

Industria y Comercio
SUPERINTENDENCIA

93
SUPERINDUSTRIA Y COMERCIO
Radicación: 04056453 00000005 Folios: 43
Fecha (HNB): 2006-03-27 17:28:35
Trámite: 011 PCT-PATENT 379 FASE NACI 400 OPOSICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

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

②

SOLICITUD
PUBLICADA

Número del expediente: 04-056453
Solicitante: PHARMACIA CORPORATION
Apoderado: CARLOS R. OLARTE
Título de la nueva creación o denominación del signo: SUSPENSIÓN
FARMACÉUTICA PARA ADMINISTRACION ORAL.
Gaceta: 559

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: PROCAPS S.A	IDENTIFICACIÓN C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Cual _____ Número <u>890.106.527-5</u>
	Dirección: CALLE 80 No. 78b-201 Nacionalidad o Domicilio: COLOMBIA Lugar de Constitución: BARRANQUILLA Teléfono: 371 91 61 Fax: 371 91 62 E-mail: _____	
REPRESENTANTE O APODERADO	Nombre: REINALDO PINILLA MORENO	IDENTIFICACIÓN C.C. ☒ NT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>80425609</u> TP <u>91563</u>
	Dirección: TRANVERSAL 13 A 119-95 OFICINA 104 Teléfono: 213 12 13 Fax: 612 19 79 E-mail: negocios@optimum-co.com	

④ FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN
Causal: No cumple con los requisitos de patentabilidad.

Signo opositor: _____

Justificación: _____

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

⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

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

⑦

NOMBRE: REINALDO PINILLA MORENO

FIRMA: [Firma manuscrita]

C.C. 80425609

TP. 91563 CSJ

COMPARECENCIA PERSONAL Y AUTENTICACIÓN DE FIRMA²

El Notario Tercero y Nueve/(E) de Bogotá, da fe que el anterior, escrito dirigido a Capital Industrial y Comercio fue presentado personalmente por: Reinaldo Pinilla Moreno

quien exhibió la C.C. No. 80425609 y T.P. No. 91563 CSJ y manifestó que la firma y huella que aparecen en el presente documento son suyas, y que acepta el contenido del mismo.

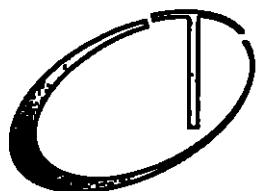


FIRMA

27 MAR. 2006

FRANCISCO JULIO RIANO
NOTARIO 39 (E)





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95
Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

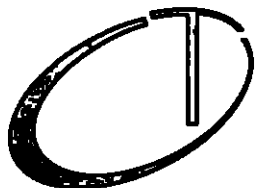
Referencia : Expediente N° 04 056.453
Asunto : Oposición a la solicitud de patente de Invención titulada
"SUSPENSIÓN FARMACÉUTICA PARA
ADMINISTRACIÓN ORAL".
Solicitante : PHARMACIA CORPORATION.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 559 del 30 de Diciembre de 2005

Yo, **REINALDO PINILLA MORENO**, abogado con tarjeta profesional N° 91563 del consejo superior de la judicatura, en mi condición de apoderado de la sociedad **PROCAPS S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la patente de Invención titulada "**SUSPENSIÓN FARMACÉUTICA PARA ADMINISTRACIÓN ORAL**", solicitada por **PHARMACIA CORPORATION.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.



Transversal 13ª N° 119-95, Of. 104 Tel. (571) 2 13 12 13 - 6 20 50 21 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia



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Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

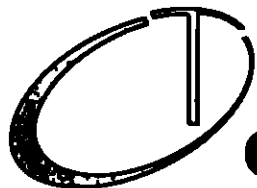
1. INTERÉS PARA ACTUAR

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

2. FUNDAMENTOS DE HECHOS

- 2.1. La solicitud objeto de la presente fue presentada el 17 de junio de 2004, reivindicando prioridad bajo las solicitudes US60/342.599 del 2001-12-20 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 559 del 30 de diciembre de 2005, página 362, N° publicación 886, cuya publicación internacional corresponde a la WO03/053403 del 2003-07-03.
- 2.2. La solicitud colombiana 04056453 objeto de la presente oposición, se refiere a una composición farmacéutica adecuada para administración oral, comprendiendo la composición un medio acuoso que tiene suspendida en el mismo una sustancia sólida de baja solubilidad en agua en forma particulada, y que comprende además un agente de suspensión y al menos un polímero no tensioactivo soluble o hinchable en agua farmacéuticamente aceptable, siendo la cantidad total de todos dichos polímeros presentes menor de un 1 % en peso de la composición; donde la



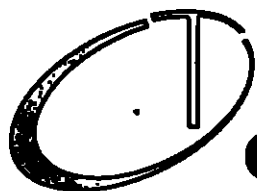


cantidad total de todos los polímeros no tensioactivos solubles o hinchables en agua farmacéuticamente aceptables presentes no es mayor de aproximadamente un 0,5% en peso de la composición; donde la sustancia sólida de baja solubilidad en agua es un fármaco en una cantidad terapéutica y/o profilácticamente eficaz; donde la sustancia sólida de baja solubilidad en agua es un excipiente y la composición es una suspensión placebo; donde la que dicho excipiente se selecciona del grupo constituido por talco, dióxido de silicio, dióxido de titanio y óxido de cinc; donde tiene una viscosidad a una baja velocidad de cizallamiento de menos de aproximadamente 5 Pa.s; donde tiene una viscosidad a una baja velocidad de cizallamiento de menos de aproximadamente; y, donde es una suspensión floculada; donde al menos un polímero no tensioactivo soluble o hinchable en agua se selecciona del grupo constituido por carbómero, carragenina, gelatina, hidroxiethylcelulosa, hidroxipropilcelulosa, HPMC, metilcelulosa, povidona, polietilenglicol y carboximetilcelulosa de sodio; donde al menos un polímero no tensioactivo soluble o hinchable en agua se selecciona del grupo constituido por gelatina, HPMC, povidona y polietilenglicol. Esta solicitud también se refiere al proceso de preparación de dicha composición farmacéutica; y, a un método de diagnóstico.

2.3. En primera instancia, se debe advertir que la reivindicación 18 en adelante se refieren al método terapéutico y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 20.- *"No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales"*.

2.4. De otra parte el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. Así las cosas, las invenciones



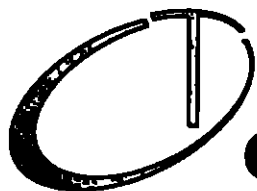


objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la novedad y el nivel inventivo de la presente solicitud:

- D1: US2904469, 15-09-1959.
- D2: US3041239, 26-06-1962
- D3: EP0052085, 10-05-1982
- D4: US5455049, 03-10-1995

2.5. Ahora bien, el documento D1, particularmente en la descripción, columna 1 línea 31 a columna 4 línea 18 y reivindicaciones, que relaciona con suspensiones acuosas estables de salicilamida sólida finamente dividida, particularmente con suspensiones que contiene una solución acuosa de polivinilpirrolidona y un jarabe acuoso azucarado. Según dicho documento D1, el método revela la forma para preparar una suspensión acuosa estable que contiene de 2 a 15% por peso de salicilamida sólida finamente dividida en un vehículo acuoso para preparar una pasta sólida en una solución acuosa que contiene al menos 0,02% por peso de la suspensión final de polivinilpirrolidona y mezclar completamente dicha pasta con una solución de jarabe acuosa azucarada para obtener una composición farmacéutica estable que contiene de 2 a 15% por peso de salicilamida sólida finamente dividida y al menos 0,0149% de polivinilpirrolidona basada en el peso final de la suspensión. Así las cosas, este documento D1, revela igualmente una solución que comprende una composición farmacéutica adecuada para administración oral, de un medio acuoso que tiene suspendida en el mismo una sustancia sólida de baja solubilidad en agua en forma sólida. Por su parte, el documento D2, particularmente en la descripción, columna 1, líneas 28 a columna 2 línea 13 y columna 3 línea 34 a columna 4 línea 17, revela con anterioridad una



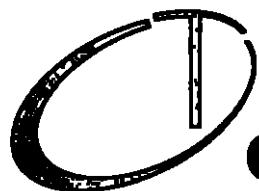


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Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

composición farmacéutica de una suspensión acuosa estable con partículas sólidas de salicilamida y el método de preparación. Según dicho documento se revela una suspensión acuosa estable que contiene entre 2 a 15% por peso de partículas de salicilamida y un agente espesante en un vehículo acuoso. Según el ejemplo, se define una formulación oral que comprende 4,9% de salicilamida; 0,02% de polivinilpirrolidona; 0,2% de silicato aluminico de magnesio; 23% de sorbitol; 49% de sacarosa; y, agua. Además se agrega que puede comprender sabor y colorantes. Por lo tanto, es claro que estos documentos D1 y D2, revelan una misma propuesta como solución que incluye un método de fabricación y el producto obtenido de una composición farmacéutica adecuada para administración oral, de un medio acuoso que tiene suspendida en el mismo una sustancia sólida de baja solubilidad en agua en forma sólida. De esta manera, a los ojos de estos documentos D1 y D2, la presente solicitud no es novedosa.

2.6. Ahora bien, los documentos D3, D4 y D5, se refieren a composiciones orales en medio acuoso que tiene suspendida en la misma una sustancia sólida de baja solubilidad en forma particulada. El documento D3, define según los ejemplos 3 y 5 una suspensión y el método de preparación donde el vehículo líquido es substancialmente agua y las partículas de vincamina tienen una dimensión máxima de 80. El documento D4, en la columna 7, líneas 49 a 54 y ejemplos, define una composición en polvo que comprende una cantidad de un antihistamínico que puede ser disuelto por agitación en una cantidad de agua para ser administrado oralmente con la composición dispersa. Por lo tanto, una persona versada en la materia, al relacionar lo referido en los documentos D1 y D2 en conjunto con lo especificado en los documentos D3 y D4 puede llegar a lo pretendido en el presente documento objeto de oposición.



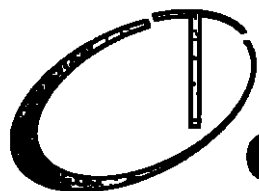
2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 04056453 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los tres requisitos necesarios para su protección.

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

2.8.1. **CARECE DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."* A la fecha de prioridad, el 20 de diciembre de 2001, ya era conocido, pues como se demostró, era parte del arte anterior con base en los documentos D1 y D2, una composición farmacéutica adecuada para administración oral, de un medio acuoso que tiene suspendida en el mismo una sustancia sólida de baja solubilidad en agua en forma sólida sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. **CARENCIA DE ALTURA INVENTIVA** Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."* A la fecha de prioridad, el 20 de diciembre de 2001, documentos D1 y D2 en conjunto con lo especificado en los documentos D3 y D4, es posible deducir la conformación de una composición farmacéutica adecuada para administración oral, de un medio acuoso que tiene suspendida en el mismo una sustancia sólida de baja





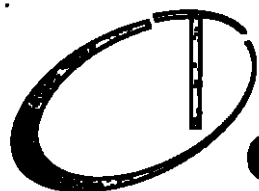
solubilidad en agua en forma sólida sobre el cual busca protección en el capítulo reivindicatorio.

2.8.3. **CARENCIA DE APLICACIÓN INDUSTRIAL** La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

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

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"SUSPENSIÓN FARMACÉUTICA PARA ADMINISTRACIÓN ORAL"**, solicitada por **PHARMACIA CORPORATION**., solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 559.





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3. PRUEBAS

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

- D1: US2904469, 15-09-1959.
- D2: US3041239, 26-06-1962
- D3: EP0052085, 10-05-1982
- D4: US5455049, 03-10-1995

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

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

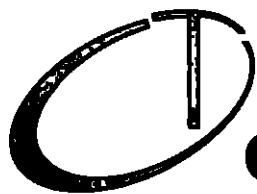
5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

- D1: US2904469, 15-09-1959.

Transversal 13ª N° 119-95, Of. 104 Tel. (571) 2 13 12 13 - 6 20 50 21 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia





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Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

- D2: US3041239, 26-06-1962
- D3: EP0052085, 10-05-1982
- D4: US5455049, 03-10-1995

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Transversal 13ª N° 119-95, Of. 104 de esta ciudad de Bogotá.

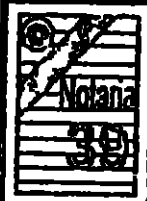
Señor Superintendente,


REINALDO PINILLA MORENO

C.C. 80'425.609 de Bogotá

T.P.A. 91563 del C.S. de la J.

COMPARECENCIA PERSONAL Y AUTENTICACIÓN DE FIRMA
El Notario Treinta y Nueve (E) de Bogotá, da fe que el anterior escrito dirigido a Reinaldo Pinilla Moreno fue presentado personalmente por: Reinaldo Pinilla Moreno quien exhibió la C.C. No. 80'425.609 de Bogotá y T.P. No. 91563 C.S. y manifestó que la firma y huella que aparecen en el presente documento son suyas, y que acepta el contenido del mismo.

  
FIRMA
27 MAR. 2006
FRANCISCO RULLO GILANO
NOTARIO 39 (E)

Transversal 13ª N° 119-95, Of. 104 Tel. (571) 2 13 12 13 - 6 20 50 21 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

MIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 06 - 24,196
FECHA : MARZO 27 DE 2006

SUPERINDUSTRIA Y COMERCIO
Radicion : 04056453 00000005 Folios: 43
Fecha (OMB): 2006-03-27 17:28:25
Tramite : 011 PCT-PATENT 379 FASE NACI 400 OPOSICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	44744453	10/03/2006	260,500.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVICIOS ADMINISTRATIVOS
			TOTAL : \$ 5,000.00

SON: CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.

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SUPERINDUSTRIA Y COMERCIO
Radicación : 04036453 00000005 Folios: 43
Fecha (AMB): 2006-03-27 17:29:25
Tramite : 011 PCT-PATENT 379 FASE NACI 400 OPOSICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 06 - 22,092
FECHA : MARZO 17 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	44744355	23/02/2006	531,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	
		99 OTROS SERVICIOS ADMINISTRATIVOS	39,000.00
		TOTAL :	\$ 39,000.00

SON: TREINTA Y NUEVE MIL PESOS



RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SUPERINDUSTRIA Y COMERCIO

Radicacion : 04056453 00000045 Folios: 43
Fecha (GMB): 2006-03-27 17:26:15
Tramite : 011 PCT-PATENT 379 FASE NACI 400 OPOSICION
Dependencia: 2029 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 06 - 5,022
FECHA : ENERO 24 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	34008881	18/11/2005	940,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-09	OTROS SERVICIOS DE PROPIEDAD I	99 OTROS SERVICIOS ADMINISTRATIVOS
			TOTAL : \$ 202,000.

SON: DOSCIENTOS DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER
SUSTITUIDA POR NINGUN RECIBO.



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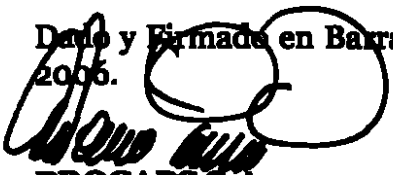
PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a **REINALDO PINILLA MORENO**, abogado titulado, identificado como aparece al pie de su firma, con tarjeta profesional No. 91563 expedida por el Consejo Superior de la Judicatura, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 04-056453, de título: **"SUSPENSIÓN FARMACÉUTICA PARA ADMINISTRACIÓN ORAL"**, publicada en la gaceta No. 559 del 30 de Diciembre de 2005.

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

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

Dado y Firmado en Barranquilla (Colombia) a los 23 días del mes de Marzo de 2006.


PROCAPS S.A.

WALTER TANAKA TATEKAWA

C.C. N° 16.251.923

Representante Legal — *avés*

Acepto,


REINALDO PINILLA MORENO

C.C. 80'425.609 de Bogotá

T.P.A. 91563 del C.S. de la J.

NOTARIA SEGURA NOTARIA SEGURA NOTARIA SEGURA NOTARIA SEGURA

ADY ISABEL NAMEN SEGURA

NOTARIA SEGURA DEL CIRCULO DE BAYAMON

DILIGENCIA DE PRESENTACION PERSONAL Y RECONOCIMIENTO

La suscrita Notaria Certifica que este escrito fue
presentado Personalmente por Milena
TANOKA TATELOPE

Identificado con: 16 251 927

Ejecutor: Milena

Quien declaró que su contenido es cierto y que la
firma puesta en el documento es:

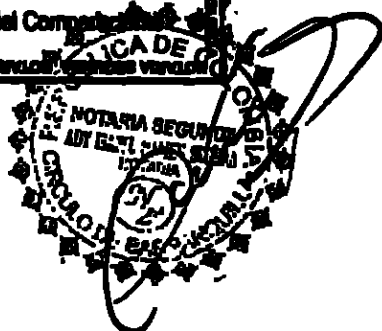
Milena

Firma

2 MAR. 2008

Huella del Compadre

NOTARIA SEGURA NOTARIA SEGURA NOTARIA SEGURA NOTARIA SEGURA





***** Pag. 1
C A M A R A D E C O M E R C I O
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08*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

EN JUNIO DE ESTE AÑO SE ELEGIRÁ JUNTA DIRECTIVA DE LA CÁMARA DE COMERCIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA QUINCENA DE MAYO. PARA INFORMACIÓN DETALLADA DIRIGIRSE A LA SEDE PRINCIPAL O COMUNICARSE AL SIGUIENTE TELEFONO: 3303911.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

Que por Escritura Pública No. 1.190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6.070 del libro respectivo, fue constituida la sociedad-----
limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA
"PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 1.307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10.039 del libro respectivo, la sociedad antes mencionada-----
se transformo en sociedad anonima bajo la denominacion social de
"PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Pública No. 3.810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12.705 del libro respectivo, la sociedad antes mencionada-----
se transformo en sociedad de responsabilidad limitada bajo al razon
social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI -
MITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 3.755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17.922 del libro respectivo, la sociedad antes mencionada-----
se transformo en sociedad anonima bajo la denominacion social de
"PRODUCTORA DE CAPSULAS DE GELATINA S.A. "PROCAPS S.A.".-----

C E R T I F I C A

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

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

Que por Escritura Pública No. 3.615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67.218 del libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A

C E R T I F I C A

Que por Escritura Pública No. 3.775 del 18 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67.704 del libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion PROCAPS S.A. -----

C E R T I F I C A

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

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9.452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13.112	1981/05/06
1.464	1982/08/27	Notaria Unica de Soledad	15.533	1982/09/08
2.744	1983/08/18	Notaria Unica de Soledad	17.416	1983/08/26
3.826	1984/07/16	Notaria Unica de Soledad	19.554	1984/07/27
3.835	1985/08/26	Notaria Unica de Soledad	22.230	1985/09/04
2.260	1986/09/10	Notaria Unica de Soledad.	24.995	1986/09/15
1.849	1989/07/11	Notaria 2a. de Barranquilla.	33.909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36.101	1990/03/16
3.090	1991/12/17	Notaria 2a. de Barranquilla	43.993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48.428	1993/02/16
2.342	1993/07/28	Notaria 2a. de Barranquilla	50.582	1993/08/10
3.652	1993/11/09	Notaria 2a. de Barranquilla	51.798	1993/11/22
3.615	1996/12/06	Notaria 2a. de Barranquilla	67.218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67.704	1997/01/23
2.070	1997/07/17	Notaria 2a. de Barranquilla	70.627	1997/07/31
2.281	1997/08/04	Notaria 2a. de Barranquilla	70.813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80.628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91.502	2001/02/23
2.608	2001/10/05	Notaria 2a. de Barranquilla	95.771	2001/11/08
1.730	2004/07/29	Notaria 2. de Barranquilla	112.999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116.364	2005/03/10
1.613	2005/07/28	Notaria 2. de Barranquilla	119.322	2005/08/18

C E R T I F I C A

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

DENOMINACION O RAZON SOCIAL:

PROCAPS S.A.-----

SIGLA: PROCAPS.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

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



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

PROCAPS S.A.-----

NIT: 890.106.527-5.

MATRICULA MERCANTIL: 24.802.

C E R T I F I C A

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

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

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

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

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

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Suscrito		
\$*****1.220.000.000	*****1.220.000	*****1.000
Pagado		
\$*****1.220.000.000	*****1.220.000	*****1.000
Autorizado		
\$*****2.000.000.000	*****2.000.000	*****1.000

C E R T I F I C A

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

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



***** Pag. 3
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

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

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

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

PROCAPS S.A.-----
NIT: 890.106.527-5.

gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente. -----

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70.838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87.250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben	CC.*****7.463.982
2. Minski Gontovnik Meyer	CC.*****7.461.324
3. Minski Gontovnik Jose	CC.*****8.671.834

Suplentes

1. Minski Zilberblum Elliot	CC.*****72.219.541
2. Minski Deitel Daniel	.*****
3. Minski Sharon	PA.*990.212.082.805

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70.838 del libro respectivo,

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

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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
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NIT: 890.106.527-5.

fueron hechos los siguientes nombramientos:	
Cargo/Nombre	Identificación
Presidente.	
Minski Gontovnik Ruben	CC.*****7.463.982
Suplente del Presidente	
Minski Minski Abraham	CC.*****802.575
Vicepresidente	
Minski Gontovnik Meyer	CC.*****7.461.324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*****8.671.834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91.273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Uribe Ochoa Guillermo Luis	CC.*****70.073.754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113.263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Tanaka Walter	CC.*****16.251.923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82.226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Ppal.	
Vargas Pertuz Ana Isabel	CC.*****32.696.645

C E R T I F I C A

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

PROCAPS S.A.-----
NIT: 890.106.527-5.

Que según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87.250 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal.	
Lozada Villareal Milena	CC.*****32.748.111

C E R T I F I C A

Que por escritura publica No. 2.608 del 5 de Octubre del 2.001, otorgada en la Notaria 2a. de Barranquilla, inscrita en esta Camara de Comercio el 8 de Noviembre del 2.001, bajo los Nos. 95.771, 2.056, 2.057, 2.058, 2.059, 2.060, 2.061, 2.062 y 2.064 del libro respectivo, se reforma totalmente el articulo 65, contenido en la escritura publica No. 3.705 de Noviembre 6 de 1.998, de la Notaria Segunda del Circuito de Barranquilla, y se constituyen los siguientes Apoderados Generales, quienes tendran las funciones que a continuacion se indican en razon de su cargo en la sociedad: 1.-Se confiere Poder Especial, Amplio y Suficiente a los senores: WALTER TANAKA TATEKAWA, C.C. No. 16.251.923; WILLIAM ALBERTO BARROS CERRA, C.C. No. 8.715.941, para que cada uno en forma independiente en nombre y representacion de PROCAPS S.A., suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad, asi como para que responda todo tipo de requerimiento o solicitudes de informacion de las autoridades tributarias, aduaneras o cambiarias, en los ordenes Distrital, Departamental y Nacional. 2.-Se confiere Poder Especial, amplio y suficiente, a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta por la suma de US\$800.000.00 (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transaccion. GUPO A: GUILLERMO LUIS URIBE OCHO C.C. No. 70.073.754, LINO LAZALA SILVA VARGAS C.C. No. 19.260.410, JAIRO MOLINA MEJIA C.C. No. 8.706.380, CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.-293. BRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, HENRY CARO DIAZ C.C. No. 19.395.298, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZGRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requiera por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C.C. No. 33.138.497, a la Doctora MARCELA CARVAJALINO PAGANO C.C. No. 22.579.748, y al Doctor DANIEL MORENO VILLALBA, C.C. No. 19.113.210; para que cada uno representen a PROCAPS S.A., ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como: Contestar e interponer demandas y requerimientos, comparecer en juicios, pedir la practica de pruebas, recibir notificaciones, interponer recursos y ejercer acciones contencioso administrativas y de tutela, transigir, conciliar, recibir en nombre de la sociedad

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



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D E B A R R A N Q U I L L A
08*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

desistir, sustituir y reasumir este mandato. Para la celebracion de cualquier acuerdo conciliatorio o transaccional, judicial o extrajudicial, cualquiera que sea su cuantia, los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la sociedad. Los Apoderados podran presentar solicitudes de devolucion y/o compensacion de impuestos y recibir los pagos por devoluciones de impuestos, firmar, notificarse y realizar todo acto necesario para cumplir con el mandato encomendado.-----

C E R T I F I C A

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

C E R T I F I C A

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

C E R T I F I C A

Que segun documento privado del 10 de noviembre del 2004, inscrito en esta Camara de Comercio el 1 de diciembre del 2.004, bajo el No. 2.753 del libro respectivo consta que RUBEN MINSNSKI GONTOVNIK, C.C. 7.463.982 de Barranquilla, actuando como Presidente y Representante

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

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

PROCAPS S.A.-----
NIT: 890.106.527-5.

Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a ANTONIO VARELA DIAZ, C.C.No.72.004.669 de Barranquilla, para que en nombre y representacion de la sociedad firme las declaraciones cambiarias a que este obligada PROCAPS S.A., a suscribir en el giro normal de sus negocios y operaciones sociales. Por lo anterior, el señor ANTONIO VARELA DIAZ, queda facultado para firmar las declaraciones comabiaras y demas documentos relacionados con las declaraciones, notificaciones, aportar y solicitar las pruebas que sean necesarias, desistir en general a realizar todo acto necesario de tal forma que pueda cumplir con el mandato dado.-

C E R T I F I C A

Que segun documento privado del 22 de Febrero de 2005, inscrito en esta Camara de Comercio el 28 de Marzo de 2.005, bajo el No. 2.820 del libro respectivo, consta que WALTER TANAKA TATEKAWA C.C. 16.251-923 de Palmira, quien actua como representante legal de la sociedad PROCAPS S.A, otorga Poder Especial, Amplio y Suficiente al señor MARLON TATIS PAREDES C.C. No. 72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones aduaneras, reportes y cualquier tipo de documentos relacionados con los tramites o registros de comercio exterior ante la direccion de impuestos y aduanas nacionales y/o cualquier entidad que haga sus veces, y para que responda todo tipo de requerimientos y/o solicitudes de informacion de las autoridades aduaneras en los ordenes distrital, departamental y nacional.-----

C E R T I F I C A

Que por Escritura Publica No.1.613 del 28 de Junio del 2.005, otorgada en la Notaria Segunda de Barranquilla, inscrita en esta Camara de Comercio el 18 de agosto del 2.005 bajo el No.2.913 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C.C.No.7.463.928, en su condicion de Presidente y Representante Legal de la sociedad PROCAPS S.A., confiere poder especial amplio y suficiente a los siguientes senores que conforman el Grupo A y el Grupo B, para que conjuntamente suscriban contratos de suministro de mercancías y servicios con entidades oficiales, hasta por la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS DE AMERICA (US\$800.000), liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transaccion. GRUPO A: MIRIAM RODRIGUEZ DIAZ, C.C.No. 41.473.569. GRUPO B: NELSON SUAREZ CHAVEZ, C.C.No.79.417.971.-----.

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 23 de Marzo de 2005.

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



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

PROCAPS S.A.-----

NIT: 890.106.527-5.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.

m. l. p. a. s.

ANEXO 1

PATENTE US2904469

United States Patent Office

2,904,469
Patented Sept. 15, 1960

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1,904,469

STABILIZED AQUEOUS SUSPENSION OF SALICYLAMIDE

Wilson Nashed, New Brunswick, N.J., assignor to Johnson & Johnson, a corporation of New Jersey

No Drawing. Application July 29, 1957
Serial No. 674,570

4 Claims. (Cl. 167-45)

This invention relates to stable aqueous suspensions of finely divided solid salicylamide, and to methods for the preparation thereof. More particularly, it relates to such suspensions containing an aqueous solution of polyvinylpyrrolidone and an aqueous sugar syrup having a specific gravity of 1.339.

In the oral administration of salicylamide medication various liquid media have been proposed heretofore. However, so far as known, all of such materials suffer from various disadvantages. A desirable form for such compositions is an aqueous suspension in a water or the like medium having a pleasant taste. However, it has been found by actual test that many of such suspensions prepared in conventional manner suffer from the drawback of instability; i.e., they tend to separate on standing giving a product which is highly undesirable.

The discoveries associated with the invention and relating to solutions of the above problems, and the objects achieved in accordance with the invention as set forth herein include: the provision of a method of preparing a stable aqueous suspension containing 3 to 15 percent by weight of finely divided solid salicylamide in an aqueous vehicle by preparing a paste of the solid in an aqueous solution containing at least 0.01% by weight (of the final suspension) of polyvinylpyrrolidone and thoroughly mixing this paste with an aqueous sugar syrup having a specific gravity in the range of 1.333 to 1.345 and the resulting stable product; the provision of such a method wherein the polyvinylpyrrolidone has a molecular weight of about 40,000 and the sugar solution contains sucrose and sorbitol in a weight ratio of about three parts of the sucrose to one part of sorbitol, and the resulting product contains 3 to 5 percent by weight of salicylamide; and other objects which will be apparent as details or embodiments of the invention are set forth hereinafter.

In order to facilitate a clear understanding of the invention, the following preferred specific embodiments are described in detail.

A solution is prepared having the following composition:

	Parts by weight
Sucrose	40
Water	17.5
Sorbitol (as 70% aqueous solution)	18.5

and this solution is mixed with finely divided salicylamide (particle size or average diameter of about 3 to 4 microns) in the following proportions:

	Parts by weight
Salicylamide	325
Solution	6.340

In preparing the mixture, the salicylamide is mixed with a small portion of the solution to form a paste, and this paste is then blended with the remainder of the solution with thorough mixing or kneading followed by passage through a colloid mill or homogenizer.

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Stability test

The stability of the resulting composition is tested by allowing it to stand for about 15 hours or more, and then testing the product for homogeneity. For a satisfactory product, there should be no separation of the salicylamide.

In accordance with the invention, just prior to or simultaneously with forming the paste, the salicylamide is mixed with an aqueous solution of polyvinylpyrrolidone having a molecular weight of about 40,000 in the following proportions (wherein the relationship of weight to volume is the same as grams to cubic centimeters):

Concentration of polyvinylpyrrolidone
(in final composition)

Example:	
1	0.01% (weight/volume)
2	0.04% (weight/volume)
3	0.2 % (weight/volume)

In the following test, the salicylamide and the suspending agent were triturated together in a mortar, and the sugar solution was added slowly with trituration.

Example:	
4	1.0% (weight/volume)

Each was tested for stability, and each was found to be satisfactory; i.e., there was no separation of the salicylamide.

In a run comparable to Example 4, using 0.01% of the polyvinylpyrrolidone, the product was unstable; i.e., there was substantial separation of the salicylamide.

The above successful results are indeed surprising when one considers the many conventional suspending or wetting or the like agents which were tested and found to give mixtures which did not have satisfactory stability; i.e., mixtures in which the salicylamide separated out and floated on top upon standing. These are typified by the following:

In the following tests, the salicylamide was mixed with the solution of suspending agent in a mortar and filtered. The filter cake was dispersed in the sugar solution.

Comparative test:	Concentration, percent (weight/volume)
A. Methylcellulose (Dow HG-4000)	0.2
B. Pectin (I.M.)	0.5
C. Egg albumin	0.5
D. Isomeric casein	0.5

In the following tests, the salicylamide and the suspending agent were triturated together in a mortar, and the sugar solution was added slowly with trituration.

Comparative test:	Concentration, percent (weight/volume)
E. Sodium alginate	0.5
F. Methylcellulose (Dow HG-50)	0.5
G. Carboxymethylcellulose (low vis.)	1.0
H. Purified magnesium aluminum silicate	0.5
I. Purified magnesium aluminum silicate	1.0
J. Ethyl Alcohol	3.5

In the following test, the salicylamide and the suspending agent were mixed in a mortar, then sufficient sugar solution was added to form a paste (about 1.5 parts by weight of solution per part of the powder), and the paste was run through a three-roll mill (Katz); then the remainder of the sugar solution was added therewith and the resulting mixture was passed through a colloid mill.

Comparative test:	Concentration, percent (weight/volume)
L. Carboxymethylcellulose (low vis.)	0.5

In the following test, the wetting agent was dissolved in a portion of the sugar solution, and the resulting mixture was added slowly to the milkylamide with trituration in a glass mortar.

Comparative test:	Concentration, percent (weight/volume)
M. Sodium alginate (extra low viscosity)	0.5
N. Polyoxyethylene sorbitan stearate (20 ethoxy units per molecule)	0.2
O. Polyoxyethylene sorbitan monolaurate (4 ethoxy units per molecule)	0.2
P. Polyoxyethylene sorbitan monolaurate (20 ethoxy units per molecule)	0.2
Q. Glycerin	1.0

Comparable results to the foregoing Examples 1 through 4 may be obtained with various modifications thereof, including the following. The concentration of the milkylamide in the final composition may be in the range of 2 to 15 percent by weight, preferably 4 to 5 percent. The particle size of the milkylamide may be in the range of 0.1 to 100 microns, or above, desirably 2 to 25, and preferably 3 to 4 microns average diameter. The molecular weight of the polyvinylpyrrolidone may be in the range of about 20,000 to about 80,000, desirably 30,000 to 50,000, preferably 40,000, average. The concentration thereof in the final composition is at least about 0.02% weight/volume (i.e., 0.0149% by weight). The maximum concentration in the stability tank thereof in the final composition; however, for practical purposes, one percent is the upper limit. Instead of the sucrose in the mixture, other sugars may be used, including hydrolyzed sucrose, glucose, fructose, or mixtures thereof. Various proportions of sugar or sugars may be used with sorbitol, providing the desired specific gravity is maintained.

If desired, there may be included in the mixture a small amount of sodium benzoate or the like preservative, as well as coloring or flavoring materials. These do not interfere with or cause any harmful effect on the stability of the resulting composition. It is desirable to use relatively low-free water.

In making up the preparation, the sorbitol may be mixed with the water using an efficient propeller-type mixer and the sucrose added thereto, together with the sodium benzoate, if desired. The mixture may be heated, e.g., up to about 175 to 200° F., in order to obtain complete solution. The specific gravity of the resulting solution should be in the range of 1.335 to 1.340, and if necessary it be adjusted by adding either water or sugar.

The polyvinylpyrrolidone may be dissolved in water, using about 5 to 10 parts by weight of the water per part of the polyvinylpyrrolidone. The resulting polyvinylpyrrolidone solution may be mixed with a portion of the sugar solution, e.g., in the proportions of about 15 to 25 parts by weight of the sugar solution per part by weight of the polyvinylpyrrolidone solution, and there may be mixed with the milkylamide in an efficient mixer, preferably one provided with means for evacuating the mixing chamber. Preferably, the milkylamide is added thereto gradually with relatively slow agitation. In a proportion such as about 0.5 part by weight of milkylamide per part by weight of the liquid mixture therein. The resulting mixture is agitated at high speed. Then the mixing chamber is evacuated, without agitation. After the

vacuum has been brought up to about 27 to 28 inches (or 130 to 50 mm.) of mercury, the agitation is started again, and the speed thereof gradually increased, and maintained at highest speed for a time to achieve thorough mixing, such as about 1/2 or 1 hour or more. Then the speed is gradually reduced, and finally the vacuum is decreased and the contents brought back to room pressure. If desired, a small amount of coloring matter and flavoring may be added thereto, e.g., as a solution in water. The resulting mixture may be added to additional syrup, if desired, to give a final composition of the desired milkylamide concentration, and this may be achieved by mixing thoroughly with a paddle or propeller type mixer, and finally by passing through a homogenizer, e.g., at about 300 to 600 p.s.i.g. (pounds per square inch gauge).

The product is pleasant tasting, and is especially useful for oral administration of milkylamide medication to children.

In view of the foregoing disclosures, variations or modifications thereof will be apparent, and it is intended to include within the invention all such variations and modifications except as do not come within the scope of the appended claims.

I claim:

1. A method for the preparation of stable aqueous suspension containing 2 to 15 percent by weight of finely divided solid milkylamide in an aqueous vehicle, which method comprises preparing a paste of the finely divided milkylamide in aqueous polyvinylpyrrolidone and thoroughly mixing said paste with an aqueous sugar solution having a specific gravity in the range of 1.335 to 1.340, the concentration of the polyvinylpyrrolidone being at least 0.0149% based on the weight of the final suspension.

2. A method of claim 1 wherein the polyvinylpyrrolidone is of an average molecular weight of about 40,000 and the sugar solution contains sucrose and sorbitol in a ratio of 3 parts of the former to 1 part of the latter by weight.

3. A stable aqueous suspension of finely divided milkylamide in an aqueous sugar solution, which solution has a specific gravity in the range of 1.335 to 1.340, which suspension contains 2 to 15 percent by weight of finely divided solid milkylamide and at least 0.0149% of polyvinylpyrrolidone based on the weight of the final suspension.

4. A suspension of claim 3 containing about 5% of the milkylamide.

References Cited in the file of this patent

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ANEXO 2
PATENTE US3041239

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2

3,041,239
STABLE AQUEOUS SALICYLAMIDE COMPOSITION AND METHOD OF PREPARING SAME
William Nashed, North Brunswick, N.J., assignor to Johnson & Johnson, a corporation of New Jersey
No Drawing. Filed May 28, 1959, Ser. No. 816,386
7 Claims. (Cl. 167-45)

This application is a continuation-in-part of application Serial Number 674,570, issued as U.S. Patent No. 2,904,469 on September 15, 1959.

This invention relates to stable aqueous suspensions of solid salicylamide and to methods for the preparation thereof. More particularly, it relates to such suspensions wherein the particle size of the salicylamide is such that substantially all of it passes through a #60 mesh sieve and preferably through a #100 mesh sieve and a major proportion thereof is retained by a #325 mesh sieve.

In the oral administration of salicylamide medication, a formulation containing finely divided salicylamide, polyvinylpyrrolidone and an aqueous sugar syrup, prepared in accordance with the above indicated parent application, has enjoyed substantial commercial success. However, in some instances, it has a disadvantageous burning aftertaste; and the art is confronted by the problem of providing desirable suspensions of this type which are free from this disadvantage.

The discoveries associated with the invention and relating to solutions of the above problems, and the objects achieved in accordance with the invention as set forth herein include: the provision of a suspension of solid salicylamide substantially free from burning aftertaste; the provision of a method for the preparation of a stable aqueous suspension containing 2 to 15 percent by weight of solid salicylamide and a thickening agent in an aqueous vehicle, which method comprises preparing an aqueous solution of the agent and adding a paste of the salicylamide in aqueous polyvinylpyrrolidone and thoroughly mixing with an aqueous sugar solution to give a final suspension having a specific gravity in the range of 1.335 to 1.340, the concentration of the polyvinylpyrrolidone being at least 0.0149% based on the weight of the final suspension, said salicylamide being of a particle size such that substantially all of it passes through a #100 mesh sieve and at least 50% thereof is retained on a #325 mesh sieve, the amount of the thickening agent being such as to provide a fluid having a viscosity in the range of 300 to 18,300 cps.; the provision of a method for the preparation of stable aqueous suspension containing 2 to 15 percent by weight of solid salicylamide and 0.1 to 1% by weight of magnesium aluminum silicate in an aqueous vehicle, which method comprises preparing an aqueous solution of the silicate and adding a paste of the salicylamide in aqueous polyvinylpyrrolidone and thoroughly mixing with an aqueous sugar solution to give a final suspension having a specific gravity in the range of 1.335 to 1.340, the concentration of the polyvinylpyrrolidone being at least 0.0149% based on the weight of the final suspension, said salicylamide being of a particle size such that substantially all of it passes through a #100 mesh sieve and at least 50% thereof is retained on a #325 mesh sieve; the provision of such a method wherein the polyvinylpyrrolidone is of an average molecular weight of about 40,000 and the sugar solution contains sucrose and sorbitol in a ratio of 3 parts of the former to 1 part of the latter by weight; the provision of a stable aqueous suspension of 2 to 15 percent by weight of solid salicylamide in an aqueous sugar solution, which solution has a specific gravity in the range of 1.335 to 1.340, which suspension contains at least 0.0149% of polyvinylpyrrolidone based on the weight of the final suspension, said salicylamide being of

a particle size such that substantially all of it passes through a #100 mesh sieve and at least 50% thereof is retained on a #325 mesh sieve, the amount of the thickening agent being such as to provide a fluid having a viscosity in the range of 300 to 18,300 cps.; the provision of a stable aqueous suspension of solid salicylamide and 0.1 to 1% by weight of magnesium aluminum silicate in an aqueous sugar solution, which solution has a specific gravity in the range of 1.335 to 1.340, which suspension contains at least 0.0149% of polyvinylpyrrolidone based on the weight of the final suspension, said salicylamide being of a particle size such that substantially all of it passes through a #100 mesh sieve and a major proportion thereof is retained on a #325 mesh sieve; the provision of such a suspension containing about 5% of the salicylamide; and other objects which will be apparent as details or embodiments of the invention are described hereinafter.

In order to facilitate a clear understanding of the invention, the following preferred specific embodiments are described in detail.

EXAMPLE I

A solution is prepared having the following composition (percent is by weight of the solution):

	Percent
Salicylamide	4.9390
Polyvinylpyrrolidone	0.0299
Magnesium aluminum silicate	0.2054
70% sorbitol (aq.)	23.2548
Sucrose	49.9586
Water	To 100.0000

This formulation is prepared by forming a heated mixture or solution of the magnesium aluminum silicate and most of the water, gradually adding most of the sucrose and sorbitol, adding thereto the salicylamide and the polyvinylpyrrolidone and blending with the remainder of the water with thorough mixing or kneading.

In this formulation the particle size of the salicylamide is such that substantially all of it passes through a #100 mesh sieve and only about 38% thereof passes through a #325 mesh sieve (U.S. Sieve series). This composition when administered orally, is found to be substantially free from the undesirable burning aftertaste. If desired, flavoring and coloring agents may be added.

Determination of Mesh Size

A saturated salicylamide solution is prepared by mixing 2000 ml. of distilled water, 0.6 gm. of polyvinylpyrrolidone and 50 gm. of salicylamide with rapid agitation for 1/4 hour. The mixture is filtered through #3 filter paper and the filtrate is collected and used as the washing solution for the evaluation.

Mix 50 gm. of salicylamide to be evaluated and 500 ml. of the saturated salicylamide solution with rapid agitation for 5 minutes. The mixture is filtered through a tared 100 mesh screen. The residue on the screen is washed several times with polyvinylpyrrolidone-salicylamide solution, above, using a rubber spatula until a clear filtrate is obtained. The residual salicylamide on the screen is dried at 120° F. overnight or about 15 hours, cooled and weighed.

Percent salicylamide retained on 100 mesh screen equals two times the residual weight on 100 mesh screen.

A saturated salicylamide solution is prepared by mixing 2000 ml. of distilled water, 0.6 gm. of polyvinylpyrrolidone and 50 gm. of salicylamide with rapid agitation for 1/4 hour. The mixture is filtered through #3 filter paper and the filtrate is collected and used as the washing solution for the evaluation.

Mix 50 gm. of salicylamide to be evaluated and 500 ml. of the saturated salicylamide solution with rapid agita-

tion for 5 minutes. The mixture is filtered through a tared #325 mesh screen. The residue on the screen is washed several times with polyvinylpyrrolidone-salicylamide solution, above using a rubber spatula until a clear filtrate is obtained. The residual salicylamide on the screen is dried at 120° F. overnight or about 15 hours, cooled and weighed.

Percent salicylamide passed through #325 mesh screen equals 100 minus 2 times residual weight on #325 mesh screen.

COMPARATIVE EXAMPLE A

Example 1 is repeated except that the salicylamide used is one of a particle size such that all of it passes through the #325 mesh sieve. Upon test, this is found to have the undesirable burning aftertaste.

COMPARATIVE EXAMPLE B

Example 1 is repeated except that the salicylamide used is one of a particle size such that it is all retained on a #100 mesh sieve. Upon test, this is found to have an undesirable gritty taste or texture.

EXAMPLE II

Example 1 is repeated except that the particle size of the salicylamide is such that it all passes through a #100 mesh sieve and is all retained on a #325 mesh sieve. Upon test the resultant product is found to be free of the undesirable burning aftertaste.

All of the foregoing formulations are satisfactory from the viewpoint of stability (no separation of the salicylamide) when tested by allowing the same to stand for about 15 hours or more, and then testing the product for homogeneity.

The formulation containing about 0.2% of the magnesium aluminum silicate is easily reconstituted by shaking (if it has been standing for a sufficient time to deposit the salicylamide as a sediment), whereas a similarly settled formulation which does not contain the magnesium aluminum silicate is not readily dispersed or reconstituted on shaking.

Comparable results to the foregoing Examples 1 and 2 may be obtained with various modifications thereof, including the following. The concentration of the salicylamide in the final composition may be in the range of 2 to 15 percent by weight, preferably 4 to 5 percent. The particle size of the salicylamide in the final composition is such that substantially all of it passes through a #100 mesh sieve and at least 50% thereof is retained on a #325 mesh sieve; i.e., the particle size or diameter thereof may average 20 microns to 40 microns (as determined by known methods, e.g., a subsieve analyzer).

It is preferred that the viscosity of the formulation be in the range of 500 to 1000 cps. (centipoises), although viscosities in the range of about 300 to 18,300 cps. are operative (rotating spindle viscometer such as the Brookfield Viscometer, using #2 spindle, 30 r.p.m. at 25° C.; Instructions, Brookfield Synchro-Lectric Viscometer, published by the Brookfield Engineering Laboratories, Inc., Stoughton, Massachusetts, Serial Number 8667, and also their Data Sheet #081-a).

The viscosity of the formulation is dependent on the concentration of the magnesium aluminum silicate and generally this may be in the range of 0.1 to 1%, preferably 0.2 to 0.5% by weight based on the weight of the formulation. In addition to controlling the viscosity, this critical amount of magnesium aluminum silicate controls or retards the sedimentation rate of the salicylamide. In addition, it appears to aid in reducing the undesirable burning aftertaste.

A high viscosity carboxymethyl cellulose or the like thickening agent may be used instead of the silicate; if desired, in an amount in the range of 0.02 to 0.3, preferably 0.1%.

The molecular weight of the polyvinylpyrrolidone may

be in the range of about 20,000 to about 80,000 desirably 30,000 to 50,000, preferably 40,000, average. The concentration thereof in the final composition is at least about 0.02% weight/volume (i.e., 0.0149% by weight). The maximum concentration is the solubility limit thereof in the final composition; however, for practical purposes, one percent is the upper limit. Instead of the sucrose in the mixture, other sugars may be used, including hydrolyzed sucrose, glucose, fructose, or mixtures thereof. Various proportions of sugar or sugars may be used with sorbitol, providing the desired specific gravity is maintained.

If desired, there may be included in the mixture a small amount of sodium benzoate or the like preservative, as well as coloring or flavoring materials. These do not interfere with or cause any harmful effect on the stability of the resulting composition. It is desirable to use relatively ion-free water.

In making up the preparation, the silicate (thickening agent) may be mixed with the water using an efficient propeller-type mixer and the sorbitol and sucrose added thereto, together with the sodium benzoate, if desired. The mixture may be heated, e.g., up to about 175 to 200° F., in order to obtain complete solution. The specific gravity of the resulting solution of silicate and sugar should be in the range of 1.352 to 1.356, and if necessary, it may be adjusted by adding either water or sugar.

The polyvinylpyrrolidone may be dissolved in water, using about 5 to 10 parts by weight of the water per part of the polyvinylpyrrolidone. The resulting polyvinylpyrrolidone solution may be mixed with a portion of the sugar solution, e.g., in the proportions of about 15 to 25 parts by weight of the sugar solution per part by weight of the polyvinylpyrrolidone solution, and these may be mixed with the salicylamide in an efficient mixer, preferably one provided with means for evacuating the mixing chamber.

Preferably, the salicylamide is added thereto gradually with relatively slow agitation, in a proportion such as about 0.5 part by weight of salicylamide per part by weight of the liquid mixture therein. The resulting mixture is agitated at high speed. Then the mixing chamber is evacuated, without agitation. After the vacuum has been brought up to about 27 to 28 inches of mercury, the agitation is started again, and the speed thereof gradually increased, and maintained at highest speed for a time to achieve thorough mixing, such as about ¼ or 1 hour or more. Then the speed is gradually reduced, and finally the vacuum is decreased and the contents brought back to room pressure. If desired, a small amount of coloring matter and flavoring may be added thereto, e.g., as a solution in water.

The resulting mixture may be added to additional syrup, if desired, to give a final composition of the desired salicylamide concentration, and this may be achieved by mixing thoroughly with a paddle or propeller type mixer.

It may be desirable to check the salicylamide particle size distribution in the final composition, especially if "grinding" occurs during the mixing operations.

In view of the foregoing disclosures, variations or modifications thereof will be apparent, and it is intended to include within the invention all such variations and modifications except as do not come within the scope of the appended claims.

I claim:

1. A method for the preparation of a stable aqueous suspension containing 2 to 15 percent by weight of solid salicylamide and a thickening agent in an aqueous vehicle, which method comprises preparing an aqueous solution of the agent and adding a paste of the salicylamide in aqueous polyvinylpyrrolidone and thoroughly mixing with an aqueous sugar solution to give a final suspension having a specific gravity in the range of 1.335 to 1.340, the concentration of the polyvinylpyrrolidone being at least 0.0149% based on the weight of the final suspension, said salicylamide being of a particle size such

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that substantially all of it passes through a #100 mesh sieve and at least 50% thereof is retained on a #325 mesh sieve, the amount of the thickening agent being such as to provide a fluid having a viscosity in the range of 300 to 18,300 c.p.s.

2. A method for the preparation of stable aqueous suspension containing 2 to 15 percent by weight of solid salicylamide and 0.1 to 1% by weight of magnesium aluminum silicate in an aqueous vehicle, which method comprises preparing an aqueous solution of the silicate and adding a paste of the salicylamide in aqueous polyvinylpyrrolidone and thoroughly mixing with an aqueous sugar solution to give a final suspension having a specific gravity in the range of 1.335 to 1.340, the concentration of the polyvinylpyrrolidone being at least 0.0149% based on the weight of the final suspension, said salicylamide being of a particle size such that substantially all of it passes through a #100 mesh sieve and at least 50% thereof is retained on a #325 mesh sieve.

3. A method of claim 2 wherein the polyvinylpyrrolidone is of an average molecular weight of about 40,000 and the sugar solution contains sucrose and sorbitol in a ratio of 3 parts of the former to 1 part of the latter by weight.

4. A stable aqueous suspension of 2 to 15 percent by weight of solid salicylamide in an aqueous sugar solution, which solution has a specific gravity in the range of 1.335 to 1.340, which suspension contains at least 0.0149% of polyvinylpyrrolidone based on the weight of the final suspension, said salicylamide being of a particle size such that substantially all of it passes through a #100 mesh sieve and at least 50% thereof is retained on a #325 mesh sieve, the amount of the thickening agent being such as to provide a fluid having a viscosity in the range of 300 to 18,300 c.p.s.

5. A stable aqueous suspension of solid salicylamide and 0.1 to 1% by weight of magnesium aluminum sil-

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cate in an aqueous sugar solution, which solution has a specific gravity in the range of 1.335 to 1.340, which suspension contains at least 0.0149% of polyvinylpyrrolidone based on the weight of the final suspension, said salicylamide being of a particle size such that substantially all of it passes through a #100 mesh sieve and a major proportion thereof is retained on a #325 mesh sieve.

6. A suspension of claim 5 containing about 5% of the salicylamide.

7. A fluid salicylamide composition adapted to be taken orally which is substantially free of burning after-taste comprising an aqueous suspension of solid salicylamide in which the particle size of the salicylamide is such that substantially all of it passes through a #100 mesh sieve and at least 50% thereof is retained on a #325 mesh sieve.

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ANEXO 3
PATENTE EP0052085



Europäisches Patentamt
European Patent Office
Office européen des brevets

⑪ Publication number:

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A2

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EUROPEAN PATENT APPLICATION

Application number: 8183216.2

⑦ Int. CL²: A 61 K 9/00

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⑪ Applicant: MAGGI FARMACEUTICI S.r.l., Viale Europa, 38/39, Brescia (IT)

⑫ Date of publication of application: 19.04.82
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⑭ Designated Contracting States: AT BE CH DE FR GB LI
LU NL SE

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⑯ Pharmaceutical composition containing vincamine.

⑰ A vincamine suspension is disclosed and claimed.
Said suspension, which retains all solution's advantages as to use's flexibility, without offering its disadvantages, is especially useful in therapy, chiefly as drug for the regulation of cerebral microcirculation.

EP 0 052 085 A2

Pharmaceutical composition containing vincamine

The present invention relates to a pharmaceutical composition for oral administration.

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More particularly the present invention relates to a pharmaceutical composition for oral administration of 13a-ethyl-2,3,5,6,12,13,13a,13b-octahydro-12-hydroxy-1H-indole - [3,2,1-dc] pyrido [3,2,1-ij] [1,5] naphthiridine-12-
10 carboxylic acid methyl ester, which is hereinafter called vincamine, characterized in that it is a suspension.

In said suspension the liquid vehicle is substantially water and, in case of suspension ready for administration,
15 the particles of vincamine have advantageously a maximum dimension of 80 μ .

Vincamine is a known compound which is already used in therapy; it is particularly used for the regulation of
20 cerebral microcirculation, that is, for example, in case of ascending cerebral circulatory failure, sclerosis and senile cerebral involution or acute cerebro-vascular events.

25 Pharmaceutical compositions previously used for the oral administration of vincamine were tablets or solutions which were dosed and administered in drops. Pharmaceutical compositions which are administrable in drops are very useful as they offer high flexibility in dosing
30 and high practicality in administration; nevertheless the vincamine solutions have certain limitations.

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Firstly, vincamine solutions are endowed with an intense bitter taste which gives rise to cases of intolerance in a considerable number of patients. Secondly, solutions, owing to vincamine's low solubility, cannot exceed concentration of about 2% and therefore it is possible to obtain the very high dosages which are now required by present therapy only by increasing very much the solution volume. Lastly, stability of active ingredient is time-limited in solution.

10

It was now surprisingly found, and this is object of the present invention, that above described limitations are overcome by a pharmaceutical composition for vincamine's oral administration, characterized in that it is a suspension.

By means of the present invention pharmaceutical compositions are obtained which offer undeniable advantages, in addition of solutions' dosing flexibility.

20

As a matter of fact, the suspensions of the present invention, together with an increase in time-stability of the active ingredient, does not taste bitterly; therefore, intolerance cases are eliminated which were risen by the taste. Moreover, the suspensions of the present invention allow to reach higher concentrations w/v and to administer higher doses without increasing the volume. Therefore, scheme of dosing can be utilized in which doses are progressively increased or are suitable for patients' individual needs without involving an excessive increase in drops' number, in order to avoid computation's errors and, consequently, dosing errors.

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Therefore, it is another advantage of the present invention that an amount of active ingredient considerably higher than in prior art can be incorporated into a given volume of the pharmaceutical composition. When dosage limits which are presently used in therapy are considered, suspensions which are object of the present invention have from 0.5% to 10% w/v of vincamine; nevertheless higher concentrations are also within the scope of the present invention.

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Suspensions which are object of the present invention have a liquid vehicle which is substantially water. An important and critical feature of the present invention lies in the degree of subdivision of the vincamine's particles. Powders to prepare granulates for reconstitution "in situ" of suspensions have particles of vincamine with a maximum dimension of 250 μ ; ready suspensions have particles with a maximum dimension of 80 μ . Ready suspensions are a preferred embodiment of the present invention.

20

Such ready suspensions contain water, as liquid vehicle, vincamine, in amount varying from 0.5% to 15% w/v, preferably from 2% to 10% w/v, and additives such as surface-active agents, inorganic electrolytes, anionic and non-ionic suspending agents, edulcorating and flavoring agents and preservatives.

In particular are conveniently present: ammonium glycyrrhizinate (from 0.04% to 0.2%), sucrose (50%), sodium carboxymethylcellulose (from 0.25% to 0.50%), polyvinylpyrrolidone (from 0.5% to 1%) or sucresether, that is

sucrose's esters with fatty acids (from 2% to 3%),
silica gel (from 0.12% to 0.25%) or sodium hexameta-
phosphate (from 1.5% to 8%). All percentages are
weight/volume and may vary independently each other.

5 Moreover, it is conveniently present liquesterol (4%
v/v), that is a mixture of p-hydroxybenzoates of methyl,
ethyl and propyl.

Granulates for reconstitution "in situ" of suspensions
10 are also preferred embodiments of the present invention.

Such granulates contain vincamine, in amount varying
from 0.5% to 10% w/v, preferably from 2% to 5% w/v, of
the reconstituted suspension, and may contain same
15 additives which are present in ready suspensions, in
same percentages, when such percentages are calculated
for reconstituted suspension's volume.

As antimicrobial preservative, sodium benzoate is conve-
20 niently used instead of liquesterol; its amount may vary
from 0.1% to 0.5% (w/v) of the reconstituted suspension.

In a further aspect of the present invention there are
provided pharmaceutical forms in which the pharmaceutic-
25 al compositions, which are object of the present inven-
tion, may be carried out. Such pharmaceutical forms may
be either granulates filled into vials for suspension's
reconstitution "in situ", or granulates filled into
single-dose containers for suspension's reconstitution
30 "in situ", or vials containing the suspending solution
and having the granulate filled in container-caps, or
ready suspensions.

The following Examples illustrate some embodiments of the present invention, without limiting it. All temperatures are in °C.

5 EXAMPLE 1

Granulate in vials for reconstitution "in situ" of the suspension (amounts are referred to 100 ml of reconstituted suspension).

The following ingredients were used:

10 Vincamine	g	2
Polyvinylpyrrolidone	mg	900
Sodium carboxymethylcellulose	mg	450
Sucrose	g	50
Ammonium glycyrrhizinate	mg	60
15 Sodium benzoate	mg	100
Silica gel	mg	250

Sucrose was sized by means of a meshed screen with apertures of 0.7 mm span-size; sucrose which passed through the screen was used for the preparation of the

20 sirup.

Polyvinylpyrrolidone, carboxymethylcellulose and flavour were sized by means of a stainless alloy meshed screen with apertures of 0.25 mm span-size, getting all the products through the screen.

25 Vincamine was treated in a granulator with stainless alloy sieve of 0.25 mm span-size, getting all the product through the sieve.

In a suitable mixer (cube-shaped, V-shaped or the like) all products were intimately mixed, till a perfectly

30 homogeneous mixture was obtained.

The granulate was then filled into suitable vials.

EXAMPLE 2

Granulate in vials for reconstitution "in situ" of the suspension (amounts are referred to 100 ml of reconstituted suspension).

5 Operating as in Example 1, the following ingredients were used:

Vincamine	g	5
Polyvinylpyrrolidone	mg	900
Sodium carboxymethylcellulose	mg	450
10 Sucrose	g	50
Ammonium glycyrrhizinate	mg	150
Sodium benzoate	mg	100
Silica gel	mg	350

15 EXAMPLE 3

Ready suspension.

The following ingredients were used:

Vincamine	g	2
: Liquesterol	ml	4
20 Ammonium glycyrrhizinate	mg	60
Sucrose	g	50
Sodium carboxymethylcellulose	mg	280
Polyvinylpyrrolidone	mg	550
Silica gel	mg	135
25 Water	to	ml 100

Carboxymethylcellulose was blended with 3% of the total weight of sucrose and milled (4600 RPM, sieve 00). De-ionized water (about half of the final volume), warmed up to 60-65°C, was added into a first stainless alloy vessel, after filtering through a 0.45 μ Millipore membrane. Ammonium glycyrrhizinate was added. After dissolution was complete, polyvinylpyrrolidone was add-

ed. While stirring at 50 RPM, the remaining sucrose was added into the first vessel and stirring was protracted for 15' after the adding was complete.

The warm sirup was filtered through a sieve (250 mesh) into a second stainless alloy vessel, while the first vessel was washed by means of deionized water.

While stirring at 50 RPM, the previously prepared mixture (sucrose + sodium carboxymethylcellulose) was slowly added into the second vessel; stirring was protracted for 15' after the adding was complete. Then the sirup was cooled to 22-25°C.

While stirring at 50 RPM, the following ingredients were added, with 3-4 minutes intervals, in that order :

- Liquesterol
- 15 - Silica gel
- Vincamine, having particles with maximum dimension 80 μ .

Stirring was protracted for 15' after the adding was complete.

20 Through a colloid-mill the sirup was transferred into the first vessel which was previously washed.

When transferring was over, the second vessel was washed, together with the mill, by means of deionized filtered water (4% of the final volume) which was then transferr-

25 ed into the first vessel.

Temperature was kept at 20-25°C.

Sirup was allowed to stand till foam disappeared; then final volume was corrected.

30 EXAMPLE 4

Ready suspension.

Operating as in Example 3, the following ingredients were

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used:

Vincamine	g	10
Liquesterol	ml	4
Ammonium glycyrrhizinate	mg	150
5 Sucrose	g	50
Sodium carboxymethylcellulose	mg	450
Polyvinylpyrrolidone	mg	900
Silica gel	mg	2000
Water	to ml	100

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EXAMPLE 5

Ready suspension.

The following ingredients were used:

Vincamine	g	2
15 Liquesterol	ml	4
Ammonium glycyrrhizinate	mg	60
Sucrose -	g	50
Sodium carboxymethylcellulose	mg	275
Polyvinylpyrrolidone	mg	550
20 Sodium hexametaphosphate	g	1,5
Water	to ml	100

Carboxymethylcellulose was blended with 3% of the total weight of sucrose and milled (4600 RPM, sieve 00). De-ionized water (about half of the final volume), warmed
25 up to 60-65°C, was added into a first stainless alloy vessel after filtering through a 0.45 μ Millipore membrane. Ammonium glycyrrhizinate was added. After dissolution was complete, polyvinylpyrrolidone was added. While stirring at 50 RPM, the remaining sucrose was add-
30 ed into the first vessel and stirring was protracted for 15' after the adding was complete.
The warm sirup was filtered through a sieve (250 mesh)

into a second stainless alloy vessel, while the first vessel was washed by means of deionized water.

While stirring at 50 RPM, the previously prepared mixture (sucrose + sodium carboxymethylcellulose) was slowly added into the second vessel; stirring was protracted for 15' after the adding was complete. Then the sirup was cooled to 22-25°C.

While stirring at 50 RPM, the following ingredients were added, with 3-4 minutes intervals, in that order:

10 - Liquesterol

- Vincamine, having particles with maximum dimension 80 μ .

Stirring was protracted for 15' after the adding was complete.

15 Stirring was increased to 100 RPM and sodium hexameta-phosphate was added very slowly (during about 15 minutes), in small quantities.

Stirring was protracted for 30 minutes after the adding was complete, at a temperature of 22-25°C.

20 The sirup, while stirring at 50 RPM, was transferred through a colloid-mill into the first vessel which was previously washed.

When transferring was over, the second vessel was washed, together with the mill, by means of deionized filtered

25 water (4% of the final volume) which was then transferr-ed into the first vessel.

Temperature was kept at 20-25°C.

Sirup was allowed to stand till foam disappeared; then final volume was corrected.

30

EXAMPLE 6

Ready suspension.

Operating as in Example 5, the following ingredients were used:

Vincamine	g	10
; Liquesterol	ml	4
5 Ammonium glycyrrhizinate	mg	150
Sucrose	g	50
Sodium carboxymethylcellulose	mg	450
Polyvinylpyrrolidone	mg	900
Sodium hexametaphosphate	g	8
10 Water	to ml	100

While the invention was described in detail and with reference to specific embodiments, it will be apparent to those skilled in the art that variations and modifications can be made without departing from the spirit and scope of the invention.

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C L A I M S

1. Pharmaceutical composition for oral administration of vincamine, characterized in that it is a suspension.

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2. Pharmaceutical composition according to claim 1, characterized in that the liquid vehicle is substantially water and vincamine particles' maximum dimension is 80 μ .

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3. Pharmaceutical composition according to claims 1 and 2, characterized in that it is a ready suspension.

4. Pharmaceutical composition according to claim 1, characterized in that it is a dry powder for reconstitution "in situ" of the suspension, in which vincamine particles' maximum size is 250 μ .

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ANEXO 4
PATENTE US5455049

United States Patent [19]
Anaebonam et al.

[11] **Patent Number:** 5,455,049
 [45] **Date of Patent:** Oct. 3, 1995

[54] **TERFENADINE ORAL POWDER**
 [75] **Inventors:** Aloysius O. Anaebonam, Burlington, Mass.; Abdel A. Fawzy, Nashua, N.H.; Emmett Clemente, Manchester, Mass.
 [73] **Assignee:** Ascent Pharmaceuticals, Inc., Billerica, Mass.
 [21] **Appl. No.:** 368,421
 [22] **Filed:** Jan. 4, 1995
 [51] **Int. Cl.⁶** A61K 9/16
 [52] **U.S. CL.** 424/499; 424/439; 424/489; 424/497; 424/501
 [58] **Field of Search** 424/499, 439, 424/489, 497, 501

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Primary Examiner—Thurman K. Page
Assistant Examiner—S. Howard
Attorney, Agent, or Firm—Welsh & Katz, Ltd.

[57] **ABSTRACT**

The present invention contemplates a dry, powdered terfenadine composition. That composition comprises

(a) a mixture of:
 (i) about 1 to about 20 parts by weight micronized terfenadine and
 (ii) about 0.2 to about 10 parts by weight a polyethylene oxide-polypropylene oxide-polyethylene oxide block copolymer having an HLB number of 24 that is a wetting agent for said terfenadine;
 that are dry-blendedly dispersed into:
 (b) about 20 to about 40 parts by weight spray-dried sorbital particles that are loosely packed, randomly oriented filamentary crystals having pores that entrap said terfenadine particles and wetting agent upon said dry-blended dispersal, said components being further dry blended with
 (c) about 2 to about 10 parts by weight dry polyvinylpyrrolidone;
 (d) about 1 to about 5 parts by weight of a dry mixture of microcrystalline cellulose and sodium carboxymethyl-cellulose; and
 (e) a dry flavorant in an amount sufficient to provide a desired taste to said powder;
 said composition being a free-flowing powder that is substantially free from the taste of terfenadine when placed on the human tongue in dry form or when dispersed in water and tasted within about five minutes of said dispersal.

8 Claims, No Drawings

TERFENADINE ORAL POWDER

DESCRIPTION

1. Technical Field

The present invention relates to an orally administrable antihistamine-containing powder, and more particularly to an orally administrable, pleasant tasting powdered form of terfenadine that when applied to the tongue is substantially free of the taste of solubilized terfenadine.

2. Background Art

Terfenadine is a well-known antihistamine that is a selective antagonist of the histamine H_1 -receptor. Terfenadine lacks sedative properties. This particularly effective drug has a particularly offensive taste when dissolved and is consequently formatted for oral administration as a pill or tablet that minimizes that offensive taste.

Although provision in a tablet form overcomes the problem of offensive taste for this valuable medicament for most of the adult population that uses terfenadine, many adults and many children have difficulty swallowing the pills or tablets or cannot swallow them, and thereby do not benefit from terfenadine.

The disclosure that follows illustrates one solution to the problem of terfenadine delivery that is applicable to adults and children that cannot swallow capsules or have difficulty doing so, as well as an alternative delivery mode for the general population.

BRIEF SUMMARY OF THE INVENTION

A dry, powdered terfenadine composition is contemplated. That composition comprises

(a) a mixture of:

(i) about 1 to about 20 parts by weight micronized terfenadine, and

(ii) about 0.2 to about 10 parts by weight a polyethylene oxide-polypropylene oxide-polyethylene oxide block copolymer having an HLB number of about 24 that is a wetting agent for the terfenadine;

Those components are jointly dry-blendedly dispersed into:

(b) about 20 to about 40 parts by weight spray-dried sorbitol particles. The particles are loosely packed, randomly oriented filamentary crystals having pores that entrap the micronized terfenadine particles and wetting agent upon dry-blended dispersal. The three blended components are further dry blended with

(c) about 2 to about 10 parts by weight dry polyvinylpyrrolidone;

(d) about 1 to about 5 parts by weight dry microcrystalline cellulose that includes sodium carboxymethylcellulose; and

(e) a dry flavorant in an amount sufficient to provide a desired taste to the powdered composition;

The resulting composition is a free-flowing powder that is substantially free from the taste of solubilized terfenadine when placed on the human tongue in dry form or when dispersed in water and tasted within about five minutes of the dispersal.

The present invention has several benefits and advantages.

One benefit is that the terfenadine oral powder disclosed can be taken by those persons that have difficulty swallowing usually supplied pills or tablets, or cannot so swallow

without experiencing the offensive taste usually associated with solubilized terfenadine.

An advantage of the invention is that the terfenadine oral powder can also be dispersed in foods or aqueous liquids and consumed without exhibiting the usual offensive taste of solubilized terfenadine.

Another benefit of the invention is that the powdered composition, once placed onto the tongue, disperses almost immediately, without having a gritty or other noticeable residue.

Another advantage of the invention is that use of dry granulation procedures provides enhanced efficiency in manpower and energy usage compared to a liquid mixing procedure in that no drying step is required.

Still further benefits and advantages of the present invention will be apparent to the worker of ordinary skill from the disclosure that follows.

DETAILS DESCRIPTION OF THE INVENTION

The present invention contemplates a free-flowing powdered form of terfenadine that is pleasant tasting, substantially free from the usual taste of solubilized terfenadine, and is designed to be taken orally as by administration of the powder directly into the mouth or upon reconstitution in a small amount of water or in food.

A contemplated composition comprises (a) a mixture of (i) about 1 to about 20 parts by weight of micronized terfenadine and (ii) about 0.2 to about 10 parts by weight of a polyethylene oxide-polypropylene oxide-polyethylene oxide block co-polymer having an HLB number of about 24 that is a wetting agent (dispersant) for the terfenadine;

(b) about 20 to about 40 parts by weight spray-dried sorbitol particles, a loosely packed, randomly oriented filamentary crystals having pores that entrap the micronized terfenadine particles and wetting agent upon the dry-blended dispersal. The dry blended (a) and (b) components are further dry blended with

(c) about 2 to about 10 parts by weight dry polyvinylpyrrolidone;

(d) about 1 to about 5 parts by weight dry microcrystalline cellulose; and

(e) a dry flavorant in an amount sufficient to provide a desired pleasant taste to the powdered composition.

The resulting powdered composition is free-flowing and is substantially free from the taste of solubilized terfenadine when placed on the human tongue in dry form or when dispersed in water and tasted within about five minutes of that dispersal.

A contemplated composition contains both micronized terfenadine and a spray-dried sorbitol. Those materials can be present at a weight ratio of 1:20 to about 1:2 terfenadine:sorbitol. That weight ratio is more preferably about 1:12.5 to about 1:3.5, and most preferably is about 1:10 in the order noted.

The wetting agent block co-polymer assists in dispersing the micronized terfenadine, but does not form micellar structures that solubilize the terfenadine. The wetting agent is present at about one-fifth to about one-half the weight of the micronized terfenadine, and more preferably at about one-half the weight of terfenadine.

Polyvinylpyrrolidone (PVP; povidone) that acts as a debittering agent to the terfenadine and secondarily can assist in building viscosity and mouth feel is present at a weight

ratio to the sorbitol particles of about 1:10 to about 1:4 of PVP:sorbitol.

A mixture of microcrystalline cellulose and sodium carboxymethylcellulose that acts as a wetting agent for the blended materials is also present. This cellulosic mixture is present at a weight ratio of about 20 to about 1:8 relative to the sorbitol. More preferably, that weight ratio is about 1:12 to about 1:9; with a weight ratio of about 1:10 being most preferred.

The composition also contains a flavorant that can be a single ingredient such as fructose or sucrose or both, or more complex mixtures of materials that provide a desired pleasant sweetness or other flavor than that of solubilized terfenadine itself. The composition is substantially free from a solubilized terfenadine taste and has a pleasant, non-medicinal taste.

The composition is also free-flowing in that its individual particles tend not to clump together or agglomerate even when in the mouth or stirred in an amount of water sufficient to form a watery suspension, as compared to a paste or cream. The dry composition therefore flows freely when poured from one vessel to another.

Turning more specifically to the individual ingredients, the terfenadine used herein is terfenadine USP that has been finely comminuted into micron-sized particles. The terfenadine is therefore often referred to herein as "micronized" to highlight its small particle size, and at other times hereinafter that material is called terfenadine. This micronized terfenadine is sized so that 100 percent of the particles are less than 10 μm , and at least 85 percent are smaller than 5 μm . Typical bulk densities for this material are about 0.1 to about 0.5 g/ml.

Micronized terfenadine is available from several commercial sources. Illustrative sources include CILag AG Schaffhausen, Switzerland (Zetapharm, Inc. of New York, N.Y.); and Erregirre Industrial Chimica, SpA, Italy (Flavine International Inc. of Closter, N.J.).

The usual antihistaminic dosage of terfenadine for adults and children over 13 years of age is 60 mg twice each day. For younger children, the dosage is usually about 15-30 mg twice each day.

As used here, a single dose of powdered composition having a total mass of 0.5, 1 or 2 grams is designed to carry the entire antihistaminic amount of terfenadine. As a consequence, the amounts of ingredients other than micronized terfenadine are based upon the amount of terfenadine preferably being calculated to be a dose of about 15, 30 or 60 mg. It should also be understood that less than the usual antihistaminic amount can be used in a single dose with several doses being supplied at about the same time or within about one hour of each other to provide an antihistaminic amount of terfenadine.

Thus, a powdered composition, when viewed only as a composition, need only define relative amounts by parts or other ratios of each ingredient to another ingredient or ingredients. However, when used to supply an antihistaminic amount of terfenadine, or contemplated in a process for use or treatment, total amounts of ingredients are considered.

In a given composition, micronized terfenadine is present at about 1-20 parts. More preferably, the micronized terfenadine is present at about 2-10 parts, and most preferably at about 3 parts by weight.

A contemplated polyethylene oxide/polypropylene oxide-polyethylene oxide block copolymer wetting agent is referred to in the nomenclature of the *International Cosmetic Ingredient Dictionary*, 5th ed., McNamee et al., eds.,

The Cosmetic, Toiletry, and Fragrance Association, Washington, D.C. (1993) as a "Poloxamer", followed by a numerical designation. A particular Poloxamer of interest here contains polyethylene oxide blocks of about equal average length on either side of the polypropylene oxide block, with the average total molar ratio of oxyethylene to oxypropylene repeating groups in each molecule being about 5 to about 6. These materials are all solids at ambient room temperature and have an HLB of 24.

Exemplary Poloxamer wetting agent molecules are sold under the trademark PLURONIC polyol F-38, F-68, F-88, F-98 and F-108 for Poloxamers 108, 188, 238, 288 and 338, respectively. Pluronic polyol F-68 is particularly preferred. These Pluronic polyols are available from BASF Corporation of Mount Olive, NJ.

The Poloxamer is present at about one-fifth to about one-half the weight of the micronized terfenadine, with more of the Poloxamer wetting agent being used when more micronized terfenadine is used. Thus, where the powder composition contains about 1 to about 20 parts micronized terfenadine, about 0.2 to about 10 parts Poloxamer wetting agent are also present. With a more preferred amount of terfenadine of about 2 to about 10 parts, one uses about 1 to about 5 parts Poloxamer, and most preferably, about 1.5 parts Poloxamer are used with 3 parts micronized terfenadine.

The spray-dried sorbitol is a specialized product produced by E. Merck of Darmstadt, and available from EM Industries Inc. of Hawthorne, N.Y. under the trademark sorbitol Instant™. Sorbitol Instant™ is spray-dried from an aqueous solution and whereas crystalline sorbitol exhibits sharp angles, a smooth particle surface and provides a gritty texture and mouth feel when tableted, sorbitol Instant™ is comprised of loosely packed, randomly oriented, interwoven filamentary crystal particles. Magnification of these particles shows pore spaces within the particles and a furry-looking particle surface appearance. Any reference to "sorbitol" herein except a specific reference to the usual "crystalline sorbitol" is to sorbitol Instant™.

Sorbitol is known to have a high capacity to adsorb some small drug particles, with the adsorption being dependent upon particle size as well as electrostatic and Van der Waals forces. Thus, some drugs such as acetaminophen do not form adsorbates to a high degree, whereas others such as erythromycin ethylsuccinate form very concentrated adsorbates.

Two forms of sorbitol Instant™ are commercially available, and both can be used herein. The first is referred to as 7703 sorbitol Instant™ Pharma, which is preferred, and the second is referred to as 11578 sorbitol Instant™ P3000. Both products are soluble at 360 g/100 ml water at 40° C. and have a specific rotation, $[\alpha]_D^{20}$ (C=1, water, borate complex) of +4.0° to +7.0°, calculated as the anhydrous material that it is.

The two materials differ in particle size and therefore bulk density. 7703 Sorbitol Instant™ Pharma has the following particle size distribution: <12 μm (70 mesh) <5 percent, <50 μm (35 mesh) <80 percent; and 850 μm (20 mesh) <5 percent, with a bulk density of 38-46 g/100 ml and a tapped density of 45-50 g/100 ml. 11578 Sorbitol Instant™ P3000 has the following particle size distribution: <53 μm (270 mesh) <15 percent, 53-106 μm (270-140 mesh) 15-20 percent, 106-212 μm (140-70 mesh) 40-50 percent, 212-500 μm (70-35 mesh) 20-30 percent, and >500 μm (35 mesh) <1 percent, with a bulk density of 45-55 g/100 ml and a tapped density of 51-56 g/100 ml. Sieve sizes are U.S. Standard Sieve Series.

The sorbitol is used in excess over the terfenadine so that when more terfenadine is present, more sorbitol Instant™ is

used. A preferred composition that contains 1 to about 20 parts micronized terfenadine therefore contains about 20 to about 40 parts sorbitol. A preferred composition containing about 2 to about 10 parts terfenadine contains about 25 to about 35 parts sorbitol Instant™, whereas a most preferred composition that contains about 3 parts terfenadine contains about 30 parts sorbitol.

Sorbitol can also be used in greater amounts to provide bulk to the composition. Any excess in the amount of sorbitol over the weight ratio to terfenadine discussed hereinbefore is so used, as compared to the primary use of sorbitol Instant™ as a dispersing and taste-masking agent for the terfenadine.

The micronized terfenadine and block copolymer wetting agent are dry-blendedly dispersed into the sorbitol. That is, the first two ingredients are blended dry with each other and with the sorbitol Instant™, and adhere to the sorbitol and fill its pores. This is preferably accomplished by a tumbling mixer with the fortunate result that both the terfenadine and block copolymer adhere to the sorbitol particles without greatly changing the particle size of the sorbitol except for the size increase due to the adsorption and without noticeable agglomeration of filled and coated sorbitol particles. This lack of agglomeration contributes to the free flowing character of the final powder composition.

The above dry blended components are thereafter dry blended further with dry PVP, dry microcrystalline cellulose and a dry flavorant, as are discussed below.

The polyvinylpyrrolidone (PVP) is a well known item of commerce that is available in several molecular weight grades from several suppliers. A particularly preferred material is sold under the trademark KOLLIDON by BASF Corp. of Mount Olive, N.J. Exemplary materials are sold as KOLLIDON 25, 30 and 90 that have weight average molecular weights of about 25,700, 42,500 and 1,100,000, respectively. These materials are free flowing powders with particle sizes in the range of about 50 to about 250 μ m. Particles smaller than 50 μ m are present at less than 10 percent for all grades, and particles greater than 250 μ m are less than 5 percent for KOLLIDON 25 and 30, and less than 20 percent for KOLLIDON 90. Bulk densities are about 0.40–0.50 g/ml, 0.35–0.50 g/ml and 0.40–0.50 g/ml for KOLLIDON 25, 30 and 90, respectively.

The highest molecular weight material, KOLLIDON 90, is preferred herein. This material, unexpectedly and primarily, provides a further taste-enhancing, de-bittering function to the terfenadine. Secondly, the PVP also provides an enhanced mouthfeel when the composition is on the tongue, and additionally provides body (viscosity) when the composition is reconstituted in water.

The PVP is used at a weight ratio of about 1:10 to about 1:4 to sorbitol. More of the PVP is used when more terfenadine and sorbitol are in the composition. Thus, about 20 to about 40 parts sorbitol are used with about 2 to about 10 parts of PVP. More preferably, about 25 to about 35 parts sorbitol are used with about 3 to about 7 parts PVP. Most preferably, about 30 parts of sorbitol are used with about 5 parts of PVP.

A mixture of microcrystalline cellulose and sodium carboxymethylcellulose (NaCMC) is also utilized in the composition as a colloidal suspending agent. The NaCMC is present at about 7 to about 20 weight percent in this mixture so the mixture is more simply referred to as microcrystalline cellulose as that material constitutes about 80 to about 93 percent of the total. This material is listed in the U.S. Pharmacopeia National Formulary as microcrystalline cellulose and carboxymethylcellulose sodium.

A preferred mixture is available from FMC Corporation, Philadelphia, Pa. under the trademarks AVICEL RC-501, RC-581, RC-591 and CL-611. These materials are solid powders that pass through a 60 mesh sieve to at least 99.9 percent and are retained on a 200 mesh sieve at not more than 40 and 35 weight percents (AVICEL RC-501 and RC-581, respectively), or 45 and 50 percents on a 325 mesh sieve (AVICEL RC-591 and CL-611, respectively). The two first designated materials typically require high shear mixing for dispersion in water, whereas the latter two materials only require moderate shear for dispersion.

AVICEL CL-611 is preferred herein and forms a thixotropic gel in water when present at greater than 1.2 percent. This material contains about 11 to about 19 percent NaCMC.

The microcrystalline cellulose mixture is present at a weight ratio of about 1:20 to about 1:8 relative to the sorbitol. As more terfenadine and sorbitol are used, more of the microcrystalline cellulose is also used. Thus, where about 20 to about 40 parts sorbitol are present, about 1 to about 5 parts of microcrystalline cellulose are also present. More preferably, about 25 to about 35 parts sorbitol are used with about 2 to about 4 parts microcrystalline cellulose. Most preferably, about 3 parts microcrystalline cellulose are used with about 30 parts sorbitol.

A flavorant is also present. Most preferably, the flavorant is a sweetener that is a mixture of saccharides such as maltodextrin and sucrose or fructose. These flavorants can comprise up to about 75 weight percent and more preferably comprise about 40 to about 60 weight percent of the final composition down to only a few percent when artificial sweeteners are used.

A preferred maltodextrin, which is a hydrolyzed corn-starch polymer having α -1 $\rightarrow$ 4-linked D-glucose having a dextrose equivalent (DE) of less than or equal to about 20, is the agglomerated product sold under the trademark MALTRIN QD. The MALTRIN QD products are sold by Grain Processing Corp., Muscatine, IA. Products are sold under the designations QD M440, M500 and M600 that have DE values of 4–7, 9–12 and 20–23, respectively.

The preferred MALTRIN QD™ M500 has a particle size specification that requires a minimal 90 percent passage through a U.S. #20 mesh sieve screen and a maximal 10 percent passage through a U.S. #200 sieve screen. A typical particle size distribution provides 95 percent through a #20 sieve screen, 50 percent through a #60 sieve screen, 25 percent through a #100 sieve screen and 6 percent through a #200 sieve screen, U.S. Sieve Series.

These agglomerated maltodextrins have low bulk densities, e.g., MALTRIN QD M500 that is preferred has a bulk density of 34 g/100cc, are relatively non-friable and do not disintegrate readily in dry mixing. These materials also disperse very rapidly in water, e.g., 100 percent of a 15 weight percent mixture of MALTRIN QD M500 in water dissolves in one minute on mixing.

The agglomerated maltodextrin has a bland flavor that helps control sweetness and is also used as a bulking and flow control agent in the powder. On dissolution or dispersion in water, the agglomerated maltodextrin also contributes to building viscosity.

Sucrose or fructose (sugar) in finely divided form is a principal flavorant, and provides sweetness as is well known. An exemplary fructose is available from Roquette Corp., Gurnee, Ill.

It is preferred to use both the agglomerated maltodextrin and either sucrose or fructose as the flavorant, or part of the flavorant. It is also preferred to use about twice the amount of sugar as agglomerated maltodextrin. The combined

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amount of maltodextrin and sugar is used at about twice the amount of sorbitol.

Broadly, where sorbitol is present at about 20 to about 40 parts, the agglomerated maltodextrin can be present at about 10 to about 40 parts, and the sugar at about 10 to about 50 parts. With a preferred amount of about 25 to about 35 parts sorbitol, about 15 to about 25 parts agglomerated maltodextrin and about 30 to about 40 parts sugar are used. With the most preferred 30 parts sorbitol, about 20 parts agglomerated maltodextrin are used with about 37.5 parts sugar.

Artificial sweeteners such as aspartame, saccharin and cyclamates can also be used as flavorants in addition to or as replacements for the above flavorants. Dried fruit flavors such as orange and lemon flavors and other well known dry flavorants can also be used in place of some or all of the above flavorants.

As noted previously, the micronized terfenadine and Poloxamer are dry-blendedly dispersed into, onto and with the sorbitol to form a homogeneous material. Using a usual tumbling mixer, blender at a slow speed, this dispersal takes about 5-15 minutes. The other ingredients are then admixed and the admixture is blended for about another 5-15 minutes or until homogeneity is achieved.

Once all of the blending is completed, a freeflowing powder composition is obtained. The composition itself has 25 preferably a pleasant taste, although whether the taste is pleasant or not is governed by the choice of the worker preparing the composition. The composition, more importantly, is substantially free from the taste of solubilized 30 terfenadine when placed on the human tongue in the composition's dry form, or when tasted within about five minutes of being dispersed in water.

By being "substantially free from the taste of terfenadine" it is meant that an average person on tasting the composition would not detect the usually offensive dissolved terfenadine taste. This definition is meant not to be all-inclusive as some people may be particularly sensitive to the terfenadine taste so that no amount of masking will overcome that offensive taste. In addition, some discriminating palates such as those of chefs and other food experts who are used to discriminating one taste from another may be able to discern the distinctive bitter solubilized terfenadine taste. Generally, most people cannot discern the solubilized terfenadine taste in the completed composition.

The resulting powdered composition can be used as is for its antihistaminic effects by simply applying an antihistaminic amount of the composition upon the tongue and permitting the composition to disperse in saliva or with an appropriate drink. An antihistaminic amount of the powdered composition can also be dispersed with shaking or stirring in a few milliliters of water, e.g. about 5 to about 15 ml, and administered by drinking the dispersed composition. The composition can also be dispersed in a food such as applesauce, mashed bananas, peanut butter or the like and

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then ingested as those foods are normally ingested.

A contemplated powdered terfenadine oral composition can be packaged for sale as a powder in a suitable container or package such as a jar or bottle from which the user measures out his or her own antihistaminic dose, as with an appropriately sized spoon or similar device. More preferably, the powdered terfenadine is prepackaged in unit dose form so that each packaged unit contains a single antihistaminic dose as discussed before such as 15, 30, 94 60 mg of terfenadine. In one preferred embodiment, the unit dose is packaged in a tear-open packet from which the unit antihistaminic dose of terfenadine can be poured directly onto the tongue or into water or food as discussed before.

BEST MODE FOR CARRYING OUT THE INVENTION

Example 1

Terfenadine Oral Powder

A composition designed to provide 60 mg of terfenadine in 2 g of dry composition was prepared as follows.

The Sorbitol Instant™, maltodextrin and fructose used in the composition were separately sieved using a #60 U.S. Standard Sieve Screen, and only material that passed through the screen was used.

Microtonized terfenadine (30 g) and the block co-polymer wetting agent (PluronicTM polyol F-68) were mixed slowly in a "V-blender" for about five minutes. Sorbitol InstantTM (300 g) was added to the mixture and blended therewith for another five minutes to form a blend of all three components.

Microcrystalline cellulose (30 g; AVICEL™ CL-611) PVP (50 g, KOLLIDON™ K-90) maltodextrin (200 g, MALTRIN™ QD M500) and 375 g of fine, granular fructose were added to the above blend, and blending was continued for another ten minutes to form a homogeneous, dry terfenadine composition that was a free flowing powder.

The blended dry composition was thereafter packaged into 2 g sachets as unit doses.

Example 2

Taste Assay

A series of ten compositions was prepared using the general procedures described in Example 1. The resulting dry, powdered terfenadine compositions were then assayed by placing 0.5–2 g of the composition individually into the mouths of two experienced taste assayers. The amount of each sample used was determined based on the amount of terfenadine present in the individual samples so that the total amount of terfenadine remained approximately constant. The composition components are shown below in amounts by weight percent of the total composition. Taste ranking scores from each of the two assayers follow each assay of composition components.

TABLE

[illegible]

TABLE-continued

Composition Components in Weight Percent									
Sucrose, fine	39.5		20.0	37.5		20.0	37.0		20.0
Mahoeextrin ⁴ , fine	20.0	20.0	39.5	20.0	20.0	37.5	15.0	15.0	20.0
Fructose, fine		39.5			37.5			37.0	20.0
Assayer #1	3	2	4	2	3	4	4	3	4
Assayer #2	3	2	3	2	3	4	4	5	4

¹AVICEL™ CL-611 was used.
²KOLLIDON™ K-90 was used.
³Poloxamer 188 was used.
⁴MALTRIN™ QD M300 was used.

Numerical taste ranking values were as follows: 1=Excellent; 2=Very good; 3=Good; 4=Satisfactory; 5=Acceptable with slight bitter aftertaste; 6=Acceptable with slight soapy taste and bitter aftertaste; and 8=Bitter/unpleasant.

As is seen from the above results, each of the dry, powdered terfenadine-containing compositions was acceptable from a taste standpoint. In contrast, a crushed commercially available terfenadine tablet containing an equal amount of terfenadine provides a taste ranking score of about 6 or 7 under these assay conditions.

Although the present invention has now been described in terms of certain preferred embodiments, and exemplified with respect thereto, one skilled in the art will readily appreciate that various modifications, changes, omissions and substitutions may be made without departing from the spirit thereof.

We claim:

1. A dry, powdered terfenadine composition that comprises

(a) a mixture of:

(i) about 1 to about 20 parts by weight micronized terfenadine and

(ii) about 0.2 to about 10 parts by weight a polyethylene oxide-polypropylene oxide-polyethylene oxide block copolymer having an HLB number of 24 that is a wetting agent for said terfenadine;

that are dry-blendedly dispersed into:

(b) about 20 to about 40 parts by weight spray-dried sorbitol particles that are loosely packed, randomly oriented filamentary crystals having pores that entrap said terfenadine particles and wetting agent upon said dry-blended dispersal, said components being further dry blended with

(c) about 2 to about 10 parts by weight dry polyvinylpyrrolidone;

(d) about 1 to about 5 parts by weight dry microcrystalline cellulose mixture that contains about 7 to about 20 weight percent sodium carboxymethylcellulose; and

(e) a dry flavorant in an amount sufficient to provide a desired taste to said powder;

said composition being a free-flowing powder that is substantially free from the taste of solubilized terfenadine when placed on the human tongue in dry form or when dispersed in water and tasted within about five minutes of said dispersal.

2. The composition according to claim 1 wherein said micronized terfenadine is present at about 2 to about 10 parts by weight, said spray-dried sorbitol is present at about 25 to about 35 parts by weight and said block copolymer is present at about 1 to about 5 parts by weight.

3. The composition according to claim 1 wherein said polyvinylpyrrolidone is present at a weight ratio relative to said spray-dried sorbitol of about 1:10 to about 1:4.

4. The composition according to claim 1 wherein said microcrystalline cellulose mixture is present at a weight ratio relative to said sorbitol of about 1:20 to about 1:8.

5. The composition according to claim 1 wherein said flavorant powder comprises up to about 60 weight percent of said composition.

6. The composition according to claim 5 wherein said flavorant includes a sweetener.

7. A dry, powdered terfenadine composition that comprises

(a) a mixture of:

(i) about 2 to about 10 parts by weight micronized terfenadine and

(ii) about 1 to about 5 parts by weight a polyethylene oxide-polypropylene oxide-polyethylene oxide block copolymer having an HLB number of 24 that is a wetting agent for said terfenadine;

that are dry-blendedly dispersed into:

(b) about 25 to about 35 parts by weight spray-dried sorbitol particles that are loosely packed, randomly oriented filamentary crystals having pores that entrap said terfenadine particles and wetting agent upon said dry-blended dispersal, said components being further dry blended with

(c) about 3 to about 7 parts by weight dry polyvinylpyrrolidone;

(d) about 2 to about 4 parts by weight dry microcrystalline cellulose mixture that contains about 7 to about 20 weight percent sodium carboxymethylcellulose; and

(e) about 40 to about 60 parts by weight of a dry flavorant in an amount sufficient to provide a desired taste to said powder, said flavorant including a sweetener;

said composition being a free-flowing powder that is substantially free from the taste of solubilized terfenadine when placed on the human tongue in dry form or when dispersed in water and tasted within about five minutes of said dispersal.

8. The composition according to claim 7 in unit dosage form in a package containing an antihistaminic dose of terfenadine.

* * * * *

2020
Bogotá, D.C.,

Doctor:
Carlos Olarte García
Apoderado

Oficio N°: 4290

ASUNTO:

Radicación PCT N°	04-56453
Trámite	011
Evento	379
Actuación	440
Folios	010

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

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

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


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

El anterior requerimiento fue notificado por fijación en lista de fecha 21 ABR 2006.

202021

Reino Copier Hasboks -
21-Apr-2008 -
Frederick H. Tong