrhythmic agents, calcium channel blocking agents, vasodilators, antiadrenergics/sympatholytics, renin
5 angiotensin system antagonists, antihypertensive combinations, agents for pheochromocytoma, agents for hypertensive emergencies, antihyperlipidemic agents, antihyperlipidemic combination products, vasopressors used in shock, potassium removing resins, edetate disodium, cardioplegic solutions, agents for patent ductus arteriosus, and sclerosing agents. Exemplary renal and genitourinary agents include
10 interstitial cystitis agents, cellulose sodium phosphate, anti-impotence agents, acetohydroxamic acid (aha), genitourinary irrigants, cystine-depleting agents, urinary alkalizers, urinary acidifiers, anticholinergics, urinary cholinergics, polymeric phosphate binders, vaginal preparations, and diuretics. Exemplary respiratory agents include
15 bronchodilators, leukotriene receptor antagonists, leukotriene formation inhibitors, respiratory inhalant products, nasal decongestants, respiratory enzymes, lung surfactants, antihistamines, nonnarcotic antitussives, and expectorants. Exemplary central nervous system agents include CNS stimulants, narcotic agonist analgesics, narcotic agonist-antagonist analgesics, central analgesics, acetaminophen, salicylates, nonnarcotic analgesics, nonsteroidal anti-inflammatory agents, agents for migraine,
20 antiemetic/antivertigo agents, anxiety agents, antidepressants, antipsychotic agents, cholinesterase inhibitors, nonbarbiturate sedatives and hypnotics, nonprescription sleep aids, barbiturate sedatives and hypnotics, general anesthetics, injectable local anesthetics, anticonvulsants, muscle relaxants, antiparkinson agents, adenosine phosphate, cholinergic muscle stimulants, disulfuram, smoking deterrents, riluzole, hyaluronic acid derivatives,
25 and botulinum toxins. Exemplary gastrointestinal agents including H pylori agents, histamine H2 antagonists, proton pump inhibitors, sucralfate, prostaglandins, antacids, gastrointestinal anticholinergics/antispasmodics, mesalamine, olsalazine sodium, balsalazide disodium, sulfasalazine, celecoxib, infliximab, tegaserod maleate, laxatives, antidiarrheals, antiflatulents, lipase inhibitors, GI stimulants, digestive enzymes, gastric
30 acidifiers, hydrocholeretics, gallstone solubilizing agents, mouth and throat products, systemic deodorizers, and anorectal preparations. Exemplary anti-infective agents including penicillins, cephalosporins and related antibiotics, carbapenem, monobactams, chloramphenicol, quinolones, fluoroquinolones, tetracyclines, macrolides, spectinomycin,

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reacting it with an acid or base as needed to form an ionically bound pair. Examples of pharmaceutically acceptable salts include conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. Suitable non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfonic, sulfamic, phosphoric, nitric and others known to those of ordinary skill in the art. The salts prepared from organic acids such as amino acids, acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and others known to those of ordinary skill in the art. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent active agent which contains a basic or acidic moiety by conventional chemical methods. Lists of other suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, the relevant disclosure of which is hereby incorporated by reference.

An anionic derivatized cyclodextrin can complex or otherwise bind with an acid-ionizable agent. As used herein, the term acid-ionizable agent is taken to mean any compound that becomes or is ionized in the presence of an acid. An acid-ionizable agent comprises at least one acid-ionizable functional group that becomes ionized when exposed to acid or when placed in an acidic medium. Exemplary acid-ionizable functional groups include a primary amine, secondary amine, tertiary amine, quaternary amine, aromatic amine, unsaturated amine, primary thiol, secondary thiol, sulfonium, hydroxyl, enol and others known to those of ordinary skill in the chemical arts.

The degree to which an acid-ionizable agent is bound by non-covalent ionic binding versus inclusion complexation formation can be determined spectrophotometrically using methods such as ¹HNMR, ¹³CNMR, or circular dichroism, for example, and by analysis of the phase solubility data for the acid-ionizable agent and anionic derivatized cyclodextrin. The artisan of ordinary skill in the art will be able to use these conventional methods to approximate the amount of each type of binding that is occurring in solution to determine whether or not binding between the species is occurring predominantly by non-covalent ionic binding or inclusion complex formation. An acid-ionizable agent that binds to derivatized cyclodextrin by both means will generally exhibit a bi-phasic phase solubility curve. Under conditions where non-covalent ionic bonding

colorant, solubility-enhancing agent, complexation enhancing agent, electrolyte, glucose, stabilizer, tonicity modifier, bulking agent, antifoaming agent, oil, emulsifying agent, cryoprotectant, plasticizer, flavors, sweeteners, other excipients known by those of ordinary skill in the art for use in preserved formulations, or a combination thereof

5 As used herein, the term "alkalizing agent" is intended to mean a compound used to provide alkaline medium for product stability. Such compounds include, by way of example and without limitation, ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium bicarbonate, sodium hydroxide, triethanolamine, diethanolamine, organic amine base,
10 alkaline amino acids and triamine and others known to those of ordinary skill in the art.

As used herein, the term "acidifying agent" is intended to mean a compound used to provide an acidic medium for product stability. Such compounds include, by way of example and without limitation, acetic acid, acidic amino acids, citric acid, fumaric acid and other alpha hydroxy acids, hydrochloric acid, ascorbic acid, phosphoric acid, sulfuric
15 acid, tartaric acid and nitric acid and others known to those of ordinary skill in the art.

As used herein, a conventional preservative is a compound used to at least reduce the rate at which bioburden increases, but preferably maintains bioburden steady or reduces bioburden after contamination. Such compounds include, by way of example and without limitation, benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl
20 alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate, phenylmercuric acetate, thimerosal, metacresol, myristylgamma picolinium chloride, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, sorbic acid, thymol, and methyl, ethyl, propyl or butyl parabens and others known to those of ordinary skill in the art.

As used herein, the term "antioxidant" is intended to mean an agent that inhibits oxidation and thus is used to prevent the deterioration of preparations by the oxidative process. Such compounds include, by way of example and without limitation, acetone, potassium metabisulfite, potassium sulfite, ascorbic acid, ascorbyl palmitate, citric acid, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid,
30 monothioglycerol, propyl gallate, sodium ascorbate, sodium citrate, sodium sulfide, sodium sulfite, sodium bisulfite, sodium formaldehyde sulfoxylate, thioglycolic acid, EDTA, pentetate, and sodium metabisulfite and others known to those of ordinary skill in the art.

however, in none of the samples of Example 3 was an increase in bioburden observed for solutions containing SAE-CD. Overall, the SAE-CD containing formulations actually had a lower microbial count after 24 and 48 hours than they did at the beginning of the study. Accordingly, the present formulation provides a substantially preserved parenteral formulation comprising an SAE-CD, an active agent and a liquid carrier. The invention also provides a method of preserving a formulation comprising the step of including in the formulation SAE-CD in an amount sufficient to slow down the rate of bioburden increase, maintain bioburden and/or reduce bioburden in a contaminated formulation. Unlike the emulsion formulation, the present formulation or composition does not require an added conventional preservative, such as detailed herein; although, a conventional preservative can be further included if desired. As such, the presently claimed formulations unexpectedly possess microbial growth retarding or preservative properties.

Additional embodiments of preserved formulations according to the invention are included in Examples 6-9. Formulations containing varying amounts of SBE7- β -CD and microbial inoculates were prepared. The microbes tested include *Pseudomonas aeruginosa* (ATCC 9027), *Escherichia coli* (ATCC 8739), *Salmonella choleraesuis* (ATCC 13311), *Staphylococcus aureus* (ATCC 6538), *Candida albicans* (ATCC 10231), and *Aspergillus niger* (ATCC 16404). As noted in the water activity versus microorganism table included in the Background section above, the above-mentioned microbes will not reproduce when the water activity of the medium in which they are found is at or below the values indicated. In other words, the microbes should proliferate when they are present in a medium having a water activity higher than the indicated values as long as the medium contains sufficient nutrients to sustain microbial growth. In order to provide a basis for unexpected results, the water activity values of the above-mentioned solutions were determined to be as follows:

CD Solution	Neat	Bound Active		Unbound Active
		10 mg/mL Propofol	20 mg/mL Ibuprofen	10 mg/mL Cyclopentolate HCl
20% w/v Captisol	0.974 (pH 5.5)	0.974 (pH 5.6)	Not Available	Not Available
40% w/v Captisol	0.951 (pH 6.0)	Not Available	0.979 (pH 5.7)	0.946 (pH 6.0)
40% w/v HPBCD	0.986 (pH 5.4)	Not Available	0.983 (pH 5.7)	0.986 (pH 6.0)

The antimicrobial preserving capability of the formulations was evaluated by testing each formulation using the procedure of USP XXV <51> test for preservative

effectiveness except that the time points analyzed were 0, 24, and 72 hours post inoculation.

In Example 6, the performance of SAE-CD to HPCD was evaluated in the presence and absence (control samples) of ibuprofen, a non-steroidal anti-inflammatory drug. Ibuprofen is known to complex with SAE-CD and HPCD. As detailed in the table above, complexation of SAE-CD with ibuprofen increased the a_w of the solution, but complexation of ibuprofen with HPCD did not increase the water activity of the HPCD-containing solution. Even so, the results indicate that a derivatized cyclodextrin, such as an SAE-CD, acts as a preservative under conditions where one would not expect it to, since the SAE-CD inhibited or retarded growth and/or kill microbes at concentrations for HPCD that are inactive. Moreover, SAE-CD retained preservative activity at water activity values in which the microbes would have been expected to proliferate. For example, SAE-CD present at a concentration of 40.0% w/v in the presence of the active ibuprofen had a measured a_w of 0.979. At that a_w value, one would not expect that a water activity-reducing agent, such as SAE-CD, would have a preservative effect. However, the inventors have discovered that SAE-CD, but not HPCD, causes a decrease in bioburden (possesses biocidal activity) at that water activity value for *P. aeruginosa*, *E. coli*, *S. chloerasuis* and *C. albicans*.

According to the above, SAE-CD unexpectedly provides preservative properties, for solutions containing it, at water activity values that one would not expect to see such a high degree of activity.

In the formulation of Example 7, cyclopentolate HCl was used as it was determined not to complex to any significant extent with SAE-CD or HPCD, since the drug is very water soluble. It is possible that minor complexation of the cyclopentolate with cyclodextrin could occur under certain circumstances. As noted above, addition of cyclopentolate to a solution containing SAE-CD or HPCD did not substantially increase or decrease the water activity of the respective solution. SAE-CD possesses better biocidal/biostatic properties against *P. aeruginosa*, *E. coli*, and *S. chloerasuis* than HPCD.

The pH at which SAE-CD expresses its preservative activity is not limited to alkaline pH values. As noted herein, SAE-CD, when present in sufficient amounts, serves as a suitable preservative for solutions having a pH from 0-14, or an acidic pH, alkaline pH, or physiological pH.

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES**

2020
Bogotá, D.C.

✓ Abogado
CARLOS R. OLARTE

ASUNTO	Radicación	06073023
	Trámite	011
	Evento	379
	Actuación	411
	Oficio	01 03 8 2
	Folios	022

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐ Cap. II ☒
No. Sol. Internacional	PCT/IB2005/000100		
Fecha de Presentación Interna.	Enero 17 de 2005.		

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

1. Documentos estudiados

- | | | | |
|------|--------------------------|--|--|
| 1.1. | <u>Descripción:</u> | Folios: 74 a 139 | como se radicó inicialmente |
| 1.2. | <u>Reivindicaciones:</u> | Folios: 140 a 142 ✓
Folios: 185-186 ✓ | como se radicó inicialmente
2010/04/05. |
| 1.3. | <u>Prioridad:</u> | Enero 30 de 2004; US; 60/540.897 | |

2. Objeto de la invención

Título de la invención: CONSERVANTES ANTIMICROBIANOS PARA LOGRAR UNA FORMULACIÓN DE DOSIS MÚLTIPLES USANDO CICLODEXTRINAS β PARA FORMAS DE DOSIFICACIÓN LÍQUIDAS.

Problema Técnico Planteado: Necesidad de composiciones farmacéuticas con Ciclodextrinas.

Solución: Composiciones farmacéuticas del compuesto de fórmula (Ia), una ciclodextrina y un conservante.

IPC: A61K47/00.

3. 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: Enero 30 de 2004.

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D1	US2003/0139443	Use of tachykinin antagonists including NK-1 receptor antagonists, to modify unwanted behavior in dogs, cats and horses	Julio 24 de 2003
D2	WO03/080079	Use of sulfoalkyl ether cyclodextrin as a preservative	Octubre 02 de 2003

D1 (folios: 173-176); D2 (folios: 187-205)

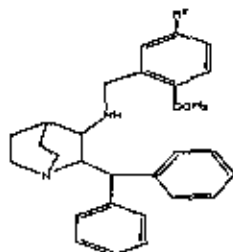
4. Análisis de patentabilidad (artículo 14 D486)

4.1 Nivel inventivo (artículo 18 D486)

La reivindicación 1, dice:

Una composición farmacéutica parenteral, que comprende:

Un cantidad terapéuticamente efectiva de un compuesto de fórmula (I):



donde R2 es tert- butyl; ó una sal farmacéutica aceptable del mismo, como antagonista del receptor NK-1

Una β -cyclodextrina

Un preservante farmacéutica aceptable que es metacresol; y

Un vehículo farmacéutica aceptable

El Estado de la Técnica más cercano es D1 (US2003/0139443) que da a conocer composiciones farmacéuticas líquidas que contienen un antagonista del receptor NK-1 ó sus sales (folio 174, pg 5, parágrafo 134) y además contienen vehículos o diluentes (folio 175, pg 6, parágrafo 148), tales como: un conservante (polietilenglicol), un vehículo (glicerina) (folio 175, pg 6, parágrafo 149) y una

ciclodextrina β (sulfobutileter SBE ciclodextrina, folio 174, párrafo 134, R2 es tert- butyl) o su sal farmacéutica aceptable); las cuales se pueden administrar por vía parenteral (soluciones isotónicas) folio 175, pg6, párrafo 150,

La composición objeto de esta solicitud se diferencia de las composiciones de D1, en que esta contiene como preservante el metacresol.

El hecho de incluir como preservante el metacresol, en las composiciones que se daban a conocer en D1, causa que la composición reclamada, presente buena estabilidad con eficacia antimicrobiana frente a los microorganismos probados (folio 118, pg 45) y con buena solubilidad, (folio 66, pg 1/4, descripción), lo cual era de esperarse.

El Problema Técnico Objetivo era "cómo obtener composiciones, alternativas, de un compuesto de formula (I) ó una sal farmacéutica aceptable del mismo, como antagonista del receptor NK-1, soluble y con eficacia antimicrobiana".

D2 (WO03/080079) describe una manera de solucionar el problema técnico planteado, mediante el uso del Sulfobutil éter ciclodextrina, (folio 190, pg4 , línea 16) en formulaciones farmacéuticas líquidas con pH ácido (folio 191, pg 5, línea 6; folio 197, pg 16, línea 3; folio 205, pg 38, línea 31), formando un complejo entre principios activos, como un agente contra la ansiedad en forma de sal citrato (folio 201, pg 27, línea 20; folio 202, pg 29, línea 6, con diferentes grados de solubilidad, folio 200, pg 25, líneas 24-27), para aumentar la solubilidad y la estabilidad de dichas preparaciones farmacéuticas (folio 188, pg 2, líneas 14-17; folio 190, pg4, líneas 20-21), que también pueden contener metacresol, pg 31, línea 21). Las formulaciones divulgadas en D2, presentaron efectividad antimicrobiana, contra los mismos microorganismos (folio 204, pg 37, líneas 13-18) para los cuales presentó efectividad antimicrobiana, la composición de la solicitud (folio 118, pg 45, tabla IV); en donde la ciclodextrina no reduce la actividad del componente preservante (metacresol) ó donde la actividad antimicrobiana de la formulación no se disminuye (lo cual es el mismo efecto alcanzado por la solicitud).

El solicitante en los folios 93, 102 y 104, afirma que el desarrollo de la formulación dio como resultado la optimización de la ciclodextrina unida al fármaco y no unida al conservante (como en D2 folio 191, pg5, líneas 9-11) lo cual muestra que es una labor de la rutina diaria del experto en la materia, lo cual no le confiere altura inventiva a las reivindicaciones reclamadas.

Por tanto, la solicitud, tal como se reivindica, es obvia, porque el Experto en la Materia enfrentado al problema de "cómo obtener composiciones, alternativas, de un compuesto de formula (I) ó una sal farmacéutica aceptable del mismo, como antagonista del receptor NK-1, con eficacia antimicrobiana, más solubles", utilizaría las enseñanzas de D1 y D2, incluyendo el metacresol, que se revela en D2, dentro de las composiciones que se enseñan en D1, para lograr de esta forma la composición objeto de esta solicitud.

Las reivindicaciones 2-6 dependientes de la 1, se caracterizan por determinar ciertas proporciones entre la ciclodextrina y el principio activo ó la ciclodextrina y el conservante. Es conocido que encontrar nuevas proporciones entre los componentes de una composición farmacéutica, es una labor de la rutina diaria del experto en la materia, lo cual no le confiere altura inventiva a las reivindicaciones reclamadas.

De lo anterior se concluye, que las reivindicaciones 1-6 no son inventivas.

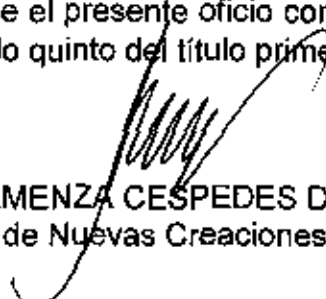
5. Conclusión:

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

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	US2003/0139443	1-6	Nivel Inventivo
D2	WO03/080079	1-6	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 numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha

13 AGO. 2010

CONCEPTO TÉCNICO No.2517	EXAMINADOR TÉCNICO Código No.202078
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