

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICION A

- ☒ 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

Numero del expediente 08-55399

Solicitante GENEREX PHARMACEUTICALS INC

Apoderado DILIA MARIA RODRIGUEZ D' ALEMAN

Título de la nueva creación o denominación del signo: *FORMULACION
FARMACEUTICA DE ABSORCIÓN ORAL Y SU METODO DE ADMINISTRACIÓN

Gaceta: 595

③ OPOSICION PRESENTADA POR

SOLICITANTE	Nombre: <u>PROCAPS S.A</u>	IDENTIFICACION	
	Dirección: <u>CALLE 80 No. 78B-201</u>	C.C. ☐	NIT ☒
REPRESENTANTE O APODERADO	Nacionalidad o Domicilio: <u>COLOMBIA</u>	C.E. ☐	Otro ☐
	Lugar de Constitución: <u>BARRANQUILLA</u>	Cual <u>890.106.527-5</u>	
	Telefono: <u>(571)3719900</u> Fax: <u>(571)3730818</u> E-mail: <u></u>	Numero <u>890.106.527-5</u>	
REPRESENTANTE O APODERADO	Nombre: <u>ELIANA ISAURA MORENO BOHORQUEZ</u>	IDENTIFICACION	
	Dirección: <u>CARRERA 13 No. 119-95 OF 104</u>	C.C. ☒	NIT ☐
	Telefono: <u>(571)2131213</u> Fax: <u>(571)6121979</u> E-mail: <u>negocios@optimum-co.com</u>	C.E. ☐	Otro ☐
		Cual <u>51.975.664 TP 83823</u>	
		Numero <u>51.975.664 TP 83823</u>	

④ FUNDAMENTOS DE LA OPOSICION

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

Signo opositor:

Justificación:

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

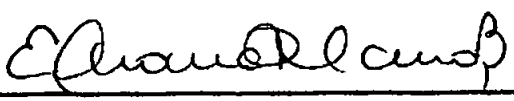
⑤ Comprobante de pago No. _____ Fecha _____

⑥ ANEXOS

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

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA: 

C.C. 51.975.664

TP. 83823

Señora Jefe,
DIVISIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Referencia : Expediente N° 08055399
Asunto : Oposición a la solicitud de patente de Invención titulada
"FORMULACIÓN FARMACÉUTICA DE ABSORCIÓN
ORAL Y SU MÉTODO DE ADMINISTRACIÓN"
Solicitante : GENEREX PHARMACEUTICALS.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 595 del 29 de agosto de 2008

Yo, **ELIANA ISaura MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **PROCAPS S.A.** conformada bajo las leyes de la Republica 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 FARMACÉUTICA DE ABSORCIÓN ORAL Y SU MÉTODO DE ADMINISTRACIÓN**", cuyo titular es **GENEREX PHARMACEUTICALS**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

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 para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular **formadores micelares**. 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 30 de mayo de 2008, reivindicando prioridad bajo la solicitud WO2005CA01816 del 2005-11-30; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 595 del 29 de agosto de 2008, cuya publicación internacional corresponde a la WO2007062494 del 2007-06-07.

2.2. La solicitud colombiana 08055399 objeto de la presente oposición, se refiere a una formulación farmacéutica para absorber por la mucosa oral que incluye una cantidad efectiva de (a) un agente farmacéutico en forma de micela combinada, (b) al menos un compuesto formador de micela seleccionado del grupo de sulfato alquilo de metal alcalino y monooleato de sorbitan polioxietileno, (c) un copolímero bloque de polioxietileno y polioxipropileno, (d) al menos un

compuesto formador de micela adicional que se selecciona del grupo de glicina trihidroxioxocolanila y sales del mismo, glicerina, poliglicerina, lecitina, ácido hialurónico, ácido glicólico, ácido láctico, extracto de manzanilla, extracto de pepino, ácido oleico, ácido linoleico, ácido linolénico, monooleína, monooleatos, monolauratos, ácido boraja, aceite de onagra, mentol, poliglicerina, lisina, polilisina, trioleína, éteres polioxietileno, éteres alquilo polidocanol, quenodeoxicolato, deoxicolato, salicilato de metal alcalino, edetato farmacéuticamente aceptable, y sales farmacéuticamente aceptables y sus análogos, y (e) un disolvente adecuado; en la que la sal de glicina trihidroxioxocolanila es glicocolato de sodio; en la que el monooleato sorbitan polioxietileno es un monooleato (x)-sorbitan mono-9-octadecenoato poli (oxi-1,2-etanodil); en el que el sulfato alquilo de metal alcalino es sulfato de lauril-sódico.

2.3. En primera instancia, se debe advertir que las reivindicaciones se refieren al uso y a un método de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- "Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)", los usos no están contemplados como patentables; y, Artículo 20.- "No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales". Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente al uso y a un método de tratamiento, no sería patentable.

2.4. Ahora bien, con base en 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 afecta la patentabilidad de la presente solicitud:

- D1: CA2354148 publicada el 29 de junio de 2000.

2.5. Ahora bien, el documento D1, particularmente en la descripción revela un aerosol que surte oralmente una formulación farmacéutica que incluye un agente farmacéutico proteico micelar, un sulfato metal alcali lauril, al menos tres compuestos formadores de micela, un fenol y un propulsor. Entre los compuestos formadores de micela es posible ser seleccionado del grupo que consiste en: lecitina, ácido hialurónico, sales farmacéuticamente aceptables de ácido hialurónico, ácido glicólico, ácido láctico, extracto de manzanilla, extracto de pepino, ácido oleico, ácido linoleico, monooleinas, monooleatos, monolauratos, aceite de rosas, mentol, glicina trihidroxí oxocholanil y sales farmacéuticamente aceptables. El documento D1 como tal enseña como la cantidad de cada formador de micela está presente en una cantidad entre 1 a 20 p/p del porcentaje total de la formulación, donde la formulación se libera a través del aparato de spray con la ayuda de un propelente. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud se puede derivar de manera evidente y partir de esta anterioridad D1, cualquier persona versada en la materia puede llegar a una formulación farmacéutica para absorber por la mucosa oral que incluye una cantidad efectiva de un agente farmacéutico en forma de micela combinada, al menos un compuesto formador de micela, un copolímero bloque de polioxietileno y polioxipropileno y al menos un compuesto formador de micela, tal y como aquella revelada en la presente solicitud.

Por lo tanto, visto dicho documento D1 la presente solicitud carece evidentemente de altura inventiva.

2.6. Por lo tanto, este documento objeto de oposición a la luz del documento D1 carece evidentemente de ALTURA INVENTIVA.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 08055399 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.

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

2.8.1. **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, 30 de noviembre de 2005, a partir del documento D1, puede llegar de manera evidente a una formulación farmacéutica para absorber por la mucosa oral que incluye una cantidad efectiva de un agente farmacéutico en forma de micela combinada, al menos un compuesto formador de micela, un copolímero bloque de polioxietileno y polioxipropileno y al menos un compuesto formador de micela, sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. **CARENCIA DE APLICACIÓN INDUSTRIAL** La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. La presente solicitud carece de aplicación industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método

terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

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

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada **"FORMULACIÓN FARMACÉUTICA DE ABSORCIÓN ORAL Y SU MÉTODO DE ADMINISTRACIÓN"**, cuyo titular es **GENEREX PHARMACEUTICALS**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 595 del 29 de agosto de 2008.

3. PRUEBAS

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

- D1: CA2354148 publicada el 29 de junio de 2000.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

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

5. ANEXOS

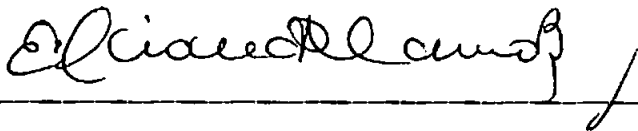
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **PROCAPS S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - DI: CA2354148 publicada el 29 de junio de 2000.

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 Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



ELLANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.



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 la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **08 055.399**, titulada "**FORMULACIÓN FARMACÉUTICA DE ABSORCIÓN ORAL Y SU MÉTODO DE ADMINISTRACIÓN**", cuyo titular es **GENEREX PHARMACEUTICALS**, publicada en la gaceta No. 595 del 29 de Agosto de 2008.

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 24 días del mes de Octubre de 2008:

PROCAPS S.A.

C.C. N° 16'251.923

NIT: 890.106.527-5

Representante Legal

Acepto:

ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

LA PRESENTE DILIGENCIA
SE PRACTICA A PETICION
DE PARTE INTERESADA

DILIGENCIA DE RECONOCIMIENTO ANTE EL
SUSCRITO NOTARIO SEXTO DE BARRANQUILLA
COMPARECIO Walter Quintero
IDENTIFICADO CON cc F 16251 923 Polina (chlla)
y declaró que es cierto el contenido del documento
anterior y suya la firma
Barranquilla **24 OCT. 2008**

LA HUELLA DE ESTA
DILIGENCIA CORRESPONDE
NOTARIO SEXTO

**DILIGENCIA DE PRESENTACION PERSONAL
Y RECONOCIMIENTO**

NOTARIA 2ª DE CHIA CUNDINAMARCA

**LA SUSCRITA NOTARIA
CERTIFICA**

NOTARIA 6A DE BARRANQUILLA
JORGE DEL GORDO FDEZ DE CASTRO
NOTARIO ENCARGADO

Que el escrito dirgido Super Interdicio de
Ind. y Comercio

fue presentado personalmente por: Eliana Isana
Mario Bohorquez T.P. 83823 C.S.

identificado(s) con C.C. 51975664 de Bta

quien(es) declaro(arón) que su contenido es cierto y que la(s)

firma(s) puesta(s) en el es (son) suya(s)

Firma E. Isana Bohorquez

Chía Cundinamarca **24 NOV 2008**

La Notaria



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 91,935
FECHA : NOVIEMBRE 25 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-055399- -00002-0000

Fecha 2008-11-25 14:37:31 Dep. 2020 NULCREACIONE
LVA 11 PATENTEYII LVA 375 FASENACIONALI
Art 400 OPDSIOBSERVIER Folios 60

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	4928873	09/10/2008	1,862,000.00
BYNOPHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	14672361	18/11/2008	1,330,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
		12 MARCAS Y LENAS COMERCIALES	266,000.00
		TOTAL :	\$ 266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____



***** 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
11*****

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

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

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad-----
limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA
"PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada-----
se transformo en sociedad anonima bajo la denominacion social de
"PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A."-----

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada-----
se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI -
MITADA".-----

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada-----
se transformo en sociedad anonima bajo la denominacion social de
"PRODUCTORA DE CAPSULAS DE GELATINA S.A. "PROCAPS S.A."-----

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del

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

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

libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion PROCAPS S.A. -----

C E R T I F I C A

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

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18

C E R T I F I C A

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

DENOMINACION O RAZON SOCIAL:

PROCAPS S.A.-----

SIGLA: PROCAPS.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.

C E R T I F I C A

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



***** Pag. 2
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
11*****

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

PROCAPS S.A.-----

NIT: 890.106.527-5.

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

C E R T I F I C A

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

C E R T I F I C A

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

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

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

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

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2,000,000,000	*****2,000,000	*****1,000
Suscrito		
\$*****1,229,071,000	*****1,229,071	*****1,000
Pagado		
\$*****1,229,071,000	*****1,229,071	*****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponde a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva.

La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente

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



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

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

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NIT: 890.106.527-5.

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

C E R T I F I C A

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

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:

PROCAPS S.A.-----
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben	CC.*****7,463,982
2. Minski Gontovnik Meyer	CC.*****7,461,324
3. Minski Gontovnik Jose	CC.*****8,671,834

Suplentes

1. Minski Zilberblum Elliot	CC.*****72,219,541
2. Minski Deitel Daniel	.*****
3. Minski Sharon	PA.*990,212,082,805

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	

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



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

Minski Gontovnik Ruben	CC.*****7,463,982
Suplente del Presidente	
Minski Minski Abraham	CC.*****802,575
Vicepresidente	
Minski Gontovnik Meyer	CC.*****7,461,324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 11 del 01 de Febrero de 2001 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 12 de Febrero de 2001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General.	
Uribe Ochoa Guillermo Luis	CC.*****70,073,754

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Gerente.	
Tanaka Tatekawa 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

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

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

S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal.	
Lozada Villareal Milena	CC.*****32,748,111

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo,-----
y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, ----
3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, ----
3.507, Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, -----
obrando como Presidente y Representante Legal de la sociedad C.I. NATURMEGA S.A., que obrando en su condicion de Presidente y -----
Representante Legaql de la sociedad PROCAPS S.A., el presidente ----
debidamente facultado por los Estatutos Sociales y por el Maximo Organ Social, otorga los siguientes poderes: Otorgar poder -----
general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN ----
MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO -----
CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con las facultades que se transcriben a continuacion: a.- Para que ----
representen a la sociedad PROCAPS S.A, ante todo tipo de -----
autoridades administrativas y jurisdiccionales, en asuntos de -----
naturaleza civil, laboral, comercial, penal, aduanera, cambiaria, tributaria, policiva, administrativa y fiscal. b.- Contestar y ----
presentar demandas, requerimientos, recursos, pedir y aportar -----
pruebas, recibir, notificarse, ejercer la accion de tutela, -----
tramitar incidente de desacato, comparecer en los procesos que ----
cursen contra la sociedad, allanarse en nombre de la sociedad en los asuntos que sean necesarios, transigir, desistir, sustituir, renunciar y reasumir el poder. c.- La facultad expresa de -----
conciliar, por tanto pueden llegar a acuerdos conciliatorios, ----
transaccionales, judiciales o extrajudiciales o extrajudiciales, cualquiera que sea su cuantia, para lo cual las apoderadas deben aportar la autorizacion simple y escrita del Representante legal de la sociedad. d.- Podran presentar solicitudes de devolucion y/o compensacion de impuestos, ventas y rentas, recibir los pagos por las devoluciones y adelantar todo tramite o proceso administrativo ante la DIAN, de tal forma que en ningun momento quede sin -----
representacion legal de la sociedad. PODERES ESPECIALES: a.- Se ----
confiere poder especial amplio y suficiente a las personas que se determinan seguidamente, que conforman el grupo A y B, para, para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), -----
liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. Grupo A. WALTER NANAKA TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO -----
CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN -----

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



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C A M A R A D E C O M E R C I O
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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA -----
DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO -----
CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME
FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial -----
amplio y suficiente al señor WILLIAM ALBERTO BARROS CERRA -----
CC.No.8.715.941, para que en nombre y representacion de PROCAPS ----
S.A., suscriban declaraciones cambiarias, aduaneras y tributarias a
que este obligada la sociedad, en el giro normal de sus negocios y
operaciones sociales, por tanto quedan facultados para firmarlas,
como tambien los demas documentos relacionados con ellas, -----
notificarse, aportar y solicitar las pruebas que sean necesarias.
c.-Otorgar poder especial amplio y suficiente al señor MARLON ----
TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS
CERRA CC.No.8.715.941, para que en nombre y representacion de -----
PROCANPS S.A., suscriban las declaraciones, reportes y cualquier
documento relacionado con los tramites o registros de Comercio ----
Exterior y o cualquier entidad del Estado que haga sus veces: d)
Otorgar poder especial amplio y suficiente a la doctora CARMEN ----
ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER
TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y -----
representacion de PROCAPS S.A.; endosen los titulos valores de la
sociedad hasta por la suma de UN MIL MILLONES DE PESOS -----
(1.000.000.000.00) M.L. CUARTO: EI representante legal de la -----
sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta
que la presente reforma fue aprobada por la Asamblea General -----
Extraordinaria de Accionista de PROCAPS S.A., con observancia de
las disposiciones legales y estatutarias.-----

C E R T I F I C A

Que por Escritura Pública No. 1,933 del 16 de Sep/bre de 2008,
otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente
se inscribió en esta Cámara de Comercio, el 06 de Octubre de 2008
bajo el No. 3,748 del libro respectivo,-----
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, que
comparece en su condicion de Presidente y Representante Legal de la
Sociedad PROCAPS S.A., confiere por medio de este instrumento -----
publico Poder especial Amplio y Suficiente a la doctora MILENA ----
ESCAFFI PARDO, C.C. No. 32.758.420, para que en nombre y -----
representacion de PROCAPS S.A., suscriba declaraciones cambiarias,
aduaneras y tributarias a que este obligada la sociedad en el giro
normal de sus negocios y operaciones sociales, por tanto queda ----
facultada para firmar, como tambien los demas documentos -----
relacionados con ellas, notificarse, aportar y solicitar las -----
pruebas que sean necesarias.-----

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

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

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

C E R T I F I C A

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

C E R T I F I C A

Que su última Renovación fue el: 19 de Marzo de 2008.

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

C E R T I F I C A

Que los actos de registro aquí certificados quedan en firme cinco días hábiles despues de la correspondiente inscripción, siempre que, dentro de dicho término, no sean objeto de los recursos de reposición ante esta entidad, y/o de apelación para ante la Superintendencia de Industria y Comercio.

m. fajon

ANEXO 1

(19)  Canadian
Intellectual Property
Office

An Agency of
Industry Canada

Office de la Propriété,
Intellectuelle
du Canada

Un organisme
d'Industrie Canada

(11) **CA 2 354 148** (13) **A1**

(40) 29.06.2000

(43) 29.06.2000

(12)

(21) 2 354 148

(51) Int. Cl. 7: **A61K 9/12, A61K 9/107**

(22) 16.12.1999

(85) 08.06.2001

(86) PCT/CA99/01231

(87) WO00/37051

(30) 60/113,239 US 21.12.1998
09/251,464 US 17.02.1999
09/386,284 US 31.08.1999

(72) MODI, PANKAJ (CA).

(71) GENEREX PHARMACEUTICALS INC.,
202-33 Harbour Square, TORONTO, O1 (CA).

(74) RIDOUT & MAYBEE

(54) FORMULATIONS D'AEROSOLS POUR APPLICATION BUCCALE ET PULMONAIRE

(54) AEROSOL FORMULATIONS FOR BUCCAL AND PULMONARY APPLICATION

(57)

²²²A mixed micellar aerosol pharmaceutical formulation includes a micellar ²proteinic pharmaceutical agent, an alkali metal lauryl sulphate, at least ²three micelle forming compounds, a phenol and a propellant. The micelle ²forming compounds are selected from the group consisting of lecithin, ²hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, ²glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, ²linoleic acid, linolenic acid, monoolein, monooleates, monolaurates, borage ²oil, evening of primrose oil, menthol, trihydroxy oxocholanyl glycine and ²pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, ²polylysine, triolein, polyoxyethylene ethers and analogues thereof, ²polidocanol alkyl ethers and analogues thereof, chenodeoxycholate and ²deoxycholate. The amount of each micelle forming compound is present in a ²concentration of from 1 to 20 wt./wt.% of the total formulation, and the total ²concentration of micelle forming compounds are less than 50 wt./wt.% of the ²formulation. The propellant, e.g., a fluorocarbon propellant, provides ²enhanced absorption of the pharmaceutical agent, particularly in the buccal ²cavity.²



Office de la Propriété
Intellectuelle
du Canada

Un organisme
d'Industrie Canada

Canadian
Intellectual Property
Office

An agency of
Industry Canada

CA 2354148 A1 2000/06/29

(21) 2 354 148

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(66) Date de dépôt PCT/PCT Filing Date: 1999/12/16
(67) Date publication PCT/PCT Publication Date: 2000/06/29
(65) Entrée phase nationale/National Entry: 2001/06/08
(86) N° demande PCT/PCT Application No.: CA 99/01231
(87) N° publication PCT/PCT Publication No.: WO 00/37051
(30) Priorités/Priorities: 1998/12/21 (60/113,233) US;
1999/02/17 (09/251,464) US; 1999/08/31 (09/386,284) US

(51) Cl.Int.⁷/Int.Cl.⁷ A61K 9/12, A61K 9/107
(71) Demandeur/Applicant:
GENEREX PHARMACEUTICALS INC., CA
(72) Inventeur/Inventor:
MODI, PANKAJ, CA
(74) Agent: RIDOUT & MAYBEE

(54) Titre : FORMULATIONS D'AEROSOLS POUR APPLICATION BUCCALE ET PULMONAIRE
(54) Title: AEROSOL FORMULATIONS FOR BUCCAL AND PULMONARY APPLICATION

(57) Abrégé/Abstract:

A mixed micellar aerosol pharmaceutical formulation includes a micellar proteinic pharmaceutical agent, an alkali metal lauryl sulphate, at least three micelle forming compounds, a phenol and a propellant. The micelle forming compounds are selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linoleic acid, linolenic acid, monoprotein, monooleates, monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy oxocholanyl glycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof, polidocanol alkyl ethers and analogues thereof, chenodeoxycholate and deoxycholate. The amount of each micelle forming compound is present in a concentration of from 1 to 20 wt./wt % of the total formulation, and the total concentration of micelle forming compounds are less than 50 wt./wt.% of the formulation. The propellant, e.g., a fluorocarbon propellant, provides enhanced absorption of the pharmaceutical agent, particularly in the buccal cavity.

Canada

<http://opic.gc.ca> • Ottawa-Hull K1A 0C9 • <http://cipo.gc.ca>

OPIC • CIPD 191

OPIC



CIPD

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

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(54) Title: AEROSOL FORMULATIONS FOR BUCCAL AND PULMONARY APPLICATION		
(57) Abstract A mixed micellar aerosol pharmaceutical formulation includes a micellar proteinic pharmaceutical agent, an alkali metal lauryl sulphate, at least three micelle forming compounds, a phenol and a propellant. The micelle forming compounds are selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linoleic acid, linolenic acid, monoolein, monooleates, monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy oxncholanyl glycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof, polidocanol alkyl ethers and analogues thereof, chenodeoxycholate and deoxycholate. The amount of each micelle forming compound is present in a concentration of from 1 to 20 wt./wt.% of the total formulation, and the total concentration of micelle forming compounds are less than 50 wt./wt.% of the formulation. The propellant, e.g., a fluorocarbon propellant, provides enhanced absorption of the pharmaceutical agent, particularly in the buccal cavity.		

AEROSOL FORMULATIONS FOR BUCCAL AND
PULMONARY APPLICATION

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Field of the Invention

The present invention relates to an improved delivery system for the administration of large-molecule pharmaceuticals, e.g. peptidic drugs, vaccines and hormones. In particular it relates to pharmaceuticals which may be administered by means of an aerosol into the mouth, for buccal or pulmonary application.

Background to the Invention

In spite of significant efforts in academic and commercial laboratories, major breakthroughs in oral peptide and protein formulation have not been achieved. Relatively little progress has been made in reaching the target of safe and effective oral formulations for peptides and proteins. The major barriers to developing oral formulations for proteins and peptides include poor intrinsic permeability, luminal and cellular enzymatic degradation, rapid clearance, and chemical stability in the gastrointestinal (GI) tract. Pharmaceutical approaches to address these barriers, which have been successful with traditional small, organic drug molecules, have not readily translated into effective peptide and protein formulations. Although the challenges are significant, the potential therapeutic benefits remain high especially in the field of diabetes treatment using insulin.

Scientists have explored various administration routes other than the injection for proteins and peptides. Oral and nasal cavities have been of greatest interest to scientists. Both the oral and nasal

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membranes offer advantages over other routes of administration. For example, drugs administered through these membranes have a rapid onset of action, provide therapeutic plasma levels, avoid first pass effect of hepatic metabolism, and avoid exposure of the drug to hostile GI environment. Additional advantages include easy access to the membrane sites so that the drug can be applied, localized and removed easily. Further, there is a good potential for prolonged delivery of large molecules through these membranes.

The oral routes have received far more attention than has the other routes. The sublingual mucosa includes the membrane of ventral surface of the tongue and the floor of the mouth whereas the buccal mucosa constitutes the lining of the cheek. The sublingual mucosa is relatively permeable thus giving rapid absorption and acceptable bioavailability of many drugs. Further, the sublingual mucosa is convenient, acceptable and easily accessible. This route has been investigated clinically for the delivery of a substantial number of drugs.

The ability of molecules to permeate through the oral mucosa appears to be related to molecular size, lipid solubility and peptide protein ionization. Small molecules, less than 1000 daltons appear to cross mucosa rapidly. As molecular size increases, the permeability decreases rapidly. Lipid soluble compounds are more permeable than non-lipid soluble molecules. Maximum absorption occurs when molecules are un-ionized or neutral in electrical charges. Therefore charged molecules present the biggest challenges to absorption through the oral mucosae.

Most proteinic drug molecules are extremely large molecules with molecular weight exceeding 6000 daltons. These large molecules have very poor lipid solubility

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and are practically impermeable. Substances that facilitate the absorption or transport of large molecules (>2000 daltons) across biological membranes are known as enhancers, (Lee et al., Critical Reviews in
5 Therapeutic drug Carrier Systems, 8, 91, 1991; Lee et al., Critical Reviews in Therapeutic drug Carrier Systems, 8, 115, 1991, 1992). Enhancers have been characterized as chelators, bile salts, fatty acids, synthetic hydrophilic and hydrophobic compounds, and
10 biodegradable polymeric compounds.

Various mechanisms of action of enhancers have been proposed. These mechanisms of action, at least for protein and peptidic drugs include (1) reducing viscosity and/or elasticity of mucous layer, (2)
15 facilitating transcellular transport by increasing the fluidity of the lipid bilayer of membranes, and (3) increasing the thermodynamic activity of drugs (Critical Rev, 117-125, 1991, 1992).

Many enhancers have been tested so far and some
20 have found to be effective in facilitating mucosal administration of large molecule drugs. However, hardly any penetration enhancing products have reached the market place. Reasons for this include lack of a satisfactory safety profile respecting irritation,
25 lowering of the barrier function, and impairment of the mucocilliary clearance protective mechanism. It has been found that some enhancers, especially those related to bile salts, and some protein solubilizing agents give an extremely bitter and unpleasant taste. This makes
30 their use almost impossible for human consumption on a daily basis. Several approaches have been utilized to improve the taste of the bile salts based delivery systems, but none one of them are commercially acceptable for human oral consumption to date. Among
35 the approaches utilized includes patches for buccal

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mucosa, bilayer tablets, controlled release tablets, use of protease inhibitors, buccally administered film patch devices, and various polymer matrices.

The basic problem associated with the above technologies is the use of large quantities of bile acids and their salts to promote the transport of the large molecules through membranes in the form of localized delivery system using patches or tablets. In spite of using protease inhibitors and polymer coatings the technologies failed to deliver proteinic drugs in the required therapeutic concentrations. Further, the problem is compounded because of the localized site effect of the patch which resulted in severe tissue damage in the mouth. Most attempts were made to deliver large molecules via the oral, nasal, rectal, and vaginal routes using single bile acids or enhancing agents in combination with protease inhibitors and biodegradable polymeric materials. However, it is extremely difficult to achieve therapeutic levels of proteinic drugs using these formulations. Single enhancing agents fail to loosen tight cellular junctions in the oral, nasal, rectal and vaginal cavities for a required period of time in order to permit passage of large molecules through the mucosal membranes without further degradation. This problem makes it impractical to use the above mentioned systems commercially.

Oral delivery offers a variety of benefits for systemic drug delivery. For example, it provides easy, non-invasive access to a permeable mucosa, which facilitates rapid drug absorption and a fast onset of action of the drug. In comparison to the GI tract and other organs, the buccal environment has lower enzymatic activity and a neutral pH.

In order to overcome the above mentioned problem of the bitter taste, irritation and the penetration of

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large molecules through the sublingual, buccal and GI tract mucosal lining, a system has now been designed where a proteinic drug is encapsulated in mixed micelles made up of a combination of enhancers.

5 A method of substantially overcoming the above disadvantages has now been found. The amount of physiologically peptide or protein in the compositions of the present invention is typically a quantity that provides an effective amount of the pharmaceutical or
10 drug to produce the physiological activity (therapeutic plasma level) for which peptide or protein is being administered. In consideration of the fact that the bioavailability of any active substance can never be 100%, it is preferable to incorporate slightly larger
15 amount than the desired dosage.

It is believed that improvements in penetration and absorption of mixed micellar formulations can be achieved by administering the mixed micellar formulation with propellants such as tetrafluoroethane,
20 heptafluoroethane, dimethylfluoropropane, tetrafluoropropane, butane, isobutane, dimethyl ether and other non-CFC and CFC propellants. Preferably they are delivered through metered dose spray devices. Metered dose inhalers are known and are a popular
25 pulmonary drug delivery form for some drugs. The present formulation, including the propellant, is intended to improve the quality of absorption, stability and performance of many formulations. The compositions have been selected to give enhancement in the
30 penetration through pores, and facilitate absorption of the drugs to reach therapeutic levels in the plasma. One of the other benefits of using an atomizer or inhaler is that the potential for contamination is minimized because the devices are self contained.

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Summary of the Invention

Accordingly the present invention provides a mixed micellar aerosol pharmaceutical formulation and a propellant, comprising 1) a pharmaceutical agent in micellar form, ii) water, iii) an alkali metal C8 to C22 alkyl sulphate in a concentration of from 1 to 20 wt./wt.% of the total formulation, iv) at least three micelle forming compounds selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linoleic acid, linolenic acid, monoolein, monocleates, monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy oxo cholanylglycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof, polidocanol alkyl ethers and analogues thereof, chenodecxycholate, deoxycholate, and mixtures thereof, wherein the amount of each micelle forming compound is present in a concentration of from 1 to 20 wt./wt.% of the total formulation, and the total concentration of micelle forming compounds are less than 50 wt./wt.% of the formulation, v) a phenolic compound selected from the group consisting of phenol and methyl phenol in a concentration of from 1 to 10 wt./wt.% of the total formulation, and vi) a propellant selected from the group consisting of C1-C2 dialkyl ether, butanes, fluorocarbon propellant, hydrogen-containing fluorocarbon propellant, chlorofluorocarbon propellant, hydrogen-containing chlorofluorocarbon propellant, and mixtures thereof.

In one embodiment, the alkali metal C8 to C22 alkyl sulphate is in a concentration of from 2 to 5 wt./wt.% of the total formulation.

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In another embodiment, the alkali metal C8 to C22 alkyl sulphate is sodium lauryl sulphate.

In another embodiment, the lecithin is saturated or unsaturated, preferably selected from the group
5 consisting of phosphatidylcholine, phosphatidyl serine, sphingomyelin, phosphatidylethanolamine, cephalin, and lysolecithin.

In yet another embodiment, at least one of the micelle forming compounds is selected from the group
10 consisting of hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, polidocanol alkyl ethers, trihydroxy oxo cholanyl glycine, polyoxyethylene ethers, triolein and mixtures thereof, the concentration such micelle forming compound being from about 1 to
15 about 5 wt./wt. %.

Preferably, the ratio of proteinic pharmaceutical agent, e.g. insulin, to propellant is from 5:95 to 25:75.

In another embodiment, the propellant is selected
20 from the group consisting of tetrafluoroethane, tetrafluoropropane, dimethylfluoropropane, heptafluoropropane, dimethyl ether, n-butane and isobutane.

In yet another embodiment, the mixed micellar
25 pharmaceutical formulation and propellant are contained in an aerosol dispenser.

For insulin-containing and some other compositions, the composition may also contains at least one inorganic salt which opens channels in the gastrointestinal tract
30 and may provide additional stimulation to release insulin. Non-limiting examples of inorganic salts are sodium, potassium, calcium and zinc salts, especially sodium chloride, potassium chloride, calcium chloride, zinc chloride and sodium bicarbonate.

35 It will be recognized by those skilled in the art

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that for many pharmaceutical compositions it is usual to add at least one antioxidant to prevent degradation and oxidation of the pharmaceutically active ingredients. It will also be understood by those skilled in the art that colorants, flavouring agents and non-therapeutic amounts of other compounds may be included in the formulation. Typical flavouring agents are menthol, sorbitol and fruit flavours.

In one embodiment the antioxidant is selected from the group consisting of tocopherol, dexteroxime mesylate, methyl paraben, ethyl paraben, ascorbic acid and mixtures thereof. A preferred antioxidant is tocopherol.

In a preferred embodiment at least one protease inhibitor is added to the formulation to inhibit degradation of the pharmaceutical agent by the action of proteolytic enzymes. Of the known protease inhibitors, most are effective at concentrations of from 1 to 3 wt./wt.% of the formulation.

Non-limiting examples of effective protease inhibitors are bacitracin, soyabean trypsin, aprotinin and bacitracin derivatives, e.g. bacitracin methylene disalicylate. Bacitracin is the most effective of those named when used in concentrations of from 1.5 to 2 wt./wt.%. Soyabean trypsin and aprotinin also may be used in concentrations of about 1 to 2 wt./wt.% of the formulation.

The pharmaceutical agent may be selected from a wide variety of macromolecular agents, depending on the disorder to be treated, generally with molecular weights greater than about 1000 and especially between about 1000 and 2 000 000. Preferred pharmaceutical agents are selected from the group consisting of insulin, heparin, low molecular weight heparin, hirulog, hirugen, uridine, interferons, interleukins, cytokines,

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mono and polyclonal antibodies, immunoglobins, chemotherapeutic agents, vaccines, glycoproteins, bacterial toxoids, hormones, calcitonins, insulin like growth factors (IGF), glucagon like peptides (GLP-1),
5 large molecule antibiotics, protein based thrombolytic compounds, platelet inhibitors, DNA, RNA, gene therapeutics, antisense oligonucleotides, opioids, narcotics, hypnotics, steroids and pain killers.

The present invention also provides a process for
10 making a pharmaceutical composition suitable for delivery through transdermal membranes comprising the steps of:

98 2 32 a) mixing ^{of mixture} a pharmaceutical agent composition in an aqueous medium with an alkali metal C8 to C22 alkyl
15 sulphate, and at least three micelle forming compounds selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linoleic acid,
20 linolenic acid, monoolein, monooleates, monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy oxo cholanyl glycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and
25 analogues thereof, polidocanol alkyl ethers and analogues thereof, chenodeoxycholate, deoxycholate, and mixtures thereof, to form a ^{of mixture} micellar pharmaceutical agent composition;

98 2 32 b) adding a phenolic compound selected from the
30 group consisting of phenol, m-cresol and mixtures thereof, in which the addition takes place at a time selected from the group consisting of before the addition of the alkali metal C8 to C22 alkyl sulphate, during the addition of the alkali metal C8 to C22 alkyl

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5 sulphate, after the addition of the alkali metal C8 to C22 alkyl sulphate, before the addition of at least one of the micelle forming compounds, during the addition of at least one of the micelle forming compounds and after the addition of at least one of the micelle forming compounds; and subsequently

d) placing the formulation into an aerosol dispenser and charging the dispenser a propellant;

wherein the composition has at least three micelle forming compounds and the amount of the micelle forming compounds are each present in a concentration of from 1 to 20 wt./wt.% of the total formulation, and the total concentration of alkali metal alkyl sulphate and micelle forming compounds is less than 50 wt./wt.% of the formulation.

In one embodiment, the process comprises:

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a) mixing a pharmaceutical agent composition in an aqueous medium with an alkali metal C8 to C22 alkyl sulphate, and at least one micelle forming compound selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamemile extract, cucumber extract, oleic acid, linoleic acid, linolenic acid, monoolein, monooleates, monooleurates, borage oil, evening of primrose oil, menthol, trihydroxy oxo cholanyl glycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof, polidocanol alkyl ethers and analogues thereof, chenodeoxycholate, deoxycholate, and mixtures thereof, to form a micellar pharmaceutical agent composition; pg 28

b) during step a) or after step a), adding at least one micelle forming compound, different from that added in step a);

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c) during step a) or after step a), adding a phenolic compound selected from the group consisting of phenol, m-cresol and mixtures thereof; and subsequently

d) placing the formulation into an aerosol dispenser and charging the dispenser a propellant;

5 wherein the composition has at least three micelle forming compounds and the amount of the micelle forming compounds are each present in a concentration of from 1 to 20 wt./wt.% of the total formulation, and the total
10 concentration of alkali metal alkyl sulphate and micelle forming compounds is less than 50 wt./wt.% of the formulation.

In another embodiment, the process comprises:

08 232 a') mixing the pharmaceutical agent composition in
15 an aqueous medium with the alkali metal C8 to C22 alkyl sulphate and optionally at least one of the micelle forming compounds, to form a micellar proteinic pharmaceutical agent composition;

b') slowly adding at least one of the micelle
20 forming compounds, different from that added in step a'), while mixing vigorously, to form a mixed micellar composition;

c') mixing the mixed micellar composition
25 resulting from steps a') and b') with the phenolic compound; and subsequently

d') placing the formulation into an aerosol dispenser and charging the dispenser a propellant.

In a further embodiment, the process comprises the steps of:

08 232 30 a") mixing the pharmaceutical agent composition in an aqueous medium with the alkali metal C8 to C22 alkyl sulphate and optionally at least one of the micelle forming compounds, while mixing vigorously, to form a mixed micellar composition;

35 b") mixing the mixed micellar composition

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resulting from step a") with the phenolic compound; and subsequently

c") placing the formulation into an aerosol dispenser and charging the dispenser a propellant.

5 In another embodiment, the alkali metal alkyl sulphate is sodium lauryl sulphate.

In yet another embodiment, the formulation has micelle forming compound combinations selected from the group consisting of sodium hyaluronate, monoolein and
10 saturated phospholipid, ii) saturated phospholipid, monoolein and glycolic acid, iii) sodium hyaluronate, polyoxyethylene ether and lecithin, iv) polyoxyethylene ether, trihydroxy oxo cholanyl and lecithin, v)
15 polidocanol 9 lauryl ether, polylysine and triolein, vi) saturated phospholipid, polyoxyethylene ether and glycolic acid, and vii) trihydroxy oxo-cholanyl glycine, lecithin and chenodeoxycholate.

The vigorous mixing may be accomplished by using high speed stirrers, e.g. magnetic stirrers or propellor
20 stirrers, or by sonication.

In one embodiment, the mixed micellar formulation is formed by sonication of the aqueous micellar pharmaceutical agent composition in which one of the micelle forming compounds is lecithin.

25 The present invention also provides a metered dose aerosol dispenser with the composition of the present invention therein, in which an aqueous solution containing the pharmaceutical agent, and the propellant, are in a single phase.

30 The present invention also provides a method for administering mixed micellar pharmaceutical formulations of the present invention, by spraying the intermixed composition into the mouth with a metered dose spray device.

35 The present invention also provides a method for

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administration of a pharmaceutical agent in a buccal cavity of a human being by spraying into the cavity, without inhalation, from a metered dose spray dispenser, a mixed micellar pharmaceutical formulation and a

5 propellant comprising:

- 1) the pharmaceutical agent in micellar form, ii) water, iii) an alkali metal C8 to C22 alkyl sulphate in a concentration of from 1 to 20 wt./wt.% of the total formulation, iv) at least three micelle forming
- 10 compounds selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linoleic acid, linolenic acid, monoolein, monooleates,
- 15 monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy oxo cholanylglycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof,
- 20 polidocanol alkyl ethers and analogues thereof, chenodeoxycholate, deoxycholate, and mixtures thereof, wherein the amount of each micelle forming compound is present in a concentration of from 1 to 20 wt./wt.% of the total formulation, and the total concentration of
- 25 micelle forming compounds are less than 50 wt./wt.% of the formulation, v) a phenolic compound selected from the group consisting of phenol and methyl phenol in a concentration of from 1 to 10 wt./wt.% of the total formulation, and vi) a propellant selected from the
- 30 group consisting of C1-C2 dialkyl ether, butanes, fluorocarbon propellant, hydrogen-containing fluorocarbon propellant, chlorofluorocarbon propellant, hydrogen-containing chlorofluorocarbon propellant, and mixtures thereof.

35 In one embodiment, the dispenser is first shaken

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prior to spraying the pharmaceutical formulation and propellant into the buccal cavity.

Detailed Description of Preferred Embodiments

The present invention provides an improved method
5 for delivery of macromolecular (high molecular weight)
pharmaceutical agents, particularly through the
membranes in the mouth or lungs. The pharmaceutical
agents cover a wide spectrum of agents, including
proteins, peptides, hormones, vaccines and drugs. The
10 molecular weights of the macromolecular pharmaceutical
agents are preferably above 1000, especially between
1000 and 2 000 000.

For example, hormones which may be administered
with the present invention include thyroids, androgens,
15 estrogens, prostaglandins, somatotropins, gonadotropins,
erythropoietin, interferons, interleukins, steroids and
cytokines. Vaccines which may be administered with the
present invention include bacterial and viral vaccines
such as vaccines for hepatitis, influenza, tuberculosis,
20 canary pox, chicken pox, measles, mumps, rubella,
pneumonia, BCG, HIV and AIDS. Bacterial toxoids which
may be administered using the present invention include
diphtheria, tetanus, pseudomonas and mycobacterium
tuberculosis. Examples of specific cardiovascular or
25 thrombolytic agents include heparin, hirugen, hirulos
and hirudine. Large molecules usefully administered
with the present invention include monoclonal
antibodies, polyclonal antibodies and immunoglobins.

As will be understood, the concentration of the
30 pharmaceutical agent is an amount sufficient to be
effective in treating or preventing a disorder or to
regulate a physiological condition in an animal or
human. The concentration or amount of pharmaceutical
agent administered will depend on the parameters
35 determined for the agent and the method of

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administration, e.g. nasal, buccal, pulmonary. For example, nasal formulations tend to require much lower concentrations of some ingredients in order to avoid irritation or burning of the nasal passages. It is sometimes desirable to dilute an oral formulation up to 10-100 times in order to provide a suitable nasal formulation.

The mixed micellar formulation may be prepared by mixing an aqueous solution of the pharmaceutical agent, the alkali metal C8 to C22 alkyl sulphate, at least three micelle forming compounds, and optionally the phenolic compound. The micelle forming compounds may be added at the same time or after addition of the alkali metal alkyl sulphate. Mixed micelles will form with substantially any kind of mixing of the ingredients but vigorous mixing is preferred in order to provide smaller size micelles.

In one method a first micellar composition is prepared which contains the pharmaceutically active agent and at least the alkali metal alkyl sulphate. The first micellar composition is then mixed with at least three micelle forming compounds to form a mixed micellar composition. In another method, the micellar composition is prepared by mixing the pharmaceutically active agent, the alkali metal alkyl sulphate and at least one of the micelle forming compounds, followed by addition of the remaining micelle forming compounds, with vigorous mixing.

The phenol and/or m-cresol may be added to the mixed micellar composition to stabilize the formulation and protect against bacterial growth. Alternatively, the phenol and/or m-cresol may be added with the micelle forming ingredients. An isotonic agent such as glycerin may also be added after formation of the mixed micellar composition. The formulation is then put into an

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aerosol dispenser and the dispenser charged with the propellant. The propellant, which is under pressure, is in liquid form in the dispenser. In the present invention, when the composition of the present invention is in a dispenser, the aqueous phase may be separated from the propellant phase. Preferably, however, the ratios of the ingredients are adjusted by simple experimentation so that the aqueous and propellant phases become one, i.e. there is one phase. If there are two phases, it is necessary to shake the dispenser prior to dispensing a portion of the contents, e.g. through a metered valve. The dispensed dose of pharmaceutical agent is propelled from the metered valve in a fine spray.

The preferred propellants are hydrogen-containing chlorofluorocarbons, hydrogen-containing fluorocarbons, dimethyl ether and diethyl ether. Even more preferred is HFA 134a (1,1,1,2 tetrafluoroethane).

Although the present invention has such wide applicability, the invention is described hereinafter with particular reference to insulin and its analogues, which are used for the treatment of diabetes.

As indicated hereinbefore, the aerosol compositions of the present invention require that the pharmaceutical formulation be in mixed micellar form.

In the case of insulin, which is intended for administration through the mouth cavity, the first micellar solution may be made by adding water, and then hydrochloric acid (typically 5M) to powdered insulin, and then stirring until the powder is dissolved and a clear solution is obtained. The solution is then neutralized with sodium hydroxide. The sodium alkyl sulphate may then be added with low speed stirring, either alone or with at least one micelle forming compound. A typical concentration of sodium lauryl

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sulphate, as the sodium alkyl sulphate, in the aqueous solution is about 3 to 20 wt./wt.% of the solution. Typically, insulin is present in the micellar solution in an amount which will give a concentration of about 2
5 to 4 wt./wt.% of the final formulation.

The micellar solution so formed may then be mixed vigorously, e.g. by sonication or high speed stirring, to form a mixed micelle liposomal solution. Other micelle forming compounds may then be added. For
10 example, one or more micelle forming compounds selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linoleic acid, linolenic acid,
15 monoolein, monooleates, monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy oxo cholanyl glycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof,
20 polidocanol alkyl ethers and analogues thereof, chenodeoxycholate, and deoxycholate may be added. The mixing may be done with a high speed mixer or sonicator to ensure uniform micelle particle size distribution within the formulation.

25 After forming the mixed micellar formulation, the phenol and/or m-cresol is added prior to charging the composition to an aerosol dispenser. As indicated above, other ingredients, such as isotonic agents, flavouring agents, anti-oxidants, salts, protease
30 inhibitors or other pharmaceutically acceptable compounds may also be added. After the formulation is in the aerosol dispenser, the dispenser is charged with propellant in a known manner.

Each of the micelle forming compounds, when
35 present, is in a concentration of from 1 to 20 wt./wt.%

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of the total formulation.

Preferred salts of hyaluronic acid are alkali metal hyaluronates, alkaline earth hyaluronates and aluminium hyaluronate. The preferred salt is sodium hyaluronate.

5 The preferred concentration of hyaluronic acid or pharmaceutically acceptable salts of hyaluronic acid is from 1 to 5 wt./wt.% of the total formulation. An even more preferred range is from 1.5 to 3.5 wt./wt.% of the total formulation.

10 The specific concentrations of the essential ingredients can be determined by relatively straightforward experimentation. It will be understood that the amounts of certain ingredients may need to be limited in order to avoid compositions which produce
15 foam when sprayed rather than forming a fine spray. For absorption through the oral cavities, it is often desirable to increase, e.g. double or triple, the dosage which is normally required through injection or administration through the gastrointestinal tract.

20 As will be understood, the amount of each component of the formulation will vary depending on the pharmaceutical agent and the site of application. Preferred formulations buccal application have the following combinations: 1) sodium lauryl sulphate, 25 polidocanol 10 lauryl ether, sodium oxo cholanyl glycine and lecithin; ii) sodium lauryl sulphate, polidocanol 10 lauryl ether, phosphatidyl choline, oleic acid; iii) sodium lauryl sulphate, polidocanol 10 lauryl ether, sodium hyaluronate and lecithin; iv) sodium lauryl
30 sulphate, polidocanol 9 lauryl ether, triolein and polylysine; v) sodium lauryl sulphate, polyoxyethylene ether (10 lauryl), trihydroxy oxo cholanyl glycine and lecithin, vi) sodium lauryl sulphate, polidocanol 20 lauryl ether, evening of primrose oil and lecithin and
35 vii) sodium lauryl sulphate, trihydroxy oxo-cholanyl

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glycine, lecithin and chenodeoxycholate.

The therapeutic compositions of the present invention may be stored at room temperature or at cold temperature. Storage of proteinic drugs is preferable
5 at a cold temperature to prevent degradation of the drugs and to extend their shelf life.

It is believed that the mixed micelles of the present invention encapsulate molecules with a high degree of efficiency (>90% encapsulation). In general
10 the size of the micelle particles in the mixed micellar composition is about 1 to 10 nm or less, and preferably from 1 to 5 nm. Such mixed micelles tend to be smaller than the pores of the membranes in the oral cavity or the GI tract. It is therefore believed that the
15 extremely small size of mixed micelles helps the encapsulated molecules penetrate efficiently through the mucosal membranes of the oral cavity.

The desired size of aerosol droplets which are sprayed from the aerosol dispenser will depend, in part,
20 on where the pharmaceutical is to be deposited. For example, for deposition in the lungs, particle sizes of less than about 5 μm are preferred whereas for absorption in the buccal cavity of the mouth, particle sizes of about 6-10 μm are preferred.

25 The amount of physiologically peptide or protein in the compositions of this invention is typically a quantity that provides an effective amount of the pharmaceutical or drug to produce the physiological activity (therapeutic plasma level) for which peptide or
30 protein is being administered. In consideration of the fact that the bioavailability of any active substance can never be 100%, that is to say the administered dose of the active drug is not completely absorbed, it is preferable to incorporate slightly larger amount than
35 the desired dosage.

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It is believed that improvements in penetration and absorption of mixed micellar formulations are achieved by mixing the mixed micellar formulation with propellants such as tetrafluoroethane, heptafluoroethane, dimethylfluoropropane, tetrafluoropropane, butane, isobutane, dimethyl ether and other non-CFC and CFC propellants. Preferably they are delivered through metered dose spray devices. Metered dose inhalers are known and are a popular pulmonary drug delivery form for some drugs. One of the benefits of using an atomizer or inhaler is that the potential for contamination is minimized because the devices are self contained.

As indicated hereinbefore, by making adjustments to the concentrations of ingredients in the formulation, the formulation in the aerosol container may be in a single phase, i.e. the propellant and the remainder of the formulation are intimately mixed together. In such instances, the single phase generally remains stable for many months. With other combinations the formulation may be in two phases, i.e. the propellant in one phase and the remainder in another phase. In such event, then the formulation should be shaken vigorously prior to spraying the formulation into the mouth, so that there is a uniform amount of pharmaceutical agent in each shot delivered from the metered dose applicator (aerosol container).

The present formulation, including the propellant, is intended to improve the quality of absorption, stability and performance of many formulations. The compositions have been selected to give enhancement in the penetration through pores, and facilitate absorption of the drugs to reach therapeutic levels in the plasma.

Administration of the formulation into the buccal cavity is by spraying the formulation into the mouth.

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without inhalation, so that the droplets stay in the mouth rather than be drawn into the lungs.

The invention is illustrated by reference to the following examples.

5 Example 1

A first experiment was conducted to provide data for comparative purposes. This example does not fall within the scope of the present invention.

Powdered insulin was placed in a glass beaker
10 equipped with a stirrer. Distilled water was added and the solution was stirred at low speed. To this solution was added 5M HCl (pH 2) solution dropwise until the insulin was solubilized completely. This solution was then neutralized with 5M NaOH solution dropwise until
15 the pH was between 7 and 8. Seven mg phenol and 7 mg m-cresol were added to the solution and mixed thoroughly. The solution was diluted with distilled water until there were 200 units insulin per millilitre of solution. One millilitre portions were then transferred to glass
20 vials, which were then charged with 10.8 g HFA 134a propellant using a Pamasol (trade mark) 2008 semi-automatic gas filling apparatus.

Ten diabetic volunteers were asked to fast overnight and not have any breakfast prior to dosing.
25 On the first day, the volunteers were given 10 units insulin by injection (regular fast acting insulin, available from Eli Lilly). On the second day, the volunteers were given 60 units insulin of this example (10 puffs of 6 units each) into the mouth, without
30 inhalation. Blood glucose levels were monitored at intervals using Bayer's glucometer Elite for 3 hours. The average results, in millimoles per litre, are shown in Table I.

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Table I

Time*:	0	15	30	60	90	120	150	180
Injection:	6.8	6.6	5.9	5.3	4.9	4.5	4.1	3.7
Spray:	6.3	6.8	6.2	6.8	6.1	6.7	6.5	6.2

5 * time in minutes

These tests indicate that compared to the injection method, the spray method with formulations without the alkali metal alkyl sulphate and absorption enhancers of the present invention failed to lower the blood glucose
10 levels in diabetic patients. Thus, combination of the formulation and the spray method of application had no metabolic effect.

Example 2

Powdered insulin was placed in a glass beaker
15 equipped with a stirrer. Distilled water was added and the solution was stirred at low speed. To this solution was added 5M HCl (pH 2) solution dropwise until the insulin was solubilized completely. This solution was then neutralized, while stirring slowly, with 5M NaOH
20 solution dropwise until the pH was between 7 and 8. To this solution was added 7 mg sodium lauryl sulphate, 7 mg polyoxyethylene ether (10 lauryl) and 7 mg trihydroxy oxo cholanyl glycine and dissolved completely. Seven mg lecithin, solubilized in a water
25 alcohol solution (7 mg/mL) was then added while stirring at high speed, i.e. 2000 rpm. The solution was stirred for 30 minutes and then stored at 10°C. The resulting mixed micellar solution had about 200 units insulin. To this mixture 5 mg phenol, 5 mg m-cresol and 10 mg
30 glycerin were added.

The solution was pipetted (1mL/vial) into 10 mL capacity glass vials. The vials were then charged with HFA 134a propellant with a Pamasol 2008 automatic gas filling apparatus. The amount of propellant was
35 adjusted to 9 mL shot size in order to deliver 2 units

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insulin per actuation of the aerosol vial. The valves of the vials were designed to deliver 100 μ L spray per actuation, containing 2 units insulin. The formulation, in the glass vial, including the propellant, was in a single phase, i.e. was homogeneous.

The aerodynamic particle size was determined by an 8-stage USP Anderson (trade mark) Cascade Impactor Mark II. The impactor was cleaned with methanol and air dried at 30°C. Glass fibre filters were placed on the collection plates. The actuator was attached to the mouthpiece of the impactor and assembled onto the USP induction port and jet stages. A vacuum pump was connected and the air flow rate set to 28.3 litres per minute. The vial was primed by shaking for 10 seconds and actuating twice to waste. The shot was delivered by discharging the actuator into the mouthpiece and repeating 25 times. The deposited insulin was collected by rinsing the mouthpiece with 0.6 mL EDTA in 10 mL water at pH 8.7. The filters were removed and placed in scintillation vials and sonicated for 15 minutes. The quantity of insulin was then analysed using RP-HPLC. The results are shown in Table II (2 units per actuation) and III (4 units per actuation).

Table II

Stage No.	0	1	2	3
Volume (mL)	10	10	10	10
Mass (mg)	0.79	0.81	0.78	*
Units	10.4	10.0	10.0	
Actuation	5	5	5	
Units per actuation	2.0	2.0	2.1	
Particle size (μ m)	8.8	5.8	5.7	

* not determined/detected

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Table III

Stage No.	0	1	2	3
Volume (mL)	10	10	10	10
Mass (mg)	0.79	0.81	0.78	**
5 Units	20.7	21.0	20.1	
Actuation	5	5	5	
Units per actuation	4.15	4.18	4.01	
Particle size (μ m)	9	5.8	4.7	
10 ** not determined				

Based on these tests, the particle size was determined to be about 7 μ m, and stages 3-8 showed no insulin deposition, indicating that most particles were larger than about 6 μ m. This suggests that there would be no deep lung deposition of the formulation and that most of the formulation would be deposited in the buccal cavity.

Further tests were conducted to determine the shot size accuracy, by firing shots into thiel tubes and weighing the tubes before and after the sample collection. The tests showed the shots for 2 units per actuation weighed between 0.075 and 0.083 grams, i.e. within about $\pm 5\%$. The tests showed the shots for 4 units per actuation weighed between 0.076 and 0.083 grams, i.e. within about $\pm 5\%$. The tests showed the shots for 6 units per actuation weighed between 0.070 and 0.082 grams, i.e. within about $\pm 8\%$. HPLC analysis showed the doses delivered to be from 2.01 units to 2.07 units for 2 units per actuation, from 3.9 units to 4.4 units for 4 units per actuation, and from 5.8 units to 6.3 units for 6 units per actuation.

Ten diabetic volunteers were asked to fast overnight and not have any breakfast prior to dosing. On the first day, the volunteers were given 10 units insulin by injection (regular fast acting insulin,

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available from Eli Lilly). On the second day, the volunteers were given 60 units insulin of this example (10 puffs of 6 units each) into the mouth, without inhalation. Plasma insulin levels were measured at 5 intervals by the RIA method for 3 hours. The average results, in micromoles per millilitre, are shown in Table IV. Blood glucose levels were also monitored at intervals using Bayer's glucometer Elite for 3 hours. The average results, in millimoles per litre, are shown 10 in Table V.

Table IV

Time*:	0	15	30	45	60	90	120	150	180
Injection:	10	9.1	11	16	31	45	32	25	20
Spray:	8.7	12.1	19.8	28	27	36	29	21	13

15 * time in minutes

This test indicated that the injection method and spray method were comparable.

Table V

Time*:	0	15	30	45	60	90	120	150	180
Injection:	6.1	6.0	5.9	5.5	5.1	4.5	3.8	4.2	4.4
Spray:	6.6	6.3	5.8	5.2	4.8	4.9	4.5	5.0	5.3

20 * time in minutes

This test indicated that the injection method and spray method were comparable in terms of glucose level.

25 Tests were also conducted with 40 units of spray at 10 puffs each, and compared to 10 units injected by measuring plasma levels and glucose levels as above. The results are shown in Table VI (plasma) and VII (glucose).

Table VI

Time*:	0	15	30	45	60	90	120	150	180
Injection:	9	9	13	19	34	45	42	35	24
Spray:	10	13	18.5	27	30	33	29	19	14

30 * time in minutes

35 This test indicated that the injection method and

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spray method were comparable in terms of plasma insulin levels.

Table VII

Time*:	0	15	30	60	90	120	150	180
5 Injection:	5.8	6.0	5.9	5.5	5.0	4.5	4.1	3.9
Spray:	6.0	5.7	5.4	5.0	5.1	4.7	4.5	4.2

* time in minutes

This test indicated that the injection method and spray method were comparable in terms of glucose levels.

10 Example 3

Powdered insulin was placed in a glass beaker equipped with a stirrer. Distilled water was added and the solution was stirred at low speed. To this solution was added 5M HCl (pH 2) solution dropwise until the
 15 insulin was solubilized completely. This solution was then neutralized, while stirring slowly, with 5M NaOH solution dropwise until the pH was between 7 and 8. To this solution was added 30.4 mg sodium lauryl sulphate per millilitre of insulin solution, 30.4 mg polidocanol
 20 9 lauryl ether per millilitre of insulin solution and 10.0 mg polylysine per millilitre of insulin solution, and dissolved completely. 15.2 mg triolein per millilitre of insulin solution was then added while stirring at high speed, i.e. 2000 rpm. The solution was
 25 stirred for 30 minutes and then stored at 10°C. The resulting solution was a mixed micellar solution. To this mixture 15.2 mg m-cresol per millilitre of insulin solution were added.

The solution was pipetted (1 mL) into glass vials.
 30 The vials were then charged with 10.8 g HFA 134a propellant per vial, with a Pamasol 2008 automatic gas filling apparatus. The valves of the vials were designed to deliver 100 µL spray per actuation, containing 6 units insulin. The formulation, in the
 35 glass vial, including the propellant, was in a single

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phase, i.e. was homogeneous.

Ten diabetic volunteers were asked to fast overnight and not have any breakfast prior to dosing. On the first day, the volunteers were given 10 units
 5 insulin by injection (regular fast acting insulin, available from Eli Lilly). On the second day, the volunteers were given 60 units insulin of this example (10 puffs of 6 units each) into the mouth, without inhalation. Plasma insulin levels were measured at
 10 intervals by the RIA method for 3 hours. The average results, in micromoles per millilitre, are shown in Table VIII. Blood glucose levels were also monitored at intervals using Bayer's glucometer Elite for 3 hours. The average results, in millimoles per litre, are shown
 15 in Table IX.

Table VIII

Time*:	0	15	30	45	60	90	120	150	180
Injection:	9	9.1	14	20	40	48	39	34	27
Spray:	10	15.1	22	32	47	36	27	21	19
* time in minutes									

This test indicated that the injection method and spray method were comparable

Table IX

Time*:	0	15	30	45	60	90	120	150	180
Injection:	6.6	6.5	6.1	5.5	4.9	4.5	3.8	3.5	4.4
Spray:	6.8	5.9	5.2	4.8	4.3	3.9	4.5	5.7	5.3
* time in minutes									

This test indicated that the injection method and spray method were comparable in terms of glucose level.

30 Example 4

A further experiment was conducted to provide data for comparative purposes.

Powdered insulin was placed in a glass beaker equipped with a stirrer. Distilled water was added and
 35 the solution was stirred at low speed. To this solution

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was added 5M HCl (pH 2) solution dropwise until the insulin was solubilized completely. This solution was then neutralized with 5M NaOH solution dropwise until the pH was between 7 and 8. The solution was diluted
5 with distilled water until there were 600 units insulin per millilitre of solution. One millilitre portions were then transferred to 10 mL capacity glass vials, which were then charged with 10.8 g HFA 134a propellant using a Pamasol (trade mark) 2008 semi-automatic gas
10 filling apparatus. This formulation does not fall within the scope of the present invention.

The gas phase and the aqueous phase were observed to be distinctly separate. Even shaking of the vials did not appear to homogenize the composition.

15 Tests were conducted to determine the shot size accuracy, by firing shots into thiel tubes and weighing the tubes before and after the sample collection. The tests showed five consecutive shots for 6 units per actuation weighed 0.094, 0.110, 0.200, 0.150 and
20 0.050 grams, i.e. within about $\pm 60\%$ of the average. This compares with $\pm 8\%$ in Example 2 (which is within the scope of the present invention).

HPLC analysis showed the average doses delivered to be 5.4 units per actuation from shots 5-10, 7.1 units
25 per actuation from shots 45-50 and 8.6 units per actuation from shots 85-90.

These results showed that such composition, without the micelle-forming ingredients, gave non-uniform dose delivery.

30 Example V

Ten millilitres of concentrated insulin containing 10 000 units per millilitre was placed in a glass beaker. To this solution was added 7 mg sodium lauryl sulphate, 7 mg polyoxyethylene ether (10 lauryl), 7 mg trihydroxy
35 oxo-cholanyl glycine and 7 mg lecithin. The components

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were stirred until they were completely dissolved. Seven mg phenol and 7 mg m-cresol were added to the solution and mixed thoroughly.

One millilitre portions of the solution were
 5 pipetted into 10 mL capacity glass vials. The vials had metered dose valves thereon. The vials were then charged with HFA 134a propellant with Pamasol 2008 (trade mark) gas filling apparatus. The amount of propellant was adjusted to 9 mL per vial in order to
 10 deliver 10 units of insulin per actuation of the valve (100 μ L shot/actuation). The formulation, in the glass vial, including the propellant, was in a single phase, i.e. was homogeneous.

Ten diabetic patients fasted overnight and did not
 15 have a breakfast prior to dosing. On the first day, each patient had 7 units regular fast acting insulin, available from Eli Lilly, administered by injection. On the second day, each patient was given 70 units insulin of this example (7 puffs of 10 units each) into the
 20 mouth, without inhalation. Blood samples were collected and plasma glucose levels were measured at intervals using Bayer's glucometer Elite for 3 hours. The average results, in millimoles per millilitre, are shown in Table X. Insulin levels were also monitored at
 25 intervals by the RIA method for 3 hours. The average results, in micromoles per litre, are shown in Table XI.

Table X

Time*:	0	15	30	45	60	90	120	150	180
Injection:	6.5	6.3	5.7	5.2	4.8	4.9	3.8	4.5	4.7
30 Spray:	6.1	6.0	6.0	5.9	5.5	4.5	3.6	4.1	4.4

Table XI

Time*:	0	15	30	45	60	90	120	150	180
Injection:	8.7	12.1	19.8	29.0	36.0	37.0	33.0	23.0	14.0
Spray:	9.1	11.0	16.0	31.0	45.0	43.0	45.0	32.0	22.0

35 * time in minutes

- 30 -

These tests indicated that the injection method and spray method were comparable.

Example VI

Ten millilitres of concentrated insulin containing
5 10 000 units per millilitre was placed in a glass beaker.
To this solution was added 15 mg sodium lauryl sulphate,
15 mg chenodeoxycholate, 15 mg trihydroxy oxo-cholanyl
glycine and 7 mg lecithin. The components were stirred
until they were completely dissolved. Seven mg phenol
10 and 7 mg m-cresol were added to the solution and mixed
thoroughly.

One millilitre portions of the solution were
pipetted into 10 mL capacity glass vials. The vials had
metered dose valves thereon. The vials were then
15 charged with HFA 134a propellant with Pamasol 2008
(trade mark) gas filling apparatus. The amount of
propellant was adjusted to 9 mL per vial in order to
deliver 10 units of insulin per actuation of the valve
(100 μ L shot/actuation). The formulation, in the glass
20 vial, including the propellant, was in a single phase,
i.e. was homogeneous.

Ten diabetic patients fasted overnight and did not
have a breakfast prior to dosing. On the first day,
each patient had 7 units regular fast acting insulin,
25 available from Eli Lilly, administered by injection.
Fifteen minutes after administering the insulin, each
patient was given a 250 calorie Sustacal (trade mark)
drink, which was drunk within 10 minutes. On the second
day, each patient was given 70 units insulin of this
30 example (7 puffs of 10 units each) into the mouth,
without inhalation. Fifteen minutes after administering
the insulin, each patient was given a 250 calorie
Sustacal (trade mark) drink, which was drunk within 10
minutes. Blood samples were collected and plasma
35 glucose levels were measured at intervals, using Bayer's

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glucometer Elite for 4 hours. The average results, in millimoles per millilitre, are shown in Table XII.

Table XII

Time*:	0	15	30	60	90	120	180	240
5 Injection:	9.2	9.0	9.5	12.3	12.4	12.6	11.3	9.7
Spray:	8.8	8.8	8.7	10.4	12.0	12.4	11.9	10.5

* time in minutes

These tests indicated that the injection method and spray method were comparable.

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CLAIMS:

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1. A mixed micellar aerosol pharmaceutical formulation and a propellant, comprising i) a ^{pharmaceutical} pharmaceutical agent in micellar form, ii) water, iii) an alkali metal C8 to C22 alkyl sulphate in a concentration of from 1 to 20 wt./wt.% of the total formulation, iv) at least three micelle forming compounds selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linoleic acid, linolenic acid, monolein, monooleates, monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy oxo cholanyl glycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof, polidocanol alkyl ethers and analogues thereof, chenodeoxycholate, deoxycholate, and mixtures thereof, wherein the amount of each micelle forming compound is present in a concentration of from 1 to 20 wt./wt.% of the total formulation, and the total concentration of micelle forming compounds are less than 50 wt./wt.% of the formulation, v) a phenolic compound selected from the group consisting of phenol and methyl phenol in a concentration of from 1 to 10 wt./wt.% of the total formulation, and vi) a propellant selected from the group consisting of C1-C2 dialkyl ether, butanes, fluorocarbon propellant, hydrogen-containing fluorocarbon propellant, chlorofluorocarbon propellant, hydrogen-containing chlorofluorocarbon propellant, and mixtures thereof.
2. A formulation according to Claim 1 wherein the alkali metal C8 to C22 alkyl sulphate is in a concentration of from 2 to 5 wt./wt.% of the total

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formulation.

3. A formulation according to Claim 1 wherein the alkali metal C8 to C22 alkyl sulphate is sodium lauryl sulphate.
- 5 4. A formulation according to Claim 2 wherein the alkali metal C8 to C22 alkyl sulphate is sodium lauryl sulphate.
5. A formulation according to Claim 1 wherein the lecithin selected from the group consisting of saturated
10 phosphatidylcholine, unsaturated phosphatidylcholine, phosphatidyl serine, sphingomyelin, phosphatidylethanolamine, cephalin, and lysolecithin.
6. A formulation according to Claim 1 wherein one of the micelle forming compounds is selected from the group
15 consisting of hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, polidocanol alkyl ethers, trihydroxy oxo cholanyl glycine and pharmaceutically acceptable salts thereof, polyoxyethylene ethers and analogues thereof,
- 20 chenodeoxycholate, and mixtures thereof, the concentration such micelle forming compound being from about 1 to about 5 wt./wt. %.
7. A formulation according to Claim 1 wherein the propellant is selected from the group consisting of
25 tetrafluoroethane, tetrafluoropropane, dimethylfluoropropane, heptafluoropropane, dimethyl ether, n-butane and isobutane.
8. A formulation according to Claim 2 wherein the propellant is selected from the group consisting of
30 tetrafluoroethane, tetrafluoropropane, dimethylfluoropropane, heptafluoropropane, dimethyl ether, n-butane and isobutane.
9. A formulation according to Claim 1 wherein the formulation comprises combinations selected from the
35 group consisting of i) sodium lauryl sulphate,

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polidocanol 10 lauryl ether, sodium oxo cholanyl glycine and lecithin; ii) sodium lauryl sulphate, polidocanol 10 lauryl ether, phosphatidyl choline, oleic acid; iii) sodium lauryl sulphate, polidocanol 10 lauryl ether, sodium hyaluronate and lecithin; iv) sodium lauryl sulphate, polidocanol 9 lauryl ether, triolein and polylysine; v) sodium lauryl sulphate, polyoxyethylene ether (10 lauryl), trihydroxy oxo cholanyl glycine and lecithin, vi) sodium lauryl sulphate, polidocanol 20 lauryl ether, evening of primrose oil and lecithin, and vii) sodium lauryl sulphate, trihydroxy oxo-cholanyl glycine, lecithin and chenodeoxycholate.

10. A formulation according to Claim 1 wherein the pharmaceutical agents are selected from the group consisting of insulin, heparin, low molecular weight heparin, hirulog, hirugen, huridine, interferons, interleukins, cytokines, mono and polyclonal antibodies, immunoglobins, chemotherapeutic agents, vaccines, glycoproteins, bacterial toxoids, hormones, calcitonins, insulin like growth factors (IGF), glucagon like peptides (GLP-1), large molecule antibiotics, protein based thrombolytic compounds, platelet inhibitors, DNA, RNA, gene therapeutics, antisense oligonucleotides, opioids, narcotics, hypnotics, steroids and pain killers.

11. A formulation according to Claim 2 wherein the pharmaceutical agent is insulin.

12. A ^{pharmaceutical} formulation according to Claim 1 wherein the ratio of pharmaceutical agent to propellant is from 5:95 to 25:75.

13. A formulation according to Claim 1 which is contained in a metered dose device.

14. A process for making a pharmaceutical composition suitable for delivery through transdermal membranes comprising the steps of:

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- mixing a ^{pharmaceutical} pharmaceutical agent composition in an aqueous medium with an alkali metal C8 to C22 alkyl sulphate, and at least one micelle forming compound selected from the group consisting of lecithin,
- 5 hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linoleic acid, linolenic acid, monoolein, monooleates, monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy
- 10 oxo cholanyl glycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof, polidocanol alkyl ethers and analogues thereof, chenodeoxycholate, deoxycholate, and
- 15 mixtures thereof, to form a ^{pharmaceutical} micellar pharmaceutical agent composition; and a phenolic compound selected from the group consisting of phenol, m-cresol and mixtures thereof; and subsequently

- b) placing the formulation into an aerosol
- 20 dispenser and charging the dispenser a propellant; wherein the composition has at least three micelle forming compounds and the amount of the micelle forming compounds are each present in a concentration of from 1 to 20 wt./wt.% of the total formulation, and the total
- 25 concentration of alkali metal alkyl sulphate and micelle forming compounds is less than 50 wt./wt.% of the formulation.

15. A process according to Claim 14 comprising the steps of:

- 30 a) mixing a ^{pharmaceutical} pharmaceutical agent composition in an aqueous medium with an alkali metal C8 to C22 alkyl sulphate, and at least one micelle forming compound selected from the group consisting of lecithin, hyaluronic acid, pharmaceutically acceptable salts of
- 35 hyaluronic acid, glycolic acid, lactic acid, chamomile

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- extract, cucumber extract, oleic acid, linoleic acid, linolenic acid, monoolein, monooleates, monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy oxo cholanyl glycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof, polidocanol alkyl ethers and analogues thereof, chenodeoxycholate, deoxycholate, and mixtures thereof, to form a micellar pharmaceutical agent composition;
- 5 salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof, polidocanol alkyl ethers and analogues thereof, chenodeoxycholate, deoxycholate, and mixtures thereof, to form a micellar pharmaceutical agent composition;
- 10 agent composition;
- b) during step a) or after step a), adding at least one micelle forming compound, different from that added in step a);
- c) during step a) or after step a), adding a phenolic compound selected from the group consisting of phenol, m-cresol and mixtures thereof; and subsequently
- 15 phenolic compound selected from the group consisting of phenol, m-cresol and mixtures thereof; and subsequently
- d) placing the formulation into an aerosol dispenser and charging the dispenser a propellant; wherein the composition has at least three micelle forming compounds and the amount of the micelle forming compounds are each present in a concentration of from 1 to 20 wt./wt.% of the total formulation, and the total concentration of alkali metal alkyl sulphate and micelle forming compounds is less than 50 wt./wt.% of the
- 20 forming compounds and the amount of the micelle forming compounds are each present in a concentration of from 1 to 20 wt./wt.% of the total formulation, and the total concentration of alkali metal alkyl sulphate and micelle forming compounds is less than 50 wt./wt.% of the formulation.
- 25 formulation.
16. A process according to Claim 14 wherein the alkali metal alkyl sulphate is sodium lauryl sulphate.
17. A process according to Claim 14 wherein the propellant is selected from the group consisting of tetrafluoroethane, tetrafluoropropane, dimethylfluoropropane, heptafluoropropane, dimethyl ether, n-butane and isobutane.
- 30 tetrafluoroethane, tetrafluoropropane, dimethylfluoropropane, heptafluoropropane, dimethyl ether, n-butane and isobutane.
18. A process according to Claim 14 wherein the formulation comprises combinations selected from the group consisting of i) sodium lauryl sulphate,
- 35 group consisting of i) sodium lauryl sulphate,

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polidocanol 10 lauryl ether, sodium oxo cholanyl glycine and lecithin; ii) sodium lauryl sulphate, polidocanol 10 lauryl ether, phosphatidyl choline, oleic acid; iii) sodium lauryl sulphate, polidocanol 10 lauryl ether, 5 sodium hyaluronate and lecithin; iv) sodium lauryl sulphate, polidocanol 9 lauryl ether, triolein and polylysine; v) sodium lauryl sulphate, polyoxyethylene ether (10 lauryl), trihydroxy oxo cholanyl glycine and lecithin, and vi) sodium lauryl sulphate, polidocanol 20 10 lauryl ether, evening of primrose oil and lecithin, and vii) sodium lauryl sulphate, trihydroxy oxo-cholanyl glycine, lecithin and chenodeoxycholate.

19. A process according to Claim 14 wherein the ^{of present} pharmaceutical agent is selected from the group 15 consisting of insulin, heparin, low molecular weight heparin, hirulog, hirugen, hiridine, interferons, interleukins, cytokines, mono and polyclonal antibodies, immunoglobins, chemotherapeutic agents, vaccines, glycoproteins, bacterial toxoids, hormones, calcitonins, 20 insulin like growth factors (IGF), glucagon like peptides (GLP-1), large molecule antibiotics, protein based thrombolytic compounds, platelet inhibitors, DNA, RNA, gene therapeutics, antisense oligonucleotides, opioids, narcotics, hypnotics, steroids and pain 25 killers.

20. A method for administration of a pharmaceutical ^{agent} in a buccal cavity of a human being by spraying into the cavity, without inhalation, from a metered dose spray dispenser, a mixed micellar pharmaceutical 30 formulation and a propellant comprising:

i) the ^{pharmaceutical} pharmaceutical agent in micellar form, ii) water, iii) an alkali metal C8 to C22 alkyl sulphate in a concentration of from 1 to 20 wt./wt.% of the total formulation, iv) at least three micelle forming 35 compounds selected from the group consisting of

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- lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linoleic acid, linolenic acid, monoolein, monooleates, 5 monolaurates, borage oil, evening of primrose oil, menthol, trihydroxy oxo cholanylglycine and pharmaceutically acceptable salts thereof, glycerin, polyglycerin, lysine, polylysine, triolein, polyoxyethylene ethers and analogues thereof,
- 10 polidocanol alkyl ethers and analogues thereof, chenodeoxycholate, deoxycholate, and mixtures thereof, wherein the amount of each micelle forming compound is present in a concentration of from 1 to 20 wt./wt.% of the total formulation, and the total concentration of 15 micelle forming compounds are less than 50 wt./wt.% of the formulation, v) a phenolic compound selected from the group consisting of phenol and methyl phenol in a concentration of from 1 to 10 wt./wt.% of the total formulation, and vi) a propellant selected from the 20 group consisting of C1-C2 dialkyl ether, butanes, fluorocarbon propellant, hydrogen-containing fluorocarbon propellant, chlorofluorocarbon propellant, hydrogen-containing chlorofluorocarbon propellant, and mixtures thereof.
- 25 21. A method according to Claim 20 wherein the pharmaceutical agent is selected from the group consisting of insulin, heparin, low molecular weight heparin, hirulog, hirugen, huridine, interferons, interleukins, cytokines, mono and polyclonal antibodies, 30 immunoglobins, chemotherapeutic agents, vaccines, glycoproteins, bacterial toxoids, hormones, calcitonins, insulin like growth factors (IGF), glucagon like peptides (GLP-1), large molecule antibiotics, protein based thrombolytic compounds, platelet inhibitors, DNA, 35 RNA, gene therapeutics, antisense oligonucleotides,

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opioids, narcotics, hypnotics, steroids and pain killers.

22. A method according to Claim 20 wherein the pharmaceutical agent is insulin.

5 23. A method according to Claim 21 wherein the alkali metal C8 to C22 alkyl sulphate is sodium lauryl sulphate.

24. A method according to Claim 22 wherein the alkali metal C8 to C22 alkyl sulphate is sodium lauryl
10 sulphate.

25. A method according to Claim 20 wherein one of the micelle forming compounds is selected from the group consisting of hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, polidocanol alkyl
15 ethers, trihydroxy oxo cholanyl glycine and pharmaceutically acceptable salts thereof, polyoxyethylene ethers and analogues thereof, and chenodeoxycholate, the concentration such micelle forming compound being from about 1 to about 5 wt.%.
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26. A method according to Claim 21 wherein the propellant is selected from the group consisting of tetrafluoroethane, tetrafluoropropane, dimethylfluoropropane, heptafluoropropane, dimethyl ether, n-butane and isobutane.

25 27. A method according to Claim 22 wherein the propellant is selected from the group consisting of tetrafluoroethane, tetrafluoropropane, dimethylfluoropropane, heptafluoropropane, dimethyl ether, n-butane and isobutane.

30 28. A method according to Claim 21 wherein the formulation comprises combinations selected from the group consisting of i) sodium lauryl sulphate, polidocanol 10 lauryl ether, sodium oxo cholanyl glycine and lecithin; ii) sodium lauryl sulphate, polidocanol 10
35 lauryl ether, phosphatidyl choline, oleic acid; iii)

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sodium lauryl sulphate, polidocanol 10 lauryl ether, sodium hyaluronate and lecithin; iv) sodium lauryl sulphate, polidocanol 9 lauryl ether, triolein and polylysine; v) sodium lauryl sulphate, polyoxyethylene 5 ether (10 lauryl), trihydroxy oxo cholanyl glycine and lecithin, vi) sodium lauryl sulphate, polidocanol 20 lauryl ether, evening of primrose oil and lecithin, and vii) sodium lauryl sulphate, trihydroxy oxo-cholanyl glycine, lecithin and chenodeoxycholate.

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2020
Bogotá, D.C.,

Doctora:
Dilia María Rodríguez D'Aleman
Apoderada

Oficio N°: 2127

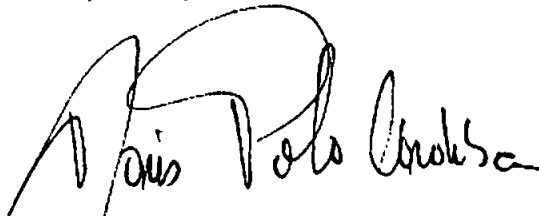
ASUNTO:

Radicación PCT N°	08-55399
Trámite	011
Evento	378
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 la doctora Eliana Isaura Moreno Bohórquez, en su calidad de apoderada 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.



DORIS ELENA POLO CORDOBA
Jefe de la División de Nuevas Creaciones (E).

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

20 FEB. 2009

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