

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMER
DIVISION DE NUEVAS CREACIONES
E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-017056- -00008-0000

Fecha: 2009-12-01 16:25:30 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eje: 379 FASENACIONALI
Act: 444 RESPUESTAREQUE Folios: 11

Re: P1.-WYETH.-Solicitud de Patente de Invención en Fase Nacional PCT para
"FORMULACIONES PARENTERALES QUE CONTIENEN UN
HIDROXIESTER DE RAPAMICINA".-Clase A61K 31/436.-Expediente
número 05-017.056.-

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista de 4 de Septiembre de 2009.

2. Con el fin de responder las objeciones presentadas por el Señor Examinador en su Concepto Técnico No. 2970 en relación con el requisito de Nivel Inventivo, me permito dirigir su atención a las siguientes modificaciones y argumentos técnicos, por medio de los cuales se superan completamente dichas objeciones.

3. **MODIFICACIONES AL CAPITULO REIVINDICATORIO:**

Antes de presentar los argumentos técnicos que permiten demostrar la altura inventiva de la presente solicitud, me permito dirigir la atención del señor Examinador a las siguientes modificaciones sobre el capítulo reivindicatorio actualmente presentado realizadas con el fin de aportar mayor claridad acerca del objeto que se desea proteger y de distinguir aún más la materia reclamada de las enseñanzas contenidas en los documentos citados como estado de la técnica más cercano.

De conformidad con lo anterior, los cambios realizados son:

- (I) Se ha modificado la estructura de la reivindicación 1 con el fin de aclarar que el concentrado cosolvente de CCI-229 reclamado está conformado por una cierta cantidad de CCI-779; un solvente parenteralmente aceptable seleccionado entre dimetilacetamida y un solvente alcohólico; y un componente antioxidante.

Dicha modificación se hace en atención a la afirmación realizada por el señor Examinador al final del folio 337 de su Concepto Técnico, según la cual "*con la modificación que se presenta para la cláusula independiente 1 en el nuevo juego de reivindicaciones, el señor solicitante cambia la modalidad de*

JOSE LLORED A CAMACHO & CO.

Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 6069700 Fax 6069701

sistema cosolvente binario y pasa a un sistema ternario constituido por la mezcla de DMAC, un solvente alcohólico y un componente antioxidante, es decir, elimina la posibilidad de que sea DMAC o un solvente alcohólico y establece la necesidad de su coexistencia en la forma de un sistema cosolvente ternario", lo que corresponde a una interpretación incorrecta de la invención, lo cual se puede corroborar por el hecho de que las reivindicaciones 2 y 3 actualmente presentadas reivindican cada una un concentrado con dimetilacetamida (reivindicación 2) o un concentrado con un solvente alcohólico (reivindicación 3), es decir, que el solvente parenteralmente aceptable no tiene que corresponder a la mezcla de los dos solventes señalados en la reivindicación 1.

Adicionalmente, el solicitante ha decidido restringir el rango de concentración de CCI-779 en el concentrado reivindicado, de forma tal que ha reemplazado el valor del límite inferior del rango actualmente presentado que es de 0.05 mg/mL, por un valor mayor correspondiente de 2.5 mg/mL. El sustento para esta modificación se puede encontrar en la línea 3 de la página 8 de la memoria descriptiva originalmente presentada.

De conformidad con lo anterior, la reivindicación 1 ahora modificada se deberá leer tal como sigue:

*"1. Un concentrado cosolvente de CCI-779 que comprende:
aproximadamente 2.5 mg/mL a aproximadamente 50 mg/mL de CCI-779,
un solvente parenteralmente aceptable seleccionado del grupo que consiste en dimetilacetamida y un solvente alcohólico, y
aproximadamente 0.001% a 1.0% p/v de un componente antioxidante";*

- (ii) Se ha modificado la reivindicación 4 actualmente presentada, con el fin de eliminar la expresión "polietilen glicol 1000" y de introducir la frase "una mezcla de los mismos" al final de dicha reivindicación, cuyo sustento se puede encontrar en la línea 34 de la página 5 de la descripción;
- (iii) Se ha eliminado la reivindicación 9 actualmente presentada;
- (iv) Se ha modificado la reivindicación 10 actualmente presentada, ahora renumerada como reivindicación 9, con el fin de incluir un límite superior a la cantidad de CCI-779 que puede estar presente en el concentrado particular allí reclamado, y de esta forma definir de manera más clara y precisa la realización específica señalada. En este sentido, se ha incluido la expresión

"a aproximadamente 50 mg/mL" al final de la misma, de conformidad con el rango de concentración reclamado en la reivindicación independiente 1 y con lo expuesto en la línea 5 de la página 8 de la descripción;

- (v) Se ha modificado la reivindicación 11 actualmente presentada, ahora renumerada como reivindicación 10, con el fin de incluir en ella la materia protegida en las reivindicaciones 13 y 15 actualmente protegidas, de forma tal que se ha introducido la expresión *"en donde CCI-779 comprende aproximadamente 1 mg/mL a aproximadamente 25 mg/mL de la formulación parenteral y el antioxidante comprende aproximadamente 0.0005 a 0.5% p/v de la formulación parenteral"* al final de dicha cláusula, para así definir de manera más clara y restringida la formulación parenteral que comprende al concentrado cosolvente de CCI-779 y que corresponde a otro de los objetos revelados por la presente solicitud;
- (vi) De conformidad con las anteriores modificaciones, se han renumerado las reivindicaciones 12, 14 y 16 a 26 como nuevas reivindicaciones 11, 12 y 13 a 23, respectivamente, corrigiendo adicionalmente sus respectivas dependencias en forma coherente con tales cambios;
- (vii) Se ha incluido la palabra *"parenteral"* en el preámbulo de las nuevas reivindicaciones dependientes 11 a 14 (actuales 12, 14, 16 y 17, respectivamente), con el fin hacer más clara su conexión con la reivindicación 10;
- (viii) Se ha incluido la expresión *"de la formulación parenteral"* al final de la nueva reivindicación 12 (actual 14), con el fin de aclarar que el contenido de CCI-779 expresado es respecto de la formulación parenteral y no del concentrado cosolvente y así evitar posibles malas interpretaciones;
- (ix) Se ha incluido la palabra *"parenteral"* al final de la reivindicación 13 (actual 16), con el fin de aclarar que el contenido de surfactante allí señalado es respecto de la formulación parenteral;
- (x) Se ha incluido la palabra *"diluyente"* junto a la palabra solvente y *"parenteral"* al final de la reivindicación 14 (actual 17), con el fin de aclarar que el solvente mencionado corresponde al solvente diluyente y que su concentración es respecto de la formulación parenteral;

JOSE LLORED A CAMACHO & CO.

Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 6069700 Fax 6069701

- (xi) Se ha reemplazado la expresión "*una formulación de CCI-779*" por la expresión "*la formulación parenteral*" al comienzo de la reivindicación de proceso 15 (actual 18), con el fin de proporcionar mayor claridad acerca del producto obtenido a través de dicho proceso.

Adicionalmente, en los pasos (a) y (b) del mencionado proceso, se han modificado las expresiones "*un solvente*", "*un componente*" y "*un surfactante*" por las expresiones "*el solvente*", "*el componente*" y "*el surfactante*", para así proporcionar mayor claridad en la lectura de los mismos al considerar las limitaciones que se han presentado a lo largo del proceso.

Finalmente, se ha eliminado la expresión "*para dar la formulación parenteral de CCI-779*" del paso (c) del proceso reivindicado, toda vez que la misma resulta redundante con respecto a la redacción presentada al principio de la reivindicación.

- (xii) Se ha modificado la reivindicación 16 (actual 19), con el fin de eliminar la expresión "*polietilen glicol 1000*" y de introducir la frase "*una mezcla de los mismos*" al final de dicha reivindicación, cuyo sustento se puede encontrar en la línea 34 de la página 5 de la descripción;
- (xiii) Se ha modificado la reivindicación 17 (actual 20) mediante la introducción de la palabra "*componente*" junto a la palabra "*antioxidante*", con el fin de proporcionar mayor claridad acerca de la naturaleza de este componente empleado en el proceso reclamado;
- (xiv) Se ha modificado la reivindicación 18 (actual 21), con el fin de eliminar la expresión "*polietilen glicol 1000*" y de introducir la frase "*una mezcla de los mismos*" al final de dicha reivindicación, cuyo sustento se puede encontrar en la línea 24 de la página 7 de la descripción;
- (xv) Se ha modificado la reivindicación 20 (actual 23), mediante la introducción de la palabra "*componente*" junto a la palabra "*antioxidante*" y el reemplazo de la expresión "*los solventes diluyentes son*" por la expresión "*el solvente diluyente es*", con el fin de proporcionar mayor claridad en cuanto al hecho de que el solvente diluyente es una mezcla de agua y polietilen glicol 400;
- (xvi) Se ha modificado la reivindicación 21 (actual 24), mediante la introducción de la palabra "*componente*" junto a la palabra "*antioxidante*";

- (xvii) Se ha modificado la reivindicación 22 (actual 25), mediante la introducción de la palabra "*componente*" junto a la palabra "*antioxidante*" y el reemplazo de la expresión "*los solventes son*" por la expresión "*el solvente parenteralmente aceptable es*", con el fin de proporcionar mayor claridad en cuanto al hecho de que el solvente parenteral es una mezcla de etanol deshidratado y propilen glicol; y
- (xviii) Se ha modificado la reivindicación 23 (actual 26), mediante la introducción de la palabra "*componente*" junto a la palabra "*antioxidante*".

De conformidad con lo anterior, y respetando los términos del artículo 34 de la Decisión Andina 486 de 2000, me permito señalar que **las modificaciones anteriormente señaladas no amplían de ninguna forma el alcance de la solicitud tal como fue originalmente presentada**, ya que las mismas tienen un sustento adecuado dentro del texto inicialmente radicado. En este sentido, cabe señalar que dichas modificaciones se presentan con el fin de proporcionar mayor claridad al texto del capítulo reivindicatorio con el ánimo de facilitar su comprensión y de diferenciar aún más el objeto de la presente solicitud de las enseñanzas del estado de la técnica.

4. NIVEL INVENTIVO.

Ahora bien, de conformidad con el análisis de patentabilidad realizado por el señor Examinador, se ha señalado en su Concepto Técnico No. **2970** que el objeto de la presente invención no cumple con el requisito de nivel Inventivo dadas las enseñanzas de los siguientes documentos:

- (1) US 5516770 (D1): citado anteriormente como D3, frente a esta referencia el señor Examinador ha manifestado que difiere de la presente solicitud en el hecho de que el concentrado de rapamicina allí descrito no incluye un solvente alcohólico o antioxidantes;
- (2) GB 2327611 (D2): citado previamente como D4, en relación con este documento el señor Examinador ha reconocido que no divulga o discute la adición de N,N-dimetilacetamida al concentrado de rapamicina, pero que sí discute el uso de aceite de ricino etoxilado con etanol y ácido cítrico;
- (3) US 5530006 (D3): citado inicialmente como D5, frente a este documento el señor Examinador ha reconocido que no enseña o discute composiciones que contengan antioxidantes y un cosolvente alcohólico; y

JOSE LLOREDA CAMACHO & CO.

Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 6069700 Fax 6069701

- (4) US 5674874 (D4): citado por primera vez, en relación con esta referencia el señor Examinador ha reconocido que no enseña ningún tipo de concentrado de rapamicina.

En relación con los anteriores documentos, el señor Examinador ha manifestado que es a partir de la combinación de los mismos que se ve afectada la altura inventiva de la solicitud, presentando como fundamento las siguientes combinaciones de D1 a D4:

- (1) La combinación de las referencias D2 y D3 podría conducir a una persona versada en la materia a superar las diferencias técnicas de cada documento con respecto a la incorporación de un antioxidante y un surfactante con el propósito de alcanzar una solubilidad mejorada para derivados de rapamicina como CCI-779.
- (2) La combinación de las enseñanzas de D1 y D3 podría conducir al versado en la materia a preparar una formulación concentrada que posteriormente es diluida con un diluyente y un surfactante, dado que es bien conocido que los alcoholes mezclados con un agente capaz de disminuir la tensión superficial, pueden mantener las moléculas solubilizadas dado que la mezcla evita la formación de cristales.
- (3) Resultaría obvio combinar D1 ó D3 con D4 para establecer un sistema cosolvente que disminuya las dificultades para mantener solubilizada una molécula estructuralmente compleja.
- (4) La incorporación de un solvente alcohólico y un agente antioxidantes resultaría obvia porque es bien sabido que la mejor manera para disminuir la descomposición de una sustancia es emplear compuestos que previenen la generación de radicales libres. Por lo tanto, la persona versada en la materia utilizaría las enseñanzas de D2 cuando trabaje con compuestos inestables tales como los macrociclos tipo lactona.

Antes de presentar los argumentos técnicos que demuestran de forma contundente el carácter inventivo de la materia objeto de la solicitud frente a las enseñanzas del arte previo citado, me permito dirigir la atención del señor Examinador nuevamente al hecho de que de acuerdo con los antecedentes técnicos de la invención, en el estado de la técnica existían diferentes limitaciones para la formulación parenteral de CCI-779, las cuales han podido superarse gracias al objeto de la presente solicitud, lo que constituye el aporte al estado del arte por parte de la invención, razón por la cual se hace necesario resaltar dicha información.

Problemático

Con este objetivo, me permito dirigir su atención a lo revelado en la página 4 de la memoria descriptiva de la solicitud, en donde el solicitante acertadamente, y por primera vez en el estado del arte, establece las principales limitaciones que, previo a los hallazgos de su invención, impidieron la eficiente implementación del principio activo CCI-779 en formulaciones parenterales.

En este sentido, cabe resaltar que al momento de abordar el problema de implementar eficientemente el compuesto CCI-779 en formulaciones parenterales, se reconoce que:

- (i) CCI-779 tiene una pobre solubilidad acuosa, la cual es de menos de 1 $\mu\text{g}/\text{ml}$.
- (ii) CCI-779 tiene solubilidad pobre en aceites vegetales farmacéuticamente aceptables.

A pesar de lo anterior, se reconoce que CCI-779 es soluble en ciertos solventes orgánicos miscibles con agua que son aceptables para administración parenteral.

Sin embargo, adicionalmente se han identificado los siguientes problemas técnicos:

- (iii) No es posible la formulación de CCI-779 en los mencionados solventes orgánicos miscibles con agua, debido a su inestabilidad química en virtualmente todos los solventes. A este respecto el solicitante señala que dicha inestabilidad puede estar asociada con la degradación oxidativa de CCI-779 o al clivaje de un enlace de lactona; y
- (iv) Las formulaciones de CCI-779 en solventes inorgánicos se precipitarían a la dilución con soluciones de infusión acuosas, tales como inyección de cloruro de sodio al 0.9% o inyecciones de dextrosa al 5%, o con sangre.

En conexión con lo anterior, me permito señalar que el problema técnico a ser solucionado por la presente invención es la provisión de formulaciones de CCI-779 más estables, preferiblemente formulaciones estables durante el almacenamiento y aún más preferiblemente, formulaciones de fácil manejo. En este sentido, los inventores han solucionado dicho problema técnico mediante los concentrados cosolventes de CCI-779, representados en las reivindicaciones 1 a 9 ahora presentadas, que son estables durante el almacenamiento y de fácil manipulación.

JOSE LLOREDA CAMACHO & CO.

Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 6069700 Fax 6069701

En este sentido, me permito llamar la atención del señor Examinador al hecho de que el solicitante ha alcanzado la meta propuesta al proporcionar una formulación de CCI-779 que tiene las siguientes características técnicas:

- Es un concentrado cosolvente,
- Contiene aproximadamente 2.5 mg/mL a aproximadamente 50 mg/mL de CCI-779,
- Contiene un solvente parenteralmente aceptable seleccionado de dimetilacetamida y un solvente alcohólico, y
- Contiene aproximadamente 0.001% a 1% p/v de un antioxidante.

Ahora bien, en relación con los argumentos presentados por el señor Examinador para fundamentar la supuesta falta de Nivel Inventivo de la presente solicitud, me permito señalar en primer lugar que, tal como ya ha sido mencionado, las referencias D1 y D3 (previas D3 y D5, respectivamente) simplemente proporcionan formulaciones parenterales de rapamicina. Estas formulaciones son preparadas mediante (a) la disolución de la rapamicina en propilen glicol o N,N-dimetilacetamida y (b) mezclar la solución del paso (a) con una solución diluyente de agua que contiene polietilén glicol y un éster de polioxitilén sorbitán. Sin embargo, **ninguno de los documentos D1 y D3 enseña o sugiere la inclusión de un antioxidante en las formulaciones, los problemas y soluciones asociadas con las formulaciones parenterales que comprende CCI-779, ni el concentrado listo para almacenar del solicitante.**

En otras palabras, la combinación de los documentos D1 y D3 no podría conducir a una persona versada en la materia a la obtención del concentrado cosolvente reivindicado en la presente solicitud, toda vez que ambas referencias son completamente silenciosas frente a aspectos técnicos que corresponden a características técnicas esenciales del objeto revelado en la invención bajo estudio, por lo que es evidente la carencia de elementos técnicos que pudieran motivar, y mucho menos conducir, a la persona versada en la materia de manera obvia al resultado alcanzado por el solicitante.

En forma similar al caso arriba señalado, me permito señalar que tal como fue mencionado en mi respuesta previa al señor Examinador, si bien la referencia D2 (anteriormente D4) discute formulaciones que contienen macrólidos y ácido, la misma **no reconoce el beneficio de utilizar agentes antioxidantes en lugar de ácidos para la estabilización de los macrólidos.**

Sobre este particular, me permito manifestar que la afirmación del señor Examinador en respuesta a los argumentos proporcionados por el solicitante en relación

con D2, de acuerdo con la cual dicha referencia "se encuentra en el mismo contexto técnico señalado por el señor solicitante para las formulaciones de Temsirolimus, dado que intenta resolver la problemática de la formación de sustancias producto de la descomposición del activo por efecto de los solventes. Para ello recurre a la formulación de un concentrado de rapamicina en aceite de ricino etoxilado, ácido cítrico y etanol, **es decir, se anticipa a la manera como el señor solicitante pretende resolver el problema**", no es correcta, toda vez que los ejemplos 2a y 3a de D2, cuando se comparan con los ejemplos 2b y 3b de la misma referencia, muestran que los preconcentrados allí obtenidos **son inestables excepto en el ambiente ácido proporcionado por el ácido masónico, e incluso son inestables en la presencia de un antioxidante conocido como el α -tocoferol.**

De conformidad con lo anterior, es completamente claro que las enseñanzas de D2 conducirían a la persona versada en la materia a creer que la inclusión de un agente antioxidante en la formulación de una molécula compleja no tendría ningún efecto estabilizador, **alejándola así de cualquier posibilidad de considerar la presencia de un agente antioxidante como una alternativa a explorar para lograr sistemas estables de moléculas complejas, mucho menos de CCI-779 específicamente.**

Finalmente, el documento D4 citado por primera vez dentro del presente proceso, proporciona información acerca de una formulación parenteral de camptotecina combinada con N,N-dimetilacetamida, un antioxidante y un solvente alcohólico. Sin embargo, D4 no contiene ninguna enseñanza acerca de la formulación de un macrólido, mucho menos del compuesto específico CCI-779, y aún menos acerca de los problemas de formulación que se presentan por las características técnicas particulares que presenta dicha sustancia. En este sentido, lo que D4 enseña es que el sistema de formulación allí empleado es efectivo para camptotecina, **pero la extrapolación de esta información a cualquier macrólido, y particularmente a CCI-779, adicionalmente con expectativas de éxito, no es sugerida ni se desprende de la misma,** toda vez que a partir de la lectura de dicho documento es perfectamente claro que el desarrollo allí propuesto está centrado únicamente en los problemas de formulación de la molécula de camptotecina.

Ahora bien, en relación con el argumento central del señor Examinador de acuerdo con el cual **es la combinación de las enseñanzas de los documentos citados la que permite afirmar la carencia de Nivel Inventivo del objeto reivindicado en la presente solicitud,** me permito manifestar que el solicitante no está de acuerdo con dicha posición, toda vez que las **características combinadas de las realizaciones**

} NI
Novedad.

JOSE LLOREDA CAMACHO & CO.

Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 6069700 Fax 6069701

reclamadas no podrían derivarse en forma obvia o evidente a partir de D1 a D4, tal como me permito demostrar a continuación.

En efecto, la persona versada en la materia no podría predecir o anticipar a partir del estado de la técnica citado que la combinación de características proporcionada por el solicitante podría conducir a formulaciones parenterales con estabilidad mejorada, toda vez que son físicamente estables durante el almacenamiento a temperatura ambiente, tal como ha sido demostrado por los inventores a través de los ejemplos incluidos en la memoria descriptiva.

En conexión con lo anterior, resulta de la mayor importancia para el correcto estudio de patentabilidad, señalar que **ninguno de los documentos D1 a D4, bien sea tomados solos o en combinación, podría sugerir a la persona versada en la materia la efectividad del concentrado cosolvente de CCI-779 en la superación de los problemas para la preparación de formulaciones parenterales de CCI-779, esto es, su inestabilidad química en virtualmente todos los solventes orgánicos y su tendencia a la precipitación cuando se diluye con soluciones acuosas, así como tampoco podrían proporcionar motivación alguna para tratar de solucionar tales problemas**, frente a los cuales dichas referencias son completamente silenciosas.

En este sentido, me permito dirigir la atención del señor Examinador al hecho de que no cabe duda alguna que la combinación de D1 a D4 falla en discutir o al menos identificar los problemas de solubilidad y estabilidad asociados con las formulaciones parenterales de CCI-779. Por lo tanto, así como es fácil identificar que de la combinación de D1 a D4 la persona versada en la materia no podría reconocer los problemas de la formulación parenteral de CCI-779, es aún más claro que dicha combinación tampoco podría sugerir una solución para los mismos, y mucho menos, la solución precisamente aportada por el solicitante mediante la presente invención, razón por la cual se puede afirmar categóricamente que la materia protegida en las reivindicaciones 1 a 9 del capítulo reivindicatorio ahora presentado, esto es, el concentrado cosolvente de CCI-779, posee el Nivel Inventivo requerido frente a las enseñanzas del estado de la técnica citado.

Adicionalmente, me permito manifestar al señor Examinador que el Nivel Inventivo de las reivindicaciones 10 a 14 ahora presentadas puede ser demostrado en forma similar a la discusión anteriormente expuesta para las reivindicaciones 1 a 9. En efecto, el problema técnico a ser solucionado es la necesidad de proporcionar formulaciones de CCI-779 con estabilidad mejorada, preferiblemente, formulaciones estables durante el almacenamiento y aún más preferiblemente, formulaciones de fácil manipulación.

Las anteriores necesidades han sido solucionadas gracias a la presente invención mediante la provisión de una formulación parenteral que contenga:

- Aproximadamente 1 a 25 mg/mL de CCI-779,
- Un solvente alcoholico,
- Aproximadamente 0.0005 a 0.5% p/v de un antioxidante,
- Un solvente diluyente, y
- Un surfactante.

Ahora bien, **ninguna combinación posible de los documentos D1 a D4 permitiría, en forma obvia o evidente, que la persona versada en la materia simultáneamente:**

- (a) Discutiera el uso de antioxidantes en la estabilización de CCI-779;
- (b) Identificara el problema técnico abordado y solucionado mediante la presente invención;
- (c) Discutiera un concentrado de cosolvente como parte de una formulación parenteral, mucho menos de CCI-779;
- (d) Mencionara o considerara un antioxidante, mucho menos de 0.001 a 0.1% de dicho agente antioxidante, en la formulación parenteral del concentrado cosolvente de CCI-779; y
- (e) Discutiera alguna formulación parenteral de CCI-779 con estabilidad mejorada del todo.

Adicionalmente, me permito dirigir la atención del señor Examinador al hecho de que, bajo ningún punto de vista técnicamente válido, puede considerarse que el establecimiento de las condiciones arriba señaladas corresponde a una tarea que la persona versada en la materia realizaría en forma obvia o evidente a partir de las enseñanzas de los documentos citados, toda vez que el grado de especificidad para ello es tal que únicamente a través de un análisis en retrospectiva de la invención, es decir, partiendo del resultado proporcionado por el solicitante, sería posible llegar a la combinación de características técnicas que representa al objeto de la invención, lo cual tal como el señor Examinador debe saber, corresponde a un análisis de patentabilidad incorrectamente practicado y, por ende, carente de validez técnica.

Tal como se ha demostrado mediante los argumentos previamente expuestos, los documentos D1 a D4 carecen de las enseñanzas necesarias para conducir a todas las características anteriormente mencionadas, y más importante aún, la persona versada en la materia no podría predecir que esta combinación de características pudiera proporcionar formulaciones parenterales de CCI-779 con estabilidad mejorada, dado que son físicamente estables a temperatura ambiente tal como ha sido demostrado por los inventores mediante los ejemplos suministrados en la descripción, de forma tal que los resultados alcanzados

JOSE LLOREDA CAMACHO & CO.

Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 6069700 Fax 6069701

corresponden a un avance técnico inesperado y sorprendente que permite afirmar que la materia de las reivindicaciones 10 a 14 ahora presentadas efectivamente posea el Nivel Inventivo requerido frente a cualquier combinación posible de las enseñanzas de los documentos citados.

Finalmente, a pesar de la ausencia de argumentos técnicos en contra de las reivindicaciones de proceso en el Concepto Técnico No. **2970**, el solicitante se permite dirigir la atención del señor Examinador al hecho de que las reivindicaciones 15 a 23 ahora presentadas se encuentran dirigidas a proteger el proceso para la preparación de de formulaciones parenterales novedosas e inventivas que implica como primera etapa la preparación de un concentrado cosolvente también novedoso e inventivo, tal como se ha demostrado anteriormente. Por lo tanto, el proceso de obtención de la formulación parenteral revelada en la presente solicitud, también es novedosa e inventiva, toda vez que no existe en los documentos citados ninguna enseñanza que condujera a una persona versada en la materia a desarrollar un procedimiento para la obtención de un objeto que tampoco le es sugerido.

De conformidad con lo anterior, queda demostrado que en la ausencia del reconocimiento de cualquiera de los problemas mencionados en la preparación de formulaciones parenterales de CCI-779, la persona versada en la materia no se encontraría en capacidad para alcanzar las formulaciones reclamadas mediante la solicitud en estudio, menos aún, sin el reconocimiento de la necesidad de emplear dentro de dichas soluciones un agente antioxidante.

En consecuencia, me permito resaltar una vez más que de conformidad con los argumentos presentados ha sido demostrado de forma contundente el evidente carácter inventivo de las formulaciones de la presente solicitud frente a las enseñanzas de los documentos D1 a D4, de forma tal que **se confirma que la materia objeto de la solicitud cumple cabalmente con lo preceptuado en el Artículo 18 de la Decisión Andina 486 de 2000, es decir cumple con el requisito de altura inventiva frente a las enseñanzas de estado del arte previo.**

5. Anexo me permito presentar:

(a) Recibo No. 09-77,226, expedido por la Superintendencia de Industria y Comercio que acredita el pago de la tasa correspondiente; y

(b) Copia del nuevo Capítulo Reivindicatorio, en el cual se han realizado las modificaciones expuestas anteriormente.



LLOREDA & CIA. S. A.

345 153

6. En vista de lo anterior, ruego a usted proceder a estudiar nuevamente la solicitud a la luz de las argumentaciones y las modificaciones presentadas y conceder el privilegio de patente solicitado.

Señor Superintendente,


ALICIA LLOREDA RICAURTE

T.P. 53.215

NOTARIA 41 DEL CÍRCULO DE BOGOTÁ D.C.
DEPARTAMENTO DE CUNDINAMARCA
REPÚBLICA DE COLOMBIA

El Notario 41 del círculo de Bogotá, da fe de que compareció personalmente Alicia Lloreda Ricaurte identificada (o) con: 39.690.713 y tarjeta profesional de abogado No. 53.215 del Consejo Superior de la Judicatura, quien autentica la firma puesta por ella (el) mismo an este escrito.
(Art. 84 C. P. C. Decreto. 2282/99 mod. 36)

5 NOV. 2009


ALICIA LLOREDA-RICAURTE
C.C. No. 39.690.713 de Usaquén



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

346
154

RECIBO OFICIAL DE CAJA : 09 - 77,226
FECHA : OCTUBRE 13 DE 2009

===== CONSIGNACION =====

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
LOREDA Y CIA S. A	RECIBO DE CAJA			76955	13/10/2009	8,133,000.00

===== CONCEPTO =====

CANT. HISTORICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEHAS COMERCIALES	111,000.00
	TOTAL :	\$ 111,000.00

SON: CIENTO ONCE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

REIVINDICACIONES

1. Un concentrado cosolvente de CCI-779 que comprende:
aproximadamente 2.5 mg/mL a aproximadamente 50 mg/mL de CCI-779,
→ un solvente parenteralmente aceptable/seleccionado del grupo que consiste
en dimetilacetamida y un solvente alcohólico, y
aproximadamente 0.001% a 1.0% p/v de un componente antioxidante.
2. El concentrado cosolvente de la reivindicación 1, en donde el solvente
parenteralmente aceptable es dimetilacetamida.
3. El concentrado cosolvente de la reivindicación 1, en donde el solvente
parenteralmente aceptable es un solvente alcohólico.
4. El concentrado cosolvente de la reivindicación 3, en donde el solvente
alcohólico comprende etanol, propilen glicol, polietilen glicol 300, polietilen
glicol 400, polietilen glicol 600, o una mezcla de los mismos.
5. El concentrado cosolvente de cualquiera de las reivindicaciones 1 a 4,
en donde el componente antioxidante comprende: ácido cítrico, glicina,
d,l- α -tocoferol, BHA, BHT, monotioglicerol, ácido ascórbico o propil galato.
6. Un concentrado cosolvente de CCI-779 que comprende, CCI-779,
ácido cítrico y etanol deshidratado.
7. Un concentrado cosolvente de CCI-779 que comprende, CCI-779,
etanol deshidratado, d,l- α -tocoferol y propilen glicol.
8. El concentrado cosolvente de la reivindicación 7, que además
comprende ácido cítrico.
9. El concentrado cosolvente de cualquiera de las reivindicaciones 1 a 8,
en donde el CCI-779 comprende aproximadamente 25 mg/mL a
aproximadamente 50 mg/mL.

10. Una formulación parenteral que comprende el concentrado cosolvente de cualquiera de las reivindicaciones 1 a 9, un solvente diluyente y un surfactante, en donde CCI-779 comprende aproximadamente 1 mg/mL a aproximadamente 25 mg/mL de la formulación parenteral y el antioxidante comprende aproximadamente 0.0005 a 0.5% p/v de la formulación parenteral.

11. La formulación parenteral según la reivindicación 10, en donde el surfactante es polisorbato 20, polisorbato 80, un ácido biliar, lecitina, un aceite vegetal etoxilado, vitamina E tocoferol propilen glicol succinato, o copolímeros de bloque polioxietilen-polioxipropileno.

12. La formulación parenteral según las reivindicaciones 10 u 11, en donde CCI-779 comprende aproximadamente 2.5 mg/mL a aproximadamente 10 mg/mL de la formulación parenteral.

13. La formulación parenteral de cualquiera de las reivindicaciones 10 a 12, en donde el surfactante comprende aproximadamente 0.5% a aproximadamente 10% p/v de la formulación parenteral.

14. La formulación parenteral de cualquiera de las reivindicaciones 10 a 12, en donde el solvente diluyente comprende aproximadamente 10% a aproximadamente 90% p/v de la formulación parenteral.

15. Un proceso para preparar la formulación parenteral de la reivindicación 10, en donde el proceso comprende:

(a) mezclar CCI-779 con el solvente parenteralmente aceptable y el componente antioxidante para dar un concentrado cosolvente;

(b) mezclar el solvente diluyente y el surfactante para producir un diluyente; y

(c) mezclar el concentrado cosolvente con el diluyente.

16. El proceso de la reivindicación 15, en donde el solvente parenteralmente aceptable es un solvente alcohólico que comprende etanol, propilen glicol, polietilen glicol 300, polietilen glicol 400, polietilen glicol 600, o una mezcla de los mismos.

17. El proceso de la reivindicación 15 o reivindicación 16, en donde el componente antioxidante comprende ácido cítrico, d,l- α -tocoferol, BHA, BHT, monotioglicerol, ácido ascórbico o propil galato.
18. El proceso de cualquiera de las reivindicaciones 15 a 17, en donde el solvente diluyente es agua, etanol, polietilen glicol 300, polietilen glicol 400, polietilen glicol 600, o propilen glicol, o una mezcla de los mismos.
19. El proceso de cualquiera de las reivindicaciones 15 a 18, en donde el surfactante es polisorbato 20, polisorbato 80, un ácido biliar, lecitina, un aceite vegetal etoxilado, vitamina E tocoferol propilen glicol succinato, o copolímeros de bloque polioxietilen-polioxipropileno.
20. El proceso de cualquiera de las reivindicaciones 15 a 18, en donde el solvente parenteralmente aceptable es etanol deshidratado, el componente antioxidante es ácido cítrico, el solvente diluyente es agua y polietilen glicol 400, y el surfactante es polisorbato 20 o polisorbato 80.
21. El proceso de cualquiera de las reivindicaciones 15 a 18, en donde el solvente parenteralmente aceptable es etanol deshidratado, el componente antioxidante es ácido cítrico, el solvente diluyente es etanol deshidratado y polietilen glicol 400, y el surfactante es polisorbato 20 o polisorbato 80.
22. El proceso de cualquiera de las reivindicaciones 15 a 18, en donde el solvente parenteralmente aceptable es etanol deshidratado y propilen glicol, el componente antioxidante es d,l- α -tocoferol, el solvente diluyente es agua y polietilen glicol 400, y el surfactante es polisorbato 20 o polisorbato 80.
23. El proceso de cualquiera de las reivindicaciones 15 a 18, en donde el solvente parenteralmente aceptable es etanol deshidratado y propilen glicol, el componente antioxidante es d,l- α -tocoferol, el solvente diluyente es etanol deshidratado y polietilen glicol 400, y el surfactante es polisorbato 20 o polisorbato 80.



US005674874A

D4
350
158

United States Patent [19]

Hausheer et al.

[11] Patent Number: 5,674,874

[45] Date of Patent: Oct. 7, 1997

[54] LACTONE STABLE FORMULATION OF 7-ETHYL-10-HYDROXY CAMPTOTHECIN AND METHODS FOR USES THEREOF

[75] Inventors: Frederick B. Hausheer; Kochat Baridas, both of San Antonio, Tex.

[73] Assignee: BioNumerik Pharmaceuticals, Inc., San Antonio, Tex.

[21] Appl. No.: 522,951

[22] Filed: Sep. 1, 1995

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 172,620, Dec. 22, 1993, Pat. No. 5,447,936.

[31] Int. Cl.⁶ A61K 31/475

[52] U.S. Cl. 514/283

[58] Field of Search 514/283

[56] References Cited

U.S. PATENT DOCUMENTS

3,219,529	11/1965	Nash	
3,689,230	10/1972	Besouchamp et al.	
4,082,881	4/1978	Chen et al.	
4,228,162	10/1980	Lauri et al.	
4,339,276	7/1982	Miyasaka et al.	491/22
4,359,282	8/1983	Miyasaka et al.	491/147
4,473,691	9/1984	Miyasaka et al.	546/448
4,545,860	10/1985	Miyasaka et al.	204/158
4,604,463	3/1986	Miyasaka et al.	544/66
4,713,246	12/1987	Begum et al.	514/27
4,794,284	3/1988	Terada et al.	
4,778,891	10/1988	Tagawa et al.	545/13
5,004,758	4/1991	Boehm et al.	514/283
5,061,800	10/1991	Wall et al.	514/219
5,180,722	1/1993	Katana	546/46
5,225,404	7/1993	Giovannella et al.	514/81
5,227,390	7/1993	Wall et al.	
5,447,936	9/1993	Hausheer et al.	514/283
5,468,754	11/1993	Hausheer et al.	514/283
5,496,830	3/1996	Shapiro	514/283
5,597,829	1/1997	Hausheer	514/283
5,604,233	2/1997	Hausheer	514/283
5,633,260	3/1997	Hausheer	514/283

OTHER PUBLICATIONS

Emerson, David L., et al.; In Vivo Antitumor Activity of Two New Seven-Substituted Water Soluble Camptothecin Analogues; *Cancer Research* 53:603-609; Feb. 1993.Gupta, Elora, et al.; Metabolic Fate of Irinotecan in Humans: Correlation Of Glucuronidation With Diarrhea; *Cancer Research* 54:3723-3725, Jul. 1994.Rass, Naomi B., et al.; Phase I Pharmacokinetic Study of Topotecan by 24-Hour Continuous Infusion Weekly; *Cancer Research* 54:1220-1226, Mar. 1994.Hinz, Hellmuth R., et al.; Pharmacokinetic of the In Vivo and In Vitro Conversion of 9-Nitro-20-(S)-Camptothecin In Humans, Dogs, and Mice; *Cancer Research* 54:3096-3100, Jan. 1994.Houghton, Peter J., et al.; Therapeutic Efficacy of the Topoisomerase I Inhibitor 7-Ethyl-10-(4-{1-piperidino}-1-piperidino)-carboxyloxy-camptothecin against Human Tumor Xenografts: Lack of Cross-Resistance In Vivo in Tumors With Acquired Resistance To The Topoisomerase I Inhibitor 9-Dimethylaminomethyl-10-hydroxycamptothecin; *Cancer Research* 53:2823-2829, Jan. 1993.Luzzio, Michael J., et al.; Synthesis And Antitumor Activity of Novel Water Soluble Derivatives Of Camptothecin As Specific Inhibitors of Topoisomerase I; *Journal Of Medicinal Chemistry*, 38:3395-401.Moertel, Charles G., et al.; Phase II Study of Camptothecin (NSC-100880) in the Treatment Of Advanced Gastrointestinal Cancer; *Cancer Chemotherapy Reports Part 1* vol. 56, No. 1, Feb. 1972.Rivory, Laurent P., et al.; Kinetics of the In Vivo Interconversion of the Carboxylate and Lactone Forms of Irinotecan (CPT-11) and of Its Metabolite SN-38 in Patients; *Cancer Research* 54:6330-6333, Dec. 1994.Supko, Jeffrey G., et al.; Pharmacokinetics of the 9-Amino and 10, 1-Methylenedioxy Derivatives of Camptothecin in Mice; *Cancer Research* 53:3062-3069, Jul. 1993.Wall, Monroe E., et al.; Camptothecin And Taxol: Discovery To Clinic-Thirteenth Bruce F. Cain Memorial Award Lecture; *Cancer Research* 55:753-760, Feb. 1995.

Wall, Monroe E., et al.; Camptothecin: AntiCancer Agents Based on Natural Product Models, Chapter 12, pp. 417-436, 1990.

Wall, Monroe E., et al.; Plant Antitumor Agents, 30th Synthesis And Structure Activity Of Novel Camptothecin Analogs; *J. Med. Chem.*, 36:2689-2700, 1993.

Primary Examiner—Donald G. Duns

Attorney Agent, or Firm—Thomas J. Dodd

[57] ABSTRACT

7-ethyl-10-hydroxy camptothecin (HECPT), an active metabolite of the camptothecin analog CPT-11 which is used as an anticancer drug, is poorly soluble in water. Because of its poor water solubility, HECPT has not been directly administered by parenteral or oral routes in human patients for the purpose of inhibiting the growth of cancer cells. There is also unpredictable interpatient variability in the metabolic production of HECPT from CPT-11 which limits the utility of CPT-11. This invention overcomes these limitations by teaching novel pharmaceutically acceptable lactone stable HECPT formulations for the direct administration of lactone stable HECPT formulations orally or parenterally to patients with various forms of cancer.

9 Claims, No Drawings

The solution is stable and free of precipitate for a period of at least two hours; sufficient time to permit administration and absorption by the patient.

It has been observed with similar solutions of etoposide, a chemically unrelated poorly water soluble anticancer drug, that the bioavailability of the drug following oral administration is substantially equivalent to that achieved by intravenous administration of a solution of etoposide (U.S. Pat. No. 4,713,246). Analogous to that of etoposide, it is believed that ingestion of the present dosage form of HECPT and resulting dilution thereof by the stomach contents, results in the formation of a micellar solution of HECPT in the stomach which is readily absorbed by the gastrointestinal tract. Applicants do not wish to be bound, however, by any theoretical explanation of the mechanism by which the superior oral bioavailability of the present HECPT formulation is achieved.

Formulations Containing HECPT

A preferred embodiment of the claimed invention is a formulation containing 7-ethyl-10-hydroxy camptothecin (HECPT) dissolved or suspended in dimethylisobutylacetamide containing from about 0.1 mg to about 5.0 mg 7-ethyl-10-hydroxy camptothecin activity per 1 (one) ml of dimethylisobutylacetamide.

A preferred embodiment of the claimed invention is an antitumor composition comprising a solution of 7-ethyl-10-hydroxy camptothecin dissolved in dimethylisobutylacetamide or dimethylacetamide containing from about 0.1 mg to about 5.0 mg 7-ethyl-10-hydroxy camptothecin activity per ml in a solution consisting of between about 500 and about 10,000 parts by weight of dimethylisobutylacetamide or dimethylacetamide by total solution weight and containing from about 1 to about 1,000 parts by weight of a pharmaceutically acceptable acid per ml of formulation. Inventors prefer to use about 50 to about 500 parts by weight of a pharmaceutically acceptable acid per parts by weight of the total solution.

Also embodied in this formulation wherein said carboxylic acid is selected from the group consisting of tartaric acid, citric acid, succinic, fumaric, maleic acid, gluconic acid, ascorbic acid, taurocholic acid, and taurocholic acid in an admixture with citric acid and wherein said carboxylic acid is selected from the group consisting of citric acid and taurocholic acid in an admixture with citric acid or wherein said mineral acid is selected from the group consisting of hydrochloric acid, and phosphoric acid. Yet another embodiment of this formulation is wherein said admixture of a carboxylic acid and a mineral acid is selected from the group consisting of hydrochloric acid in an admixture with taurocholic acid, phosphoric acid in an admixture with taurocholic acid, citric acid in an admixture with phosphoric acid and citric acid in an admixture with hydrochloric acid. Also, the acid of this formulation is in an amount sufficient to result in a final pH of between about 2.0 and about 6.0 or is in an amount sufficient to result in a final pH of between about 3.0 and about 5.0.

An additional embodiment of the claimed subject matter is wherein said part by weight of a pharmaceutically acceptable acid is from about 1 to about 1,000 parts by weight of the total solution and the acid is selected from the following group, alone or in any combination: citric acid, hydrochloric acid and phosphoric acid.

Another embodiment of this invention is the formulation or an antitumor composition comprising a solution or suspension of about 0.1 to about 15.0 mg of 7-ethyl-10-hydroxy camptothecin per 1 (one) ml of a formulation consisting of

500 to 10,000 parts by weight of dimethylisobutylacetamide or dimethylacetamide by weight of the total formulation in the presence of a pharmaceutically acceptable acid and a glycol selected from the group consisting of polyethylene glycol, propylene glycol, and a combination of a polyethylene glycol and propylene glycol.

Another aspect of this invention is this formulation or antitumor composition comprising a solution or suspension of about 0.1 to about 15.0 mg of 7-ethyl-10-hydroxy camptothecin per 1 (one) ml of a formulation consisting of dimethylisobutylacetamide or dimethylacetamide in the presence of a pharmaceutically acceptable acid, wherein said solution or suspension further comprises taurocholic acid or a pharmaceutically acceptable salt thereof, and a glycol selected from the group consisting of polyethylene glycol, propylene glycol, and a combination of a polyethylene glycol and propylene glycol.

Yet another aspect of this invention is a formulation or solution or suspension of antitumor composition having about 0.1 to about 15.0 mg of 7-ethyl-10-hydroxy camptothecin per 1 (one) ml of a formulation containing 500 to 10,000 parts by weight dimethylisobutylacetamide or dimethylacetamide based on the weight of the total formulation, between about 1 and about 1,000 parts by weight of a pharmaceutically acceptable acid, between about 10 and about 2,500 parts by weight of taurocholic acid or a pharmaceutically acceptable salt thereof, 20 to 8,000 parts by weight of a polyethylene glycol or propylene glycol per total solution weight. An additional embodiment is wherein said acid is an organic carboxylic acid and the inventors prefer citric acid.

Embodied in this invention is the formulation wherein said carboxylic acid is selected from the group consisting of tartaric acid, citric acid, succinic, fumaric, maleic acid, gluconic acid, ascorbic acid, taurocholic acid, and taurocholic acid in an admixture with citric acid. Also, this formulation is further defined wherein said carboxylic acid is selected from the group consisting of citric acid and taurocholic acid in an admixture with citric acid and wherein said mineral acid is selected from the group consisting of hydrochloric acid, and phosphoric acid. Also embodied, wherein said acid is an admixture of a carboxylic acid and a mineral acid is selected from the group consisting of hydrochloric acid in an admixture with taurocholic acid, phosphoric acid in an admixture with taurocholic acid, citric acid in an admixture with phosphoric acid and citric acid in an admixture with hydrochloric acid and wherein said acid is in an amount sufficient to result in a final pH of between about 2.0 and about 6.0 or said acid is in an amount sufficient to result in a final pH of between about 3.0 and about 5.0.

Another aspect of this invention is the formulation or antitumor composition further comprises a lower alcohol. Many different alcohols would be effective in this invention, but the inventors prefer to use ethanol, benzyl alcohol or a combination of ethanol and benzyl alcohol. For this invention, ethanol, ethyl alcohol and dehydrated ethyl alcohol are used interchangeably. Another embodiment of the claimed invention is the formulation or antitumor composition further comprises glycerin as a co-solvent.

A further aspect of this invention is an oral 7-ethyl-10-hydroxy camptothecin formulation comprising 7-ethyl-10-hydroxy camptothecin, dimethylacetamide, a pharmaceutically acceptable acid selected from the group consisting of a carboxylic acid, mineral acid and a carboxylic acid in an admixture with a mineral acid, taurocholic acid or a pharmaceutically acceptable salt thereof, and a glycol selected

35T
159

from the group consisting of polyethylene glycol, propylene glycol and polyethylene glycol in an admixture with propylene glycol. This oral formulation has between about 0.1 and about 15.0 mg of 7-ethyl-10-hydroxy camptothecin per one ml of formulation having between about 500 and about 10,000 parts by weight dimethylacetamide based on the weight of the total formulation, between about 1 and about 1,000 parts by weight of said acid, between about 10 and about 2,500 parts by weight of taurocholic acid or a pharmaceutically acceptable salt thereof, and between about 20 and about 8,000 parts by weight of said glycol per total formulation weight. Also, this oral formulation further has between about 20 parts and about 7,000 parts of a lower alcohol selected from the group consisting of ethanol, benzyl alcohol, and ethanol in an admixture with benzyl alcohol and between about 1 part and about 1,000 parts of glycerin. And, the carboxylic acid in this oral formulation is selected from the group consisting of tartaric acid, citric acid, succinic, fumaric, maleic acid, gluconic acid, ascorbic acid, taurocholic acid, and taurocholic acid in an admixture with citric acid.

Yet another embodiment of this invention is an antitumor composition comprising a solution or suspension containing about 0.1 to about 15.0 mg of 7-ethyl-10-hydroxy camptothecin per 1 (one) ml of a formulation containing 500 to 10,000 parts by weight of dimethylisobutide or dimethylacetamide based on the weight of the total formulation in the presence of a pharmaceutically acceptable acid, wherein said solution further comprises taurocholic acid or a pharmaceutically acceptable salt thereof, a glycol selected from the group consisting of polyethylene glycol, propylene glycol, and a combination of both, ethanol, glycerin, and a buffer, such as sodium acetate, to maintain an acidic pH upon dilution with an aqueous vehicle of less than 6.0 and greater than 2.0.

An additional aspect of this invention is wherein said solution or suspension contains about 0.1 to about 15.0 mg of 7-ethyl-10-hydroxy camptothecin per 1 (one) ml of a formulation containing 500 to 10,000 parts by weight of dimethylisobutide or dimethylacetamide in based on the weight of the total formulation, 1 to 1,000 parts by weight of a pharmaceutically acceptable acid, 10 to 2,500 parts by weight of taurocholic acid or a pharmaceutically acceptable salt thereof, 20 to 8,000 parts by weight of a polyethylene glycol or propylene glycol or a combination of a polyethylene glycol and propylene glycol, 1 to 1,000 parts by weight of glycerin, 20 to 7,000 parts by weight of lower alcohol selected from the group consisting of ethanol, benzyl alcohol and a combination of both, 0.1 to 750 parts by weight of a buffer based on the weight of the total formulation.

This oral formulation is further defined wherein said carboxylic acid is selected from the group consisting of tartaric acid, citric acid, succinic, fumaric, maleic acid, gluconic acid, ascorbic acid, taurocholic acid, and taurocholic acid in an admixture with citric acid and wherein said acid is selected from the group consisting of citric acid and taurocholic acid in an admixture with citric acid. Also embodied in this invention is wherein said acid is taurocholic acid in an admixture with citric acid and wherein said mineral acid is selected from the group consisting of hydrochloric acid, and phosphoric acid. Further, the admixture of a carboxylic acid and a mineral acid is selected from the group consisting of hydrochloric acid in an admixture with taurocholic acid, phosphoric acid in an admixture with taurocholic acid, citric acid in an admixture with phosphoric acid and citric acid in an admixture with hydrochloric acid.

Also, the acid is in an amount sufficient to result in a final pH of between about 2.0 and about 6.0 or the acid is in an amount sufficient to result in a final pH of between about 3.0 and about 5.0.

Another embodiment of this invention is wherein said polyethylene glycol has a molecular weight of about 300 to 400 and the antitumor composition further comprises a non-ionic surfactant. There are many different surfactants but the inventors prefer a poloxamer. The preferred poloxamer is poloxamer 127.

Yet another embodiment of this invention is a formulation or an antitumor composition comprising a solution or suspension of about 0.1 to about 15.0 mg of 7-ethyl-10-hydroxy camptothecin per 1 (one) ml of a formulation consisting of 500 to 10,000 parts by weight of dimethylisobutide or dimethylacetamide based on the weight of the total formulation in the presence of a pharmaceutically acceptable acid, wherein said solution further comprises a lower alcohol and a glycol selected from the group consisting of polyethylene glycol, a propylene glycol, and a combination of a polyethylene glycol and propylene glycol.

Yet another embodiment of this invention is a formulation or an antitumor composition comprising a solution or suspension of about 0.1 to about 15.0 mg of 7-ethyl-10-hydroxy camptothecin per 1 (one) ml of a formulation consisting of 500 to 10,000 parts by weight of dimethylisobutide or dimethylacetamide based on the weight of the total formulation in the presence of a pharmaceutically acceptable acid, wherein said solution further comprises a lower alcohol, polyethylene glycol or propylene glycol, or a combination of a polyethylene glycol and propylene glycol, and surfactant.

As a more preferred embodiment for this antitumor composition, the pharmaceutically acceptable organic acid is citric acid, the polyethylene glycol is PEG 300, the lower alcohol is ethanol and the surfactant is polysorbate-80.

An aspect of this invention is an oral 7-ethyl-10-hydroxy camptothecin formulation comprising 7-ethyl-10-hydroxy camptothecin, dimethylacetamide, a pharmaceutically acceptable acid selected from the group consisting of a carboxylic acid, mineral acid and a carboxylic acid in an admixture with a mineral acid, taurocholic acid or a pharmaceutically acceptable salt thereof, and a glycol selected from the group consisting of polyethylene glycol, propylene glycol and polyethylene glycol in an admixture with propylene glycol, ethanol, glycerin, and a buffer to maintain an acidic pH in a range between about 2.0 and 6.0 upon dilution with an aqueous vehicle, wherein said oral formulation has between about 0.1 and about 15.0 mg of 7-ethyl-10-hydroxy camptothecin per one ml of formulation having between about 500 and about 10,000 parts by weight of dimethylacetamide based on the weight of the total formulation. This formulation has between about 1 part and about 1,000 parts by weight of said pharmaceutically acceptable acid, between about 10 parts and about 2,500 parts by weight of taurocholic acid or a pharmaceutically acceptable salt thereof, between about 20 parts and about 8,000 parts by weight of said glycol, between about 1 part and about 1,000 parts by weight of glycerin, between about 20 parts and about 7,000 parts by weight of ethanol, between about 0.1 part and about 750 parts by weight of a buffer based on the weight of the total formulation and wherein said buffer is sodium acetate. Also, the glycol in this oral formulation is selected from the group consisting of polyethylene glycol 300 and polyethylene glycol 400 and this oral formulation further has a surfactant wherein said surfactant is poloxamer and more specifically wherein said poloxamer is poloxamer 127.

352
160

HECPT in DMI or DMA when administered parenterally, can be diluted with an appropriate volume of a parenteral vehicle to a concentration of about 0.1 mg/ml or a lower concentration of HECPT activity. A further embodiment of the claimed invention is a sterile solution of any of the claimed HECPT compositions and formulations for sterile administration to a patient with cancer upon dilution with a sterile parenteral vehicle. For the purposes of this invention, parenteral vehicles include dextrose 5 to 10% in water, 0.9% NaCl in water with or without 5% or 10% Dextrose, 0.45% NaCl in water with or without 5% or 10% Dextrose, and 3% NaCl in water with or without 5% to 10% Dextrose, or sterile lipid formulations, such as intralipid, used for parenteral nutritional support for cancer patients.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

In its preferred embodiments, this invention involves preparation and administration of novel lactone stable HECPT formulations as described below.

EXAMPLES

The following examples illustrate selected modes for carrying out the claimed invention and are not to be construed as limiting the specification and claims in any way.

The foregoing description of the formulation invention has been directed to particular preferred embodiments in accordance with the requirements of the patent statutes and for purposes of explanation and illustration. Those skilled in the art will recognize that many modifications and changes may be made without departing from the scope and the spirit of the invention.

Example 1

Formulation #1 of HECPT and DMI

For injection or infusion into aqueous body fluids, a formulation containing about 0.1 to about 2.5 mg of HECPT dissolved in 500 to 10,000 parts by weight of dimethylisorbide based on the total weight of the formulation, about 1 to 1,000 parts by weight of a pharmaceutically acceptable acid, about 20 to 7,000 parts by weight of a pharmaceutically acceptable alcohol, about 20 to about 8,000 parts by weight of a polyethylene glycol, and about 20 to about 8,000 parts of a non-ionic surfactant. Suitable alcohols include ethyl alcohol and benzyl alcohol. Suitable polyether glycols for this formulation include polyethylene glycol 300, polyethylene glycol 400 and propylene glycol. Suitable non-ionic surfactants include polysorbate-80. In a preferred embodiment, the formulation of HECPT is supplied as an intravenous injectable in a unit dose sealed vial comprising a sterile, non-aqueous solution of drug in a vehicle comprising dimethylisorbide, ethyl alcohol with or without benzyl alcohol, citric acid, polyethylene glycol 300, and polysorbate (Tween 80) in acidified medium with a pH of 3 to 4 at a final concentration of 0.1 to 1.0 mg of HECPT per 1 ml of formulation.

Example 2

Formulation #2 of HECPT and DMI

A second formulation comprises from about 0.1 mg to about 2.5 mg of HECPT dissolved in a formulation containing 20 to 7,000 parts by weight of a pharmaceutically acceptable alcohol and about 20 to 8,000 parts by weight of

formulation of a non-ionic surfactant. Suitable alcohols include dehydrated ethyl alcohol USP with or without benzyl alcohol. Suitable non-ionic surfactants include the polyoxyethylated oils, such as polyoxyethylated vegetable oils, such as castor oil, peanut oil, and olive oil. In a preferred embodiment 0.1 mg to 1.0 mg HECPT per ml of formulation consists of 500 to 10,000 parts by weight of dimethylisorbide, 20 to 8,000 parts by weight of Cremaphor EL (polyoxyethylated castor oil), 20 to 7,000 parts by weight of ethyl alcohol and 1 to 1,000 parts by weight of total solution weight of citric acid.

Example 3

Oral Formulation of HECPT and DMI

An oral formulation of HECPT in soft gelatin capsules (comprised of gelatin/glycerin/sorbitol/purifiers/purified water) containing HECPT in a final concentration of 0.1 to 1.0 mg per ml in a formulation containing 500 to 10,000 parts of dimethylisorbide by weight of total solution, citric acid 1 to 1,000 parts by weight, glycerin 1 to 1,000 parts by weight, and polyethylene glycol 300 or polyethylene glycol 400 20 to 8,000 parts by weight, ethyl alcohol 20 to 7,000 parts by weight, sodium acetate 0.1 to 250 parts by weight, pluronic F-127 poloxamer 0.1 to 800 parts by weight, and taurocholic acid 10 to 2,500 parts by weight of total solution weight. The soft gelatin capsules may also be composed of any of a number of compounds used for this purpose including, for example, a mixture of gelatin, glycerin, sorbitol, purified water, and parabens.

Example 4

Formulation #1 of HECPT and DMA

For injection or infusion into aqueous body fluids, a formulation comprises from about 0.1 to about 5.0 mg of HECPT dissolved in 500 to 10,000 parts by weight of total solution weight of dimethylacetamide (DMA), about 1 to about 1,000 parts by weight of a pharmaceutically acceptable acid, about 20 to about 7,000 parts by weight of an alcohol, about 20 to about 8,000 parts by weight of a polyether glycol including polyethylene glycol, and about 20 to about 8,000 parts of a non-ionic surfactant. Suitable pharmaceutically acceptable acids include citric acid, hydrochloric acid and phosphoric acid alone or in any combination. Suitable alcohols include dehydrated ethyl alcohol, benzyl alcohol. Suitable polyether glycols, which can be used individually or in any combination include polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400 and propylene glycol. Suitable non-ionic surfactants include polysorbate-80. In a preferred embodiment, the formulation of HECPT is supplied as an intravenous injectable in a sealed unit dose vial comprising a sterile, non-aqueous solution of drug in a vehicle comprising ethyl alcohol, benzyl alcohol, citric acid, polyethylene glycol 300, and polysorbate (Tween 80) in an acidified medium with a pH of 3 to 4 containing HECPT at a final concentration of 0.2 mg per ml.

Example 5

Formulation #2 of HECPT and DMA

A second formulation contains about 0.1 mg to about 5.0 mg of HECPT dissolved in 500 to about 10,000 parts by weight of dimethylacetamide, 1 to 1,000 parts by weight of citric acid, 20 to 7,000 parts by weight of an alcohol and

354/162

27

about 20 to 8,000 parts by weight of a non-ionic surfactant. Suitable alcohols include dehydrated ethyl alcohol USP or dehydrated ethyl alcohol and benzyl alcohol. Suitable non-ionic surfactants include the polyoxyethylated oils, such as polyoxyethylated vegetable oils, such as castor oil, peanut oil, and olive oil. In a preferred embodiment 0.1 to 5 mg HECPT is formulated in 500 to 10,000 parts by weight of dimethylacetamide (DMA), 20 to 8,000 parts by weight of Cremaphor EL (polyoxyethylated castor oil), 20 to 7,000 parts by weight dehydrated ethyl alcohol USP, and 50 to 750 parts by weight of citric acid to adjust the final pH between 3 to 4.

Example 6

Oral Formulation of HECPT and DMA

An oral formulation of HECPT in soft gelatin capsules (comprised of gelatin/glycerin/sorbitol/purifiers/purified water) containing 0.1 to 15 mg of HECPT dissolved or suspended in 500 to 10,000 parts of dimethylacetamide, citric acid 1 to 1,000 parts by weight, glycerin 1 to 1,000 parts by weight, and polyethylene glycol 300 or polyethylene glycol 400 20 to 8,000 parts by weight, dehydrated ethyl alcohol 20 to 7,000 parts by weight, sodium acetate 0.1 to 250 parts by weight, pluronic F-127 poloxamer 0.1 to 800 parts by weight, and taurocholic acid 10 to 2,500 parts by weight. The soft gelatin capsules may also be composed of any of a number of compounds used for this purpose including, for example, a mixture of gelatin, glycerin, sorbitol, purified water, and parabens.

Example 7

Administration of HECPT and DMA or DMI Formulations

To allow a prolonged parenteral infusion of HECPT to patients with cancer for clinical infusions, the drug may be diluted in 5% Dextrose in water (D5W) to a final concentration of 0.001 mg/ml to about 0.01 mg/ml of HECPT prior to injection or infusion.

Maintaining an acidic pH (3 to 4) in the formulation is particularly important to reduce the slow conversion of HECPT lactone to the E-ring-hydrolyzed carboxylate form, which occurs at physiological pH. At equilibrium under physiologic pH, the ratio of the open-ring carboxylate form to lactone form increases. Hydrolysis of the HECPT lactone E-ring will be substantially reduced if the drug is kept in an acidic environment. Some of the unpredictable toxicity seen in earlier clinical trials using sodium camptothecin may have been due to the formation of greater amounts of the lactone form of camptothecin, which is 10-fold more toxic than sodium camptothecin in mice. The lactone form of camptothecin, as in HECPT, is less water soluble than the carboxylate E-ring form. When early clinical trials were first conducted with camptothecin formulated using NaOH, the significance of maintaining the closed lactone E ring for uniform efficacy in treating patients with cancer was poorly understood. The early reported unpredictable clinical toxicities associated with camptothecin administration may have been exacerbated by the NaOH formulation which promotes the formation of the carboxylate form, and by the relative lack of understanding of the significance of the lactone form of camptothecin as it relates to antitumor activity.

Example 8

Solubility of Camptothecin in Various Solvents

This Example was designed to test the solubility of camptothecin, which is used as a reference compound for

7-ethyl-10-hydroxy camptothecin in different solvents. For this Example, BNPT-1028 is camptothecin. The solubility of camptothecin was tested in water, ethanol, benzyl alcohol, propylene glycol, PEG 300, DMI and DMA. For this Example, the maximum amount of camptothecin that would dissolve in 1 ml of the indicated solvent at 4° C. or at 25° C. was measured. For example, referring to Table 4, 0.928 mg camptothecin dissolved in 1 ml of DMI at 25° C., 5.0 mg camptothecin was dissolved in 1 ml of DMA at 25° C., while only 0.051 mg camptothecin dissolved in 1 ml of ethanol (200 proof) 25° C. See Table 4 below. See Table 4. The numbers in the Parentheses are greater than highest calibration standard. They are considered acceptable because of the linear response of the method.

This Example confirmed the poorly water soluble nature of camptothecin and demonstrated that camptothecin is relatively insoluble in water and polar solvents (i.e. ethanol, propylene glycol). This Example also showed that camptothecin was much more soluble in non-polar solvents such as benzyl alcohol, dimethyl isosorbide and dimethylacetamide. From this data, it can be concluded that maximum dissolution of camptothecin depends on the temperature (4° C. versus 25° C.) and solvent. As is evident, camptothecin dissolves better in DMI and DMA than in ethanol or water. Also, camptothecin is much more soluble in DMA than in DMI.

TABLE 4

Solubility of Camptothecin in DMA or DMI in Different Solvents

Solvent	Target Concentration (µg/ml)	4° C. Actual Concentration (µg/ml)	25° C. Actual Concentration (µg/ml)
Mili-Q Water	2620	0.7	0.2
Ethanol (200 Proof)	2620	41	51
Benzyl Alcohol	2710	(2663)	1674
Propylene Glycol	3130	296	381
PEG 300	2660	650	(706)
Dimethylacetamide	2460	510	928
N,N-Dimethyl Acetamide	10000	5500	5000

Example 9

Solubility of HECPT in DMA with Additional Components

(Range in Parts by Weight)

This Example was designed to determine the range in parts by weight for a variety of different components added to an initial solution of HECPT and DMA. Table 5 is a compilation of these ranges. Various combinations of the components are presented in Tables 6, 7, and 8.

TABLE 5

SOLUBILITY OF SN3S (0.1 MG/ML TO 10 MG/ML) IN DMA WITH ADDITIONAL COMPONENTS (RANGE IN PARTS BY WEIGHT)

COMPONENT	RANGE IN PARTS BY WEIGHT	TABLE NUMBER
Dimethylacetamide (DMA)	500-10,000	6, 7, 8
Total Acid	1-3,500	6, 7, 8
Citric Acid	1-1,000	6, 7, 8
Taurocholic Acid	10-2,500	8
PEG 300, PEG 400	20-8,000	7, 8

TABLE 5-continued

SOLUBILITY OF SN38 (0.1 MG/ML TO 10 MG/ML) IN DMA WITH ADDITIONAL COMPONENTS (RANGE IN PARTS BY WEIGHT)		
COMPONENT	RANGE IN PARTS BY WEIGHT	TABLE NUMBER
Glycerin	1-1,000	8
Benzyl Alcohol	20-4,000	6
Dehydrated Ethyl Alcohol USP (Ethanol)	20-7,000	6, 7, 8
Polysorbate - 80	20-8,000	6
Cremaphor EL (Polyoxyethylene castor oil)	20-8,000	7
Propylene Glycol	20-8,000	
Poloxamer (Poloxamer 127)	0.1-800	8
Sodium Acetate	0.1-250	8

Example 10

Modified Parenteral Formulation Version 1
HECPT with DMA

This Example presents one preferred parenteral formulation of HECPT and DMA in combination with a variety of

succinic, fumaric, maleic acid, gluconic acid, ascorbic acid, taurocholic acid, and taurocholic acid in an admixture with citric acid. These are examples only and not intended to be the only carboxylic acids for this invention.

Examples of different combinational parenteral formulations are presented in Table 6 below. This parenteral formulation includes between about 0.1 to about 0.25 mg per ml of HECPT per ml of formulation, ethanol (about 20 to about 7,000 parts by weight), benzyl alcohol (about 500 to about 5,000 parts by weight), citric acid (about 1 to about 1,000 parts by weight), polyethylene glycol 300 (PEG 300; about 20 to about 8,000 parts by weight), DMA (also called DMAC; about 500 to about 10,000 parts by weight) and Tween 80 (polysorbate-80, a non-ionic surfactant; about 20 to about 8,000 parts by weight).

TABLE 6

Modified Oral or Parenteral Formulation Version 1 (with DMAC)												
Formulation Number	Ethanol		Benzyl Alcohol		Citric Acid		PEG 300		DMAC		Tween 80	
	Nominal (mL)	Exact (mL)	Nominal (mL)	Exact (mL)	Nominal (G)	Exact (G)	Nominal (G)	Exact (G)	Nominal (mL)	Exact (mL)	Nominal (G)	Exact (G)
4 - DMAC	6.337	6.337	—	—	1.0000	1.0077	50.0000	49.9909	10.584	10.584	10.0000	10.0097
9 - DMAC	1.901	1.901	—	—	1.5000	1.5085	15.0000	15.0179	32.051	32.051	30.0000	29.9929
10 - DMAC	20.279	20.279	3.444	3.444	4.0000	3.9962	40.0000	40.2157	8.547	8.547	8.0000	8.0297

different components. For each formulation approximately 2.5 mg of HECPT was dissolved in 1000 parts of a pure form of DMA at 25° C. Dissolution was achieved with gentle agitation until a clear solution resulted within about 2 hours. Approximately one hundred (100) parts of a mineral acid is added to this solution of HECPT and DMA to obtain a final pH of between 2 and 6. A more preferred pH range is between 3 and 4. Examples of mineral acids are pure hydrochloric acid (0.1N) and phosphoric acid. These are examples only and not intended to be the only mineral acids used in this invention. Range of HECPT in DMA is 0.1 mg to 0.25 mg HECPT per ml of formulation.

Example 11

Modified Parenteral Formulation Version 1
HECPT with DMA

This Example presents another preferred parenteral formulation of HECPT and DMA in combination with a variety of different components. For each formulation approximately 2.5 mg of HECPT was dissolved in 1000 parts of a pure form of DMA at 25° C. Dissolution was achieved with gentle agitation until a clear solution resulted within about two hours. About five hundred (500) parts of a carboxylic acid is added to this solution of HECPT and DMA. Examples of carboxylic acids are tartaric acid, citric acid,

Example 12

Modified Parenteral Formulation Version 2
HECPT with DMA

This Example presents yet another preferred parenteral formulation of HECPT and DMA in combination with a variety of different components. For each formulation approximately 2.5 mg of HECPT was dissolved in 1000 parts of a pure form of DMA at 25° C. Dissolution was achieved with gentle agitation until a clear solution resulted within about two hours. About five hundred (500) parts of a carboxylic acid is added to this solution of HECPT and DMA. Examples of carboxylic acids are tartaric acid, citric acid, succinic, fumaric, maleic acid, gluconic acid, ascorbic acid, taurocholic acid, and taurocholic acid in an admixture with citric acid. These are examples of carboxylic acids only and not intended to be the only carboxylic acids for this invention.

Examples of different combinational parenteral formulations are presented in Table 7 below. This parenteral formulation contains HECPT between about 0.1 to about 0.25 mg per ml, ethanol (about 20 to about 7,000 parts by weight), citric acid (about 1 to 1,000 parts by weight), DMA (also called DMAC; about 500 to about 10,000 parts by weight) and Cremaphor EL (20-8,000 parts by weight).

TABLE 7

Modified Oral or Parenteral Formulation Version 2 (with DMAC)								
Formulation Number	Cremaphor EL		Ethanol		Citric Acid		DMAC	
	Nominal (G)	Exact (G)	Nominal (mL)	Exact (mL)	Nominal (G)	Exact (G)	Nominal (mL)	Exact (mL)
1	40.0000	39.9927	25.349	25.349	4.0000	4.0000	42.735	42.735
2	100.0000	100.0010	6.337	6.337	5.0000	5.0008	10.684	10.684
3	10.0000	10.0100	6.337	6.337	5.0000	5.0012	106.838	106.838
9	4.0000	4.0438	50.697	50.697	2.0000	2.0010	42.735	42.735

Example 13

Oral Formulations—Version 2

HECPT with DMA

This Example a preferred oral formulation of HECPT and DMA in combination with a variety of different components. For each formulation approximately 2.5 mg of HECPT was dissolved in 1000 parts of a pure form of DMA at 25° C. Dissolution was achieved with gentle agitation until a clear solution resulted within about two hours. About five hundred (500) parts by weight of a carboxylic acid is added to this solution of HECPT and DMA. Examples of carboxylic acids are tartaric acid, citric acid, succinic, fumaric, maleic acid, gluconic acid, ascorbic acid, taurocholic acid, and taurocholic acid in an admixture with citric acid. These are examples of carboxylic acids only and not intended to be the only carboxylic acids for this invention.

Examples of different combinational oral formulations are presented in Table 8 below. This oral formulation contains about 0.1 to about 0.25 mg per ml of HECPT, citric acid

(about 1 to about 1,000 parts by weight), glycerin (about 1 to about 1,000 parts by weight), PEG 300 (about 20 to about 8,000 parts by weight), ethanol (about 20 to about 7,000 parts by weight), DMA (about 500 to about 10,000 parts by weight), A surfactant (Polaxomer 127) about 0.1 to about 800 parts by weight), Sodium Acetate (about 0.1 to about 250 parts by weight), and taurocholic acid (about 10 to about 2,500 parts by weight).

TABLE 8

Oral Formulations - Version 2 (with DMAC and Polaxomer 127)								
Formulation Number	Citric Acid		Glycerine		PEG 300		Ethanol	
	Nominal (G)	Exact (G)	Nominal (G)	Exact (G)	Nominal (G)	Exact (G)	Nominal (mL)	Exact (mL)
1*	10.0000	10.0000	6.0000	6.0269	45.0000	45.0118	10.111	10.111
2	0.2000	0.2001	—	—	36.0000	36.5737	10.849	10.849
3	0.4000	0.4001	—	—	40.0000	40.0169	18.276	18.276
4	0.3000	0.1000	—	—	18.0000	18.0109	10.488	10.488
5*	6.0000	6.0012	—	—	15.0000	15.0052	5.725	5.725
6	0.1500	0.1503	3.6000	3.6014	15.0000	15.2513	5.475	5.475
7	0.2000	0.2023	4.8000	4.8090	20.0000	20.0186	20.659	20.659
8*	10.0000	10.0029	6.0000	6.0084	45.0000	45.0218	10.111	10.111
9	8.0000	8.0002	—	—	20.0000	20.0190	10.139	10.139
10	8.0000	8.0096	4.8000	4.8438	36.0000	36.0201	16.793	16.793
11	0.1000	0.1001	—	—	18.0000	18.0001	10.488	10.488
12	0.1000	0.1000	2.4000	2.4169	18.0000	18.0392	7.534	7.534
13	2.5000	2.5003	1.5000	1.5247	6.2500	6.4536	9.846	9.846
14	0.2000	0.2022	—	—	36.0000	36.0383	10.849	10.849
15	2.5000	2.5017	—	—	11.2500	11.2540	10.579	10.579
16*	6.0000	6.0001	—	—	15.0000	15.0010	5.725	5.725

Formulation Number	DMAC		Polaxomer 127		Na Acetate		Taurocholic A.	
	Nominal (mL)	Exact (mL)	Nominal (G)	Exact (G)	Nominal (G)	Exact (G)	Nominal (G)	Exact (G)
1*	5.342	5.342	5.0000	5.0021	0.8000	0.8035	—	—
2	42.735	42.735	0.2000	0.2025	0.6400	0.6404	—	—
3	8.347	8.347	8.0000	8.0011	1.2800	1.2796	—	—
4	2.137	2.137	2.0000	2.0016	—	—	11.0000	11.0139
5*	3.205	3.205	0.1500	0.1501	—	—	16.3000	16.6099



US006022852A

D₅

United States Patent [19]

[11] Patent Number: 6,022,852

Klokke et al.

[45] Date of Patent: Feb. 8, 2000

357
165[54] PHARMACEUTICAL COMPOSITION
CONTAINING CYCLOSPORIN A

[56] References Cited

[75] Inventors: Karin Klokke, Wilfried Fischer,
both of Holzkirchen, Germany

U.S. PATENT DOCUMENTS

5,430,021 7/1995 Rudie et al. 514/14

[73] Assignee: Hexal AG, Holzkirchen, Germany

OTHER PUBLICATIONS

[21] Appl. No.: 09/076,175

Sokol et al., "Improvement of cyclosporin absorption in
children after liver transplantation by means of water-
soluble vitamin E", vol. 228, pp. 212-215, Jul. 1991.

[22] Filed: May 11, 1998

Related U.S. Application Data

Primary Examiner—Raymond Henley, III
Attorney, Agent, or Firm—Cohen, Pontani, Lieberman &
Pavane[63] Continuation-in-part of application No. 08/633,823, Jun. 27,
1996, abandoned.

[30] Foreign Application Priority Data

[57] ABSTRACT

Oct. 22, 1993 [DE] Germany 43 36 163

The invention relates to a pharmaceutical composition con-
sisting of or containing cyclosporin A and α -tocopherol or
one of the derivatives thereof.[51] Int. Cl.⁷ A61K 38/00; A61K 31/355

[52] U.S. Cl. 514/11; 514/458

[58] Field of Search 514/11, 458

6 Claims, No Drawings

1

PHARMACEUTICAL COMPOSITION CONTAINING CYCLOSPORIN A

RELATED APPLICATIONS

This application is a continuation-in-part of application Ser. No. 08/633,823, filed Jun. 27, 1996, now abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to pharmaceutical compositions containing an effective amount of cyclosporin A in combination with vitamin E, vitamin E derivatives or vitamin E concentrates in which natural vitamin E is present together with vegetable-oil components.

2. Prior Art

Cyclosporin A is a cyclic, water-insoluble, non-polar undecapeptide. The compound is an effective immunosuppressant obtained from fungal cultures (Cane et al., Transplant TROC. 13: 349-358 (1981); Ferguson et al., Surgery 92: 175-182 (1952)). The medicament is used to prevent the rejection of transplanted allogeneic organs (Bennett & Norman, Arzn. Rev. Med. 37: 215-224 (1936); Van Basen, Surg. Clin. North Am. 66: 435-449 (1986)). Its immunosuppressive action is based on selective inhibition of cell function which allows the survival of, for example, heart transplants, without myelocyte suppression (Myers et al., New England Journal of Medicine 311: 699 (1994)). In addition to its use in transplantation, more recent clinical trials have shown that cyclosporin A is effective in the treatment of a large number of autoimmune diseases. For example, clinical trials of the treatment of polymyositis, systemic lupus erythematosus, rheumatoid arthritis or even of early-onset insulin-dependent diabetes have been carried out (see the corresponding chapter in: Cyclosporine in Autoimmune Diseases, ed. Schindler, Springer Verlag, Berlin 1985).

Cyclosporin is a lipophilic molecule having a molecular weight of 1202 daltons. Owing to the poor solubility in water and the high lipophilicity of cyclosporin A, pharmaceutical compositions of cyclosporin A with customary solid or liquid pharmaceutical carriers often have disadvantages. For example, the cyclosporins are not satisfactorily absorbed from such compositions (Cavanak & Sucker, Formulation of Dosage Forms, Prog. Allergy 38: 65-72 (1956)), or the compositions are not well tolerated, or they are not sufficiently stable when stored, for example with regard to crystallising out of the cyclosporin. Often the dissolved concentration is low in relation to the daily dose of up to 1 g, for example only 3%, which means that 30 g of solution have to be taken. Greater solubility is indicated in DE-B-2 907 460 wherein a solution of cyclosporin in vegetable oil, such as olive oil or corn oil, ethanol and an emulsifier consisting of a non-ionic ester of a triglyceride with a polyalkylene glycol is described. Examples of the compositions indicated in that patent as being preferred are drinkable solutions, drinkable emulsions, injection solutions and solutions in capsules.

The above composition is administered preferably intramuscularly, or subcutaneously, or especially orally. Cyclosporin A administered in the above medicament forms is distinguished by good bioavailability. Once it has been absorbed, the substance binds rapidly to plasma proteins and has a terminal half-life of 24 hours. A high percentage thereof is metabolized in the liver, biliary excretion being the main elimination route (Beverige, Cyclosporin A, in: Pro-

ceedings of International Symposium, Cambridge, ed. White, pages 35-44 (1982).

Despite its great value as an immunosuppressant, the clinical use of cyclosporin is limited by the main side effect of chronic administration which is the nephrotoxicity of the active ingredient itself (Van Buren, Surg. Clin. North Am. 66: 435-449 (1986)). In addition, renal toxicity occurs in approximately 80% of kidney transplant patients (Kahan, Dial. Transplant. 12: 620-630 (1983)) as a result of the very side effect inherent in the substance which is used to protect the transplant against rejection.

Frequent side effects of cyclosporin treatments in various autoimmune diseases include nephrotoxicity, hypertension, hyperkalaemia, hyperuricaemia, hepatotoxicity, anaemia, hypertrichosis, gingival hyperplasia, gastrointestinal side effects, tremors and paraesthesia (Van Graffoort et al., Cyclosporine in Autoimmune Diseases, ed. Schindler, Springer Verlag, Berlin, pages 59-73 (1985)). Of the side effects quoted here, nephrotoxicity is the most frequent. Acute, cyclosporin-induced nephrotoxicity is dosage-dependent and correlates with the cyclosporin blood levels. It is reversible after a reduction in dosage or when the cyclosporin treatment has been completed (Chapman et al., Lancet I: 128 (1985)).

Acute cyclosporin nephrotoxicity is accompanied morphologically by tubular lesions characterised by inclusion bodies, isometric vacuolation and microcalcification (Mihatsch et al., Transplant. Proc. 15: 2821 (1983)). That leads to a decrease in the glomerular filtration rate, which can be identified by the rapid increase in serum creatinine in patients treated with cyclosporin. One reason could be disturbance of the microcirculation as a result of the interaction of cyclosporin with local prostacyclin synthesis (Neild et al., in: Cyclosporine, ed. Kahan, Gruen & Stratton, Orlando, Fla., page 182 (1984)).

Although the mechanism of renal dysfunction is not yet fully explained, it has been shown that renal synthesis of thromboxane occurs during the progression of immunomediated and non-immuno-mediated models of renal damage (Lianos et al., J. Clin. Invest. 72: 1439-1448 (1983); Okegawa et al., J. Clin. Invest. 71: 81-90 (1983)). Thromboxane is a prostanoid and hence a metabolite of arachidonic acid from the cyclo-oxygenase cycle. The other prostanoids are prostaglandins and prostacyclins. Prostanoids are very effective mediators that are formed during immunologically generated inflammation processes. They can fundamentally alter the renal haemodynamics (Morley, in: Lymphokines, ed. Pic, Academic Press, New York, 4: 377-391 (1981)).

EP-A-0 305 400 describes the connections between disturbed prostanoid synthesis and nephrotoxicity. According to that specification, the administration of cyclosporin is accompanied by increased synthesis of thromboxane B2, a mediator of inflammation. Cyclosporin is accordingly said also to promote the formation of prostaglandins of the E series, which are likewise inflammation mediators. The rejection of human kidney transplants was linked to a rapid increase in renally eliminated thromboxane B2.

EP-A-0 035 400 also describes the use of ω -3-unsaturated fatty acids in combination with cyclosporin A in the inhibition of prostaglandin or thromboxane formation.

A disadvantage of longer-term administration of ω -3-fatty acids is the development of vitamin E deficiency states. Symptoms of deficiency are, for example, haemolysis and a reduction in the life of erythrocytes. In animal experiments, vitamin E deficiency leads to degenerative muscle changes, creatinuria and increased haemolysis of erythrocytes and

affects certain hormones and enzymes and the metabolism of proteins and arachidonic acid (Machlin, Vitamin E, in: Machlin, Handbook of Vitamins: Nutritional, Biochemical and Clinical Aspects, pages 99-145. Marcel Dekker, New York, 1984).

A further disadvantage of the composition containing ω -3-unsaturated fatty acids (fish oils) is the concentration, obviously low, of active ingredient that can be achieved in that oil. For example, EP-A-0 305 400 described a concentration of only 12.5 mg of cyclosporin A per gram of fish oil. At a customary daily dose of more than 300 mg of cyclosporin A, that means a total intake of approximately 24 grams of preparation, at 1 g of cyclosporin A per 80 g of preparation. That is an unacceptably large amount of oil for a patient; for example, encapsulated in soft gelatin capsules, it would mean a daily intake of 24 capsules containing 300 mg of cyclosporin A. Parenteral administration by infusion would, in the case of an infusion emulsion containing, at an optimistic estimate, 10% oil, involve an amount of approx. 240 ml of emulsion containing 300 mg of cyclosporin A, a volume that can be infused only over a relatively long period of time. Both features militate totally against the chronic administration required in the case of transplant patients.

Although the formulations according to DE-B-2 907 460 are distinguished by their large dissolving capacity for cyclosporin A, they have the disadvantage that they comprise only vegetable oils, which do not contain any substances that inhibit prostaglandin or thromboxane synthesis. That means that those preparations do not inhibit the nephrotoxicity of the cyclosporin A. The commercially available parenteral solution of cyclosporin A (Sandimmun®; made by Sandoz) contains, in 1 ml of solution, 50 mg of cyclosporin A, 32.5% ethanol and 650 mg of Cremeopher EL, an ethoxylated, hydrogenated castor oil. In addition to the amount of 2 g of ethanol per application, which represents a burden for the liver, according to reports in the literature Cremeopher EL is nephrotoxically similar to cyclosporin A itself (Friel et al., Clin. Nephrol. 25 (Suppl. 1), 540-542 (1986); Finn et al., Renal Failure 11, 3-15 (1989)). For example, in isolated, perfused rat kidney, Cremeopher EL leads to marked renal vasoconstriction with reduced renal blood flow and tubular dysfunction (Basarab et al., Transplantation 44, 195-201 (1987); Luke et al., Transplantation 43, 795-799 (1987)). Furthermore, Cremeopher EL causes anaphylactic reactions, which may be as severe as anaphylactic shock (Chupuis et al., Engl. J. Med. 312, 1259 (1985); Lounissen et al., Lancet 1, 637 (1986); Magalini et al., Transplantation 42, 443-444 (1986)). Cremeopher EL is regarded as the cause of the anaphylactoid reaction as it leads to histamine liberation (Ennis et al., Agents Action 12, 64-80 (1982)). In some cases of therapy using the i.v. solution, the allergic reaction was observed in humans on the first administration (Friedman et al., Ann. J. Med. 78, 343-345 (1985); Magalini et al., Transplantation 42, 443-444 (1986)). A disadvantage of the commercially available parenteral preparation is accordingly the constituent Cremeopher EL. Efforts should be made to obtain a formulation that does not contain that excipient, in order to avoid the above side effects and to increase the safety of the medicament.

The advantageous immunosuppressive properties of cyclosporin A are exploited in the treatment of psoriasis. Owing to its high molecular weight and its very high degree of lipophilicity, cyclosporin A is not, however, capable of penetrating intact skin, especially the horny layer. For that reason, severe cases of psoriasis are treated with oral and parenteral administration of cyclosporin. Disadvantages of

such administration are the systemic side effects on the circulation (hypertension) and kidney function. Topical preparations for the treatment of psoriasis, which would reduce the systemic side effects, require absorption promoters, such as, for example, propylene glycol and azone (Duncan et al., British Journal of Dermatology 123: 631-640 (1990)). It is, however, known that the permeation-promoting properties of azone are attributable to disturbances, or even destruction, of the protective function of the horny layer. Propylene glycol leads to drying-out of the skin. The two substances would therefore hinder rather than assist the healing of the psoriasis. For that reason a topical preparation containing a therapeutically adequate amount of cyclosporin A in combination with substances that assist the healing process would be desirable. In addition, the combination should promote the permeation of cyclosporin A through intact skin.

3. THE PROBLEM OF THE INVENTION

The problem of the present invention is to find an advantageous solvent system that dissolves cyclosporin A in sufficient quantities for it to be taken orally in the therapeutically customary daily dose; that is capable of reducing nephrotoxic activity; that, when applied topically, is capable both of promoting permeation through the skin and of assisting the healing process in the treatment of psoriasis and that, in addition, ensures parenteral administration that is well tolerated.

4. SUMMARY OF THE INVENTION

The problem underlying the invention is solved by a pharmaceutical preparation that consists of or contains cyclosporin A and α -tocopherol or one of the derivatives thereof.

That pharmaceutical preparation can be characterised by α -tocopherol succinate, α -tocopherol acetate or D- α -tocopherol polyethylene glycol 1000 succinate as the α -tocopherol derivative.

The pharmaceutical preparation can be characterised further by the fact that it contains α -tocopherol in the form of an α -tocopherol concentrate in vegetable oil.

The pharmaceutical preparation is obtainable by mixing cyclosporin A with an α -tocopherol concentrate in vegetable oil.

The pharmaceutical preparation can also be characterised by the fact that it contains α -tocopherol or one of the derivatives thereof in an amount of up to 900%, based on cyclosporin A.

The pharmaceutical preparation can also be characterised by the fact that it contains cyclosporin A in an amount of $\geq 10\%$, based on the composition.

The pharmaceutical preparation can also be characterised by the fact that it contains ethanol or isopropanol as processing auxiliary, especially in amounts of up to 20%.

The pharmaceutical preparation can also be characterised by the fact that it contains an emulsifier.

The pharmaceutical preparation can also be characterised by the fact that it contains a thickener.

The pharmaceutical preparation can, finally, be provided in the form of an injection concentrate for formulations for parenteral use containing physiologically tolerable excipients customary therefor.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

According to the invention, it has also been found, surprisingly, THAT α -tocopherol and its chemical

359
167

derivatives, such as α -tocopherol succinate and D- α -tocopherol polyethylene glycol 1000 succinate and α -tocopherol acetate, but especially highly concentrated concentrates of D- α -tocopherol in vegetable oils, have an excellent dissolving capacity for cyclosporin A, at the same time inhibit the synthesis of prostanooids, such as prostaglandins and thromboxanes, which can be exploited to reduce nephrotoxicity and to cause inflammation reactions in the skin to subside, and at the same time promote the absorption of cyclosporin A through intact skin. In addition, solutions according to the invention, optionally with the assistance of physiologically tolerable customary excipients for the preparation of formulations for parenteral use, can be formulated as injection concentrates. The special advantage of the solutions according to the invention, in addition to the achievement of high concentrations of dissolved cyclosporin A of more than 10%, is that D- α -tocopherol, as natural vitamin E, and its derivatives have inherent effects which on the one hand counteract toxic effects of cyclosporin A at the customary high doses used in the case of oral and parenteral administration and on the other hand reinforce the intended immunosuppressive effect in the case of the topical treatment of psoriasis by means of their absorption-promoting effect.

For example vitamin E affects the metabolism of arachidonic acid by inhibiting prostaglandin, thromboxane and leucotriene biosynthesis and increasing prostacyclin formation. Those properties are associated with biological inhibition of inflammation and with thrombotic disorders (Machlin, Vitamin E, in: Machlin, Handbook of Vitamins: Nutritional, Biochemical and Clinical Aspects, pages 99-145, Marcel Dekker, New York, 1984). When taken orally, vitamin E can likewise promote the activity of non-steroidal anti-inflammatory medicaments (Bertolini et al., Rivista di Farmakologia et Therapie 3, pages 27-34 (1982); Klein & Blankenhorn, Vergleich der klinischen Wirksamkeit von Vitamin E und Diclofenac Natrium bei Spondylitis Ancylosans (Morbus Bechterew), Vitaminspur 2, pages 137-142 (1987)). When applied topically, vitamin E permeates the horny layer very well. Quantitative absorption studies have been carried out on the skin of experimental animals. For example, 16 hours after the application of 300 μ g of a 5% vitamin E solution in ethanol per cm², 0.7% of the vitamin E; was recovered in the horny layer and approx. 40.9% in layers of skin below the horny layer (Djerassi et al., Vitamin E: Biochemical function and its role in cosmetics, Drug & Cosmetic Industry 13: No. 1, pages 29-31, 34, 78 (1986)). When applied locally, vitamin E acts as a membrane-stabilising antioxidant and inhibits the liberation of histamine and hydrolytic enzymes, for example from mast cells and lysosomes by stabilising the membranes thereof. Likewise, it inhibits the synthesis of certain prostaglandins, deactivates oxygen radicals and detoxifies corresponding secondary products (Sies, Bildung, von Superoxidradikalen und Peroxiden, in: Superoxiddismutase—Biochemie und therapeutischer Einsatz; ed. Publ & Ries, Perimed Verlag, Erlangen, 1982). In addition, vitamin E increased skin moisture and acts as a quasi-occlusion agent. All of those properties that have been described are advantageous in the treatment of psoriasis.

Cyclosporin A dissolves, entirely unexpectedly, in vitamin E preparations, such as vitamin E concentrates (Copherol F 1300), in a high concentration of >10%, with the result that a combination thereof in the form of a solution can be used to therapeutic effect both in soft gelatin capsules and in topical formulations. In order to assist their processability, the formulations may contain small amounts

of alcohol, such as ethanol or isopropanol in amounts of up to 20% of the total formulation, and, in order to promote wetting, may contain physiologically tolerable surface-active substances, i.e. emulsifiers. Emulsifiers that are tolerable both orally and topically are, for example, phospholipids, such as lecithins, lysolecithins, ethoxylation products of fatty acids and fats, alkali soaps, sucrose esters and others, but are not limited thereto. In addition, the formulations may contain thickeners, such as colloidal silica or polyacrylic acid or polyacrylic acid derivatives or cellulose derivatives and antioxidants and flavour enhancers.

5. EXAMPLES

Example 1

Composition for a Soft Gelatin Capsule

cyclosporin A	100 mg
tocopherol (Copherol F1300)	900 mg

Example 2

Composition for a Soft Gelatin Capsule

cyclosporin A	100 mg
ethanol	100 mg
soya lecithin	200 mg
tocopherol (Copherol F1300)	900 mg

Example 3

Composition for a Soft Gelatin Capsule

cyclosporin A	125 mg
abs. ethanol	125 mg
D- α -tocopherol	325 mg
D- α -tocopherol ethylene glycol 1000 succinate	425 mg

Example 4

Topical Preparation

cyclosporin A	10 mg
tocopherol (Copherol F1300)	90 mg
lecithin	100 mg
isopropanol	200 mg
polyacrylic acid	25 mg
triethanolamine	5 mg
water ad	1000 mg

7

Example 3
Injection Concentrate

cyclosporin A	50 mg
ascopheryl (Copheryl F1500)	100 mg
lecithin	200 mg
ethanol	100 mg
nutraceutical	500 mg

Example 6

Test (Hard Gelatine Capsules)

The composition of the formulation was as follows:

Cyclosporin A	100 mg
Ethanol 96%	200 mg
Tocopherol PEG 100 succinate	300 mg
Polyethoxylated castor oil	200 mg
Polyethylene glycol 400 (PEG 400)	200 mg

This mixture was filled into hard gelatine capsules and tested with dogs in a cross-over test in comparison to a

8

product of the market, i. e. Sandimmun (Optival®). Plasma levels were analyzed by means of a fluorescence immuno assay.

We claim:

1. Pharmaceutical preparation comprised of cyclosporin A, tocopherol polyethylene glycol 1000 succinate and optionally an emulsifier, with the exception of vegetable oil or fat.

2. Pharmaceutical preparation according to claim 1, which contains tocopherol in an amount of up to 900% based on cyclosporin A.

3. Pharmaceutical preparation according to either of the preceding claims, which contains cyclosporin A in an amount of >10% based on the composition.

4. Pharmaceutical preparation according to claim 1 which contains ethanol or isopropanol as processing auxiliary, in an amount of up to 20%.

5. Pharmaceutical preparation according to claim 1 which contains a thickener.

6. Pharmaceutical preparation according to claim 1 which is in the form of an injection concentrate for formulations for parenteral use containing physiologically tolerable excipients.

* * * * *

(12) **United States Patent**
Sonne

(10) Patent No.: **US 6,193,985 B1**
 (45) Date of Patent: ***Feb. 27, 2001**

(54) **TOCOPHEROL COMPOSITIONS FOR DELIVERY OF BIOLOGICALLY ACTIVE AGENTS**

(75) Inventor: **Mette Rydahl Sonne, Brøndby Strand (DK)**

(73) Assignee: **A/S Dumex (Dumex Ltd), Copenhagen (DK)**

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

70937/91 8/1991 (AU).
 3405240 8/1995 (DE).
 0 001 851 A1 5/1979 (EP).
 0387647 9/1990 (EP).
 0514967 11/1992 (EP).
 0539215 4/1993 (EP).
 0572190 12/1993 (EP).
 0636618 2/1995 (EP).
 WO 86/04233 7/1986 (WO).
 WO 89/03680 5/1989 (WO).
 WO 91/14463 10/1991 (WO).
 WO 91/16929 11/1991 (WO).
 WO 93/03720 3/1993 (WO).
 WO 93/08753 9/1993 (WO).
 WO 93/21905 11/1993 (WO).
 WO 94/20143 9/1994 (WO).
 WO 95/01785 1/1995 (WO).
 WO 95/11039 4/1995 (WO).
 WO 95/24892 9/1995 (WO).
 WO 95/30420 11/1995 (WO).

OTHER PUBLICATIONS

Sokol et al.; "Improvement of cyclosporin absorption in children after liver transplantation by means of water-soluble vitamin E"; *The Lancet*; vol. 338; Jul. 27, 1991; pp. 212-215.

Lau et al.; "Absorption of diazepam and lorazepam following intranasal administration"; *International Journal of Pharmaceutics*; 54 (1989) pp. 171-174.

Ismailos et al.; "Enhancement of cyclosporin A solubility by α -phosphatocopheryl-polyethylene-glycol-1000 succinate (TPGS)"; *European Journal of Pharmaceutical Sciences*, 1 pp. 269-271 (May 1994).

* cited by examiner

Primary Examiner—Jelley C. Mullis
 (74) Attorney, Agent, or Firm—Watson & Kippes, P.C.; Allen R. Kippes

(57) ABSTRACT

The present invention provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions. Such compositions are particularly suitable for transmucosal, and especially intranasal or rectal administration, or administration via the oral cavity.

(21) Appl. No.: **08/856,054**

(22) Filed: **May 14, 1997**

Related U.S. Application Data

(63) Continuation of application No. 08/441,759, filed on May 16, 1995, now abandoned.

(30) Foreign Application Priority Data

May 16, 1994 (GB) 9409778

(51) Int. Cl.⁷ A61K 9/00; A61K 9/107

(52) U.S. Cl. 424/400; 424/439; 424/484; 424/486; 514/772

(58) Field of Search 424/439, 450, 424/485, 486, 400, 484; 514/772

(56) References Cited

U.S. PATENT DOCUMENTS

4,439,432 3/1984 Peat.
 4,628,052 * 12/1986 Peat 514/171
 4,847,072 * 7/1989 Russell et al. 424/59
 4,863,720 9/1989 Burghart et al. .
 4,950,664 8/1990 Goldberg.
 4,960,814 10/1990 Wu et al. .
 5,179,122 * 1/1993 Greene et al. 514/458
 5,364,631 * 11/1994 Janoff et al. 424/490
 5,430,021 * 7/1995 Rudnic et al. 514/14

FOREIGN PATENT DOCUMENTS

24213/88 3/1989 (AU).

30 Claims, 2 Drawing Sheets

D₆

362

170

TOCOPHEROL COMPOSITIONS FOR DELIVERY OF BIOLOGICALLY ACTIVE AGENTS

This is a continuation application of U.S. Ser. No. 08/441,759 filed on May 16, 1995 now abandoned.

The present invention is directed to new pharmaceutical compositions for delivery of biologically active agents. More particularly, the invention concerns the use of a tocopherol or a derivative thereof to prepare compositions having low irritability suitable for administration to mucosal membranes and which may be used efficiently to administer drugs, which are substantially insoluble or only sparingly soluble in water.

For systemic action, drugs are normally administered by mouth and are then absorbed in the gastrointestinal tract. However, this mode of administration is not suitable in all circumstances, for example in the case of drugs which are metabolised to any significant degree by the liver or which are poorly absorbed. In other cases, the oral route may be impractical, for example in patients suffering from nausea or who are unconscious. Before surgery, oral administration is not advisable because of the risk of vomiting and in many cases, a more rapid effect may be required than can be achieved by the oral route.

In these circumstances the parenteral route is frequently used, most notably intravenous or intramuscular injection. However, whilst this provides a convenient way of achieving a strong and rapid systemic effect, it has a number of disadvantages including the requirement for sterile equipment and trained personnel. It is also unpleasant to the patient.

Moreover, in cases where a systemic effect is not required, local administration may be preferable, for example to avoid side effects, to reduce the dosage, or simply to facilitate the administration.

Such problems have led in recent years to an increasing interest in developing formulations for the topical administration of drugs, and in particular for topical administration involving absorption from mucous membranes.

Topical administration has the advantage that drugs may be administered readily and simply to achieve a systemic or dermal, regional or localised effect, as required. However, topical absorption of drugs through the skin can be slow, and in many cases transmucosal routes of delivery are preferred. Since it may be performed by untrained personnel and permits therapeutic plasma levels of drugs rapidly to be achieved, intranasal administration has received particular attention in this regard.

For topical delivery, biologically active drugs are normally administered in the form of aqueous solutions. However, many biologically active compounds are substantially insoluble or only sparingly soluble in water and in such cases, organic solvents are required to dissolve these agents. The problem here is that mucosal tissues are generally very sensitive and such solvents are frequently too irritant to be of clinical use. Thus for example, Lau and Slattery [Int. J. Pharm. 1989, p. 171-74] attempted to administer the benzodiazepines diazepam and lorazepam by dissolving these compounds in a range of solvents including: triacetin, DMSO, PEG 400, Cremophor EL, Lipal-9-LA, isopropylalipate and azoxe dodecyl-aza-cycloheptane-2-one. Whilst many of the solvents dissolved diazepam and lorazepam in the desired concentrations, when administered to the nose they were too irritant to be of use. Thus, Cremophor EL was found to be the least irritative for mucosal tissue, but nasal absorption using this solvent is rather slow and peak concentration is low relative to that found after iv. administration.

Triglycerides such as vegetable oils are generally non-irritant, but usually these oils are too poor as solvents to be of any use.

Attempts have been made to develop various other vehicles for transmucosal delivery of drugs, such as benzodiazepines, having limited water solubility. Thus, for example WO 86/04233 of Riker discloses a pharmaceutical composition wherein the drug (eg. diazepam) is dissolved in a mixture of propellant and co-solvent eg. glycerolphosphate. The composition requires a pressurized system and at least one halogenated hydrocarbon aerosol propellant.

In U.S. Pat. No. 4,863,720 of Burghardt, a sublingual sprayable pharmaceutical preparation is disclosed, in which the active drug can be a benzodiazepine, optionally comprising polyethylene glycol (PEG) and requiring ethanol, di-and/or triglyceride of fatty acids and a pharmaceutically acceptable propellant gas.

U.S. Pat. No. 4,950,664 of Rugby-Darby describes the nasal administration of benzodiazepines in a pharmaceutically acceptable nasal carrier. The carrier may be a saline solution, an alcohol, a glycol, a glycol ether or mixtures thereof.

In PCT WO 91/16929 of Novo Nordisk, glycofurols or ethylene glycols are suggested as carriers for a variety of drugs, including benzodiazepines, which may be used on mucous membranes.

Another solution proposed to this problem, has been the use of micelles or liposomes, but these are frequently difficult to produce on a technical scale.

A further constraint concerning nasal administration is that a small administration volume is required; it is not generally possible to administer more than about 0.1 ml per dose per nostril. Therefore, a great need exists for solvents, in which, on the one hand the solubility of the active drug is high, and which, on the other hand, are non-irritating to the mucosa.

The aim of the present invention is to provide a solution to the above mentioned problems.

Tocopherols and their derivatives such as esters for example, are widely used in vitamin supplementation and as antioxidants in the food industry and in many pharmaceutical compositions. However, although in a few cases, a potential use in formulating pharmaceutical compositions has been reported, tocopherols and derivatives thereof have not generally previously been proposed as drug carriers.

Thus for example, European Patent Application No. 539,215 of Stafford-Miller suggests a possible use of Vitamin E and its derivatives as penetration enhancers in topical compositions.

WO 89/03689 of The Liposome Co., describes a liposome system based on acid derivatives of α -tocopherol in a low pH aqueous medium for delivery of drugs which tolerate, or require, acid conditions.

The present invention is based on the surprising observation that tocopherols and derivatives thereof are excellent solvents for drugs which are substantially insoluble or sparingly soluble in water, whilst at the same time having a very low irritative potential for mucosal tissues.

As will be described in more detail below, it has also been found that certain tocopherol derivatives are efficient, non-irritant emulsifiers for such drugs, when dissolved in a tocopherol-based solvent.

In one aspect, the present invention thus provides the use of a tocopherol or a derivative thereof as a solvent and/or emulsifier for substantially insoluble and sparingly soluble biologically active agents, especially in the manufacture of pharmaceutical compositions.

A further aspect of the invention provides a composition for delivery of a substantially insoluble or sparingly soluble biologically active agent, comprising said agent dissolved in a tocopherol or a derivative thereof.

Tocopherols are a range of natural and synthetic compounds, also known by the generic term Vitamin E. α -Tocopherol (chemical name: 2,5,7,8-tetramethyl-2-(4',8',12'-trimethyldecyl)-6-chromanole) is the most active and widely distributed in nature, and has been the most widely studied. Other members of the class include beta, gamma, and delta tocopherols but these are not used in pure form in therapeutics, although they are present in foodstuffs. Tocopherols occur in a number of isomeric forms, the D and DL forms being most widely available.

As used herein, the term "tocopherol" includes all such natural and synthetic tocopherol or Vitamin E compounds.

The melting point of natural α -tocopherol is between 2.5 and 3.5° C. α -Tocopherol is a viscous oil at room temperature, is soluble in most organic solvents, but insoluble in water.

Although tocopherols are available naturally in foodstuffs and may be extracted from plants, α -tocopherol is now mainly produced synthetically.

Any of the forms or isomers of tocopherols and their derivatives, eg. esters may be used according to the present invention. Thus for example, α -tocopherol can be used as such or in the form of its esters such as α -tocopherol acetate, linoleate, nicotinate or hemi succinate-ester, many of which are available commercially.

A special article of commerce is called Tenox GT-2 and consists of 70% tocopherol of natural origin, which has been concentrated from vegetable oil. This oil has a mild odour and a gentle taste.

The compositions of the present invention are particularly suited for application to mucous membranes in animals or humans, to deliver systemically substantially insoluble or sparingly soluble biologically active agents in a manner which ensures that a clinical effect is reached at least as rapidly as by conventional oral administration, with for instance tablets.

Thus, the compositions of the invention may be used for controlled release delivery of bioactive agents to achieve a beneficial or therapeutic effect over a prolonged period of time.

The compositions of the invention may also be applied to achieve a local effect, where desired, on the mucous membranes or the underlying tissue.

However, whilst the beneficial effects of the invention are particularly apparent in transmucosal delivery, the utility of the invention is not limited and compositions according to the invention may also be administered topically to all body surfaces, including the skin and all other epithelial or serosal surfaces, as well as parenterally or enterally, eg. as implants or by intravenous, intramuscular or subcutaneous injection, by infusion, or orally.

Transmucosal delivery is preferred however, and compositions according to the invention may be administered to mucosal membranes for example in the nose, vagina, rectum, ears, eyes, oral cavity, lungs, genito-urinary tracts, and gastro-intestinal tract. Nasal, rectal and oral cavity administrations are particularly preferred.

The compositions of the invention may be used directly as solutions of the bioactive agent in the tocopherol solvent. However such solutions are viscous, and the viscosity may be too high for certain applications, for example to achieve a sprayable formulation for nasal application.

Viscosity can be reduced by addition of co-solvents such as ethanol, but this is less desired, since solutions of this kind tend to be irritating to certain mucosal tissues.

Alternatively, the tocopherol solutions may be emulsified, to obtain formulations of lower viscosity. This may be achieved in known manner, by mixing the tocopherol-based "oil phase" containing the dissolved bioactive agent with an appropriate aqueous phase, eg. water, saline or buffer solutions.

Methods and appropriate aqueous media for obtaining emulsions are well known in the art and described in the literature. Emulsions according to the invention may be oil-in-water (O/W) or water-in-oil (W/O) emulsions. Generally speaking, O/W emulsions may be achieved when the oil phase contains up to about 70% lipids. W/O emulsions are formed when the oil phase exceeds c.a. 70%.

For nasal administration, due to the small administration volume required, it has generally been found that a high concentration of the oil (or lipid) phase is required. Emulsions with high lipid content are technically difficult to achieve and may be unstable. It may therefore be necessary to employ an emulsifier in order to form a stable emulsion. A wide range of emulsifiers are well known, both in the food and pharmaceutical arts, and are widely described in the literature. However, stability and viscosity may still be a problem, where very high contents of the oil phase are required. Moreover, some of the more widely available commercial emulsifiers, eg. phospholipids, polysorbates or various sorbitan esters of fatty acids may be irritating to the more sensitive mucosal tissues, such as those of the nose.

The inventors have surprisingly found however that tocopherol derivatives, particularly certain esters, may themselves form efficient, non-irritating emulsifiers to enable stable emulsions to be formed, even where high lipid levels are involved eg. about 50-70%. Particular mention may be made in this regard of Vitamin E TPQS which is a water soluble derivative of Vitamin E and consists of α -tocopherol, which is esterified with succinic acid, the other acidic group of the latter being esterified with polyethylene glycol 1000. Vitamin E TPQS is an almost odourless waxy amphiphilic substance with a molecular weight about 1513. The melting point is about 36° C. and its solubility in water is about 20%.

Stable emulsions may readily be achieved according to the invention using a range of tocopherols or derivative compounds as solvents, with Vitamin E TPQS as emulsifier, and any suitable aqueous medium.

A further aspect of the invention thus provides a composition suitable for delivery of substantially insoluble or sparingly soluble biologically active agents, comprising a tocopherol or a derivative thereof, and Vitamin E TPQS as emulsifier.

The tocopherol derivative emulsifier of the invention may be used alone or in conjunction with other known emulsifiers eg. phospholipids, polysorbates, sorbitan esters of fatty acids, cetylal glucoside or poloxamers.

It has furthermore surprisingly been shown that various other solvents may be used in the emulsion system described above, without compromising the stability of the emulsion.

When the emulsion according to the present invention is of the oil-in-water type, it is desirable that the droplet size is as small as possible. It has been shown that by using systems according to the invention, for example, α -tocopherol, water, Vitamin E TPQS and bioactive agent, it is possible to form stable emulsions with an initial droplet size in the range 0.01-100 μ m, preferably 0.01-50 μ m, most preferably 0.1-20 μ m.

The compositions which may be prepared according to the present invention, may contain any biologically active agent which is insoluble or sparingly soluble in water, ie.

with a solubility in water (w/v) which is 3% or less. For example such agents may include any bioactive agent which has less than 1% (w/v) solubility in water. Representative active agents from a range of different therapeutic groups are listed below, by way of exemplification.

Hormones and hormone-like substances of the steroid group:

Corticosteroids such as cortisone, hydrocortisone, prednisone, prednisolone, triamcinolone acetonide, dexamethasone, flunisolide, budesonide, triamcinolone pivalate, betametasone, beclomethasone dipropionate, fluticasone etc;

Sex-hormones such as: estradiol, progesterone, testosterone etc;

Antibiotics: Tetracyclines such as tetracycline, doxycycline, oxytetracycline, chloramphenicol etc; Macrolides such as erythromycin and derivatives, etc;

Antivirals: such as acyclovir, idoxuridine, tromantadine etc;

Antimycotics: Miconazole, ketoconazole, fluconazole, itraconazole, econazole, terconazole, griseofulvin, and polyenes such as amphotericin B or nystatin etc;

Anti-amoebics: Metronidazole, metronidazole benzoate and tinidazole etc;

Anti-inflammatory drugs: NSAID's such as indomethacin, ibuprofen, piroxicam, diclofenac etc;

Anti-allergics: Disodium cromoglycate etc;

Immunosuppressive agents: cyclosporin etc;

Coronary drugs: including vasodilators such as nitroglycerin, isosorbide dinitrate, Calcium-antagonists such as verapamil, nifedipine and diltiazem, Cardiac-glycosides such as digoxin.

Analgesics: eg. morphine, buprenorphine, etc;

Local anaesthetics: eg. lidocaine, etc;

Anxiolytics, sedatives & hypnotics: diazepam, nitrazepam, flurazepam, estazolam, flunitrazepam, triazolam, alprazolam, midazolam, temazepam, lorazepam, bromizolam, clobazam, clonazepam, lorazepam, oxazepam, buspiron, etc;

Migraine relieving agents: sumatriptan, ergotamines and derivatives etc;

Drugs against motion sickness: eg. cinnarizine, antihistamines, etc;

Anti-emetics: eg. ondansetron, tropisetron, granisetron, metoclopramide, etc.

Others: such as disulfiram, vitamin K, etc.

The emulsions according to the present invention are especially suitable for nasal application because of their low index of irritability and are therefore particularly well suited to the delivery of biologically active drugs influencing the central nervous system (CNS).

Other biologically active agents which may be used include peptides, hormones, etc. The active substance may be present in an amount of from about 0.001% to 50% of the total composition, preferably 0.001% to 40% (w/w).

Generally speaking compositions of the invention may contain from 1 to 99.99% (w/w), preferably 20 to 99.99%, most preferably 40 to 99.99% (w/w) of the tocopherol or tocopherol derivative solvent. The emulsion used in compositions of the invention may contain 1 to 95% (w/w) of the tocopherol or derivative thereof, preferably 20 to 95% (w/w), most preferably 35 to 80% (w/w).

As mentioned above, the emulsions of the present invention can be prepared by conventional means, by heating the oil and aqueous phases separately, and then mixing the two phases. The active ingredient can be dissolved in the lipid fraction of the tocopherol solvent and other solvents may be added if desired. The emulsifier, eg. Vitamin E TPGS, and

optionally other emulsifiers, can be added to either the oil and/or the water phase. The water phase is then vigorously mixed with the oil phase. Mixing, eg. stirring may be continued as required eg. for up to 2 hours. Depending on the viscosity of the emulsion, a magnetic stirrer, a low shear mixer or the like can be used. If necessary, the emulsion can be processed by a low shear mixer and a high pressure homogenizer to achieve the desired droplet size. The formulations may be inspected microscopically to measure the droplet size and to be sure that no precipitation has taken place. The type of emulsion formed may be determined readily by a colour test using an oil- and/or water-soluble dye. To confirm the result, it may be examined whether the emulsion is easy to wash off with water or not. An O/W emulsion is coloured with the water-soluble dye and is very easy to wash off with water. A W/O emulsion is coloured with the oil-soluble dye and is very difficult to wash off with water.

In a further aspect, the present invention thus provides a method of preparing a composition for delivery of a substantially insoluble or sparingly soluble biologically active agent, said method comprising dissolving said agent in an amount of a tocopherol or a derivative thereof, sufficient to dissolve said agent.

In a preferred aspect, the method of the invention further comprises forming an emulsion of said tocopherol/biologically active agent solution, by mixing with an aqueous phase, optionally in the presence of an emulsifier, preferably vitamin E TPGS.

The compositions of the invention may take any of the conventional pharmaceutical forms known in the art, and may be formulated in conventional manner, optionally with one or more pharmaceutically acceptable carriers or excipients. Thus for example the compositions may take the form of ointments, creams, solutions, gels, emulsions, lotions, liniments, aerosols, sprays, drops, pessaries, suppositories, tablets, capsules or lozenges.

In a still further aspect, the present invention provides the use of a tocopherol or a derivative thereof for the preparation of a composition for delivery of a substantially insoluble or sparingly soluble biologically active agent to a human or non-human animal subject.

Alternatively viewed, the invention can be seen to provide a method of treatment of a human or non-human animal subject by delivery of a substantially insoluble or sparingly soluble biologically active agent, said method comprising administering to said subject a composition of the invention as hereinbefore defined.

The formulations according to the invention may be optimized with respect to bioadhesion, sprayability and viscosity, as desired. Thus for example, the following co-solvents may be added:

Vegetable oils such as sesame- or olive- or fractionated coconut oil, alcohols such as ethanol, propylene glycol, glycerol, polyethylene glycol or benzyl alcohol; or inositol.

To optimize the stability of the emulsions, it may be appropriate to add surfactants such as Vitamin E TPGS poloxamers (eg. Pluronic®), cetearyl glucoside, polysorbates or sorbitan esters of fatty acids, or any of the other surfactants well known in the art, or other stabilisers such as xanthan gum, or propylene glycol alginate.

It is also possible to enhance the bioadhesive properties of the formulations according to the present invention by addition of bioadhesive polymers such as:

polyacrylic polymers such as carbomer and carbomer derivatives, eg. Polycarbophil or Carbopol etc;

cellulose derivatives such as hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropyl-cellulose or sodium carboxymethylcellulose etc;

367
175

natural polymers like gelatin, sodium alginate, pectin etc; more generally, any physiologically acceptable polymer showing bioadhesive characteristics may be used.

To ensure that the formulations have a reasonable shelf-life it may be desirable to include preservatives such as benzalkonium chloride, sodium edetate, sorbic acid, potassium sorbate, phenoxylethanol, phenetanol, parabens or others known in the art. Addition of odour- or taste-masking compounds can also be desirable.

The invention will now be described in more detail in the following non-limiting Examples, with reference to the drawings in which:

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing mean serum concentrations (ng/ml) against time (minutes) after intranasal administration of 2.5 mg diazepam (Formulation C) -▲- Desmethyldiazepam -■- Diazepam;

FIG. 2 is a graph showing mean serum concentrations (ng/ml) against time (minutes) after oral administration of 2.0 mg diazepam (Formulation D) -■- Desmethyldiazepam -◆- Diazepam;

EXAMPLES

As already mentioned, administration of drugs with very low water solubility to the nose is difficult, because of the limited volume which is acceptable for the nose (about 100 μ l). The first example has a very high concentration of diazepam, and it is possible to administer diazepam to the nose and to achieve a rapid clinical effect.

Example 1

A diazepam nosedrop preparation is made as follows: (100 g)

5 g of diazepam is mixed with 44 g of Tenox GT2, and 22 g of triacetin, and 5 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 1.45 g of Pluronic F-68 (poloxamer 188) and 0.01 g of benzalkonium chloride are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed into the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion was a pale yellow o/w emulsion, where the mean droplet size was about 1-2 μ m.

This formulation (1) was tested in 8 rabbits in a randomized cross-over study compared with a commercially available diazepam formulation, Siesolido 5mg/ml for injection, (2).

Formulation 1 was given intranasally (i.n.) with a Eppendorf Multipette® 4780. Each rabbit was held in a supine position during and one minute after i.n. dosing in one nostril. The rabbits receive a volume that equals 2 mg diazepam, 40% of formulation 1. After each administration the actual dose received is estimated by visual inspection of the pipette tip and the rabbit nostrils. Only applications volumes estimated to 80% are accepted.

Formulation 2 was given as an ear-vein infusion during 10 minutes. The rabbits received 0.4 ml Siesolido 5 mg/ml (equals 2 mg diazepam). The rabbits were placed in a supine position for half a minute to attain the same experimental conditions as for i.n. dosing.

The rabbits were then tested with respect to pharmacodynamic response in the following way:

Hind legs to one side and the rabbit must stay in this position even after a firm tip with a finger on the hip.

The test is immediately repeated with both legs placed on the other side.

The rabbits were tested approximately once per minute until positive pharmacodynamic response, and thereafter tested every 2 minutes. Total test period is 20 minutes. The same person has dosed and tested all the rabbits in the present study.

The time to pharmacodynamic response is 4.4 minutes (mean, n=8) using formulation 1 and 1.6 minutes (mean, n=8) using formulation 2.

Example 2

A diazepam nosedrop preparation is made as follows: (100 g)

5 g of diazepam is mixed with 45.4 g of Tenox GT2, and 22.7 g of triacetin, and 15 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 1.45 g of Pluronic F-68 (poloxamer 188) and 0.01 g of benzalkonium chloride are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a clear orange w/o emulsion.

A less concentrated formulation of diazepam is required for the rectal administration, but still it can be very difficult to find an acceptable vehicle with low irritation.

Example 3

A diazepam enema preparation is made as follows: (100 g)

1 g of diazepam is mixed with 40 g of α -tocopherol, and 15 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. 5 g of ethanol is added to the oil phase immediately before mixing with the water phase. To the water phase, 2.5 g of Pluronic F-68 (poloxamer 188), and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a white o/w emulsion.

Cinnarizine is used for motion sickness. Like diazepam, the drug has a very low water solubility. It will be a great advantage if the patient can administer the drug easily and have a rapid effect.

Example 4

A cinnarizine nosedrop formulation is made as follows: (100 g)

5 g of cinnarizine is mixed with 64 g of α -tocopherol, and 8 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 1.5 g of Pluronic F-68 (poloxamer 188), and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a white o/w emulsion.

Miconazole is used for the local treatment of infections caused by fungi. The next two formulations show formulations for use in the oral cavity and the vagina.

Example 5

A miconazole preparation for the oral cavity is made as follows: (100 g)

20 g of miconazole is mixed with 58.8 g of α -tocopherol, and 13 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. 5 g of ethanol is added to the oil phase immediately before mixing with the water phase. To the water phase, 1.5 g of Pluronic F-68 (poloxamer 188), and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is added very slowly to the oil phase under vigorously mixing by using a magnetic stirrer. Thereafter, the emulsion is cooled to room temperature still on the magnetic stirrer. The emulsion is a yellow to brown w/o emulsion.

Example 6

A miconazole vaginal cream is made as follows: (100 g) 5 g of miconazole is mixed with 38 g of α -tocopherol, and 38 g of Vitamin E TPGS. The oil phase is heated slowly to a homogeneous phase is achieved. To the water phase, 2.5 g of Pluronic F-681 (poloxamer 188) and 0.01 g of benzalkonium chloride, and 0.05 g of disodium edetate are added, the water phase is heated slowly to a homogeneous phase is achieved. The water phase is vigorously mixed to the oil phase by using a low shear mixer. Thereafter, the emulsion is cooled to room temperature still mixed by the low shear mixer. The emulsion is a glossy, beige w/o emulsion. The emulsion has a consistency as an ointment and is very sticky.

The following Examples are divided into three subsections covering 1) Solubility; 2) Compositions and 3) Pharmacology/toxicology.

Example 7

Solubility

For the following, non-limiting, sparingly soluble drugs in water, the solubility in α -tocopherol and sesame oil are listed in Table 1:

Sesame oil was chosen as the reference, because it is a very commonly used and well tolerated vegetable oil. The solubilities in sesame oil and α -tocopherol were investigated by visual inspection of the saturation point.

TABLE 1

Active agent	g drug in 100 g of α -tocopherol	g drug in 100 g of sesame oil
Diazepam	12	2
Alprazolam	4 < α < 6	< 0.2
Midazolam	> 13	1 < α < 2
Cinnazolin	11 < α < 18	2 < α < 4
Melocloptamide	2 < α < 4	< 2
Rufesamide	1 < α < 2	< 0.2
Miconazole	60	5 < α < 10
Metronidazole	12 < α < 14	< 2
benzazole		
Indocaine	> 45	> 18
Diazepam	5	3 < α < 4
Progesterone	> 30	2 < α < 4
Testosterone	16 < α < 18	0.6 < α < 2

All the investigated biologically active agents show a surprisingly high solubility in α -tocopherol.

Compositions

In the following, non-limiting Examples, several drugs are shown in a number of different types of administration forms.

The emulsions were prepared as follows:

The oil and the water phase were heated slowly until homogeneous phases were achieved.

The warm water phase was vigorously mixed into the oil phase. Then, the emulsion was slowly cooled to room temperature while stirring. The emulsion may be homogenized.

The preparation of the solutions was made as simple solution, in which the preparations were stirred until the drug was completely dissolved.

As already mentioned, administration of drugs with low water solubility to the nose is very difficult, because of the limited acceptable volume for the nose (about 100 μ l). The following examples have very high concentration of diazepam, so it was possible to administer diazepam to the nose and to get a fast clinical effect.

Example 8

An O/W emulsion of diazepam as a nosedrop (100 g):

Oil phase:	Diazepam	5.000 g
	α -Tocopherol	59.000 g
	Vitamin E TPGS	5.000 g
Water phase:	Disodium edetate	0.050 g
	Potassium acetate	0.200 g
	Xanthan gum	0.025 g
	Purified water to	100.000 g

The water phase was adjusted to pH 4.7 by 1N HCl.

Example 9

An O/W emulsion of diazepam as nosedrop (100 g):

Oil phase:	Diazepam	5.000 g
	α -Tocopherol	59.000 g
	Sorbitan trioleate	0.500 g
	Fractionated coconut oil	5.000 g
Water phase:	Potassium sorbate	0.200 g
	Poloxamer 188	1.000 g
	Xanthan gum	0.030 g
	Polysorbate 80	0.500 g
	Purified water to	100.000 g

The water phase was adjusted to pH 4.5 by 2N HCl.

Example 10

An O/W emulsion of diazepam as nosedrop (100 g):

Oil phase:	Diazepam	5.000 g
	α -Tocopherol	59.000 g
	Triacetin	10.000 g
	Cetylal glucoside	2.000 g
	Methylparahydroxybenzoate (MPHB)	0.080 g
	Propylparahydroxybenzoate (MPHB)	0.040 g
Water phase:	Poloxamer 188	3.000 g
	Xanthan gum	0.030 g
	Purified water to	100.000 g

11

Example 11

A solution of diazepam, eg. as nosedrop, (25 g):

Diazepam	1.250 g
α -Tocopherol	10.000 g
Triacetin	13.750 g

A less concentrated formulation of diazepam is needed for the rectal administration, but still it can be very difficult to find an acceptable vehicle with low irritation.

Example 12

A solution of cinnarizine, eg. as drops for administration to the oral cavity (25 g):

Cinnarizine	1.250 g
α -tocopherol	17.500 g
ethanol	7.250 g
fractionated coconut oil	5.00 g

A study has shown, that cinnarizine has a higher oral bioavailability, if it is dissolved in a vehicle before administration, [J. Pharm. Sci., vol 76, no. 4, p. 286-288, 1987], an example of such a vehicle could be α -tocopherol.

Example 13

A solution of cinnarizine, eg. for oral administration in capsules, (25 g):

Cinnarizine	0.750 g
α -Tocopherol	24.250 g

Miconazole is used locally for treatment of infections caused by fungi. The following examples show formulations for the oral cavity and the vagina.

Example 14

A solution of miconazole e. g. as drops for administration to the oral cavity (25 g).

Miconazole	6.250 g
α -Tocopherol	16.875 g
Ethanol	1.875 g

Budesonide is a very potential drug, and is used as a local corticoid, e. g. for rhinitis.

Example 15

An O/W emulsion of budesonide as nosedrop or nasal spray (50 g).

Oil phase:	Budesonide	0.025 g
	α -tocopherol	12.500 g
	Vitamin E TPGS	5.000 g
Water phase:	Potassium sorbate	0.100 g

12

-continued

Xanthan gum	0.020 g
Purified water to	100.000 g

The water phase is adjusted to pH 4.5 with 2N HCl.

Example 16

A solution of budesonide as nosedrop (25 g).

Budesonide	0.025 g
α -tocopherol	10.000 g
Sesame oil	14.975 g

Alprazolam is a benzodiazepine which is used for the treatment of e. g. anxiety, therefore a rapid effect is desired in a easy way.

Example 17

An o/w emulsion of alprazolam as nosedrop or nasal spray (100 g).

Oil phase:	Alprazolam	0.500 g
	α -tocopherol	20.000 g
	Vitamin E TPGS	10.00 g
Water phase:	Potassium sorbate	0.200 g
	Xanthan gum	0.050 g
	Purified water to	100.000 g

The water phase is adjusted to pH 4.5 with 2N HCl.

Example 18

A solution of alprazolam, e. g. as drops for administration in the oral cavity (25 g).

alprazolam	0.125 g
α -tocopherol	23.750 g
sesame oil	21.125 g

Midazolam is a benzodiazepine tranquiliser with a sedative effect e. g., and is used for the treatment of anxiety and tension states, and as a sedative and for premedication. Midazolam has a very high first-pass effect after oral administration.

Example 19

An O/W emulsion of midazolam as nosedrop (50 g).

Oil phase:	Midazolam	1.250 g
	α -Tocopherol	29.500 g
	Vitamin E TPGS	2.500 g
Water phase:	Potassium sorbate	0.100 g
	Xanthan gum	0.013 g
	Poloxamer 188	0.750 g
	Dipotassium edetate	0.025 g
	Purified water to	100.000 g

The water phase is adjusted to pH 4.5 with 2N HCl. Disulfiram is used in the treatment of chronic alcoholism.

370
178

13

Example 20

A solution of diazepam, e. g. as an oral solution or for oral administration by capsules (25 g).

Diazepam	1.125 g
α -Tocopherol	23.875 g

Example 21

An O/W emulsion of lidocaine for treatment of e.g. insect bites (100 g).

Oil phase:	Lidocaine	5.000 g
	α -Tocopherol	40.000 g
	Ceteryl glucoside	4.000 g
	MPFB	0.080 g
Water phase:	PFBB	0.040 g
	Pelonomer 188	2.000 g
	Xanthan gum	0.030 g
	Purified water to	100.000 g

Example 22

Pharmacology

Studies on Rabbits

Preparations containing CNS active and muscle relaxing drugs such as diazepam and midazolam were tested in a pharmacodynamic model in rabbits.

The model consists of the following tests:

Test 1:

Hind legs to one side and the rabbit must stay in this position even after a firm tip with a finger on the hip. The test is immediately repeated with both legs placed on the other side.

Test 2:

Hind legs stretched out backwards and the rabbit must stay in this position even after a firm tip with a finger on the hip.

Test 3:

The rabbit must stay in a supine position, when placed in such a position.

After administration of the formulations (i.n., oral or i.v.) the rabbits were exposed to the three tests approximately once per minute until positive pharmacodynamic response, and thereafter every 2 minutes. The total test period was 20 minutes after i.n. and i.v. administration and 30 minutes after peroral administration.

The time elapsed from administration until the first positive response in test 1 was used to compare the onset of action of the different formulations.

Study 1

This pharmacodynamic study compared the nasal formulation of Example 8 (C) containing 5% of diazepam to a commercially available diazepam formulation, Stesolid 2mg tablet, Dumex (D). The study was run in 8 rabbits in a randomized cross-over study. The rabbits were tested for pharmacodynamic response as described previously, but the test period was 30 minutes after peroral administration to be sure to obtain a pharmacodynamic effect.

Formulation C was given intranasally (i.n.) with a laboratory pipette. Each rabbit was held in a supine position

14

during and one minute after i.n. dosing in one nostril. The rabbits received a volume equivalent to 2.5 mg diazepam. After each administration the actual dose received is calculated by subtraction of the weight of the pipette before and after administration. Only applications determined to 80% (2 mg diazepam) were accepted.

Formulation D was given as an oral administration using a stomach pump. The tablet was dissolved in 5 ml water immediately before administration. The tube was rinsed with 10 ml water.

The time to onset of pharmacodynamic response in test 1 is 4.5 minutes (median, n=7) using formulation C and 19.4 minutes (median, n=8) using formulation D.

Study 2

This pharmacokinetic study compared the nasal formulation of Example 8 (C) containing 5% of diazepam to a commercially available diazepam formulation, Stesolid 2mg tablet, Dumex (D). The study was run in 8 rabbits in a randomized cross-over study.

Formulation C was given intranasally (i.n.) as described in study 1.

Formulation D was given by oral administration as described in study 1 using a stomach pump.

Blood samples from the ear-vein were taken before administration (time=0) and at 2, 5, 10, 15, 30, 45, 60, 75, 90, 120, 180 and 240 minutes.

Serum was analyzed for diazepam and the metabolite, desmethyldiazepam using Gas Chromatography (GC). The limit of detection was 5ng/ml for both substances.

The pharmacokinetic parameters found for diazepam were t_{max} =23 minutes (median, n=6), C_{max} =68.2 ng/ml (median, n=6) after administration of formulation C and t_{max} =45 minutes (median, n=6), C_{max} =9.7 ng/ml (median, n=6) after administration of formulation D.

FIGS. 1 and 2 illustrate the mean serum concentrations of diazepam and desmethyldiazepam after administration of formulations C and D.

Study 3

This pharmacodynamic study compared Example 8(C) containing 5% of diazepam with Example 19 (E) containing 2.5% of midazolam. The study was using 6 rabbits.

Formulations C and E were given intranasally (i.n.) with a laboratory pipette. Each rabbit was held in a supine position during and one minute after i.n. dosing in one nostril. The rabbits received a volume equivalent to 2.5 mg diazepam or 1.25 mg midazolam, respectively.

After each administration the actual dose received was calculated by subtraction of the weight of the pipette before and after administration. Only doses equivalent to 80% were accepted.

The time to onset of pharmacodynamic response in test 1 was 3.1 minutes (median, n=6) using formulation C containing diazepam and 2.5 minutes (median, n=6) using formulation E containing midazolam.

Example 23

Toxicology

Local Irritancy in Humans:

The investigation was carried out in order to estimate irritation after nasal application of 10 mg of diazepam; 100 mg of the preparation from Example 8 in each nostril.

37A
179

6 volunteers, 3 male and 3 female participated in the trial.

The investigator inspected both nostrils macroscopically for local irritation at the following times: immediately after medication, at 30 minutes, and 1, 2, 4, and 6 hours.

In one volunteer the macroscopic inspection showed light blush of both nostrils immediately after medication. None of the six volunteers had local irritation of the nostrils 30 minutes after application, see table 2.

Conclusion

The total results of the trial have shown that preparation of Example 8 does not cause unacceptable irritation of the nostrils.

TABLE 2

Individual local irritation of the nostrils after intranasal administration of 10 mg diazepam, (Example 8)

Volunteer no	Local irritation											
	Immediately after medication	30 min	1 h	2 h	4 h	6 h						
	R	L	R	L	R	L	R	L	R	L	R	L
1	—	—	—	—	—	—	—	—	—	—	—	—
2	—	—	—	—	—	—	—	—	—	—	—	—
3	—	—	—	—	—	—	—	—	—	—	—	—
4	Light blush	Light blush	—	—	—	—	—	—	—	—	—	—
5	—	—	—	—	—	—	—	—	—	—	—	—
6	—	—	—	—	—	—	—	—	—	—	—	—

R: right nostril
L: left nostril

What is claimed is:

1. A composition for the non-topical delivery of an active agent in the form of a non-liposomal emulsion comprising two phases:

a) a first tocopherol-based phase comprising an active agent which is no more than sparingly soluble in water and which is not a tocopherol; and

an amount of 20% to 95% w/w based on the total weight of the composition of at least one tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof sufficient to dissolve the active agent in the tocopherol-based phase;

b) a second phase comprising an emulsifying agent wherein the emulsifying agent is vitamin E TPGS; wherein said active agent is selected from the group consisting of antibiotics; antivirals; antimycotics; anti-amoebics; non-steroidal anti-inflammatory drugs; anti-allergics; immunosuppressive agents; coronary drugs; analgesics; local anaesthetics; anxiolytics; sedatives and hypnotics; migraine relieving agents; drugs against motion sickness; anti-emetics; disulfiram and vitamin K.

2. A composition as claimed in claim 1 wherein the tocopherol is α -tocopherol or an acetate, linoleate, nicotinate or hemi-succinate derivative thereof.

3. A composition as claimed in claim 1 in a form suitable for transmucosal, peroral, enteral or parenteral application.

4. A composition as claimed in claim 2, in a form of suitable for intranasal, buccal, vaginal or rectal application or for administration via the oral cavity.

5. A composition as claimed in claim 1 wherein the active agent is selected from the group consisting of tetracycline, doxycycline, oxytetracycline, chloramphenicol,

erythromycin, acyclovir, idoxuridine, tromantadine, miconazole, ketoconazole, fluconazole, itraconazole, econazole, griseofulvin, amphotericin B, nystatine, metronidazole, metronidazole benzoate, tiadazole, indomethacin, ibuprofen, piroxicam, diclofenac, disodium cromoglycate, nitroglycerin, isosorbide dinitrate, verapamil, nifedipine, diltiazem, digoxin, morphine, cyclosporins, buprenorphine, lidocaine, diazepam, nitrazepam, flurazepam, estazolam, flunitrazepam, triazolam, alprazolam, midazolam, temazepam, lorazepam, oxazepam, busiprone, sumatriptan, ergotamine derivatives, cinnarizine, anti-histamines, ondansetron, tropisetron, granisetron, metoclopramide, disulfiram, and vitamin K.

6. A composition as claimed in claim 1, wherein the active agent is a coronary drug selected from the group consisting of vasodilators; calcium-antagonists and cardiac-glycosides.

7. A composition as claimed in claim 1, wherein the active agent is a benzodiazepine or an antimycotic.

8. A composition as claimed in claim 1, wherein the active agent is selected from the group consisting of diazepam, midazolam and miconazole.

9. A composition as claimed in claim 1, wherein the amount of the tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof is from 35 to 80% (w/w).

10. A composition as claimed in claim 1, further comprising at least one additional component selected from the group consisting of solvents, surfactants, stabilizers, bioadhesive polymers, preservatives, odor-masking agents and taste-masking agents.

11. A composition for the non-topical delivery of an active agent in the form of a non-liposomal emulsion comprising two phases:

a) a first tocopherol-based phase comprising an active agent which is no more than sparingly soluble in water and which is not a tocopherol; and

an amount of 20% to 95% w/w based on the total weight of the composition of at least one tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof sufficient to dissolve the active agent in the said tocopherol-based phase;

b) a second phase comprising an emulsifying agent wherein the emulsifying agent is vitamin E TPGS.

12. A composition as claimed in claim 11 wherein the active agent is selected from the group consisting of antibiotics; antivirals; antimycotics; anti-amoebics; non-steroidal anti-inflammatory drugs; anti-allergics; immunosuppressive agents; coronary drugs; analgesics; local anaesthetics; anxiolytics, sedatives and hypnotics; migraine relieving agents; drugs against motion sickness; anti-emetics; disulfiram and vitamin K.

13. A composition as claimed in claim 12 wherein the active agent is selected from the group consisting of tetracycline, doxycycline, oxytetracycline, chloramphenicol, erythromycin, acyclovir, idoxuridine, tromantadine, miconazole, ketoconazole, fluconazole, itraconazole, econazole, griseofulvin, amphotericin B, nystatine, metronidazole, metronidazole benzoate, tiadazole, indomethacin, ibuprofen, piroxicam, diclofenac, disodium cromoglycate, nitroglycerin, isosorbide dinitrate, verapamil, nifedipine, diltiazem, digoxin, morphine, cyclosporins, buprenorphine, lidocaine, diazepam, nitrazepam, flurazepam, estazolam, flunitrazepam, triazolam, alprazolam, midazolam, temazepam, lorazepam, oxazepam, busiprone, sumatriptan, ergotamine

17

derivatives, cinnarizine, anti-histamines, ondansetron, tropisetron, granisetron, metoclopramide, disulfiram, and vitamin K.

14. A composition as claimed in claim 11 wherein the tocopherol is α -tocopherol or an acetate, linoleate, nicotinate or hemi-succinate derivative thereof.

15. A composition as claimed in claim 11 in a form suitable for trans-mucosal, peroral, enteral or parenteral application.

16. A composition as claimed in claim 11, in a form suitable for intranasal, buccal, vaginal or rectal application or for administration via the oral cavity.

17. A composition as claimed in claim 11, wherein the active agent is a coronary drug selected from the group consisting of vasodilators; calcium-antagonists and cardiotonic glycosides.

18. A composition as claimed in claim 11, wherein the active agent is a benzodiazepine or an antimycotic.

19. A composition as claimed in claim 11, wherein the active agent is selected from the group consisting of diazepam, midazolam and miconazole.

20. A composition as claimed in claim 11, wherein the amount of the tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof is from 35 to 80% (w/w).

21. A composition as claimed in claim 11, further comprising at least one additional component selected from the group consisting of solvents, surfactants, stabilizers, bioadhesive polymers, preservatives, odor-masking agents and taste-masking agents.

22. A composition for the parenteral delivery of an active agent in the form of a non-liposomal emulsion comprising two phases:

a) a first tocopherol-based phase comprising an active agent which is no more than sparingly soluble in water and which is not a tocopherol; and

an amount of 20% to 95% w/w based on the total weight of the composition of at least one tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof sufficient to dissolve the active agent in the tocopherol-based phase;

b) a second phase comprising an emulsifying agent wherein the emulsifying agent is vitamin E TPGS.

23. A composition as claimed in claim 22 wherein the active agent is selected from the group consisting of antibiotics; antivirals; antimycotics, anti-amoebics; non-

18

steroidal anti-inflammatory drugs; anti-allergics; immunosuppressive agents; coronary drugs; analgesics, local anaesthetics; anxiolytics, sedative and hypnotics; migraine relieving agents; drugs against motion sickness; anti-emetics; disulfiram and vitamin K.

24. A composition as claimed in claim 23 wherein the active agent is selected from the group consisting of tetracycline, doxycycline, oxytetracycline, chloramphenicol, erythromycin, acyclovir, idoxuridine, tromantadine, miconazole, ketoconazole, fluconazole, itraconazole, econazole, griseofulvin, amphotericin B, nystatine, metronidazole, metronidazole benzoate, tinidazole, indomethacin, ibuprofen, piroxicam, diclofenac, Disodium cromoglycate, nitroglycerin, isosorbide dinitrate, verapamil, nifedipine, diltiazem, digoxin, morphine, cyclosporin, buprenorphine, lidocaine, diazepam, nitrazepam, flurazepam, estazolam, flunitrazepam, triazolam, alprazolam, midazolam, temazepam, lorazepam, bromazepam, clobazam, clonazepam, lorazepam, oxazepam, busiprone, sumatriptan, ergotamine derivatives, cinnarizine, anti-histamines, ondansetron, tropisetron, granisetron, metoclopramide, disulfiram, and vitamin K.

25. A composition as claimed in claim 22 wherein the tocopherol is α -tocopherol or an acetate, linoleate, nicotinate or hemi-succinate derivative thereof.

26. A composition as claimed in claim 22, wherein the active agent is a coronary drug selected from the group consisting of vasodilators; calcium-antagonists and cardiotonic glycosides.

27. A composition as claimed in claim 22, wherein the active agent is a benzodiazepine or an antimycotic.

28. A composition as claimed in claim 22, wherein the active agent is selected from the group consisting of diazepam, midazolam and miconazole.

29. A composition as claimed in claim 22, wherein the amount of tocopherol or acetate, linoleate, nicotinate or hemi-succinate derivative thereof is from 35 to 80% (w/w).

30. A composition as claimed in claim 22, further comprising at least one additional component selected from the group consisting of solvents, surfactants, stabilizers, bioadhesive polymers, preservatives, odor-masking agents and taste-masking agents.

* * * * *

374 182 D₂

Examples 2a and 2b, and rapamycin in Examples 3a and 3b as active agent. In Example 2, the active agent 40-0-(2-hydroxy)ethyl rapamycin is abbreviated to "active agent R".

Intact drug content and main degradation product are determined by HPLC with an analytical error of +/- 2%.

Composition	Example 2a active agent R	Example 2b active agent R malonic acid	Example 3a Rapamycin	Example 3b Rapamycin malonic acid
Cremophor RH 40	44.0 %	43.0 %	41.5 %	40.5 %
Cornoil glyceride	26.3 %	25.7 %	24.8 %	24.2 %
Propylene glycol	17.6 %	17.2 %	16.6 %	16.2 %
Ethanol abs.	10.0 %	10.0 %	15.0 %	15.0 %
DL- α -Tocopherol	0.1 %	0.1 %	0.1 %	0.1 %
active agent R	2.0 %	2.0 %	-	-
Rapamycin	-	-	2.0 %	2.0 %
Malonic acid	-	2.0 %	-	2.0 %
Intact drug content and main degradation product (<i>seco</i> acid) expressed as percentages of amount (HPLC evaluation by external standardization)				
4 weeks at 25°C	86.0% (16.1 %)	99.5 % (0.5 %)	83.5 % (15.4 %)	98.4 % (0.7 %)

Amount of main degradation product is shown in brackets. Main degradation product of rapamycin is referred to as secorapamycin.

The above examples demonstrate that malonic acid exhibits a pronounced stabilizing effect on the degradation of 40-0-(2-hydroxy)ethyl rapamycin and of rapamycin.

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

2020
Bogotá, D.C., 04/02/2010

Abogado
Alicia Lloreda Ricaurte
(Apoderado)

ASUNTO	Radicación	05 17056
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	
	Folios	011

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

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: 47 a 57 | | | | | | | | | | | | | | |
| 1.2. | <u>Reivindicaciones:</u> | Folios: 58 a 61
Folios: 87 a 90 Memorial de 26/01/2006
Folios: 347 a 349 Memorial de 01/12/2009 | | | | | | | | | | | | | | |
| 1.3. | <u>Datos PCT:</u> | <table border="0"> <tr> <td>Solicitud Internacional:</td> <td>PCT/US03/023276</td> </tr> <tr> <td>Capítulo II</td> <td></td> </tr> <tr> <td>Fecha Sol. Internacional:</td> <td>25/07/2003</td> </tr> <tr> <td>Publicación Internacional:</td> <td>WO04/011000</td> </tr> <tr> <td>Fecha Pub. Internacional:</td> <td>05/02/2004</td> </tr> <tr> <td>Fecha Inicio Fase Nacional:</td> <td>30/02/2005</td> </tr> <tr> <td>Fecha Sol. Nacional:</td> <td>23/02/2005</td> </tr> </table> | Solicitud Internacional: | PCT/US03/023276 | Capítulo II | | Fecha Sol. Internacional: | 25/07/2003 | Publicación Internacional: | WO04/011000 | Fecha Pub. Internacional: | 05/02/2004 | Fecha Inicio Fase Nacional: | 30/02/2005 | Fecha Sol. Nacional: | 23/02/2005 |
| Solicitud Internacional: | PCT/US03/023276 | | | | | | | | | | | | | | | |
| Capítulo II | | | | | | | | | | | | | | | | |
| Fecha Sol. Internacional: | 25/07/2003 | | | | | | | | | | | | | | | |
| Publicación Internacional: | WO04/011000 | | | | | | | | | | | | | | | |
| Fecha Pub. Internacional: | 05/02/2004 | | | | | | | | | | | | | | | |
| Fecha Inicio Fase Nacional: | 30/02/2005 | | | | | | | | | | | | | | | |
| Fecha Sol. Nacional: | 23/02/2005 | | | | | | | | | | | | | | | |
| 1.4. | <u>Prioridad:</u> | US 60/399,526 de 30/07/2002 | | | | | | | | | | | | | | |
| 1.5. | <u>Respuesta del solicitante:</u> | Folios: 317 a 327 Memorial de 30/04/2009
Folios: 339 a 349 Memorial de 01/12/2009 | | | | | | | | | | | | | | |

2. Objeto de la invención

Título de la solicitud

Formulaciones parenterales que contienen un hidroxi-éster de rapamicina

Reivindicaciones

Reivindicaciones 1 a 9: Se reivindica un concentrado cosolvente de CCI-779 que comprende 2,5mg/ml a aproximadamente 50mg/ml de CCI-779, un solvente parenteralmente aceptable seleccionado del grupo que consiste en dimetilacetamida y un solvente alcohólico y aproximadamente 0,001% a 1%p/v de un componente antioxidante.

Reivindicaciones 10 a 14: Se reivindica una formulación parenteral que comprende el concentrado cosolvente, un solvente diluyente y un surfactante.

Reivindicaciones 15 a 23: Se reivindica un proceso para preparar una formulación parenteral de CCI-779 que comprende:

- a) Mezclar CCI-779 con un solvente parenteralmente aceptable y un componente antioxidante para dar un concentrado cosolvente,
- b) Mezclar un solvente diluyente y un surfactante para producir un diluyente, y
- c) Mezclar el concentrado cosolvente con el diluyente para dar la formulación parenteral de CCI-779.

Sustento Descriptivo

La invención proporciona formulaciones parenterales que contienen un hidroxi-éster de rapamicina con ácido 3-hidroxi-2(hidroximetil)-2-metil-propiónico (CCI-779).

Se sabe que uno de los obstáculos primarios para la formulación de CCI-779 en la forma de dosis parenteral constituye la baja solubilidad en medio acuoso que es de menos de 1µg/ml. Debido a que el fármaco es un no electrolito los criterios de ajuste de pH y formación de sales no resultan útiles para mejorar la solubilidad en medio acuoso. El fármaco tiene solubilidad pobre en aceites vegetales farmacéuticamente aceptables pero es soluble en ciertos solventes orgánicos miscibles con agua como etanol, propilenglicol y dimetilacetamida, que han sido aceptados para la administración parenteral. Sin embargo, existe dos problemas relacionados con la administración del activo en estos solventes, el primero corresponde a la inestabilidad en términos de degradación oxidativa de CCI-779 o a clivaje de un enlace lactona produciendo la formación del sec-CCI-779 de anillo abierto. En segunda medida las formulaciones se precipitan por efecto de la dilución con soluciones de infusión acuosas, tales como inyección de cloruro de sodio al 0,9% o de dextrosa al 5% o con sangre. Esta es una limitación primaria para usar solventes orgánicos miscibles con agua o cosolventes por ello la invención resuelve los problemas de estabilidad mediante la adición de antioxidantes y un agente de quelación a la solución, así como de un surfactante parenteralmente aceptable.

- Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K³¹₁₄₃₆// A 61 P³¹₁₀₄** de la Clasificación Internacional de Patentes.

3. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 30/07/2002, se procedió a efectuar la búsqueda de

documentos relacionados en el estado de la técnica con fecha de publicación anterior a ésta.

Nº	Documento	Título	Fecha de Publicación
D1	US5516770	"Rapamycin formulation for IV injection"	14/05/1966
D2	GB2327611	"Stabilisation of macrólida compositions"	03/02/1999
D3	US5530006	"Rapamycin formulation for IV injection"	25/06/1996
D4	US5674874	"Lactone stable formulation of 7-ethyl 10-hydroxy camptothecin and methods for uses thereof"	07/10/1997
D5	US6022852	"Pharmaceutical composition containing cyclosporine A"	08/02/2000
D6	US6193985	"Tocopherol compositions for delivery of biologically active agents"	27/02/2001

Anterioridades D1 a D3 en los folios 105 a 115. Anterioridad D4 en los folios 350 a 356. Antecedentes D5 y D6 en los folios 357 a 373. Resultados del antecedente D2 en el folio 374.

4. Análisis de patentabilidad (artículo 14 D. 486)

4.1 Nivel inventivo (artículo 18 D. 486)

El nivel inventivo del objeto reclamado se evaluó por comparación entre las características esenciales del concentrado reivindicado, la formulación parenteral que lo contiene y los elementos esenciales de las composiciones reveladas por el estado del arte.

- **Se reivindica:**

Un concentrado cosolvente de CCI-779 que comprende 2,5mg/ml a aproximadamente 50mg/ml de CCI-779, un solvente parenteralmente aceptable seleccionado del grupo que consiste en dimetil-acetamida y un solvente alcohólico y aproximadamente 0,001% a 1%p/v de un componente antioxidante.

Y una formulación parenteral que comprende el concentrado cosolvente, un solvente diluyente y un surfactante.

- **El estado del arte relacionado con el concepto común (concentrado cosolvente) presenta los siguientes documentos:**

Anterioridad D2:

La publicación D2 presenta composiciones estables que contienen macrólidos como rapamicina, en especial el análogo estructural de Temsirolimus, FK506 cuya denominación común es Tacrolimus.

Las composiciones farmacéuticas contienen el macrólido y una sustancia ácida elegida entre. Ácido malónico, ácido fumárico, ácido maléico, ácido D-málico, ácido L-málico, ácido cítrico, ácido ascórbico, ácido succínico, ácido oxálico, ácido benzoico o ácido láctico.

Anterioridad D4:

La publicación D4 hace referencia a una formulación estable de un lactona como la 7-etil-10-hidroxi camptotecina (CPT-11) utilizado como anticancerígeno y que

presenta baja solubilidad en agua, por lo que no había sido posible administrarlo por vía oral o parenteral.

Dentro de las modalidades particulares la publicación se mencionan las del ejemplo 11, en las que se combinan 2,5mg de 7-etil-10-hidroxi campotecina (HECPT) con 1000 partes de dimetilacetamida a 25°C y 500 partes de un ácido carboxílico elegido entre ácido cítrico o ácido ascórbico, entre otros. Estos ejemplos se encuentran registrados en la tabla 6 del antecedente D4 (folios 354 y 355).

Anterioridad D5:

La publicación D5 revela un concentrado para inyección de ciclosporina A que combina efectivamente tocoferol con etanol junto al agente de tensión superficial lecitina, a fin de superar los problemas asociados a la baja solubilidad del agente activo en solventes acuosos y a la estabilidad disminuida durante el almacenamiento del producto.

Anterioridad D6:

La publicación D6 hace referencia a una formulación farmacéutica que contiene un principio activo insoluble o levemente soluble en medio acuoso, debido a su estructura complejo y altamente lipofílica. Las formulaciones presentan dos fases, la primera contiene tocoferol y la segunda fase comprende el agente activo emulsificado con vitamina E TPGS y pueden ser administradas a través de las mucosas, por vía peroral, enteral o parenteral.

Tabla 1. Comparación entre los elementos técnicos relacionados con el sistema cosolvente y los antecedentes D2, D4, D5 y D6

MATERIA REIVINDICADA	D2 (GB2327611)	D4 (US5674874)	D5 (US6022892)	D6 (US6193983)
Concentrado cosolvente de CCI-779 Que comprende aproximadamente 2,5 mg/ml a aproximadamente 50mg/ml de CCI-779	Concentrado para infusión de 40-0-(2-hidroxi)etil-rapamicina (Tacrolimus)	Formulación estable de campotecina	Concentrado inyectable de Ciclosporina A	Composición para aplicación parenteral que permite la liberación de un agente activo
Un solvente parenteralmente aceptable seleccionado entre: 1. Dimetilacetamida o 2. Un solvente alcohólico, tal es el caso de etanol, propilenglicol, polietilenglicol 300, 400, 600 o mezclas	Acosito ricino etoxilado (CREMOPHORE) Etanol	Dimetilacetamida (DMAC)	Etanol Lecitina	Tocoferol-esterificado con polietilenglicol 1000
Aproximadamente 0,001% a 1,0% de un componente antioxidante que comprende: 1. ácido cítrico, 2. glicina, 3. tocoferol, 4. BHA, 5. BHT, 6. monotilglicerol, 7. ácido ascórbico o 8. propil-galato	Ácido cítrico	Ácido carboxílico elegido entre: 1. Ácido cítrico, o 2. Ácido ascórbico	Tocoferol	α -Tocoferol

CCI-779

Nombre químico: Éster 42 de rapamicina con ácido 3-hidroxi-2-(hidroximetil)-2-metilpropiónico

Nombre común: Temsirolimus

Evaluación de diferencias técnicas con respecto a los documentos D2, D4, D5 y D6:

Teniendo en cuenta el contenido de las anticipaciones más cercanas a la invención

fue posible identificar las siguientes diferencias técnicas con respecto a la materia reivindicada en la cláusula independiente 1 y sus dependientes 2 a 9 (ver tabla 1):

Con relación al antecedente D2 las diferencias estriban en que las composiciones allí reveladas no comprenden Temsirolimus (CCI-779) sino el éster 40-0-(2-hidroxi)etil-rapamicina comúnmente denominado *Tacrolimus* y además agregan una sustancia lipófila como aceite de ricino para estabilizar la formulación. En este caso el sistema se forma por combinación de un solvente alcohólico como etanol y el componente antioxidante ácido cítrico junto a una sustancia lipofílica.

Y en lo concerniente a la publicación D4 la diferencia estriba en que las composiciones allí reveladas no formulan Temsirolimus (CCI-779) sino el anticancerígeno campotecina. En este caso, el sistema puede ser binario y se forma por combinación de dimetilacetamida (DMAC) y un ácido carboxílico elegido entre el ácido cítrico o el ácido ascórbico.

Con relación al antecedente D5 la diferencia estriba en que las composiciones no formulan el agente Temsirolimus sino al activo Ciclosporina A y por otra parte, incluyen un agente tensioactivo para garantizar que el fármaco permanezca soluble. En este caso, el sistema se forma por combinación de un solvente alcohólico como etanol y un antioxidante como tocoferol.

Con respecto al antecedente D6 la diferencia estriba en que el antecedente no precisa que el agente activo susceptible de formular corresponda a Temsirolimus, sino que presenta un sistema de entrega farmacéutico general cuyo vehículo está constituido por tocoferol esterificado con PEG 1000 y una fase adicional de tocoferol, el cual permite formular un variado grupo de moléculas que tienen como propiedad común la solubilidad disminuida en medio acuoso y la alta lipofilidad derivada de sus características estructurales.

De esta manera, al combinar las enseñanzas de los documentos [D4 y D2] o [D4 y D5] o [D4 y D6] se subsanan las diferencias técnicas relacionadas con la incorporación de un agente tensioactivo para conseguir una mejor solubilidad de agentes farmacológicamente activos con estructuras complejas y solubilidad pobre en medio acuoso, como es el caso de Temsirolimus (CCI-779) y por consiguiente una mejor estabilidad con el diseño de un sistema cosolvente que presente una alta concentración del agente activo. Lo anterior, debido a que en el documento D4 se consigna la posibilidad de combinar un solvente parenteralmente aceptable como DMAC con un antioxidante de tipo ácido como el ácido cítrico o el ácido ascórbico.

De esta manera, el problema técnico asociado a la formulación de sustancias con solubilidad disminuida en medio acuoso ya se había resuelto acudiendo a la utilización de solventes orgánicos biocompatibles para administración parenteral como es el caso de DMAC o etanol, ácido cítrico o ácido ascórbico y tocoferol. Por lo que esta Superintendencia infiere razonablemente que la solicitud presenta la misma solución planteada por el estado de la técnica para solubilizar sustancias como Campotecina, Ciclosporina o cualquier agente activo que presente dificultad para formularlo en medio acuoso y administrarlo por vía parenteral, para el caso particular del agente Temsirolimus, es decir, recurre a medios técnicos conocidos para dar solución técnica al mismo problema de formulación pero para un agente activo diferente.

Esta situación evidencia la obviedad de la solución aportada al estado del arte, toda vez que el efecto técnico alcanzado con la combinación de etanol (un solvente alcohólico) o DMAC con ácido cítrico, ácido ascórbico o tocoferol (agentes

antioxidantes) ya lo había previsto el estado del arte, aunque aplicado a otra clase de sustancias activas.

- El estado del arte relacionado con las formulaciones parenterales que comprenden el concentrado cosolvente presenta los siguientes documentos:

Anterioridad D1:

El documento **D1** revela formulaciones farmacéuticas inyectables cuyo principio activo es el agente Rapamicina en concentración de 0,5mg/ml a 10mg/ml con un vehículo compuesto por ésteres de polioxietilen-sorbitán y polietilenglicol 200, 300 ó 400.

Anterioridad D3:

El documento **D3** hace referencia a composiciones inyectables solubles y acuosas de rapamicina en concentración de 0.1 a 10% de la solución en solvente N,N-dimetilacetamida. El sistema de excipientes comprende 0.1 a 10% en peso de un éster de polioxietilen sorbitán, 10 a 60% de polietilenglicol 200, 300 o ambos y 30 a 90% en volumen de agua.

Anterioridad D4:

El documento **D4** revela en el ejemplo 4 una formulación farmacéutica de campotecina en concentraciones que oscilan entre 0,1 y 5,0 mg de HECPT disueltos en 500 a 10000 partes por peso de la solución total cuyo solvente principal corresponde al excipiente DMAC. La formulación incluye 1 a 1000 partes de un ácido carboxílico, 20 a 7000 partes de un alcohol y 20 a 8000 partes de polietilenglicol, así como 20 a 8000 partes de un agente de tensión superficial no iónico.

El ácido carboxílico adicionado a la formulación corresponde a ácido cítrico o ascórbico, entre otros, el polietilenglicol se elige entre polietilenglicol 200, 300 ó 400 y el agente de tensión superficial es polisorbato 80.

Tabla 2. Comparación entre los elementos técnicos relacionados con la formulación parenteral y los divulgados en los antecedentes D1, D3 y D4.

MATERIA REIVINDICADA	D1 (US5516770)	D3 (US5530006)	D4 (US5674874)
Formulación parenteral que comprende:	Soluciones de rapamicina 1.0mg/ml	Dilución del concentrado de rapamicina 50mg/ml	Formulación de la lactona Campotecina
Un concentrado cosolvente de Temsirolimus en concentraciones de 1 mg/ml a aproximadamente 25 mg/ml a base de un solvente parenteralmente aceptable elegido entre DMAC o un solvente alcohólico y un agente antioxidante en proporción 0.0005% a 0.5% p/v.	Concentrado de rapamicina en propilenglicol	Concentrado de rapamicina en dimetilacetamida (DMAC)	DMAC, alcohol bencilico y ácido cítrico
Un solvente diluyente	Polietilenglicol	Polietilenglicol 300	Polietilenglicol 200, 300, 400 y propilenglicol
Un tensioactivo elegido entre: 1. polisorbato 80, 2. polisorbato 20, 3. Ácido biliar, 4. Lecitina, 5. Aceite vegetal etoxilado, 6. Vitamina E-Tocoferol-Propilenglicol-succinato o 7. Copolímeros de bloque polioxietilen-polióxipropileno	Polisorbato 80	Polisorbato 80	Polisorbato 80

Evaluación de diferencias técnicas con respecto a los documentos D1, D3 y D4:

Teniendo en cuenta el contenido de las anticipaciones más cercanas fue posible identificar las siguientes diferencias técnicas con respecto a la materia reivindicada en las cláusulas dependientes 10 a 14 (ver tabla 2):

Con relación a las enseñanzas reveladas en el documento D1 la diferencia estriba en que el concentrado que se adiciona a la formulación parenteral no adiciona un agente antioxidante, sino que el concentrado se obtiene exclusivamente en un solvente alcohólico como propilenglicol. No obstante adicionan al concentrado un solvente diluyente como polietilenglicol y un agente de tensión superficial como polisorbato.

Con respecto a las enseñanzas reveladas en el documento D3 la diferencia estriba en que el concentrado obtenido allí sólo se forma en el vehículo DMAC sin que se agregue un agente antioxidante. Sin embargo, a la formulación se agrega un solvente diluyente como polietilenglicol y un agente de tensión superficial como polisorbato 80 para obtener la dilución del concentrado de rapamicina en concentración de 50mg/ml.

Con relación al documento D4 la única diferencia estriba en que el principio activo allí formulado no corresponde a rapamicina sino a la lactona Campotecina –un inhibidor de topoisomerasa (I)-, y en que en la composición del vehículo utilizado para solubilizar esta sustancia orgánica se agrega alcohol bencílico.

Del problema técnico objetivo y del efecto inesperado:

El problema técnico objetivo resuelto con el diseño de un concentrado de Temsirolimus es precisamente el derivado de la solubilidad disminuida en medio acuoso que es de menos de 1µg/ml, situación que hace difícil el diseño de un vehículos para administración parenteral.

El problema se resuelve con el diseño de un sistema cosolvente que aumenta la solubilidad del agente activo y lo presenta en forma concentrada, para luego agregar un vehículo diluyente que contiene un solvente diluyente y un tensioactivo.

En el folio 49 la solicitud se indica que el sistema cosolvente concentrado se forma solubilizando Temsirolimus en un solvente alcohólico y un antioxidante.

En el folio 50 de la memoria descriptiva de la solicitud se indica que el segundo aspecto de la invención tiene que ver con la formulación de un vehículo parenteral que contienen: el agente activo Temsirolimus, un solvente alcohólico, un antioxidante, un diluyente y un agente que disminuya la tensión superficial. De hecho los ejemplos 1 a 9 del sustento descriptivo presentan varias alternativas para la obtención del concentrado cosolvente, alternativas que presentan buenos resultados en términos del incremento en la solubilidad del agente activo.

La primera de ellas utiliza etanol y ácido cítrico, la segunda utiliza etanol, ácido cítrico, tocoferol y propilenglicol, la tercera utiliza ácido cítrico, tocoferol y DMAC y la cuarta polisorbato 80, PEG 400 y agua para conseguir un concentrado del compuesto Temsirolimus.

En consecuencia, el señor solicitante tiene claridad sobre los resultados alentadores que se consiguen cuando se genera un sistema de cosolvencia con una mezcla de diferentes solventes. Además sabe que los resultados son equivalentes aún cuando

se utilice un solvente alcohólico con un antioxidante o DMAC con un antioxidante.

Por lo que en virtud de las enseñanzas del estado de la técnica es posible concluir que existen anticipaciones claras en los que se consigna el efecto técnico observado por el señor solicitante, en particular, el documento D4 indica que es posible adicionar polisorbato 80 y un diluyente a un sistema cosolvente compuesto por DMAC y ácido cítrico o ácido ascórbico y el documento D3 señala que es posible obtener un vehículo que solubilice rapamicina incluso hasta una concentración de 100mg/ml cuando se utiliza incluso sólo DMAC.

En consecuencia, una persona medianamente versada en la materia se encontraba en capacidad de derivar los elementos característicos del concentrado, con base en las enseñanzas que en conjunto revelan los documentos [D4 y D2] o [D4 y D5] o [D4 y D6], toda vez que la diferencia sólo estriba en el intercambio del principio activo pero conservando las características del vehículo a fin de conseguir el mismo efecto técnico. Tan es así que cada uno de los documentos D4, D5 y D6 describe el mismo problema técnico que desea resolver el señor solicitante pero para el caso particular de Temsirolimus.

Ahora bien, con respecto a las formulaciones es posible concluir en el mismo sentido que en el caso del concentrado toda vez que al combinar las enseñanzas de la publicación D4 con cualquiera de los documentos D1 ó D3 es posible derivar todos los elementos característicos de las composiciones.

Y como se indicó para el caso de las publicaciones D4, D5 y D6, las publicaciones D1 y D3 también anticipan el problema técnico asociado a compuestos con solubilidad acuosa disminuida y aportan una solución que estriba precisamente en la elección correcta de los solventes orgánicos por medio de pruebas de solubilidad, situación que demuestra que en la mayoría de los casos para las lactonas macrocíclicas o compuestos estructuralmente complejos se recurre a la utilización de DMAC o etanol, propilenglicol o polietilenglicol en combinación con un antioxidante, con el fin de asegurar que se retarda la descomposición química del activo.

Además, la estrategia de diseñar concentrados para luego diluirlos en un vehículo compuesto por un diluyente y un agente tensioactivo, también fue anticipada por cada una de las publicaciones D1 y D3 y de hecho, es bien sabido que los alcoholes en combinación con un agente que reduzca la tensión superficial mantiene las moléculas solubilizadas y evitan su agregación y formación de núcleos de cristalización.

Así las cosas, con base en las enseñanzas que en conjunto revelan los documentos del estado del arte [D4 y D2] o [D4 y D5] o [D4 y D6] era posible derivar los elementos característicos de los concentrados y en el caso de las formulaciones parenterales que contienen Temsirolimus basta con estudiar de manera combinada el contenido de las publicaciones [D4 y D1] o [D4 y D3] para anticipar la solución aportada al estado de la técnica que reivindica el señor solicitante.

Por las razones expuestas anteriormente esta dependencia encuentra que el arte previo, afecta la altura inventiva de la materia reclamada y por consiguiente considera que existe incumplimiento de las disposiciones contempladas en el artículo 18 del ordenamiento jurídico andino.

5. Conclusión:

A) respecto es preciso señalar que los agentes activos formulados en los antecedentes presentaban las mismas limitaciones que encontró el señor solicitante para la formulación de Temsirolimus, tal es el caso de la solubilidad acuosa disminuida, lo que hace prácticamente imposible su formulación en medios acuosos, por ello, para el caso de agentes como Campotecina se efectuaron pruebas de solubilidad en solventes orgánicos, toda vez que esta es la salida convencionalmente aceptada para lograr formular agentes inestables en solventes biocompatibles para su administración por vía parenteral y no en vano en el documento D4 se recurre a la utilización de DMAC y ácidos carboxílicos como el ácido cítrico o el ácido ascórbico para lograr estabilizar el sistema cosolvente.

O bien podría citarse el contenido de la publicación D6 en el que se menciona el mismo problema técnico pero asociado una gran variedad de moléculas, las que se pueden formular en un antioxidante como tocoferol y en su derivado esterificado con polietilenglicol a fin de conseguir la estabilidad de los sistemas y garantizar la solubilidad de los agentes activos (ver columna 5 del folio 367 antecedente D6).

Así las cosas, el señor solicitante acude a medios técnicos conocidos para resolver el problema particular de Temsirolimus, el que en esencia, constituye un problema común para otras sustancias farmacológicamente activas y el que además soluciona con base en las enseñanzas del estado del arte.

- "(...) ninguno de los documentos D1 y D3 enseña o sugiere la inclusión de un antioxidante en las formulaciones, los problemas y soluciones asociadas con las formulaciones parenterales que comprende CCI-779 ni el concentrado listo para almacenar del solicitante".

Al respecto es preciso agregar que lo único que no agregan los concentrados divulgados en D1 y D3 corresponde al agente antioxidante. Sin embargo, dichas diferencias se superan en la medida que sus enseñanzas se estudian en combinación con la publicación D4, en la que evidentemente se formula inicialmente un agente activo como campotecina en un vehículo compuesto por DMAC y un agente antioxidante como el ácido cítrico o el ácido ascórbico.

De esta manera, una persona versada en ciencias farmacéuticas derivaría las características del sistema cosolvente a partir de las enseñanzas que en conjunto revelan los antecedentes mencionados [D4 y D1] o [D4 o D3].

- "(...) si bien la referencia D2 (anteriormente D4) discute formulaciones que contienen macrólidos y ácido, la misma no reconoce el beneficio de utilizar agentes antioxidantes en lugar de ácidos para la estabilización de los macrólidos".

Frente al argumento del señor solicitante es preciso indicar que en la cláusula 5 del pliego reivindicatorio se aclara la funcionalidad técnica del ácido cítrico, al que se le atribuye actividad como agente antioxidante. Así pues, derivado de este hecho es claro que el ácido divulgado en D2 presentan la misma funcionalidad técnica dentro del sistema de entrega farmacéutico, no obstante en este se agregue de manera adicional Cremophor EL, es decir, aceite de ricino etoxilado.

- "(...) es completamente claro que las enseñanzas de D2 conducirían a la persona versada en la materia a creer que la inclusión de un agente antioxidante en la formulación de una molécula compleja no tendría ningún efecto estabilizador, alejándola así de cualquier posibilidad de considerar la presencia de un agente antioxidante como una alternativa a explorar para lograr sistemas estables de moléculas complejas, mucho menos de CCI-779 específicamente".

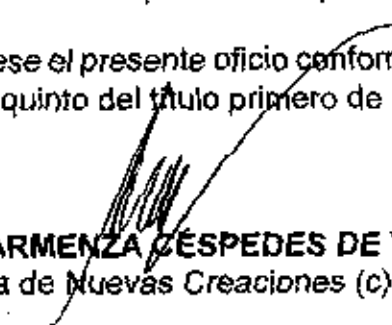
Al respecto es preciso señalar que los ejemplos 2a y 2b utilizan tocoferol para lograr estabilizar la composición y evitar la precipitación del activo y evidentemente allí no se agrega ácido cítrico ni ácido malónico. Y de acuerdo con los resultados de degradación del activo aún cuando no se adiciona ácido, la cuantificación de rapamicina indica que solo el 16% se ha descompuesto de la fórmula 2a cuatro semanas después de haberla preparado y en el caso de la fórmula 2b sólo el 0,5% del activo toda vez que allí se agregaron dos antioxidantes: tocoferol y ácido malónico.

Ahora bien, con respecto a la fórmula 3a se produjo mayor degradación debido a que en esta fórmula solo se agregó tocoferol como antioxidante, por lo que se descompuso el 15,4% del activo. Y en el caso de la fórmula 3b que incluye ácido malónico y tocoferol es evidente que se produce menor degradación por el efecto sinérgico entre los dos antioxidantes, por lo que el porcentaje de rapamicina degradado apenas es del 0,7%.

Así las cosas, las conclusiones del señor solicitante resultan equivocadas toda vez que no toma en cuenta el hecho que el excipiente tocoferol también ejerce funciones de antioxidante (ver folio 374 de D2), toda vez que en virtud de los resultados obtenidos en los ensayos 2a, 2b, 3a y 3b una persona versada en ciencias farmacéuticas claramente acudiría al uso de un ácido como antioxidante, bien sea el ácido cítrico como en el caso del ejemplo 5 de la misma publicación o acudirían a combinar ácido malónico con tocoferol por el efecto sinérgico antioxidante que exhiben, tal y como se evidencia en los ejemplos 2a, 2b, 3a y 3b.

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 CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha
12 FEB, 2016

CONCEPTO TÉCNICO No. 573

EXAMINADOR TÉCNICO
Código No. 202044