4
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Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04009302 04009303 Folios 73
Fecha (AMD) : 2005-12-19 16:18:07
Tramite : 811 PCT-PATENT 379 PAGE MAIL 400 OPOSICION
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE OPOSICIÓN

① OPOSICIÓN A :

- [X] Patente de Invención.
- [ ] Patente de Modelo de Utilidad.
- [ ] Diseño Industrial.
- [ ] Esquema de Trazado para Circuitos Integrados.
- [ ] Marcas de Productos o Servicios.
- [ ] Marca Colectiva.
- [ ] Marca de Certificación.
- [ ] Lema Comercial.

② SOLICITUD PUBLICADA

Número del expediente: 04-009302
Solicitante: PHARMACIA CORPORATION
Apoderado: RAMIRO CASTRO DUQUE
Título de la nueva creación o denominación del signo: FORMULACION DE SUSPENSIÒN ORAL ESTABILIZADA
Gaceta: 556

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: PROCAPS S.A. Dirección: CALLE 80 No. 78b-201 Nacionalidad o Domicilio: COLOMBIA Lugar de Constitucion: BARRANQUILLA Teléfono: 371 99 00 Fax: 373 08 18 E-mail:	**IDENTIFICACIÓN** C.C. [ ] NIT [X] C.E. [ ] Otro [ ] Cual ____ Número 890.106.527-5
REPRESENTANTE O APODERADO	Nombre: REINALDO PINILLA MORENO Dirección: TRNSVERSAL 13 A N°. 119-95 OFICINA 104 Teléfono: 613 34 18 Fax: 24 47 87 E-mail: negocios@optimum-co.com	**IDENTIFICACIÓN** C.C. [X] NIT [ ] C.E. [ ] Otro [ ] Cual ____ Numero 79.532.186 TP 113438

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".

2000-F04

247

⑤. Comprobante de pago No. _____ Fecha _____

⑥ ANEXOS

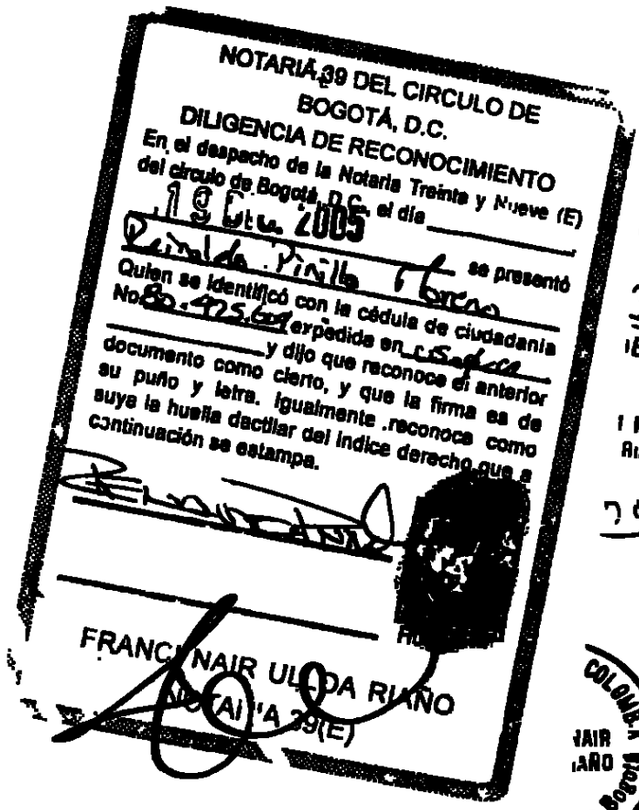
- [x] Comprobante de pago de la tasa.
- [x] Poderes. si fuere el caso.
- [x] Pruebas de los fundamentos de la oposición.
- [ ] Documentos que acrediten el legítimo interés. si fuere el caso.
- [x] Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

⑦

NOMBRE: REINALDO PINILLA MORENO

FIRMA: _____

C.C. 80.425.609 **TP.** 91563 CSJ


NOTARÍA 39 DEL CIRCULO DE BOGOTÁ, D.C.
DILIGENCIA DE RECONOCIMIENTO
En el despacho de la Notaria Treinta y Nueve (E) del circulo de Bogotá, D.C. el dia 18 Oct. 2005
Reinaldo Pinilla Moreno se presentó
Quien se identificó con la cédula de ciudadania No 80.425.609 expedida en Bogotá
y dijo que reconoce el anterior documento como cierto, y que la firma es de su puño y letra. Igualmente .reconoce como suya la huella dactilar del índice derecho que a continuación se estampa.
FRANCY NAIR ULLOA RIAÑO
NOTARIA 39(E)

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

Optimum

Derecho de la Competencia, Propiedad
Industrial y Comerci Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia	: Expediente N° 04-009.302
Asunto	: Oposición a la solicitud de patente de Invención titulada "FORMULACIÓN DE SUSPENSIÓN ORAL ESTABILIZADA.".
Solicitante	: PHARMACIA CORPORATION.
Opositora	:PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 556 del 30 de Septiembre 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 ***"FORMULACIÓN DE SUSPENSIÓN ORAL ESTABILIZADA"*** de ***PHARMACIA CORPORATION.***, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

Calle 119 A N° 53-99 Tel. (571) 6 13 34 16 – 6 13 33 74 – Fax. (571) 6 24 47 87
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

1. INTERÉS PARA ACTUAR

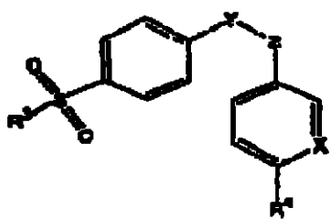
Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada debido a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida atentaría directamente a la comercialización que pretende mi representada, en materia de Celecoxib 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 25 de noviembre de 2002, reivindicando prioridad bajo la solicitud US60/310.372 del 2001-08-06 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial Nº 556 del 30 de Septiembre de 2005, página 473, Nº publicación 559, cuya publicación internacional corresponde a la WO03013473 del 2003-02-20.

2.2. La solicitud colombiana 04-009.302 objeto de la presente oposición, se refiere a una composición farmacéutica físicamente estable, tixotrópica, que comprende una droga de baja solubilidad en agua, para administrar en forma oral y un vehículo líquido acuoso que comprende (a) un agente humectante aceptable para uso farmacéutico, (b) un agente espesante tixotrópico aceptable para uso farmacéutico presente en una cantidad tixitrópica de por lo menos aproximadamente 0,25%, y (c) un agente de suspensión inorgánico aceptable para uso farmacéutico, donde la

droga inhibidora selectiva de ciclooxigenasa-2 es un compuesto de fórmula:



donde R^3 es un grupo metilo o amino, R^4 es hidrógeno o un grupo alquilo C_{1-4} o alcoxi, X es N o CR^5 donde R^5 es hidrógeno o halógeno e Y y Z son independientemente átomos de carbono o nitrógeno que definen átomos adyacentes de un anillo de entre cinco y seis miembros, que no está constituido o está constituido en una o más posiciones con grupos oxo, halo, metilo o halometilo. Adicionalmente, la solicitud se refiere a un método para aumentar la estabilidad física de una composición farmacéutica acuosa, tixotrópica de una droga de baja solubilidad en agua, donde el método comprende agregar a la composición un agente espesante tixotrópico aceptable para uso farmacéutico en una cantidad tixotrópica de por lo menos aproximadamente 0,25%, y un agente de suspensión inorgánico aceptable para uso farmacéutico en cantidades que actúan en forma sinergética para aumentar la estabilidad física de la composición.

2.3. Por su 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: WO9320798, 1993-10-26.

- D2: WO9108734, 1991-06-27
- D3: EP0257288, 1988-03-02

2.4. Ahora bien, el documento D1, particularmente en el resumen y en la descripción, que se refiere a suspensiones orales que comprenden un fármaco de baja solubilidad, un polisorbato, goma xantan y dioxido de silicio en la página 10 tabla 1 y pagina 12 tabla 3. Dichas suspensiones son estables por un periodo de tiempo prolongado según se indican en la página 2 líneas 21 a 29. Para dicho documento D1, la cantidad usada del agente tixotrópico está entre 0.02 y 0.1%. Según se expone, la combinación de goma xantan y un dioxido coloide es conocido y su uso en composiciones tixotrópicas es ampliamente divulgado y se considera que es la base experimental estándar para llegar al un viscosidad especifica. Así las cosas, es claro que este documento D1, revela una misma propuesta como solución que incluye un vehículo acuoso que comprende un agente espesante tixotrópico. Por lo tanto, a los ojos de este documento D1, la presente solicitud no comprende altura o nivel inventivo.

2.5. Por su parte, el documento D2, particularmente en el resumen, página 1 parágrafo 2; pagina 3 líneas 11 a 12 y último párrafo hasta la página 4 primer párrafo; y, ejemplo 10, se revelan una suspensión líquida anhídrida de base aceitosa para liberación de un medicamento donde se referencia la función de los agentes necesarios para suspender el fármaco uniformemente en vehículos de base aceitosa para dosis uniformes. Para ello, dicho documento D2 revela variedad de agentes de suspensión para uso farmacéutico. De hecho se especifica una formulación que comprende un agente de suspensión en el ejemplo 10. Como se nota, es ampliamente conocido el hecho de utilizar un agente de suspensión para aumentar

la estabilidad física de una composición farmacéutica. Por lo tanto, este documento objeto de oposición a la luz del documento D2, carece de altura o nivel inventivo.

2.6. Por su parte, el documento D3 según el resumen y su descripción, revela un jarabe líquido estable que comprende ibuprofeno en suspensión, bentonita y PVP según las páginas 28 a 44 y en el ejemplo 3. La viscosidad de reivindicada en el rango de 1 a 3 Pascales por segundo. Así las cosas, este documento D3 revela con anterioridad agentes estabilizantes tales como la bentonita que provee funciones de ayuda en la dispersión y la suspensión de partículas de ibuprofeno y formando una protección molecular en cubiertas delgadas alrededor de cada partícula del fármaco en suspensión. Obviamente ello proporciona una estabilidad física dado que la bentonita es un agente tixotrópico. Por lo tanto, es claro que este documento D3, revela una misma propuesta como solución que incluye un vehículo acuoso que comprende un agente espesante y de suspensión. Por lo tanto, a los ojos de este documento D3, la presente solicitud no es novedosa.

2.7. Ahora bien, cualquier persona versada en la materia, pues de deducir de manera evidente, con base en lo revelado en los documentos D1, D2 y D3 en combinación, el objeto de aumentar la estabilidad física de una composición farmacéutica acuosa que comprende un agente humectante; un agente espesante; y, un agente de suspensión. Por lo tanto, a los ojos de los documentos D1, D2 y D3 en combinación, la presente solicitud carece de altura o nivel inventivo.

2.8. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana **04-009302** no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

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

Calle 119 A Nº 53-99. Tel. (571) 6 13 34 18 - 6 13 33 74 - Fax. (571) 6 24 47 87
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

2.9.1. 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, 06 de marzo de 2001, ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D3, revela una misma propuesta como solución que incluye un vehículo acuoso que comprende un agente espesante y de suspensión, sobre el cual busca protección en el capítulo reivindicatorio.

2.9.2. 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, 06 de marzo de 2001, a partir de los documentos D1, D2, y D3 en combinación, es posible deducir una misma propuesta como solución que incluye un vehículo acuoso que comprende un agente espesante tixotrópico; un agente de suspensión y un agente humectante, según lo definido en las reivindicaciones de la presente solicitud.

2.10. 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 dos de los tres requisitos de patentabilidad.

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

2.12. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada ***"FORMULACIÓN DE SUSPENSIÓN ORAL ESTABILIZADA"*** de ***PHARMACIA CORPORATION.***, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 556.

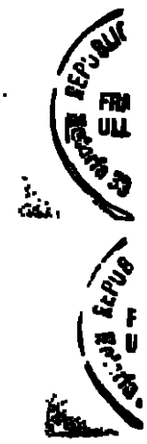
3. PRUEBAS

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

- D1: WO9320798, 1993-10-28.
- D2: WO9108734, 1991-06-27
- D3: EP0257288, 1988-03-02

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:



Numeral 1 del artículo 581 del Código de Comercio.

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: WO9320798, 1993-10-28.
- D2: WO9108734, 1991-06-27
- D3: EP0257288, 1988-03-02

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 Nº 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[2]

El Notario Treinta y Nueve (E) de Bogotá, da fé que el anterior escrito dirigido a: División de Hurtos Creaciones
fué presentado personalmente por: Reinaldo Pinilla Moreno
quien exhibió la C.C. No. 80.425.614 de Usaquén
y T.P. No. _____ y manifestó que la firma y huella que aparecen en el presente documento son suyas, y que acepta el contenido del mismo.

FIRMA

19 DIC. 2005

FRANCI NAIR ULLOA PRIAÑO
NOTARIA 39 (E)

PROCAPS

256

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. 04-09302, de título: **"FORMULACIÓN DE SUSPENSIÓN ORAL ESTABILIZADA"**, publicada en la gaceta No. 556 del 30 de septiembre 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.

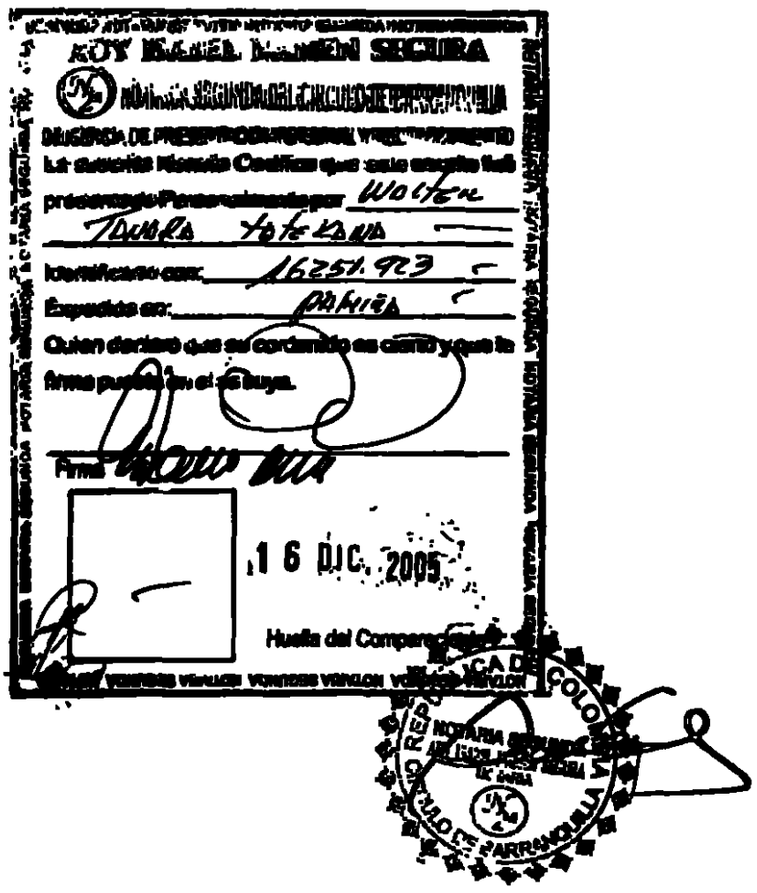
De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 12 días del mes de diciembre de 2005.

PROCAPS S.A.
WALTER TANAKA TATEKAWA
C.C. Nº 16.251.923 de Palmira
Representante Legal

Acepto,

REINALDO PINILLA MORENO
C.C. 80'425.609 de Bogotá
T.P.A. 91563 del C.S. de la J.


NOTARIA SEGUNDA DEL CIRCULO DE BARRANQUILLA

DILIGENCIA DE PRESENTACION PERSONAL Y RECONOCIMIENTO

La suscrita Notaria Certifica que: este escrito fué presentado Personalmente por Wolfen Tomás Hoffmann

Identificado con: 16251.923

Expedida en: Barranquilla

Quien declaró que su contenido es cierto y que la firma puesta en el es suya.

Firma

16 DIC. 2005

Huella del Compareciente

REPUBLICA DE COLOMBIA
NOTARIA SEGUNDA
DEL CIRCULO DE BARRANQUILLA

CAMARA DE COMERCIO DE BARRANQUILLA

********** Pag. 1

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A

07**********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.----------

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, torgada 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, t rgada 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 s cial 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

Que por Escritura Pública No. 3.615 del 06 de Dic/bre de 1996, t rgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comerci , el 20 de Dic/bre de 1996 bajo el No. 67.218 del libro respectivo, la s ciedad antes mencionada----------
cambi de raz n social, por la denominaci n LABORATORIOS PROCAPS S.A

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

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

PROCAPS S.A.----------

C E R T I F I C A

Que por Escritura Pública No. 3.775 del 18 de Dic/bre de 1996, torgada 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----------
cambi 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.
MATRICULA MERCANTIL: 24.802.

C E R T I F I C A

Direcci n para notificaciones judiciales:
CL 80 No 78 B - 201.
De la ciudad de Barranquilla.

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

CAMARA DE COMERCIO DE BARRANQUILLA

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
07**********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
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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 l s 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 dis-distribucion de dulces, confites, galletas y todo tipo de g l sinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionacionales y extranjeras en la realizacion de operaciones o transacci nes relacionadas con la industria farmaceutica y en especial c n cualquiera de las actividades descritas en los literales a), b), c). d) y e) antes descritos; g) Prestar los servici s de ases ria y consultoria en las areas administrativas, de mercade , analisis clinico, asistencia tecnica, investigacion, c st s 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 industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titul , empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objet principal, la sociedad podra tomar interes social como accionista, s ci o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuest s requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las peraciones comerciales que celebre c n terceros relativas a su objeto; celebrar y ejecutar todo

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

PROCAPS S.A.----------

tipo de act s y contratos necesarios para desarrollar sus peraciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravamenes sobre bienes muebles e inmuebles; designar representantes apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarroll 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 gravamenes reales s bre sus bienes de cualquier naturaleza.----------

C E R T I F I C A

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

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad c rresponderа 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 superi r 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 s cios, se requerira que la operacion sea aprobada con el voto de por l menos 2/3 partes de los integrantes de la Junta Directiva.
La s ciedad 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 c n lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunt judicial. Aprobar y celebrar en nombre de la socieda todo act 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 c rrespondan como Representante Legal por disposicion de la ley, de est s estatutos o de la Junta Directiva. El Presidente tendra un

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

CAMARA DE COMERCIO DE BARRANQUILLA

CAMARA DE COMERCIO
DE BARRANQUILLA

07**********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
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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 separadamente con el Presidente. El vicepresidente tendra las siguentes 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 interrogat ri s 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 cient cincuenta mil dolares de los Estados Unidos de America (US$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fij de la sociedad, inclusive de naturaleza muebles, acci nes, cu tas o partes de interes inversiones y todo tipo de derech s de la sociedad, o de constituir gravamenes sobre cualquiera de l s anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junra Directiva, quien lo reemplazara conjunta separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesari para ell 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 gerente general, llevaran la representacion legal de la sociedad, c n 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 s ciedad, en todos los actos y contratos que se requieran para el desarroll del objeto social, de conformidad c n lo previsto en las leyes y en l s presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto c ntrat cuya cuantia sea igual inferior

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

al equivalente en pesos Colombianos a Cincuenta Mil dolares de l s Estados Unidos de America (US$50.000), liquidados a la tasa de cambi 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 fij de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad de constituir gravamenes sobre cualquiera de las anteri res 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 Comerci , 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
2. Minski Gontovnik Meyer
3. Minski Gontovnik Jose

Suplentes
1. Minski Zilberblum Elliot
2. Minski Deitel Daniel
3. Minski Sharon

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 Comerci , el 15 de Agosto de 1997 bajo el No. 70.838 del libro respectivo, 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 O N T I N U A **********

No. 9808108

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CAMARA DE COMERCIO
DE BARRANQUILLA

07**********

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

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

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

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

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Que por escritura publica N . 2.608 del 5 de Octubre del 2.001, t rgada 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 continuaci n se indican en razon de su cargo en la sociedad: 1.-Se c n fiere Poder Especial, Amplio y Suficiente a los senores: WALTER TANAKA TATEKAWA, C.C. No. 16.251.923; WILIIAM 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 solicitudes de informacion de las autoridades tributarias, aduaneras o cambiarias,en los ordenes Distrital, Departamental y Nacional. 2.-Se confiere Poder Especial,amplio y suficiente,a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancias y servicios con entidades oficiales, hasta por la suma de US$800.000.oo (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. GUPO A: GUILLERMO LUIS URIBE OCHO C.C. No. 70.073. 754, LINO LAZALA SILVA VARGAS C.C. No. 19.260.410, JAIRO MOLINA MEJIA C.C. No. 8.706.380, CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.-293. BRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, HENRY CARO DIAZ C.C. No. 19.395.298, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZGRANADOS C.C. No. 22.377.540. Para el ejercici de estas facultades se requerira por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C.C. No. 33.138.497, a la D ctora MARCELA CARVAJALINO PAGANO C.C. No. 22.579.748, y al Doct r 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 notificaci nes,interponer recursos y ejercer acciones contencioso administrativas y de tutela,transigir,conciliar,recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato. Para la celebraci n 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 s ciedad. 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 document privado de fecha 7 de junio de 2000, inscrito en esta Camara de Comercio el 8 de juni de 2000, bajo el No.1.786

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
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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 Exteri r y/ 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 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 suscribrir en el giro normal de sus negocios y operaciones s ciales. Por lo anterior, el senor ANTONIO VARELA DIAZ, queda facultado para firmar las declaraciones comabiarias y demas documentos relaci nados con las declaraciones, notificaciones, aportar y solicitar las pruebas que sean necesarias, desistir en general a realizar t do act necesario de tal forma que pueda cumplir con el mandato dado.-

C E R T I F I C A

Que segun document privado del 22 de Febrero de 2005, inscrit en

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

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

PROCAPS S.A.----------

esta Camara de Comerci 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 senor MARLON TATIS PAREDES C.C. No. 72.176.874, para que en representaci n 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 tod tipo de requerimientos y/o solicitudes de informacion de las aut ridades 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, torgada 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 mercancias 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 dia 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.------.

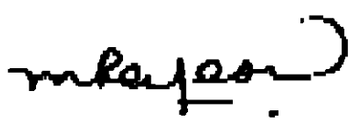
C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteri res de documentos referentes a reforma, disolución, liquidación 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.

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



PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
A61K 9/00, 9/16, 9/51	A1	WO 93/20798
		(43) International Publication Date: 28 October 1993 (28.10.93)

(21) International Application Number: PCT/US92/03220

(22) International Filing Date: 20 April 1992 (20.04.92)

(71) Applicant: RIKER LABORATORIES, INC. [US/US]; 3M Center, P.O. Box 33427, Saint Paul, MN 55133-3427 (US).

(72) Inventors: BEAURLINE, Joseph, M. ; P.O. Box 33427, Saint Paul, MN 55133-3427 (US). BERGE, Stephen, M. ; P.O.Box 33427, Saint Paul, MN 55133-3427 (US). SCHULTZ, Robert, K. ; P.O. Box 33427, Saint Paul, MN 55133-3427 (US).

(74) Agents: REEDICH, Douglas, R. et al.; Minnesota Mining and Manufacturing Company, Office of Intellectual Property Counsel, Post Office Box 33427, Saint Paul, MN 55133-3427 (US).

(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE).

Published
With international search report.

(54) Title: ORAL SUSPENSION FORMULATION

(57) Abstract

An aqueous suspension for oral administration of a drug, which suspension is storage stable for a prolonged period and maintains the drug in suspension during such period.

ORAL SUSPENSION FORMULATION

BACKGROUND OF THE INVENTION

Field of the Invention

This invention pertains to pharmaceutical liquid suspension formulations suitable for oral administration In another aspect, it pertains to sustained release suspensions. In yet another aspect, this invention pertains to theophylline formulations.

Description of Related Art

Theophylline is an antiasthmatic drug with a narrow therapeutic window. It is available in a number of different dosage forms including conventional tablets, sustained release tablets, elixirs and suspensions. The currently available suspensions settle to the bottom of the container upon standing for several days. If the container is not shaken adequately, the contents will not resuspend in a uniform fashion and the amount of theophylline present per dose will vary.

European Patent Application 0,101,418 (Kallstrand et al.) discloses what is said to be a controlled release pharmaceutical mixture which masks bad taste and increases stability of an active substance, characterized in that an encapsulated active substance is combined with a substance controlling the release of the active substance. The release-controlling substance is a carbohydrate or a carbohydrate-related material and microencapsulated theophylline is among the enumerated actives.

UK Pat. No. GB 2166651B discloses a suspension of pharmasomes containing theophylline. The suspension vehicle consists of (by weight): 85.3% 70% sorbitol solution, 0.7% Avicel RC 591, 0.3% potassium sorbate, 2.7% of a solution containing titanium dioxide 25% in 70% sorbitol, 0.01% simethicone 10% emulsion,

10.8% glycerine, 0.3% citric acid and 0.04% sodium lauryl sulphate.

SUMMARY OF THE INVENTION

This invention provides an aqueous pharmaceutical suspension for oral administration which suspension, based on the total weight of the suspension, comprises from about 0.1 to 15 percent by weight of a particulate medicament with an average particle size of less than about 150 μm; about 0.02 percent to about 5 percent by weight of a pharmaceutically acceptable wetting agent; about 0.02 to about 0.10 percent by weight of a hydrocolloid gum; about 0.2 to about 2.0 percent by weight of colloidal silicon dioxide; about 0.1 to 0.3 percent by weight of an antifoaming agent; a carbohydrate which is dissolved in the suspension; and water; the suspension being further characterized in that the medicament remains suspended uniformly for a period of at least about 90 days when tested according to the Test Method.

Due to the presence of the hydrocolloid gum and the colloidal silicon dioxide, the suspension of the invention maintains the medicament in suspension for a prolonged period of time without shaking. The amount of medicament therefore remains uniform from dose to dose during this period. Dosage uniformity is of particular importance when the medicament comprises a drug with a narrow therapeutic window such as theophylline.

In a preferred embodiment, the medicament is in the form of a controlled release polymeric particle comprising a drug, which drug is dispersed throughout the polymeric particle.

DETAILED DESCRIPTION OF THE INVENTION

A suspension of the invention contains from about 0.02 percent to about 5 percent, preferably from

about 0.1 to about 0.8 percent, by weight of a pharmaceutically acceptable wetting agent based on the total weight of the suspension. If the wetting agent is a solid, it is soluble in the suspending medium. The choice of wetting agent can influence the in vitro release rate of a controlled-release particulate medicament. Preferred wetting agents include sorbitan monolaurate, polysorbate 21, sodium lauryl sulfate and sorbitan monolaurate in combination with polysorbate 20. The most preferred wetting agent is a 4:1 sorbitan monolaurate:polysorbate 20 combination.

A hydrocolloid gum in combination with colloidal silicon dioxide serves as a suspending agent. The gum is present in an amount of from about 0.02 to about 0.10 percent, preferably 0.04 to about 0.08 percent by weight based on the total weight of the suspension. The gum can be, e.g., guar gum, locust bean gum, gum tragacanth, xanthan gum, and the like. Xanthan gum is preferred. The colloidal silicon dioxide is present in an amount of from about 0.2 to 2.0 percent, preferably 0.2 to about 0.8 percent, and more preferably 0.4 to about 0.7 percent by weight based on the total weight of the suspension. Colloidal silicon dioxide is available from DeGussa under the trade designation Aerosil™ or under the trade designation Cab-O-Sil™. A preferred colloidal silicon dioxide is Aerosil™ 200 brand colloidal silicon dioxide.

A suspension of the invention also comprises from about 0.1 to about 0.3 percent by weight based on the total weight of the suspension of a conventional antifoaming agent which is preferably simethicone emulsion.

The suspension further comprises a carbohydrate and water. As is conventional, for a given volume f water used, the carbohydrate is

preferably present in the suspension in an amount which binds substantially all of the free water in the suspension so that the solubility of the drug, whether in particulate form, microencapsulated, or dispersed throughout a polymeric particle, is minimized as a result of having minimized the solvent activity of the water contained in the suspension. Suitable suspending media include conventional syrups used in pharmaceutical suspensions. Preferred suspending media are selected from the group consisting of 70% sorbitol in water solution (w/v), simple syrup, and mixtures thereof. Simple syrup and 70% sorbitol in water solution (w/v) are described, e.g., in U.S.P. XXII, the disclosure of which is incorporated by reference herein. The most preferred suspending medium is a 1:1 mixture of 70% sorbitol:simple syrup.

A suspension of the invention can optionally further comprise from about 0.1 to about 1 percent by weight based on the total weight of the suspension of a pharmaceutically acceptable preservative. Preferred preservatives include sodium benzoate, methyl paraben, propyl paraben, potassium sorbate, potassium sorbate in combination with citric acid, and mixtures thereof. Commercially available Simple Syrup, N.F. contains a suitable preservative, e.g., 0.1% sodium benzoate.

A suspension of the invention can optionally further comprise from about 3 to about 5 percent by weight based on the total weight of the suspension of a pharmaceutically acceptable dispersing aid such as propylene glycol or preferably glycerin.

A suspension of the invention can optionally further comprise a pharmaceutically acceptable flavoring agent.

A suspension of the invention can also optionally further comprise a pharmaceutically acceptable dye.

A suspension of the invention comprises from about 0.1 to about 15 percent, preferably from about 1 to 10 percent, and most preferably from about 2 to about 7 percent, by weight based on the total weight of the suspension of a particulate medicament with an average particle size of less than about 150 μm, preferably between about 50 μm and about 125 μm.

The medicament can be employed as is in particulate form.

Alternatively, the particulate drug can be microencapsulated using, for example, a conventional material such as hydroxypropyl cellulose, beeswax, hydrogenated castor oil, hydrogenated vegetable oil, hydrogenated tallow, glyceryl stearate, glyceryl palmito stearate, or the like.

Still alternatively and preferably, the medicament is in the form of an active ingredient dispersed throughout a polymeric particle. Preferred polymeric particles contain an active ingredient (e.g., a drug) and optionally an excipient in intimate admixture with at least one non-toxic polymer, with the active ingredient and the excipient, if present, substantially uniformly distributed throughout the polymeric particle. The particles have an average size of between 0.1 and 125 μm and have a predetermined release of active ingredient when the dissolution thereof is measured according to the Paddle Method of U.S. Pharmacopoeia XXII. The dissolution rate of the particles is substantially proportional to the square root of time.

Non-toxic polymers useful in preparing polymeric particles are alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, polymers of acrylic and methacrylic acids and esters thereof, polyamides, polycarbonates, polyalkylenes, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl

alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes and polyurethanes and copolymers thereof.

Most drugs can be prepared in suitable form and are thus suitable for use in suspensions of the invention. The drug can, for example, be an antiallergic, antiinflammatory, antihistamine, antitussive, antibiotic, antiarrhythmic, vasodilator, psychotropic, analgesic, anticonvulsant, bronchodilator, antiasthmatic, antibacterial, antihypertensive or a mixture thereof. A particularly preferred drug is theophylline.

The optional excipient used in association with the drug can affect the release of the drug. For example, the excipient can be a surfactant that facilitates the transport of water into a polymeric particle. It can be an organic acid that facilitates the dissolution of active ingredients that are poorly soluble in alkaline media. It can be a base that facilitates the dissolution of active ingredients that are poorly soluble in acidic media.

A stable, uniform sustained-release theophylline suspension of the invention is suitable for oral administration and, based on the total weight of the suspension, comprises from about 0.1 to about 15 percent by weight of polymeric particles comprising theophylline.

The most preferred non-toxic polymer for the preparation of polymeric particles containing theophylline is cellulose acetate butyrate. Suitable particles comprising theophylline and methods of preparation therefor are disclosed in UK Patent GB 2166651B. Example 1 of said patent discloses a method by which suitable particles may be made. Other methods for preparing suitable particles are also disclosed in said patent.

The amount of drug in the particles can be varied as desired, e.g., to affect the amount of particles required for an effective dose or to affect the release profile of the particles. Preferred theophylline suspensions of the invention contain from about 100 to about 300 mg of theophylline per 5 mL of suspension.

Suspensions of the invention can be prepared by first blending together the suspension medium, the hydrocolloid gum, the colloidal silicon dioxide, the preservative, if any, and the dispersing aid, if any. The polymeric particles, wetting agent and antifoaming agent can then be combined to give a concentrate. This concentrate can then be combined with the previously prepared blend. The suspensions of the invention can be prepared using conventional vacuum or non-vacuum liquid processors. They are preferably prepared in liquid vacuum processors such as the VME™ brand mixer (available from Fryma Inc.) and the Unimix™ brand mixer (available from Haagen & Rinao Mischtechnik GmbH). It is particularly desirable to use liquid vacuum processors when the suspensions being prepared contain a low level of suspending agent, i.e., less than 0.04% hydrocolloid gum and/or less than 0.4 % colloidal silicon dioxide.

Prior to being used in the suspensions of the examples below, the polymeric particles to be used were analyzed for particle size, theophylline content and dissolution rate. The theophylline content was measured using conventional high-pressure liquid chromatography methodology. The dissolution rate was measured according to the Paddle Method of U.S. Pharmacopoeia XXII.

The polymeric particles used to prepare the suspensions of Examples 1, 2 and 3 below had the following characteristics: the polymer used was

cellulose butyrate acetate, 99.8% passed through a 125 μm screen, they contained 532 mg of theophylline per gram of polymeric particles, and the dissolution rate was 36.2% at 1 hour, 72.1% at 4 hours and 98.3 % at 12 hours.

Test Method for Suspension Uniformity

A suspension of the invention is capable of maintaining the medicament in suspension so that the top and bottom medicament concentrations are within ± 10% when maintained at 40°C. for at least about 90 days, preferably at least about 120 days, and most preferably at least about 180 days without shaking at any point during the test period.

Top and bottom medicament concentrations are determined according to the following procedure.

This test is done using a 225 mL bottle which contains 200 mL volume of suspension. A 5 or 10 mL polypropylene syringe with a 12 or 14 gauge 6 inch needle is used and the needle is marked such that it will penetrate the suspension 1/2 inch. The needle is placed 1/2 inch into the top of the suspension and 5 mL is drawn. The needle is removed from the syringe, the plunger is pulled back to allow for headspace, the syringe is shaken until well mixed, and 3 mL of the sample is discarded. The end of the syringe is capped. For bottom sampling, another 5 or 10 mL polypropylene syringe with a 12 or 14 gauge, 6 inch needle is used. The needle is placed all the way to the bottom of the bottle and 5 mL is drawn. The needle is removed, the plunger is pulled back to allow for headspace, the syringe is shaken until well mixed and 3 mL of the sample is discarded. The end of syringe is capped. A known weight from the 2 mL of the sample is analyzed for drug content.

This Test Method for Suspension Uniformity is referred to as the "Test Method" in the instant specification and claims.

The following examples are provided to illustrate the invention and are not intended to be limiting thereof.

Example 1

Simple syrup (29,763.11 g), 29,763.11 g of 70% sorbitol and 130.0 g of potassium sorbate were placed in a Unimix™ brand mixer then blended and homogenized under vacuum until all of the potassium sorbate was dissolved. The citric acid (227.5 g) was added and blended. The glycerin (2,600.0 g) and 39.0 g of xanthan gum were placed in a stainless steel beaker and mixed with a spatula until homogeneous. The glycerin/xanthan gum dispersion was added to the blend in the mixer and blended and homogenized under vacuum. Aerosil™ 200 brand colloidal silicon dioxide was added and then blended and homogenized under vacuum. Theophylline polymeric particles (1,794.0 g), 26.0 g of sorbitan monolaurate, 104.0 g polysorbate 20, 130.0 g simethicone emulsion, 32.5 g of cherry flavor, and about 400 g of the blend from the mixer were placed in a stainless steel beaker and blended to give a paste. This paste and 0.78 g of Red #40 FD&C were added to the remainder of the blend in the mixer and blended under vacuum until homogeneous. The resulting suspension contained 100 mg of theophylline per 5 ml of suspension and had the composition shown in Table 1. Dissolution data are shown in Table 2.

TABLE 1

Ingredient (%w/w)	Example 1	2	3
Simple syrup	45.79	45.76	44.42
70% Sorbitol solution	45.79	45.76	44.42
Potassium sorbate	0.20	0.20	0.20
Citric acid	0.35	0.35	0.35
Xanthan gum	0.06	0.06	0.06
Glycerin	4.00	4.00	4.00
Silicon dioxide	0.60	0.60	0.60
Red #40 FD&C	0.0012	0.0012	-
Sorbitan monolaurate	0.04	0.04	0.04
Polysorbate 20	0.16	0.16	0.16
Simethicone emulsion	0.20	0.20	0.20
Theophylline Polymeric Particles	2.76	2.76	5.52
Cherry flavor	0.05	-	-
Strawberry flavor	-	0.10	-
Mint flavor	-	-	0.025

TABLE 2

	% Release						
Time (min)	30	60	120	240	360	720	1200
Example 1	28.5	38.5	50.9	65.0	74.3	89.3	96.2
Example 2	30.9	40.9	53.0	67.2	76.8	92.0	98.2

Example 2

Using the general method of Example 1, a suspension containing 100 mg of theophylline per 5 ml of suspension and having the composition shown in Table 1 was prepared. Dissolution data are shown in Table 2 above.

Example 3

Using the general method of Example 1, a suspension containing 200 mg of theophylline per 5 ml of suspension and having the composition shown in Table 1 above was prepared. The general method of this Example was repeated except that 44.4075 weight percent of each of the simple syrup and sorbitol solution were used and 0.05 weight percent of cherry flavor was substituted for the mint flavor.

Example 4

Simple syrup (2843.7 g) and 70% sorbitol in water solution (2843.7 g) were blended in a glass beaker. Citric acid (21.0 g) was added and the mixture was stirred until the citric acid was dissolved. Potassium sorbate (12.0 g) was added and the mixture was blended for about 10 minutes. A dispersion of xanthan gum (3.6 g) and glycerin (240 g) was prepared, added to the mixture, and blended for about 15 minutes in a Gifford-Wood homogenizer. Colloidal silicon dioxide (36.0 g of Aerosil™ 200 brand colloidal silicon dioxide) was added and homogenization was continued for about 15 minutes to provide a vehicle. A concentrate was prepared by mixing salicylsalicylic acid powder with a particle size of less than 125 μm (14.0 g), simethicone emulsion (0.97 g), vehicle as prepared above (50 g), and an 80/20 (w/w) blend of Tween™ 20 brand polysorbate 20 and Span™ 20 brand sorbitan monolaurate (0.97 g) in a mortar. The concentrate was then blended into the vehicle as prepared above (417 g) and homogenized to afford the suspension of Example 4 with the composition shown in Table 3.

TABLE 3

Ingredient	% w/w
Salicylsalicylic acid	2.90
Ethyl cellulose-coated salicylsalicylic acid	---
Silicon dioxide	0.58
Xanthan gum	0.06
potassium sorbate	0.19
simethicone emulsion	0.20
glycerin (99%)	3.87
citric acid	0.34
70% sorbitol	45.83
simple syrup	45.83
Span/Tween	0.20

WHAT IS CLAIMED IS:

1. An aqueous pharmaceutical suspension for oral administration which suspension, based on the total weight of the suspension, comprises from about 0.1 to 15 percent by weight of a particulate medicament with an average particle size of less than about 150 μm; about 0.02 percent to about 5 percent by weight of a pharmaceutically acceptable wetting agent; about 0.02 to about 0.10 percent by weight of a hydrocolloid gum; about 0.2 to about 2.0 percent by weight of colloidal silicon dioxide; about 0.1 to 0.3 percent by weight of an antifoaming agent; a carbohydrate which is dissolved in the suspension; and water; the suspension being further characterized in that the medicament remains suspended uniformly for a period of at least about 90 days when tested according to the Test Method.

2. A suspension according to Claim 1, wherein the hydrocolloid gum is xanthan gum.

3. A suspension according to Claim 1, wherein the colloidal silicon dioxide is present in an amount of between about 0.2 to about 0.8 percent by weight based on the total weight of the suspension.

4. A suspension according to Claim 1, wherein the particulate medicament has an average particle size of between about 50 μm and about 125 μm.

5. A suspension according to Claim 1, wherein the medicament is present in an amount of from about 1 to about 10 percent by weight based on the total weight of the suspension.

6. A suspension according to Claim 5, wherein the medicament is present in an amount of from about 2 to about 7 percent by weight based on the total weight of the suspension.

7. A suspension according to Claim 1, wherein the medicament is in the form of a microencapsulated drug.

8. A suspension according to Claim 1, wherein the medicament is in the form of controlled release polymeric particles comprising a drug and optionally an excipient in intimate admixture with at least one non-toxic polymer, with the drug and the excipient, if present, substantially uniformly distributed throughout the polymeric particle, and which particles have a predetermined release of the drug when the dissolution rate thereof is measured according to the Paddle Method of U.S. Pharmacopoeia XXII.

9. A suspension according to Claim 8, wherein the non-toxic polymer is selected from the group consisting of an alkyl cellulose, a hydroxyalkyl cellulose, a cellulose ether, a cellulose ester, a nitro cellulose, a polymer of acrylic and methacrylic acids and esters thereof, a polyamide, a polycarbonate, a polyalkylene, a polyalkylene glycol, a polyalkylene oxide, a polyalkylene terephthalate, a polyvinyl alcohol, a polyvinyl ether, a polyvinyl ester, a polyvinyl halide, a polyvinylpyrrolidone, a polyglycolide, a polysiloxane, and a polyurethane.

10. A suspension according to Claim 9, wherein the non-toxic polymer is cellulose acetate butyrate.

11. A suspension according to Claim 1, wherein the medicament comprises a drug selected from the group consisting of an antiallergic, an antiinflammatory, an antihistamine, an antitussive, an antibiotic, an antiarrhythmic, a vasodilator, a psychotropic, an analgesic, an anticonvulsant, a bronchdilator, an antiasthmatic, an antibacterial, an antihypertensive, and a mixture of any two or more of the foregoing thereof.

12. A suspension according to Claim 11, wherein the drug is theophylline.

13. A suspension according to Claim 1, wherein the carbohydrate is present in an amount that minimizes the solvent activity of the water contained in the suspension.

14. A suspension according to Claim 7, wherein the carbohydrate is present in an amount that minimizes the solvent activity of the water contained in the suspension.

15. A suspension according to Claim 8, wherein carbohydrate is present in an amount that minimizes the solvent activity of the water contained in the suspension.

16. A suspension according to Claim 1, further comprising from about 0.1 to 1 percent by weight based on the total weight of the suspension of a pharmaceutically acceptable preservative.

17. A suspension according to Claim 16, wherein the preservative is selected from the group consisting of sodium benzoate, methyl paraben, propyl paraben, potassium sorbate, potassium sorbate in combination with citric acid and mixtures thereof.

18. A suspension according to Claim 1, further comprising from about 3 to about 5 percent by weight based on the total weight of the suspension of a pharmaceutically acceptable dispersing aid.

19. A suspension according to Claim 18, wherein the dispersing aid is glycerin.

20. A suspension according to Claim 1, further comprising a pharmaceutically acceptable flavoring agent.

21. A suspension according to Claim 1, further comprising a pharmaceutically acceptable dye.

22. A suspension according to Claim 1, wherein the wetting agent is selected from the group consisting of sorbitan monolaurate, polysorbate 21, sodium lauryl sulfate, and sorbitan monolaurate in combination with polysorbate 20.

23. A suspension according to Claim 22, wherein the wetting agent is present in an amount of from about 0.1 to about 0.8 percent by weight based on the total weight of the suspension.

24. A suspension according to Claim 1, wherein the antifoaming agent is simethicone emulsion.

25. A suspension according to Claim 1, wherein the gum is present in an amount of from about 0.04 to about 0.08 percent by weight based on the total weight of the suspension.

26. A suspension according to Claim 1, wherein the colloidal silicon dioxide is present in an amount of from about 0.4 to about 0.7 percent by weight based on the total weight of the suspension.

27. A suspension according to Claim 1, wherein the medicament remains suspended uniformly for a period of at least about 90 days when tested according to the Test Method.

28. A suspension according to Claim 1, wherein the medicament remains suspended uniformly for a period of at least about 180 days when tested according to the Test Method.

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(54) Title: ANHYDROUS OIL-BASED LIQUID SUSPENSION FOR DELIVERING A MEDICAMENT

(57) Abstract

Oil-based non-aqueous liquid suspension drug delivery vehicles, suitable for the administration of drugs which are sensitive to water or which have an unpalatable taste comprise an edible oil, a sugar, and a suspending agent. The average particle size of all solid components of the formulation is 30 μ or less which results in formulations which have excellent physical stability including resistance to particle agglomeration, settling and caking.

ANHYDROUS OIL-BASED LIQUID SUSPENSION FOR DELIVERING A MEDICAMENT

Cross-Reference to Related Applications

This application is a continuation-in-part of copending application U.S. Serial No. 365,409 filed June 13, 1989 which is a continuation-in-part of U.S. Serial No. 227,559 filed August 4, 1988, now abandoned, which is a continuation-in-part of U.S. Serial No. 096,892 filed September 14, 1987, now abandoned.

Technical Field

This invention relates to liquid drug vehicles. More particularly, this invention concerns liquid oil-based drug vehicles having improved shelf life and stability.

Background of the Invention

Many useful drugs are available only in solid dosage forms (e.g. capsules and tablets), primarily because the drug is unstable in or incompatible with water. Drugs which are unstable in water cannot be formulated as water-based solutions or suspensions and these convenient dosage forms cannot be used, often leading to complaints among juvenile or elderly patients who have difficulty swallowing capsules or tablets. For example, clorazepate dipotassium (sold by Abbott Laboratories under the trade name of TRANXENE®) is one such drug that is not available in liquid form. Clorazepate dipotassium is a minor tranquilizer used for the management of anxiety disorders and for short-term relief of symptoms of anxiety. It is also used as adjunctive therapy in the management of partial seizures and in the symptomatic relief of acute alcohol withdrawal. A description of this drug and its method of manufacture is found in U.S. Patent No. Re. 28,315.

Vehicles for clorazepate dipotassium are unavailable in liquid form primarily because the drug has significant aqueous stability problems. In the presence of even minute quantities of moisture greater than about 0.3% w/v (i.e. 0.3g/100ml) clorazepate dipotassium rapidly hydrolyzes to nordiazepam. This occurs even more rapidly in an acid environment.

In other cases, although a particular drug may be chemically stable in water, liquid formulations such as aqueous solutions and suspensions for oral administration are not used because of the unpalatability of the particular drug. Unpalatable drugs which are carried in aqueous media are tasted almost immediately upon ingestion and produce an unpleasant taste or after-taste. For example, the antibiotics clarithromycin and erythromycin are valuable therapeutic agents for treating infections and are somewhat unpalatable.

Attempts to solve these problems in the prior art have centered around the formulation of non-aqueous oil-based liquid vehicles for oral administration of such drugs. However, while the

formulation of liquid dosage forms of water-sensitive drugs in non-aqueous oil-based vehicles may produce *chemically stable* suspensions, the suspensions are often not *physically stable*. That is, such formulations being free of water, do not suffer hydrolysis or other degradation of the active drug component, but are often subject to particle agglomeration, stratification, and caking upon standing and thus have poor shelf life.

There is thus a need in the pharmaceutical formulation arts for a liquid vehicle for drugs which are unstable in water or which produce an unpalatable sensation when administered orally in the form of an aqueous solution or suspension.

United States Patent No. 4,080,445 discloses non-aqueous suspensions for oral administration comprising a therapeutically effective amount of a water sensitive drug in an anhydrous vehicle comprising a sugar and a vegetable oil.

Brief Description of the Drawing

In the Drawing:

FIGURE 1 represents a graph of the particle size distribution of an unmilled prior art drug formulation immediately after formulation and after two weeks of standing at 25°C.

FIGURE 2 represents a graph of the particle size distribution of a milled prior art drug formulation immediately after formulation and after two weeks of standing at 25°C.

FIGURE 3 represents a graph of the particle size distribution of an unmilled prior art drug formulation immediately after formulation and after two weeks of standing at 40°C and 80% relative humidity.

FIGURE 4 represents a graph of the particle size distribution of a milled prior art drug formulation immediately after formulation and after two weeks of standing at 40°C and 80% relative humidity..

FIGURE 5 represents a graph of the particle size distribution of a milled drug formulation in accordance with the present invention immediately after formulation and after standing at 25°C for periods of one, two and four weeks.

FIGURE 6 represents a graph of the particle size distribution of a milled drug formulation in accordance with the present invention immediately after formulation and after standing at 40°C and 80% relative humidity. for periods of one, two and four weeks.

FIGURE 7 represents the stratification rates of prior art milled and unmilled drug formulations and milled and unmilled drug formulations in accordance with the present invention after eight weeks' storage at room temperature.

Summary of the Invention

The present invention relates to a pharmaceutical formulation comprising an essentially anhydrous liquid vehicle containing a therapeutically effective amount of a water-sensitive or unpalatable drug. The essentially anhydrous liquid vehicle comprises an oil, a sugar, and a suspending agent. The average particle size of all solid components of the formulation is 30μ or less.

In a preferred embodiment, the formulation also contains a drying agent to help bind any residual water that would otherwise degrade the active therapeutic agent. It is also preferred that a buffer be present to stabilize the suspension at a pH favorable to the drug being delivered. In another preferred embodiment the suspension also contains one or more ingredients such as salt and flavor to aid the palatability of the formulation.

The suspension of the present invention provides an environment for water-sensitive or unpalatable drugs which is both chemically and physically stable. Furthermore, there is no oily taste or mouthfeel or bitter after-taste of the suspension made according to the embodiments containing sugar, salt and flavorings.

The foregoing features and advantages of the present invention will be further understood upon consideration of the following description of the preferred embodiments.

Description of the Preferred Embodiments

Generally, the suspension of the present invention is an anhydrous oil-based liquid suspension for delivering a medicament. As used herein, the term "anhydrous" means having less than about 0.8% w/v moisture. In the preferred embodiments, the suspension contains less than about 0.3% w/v moisture. In addition to oil, the suspension contains a suspending agent which forms a protective colloid around the drug to protect the drug from moisture and assure that the medicament is uniformly dispersed within the suspension.

The oil is preferably one that is considered safe for oral consumption, and is relatively stable. Furthermore, the oil should not be incompatible with the drug being delivered. Preferred oils are selected from mixed triglycerides derived from capric, caproic, and caprylic acids. Furthermore, the vegetable oils containing glycerides of saturated or unsaturated aliphatic acids, such as stearic, palmitic, lauric, margaric, linoleic, linolenic, and myristic acids are suitable for use in the present invention. The most preferred embodiments presently use a winterized safflower oil, available from California Oils, Richmond, California.

Generally, suspending agents function to suspend the drug uniformly in the oil-based vehicle so that dosages of the drug are uniform. Suitable suspending agents for use in the formulations of the present invention include bentonite (a finely powdered montmorillonite aluminum silicate which is available under the tradename Bentone® from American Colloid

Corporation); finely powdered sodium calcium alginate (available under the trade name Kelset® from Kelco, a division of Merck & Company); trihydroxystearin and hydrogenated castor oil (available under the tradename Thixcin® from NL Chemicals, Highstown, New Jersey); cellulose derivatives; silicates; bentonites; stearates; silicon dioxide; and acacia. In a preferred embodiment of the present invention, the suspending agent is finely powdered sodium calcium alginate. Suspending agents act to slow down stratification and sedimentation of suspended particles by increasing the viscosity of the liquid and thereby improving the bouyancy of the solids suspended in the liquid. It is theorized that the powdered sugar and finely powdered sodium calcium alginate react with the drug to form a protective colloid around the drug particles in the oil-based vehicle resulting in a dispersed system that is highly stabilized. Further, the complex formed by the drug, suspending agent, and sugar provides a complex pathway for moisture to diffuse through. In those cases where the active drug component of the formulation is moisture sensitive, the drug is shielded by the protective colloid and any moisture that is present in the oil-based vehicle is kept away from the drug. In those cases where the active drug component of the formulation has an unpalatable taste, the protective colloidal shield formed around the drug diminishes the undesirable taste effect while the liquid formulation is in the mouth cavity.

In one preferred embodiment, a drying agent is also included in the suspension. The drying agent is a hygroscopic compound that absorbs or adsorbs water found in the suspension and which may degrade the drug. The drying agent may, in some circumstances, also function as the suspending agent. For example, silica gel has been found to have good suspending properties as well as good water absorbing properties. A preferred drying agent in formulations of the present invention is silica gel.

Virtually any sweetener or sugar that is physically and chemically compatible with the drug being delivered is suitable for use in the formulations of this invention.. The preferred sweetener used is sucrose, and is most advantageously micronized and superfine so as to disperse easily in the suspension. Other sugars, however, such as maltose, fructose, sorbitol and xylitol may also be used.

Other preferred embodiments also contain flavor and salt. These ingredients help to make the otherwise unpalatable oil-based suspension palatable, in cases where the oil employed has an unpleasant taste or the active drug component of the formulation is bitter or has an unpalatable taste. A preferred flavoring agent is a mixture of vanilla and peppermint extracts, but may also include other oil compatible flavoring agents, such as cherry, chocolate, cinnamon, coconut, coffee, orange, lemon, lime, strawberry, banana and peanut. In preferred embodiments the flavoring agents are free of glycol and alcohol, both of which degrade some drugs such as clorazepate dipotassium.

The salt is believed to function primarily as a flavor enhancer to avoid a bland tasting product. The salt also masks the oiliness of the vehicle. It should be present in an amount sufficient to mask the oiliness of the oil based suspension without producing a noticeable salty taste. Sodium chloride is the preferred flavor masking agent. Another suitable masking agent is potassium chloride.

In other preferred embodiments, the formulations of the present invention contain an alkaline buffer and a preservative. The alkaline buffer maintains the pH at a level at which the drug is stable. Clorazepate dipotassium, for example, is most stable at a pH greater than about 9.0. In such cases, potassium carbonate is the preferred buffer; however, other carbonates, hydroxides, oxides and organic amines may be used. Suitable preservative agents include the paraben class of compounds. Most preferred is a combination of parabens, such as those marketed under the tradename Aseptoform-M® (methylparaben) and Aseptoform-P® (propylparaben) available from Mallinckrodt, Inc. of St. Louis, Missouri. Any biologically acceptable benzoate or other preservative system that does not complex with or solubilize the drug to be delivered is also suitable.

The presence of surfactants has also been found to be advantageous to the physical stability of the suspension. Most surfactants that are compatible with the drug to be delivered as well as the oil vehicle are deemed suitable for use in the present invention. The preferred surfactant is marketed under the tradename Emulphor EL 719P® by GAF Corp., Wayne, N.J., a polyoxyethylated vegetable oil having low dioxin levels.

Generally, the ingredients of the suspension of the preferred embodiments of the present invention are present in the following amounts: a therapeutically effective amount of a medicament, about 30% w/v to about 75% w/v sugar, about 30% w/v to about 75% w/v oil, about 0.05% w/v to about 5% w/v suspending agent, about 0.05 w/v to about 2% w/v salt, about 0.01% w/v to about 2% w/v alkaline buffer, about 0.01% w/v to about 3% w/v preservative, less than about 5% w/v surfactant, and about 0.01% w/v to about 5% w/v flavor. Formulations having less than about 30% w/v sugar are generally unpalatable, while those having more than about 75% w/v generally have a consistency that is too thick.

More preferably, the ingredients are present in the following ranges: a therapeutically effective amount of a medicament, about 40% w/v to about 65% w/v sugar, about 45% w/v to about 65% w/v oil, about 0.1% w/v to about 2% w/v suspending agent, about 0.2% w/v to about 1% w/v salt, about 0.05% w/v to about 1% w/v alkaline buffer, about 0.1% w/v to about 1% w/v preservative, less than about 2% w/v surfactant, about 0.01% w/v to about 3% w/v flavoring.

It has been found, in accordance with the present invention, that even with the use of a suspending agent to help maintain the uniformity of the suspension over time, there is still a tendency for the suspensions to stratify, cake, and/or undergo particle agglomeration over time.

To counteract this tendency, the formulations in accordance with the present invention are subjected to milling to reduce the average particle size of all solid contained in the mixture to less than about 30μ, preferably to less than 10μ-20μ. The milling step may be performed by any conventional technique known to those skilled in the pharmaceutical formulations arts as, for example, liquid milling. In the illustrative Examples presented below, the preformulations were passed through either a Fryma MZM-Vk7 Delmix mixer or a Manton-Gaulin homogenizer. In most cases a single pass is sufficient to reduce the average particle size of the solids contained in the formulations to a value below the desired level of 30μ, often below about 20μ. If needed, the material can be subjected to two or more passes through the mill to obtain the desired average particle size.

As shown by Examples 16 - 20 below, when this is not done, the rate of stratification, particle agglomeration and caking is accelerated with attendant decrease in the shelf life of the finished formulation.

Example 1

Neobee® oil (320 g) was combined with 5 g of Bentone 34 and 290 g sugar. Sodium chloride powder (1.84 g) was then added. To 100 ml of the above mixture was added 180 mg of clorazepate dipotassium. The ingredients were mixed well. The resulting formulation tasted slightly saline, moderately sweet, with an oily and slightly bitter aftertaste.

Example 2

To 244 g of the mixture of Example 1 was added 4 g surfactant PVP K30 (polyvinyl pyrolidone having an average molecular weight of about 30,000). The resulting mixture was smooth, thin, and free flowing. To this mixture was then added 0.59 g of vanilla flavor. The taste was good, but the mixture turned very thick. An additional 244 g of the mixture of Example 1 was added to thin out the suspension. The resulting mixture was thick but pourable and had excellent taste.

Example 3

Clorazepate dipotassium (375 mg)was mixed with 250 ml of a vehicle produced in accordance with the method of Example 2. The taste of the resulting formulation was excellent, but some bitterness of the drug was noted.

Example 4

Neobee oil M5, (300 g), 300 g powdered sugar 12X and 8.85 g of Bentone 34 were combined. Some evidence of thixotropy was noted at final volume. Vanilla flavor (1.0 g) was added, causing the suspension to thicken significantly. The ingredients were mixed well at high speed for 15 minutes.

An additional 70.38 g of Neobee oil M5 was added to 2.0 g sodium chloride which had been reduced to a fine powder in a mortar/pestle before addition to the suspension. In order to formulate a suspension containing 7.5 mg drug per 5ml of suspension, 300mg of clorazepate dipotassium was added to 200 ml of a vehicle produced as above and then mixed well. The resulting mixture was heavy, thixotropic and tasted good.

Example 5

Neobee oil M5 (600 g) and 8.85 g of Bentone 34 were mixed together well. Powdered sodium chloride (3.60 g) was added with good mixing. Powdered sugar 12X (517 g) was added and mixed until smooth. The resulting mixture was allowed to deaerate. An additional 34 g of Neobee M5 oil was then added to bring the volume of the mixture to 1.0 liter, and then mixed until uniform. A small amount of vehicle was removed and mixed with 1.50 g of clorazepate dipotassium until smooth, and then added back into the main batch and mixed well. Vanilla flavor (1.80 g) was added. The mixture became thixotropic after the addition of vanilla. The taste of the suspension was good.

Example 6

To 6.30 kg Neobee M5 oil was mixed 86.0 g of Bentone-34®. Powdered potassium carbonate (10.0 g) and 35.0g of powdered sodium chloride were mixed with above oil mixture to make a smooth paste. The paste was diluted with additional oil and mixed until uniform consistency was attained. The diluted paste was then added to the main batch. Clorazepate dipotassium was mixed with a small amount of oil until smooth, and then diluted further and added to the main batch. 5.20kg powdered sugar 12X was slowly added to the main batch and mixed for approximately 1 hour. Immediately after all the sugar was added the suspension showed thixotropic character. After 1 hour of mixing the mixture became smooth and uniform, and lost its thixotropic character. Flavor (15 ml) was then added. Emulphor El 719P surfactant was added to thicken the mixture. The mixture was passed through a Manton-Gaulin homogenizer at 1500 psi to yield a smooth and uniform product. The product was placed in a vacuum for 1 hour to deaerate. The taste of the suspension was good.

Example 7

From an initial amount of 1833 g Neobee oil, 1 liter Neobee oil was taken and mixed with 39 g Emulphor EL 719P. Bentone 34 (25 g) was blended with Neobee oil and added to the main batch. Powdered sodium chloride (10 g) was blended with a small amount of Neobee oil and then added to the main batch. A preservative agent having 6.8 g Aseptoform M and 3.4 g Aseptoform P was mixed in 40 g of oil and heated until completely in solution, and then added to the main batch.

The balance of the oil was then added and blended with a small amount of oil and added to the main batch. Clorazepate dipotassium (4.46 g) was blended with a small amount of oil and added to the main batch. The balance of the oil was added and blended. Powdered sugar (1513.0 g) was mixed in and deaerated. Natural and artificial vanilla/peppermint extract (4.5 ml, obtained from Florasynth, Des Plaines, Illinois) was also mixed in. The entire mixture was passed through a Manton & Gaulin homogenizer to obtain a mixture with an average particle size below about 30 μ. The mixture was smooth, uniform and had good taste.

Example 8

A placebo vehicle was prepared by mixing a small amount of Neobee M5 oil with 85.5 g of Bentone 34. The Bentone 34/Neobee oil mixture was then added to approximately 6.0 kg of Neobee oil. Powdered sugar 12X (6.17kg) and 36.00 g powdered sodium chloride were mixed in. The resulting mixture was thick after the first hour of mixing with a turbine blade, but thinned out after 3 hours mixing. The taste of the suspension was good.

Example 9

A prototype stability batch was prepared by mixing 2.95 kg safflower oil with 5.0 g Aseptoform-M® and 1.0 g Aseptoform-P®. The mixture was heated to approximately 80°C and 45.0 g and 12.5 g Thixcin-R were added. After dissolving the ingredients, the mixture was cooled to room temperature, and vacuum placed on the vehicle. Clorazepate dipotassium (7.5 g) and 10 g potassium carbonate were then added while the vehicle was being mixed under vacuum. Sodium chloride (17.5 g) and 3.0 kg of powdered sugar were added and homogenized using a Fryma MZM-Vk7 Delmix mixer while still under vacuum. Flavor (7.5 g) was then added and the resulting mixture mixed for approximately 15 minutes. The resulting mixture was milled using a Fryma M5-18 Coball mill (obtained from Fryma, Inc., 40 Ethel Road, Edison, N.J.) to obtain a smooth, uniform formulation having the desired average particle size and acceptable taste and stability requirements.

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Example 10

Ingredient	w/v Percent	Amount/Liter
Neobee M5 Oil	44.00	480.00 g
Aseptoform M Powder	0.20	2.00 g
Aseptoform P Powder	0.02	0.20 g
Sodium Chloride	0.35	3.50 g
Kelset®	0.90	9.00 g
Thixcin-R	0.15	1.50 g
Cab-O-Sil	0.50	5.00 g
Tween 80	2.00	20.00 g
Powdered Sugar, 12X	48.00	480.00 g
Iron Oxide	0.01	0.10 g
Chocolate	0.05	0.50 g
Flavor Enhancer, Prosweet®	0.75	7.80 g
Vanilla Peppermint Flavor	0.15	1.50 g
8-Chloro-6-phenyl-4H-[1,2,4]triazolo-[4,3-a][1,4]benzodiazepine (Estazolam)	0.02	0.20 g
Neobee M5 Oil	q.s. 1 Liter	q.s. 1 Liter

[1] The preparation and use of 8-chloro-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine, having the generic name estazolam, is disclosed in United States Patent No. 3,701,782.

Neobee M5 oil (400 ml) was heated to approximately 90°C and then allowed to stand for approx. 1 hour to equilibrate. Aseptoform M and P powders were mixed in until dissolved. Kelset,® Thixcin®, and Tween 80 were mixed to form an uniform dispersion. Estazolam was added and homogenized in a beadmill or a high energy mill. Flavors were then added until the resulting product was uniform. The volume of the resulting product was adjusted to 1 liter with Neobee Oil as required.

The formulations of Examples 11-16 were prepared using the general method detailed in Example 9.

Example 11

Ingredient	w/v Percent	Amount/15 Liters
Safflower oil	41.70	6.30 Kg
Methylparaben	0.20	30.00 g
Propylparaben	0.10	15.00 g
Potassium carbonate	0.20	30.00 g
Sodium chloride	0.35	52.50 g
Kelset®	0.90	135.00 g
Powdered sugar, 12X	56.00	8.4 Kg
Flavor enhancer Prosweet®	0.25	37.50 g
Vanilla peppermint flavor	0.15	22.50 g
Clorazepate dipotassium	0.15	22.5 g
Safflower oil	q.s.	

Nitrogen gas was used to drive air out of the product.

Example 12

Ingredient	w/v Percent
Clarithromycin[2]	5.00
Methylparaben	0.20
Propylparaben	0.10
Sodium chloride	0.35
Kelset®	0.90
Powdered sugar, 12X	45.00
Flavor enhancer, Prosweet®	0.25
Safflower oil, q.s.	100.00

[2] The preparation of clarithromycin is disclosed in United States Patent No. 4,331,803.

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Example 13

Ingredient	w/v Percent
N-2-[benzo[b]thien-2-yl]ethyl-N-hydroxyurea[3]	5.00
Methylparaben	0.20
Propylparaben	0.10
Sodium chloride	0.35
Kelset®	0.90
Powdered sugar, 12X	45.00
Flavor enhancer, Prosweet®	0.25
Safflower oil, q.s.	100.00

[3] N-2-[benzo[b]thien-2-yl]ethyl-N-hydroxyurea is an inhibitor of the lipoxygenase enzymes and is useful in the treatment of inflammatory and allergic disease states. Its preparation and use is disclosed in United States Patent No. 4,873,159.

Example 14

Ingredient	w/v Percent
8-Chloro-6-phenyl-4H-[1,2,4]-triazolo[4,3-a][1,4]benzodiazepine	5.00
Methylparaben	0.20
Propylparaben	0.10
Sodium chloride	0.35
Kelset®	0.90
Powdered sugar, 12X	45.00
Flavor enhancer, Prosweet®	0.25
Safflower oil, q.s.	100.00

Example 15

Ingredient	w/v Percent
Valproic acid	5.00
Methylparaben	0.20
Propylparaben	0.10
Sodium chloride	0.35
Kelset®	0.90
Powdered sugar, 12X	45.00
Flavor enhancer, Prosweet®	0.25
Safflower oil, q.s.	100.00

Example 16

Ingredient	w/v Percent
α-Methyl-4-(2-methylpropyl)benzeneacetic acid[4]	5.00
Methylparaben	0.20
Propylparaben	0.10
Sodium chloride	0.35
Kelset®	0.90
Powdered sugar, 12X	45.00
Flavor enhancer, Prosweet®	0.25
Safflower oil, q.s.	100.00

The preparation and use of α-methyl-4-(2-methylpropyl)benzeneacetic acid, having the generic name ibuprofen, is disclosed in United States Patents No.'s 3,228,831 and 3,385,886.

Example 17

An oil-based aspirin suspension was prepared in accordance with the teachings of United States Patent 4,080,445 to Lin, et al. The composition of the formulation was as follows:

Ingredient	Weight (g)
Aspirin	6.0
Sucrose, powdered	27.5
Syloid®	1.0
Sesame oil	100.0

The sample was not milled following thorough mixing. The composition was tested for particle size distribution just after formulation and two weeks later at two different temperatures (25°C and 40°C) . The particle size distribution graphs for this formula at 25°C and 40°C and 80% relative humidity appear in Figures 1 and 3, respectively. As can be seen from those graphs, considerable separation was noted after two weeks standing. Particle agglomeration and caking was noted since thorough shaking of the bottle and its contents after two weeks standing did not yield a uniform suspension. Gross separation and caking was noted in the formulation after standing for four weeks.

Example 18

A formulation having the same composition as Example 17 was prepared with the exception that, following thorough mixing of the ingredients, the formulation was subjected to milling to reduce the average particle size to a value below 30μ in accordance with the teachings of this invention. The formulation was subjected to particle size analysis immediately after formulation and again after two weeks standing at 25°C and at 40°C and 80% relative humidity. The results of these particle size analyses appear in Figures 2 and 4, respectively.

As can be seen by the data appearing in those graphs, the formulation had considerably greater physical stability than the similar formulation which had not been subjected to milling.

Example 19

A formulation containing clorazepate dipotassium was made having the same composition as that given in Example 11 above, but omitting the milling step. The formulation was subjected to particle size analysis immediately after formulation and again after two weeks and four weeks standing at 25°C and at 40°Cand 80% relative humidity. The results of these analyses appear in Figures 5 and 6. As can be seen by those data, the formulations are quite stable with even a slight, but unexplainable decrease in average particle size upon standing.

Example 20

The tendency of each of the formulations of Examples 11 (present invention, milled), 17 (prior art formulation, unmilled), 18 (prior art formulation, milled) and 19 (present invention, unmilled) to undergo stratification upon standing was measured by checking the average stratification rate and main separated solid volume at different levels in the formulation after standing. The results of these tests appear in Figure 7 where it can be seen that formulations made in accordance with the present invention have exceptional physical stability.

The foregoing examples are provided to enable one skilled in the art to practice the present invention, but are merely illustrative thereof and are not to be read as limiting the scope of the invention as defined by the appended claims.

Although the present invention has been described in connection with the presently preferred embodiments, those skilled in the art will recognize many modifications to sequence, arrangement, portions, elements, and materials which can be used in the practice of the invention without departing from its scope. It is intended that such changes and modifications can be covered by the following claims.

WE CLAIM:

1. A non-aqueous liquid suspension drug delivery system for water-unstable or unpalatable drugs having improved physical stability comprising a therapeutically effective amount of a water-unstable or unpalatable drug; an edible oil; a sugar; and a suspending agent; said liquid suspension drug delivery system characterized by an average particle size of all solid components of less than about 30 μ

2. A non-aqueous liquid suspension drug delivery system for water-unstable or unpalatable drugs as defined by Claim 1 characterized by an average particle size of all solid components of less than about 20μ.

3. A non-aqueous liquid suspension drug delivery system in accordance with Claim 1 comprising a therapeutically effective amount of a medicament; between about 30% w/v to about 75% w/v sugar; between about 30% w/v to about 75% w/v oil; between about 0.05% w/v to about 5% w/v suspending agent between about 0.05 w/v to about 2% w/v salt; between about 0.01% w/v to about 2% w/v alkaline buffer; between about 0.01% w/v to about 3% w/v preservative; less than about 5% w/v surfactant; and about 0.01% w/v to about 5% w/v flavor.

4. A non-aqueous liquid suspension drug delivery system in accordance with Claim 2 comprising a therapeutically effective amount of a medicament; between about 40% w/v to about 65% w/v sugar; between about 45% w/v to about 65% w/v oil; between about 0.1% w/v to about 2% w/v suspending agent; between about 0.2% w/v to about 1% w/v salt; between about 0.05% w/v to about 1% w/v alkaline buffer; between about 0.1% w/v to about 1% w/v preservative; less than about 2% w/v surfactant; and between about 0.01% w/v to about 3% w/v flavoring.

5. A non-aqueous liquid suspension drug delivery system in accordance with Claim 1 wherein said medicament is clorazepate dipotassium.

6. A non-aqueous liquid suspension drug delivery system in accordance with Claim 1 wherein said medicament is clarithromycin or a pharmaceutically acceptable salt thereof.

7. A non-aqueous liquid suspension drug delivery system in accordance with Claim 1 wherein said medicament is erythromycin or a pharmaceutically acceptable salt thereof.

8. A non-aqueous liquid suspension drug delivery system in accordance with Claim 1 wherein said medicament is N-2-[benzo[b]thien-2-yl]ethyl-N-hydroxyurea or a pharmaceutically acceptable salt thereof.

9. A non-aqueous liquid suspension drug delivery system in accordance with Claim 1 wherein said medicament is α-methyl-4-(2-methylpropyl)benzeneacetic acid or a pharmaceutically acceptable salt thereof.

10. A non-aqueous liquid suspension drug delivery system in accordance with Claim 1 wherein said medicament is valproic acid or a pharmaceutically acceptable salt thereof.

11. A non-aqueous liquid suspension drug delivery system in accordance with Claim 1 wherein said medicament is 8-chloro-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepine or a pharmaceutically acceptable salt thereof.

FIG. 1

PARTICLE SIZE ANALYSIS
PRIOR ART FORMULATION (UNMILLED)
25° C

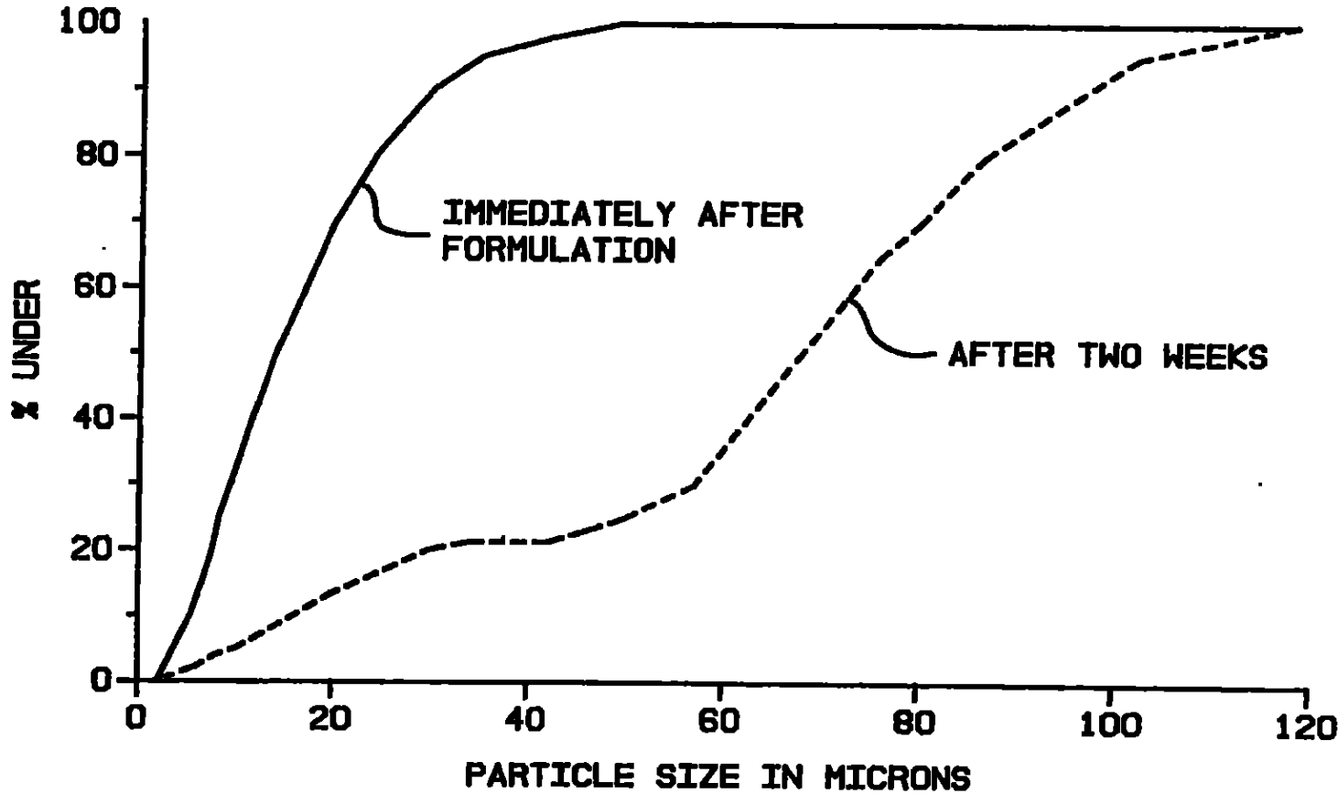

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FIG. 2

PARTICLE SIZE ANALYSIS
PRIOR ART FORMULATION (MILLED)
25°C

FIG. 3

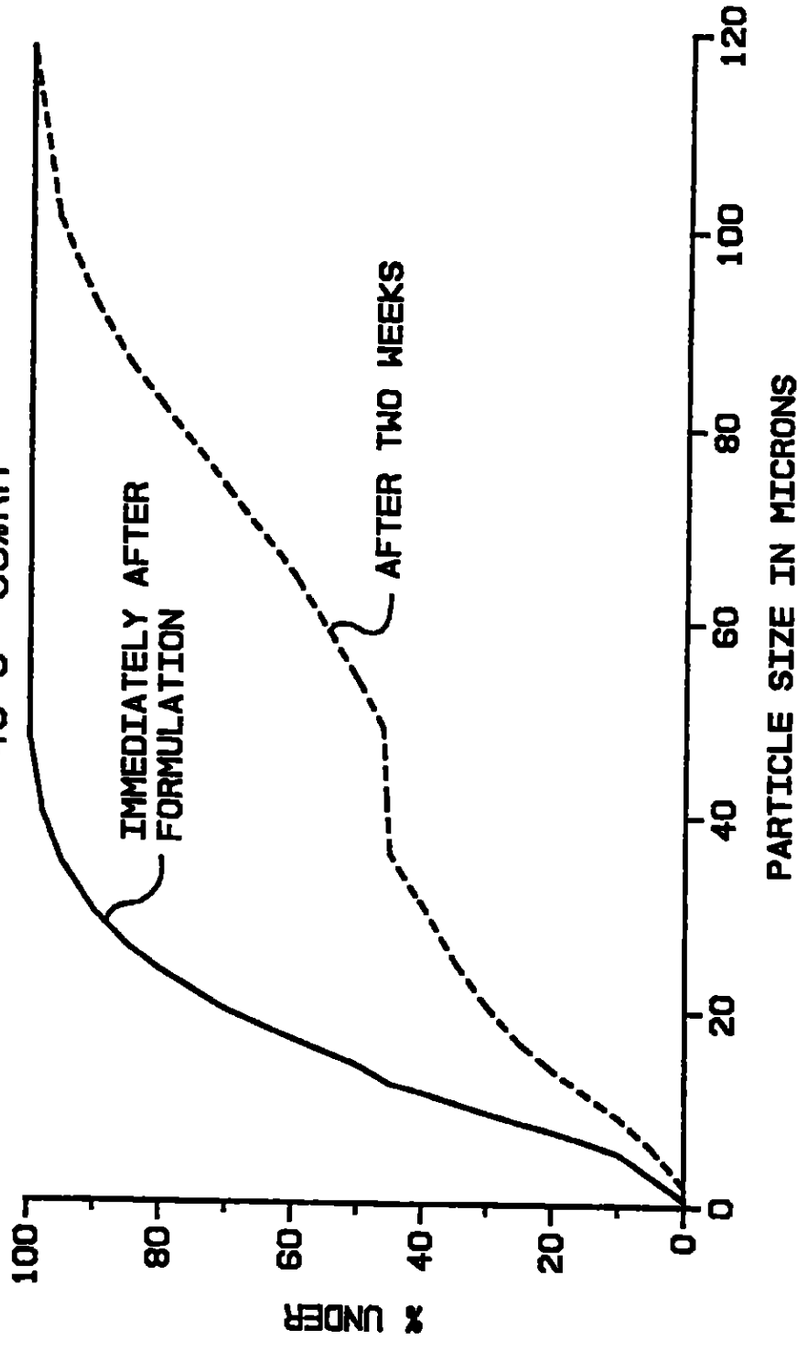
PARTICLE SIZE ANALYSIS
PRIOR ART FORMULATION (UNMILLED)
40°C 80%RH
IMMEDIATELY AFTER FORMULATION
AFTER TWO WEEKS
% UNDER
100
80
60
40
20
0
0
20
40
60
80
100
120
PARTICLE SIZE IN MICRONS

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FIG. 4

PARTICLE SIZE ANALYSIS
PRIOR ART FORMULATION (MILLED)
40°C 80%RH

FIG. 5

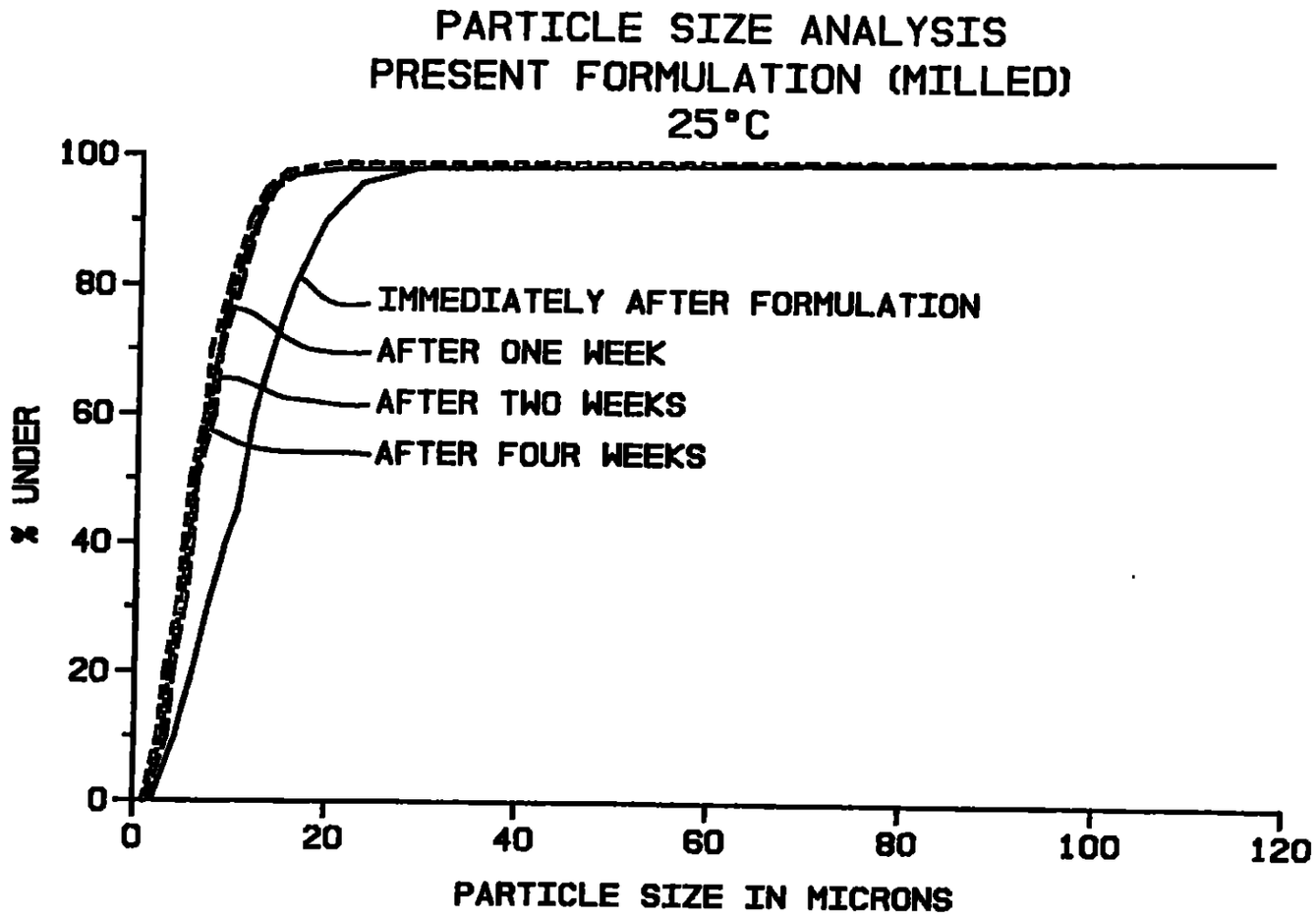

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FIG. 6

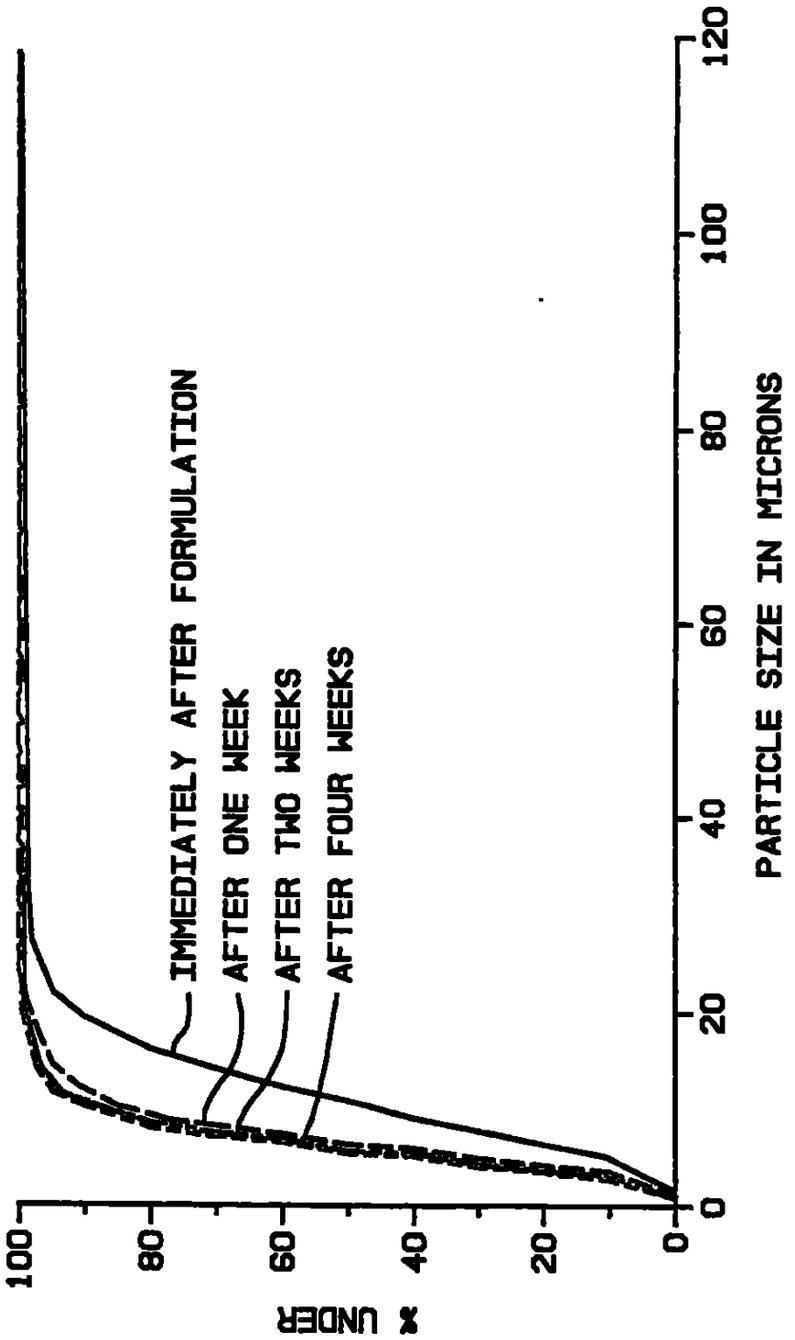
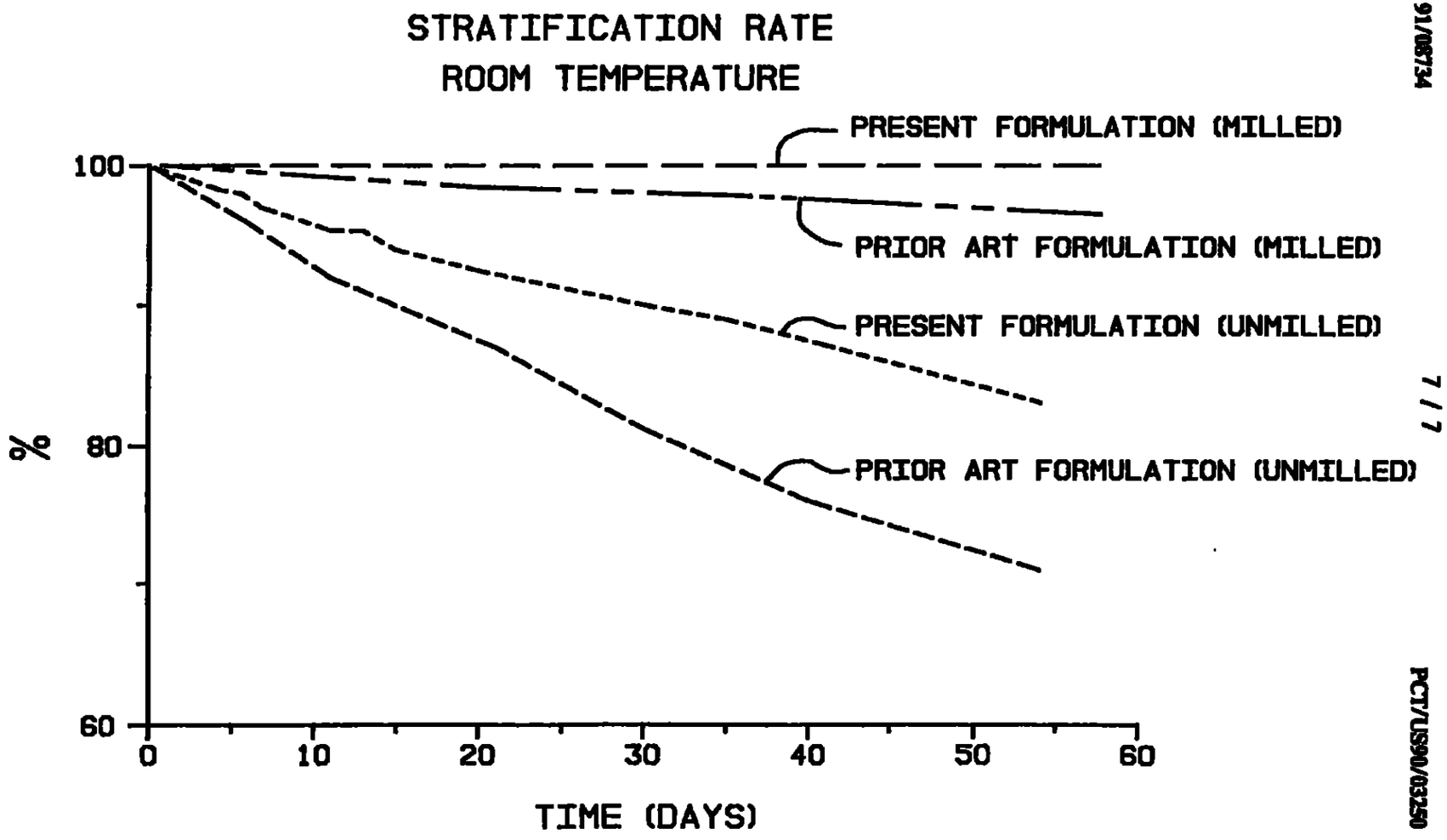

PARTICLE SIZE ANALYSIS
PRESENT FORMULATION (MILLED)
40°C 80%RH
IMMEDIATELY AFTER FORMULATION
AFTER ONE WEEK
AFTER TWO WEEKS
AFTER FOUR WEEKS
% UNDER
100
80
60
40
20
0
0
20
40
60
80
100
120
PARTICLE SIZE IN MICRONS

FIG. 7



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(54) Stabilized liquid analgesic compositions.

(57) A stabilized liquid ibuprofen syrup suitable for oral administration comprising: from 50 to 400 mg of ibuprofen per 5 ml of syrup; said ibuprofen suspended in an aqueous liquid having more than 50% by weight of a pharmaceutically acceptable polyhydric alcohol bodying agent; a sweetening agent; and a pH of higher than 7.0 and below 7.7.

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STABILIZED LIQUID ANALGESIC COMPOSITIONS

A. Field of the Invention

This invention relates to medicinal orally administrable stabilized liquid analgesic compositions, and more specifically relates to stabilized liquid analgesic compositions having ibuprofen (p-isobutylhydratropic acid) as their active ingredient. These compositions, which have the form of moderately viscous syrups, are useful for the treatment of pain, inflammatory conditions and other conditions including adult respiratory distress syndromes.

Ibuprofen is a non-steroidal anti-inflammatory drug widely used in the treatment of minor pain and degenerative and rheumatic diseases of the joints. Despite its wide use in several classes of patients, and its suitability for administration to pediatric and geriatric patients who frequently can not take solid oral dosage forms such as tablets and capsules, the industry has not been successful in developing stable, elegant and palatable preparations. Because of ibuprofen's low water solubility, unpleasant bitter taste and lack of stability in water, previous preparations displayed the problems of chemical and visual instability, resulting in products of short storage life. Thus, pediatric and geriatric patients, and others who can not, for a variety of reasons, swallow tablets or capsules, have been limited to liquid acetaminophen products for the relief of pain. While acetaminophen is a widely used analgesic and anti-pyretic agent, it lacks anti-inflammatory activity and is not as an effective pain reliever as ibuprofen.

B. Prior Art

Nicholson et al., U.S. patent 3,385,888, discloses liquid suspensions and mixtures of ibuprofen containing chloroform water, with and without orange flavor, and an unsweetened elixir containing ethanol and glycerol. These products have limited shelf life, poor flavor and substantial turbidity, not to mention the unsuitability of chloroform-containing liquid products for administration to infants, small children and elderly patients.

Mueller, U.S. patent 4,447,451, exemplifies an oral suspension containing 80 mg of ibuprofen aluminum salt per ml consisting of about 98% sucrose and 1.4% other inactive ingredients dissolved in water. This suspension rapidly develops cloudiness and is not chemically stable for long periods.

Moore et al. report a clinical trial using a liquid ibuprofen product, International Journal of Clinical Pharmacology, Therapy and Toxicology, Vol. 23 No. 11-1985 (pp 573-577). While the Moore suspension formulation is not disclosed in the body of the paper, a footnote reveals that it was compounded by the assignee of the Mueller patent and was 400% more concentrated than that of the patent on an active ingredient basis.

Despite the well-recognized efficacy of ibuprofen, and its wide use, there remains a long standing need for a suitable liquid oral dosage form of this valuable drug which is not only stable, but is especially suitable for administration to pediatric and geriatric patients. The present invention fulfills that need.

Detailed Description of the Invention

The liquid compositions of this invention are aqueous ibuprofen-containing syrups containing from 50 to 400 mg of ibuprofen per 5 ml of syrup and comprising: a therapeutically effective amount of ibuprofen or a pharmaceutically acceptable salt or ester thereof; more than 50% by weight water compatible bodying agent; less than 1% stabilizers; an alkalinizing agent in an amount suitable to provide a final composition pH of above 7.0 and preferably between 7.0 and 7.7, most preferably 7.3 to 7.5; a sweetening agent; and a pharmaceutically acceptable antioxidant.

The stabilized liquid ibuprofen formulations of this invention include both sucrose sweetened and sugar free formulations suitable for administration to diabetics and other patients whose sugar intake should be restricted. Because of the bitter and unpleasant flavor of ibuprofen, it is desirable to have a product of high sweetness.

The term "water compatible bodying agent" means a pharmaceutically acceptable water miscible or dissolvable material that yields a water-clear aqueous suspension or solution of increased viscosity.

The term "stabilizer" as used in this specification means a material having dispersing, suspending or hydrophilic emulsifying properties that does not substantially modify clarity or viscosity of water solutions at low levels; and is capable of forming a particulate or molecular film which surrounds ibuprofen molecules.

"Alkalinizing agent" means a pharmaceutically acceptable hydroxide compound capable of rendering the final syrup above pH 7.0.

"Sweetening agent" as used herein means nutritive and non-nutritive sweeteners that are pharmaceutically acceptable and are stable in aqueous solution.

The term "antioxidant" means a pharmaceutically acceptable water soluble antioxidant stable at alkaline pH.

An important aspect of this invention is the inclusion of a major portion of water compatible material or materials that contribute to a rather heavy and uniform viscosity in the final composition. Suitable materials must be capable of being freely incorporated into water without affecting clarity of the resultant suspension or solution, and not have pronounced or undesirable effect upon the flavor of the product. Pharmaceutically acceptably polyhydric alcohols are highly useful as bodying agents because of their solvent and miscibility properties, contribution to viscosity and generally pleasant taste. Those that are preferred include glycerol, sorbitol, mannitol and propylene glycols. Particularly suitable components include sorbitol and glycerol. These should be incorporated at a level of from about 50% to 75% by weight of the final composition. An especially preferred combination is the use of 1 part of glycerol to about 3 to 4 parts of sorbitol.

It is permissible to use other materials such as sucrose as an incidental part of the bodying agent component but such inclusions should not constitute a major part thereof because of the general metabolic undesirability of including larger amounts of sugar and the visual haze that develops in the syrup from its use unless special precautions are taken. While there has been no recognition by the prior art, the use of high levels of sucrose, both cane and beet, results in shortened stability of the ibuprofen liquid products by reason of haze formation when usual commercial sugar prodducts are added. If sucrose is incorporated in any quantity, and the maximum should be less than 40%, it is essential that high purity sugar such as Bottler's Grade Extra Fine, No Floc, sold by Holly Sugar be used in order to minimize haze development in storage.

Stabilizing agents provide protection for the ibuprofen active medicament by shielding it from other components, as well as aiding mixing during processing. While they are employed at very low levels, less than 1% by weight of the total syrup, they provide multiple very useful functions by first aiding in dispersing and suspending the ibuprofen particles and then forming a protective molecular or fine particle coat around the suspended drug in the final product.

Several classes of compounds suitably serve this function, especially hydrophilic emulsifying agents and colloidal clays. Natural emulsifiers of plant and animal origin are not preferred because they are susceptible to discoloration and precipitation under storage conditions. These include gelatin, lecithin tragacanth and acacia. Finely dispersed solids such as colloidal clays are highly preferred. These include bentonite, aluminum silicate, colloidal magnesium aluminum silicate such as Veegum brand supplied by Vanderbilt. Another particularly preferred stabilizing agent is the synthetic polymer, polyvinylpyrrolidone (PVP).

Optimally, a combination of stabilizing ingredients is included. One such combination is 1 part of PVP to 2 parts of colloidal magnesium aluminum silicate. These are included in a total amount of from 0.25% to 1.0% by weight. Particularly preferred is a blend of 0.11% PVP to 0.22% Veegum. It is not necessary and is undesirable to employ amounts over 1.0% because of possible slight turbidity that may result under adverse storage conditions.

It is essential to the optimum stability of the final product that the pH be maintained in the alkaline range at all times. An acceptable range is above 7.0 and below 7.7, although best results are achieved at a pH of 7.3 to 7.5. In order to maintain this level, an alkalizing agent such as a hydroxide must be used. Suitable compounds include potassium hydroxide and sodium hydroxide. While other hydroxides are useful they are not preferred. For example, while calcium hydroxide is a pharmaceutically acceptable material, and its solutions exhibit strong alkalinity, reaction between it and air causes production of haze and formation of calcium carbonate precipitate which renders the syrup undesirable for long term storage unless air is excluded. Because of the unpleasant taste characteristics of ibuprofen which are enhanced by being placed in suspension, it is most desirable to mask its natural flavor with sweetness.

Because of the stability problems encountered with sucrose, coupled with the general undesirability of using a metabolizable sugar in most patients, the preferred sweetener is sodium saccharin. While other sweeteners may be used, water stability is necessary for products expected to have an extended shelf life. Aspartame is suitable from the organoleptic standpoint but decomposes in water solution over an extended time period, making it less desirable.

A further necessary aspect of this invention is the protection of the product from entrapped air which results in oxidation and lessened stability. An antioxidant which is water soluble and suitable for inclusion in an oral drug preparation should be included. While compounds such as ascorbic acid derivatives such as ascorbyl palmitate may be employed, they are not preferred because of their acidic nature and generally lower solubilities. The preferred antioxidant is sodium metabisulfite because of its effective scavenging of oxygen incorporated within the product during manufacture or later contacting the product. The acceptable range of antioxidant is from about 0.10% to 0.25%, with 0.18% optimally being used.

Viscosity of the product should be controlled for optimum stability. A viscosity of about 1000 to 3000 centipoise at 20°C, as measured by the Brookfield Synchro-Lectric viscometer, is the preferred range. Finished product of somewhat less thickness are capable of being stored for commercially acceptable time periods, but they are less able to withstand adverse conditions which may be encountered in storage and shipment.

In addition to the necessary components of the compositions, many desirable ingredients may be added. These include flavoring, colorings, alcohol and other preservatives such as parabens. Ethanol, included at a level of about 12% to 25%, and preferably about 15% to 20%, serves as both a microbial inhibiting preservative and a mixing aid of benefit during processing of the product. Butyl paraben, at about 0.014% coupled with propyl paraben at a lower level approaching its limit of solubility about 0.008%, together inhibit an extended range of organisms.

Fruit flavors such as cherry and citrus, which have a slight bitter component to their flavor profile, are most suitable.

During compounding and processing of the compositions, it is very desirable to minimize or exclude air. Observing this precaution assists in obtaining a better quality product of satisfactory shelf life.

The following examples are illustrative of the invention and are not intended to be limiting.

Example I

A 1,000 gallon batch of aqueous syrup for oral use, containing 200 mg of ibuprofen per 5 ml, one teaspoon, dose is prepared from the following:

Ibuprofen (micronized)	151 kg
Sorbitor	2322 kg
Glycerol	710 kg
Ethanol (95%0	800 kg
Veegum	10 kg
PVP	5 kg
Sodium metabisulfite	8 kg
Sodium hydroxide	21 kg
Carmine solution *	61 kg
Wild cherry flavor (Cosmo #37)	7 kg
Sodium saccharin	20 kg
Butyl paraben	0.65 kg
Propyl paragen	0.36 kg
Deionized water, q.s.	1000 gal

Separate solutions of the Veegum, PVP and sodium hydroxide are prepared by dissolving each in water and cooling to 25-30°C. About 800 kg of water is added to a mixing tank and ibuprofen is dissolved, followed by the addition of sodium hydroxide solution until a pH of 7.3 to 7.5 is reached. The glycerol is added to the tank which is heated to 85°C. and sorbitol, the parabens and saccharin are added. The metabisulfite is dissolved in twice its weight of water and added to the batch which has been cooled to

*The Carmine solution is prepared from the following ingredients:

Propylene glycol	23468 gm
Carmine No. 40 Powder	4068 gm
Sodium Hydroxide Pellets	1398 gm
Hydrochloric acid	3248 gm
Deionized water, q.s.	67133 gm

25°C. With constant mixing the PVP and the Veegum solutions are incorporated. The carmine solution is added and after mixing the Ibuprofen solution is placed in the compounding tank, followed by the cherry flavoring. The batch is purged with nitrogen, followed by homogenization and deaeration by passage through an Oakes mixer and a Versator.

Example II

Following the procedure of Example I, a stable syrup group containing 100 mg of Ibuprofen aluminum salt per 5 ml is prepared from the following ingredients.

Ingredient	Amount (Kg)
Ibuprofen, aluminum salt	7.57
Sorbitol	160.00
Propylene glycol	80.00
Ethanol (95%)	80.00
Veegum	1.00
PVP	0.50
Sucrose (Holly Extrafine	113.00
Sodium metabisulfite	0.80
Potassium hydroxide	2.37
Carmine solution	6.10
Citrus lemon peel flavor	0.66
Butyl paraben	0.065
Propyl paraben	0.033
Deionized water, q.s.	100 gal

Example III

Following the process of Example I, a syrup containing 400 mg of Ibuprofen per 5 ml is provided from the following ingredients:

Ingredient	Amount (Kg)
Ibuprofen	30.28
Sorbitol	160.00
Glycerine	95.00
Ethanol 190 proof	75.00
Bentonite	1.00
PVP	0.50
Sodium saccharin	2.00
Sodium metabisulfite	0.80
Sodium hydroxide	2.00
Carmine solution	6.10
Lemon oil flavor	0.66
Butyl paraben	0.068
Propyl paraben	0.036
Deionized water, q.s.	100 gal

Example IV

Following the process of Example I, a syrup containing 50 mg of Ibuprofen per 5 ml is provided from the following ingredients:

Ingredient	Amount (Kg)
Ibuprofen	3.78
Veegum	10.00
PVP	5.00
Sodium hydroxide	21.00
Alcohol USP 190 proof	80.00
Glycerine	70.00
Sodium metabisulfite	0.80
Carmine solution	6.10
Wild cherry flavor	0.66
Butyl paraben	0.065
Propyl paraben	0.035
Calcium saccharin	20.00
Sorbitol	218.00
Deionized water, q.s.	100 gal

The above description has been given by way of illustration. It will be understood by those skilled in the art that modifications may be made without departing from the spirit and scope of the claimed invention.

Claims

1. A stabilized Ibuprofen-containing syrup containing from 50 to 400 mg of Ibuprofen per 5 ml of syrup and comprising: a therapeutically effective amount of Ibuprofen or a pharmaceutically acceptable salt thereof; more than 50% by weight water compatible bodying agent; less than 1% stabilizer adapted to form a particulate or molecular film about the Ibuprofen particles; an alkalinizing agent in an amount suitable to provide a final composition pH of from above 7.0 to 7.7; less than 40% by weight of a sweetening agent; and a pharmaceutically acceptable antioxidant.

2. The stabilized Ibuprofen liquid formulation of Claim 1 wherein the pH of the final composition is between 7.3 and 7.5 inclusive.

3. The stabilized Ibuprofen liquid formulation of Claim 2 wherein said sweetening agent is extrafine, no floc sugar.

4. The stabilized Ibuprofen liquid formulation of Claim 1 wherein said sweetening agent is sodium saccharin.

5. The stabilized Ibuprofen liquid formulation of Claim 1 wherein said bodying agent is a polyhydric alcohol bodying agent.

6. A stabilized liquid Ibuprofen syrup containing from 50 to 400 mg of Ibuprofen per 5 ml of syrup comprising: from 40 to 50 weight percent of sorbitol; from 0.05 to 0.25 weight percent of polyvinylpyrrolidone; from 0.15 to 0.5 weight percent colloidal clay; sodium saccharine in an amount to render the syrup sweet; from 0.1 to 0.25 weight percent sodium metabisulfite; and a therapeutically effective amount of Ibuprofen or a pharmaceutically acceptable salt or ester thereof, said syrup having a pH of from 7.3 to 7.5 inclusive.

7. A stabilized liquid Ibuprofen syrup suitable for oral administration: comprising from 50 to 400 mg of Ibuprofen per 5 ml of syrup; said Ibuprofen suspended in an aqueous liquid having more than 50% by weight of a pharmaceutically acceptable polyhydric alcohol bodying agent; a sweetening agent; and a pH of from 7.0 to 7.7.

8. The stabilized liquid Ibuprofen syrup of Claim 7 wherein said pH is 7.3 to 7.5 inclusive.

9. The syrup of Claim 1 wherein the viscosity is about 1000 to 3000 centipoise at 20°C.

10. The syrup of Claim 6 wherein the viscosity is about 1000 to 3000 centipoise at 20°C.
11. The syrup of Claim 7 wherein the viscosity is about 100 to 3000 centipoise at 20°C.

Claims for the following Contracting States : AT, ES, GR

1. A process for the production of a stabilized ibuprofen-containing syrup containing from 50 to 400 mg of ibuprofen per 5 ml of syrup, characterized by combining a therapeutically effective amount of ibuprofen or a pharmaceutically acceptable salt thereof, more than 50% by weight water compatible bodying agent, less than 1% stabilizer adapted to form a particulate or molecular film about the ibuprofen particles, an alkalinizing agent in an amount suitable to provide a final composition pH of from above 7.0 to 7.7, less than 40% by weight of a sweetening agent, and a pharmaceutically acceptable antioxidant.
2. The process of Claim 1, wherein the pH of the final composition is between 7.3 and 7.5 inclusive.
3. The process of Claim 2, wherein said sweetening agent is extrafine, no floc sugar.
4. The process of Claim 1, wherein said sweetening agent is sodium saccharin.
5. The process of Claim 1, wherein said bodying agent is a polyhydric alcohol bodying agent.
6. A process for the production of a stabilized liquid ibuprofen syrup containing from 50 to 400 mg of ibuprofen per 5 ml of syrup, characterized by combining from 40 to 50 weight percent of sorbitol, from 0.05 to 0.25 weight percent of polyvinylpyrrolidone, from 0.15 to 0.5 weight percent colloidal clay, sodium saccharine in an amount to render the syrup sweet, from 0.1 to 0.25 weight percent sodium metabisulfite, and a therapeutically effec tive amount of ibuprofen or a pharmaceutically acceptable salt or ester thereof, said syrup having a pH of from 7.3 to 7.5 inclusive.
7. A process for the production of a stabilized liquid ibuprofen syrup suitable for oral administration, characterized by combining from 50 to 400 mg of ibuprofen per 5 ml of syrup, said ibuprofen suspended in an aqueous liquid having more than 50% by weight of a pharmaceutically acceptable polyhydric alcohol bodying agent, a sweetening agent, and a pH of from 7.0 to 7.7.
8. The process of Claim 7, wherein said pH is 7.3 to 7.5 inclusive.
9. The process of Claim 1, wherein the viscosity is about 1,000 to 3,000 centipoise at 20°C.
10. The process of Claim 6, wherein the viscosity is about 1,000 to 3,000 centipoise at 20°C.
11. The process of Claim 7, wherein the viscosity is about 100 to 3,000 centipoise at 20°C.

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SUPERINTENDENCIA Y COMERCIO
Radicacion : [illegible]
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Tramite : 011 PCT-PATENTE 379 FASE NAL 440 CALIFICACION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 96.332
FECHA : DICIEMBRE 19 DE 2005

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
SYNOPHARM S.A.	CONSIGNACION	BANCO POPULAR	050-00110-6	17963487	25/10/2005	705,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	235,000.00
		TOTAL : $	235,000.00

SON: DOSCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Industria y Comercio
SUPERINTENDENCIA

311

2020
Bogotá, D.C.,

Doctor:
Ramiro Castro Duque
Apoderado

Oficio N°: 13099

ASUNTO:

Radicación PCT N°	04-9302
Trámite	011
Evento	379
Actuación	440
Folios	009

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.

CLARA DE JAIMES
Jefe de la División de Nuevas Creaciones (E).

El anterior requerimiento fue notificado por fijación en lista de fecha, 30 DIC. 2005.

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Alex.