110

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 05-124706- -00005-0000
Fec: 2007-03-28 13:51:18 Dep. 2020 NUECREACIONES
Tra. 11 PATENTEYII
Eve: 378 FASENACIONALII
Act 400 OPOSIOBSERVTER Folios: 38

FORMULARIO ÚNICO DE OPOSICIÓN

① OPOSICIÓN A :

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

② SOLICITUD PUBLICADA

Número del expediente: 05-124706
Solicitante: ALLERGAN INC
Apoderado: JERÓNIMO CASTILLO BONILLA
Título de la nueva creación o denominación del signo: "FORMAS FARMACÉUTICAS ORALES DE MEMANTINA".
Gaceta: 571

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE

Nombre: PROCAPS S.A
Dirección: CALLE 80 No. 78b-201
Nacionalidad o Domicilio: COLOMBIA
Lugar de Constitución: BARRANQUILLA
Teléfono: (571)371 99 00 Fax: (571)373 08 18
E-mail:

IDENTIFICACIÓN
C.C. [ ] NIT [X]
C.E. [ ] Otro [ ]
Cual
Número 890.106.527-5

REPRESENTANTE O APODERADO

Nombre: LAURA CATALINA SILVA BARRERA
Dirección: CARRERA 13 #119-95 OFICINA 104
Teléfono: (571)2131213 Fax: (571) 6121979
E-mail: negocios@optimum-co.com

IDENTIFICACIÓN
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número 52.455.803 TP 147399

④ FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

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

⑤ **Comprobante de pago No.** _____ **Fecha** _____

⑥ **ANEXOS**

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

⑦

NOMBRE: LAURA CATALINA SILVA BARRERA

FIRMA: 

C.C. 52.455.803 **T.P.** 147399

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

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PROCAPS

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 **LAURA CATALINA SILVA BARRERA,** abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 147399, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **05 124706,** titulada **"FORMAS FARMACÉUTICAS ORALES DE MEMANTINA"** de **ALLERGAN INC,** publicada en la gaceta No. 571 del 29 de Diciembre de 2006.

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 26 días del mes de Marzo de 2007.

PROCAPS S.A.
WALTER TANAKA TATEKAWA
C.C. N° 16.251.923 de Palmira
Representante Legal

Acepto:

LAURA CATALINA SILVA BARRERA
C.C. 52'455.803 de Bogotá
T.P.A. 147399 del C.S. de la J.

SEGUNDA NOTARIA SEGUNDA NOTARIA SEGUNDA NOTARIA SEGUNDA

ADY ISABEL NAMEN SEGURA

NOTARIA SEGUNDA DEL CIRCULO DE BARRANQUILLA

DILIGENCIA DE PRESENTACION PERSONAL Y RECONOCIMIENTO

La suscrita Notaria Certifica que este escrito fué presentado Personalmente por WALTER TANAKA TATEKAWA

Identificado con: 16.251.923 -

Expedido en: PALMIRA -

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

Firma

26 MAR. 2007

Huella del Compareciente

REPUBLICA DE COLOMBIA EL NOTARIO SEGUNDA DEL CIRCULO DE BARRANQUILLA

DILIGENCIA DE RECONOCIMIENTO

ANTE MI: JUAN ENRIQUE NIÑO GUARIN Notario cuarenta y tres del circulo de Bogotá, D.C. Compareció: Laura Cabezas Silva Barrera

Identificado con C.C. No. 52.488.803 de Bta

Declaró que reconoce el contenido del presente documento por ser cierto y que la firma igual que la huella (indice derecho) puestas en él son suyas.

27 MAR. 2007

Fecha:

JUAN ENRIQUE NIÑO GUARIN NOTARIO CUARENTA Y TRES

NOTARIA CUARENTA Y TRES DEL CIRCULO JUAN ENRIQUE NIÑO GUARIN NOTARIO CUARENTA Y TRES DE BOGOTÁ, D.C.

No. 10391267

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CAMARA DE COMERCIO DE BARRANQUILLA

10**********

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,

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 libro respectivo, la sociedad antes mencionada----------

********** 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.

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 **********

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 hospitalari s para la salud humana y animal. e)La compra,venta,exportacion y disdistribucion 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, naci - 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, socio ó fundador de empresas que tengan igual o similar objeto, com-

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

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

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prar, 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 gravamenes 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 gravamenes 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		
$**********1,224,500,000	**********1,224,500	**********1,000
Pagado		
$**********1,224,500,000	**********1,224,500	**********1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponderа 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 socieda todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los

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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 siguentes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver 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 gravamenes 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 Junra 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 que el Gerente General y sin que sea necesario para ello acreditar

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

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

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 gravamenes 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.	
Minski Gontovnik Ruben	CC.*******7,463,982

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

CAMARA DE COMERCIO DE BARRANQUILLA

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
10**********

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

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

C E R T I F I C A

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

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

C E R T I F I C A

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

Cargo/Nombre Identificación
Suplente del Gerente.
Tanaka Walter CC.******16,251,923

C E R T I F I C A

Que según Acta No. 124 del 29 de Marzo de 1999 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 04 de Agosto de 1999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre Identificación
Revisor Fiscal Ppal.
Vargas Pertuz Ana Isabel CC.******32,696,645

C E R T I F I C A

Que según Acta No. 127 del 22 de Marzo de 2000 c rrespondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio,

********** 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.

el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

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

C E R T I F I C A

Que por escritura publica No. 2.608 del 5 de Octubre del 2.001,otorgada en la Notaria 2a. de Barranquilla, inscrita en esta Camara de Comercio el 8 de Noviembre del 2.001, bajo los Nos. 95.771, 2.056, 2.057, 2.058, 2.059, 2.060, 2.061, 2.062 y 2.064 del libro respectivo, se reforma totalmente el articulo 65, contenido en la escritura publica No. 3.705 de Noviembre 6 de 1.998, de la Notaria Segunda del Circuito de Barranquilla, y se constituyen los siguientes Apoderados Generales, quienes tendran las funciones que a continuacion se indican en razon de su cargo en la sociedad: 1.-Se confiere Poder Especial, Amplio y Suficiente a los senores: WALTER TANAKA TATEKAWA, C.C. No. 16.251.923; WILIIAM ALBERTO BARROS CERRA, C.C. No. 8.715.941, para que cada uno en forma independiente en nombre y representacion de PROCAPS S.A., suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad, asi como para que responda todo tipo de requerimiento o solicitudes de informacion de las autoridades tributarias, aduaneras o cambiarias,en los ordenes Distrital, Departamental y Nacional. 2.-Se confiere Poder Especial,amplio y suficiente,a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancias y servicios con entidades oficiales, hasta por la suma de US$800.000.oo (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. GUPO A: CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.293. BRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZGRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requerira por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C.C. No. 33.138.497, a la Doctora MARCELA CARVAJALINO PAGANO C.C. No. 22.579.748, y al Doctor DANIEL MORENO VILLALBA, C.C. No. 19.113.210; para que cada uno representen a PROCAPS S.A., ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como: Contestar e interponer demandas y requerimientos, comparecer en juicios,pedir la practica de pruebas,recibir notificaciones,interponer recursos y ejercer acciones contencioso administrativas y de tutela,transigir,conciliar,recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato. Para la celebracion de cualquier acuerdo conciliatorio o transaccional, judicial o extrajudicial, cualquiera que sea su cuantia,los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la sociedad. Los Apoderados podran presentar solicitudes de devolucion y/o compensacion de impuestos y recibir los pagos por devoluciones de

********** 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.

impuestos, firmar, notificarse y realizar todo acto necesario para cumplir con el mandato encomendado.----------

C E R T I F I C A

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

C E R T I F I C A

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

C E R T I F I C A

Que segun documento privado del 10 de noviembre del 2004, inscrito en esta Camara de Comercio el 1 de diciembre del 2.004, bajo el No. 2.753 del libro respectivo consta que RUBEN MINSNSKI GONTOVNIK, C.C. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a ANTONIO VARELA DIAZ, C.C.No.72.004.669 de Barranquilla, para que en nombre y representacion de la sociedad firme las declaraciones cambiarias a que este obligada PROCAPS S.A., a suscribrir en el giro normal de sus negocios y operaciones sociales. Por lo anterior, el senor ANTONIO VARELA DIAZ, queda facultado

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

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

para firmar las declaraciones comabiarias y demas documentos relacionados con las declaraciones, notificaciones, aportar y solicitar las pruebas que sean necesarias, desistir en general a realizar todo acto necesario de tal forma que pueda cumplir con el mandato dado.-

C E R T I F I C A

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

C E R T I F I C A

Que por Escritura Pública No. 2,011 del 10 de Octubre de 2006, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Dic/bre de 2006 bajo el No. 3,183 del libro respectivo,----------
Consta que RUBEN MINSKI GONTOVNIK CC.No.7.463.928, quien manifesto que en su condicion de Presidente y Representante Legal de la ------ sociedad PROCAPS S.A.,confiere poder especial amplio y suficiente a los siguientes senores que conforman el Grupo A y el Grupo B, para que conjuntamente suscriban contratos de suministro de mercancias y servicios con entidades oficiales, hasta por la suma de ochocientos mil dolares de los Estados Unidos de America (US$800.000.00), ---- liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. Grupo A: IVAN VILLAREAL CAMACHO CC.No.91.201.749. FERNANDO RINCON RIVERA CC.No.79.484.187. CLAUDIA TANGARIFE CASTILLO CC.No.41.660.293.Grupo B. WALTER TANAKA TATEKAWA CC.No.16.251.923. CARMEN ALICIA FLOREZ DE LA ROTA --------- CC.No.22.434.044. RICARDO DORADO HURTADO CC.No.79.715.772.----------

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: 20 de Marzo de 2007.

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

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

N-10391272

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CAMARA DE COMERCIO
DE BARRANQUILLA

10**********

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

Certificados Especiales.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 25.451
FECHA : MARZO 28 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 05-124706- -00005-0000
Fec. 2007-03-28 13:51:18 Dep. 2020 NUECREACIONES
Tra. 11 PATENTEIYII
Eve: 379 FASENACIONALII
Act 400 OPOSIOBSERVTER Folios. 38

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	60060431	07/03/2007	512,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	256,000.00
		TOTAL : $	256,000.00

SON: DOSCIENTOS CINCUENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia	**: Expediente N° 05124706**
Asunto	**: Oposición a la solicitud de patente de Invención titulada "FORMAS FARMACÉUTICAS ORALES DE MEMANTINA.".**
Solicitante	**: ALLERGAN INC.**
Opositora	**:PROCAPS S.A.**

Publicada en la Gaceta de la Propiedad Industrial

N° 571 del 29 de Diciembre de 2006

Yo, ***LAURA CATALINA SILVA BARRERA***, abogada en ejercicio, identificada como aparece al pie de mi firma, con tarjeta profesional No. 147399 del consejo superior de la judicatura, en mi condición de apoderada de la sociedad ***PROCAPS S.A.*** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la patente de Invención titulada ***"FORMAS FARMACÉUTICAS ORALES DE MEMANTINA"***, solicitada por ***ALLERGAN INC.***, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

Carrera 13 N° 119-95, Oficina 104. Tel. (571) 2 13 12 13 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

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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, en particular relacionado con memantina. 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 diciembre de 2005, reivindicando prioridad bajo la solicitud US60/478.979 del 2003-06-16 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial Nº 571 del 29 de diciembre de 2006, página 451, Nº publicación 906, cuya publicación internacional corresponde a la WO2004112768.

2.2. La solicitud colombiana 05124706 objeto de la presente oposición, se refiere a una forma farmacéutica oral que contiene entre 1 mg y 100 mg de memantina, en donde dicha forma farmacéutica no contiene 10 mg de memantina, y en donde dicha forma farmacéutica no se prepara por el paciente o una persona que administra el medicamento al paciente, quien divide la forma farmacéutica que contiene una dosis mayor de memantina; donde, la forma farmacéutica oral es una

forma sólida de una tableta. Igualmente, la presente solicitud se refiere a un método de administrar memantina a un paciente en una cantidad que no es alrededor de 10 mg, que comprende administrar al paciente una forma farmacéutica oral de memantina, en donde dicha forma farmacéutica no se prepara por el paciente o una persona que administra el medicamento al paciente, quien divide la forma farmacéutica que contiene una dosis mayor de memantina.

2.3. En primera instancia, se debe advertir que la reivindicación 17 y 18 se refieren al método terapéutico y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 20.- "*No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales*". Solo serán patentables los productos o procedimientos.

2.4.De otra parte el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: "*Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*". Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la altura inventiva de la presente solicitud:

- D1: US4'273.774, 1981-06-16.
- D2: US5'382.601. 1995-01-17.

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2.5.Ahora bien, el documento D1, particularmente en el resumen y en los ejemplos 1 a 9 de la descripción y particularmente en la columna 7, línea 44 a columna 8, línea 42 y reivindicaciones, se refiere a un derivado de amantadina, que según el ejemplo 3, puede conformarse como una presentación en forma de tabletas que incluye 10 mg de 1,3-dimetil-5-aminoadamantane. Según la descripción de dicho documento D1, este compuesto puede administrarse para tratar enfermedades relacionadas con el Parkinson y puede administrarse simultáneamente con al menos un compuesto de metilxantinas tal como cafeina.

2.6.Por su parte, el documento D2, revela según la descripción y las reivindicaciones, una forma sólida tal como una tableta, que comprende una cantidad efectiva entre 0,01% y 90% del total del peso de la composición de un compuesto activo tal como memantina (reivindicaciones 1 y 9 de D1).

2.7.Visto estos dos documentos anteriores D1 y D2, se evidencia que la técnica ya mostraba para la época, formas orales que comprenden memantina en dosis orales sólidas tal como tabletas. Por lo tanto, a los ojos del documento D1, en combinación con el documento D2, cualquier persona versada en la materia puede llegar a deducir, una forma farmacéutica oral que contiene entre 1 mg y 100 mg de memantina, en donde dicha forma farmacéutica no contiene 10 mg de memantina, y en donde dicha forma farmacéutica no se prepara por el paciente o una persona que administra el medicamento al paciente, quien divide la forma farmacéutica que contiene una dosis mayor de memantina; donde, la forma farmacéutica oral es una forma sólida de una tableta. Igualmente, a partir de estos documentos, es posible llegar a un método de administrar memantina a un paciente en una cantidad que no es alrededor de 10 mg, que comprende administrar al paciente una forma

farmacéutica oral de memantina, en donde dicha forma farmacéutica no se prepara por el paciente o una persona que administra el medicamento al paciente, quien divide la forma farmacéutica que contiene una dosis mayor de memantina. Por lo tanto, a la luz de estos documentos D1 y D2, la presente solicitud carece evidentemente de altura o nivel inventivo.

2.8. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana **05124706** no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con uno de los tres requisitos necesarios para su protección.

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

2.9.1. <u>CARENCIA DE ALTURA INVENTIVA</u>. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."*. A la fecha de prioridad, el 16 de junio de 2003, a partir de los documentos D1 y D2 en combinación, es posible deducir una forma farmacéutica oral que contiene entre 1 mg y 100 mg de memantina, en donde dicha forma farmacéutica no contiene 10 mg de memantina, donde, la forma farmacéutica oral es una forma sólida de una tableta y que además deducir un método de administrar memantina a un paciente en una cantidad que no es alrededor de 10 mg, que comprende administrar al paciente una forma farmacéutica oral de memantina, en donde dicha forma farmacéutica no se prepara, conforme a lo reivindicado en la

presente solicitud objeto de oposición según lo definido en las reivindicaciones de la presente solicitud.

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

2.11. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada ***"FORMAS FARMACÉUTICAS ORALES DE MEMANTINA"***, solicitada por ***ALLERGAN INC.,*** solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 571.

3. PRUEBAS

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

- D1: US4'273.774, 1981-06-16.
- D2: US5'382.601. 1995-01-17.

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4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

4.1. Numeral 1 del artículo 586 del Código de Comercio.

4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

4.3. En las demás normas concordantes.

5. ANEXOS

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

- D1: US4'273.774, 1981-06-16.
- D2: US5'382.601. 1995-01-17.

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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 Nº 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

LAURA CATALINA SILVA BARRERA
C.C. 52'455.803 de Bogotá
T.P.A. 147399 del C.S. de la J.

ANEXO 1

Carrera 13 Nº 119-95, Oficina 104. Tel. (571) 2 13 12 13 – Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

United States Patent [19]

Scherm

[11] **4,273,774**

[45] **Jun. 16, 1981**

[54] **CENTRAL NERVOUS SYSTEM COMPOSITIONS AND METHOD**

[75] Inventor: **Arthur Scherm, Bad Homburg, Fed. Rep. of Germany**

[73] Assignee: **Merz & Co., Frankfurt, Fed. Rep. of Germany**

[21] Appl. No.: **105,419**

[22] Filed: **Dec. 19, 1979**

[30] **Foreign Application Priority Data**

Dec. 27, 1978 [DE] Fed. Rep. of Germany 2856393

[51] **Int. Cl.**[3] **A61K 31/52; A61K 31/135**

[52] **U.S. Cl.** **424/253; 424/330**

[58] **Field of Search** 424/330; 253

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,864,489	2/1975	Biscardi	424/253
3,961,060	6/1976	Fuxe	424/253
4,122,193	10/1978	Sherm et al.	424/330

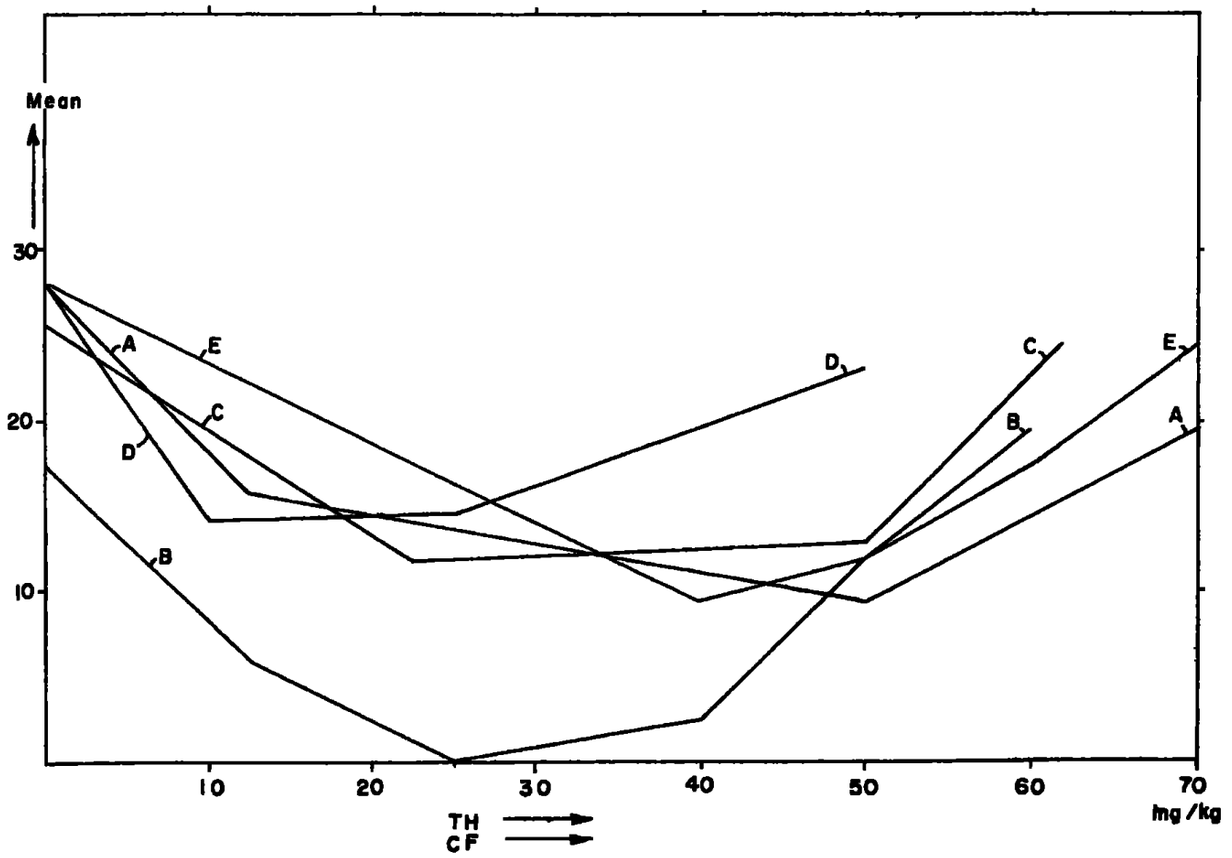
Primary Examiner—Stanley J. Friedman

Attorney, Agent, or Firm—Gordon W. Hueschen

[57] **ABSTRACT**

The present application relates to compositions which influence the central nervous system and which are especially useful in the treatment of hyperkinesis and rigidity. These compositions contain as active ingredient 1,3-dimethyl-5-aminoadamantane in the form of the free base or a pharmaceutically-acceptable salt thereof, together with a methylxanthine compound, e.g., caffeine or theophylline, in an amount up to about fifteen milligrams of the methylxanthine compound per each milligram of the 1,3-dimethyl-5-aminoadamantane compound. These compositions are useful in the treatment of central nervous system disorders, particularly of Parkinson's disease, depressions, spasticity, rigidity, hyperkinesis, and the like. The compositions possess unpredictable beneficial properties of a synergistic nature. The application also relates to the treatment of such central nervous system ailments or conditions with a combination of the said two active agents either concurrently or together in the same dosage form or unit.

11 Claims, 1 Drawing Figure


Mean
30
20
10
A
E
C
D
B
D
C
E
B
A
10
20
30
40
50
60
70
mg /kg
TH
CF

CENTRAL NERVOUS SYSTEM COMPOSITIONS AND METHOD

BACKGROUND OF THE INVENTION

1. Field of Invention

Dopaminergic, anticataleptic central nervous system compositions useful in the treatment of central nervous system ailments and disorders, particularly Parkinson's disease, depressions, spasticity, hyperkinesis, and rigidity. Treatment of such central nervous system disorders or ailments with combination therapy including a 1,3-dimethyl-5-aminodamantane compound.

2. Prior Art

In the past, numerous proposals have been made for drugs which influence the central nervous system and are useful for the treatment of ailments or disorders thereof, particularly including Parkinson's disease, depressions, spasticity, hyperkinesis, rigidity, and the like. At present, such treatment is predominantly carried out with the employment of three separate therapeutically active agents, having different modes of action and having widely different structures. These products are L-dopa, aminoadamantanes, and anticholinergics. Dependent on the form and intensity of the disease involved, rigor, tremor, and bradyphrenia are the target of the treatment. In many cases, however, single doses of 200 to 300 milligrams of the active agent are necessary to achieve a satisfactory effect on rigidity, but such dosages are already regarded as undesirably pathological. Such drugs act on akinesia and rigidity, but a wide range of effects, including also desirable reduction of tremor and treatment of bradyphrenia, can in most cases only be effected through the employment of greatly increased dosages. It is therefore obviously necessary to provide new active ingredients or agents or combinations thereof, whereby the desirable effects can be accomplished without the undesirable and even pathological increase in dosage. It is therefore highly desirable to provide combinations of active agents which potentiate each other, or in which one potentiates the activity of the other, both of which active agents are preferably already known and established in therapy. At the same time, any such combination should present, if at all possible, an improved therapeutic ratio and diminished side effects. This is sometimes possible when the potentiating effect of the one active ingredient upon the other is sufficient to permit a significant reduction in dosage.

Among the substances previously proposed for influencing the central nervous system and as especially useful in the treatment of hyperkinesis and rigidity, and particularly in the treatment of Parkinson's disease, is the compound 1,3-dimethyl-5-aminoadamantane or a pharmaceutically-acceptable salt thereof, which acts upon rigor, tremor, and akinesia. Animal experiments have revealed the anticataleptic and locomotor activity of this compound at doses of five through twenty milligrams per kilogram of body weight.

Many recent publications have dealt with the range of activity of 1,3-dimethyl-5-aminoadamantane and its pharmaceutically-acceptable salts, e.g.:

Drugs of the Future Vol. I, No. 9 (1976), 427 ff; Arzneimittel-Forschung "Drug Research" 27 (II), No. 7 (1977), 1477–1487 ff; European Journal of Pharmacology 26 (1974), 9–14, North-Holland Publishing Company; Arzneimittel-Forschung "Drug Research" 23, No. 12 (1973), 1737–1739. See also U.S. Pat. No. 4,122,193, issued Oct. 24, 1978, claiming compositions of 1,3-dimethyl-5-aminoadamantane and pharmaceutically-acceptable salts thereof and a method of treating hyperkinesis therewith.

The second active ingredient, which also plays an important part in the unpredictable effectiveness of the new combinations and method of the present invention, is a methylxanthine compound, e.g., caffeine or theophylline, both of which are old and well-known in the art and the therapeutic action of which is sufficiently described in the literature.

With regard to the prior art concerning potentiation of dopaminergic activity by means of drug combinations and combination therapy, reference is made herein to German OL No. 2518677, filed Apr. 26, 1975, and laid open on Nov. 20, 1975, which discloses dopaminergic stimulating compositions comprising certain alkaloids together with phosphodiesterase inhibitors. Although caffeine and theophyllamine are reported to be phosphodiesterase inhibitors, any potentiation which might result from a combination thereof with certain alkaloids certainly is no teaching or suggestion that they might be used to potentiate the activity of 1,3-dimethyl-5-aminoadamantane or a pharmaceutically-acceptable salt thereof, which indeed possess a far different chemical structure and activity than the alkaloids of the German OL.

As far as combination therapy, reference is also made to U.S. Pat. No. 3,961,060, issued June 1, 1976, wherein a phosphodiesterase inhibitor such as caffeine is combined with dopa, m-tyrosine, apomorphine, or a compound designated ET495, for purposes of allegedly potentiating dopaminergic effect. All the compounds disclosed in that patent, the dopaminergic activity of which is allegedly potentiated, have structures far different than the 1,3-dimethyl-5-aminoadamantane employed in the compositions and method of the present invention, and of course are also presumed to operate along entirely different metabolic pathways. Further, the evidence apparently presented in the U.S. Pat. No. 3,961,060 appears to be limited to potentiation of the dopaminergic effect of dopa itself by caffeine, which of course is hardly any suggestion to combine a methylxanthine such as caffeine or theophylline with a compound such as 1,3-dimethyl-5-aminoadamantane or a pharmaceutically-acceptable salt thereof, inasmuch as such compound contains three (3) rings compared to the single ring in dopa, as well as three (3) less functional groups than dopa, much less that caffeine or theophylline or any methylxanthine compound would in fact serve to potentiate the highly desirable activity of 1,3-dimethyl-5-aminoadamantane or a pharmaceutically-acceptable salt thereof, particularly with respect to what is undoubtedly the most important result of such combination therapy, namely, reduction in rigidity.

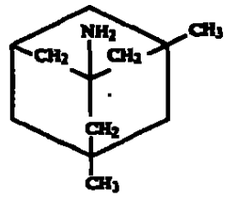
Accordingly, in the compositions of the present invention and according to the method of the present invention, the methylxanthine compound such as caffeine or theophylline unpredictably, and to an unpredictable and highly desirable extent, potentiates the activity of the 1,3-dimethyl-5-aminoadamantane or pharmaceutically-acceptable salt thereof and provides another important addition to the physician's armamentarium of useful drugs in this area.

SUMMARY OF THE INVENTION

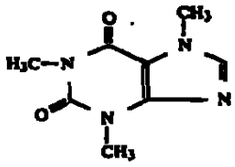
The present application relates to compositions which influence the central nervous system and which

are especially useful in the treatment of hyperkinesis and rigidity. These compositions contain as active ingredient a 1,3-dimethyl-5-aminoadamantane in the form of the free base or a pharmaceutically-acceptable salt thereof, together with a methylxanthine compound, e.g., caffeine or theophylline, in an amount up to about fifteen milligrams of the methylxanthine compound per each milligram of the 1,3-dimethyl-5-aminoadamantane compound. These compositions are useful in the treatment of central nervous system disorders, particularly of Parkinson's disease, depressions, spasticity, rigidity, hyperkinesis, and the like. The compositions possess unpredictable beneficial properties of a synergistic nature. The application also relates to the treatment of such central nervous system ailments or conditions with a combination of the said two active agents either concurrently or together in the same dosage unit to produce unprecedented and unpredictable results, including the highly desirable but difficultly-attained diminution of rigidity. Preferably the active ingredient is up to about ten milligrams of the 1,3-dimethyl-5-aminoadamantane compound, especially up to about five milligrams of the 1,3-dimethyl-5-aminoadamantane compound, where such lower dosage are adequate, and preferably the combined therapy is administered orally or parenterally in dosage unit form, generally with a conventional pharmaceutically-acceptable carrier also being present in the pharmaceutical form administered.

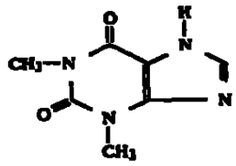
It has now unexpectedly been found that, by the administration of a combination of 1,3-dimethyl-5-aminoadamantane, having the following formula:



or a pharmaceutically-acceptable salt thereof (A) and a methylxanthine, e.g. caffeine or theophylline, having the following formulas:



1,3,7-trimethylxanthine (Caffeine)



1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropurine (Theophylline)

the respective dosage of B being up to fifteen (15) parts or milligrams per part or milligram of A, it is now possible:

(a) to maintain the dosage necessary to produce a certain action or effect upon rigidity at a lower level than has previously been possible with administration of A only;

(b) to achieve a stronger effect upon rigidity at a given dosage of the substance than with the administration of A alone; and, importantly,

(c) to reduce the side-effects and thereby produce a more favorable therapeutic ratio than previously attainable.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide valuable compositions influencing the central nervous system of the type just described, having advantageous and unpredictable properties which make them especially useful in the treatment of hyperkinesis and rigidity. It is another object of the invention to provide a method of combination therapy involving the concurrent treatment with the two active ingredients involved, as aforementioned, preferably in the form of a single dosage unit. Other objects of the invention will become apparent hereinafter, and still others will be obvious to one skilled in the art.

THE DRAWING

Reference is now made to the drawing, wherein the single FIGURE is a graph comprising several curves A–E. In the FIGURE, the abscissa represents the amount of the methylxanthine employed in mg/kg whereas the ordinate represents the mean degree of rigidity. The curves in the FIGURE correspond to the pharmacological data presented herein under "PHARMACOLOGY", the variations in the numbers on the abscissa and on the ordinate being obtained upon administration of constant dosages of the 1,3-dimethyl-5-aminoadmantane compound and upon variation of the dosage of the methylxanthine compound.

PHARMACOLOGY

The effectiveness of the new combination of A and B is based on the following synergistic effect:

When given separately, caffeine and theophylline have no effect on rigidity as can be taken from the curves. A combination of A (up to 10 mg) and B (up to 70 mg), however, has a marked effect on rigidity. Upon administration of a combination of A and B, the following synergistic effects can be demonstrated on a model, within a ratio of up to 15 parts of B per 1 part of A.

1. A acts on rigidity, whereas B does not act on rigidity at all. The administration of a combination of A and B, however, brings about a significant effect upon rigidity which is markedly stronger than the effect of A alone.

2. Upon administration of a combination of both substances, low doses of B are already sufficient to intensify the antiparkinsonism effect of A. This potentiating effect is markedly stronger than the effect of A alone. This action can be demonstrated by all model experiments carried out.

The effect of the combination of A and B will be explained by the following pharmacological examples:

(a) Decrease of rigidity by the combination of A and B in experimentally-induced catalepsy.

The tests were carried out on male Wistar rats receiving food ad libitum. Catalepsy was induced by administration of Spiroperidol according to the well-known, accepted, and published method of Delini-Stula and Merpurgo, and was examined every thirty (30) minutes during a period of 2½ hours. According to standard procedure, before injecting 1,3-dimethyl-5-aminoadamantane, a peripheral decarboxylase inhibitor (RO-4-4602) was also administered. The combinations of A and B, in the doses set forth in the table, were adminis-

tered to the animals for ten days by the peroral route. The results are summarized in the following tables.

A dosage of B in the combination of A and B has a stronger rigor-reducing effect than a single dose of compound A. A dose increase of component B potentiates the action and shows a maximum at 50 mg/kg (Curve A).

According to Curve B, the action of A is still more intensified by combination with 10 mg/kg of theophylline (Component B), resulting in a maximum of rigor-reduction. Similar results can be taken from Curve C.

The effect of theophylline (TH), caffeine (CF), and 1,3-dimethyl-5-aminoadamantane (A) on rats (catalepsy induced by Spiroperidol):

	Test No.	Substance and Dosage (mg/kg)	Mean ±	Standard error of the mean (s.e.m.)	P
Curve A	I	A 5	28,8 —	0,8	
	II	CF 12,5 + A 5	16,3 —	3,9	
	III	CF 25 + A 5	13,2 —	4,5	
	IV	CF 50 + A 5	9,3 —	4,6	
	V	CF 60 + A 5	13,0		
	VI	CF 70 + A 5	19,5		
Curve B	VII	TH 12,5 + A 10	5,5 —	4,6	
	VIII	TH 25 + A 10	0,7 —	0,4	
	IX	TH 40 + A 10	2,5		
	X	TH 50 + A 10	11,8		
	XI	TH 60 + A 10	19,5		
Curve C	XII	TH 0 + A 5	25,3 —	2,2	
	XIII	TH 25 + A 5	11,5 —	2,8	
	XIV	TH 50 + A 5	13,0		
	XV	TH 60 + A 5	22,5		

(b) Decrease of rigidity by the combination of A and B in experimentally-induced catalepsy

The test was carried out in analogy to (a) with the exception that catalepsy was induced by Reserpine. The results showed that, under the aforementioned test conditions, A did not effect any reduction in rigidity, even at doses of 5 mg/kg.

A combination of A and B, however, brings about a marked decrease in rigidity (Curve D) even at a low dosage of B (10 mg/kg). Upon repeating the test with theophylline, an action maximum could be found at 40 mg/kg theophylline.

The effect of theophylline (TH), caffeine (CF), and 1,3-dimethyl-5-aminoadamantane (A) on rats (catalepsy induced by Reserpine):

	Test No.	Substance and Dosage (mg/kg)	Mean ±	Standard error of the mean (s.e.m.)	P
Curve D	I	CF 0 + A 5	28,0 —		
	II	CF 10 + A 5	14,0 —		
	III	CF 25 + A 5	14,0 —	4,2	
	IV	CF 50 + A 5	23,2 —	1,1	
Curve E	V	TH 0 + A 5	28,0 —	1,4	
	VI	TH 10 + A 5	22,7 —	1,3	
	VII	TH 25 + A 5	15,3 —	3,8	
	VIII	TH 40 + A 5	9,3		
	IX	TH 50 + A 5	12,0		
	X	TH 60 + A 5	17,5		
	XI	TH 70 + A 5	24,5		

SPECIFIC EMBODIMENTS OF THE INVENTION

The following examples are given to illustrate specific compositions which may be employed in carrying out the method of the invention and which are representative of the compositions of the present invention, but are not to be construed as limiting.

EXAMPLE 1

Injectible Solutions

1,3-Dimethyl-5-aminoadamantane and theophylline are dissolved in double-distilled water with addition of sodium chloride. Subsequently, the solution is filtered through degerminating layers, filled into two ml ampules and subjected to thermal sterilization for twenty minutes at 120° C.

Injectible solution containing 10 mg of 1,3-dimethyl-5-aminoadamantane and 100 mg of theophylline (10 ml ampule):

1,3-Dimethyl-5-aminoadamantane	0.1 g*
Theophylline	1.0 g
Sodium chloride	0.6 g
Double-distilled water	ad 100 ml

*If the hydrochloride is employed, an equivalent amount of the free base is utilized.

EXAMPLE 2

Solution

1,3-Dimethyl-5-aminoadamantane and theophylline are dissolved in an ethanol-water mixture. The solution is filtered until it remains clear.

Solution containing 5 mg of 1,3-dimethyl-5-aminoadamantane and 30 mg of theophylline per 20 drops=0.5 ml:

1,3-Dimethyl-5-aminoadamantane	1 g*
Theophylline	6 g
Ethanol	10 g
Demineralized water	83 g
	100 g

*If the hydrochloride is employed, an equivalent amount of the free base is utilized. The same is true if another salt, e.g., the hydrobromide or sulphate, is employed.

EXAMPLE 3

Tablets

Tablets containing 10 mg of 1,3-dimethyl-5-aminoadamantane and 100 mg of caffeine per tablet of 300 mg:

1,3-Dimethyl-5-aminoadamantane	100 g
Caffeine	1000 g
Lactose	1530 g
Polyvinylpyrrolidone	40 g
Polyvinylpyrrolidone solution (10% in isopropanol)	100 g
Potato starch	250 g
Talcum	49 g
Magnesium stearate	21 g
	3000 g

The 1,3-dimethyl-5-aminoadamantane, caffeine, lactose and PVP are mixed and subjected to wet granulation with the PVP solution. After drying, potato starch, talcum and stearate are admixed with the granulate, and tablets of 300 mg compressed.

EXAMPLE 4

Coated Tablets

For the manufacture of coated tablets, tablet cores of 100 or 300 mg are compressed as described in Example 3. These tablet cores are then coated, e.g., according to the sugar-coating procedure: The core is covered with the coating suspension, colored with colored syrup, and polished.

An example for the coating of a 100 or 300 mg tablet core, containing 10 mg of 1,3-dimethyl-5-aminoadamantane and 100 mg of caffeine per core, follows:

Core	100.0 mg
Sugar	65.0 mg
Talcum	39.0 mg
Calcium carbonate	13.0 mg
Gum arabic	6.5 mg
Corn starch	3.7 mg
Shellac	1.1 mg
Polyethylene glycol	0.2 mg
Magnesia usta	1.3 mg
Colorant	0.2 mg
	230.0 mg

It has accordingly been shown from the foregoing that the subject matter of the present invention is a composition for influencing the central nervous system and which is especially useful in the treatment of hyperkinesis and rigidity, particularly in the treatment of Parkinson's disease, comprising a combination of 1,3-dimethyl-5-aminoadamantane or a pharmaceutically-acceptable acid addition salt thereof, together with at least one methylxanthine compound, such as caffeine or theophylline, wherein the combination therapy or combination composition comprises up to fifteen milligrams or parts of the methylxanthine compound per each milligram or part of 1,3-dimethyl-5-aminoadamantane.

THe compositions made available according to the present invention are especially suitable for use in human medicine, being useful in the treatment of central nervous system ailments and afflictions generally, particularly of Parkinson's disease, depressions, spasticity, rigidity, hyperkinesis, and the like.

According to the present invention, the active ingredients are administered either contemporaneously, simultaneously, or together in a unit dosage form. They may be administered by the oral or parenteral, e.g., intraperitoneal, route. For these purposes, tablets, capsules, solutions, and injectable solutions are particularly suitable. Carrier substances, if desired, may be administered together therewith and the common organic and inorganic adjuvants which do not react with the active ingredients, for example, water, ethanol, polyethylene glycol, gelatine, lactose, starch, magnesium stearate, talcum, cellulose, and the like may be employed for this purpose. If necessary, the formulations may be stabilized and/or sterilized by a mixture with one or more of preservatives, wetting agents, buffers, colors, and essences or flavors. Preparations providing sustained release of the active ingredients may also be provided in known manner. In all of these compositions, the 1,3-dimethyl-5-aminoadamantane compound is either present as the free base or as a pharmaceutically-acceptable salt thereof.

Suitable salts of 1,3-dimethyl-5-aminoadamantane, which can be employed in the compositions and according to the method of the invention, are well known and are the usual amine acid addition salts, either of an organic or inorganic nature, such as the hydrochloride, hydrobromide, sulphate, citrate, tartrate, and the like, as disclosed in the aforesaid U.S. Pat. No. 4,122,193 and elsewhere in the prior art. These salts are made from the free basic compound in known manner according to the skill of the art, and in accord with the aforesaid disclosure of U.S. Pat. No. 4,122,193 and the examples thereof.

Thus, the active ingredient is the free 1,3-dimethyl-5-aminoadamantane base or a pharmaceutically-acceptable salt thereof, numerous of which are disclosed in the aforesaid U.S. Pat. No. 4,122,193.

The method of the invention, accordingly, comprises administering, by any suitable route, preferably orally, to a subject in need thereof, the 1,3-dimethyl-5-aminoadamantane or a pharmaceutically-acceptable salt thereof together with a methylxanthine compound, e.g., caffeine or theophylline, in an amount up to about fifteen milligrams or parts of the methylxanthine compound for each milligram or part of the 1,3-dimethyl-5-aminoadamantane. The administration may be simultaneous, concurrent, or in a single unit dosage form. The compounds may be utilized either per se or preferably in the form of pharmaceutical compositions in admixture together with the usual pharmaceutical diluents, carriers, or adjuvants, according to the customary procedure of the art. They may, in this manner, be embodied into pharmaceutical compositions comprising an effective anti-hyperkinesically effective amount of the combination of active ingredients according to the invention together with the pharmaceutically-acceptable carrier. They may be administered in the form of such pharmaceutical compositions wherein the amount of 1,3-dimethyl-5-aminoadamantane compound is up to give milligrams and, where higher dosages are required, up to ten milligrams, depending upon the patient involved and the exact syndrome being treated, or even greater or lesser amounts, depending of course upon the judgment of the physician in charge, body weight of the patient, degree of central nervous system affliction, etc. The daily regimen is accordingly any number, e.g., 2-4, of such unit dosages as previously mentioned for ameliorative or maintenance treatment of the exact condition involved. When the combination of compounds or compositions of the invention are employed for such purpose, they are administered to a subject in need thereof, particularly a subject suffering from Parkinson's disease, hyperkinesis, and rigidity, but also possibly for the relief of depressions, spasticity, and the like, the amount of the methylxanthine compound being present in an amount up to about fifteen milligrams or parts per each milligram or part of the 1,3-dimethyl-5-aminoadamantane active ingredient, the amount of the two ingredients together constituting an effective anti-hyperkinesically effective amount. As previously stated, the exact amounts and dosage regimens employed will depend upon the patient involved, the exact syndrome being treated, the gravity of the central nervous system affliction, the judgment of the physician in charge, the body weight of the patient, and so on but, as previously indicated, the amount of the 1-amino-3,5-dimethyladamantane, when given in a composition of the present inivention or concurrently with the methylxanthine such as caffeine or theophylline, is generally less than the effective anti-hyperkinesic amount of the same compound when given alone, so that the dosages and

dosage regiments can be accordingly decreased in practice.

It is to be understood that the invention is not to be limited to the exact details of operation or exact compounds, compositions, methods, or procedures shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the full scope of the appended claims.

I claim:

1. A composition which influences the central nervous system and is especially useful in the treatment of hyperkinesis and rigidity, which contains the compound 1,3-dimethyl-5-aminoadamantane or a pharmaceutically-acceptable salt thereof, characterized in that it contains a potentiating amount of a methylxanthine compound selected from caffeine and theophylline, the methylxanthine compound being present in said composition in a potentiating amount up to about fifteen milligrams per milligram of the 1,3-dimethyl-5-aminoadamantane.

2. Composition of claim 1 containing up to about ten milligrams of the 1,3-dimethyl-5-aminoadamantane compound.

3. Composition of claim 1 containing up to about five milligrams of the 1,3-dimethyl-5-aminoadamantane compound.

4. A composition of claim 1, adapted to be administered orally or parenterally in dosage unit form.

5. A composition of claim 1, wherein a pharmaceutically-acceptable carrier is also present.

6. A method for influencing the central nervous system which is especially useful in the treatment of hyperkinesis and rigidity, comprising concurrently administering to a host in need of such treatment the compound (a) 1,3-dimethyl-5-aminoadamantane or a pharmaceutically-acceptable salt thereof and (b) a methylxanthine compound, selected from caffeine and theophylline, in an amount up to about fifteen milligrams of the methylxanthine compound per milligram of the 1,3-dimethyl-5-aminoadamantane compound, the combination of (a) and (b) constituting an effective antihyperkinesic dose.

7. A method of claim 6, wherein the treatment is effected by administering a composition of claim 1.

8. A method of claim 6, wherein the treatment is effected by administering a composition of claim 2.

9. A method of claim 6, wherein the treatment is effected by administering a composition of claim 3.

10. A method of claim 6, wherein the treatment is effected by administering a composition of claim 4.

11. A method of claim 6, wherein the treatment is effected by administering a composition of claim 5.

* * * * *

ANEXO 2

Carrera 13 Nº 119-95, Oficina 104. Tel. (571) 2 13 12 13 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

US005382601A

United States Patent [19]

Nürnberg et al.

[11] Patent Number: 5,382,601

[45] Date of Patent: Jan. 17, 1995

[54] **MEMANTINE-CONTAINING SOLID PHARMACEUTICAL DOSAGE FORMS HAVING AN EXTENDED TWO-STAGE RELEASE PROFILE AND PRODUCTION THEREOF**

[75] Inventors: Eberhard Nürnberg, Uttenreuth/Weiher; Erhard Seiller, Nidderau; Stefan Ritsert, Eberbach, all of Germany

[73] Assignee: Merz + Co. GmbH & Co., Frankfurt am Main, Germany

[21] Appl. No.: 96,952

[22] Filed: Jul. 23, 1993

[30] Foreign Application Priority Data

Aug. 4, 1992 [DE] Germany 4225710

[51] Int. Cl.[6] A61K 9/38; A61K 9/64; A61K 37/16

[52] U.S. Cl. 514/775; 530/360; 424/465; 424/469; 424/470

[58] Field of Search 424/465, 469, 470; 514/775; 530/360

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Primary Examiner—Shep K. Rose
Attorney, Agent, or Firm—Gordon W. Hueschen

[57] ABSTRACT

The present invention provides solid pharmaceutical compositions in dosage form containing an active ingredient or principle, preferably memantine, which exhibit an extended two-phase release profile and which are characterized by the presence of both a water-soluble and a water-insoluble salt of casein, preferably sodium and calcium caseinate, in the matrix thereof, in broad proportions and in a total amount between 5 and 98% by weight of the composition, and with a process for the production thereof.

22 Claims, 3 Drawing Sheets

FIG. 1

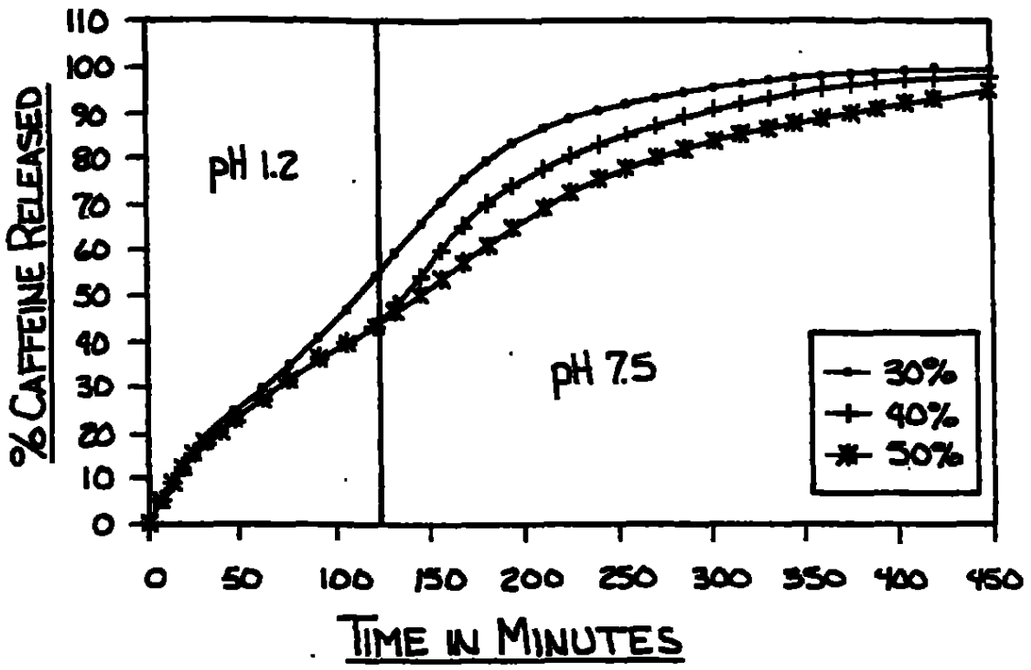


FIG. 2

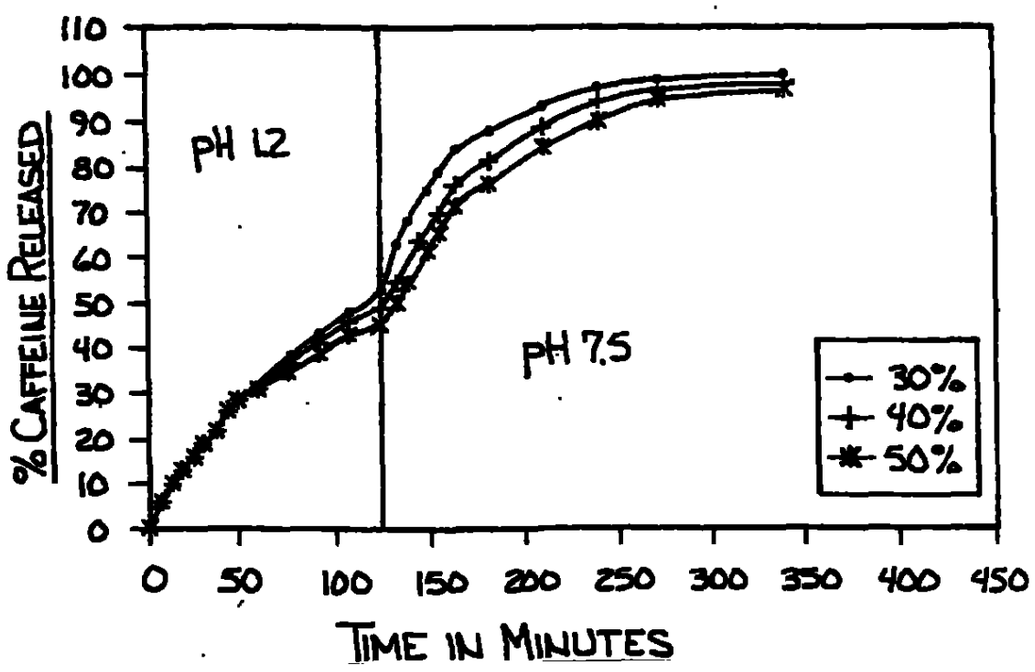
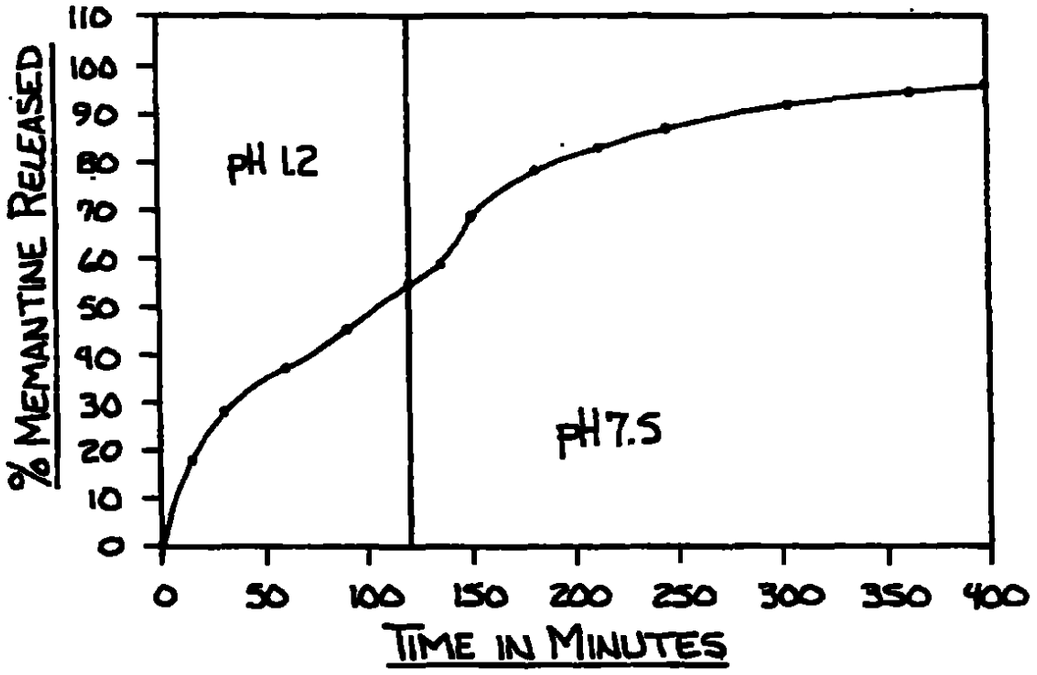


FIG. 3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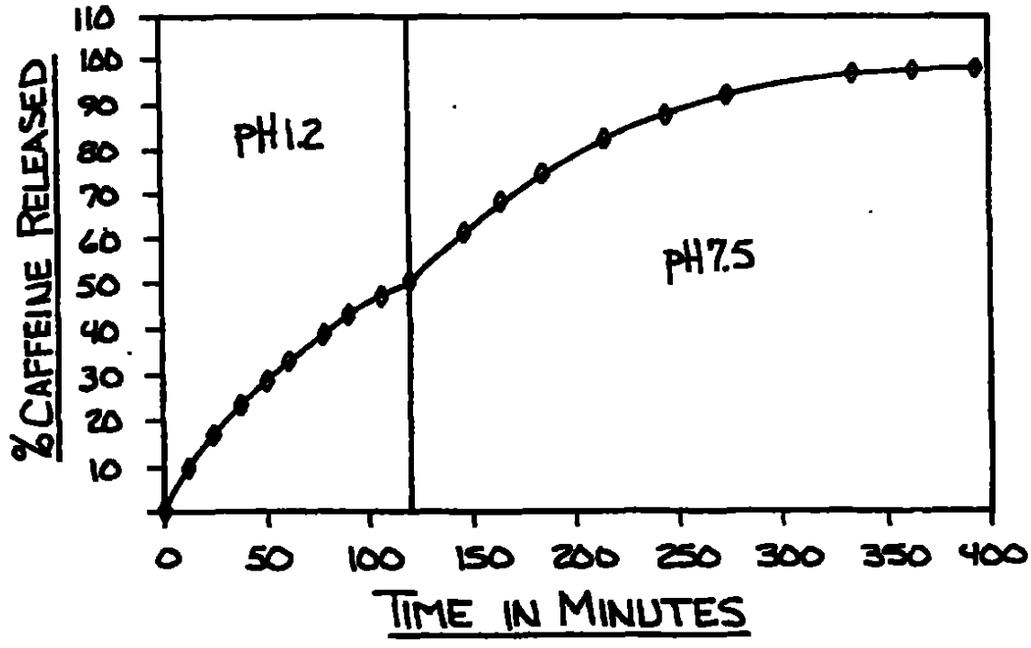
0
10
20
30
40
50
60
70
80
90
100
110
pH 1.2
pH7.5
0
50
100
150
200
250
300
350
400
TIME IN MINUTES

FIG. 4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10
20
30
40
50
60
70
80
90
100
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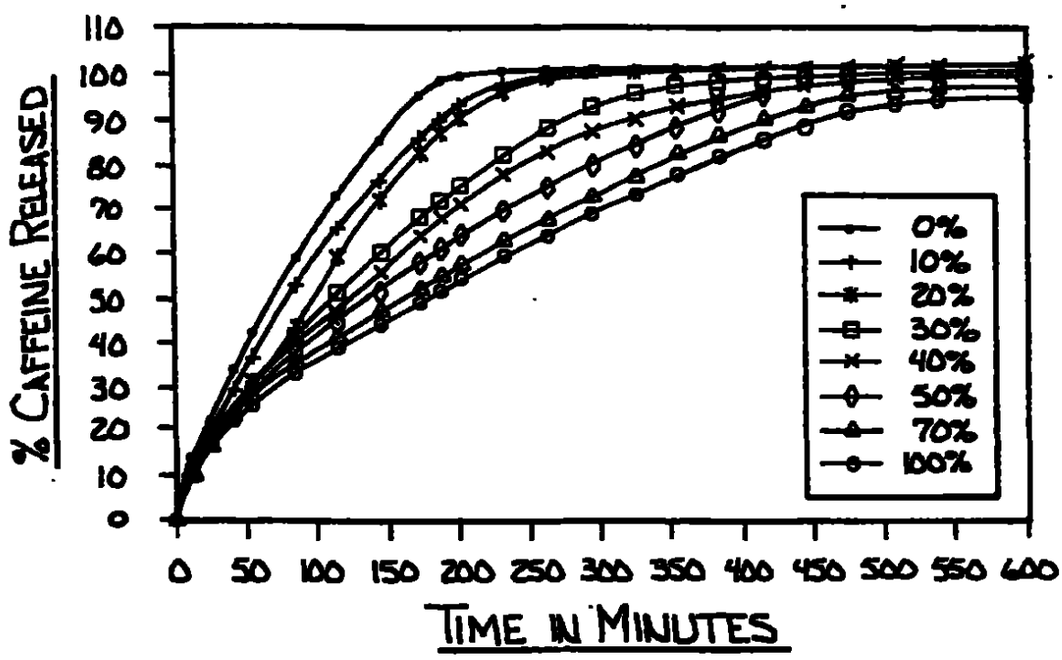
pH7.5
0
50
100
150
200
250
300
350
400
TIME IN MINUTES

FIG. 5


% CAFFEINE RELEASED
110
100
90
80
70
60
50
40
30
20
10
0
0 50 100 150 200 250 300 350 400 450 500 550 600
TIME IN MINUTES
0%
10%
20%
30%
40%
50%
70%
100%

MEMANTINE-CONTAINING SOLID PHARMACEUTICAL DOSAGE FORMS HAVING AN EXTENDED TWO-STAGE RELEASE PROFILE AND PRODUCTION THEREOF

BACKGROUND OF THE INVENTION

1. Field of Invention

The present invention is concerned with solid pharmaceutical compositions in dosage form which exhibit an extended matrix-controlled two-phase release profile and which are characterized by the presence in the matrix of both a water-soluble and a water-insoluble salt of casein, preferably sodium and calcium caseinate, respectively, in a total amount between 5 and 98% by weight of the composition, and with a process for the production thereof. A part or all of the insoluble casein salt may be replaced by a salt or solution of a polyvalent including bivalent cation, e.g., the calcium cation, adapted to form the water-insoluble casein salt in situ. The invention is particularly suitable for the provision of solid pharmaceutical dosage forms in which the active substance or principle is memantine.

2. Background of the Invention and Prior Art

Solid oral drug compositions or preparations having a retarded release, so-called retarder or extended-release preparations, are products from which the active ingredient is released over an extended period of time and hence exhibit a prolonged effect, with resultant plasma levels being adapted to therapeutic requirements. Also, a polyphase release profile can be employed to attain the desired therapeutic objectives. However, this does not necessarily mean that long-lasting effective blood level concentrations are consistently achieved. Moreover, systemic side effects and undesirable local effects within the gastrointestinal tract due to excessive local concentrations and resulting erratic plasma levels, respectively, are to be avoided.

In conventional procedures for the preparation of solid pharmaceutical dosage forms having an extended-release profile or pattern, the active substance in the majority of cases is either given extended-release properties by the application of various coatings or by being embedded in a macromolecular substance from which it is slowly released.

The most important control procedures for the release of an active pharmaceutical from a solid dosage form are the film-coating and the matrix procedures. In film coating procedures, film-forming polymers are employed to provide sustained release of the active substance in a diffusion-controlled manner. However, such an approach is disadvantageous if, during ingestion of the oral dosage form, the film is prematurely breached, as by chewing or abrasion, thereby releasing an excessive amount of active ingredient, which can result in undesirable effects from such excessive single-shot drug release.

In the matrix-controlled release approach, lipophilic substances, e.g., higher alcohols, waxes, or insoluble thermoplasts, are employed, it being a disadvantage that synthetic polymers not only generally contain varying amounts of undesirable monomers but that moreover a complete release of drug from the matrix is frequently not effected in practice.

The U.S. Pat. No. 4,665,081 describes a nifedepin formula for oral administration, which contains casein and inorganic additives selected from magnesium silicate, oxide, or aluminatemetasilicate, synthetic hydrotalc and magnesium aluminum oxide, thereby ensuring that the active substance—provided that a gastric juice-resistant auxiliary agent is included—is not released in the stomach but is rather rapidly released in the intestine. Such formulation will cause, on the one hand, a retarded release relative to the time of administration but, on the other hand, due to the rapid dissolution in the intestine, a high plasma concentration which is likely to result in undesirable side effects.

Pharm. Acta Helv. 66, No. 4, 120–124 (1991) describes an ibuprofen formula containing casein or gelatine which causes an elevated rate of dissolution and release, respectively, of the active substance.

Pharmaceutical Technology 9, 360–374 (1990) examines the influence of the presence of sodium caseinate on the rate of release of an active substance. Here, too, an enhanced dissolution, in particular, of chlorothiazide and hydrochlorothiazide, is reported.

The EP-A 0 447 100 Patent discloses formulations permitting controlled release in the stomach and in the intestine in response to the enzymes contained therein. For this purpose, a gel matrix, e.g., of alginate or carboxymethyl cellulose, carrageenin, or the like is employed, which contains imbedded therein a protein, such as calcium caseinate, and which comprises a further drug or food substance which is bondable to the protein. Although a controlled release is enabled thereby, such effect is achieved by the incorporation of protein in a surrounding matrix-forming gel.

GB-A 2 207 353 also describes formulations with a controlled release, containing calcium-free mixtures of alginic acid salts and caseinats. The protracted release is, however, based on a surrounding gel-matrix principle of the type referred to above.

It is apparent to one skilled in the art that the available technology for effective and reliable extended release, especially multistage release pharmaceutical dosage forms, still leaves much to be desired.

OBJECTS OF THE INVENTION

It is accordingly an object of the present invention to provide a pharmaceutical dosage form which is characterized by an extended controlled-release profile such that the active substance can be conveniently and reliably released over an extended period in at least two (2) stages and a process for the production thereof. Other objects of the invention will become apparent hereinafter, and still others will be obvious to one skilled in the art to which the present invention pertains.

SUMMARY OF THE INVENTION

The invention then, comprises the following, inter alia, separately or in combination:

A solid pharmaceutical composition in dosage form having a matrix-controlled extended two-stage release profile comprising an effective amount of at least one pharmaceutically-active ingredient or principle, wherein the matrix consists essentially of a combination of a water-soluble salt of casein and a water-insoluble salt of casein, the total water-soluble and water-insoluble casein salt content comprising between 5% and 98% of the total weight of the pharmaceutical composition, all salts and cations being pharmacologically acceptable; such a

composition wherein the water-soluble and water-insoluble casein salts comprise between 10% and

90% by weight of the pharmaceutical composition, preferably

between 30% and 80% by weight; such a

composition wherein the pharmaceutical composition comprises between about 5% and 95% of a water-insoluble casein salt based upon the total casein salt content, preferably

between about 20% and 70% by weight; such a

composition wherein the water-insoluble casein salt is calcium caseinate; such a

composition wherein the water-soluble calcium salt is sodium caseinate; such a

composition wherein the pharmaceutical composition comprises an enzyme; such a

composition wherein the enzyme is pancreatin or pepsin or both, and such a

composition wherein the active ingredient is memantine.

Moreover, a process for the preparation of a solid pharmaceutical composition in dosage form having a matrix-controlled two-stage release profile comprising an effective amount of at least one pharmaceutically-active ingredient or principle, wherein the matrix consists essentially of a combination of a water-soluble salt of casein and a water-insoluble salt of casein, comprising the step of compressing, granulating, extruding, pelletizing, or tabletting, in dry or wet manner, of a mixture comprising the at least one active ingredient in admixture with both a water-soluble and a water-insoluble salt of casein or, alternatively, a water-soluble salt of casein and a salt or solution of a polyvalent cation which is adapted to form a water-insoluble salt of casein in situ, the total water-soluble and water-insoluble casein salt content of the admixture in the final composition comprising between 5% and 98% of the total weight of the pharmaceutical composition, all salts and cations being pharmacologically acceptable; such a

process wherein the water-soluble and water-insoluble casein salts are included in the mixture to the extent of between 10% and 90% by weight of the pharmaceutical composition, preferably

between 30% and 80% by weight; such a

process wherein between about 5% and 95% of a water-insoluble casein salt, based upon the total casein salt content, is mixed into the composition, preferably

between about 20% and 70% by weight; such a

process wherein the water-insoluble casein salt mixed into the composition is calcium caseinate, and such a process wherein the water-soluble casein salt is sodium caseinate; such a

process wherein a water-soluble casein salt and a polyvalent cation salt is employed in the process, the percentage of the water-insoluble casein salt content to the final resultant casein salt content being between about 5% and 90%, preferably

between 20% and 70%; such a

process wherein the cations are calcium ions; such a

process wherein the water-soluble casein salt employed is sodium caseinate; such a

process wherein an enzyme is also mixed into the pharmaceutical composition; such a

process wherein the enzyme is pancreatin or pepsin or both; and such a

process wherein the active ingredient mixed into the composition is memantine.

The Present Invention

According to the practice of the present invention, the problem is solved by providing a solid pharmaceutical composition in dosage form containing a pharmacentically-effective amount of one or more active substances and the usual auxiliary agents and additives, but also a total of between 5 and 98%, preferably 10 to 90%, and especially 30 to 80%—based on the total weight of the composition—of a combination of a water-soluble and a water-insoluble salt of casein. A pharmaceutical formulation of this type can then be treated in the usual way to provide a variety of solid dosage forms having a two-phase matrix-controlled extended release profile. This includes the employment of procedures known in the pharmaceutical industry, such as compressing, granulating, extruding, pelletizing, and tabletting in dry or wet manner. It is of course also possible to combine a variety of procedures to provide the desired product formulation in any one of various forms such as tablets, dragees, pellets, granules, and the like. The amount of active substance present can be varied widely depending on the indication to be treated and the type of dosage form desired, for example, from 0.01 to 90%, based on the total weight of the pharmaceutical composition.

Quite unpredictably, it has been found that the pharmacokinetic properties of the solid dosage forms according to the present invention are not affected by the manufacturing method employed or the variations arising in practice, e.g., the compression forces utilized.

The casein employed can be a commercially available product, and the molecular weight and water content thereof may vary considerably, for example between MW 18000 and MW 30000 Daltons—depending upon the origin thereof, without detracting from its operativeness according to the present invention. Casein is of course a substance approved for use under food legislation throughout the civilized world.

A casein salt of a monovalent cation, such as lithium, potassium, ammonium, and preferably sodium, is used as the water-soluble casein salt.

The water-insoluble caseinate is a salt of casein with a bi- or polyvalent cation, both referred to herein as a polyvalent cation. These include, e.g., calcium, magnesium, zinc, manganese, aluminum, iron, or mixtures thereof. Particularly preferred is calcium. The water-insoluble caseinate can be used as such.

In addition, it is possible to include in the composition, containing a soluble casein salt, a physiologically-compatible polyvalent cation, in the form of a salt thereof which is soluble in water or gastric fluid, optionally in solution in water, in amounts such that a part of the soluble caseinate is converted to an insoluble caseinate, thereby transforming a part of the soluble casein salt to an insoluble casein salt in situ, as by gastric fluid upon ingestion. A part or all of the insoluble salt may be provided in this manner. Preferred cations are the chloride, gluconate, carbonate, lactate, and saccharate cations and, in particular, calcium chloride, calcium gluconate, calcium hydrogen phosphate, calcium lactate, calcium D-saccharate, calcium levulinate, and their hydrates, or mixtures thereof, are preferred salts for providing the aqueous polyvalent, including bivalent, cation, which may be used as such or, if desired, be solvated by simple dissolution of the salt, e.g., in water, and optionally used in a normal granulation procedure.

The weight/weight ratio of soluble to insoluble caseinate is between 5 and 95%, preferably between 5 and 90%, and more preferably between 20 and 70%, based on the total caseinate content of the composition. Most preferred is a weight/weight ratio of between 30 and 60%. The amounts of the aforementioned ionic compounds and their solutions required for the production of the desired amount and ratio of insoluble caseinate in situ are dependent on the type of cation, its counter-ion, and the molecular weight of the casein employed, as will be readily understood by and as can be readily determined by one skilled in the art since it involves only basic chemistry.

According to the invention, quite unpredictably and advantageously, a controlled bi-phase matrix-controlled extended release of active pharmaceutical ingredient is thus achieved with the specified combination of matrix-forming substances alone and without the necessity of any embedded or surrounding external protein.

Common auxiliary agents and additives or excipients which may be employed to complete the pharmaceutical composition used as matrix are components well known in the pharmaceutical industry. These include, for example, tabletting aids, such as highly disperse silicic acid, magnesium stearate, microcrystalline cellulose, lactose, talc, colorants such as iron oxides or quinoline yellow, pigments such as titanium dioxide and calcium carbonate, glyceryl monostearate, glyceryl behenate, sodium stearylfumarate, stearic acid, cetyl palmitate, long-chain partial glycerides, cellulose powder, mannitol, calcium phosphate, silicon dioxide, colloidal silicon dioxide, silicon dioxide hydrate, and polyethylene glycol, preferably of a molecular weight 1,500 to 6,000 Dalton, and the like.

Active ingredients or mixtures thereof, which can be used to provide an effective amount of the active pharmaceutical principle or ingredient in the compositions of the invention, encompass innumerable pharmaceutically-active compounds which are suitable for extremely varied fields of end-use application. They include tranquillizers such as chlorpromazine and benzodiazepines such as diazepam; muscle relaxants such as mephenesin; antihypertensive agents such as α-methyldopa; centrally-acting analgetics such as morphine; peripherally-acting analgetics such as paracetamol; non-steroidal antiphlogistics such as ibuprofen; local anesthetics such as benzocaine; spasmolytics such as papaverine; prostaglandins such as PEG2, antibiotics such as penicillin and tetracycline; agents influencing the demential syndrome such as memantine; anti-Parkinsonism therapeutic agents such as amantadine, L-dopa, selegiline, bromocriptine, and metixene; antimalarials such as chloroquine; corticosteroids such as dexamethasone; androgens such as methyltestosterone; estrogens such as ethinylestradiol; gestagens such as levonorgestrel; sympathomimetics such as adrenalin; substances having cardiovascular effect such as nitroglycerin; diuretics such as hydrochlorothiazide; anthelmintics such as praziquantel; β-blockers such as timolol; H2-blockers such as cimetidine; vitamins such as ascorbic acid, and the like. Effective amounts of such pharmaceutically-active principles or ingredients are well known in the art.

Most preferred is memantine.

The readily-produced formulations according to the invention, upon ingestion, advantageously result in a controlled two-phase release of the active ingredient, with an amount of active substance adapted to the therapeutical goal being released and available in the first phase, i.e., in the stomach, as well as in the second phase, i.e., in the intestines where, after a slight delay, a renewed liberation of active ingredient is effected, the remainder of the active ingredient being released over a predetermined time period, thereby attaining an effective adaptation to the total active substance availability requirements, with the partial release in each stage resulting in corresponding desirable plasma levels. Local excess concentrations of active substance are thus avoided.

This two-phase pharmaceutically-active ingredient, e.g., drug or vitamin, liberation profile is substantially independent of the enzymes contained in the physiological environment of the stomach and intestines, as shown in the following examples, a result which hitherto has not been realizable by conventional dosage formulations.

However, if a change in the release rate is required in one or the other of the two liberation phases which might be necessary or desirable in view of the type of active substance employed, the physiology of the patient, or the degree of seriousness of the ailment treated, enzymes such as pepsin and/or pancreatin can of course be included in the formulation in suitable amounts, as well as numerous other enzymes or polymer-enzyme products such as neutral, acid, or alkaline protease, or any of the foregoing enzymes insolubilized by attachment to an ethylenemaleic acid or anhydride (EMA) polymer (as in U.S. Pat. No. 3,751,561). This does not change the two-phase profile. It is only the rate of liberation within the phases which can thus be slightly varied.

The mechanism of the extended two-stage release can be explained as follows:

The use of a water-insoluble caseinate, e.g., calcium caseinate, results in the formation of a matrix tablet. The drug is released independently of the pH of the dissolution medium in a diffusion-controlled manner. In other words, due to the presence of the insoluble caseinate, there is an extended release in both stages, the extent of retardation being dependent on the amount of insoluble caseinate in the formulation, as shown in Study 5 and corresponding FIG. 5.

In alkaline medium, the insoluble caseinate gradually becomes degraded, equivalent to an attenuation of the matrix-effect. Subsequently, the retardation is diminished and the drug release rate increases, which can be seen in the second stage, although also in this second stage drug release is extended.

BRIEF DESCRIPTION OF THE DRAWINGS

Reference is now made to the accompanying drawings, for a better understanding of the present invention, wherein:

FIG. 1 is a graph of a biphasic drug liberation profile showing release of caffeine over a period of time in accord with Study 1 of this application without enzyme and with medium change after two hours.

FIG. 2 is the same according to Study 2 of this application with enzyme and with medium change after two hours.

FIG. 3 is a graph showing the biphasic release of Memantine over a period of time in accord with Study 3 of this application without enzyme and with medium change after two hours.

FIG. 4 is the same as FIGS. 1 and 2, but in accord with Study 4 of this application without enzyme and with medium change after two hours, and

FIG. 5 is a graph illustrating the dependence of drug release on the insoluble caseinate content of a dosage form according to the invention, showing the percent caffeine released over a period of time with calcium caseinate content of the formulation varying from 0 to 100%, this liberation profile being determined in a simulated gastric environment at a pH of 1.2 without added enzyme.

SPECIFIC DESCRIPTION OF THE INVENTION

The invention will now be described in greater detail with references to the following Examples, which are not to be construed as limiting.

I. Production of the Drug Formulation

Example 1

Active Substances and Additives	Percent by Weight
memantine HCl	20.0
sodium caseinate	46.8
calcium caseinate	31.2
Aerosil 200 TM (finely-divided SiO_2)	1.0
magnesium stearate	1.0

All components with the exception of magnesium stearate are homogeneously distributed in a suitable mixer such as a Diosna TM mixer; subsequently magnesium stearate is added and the mixture passed through a screen of an average (U.S. Standard Sieve Series) mesh size of 300 μm. After a further mixing of the material to be compressed, tablets having a mass of 100 mg and a diameter of 6 mm are produced on a suitable tabletting machine, using a force of compression of 8 kN.

Example 2

Active Substances and Additives	Percent by Weight
caffeine	20.0
sodium caseinate	75.0
calcium chloride × $2H_2O$	3.0
Aerosil 200 TM	1.0
magnesium stearate	1.0

The caffeine and sodium caseinate components are mixed in a suitable fluidized bed granulation machine, such as the Aeromatic STREA 1 TM. The granulation of a 500 g batch is effected with 400 ml of an aqueous fluid containing 3 g calcium chloride dihydrate in dissolved form at a pump rate of 10 ml/min, an inlet temperature of 60° C., an outlet temperature of 32° C., and at an atomizing pressure on the binary nozzle of about 2 bar. After a redrying of 10 min at 60° C. and a weak supply of fresh air, the granulate is separated from the coarse portion (>1.0 mm) and from the fine portion (<0.15 mm) and, after admixing with Aerosil and magnesium stearate, is compressed using a force of compression of 8 kN into tablets having a weight of 100 mg and a diameter of 6 mm.

Example 3

Active Substances and Additives	Percent by Weight
piroxicam	20.0
sodium caseinate	65.0
calcium hydrogen phosphate + $2H_2O$	3.8
Avicel PH 102 TM - microcrystalline cellulose	9.2
Aerosil 200	1.0
magnesium stearate	1.0

All components except for magnesium stearate are homogeneously distributed in a suitable mixer, e.g., a Diosna TM mixer, magnesium stearate then added, and the mixture passed through a screen of an average (U.S. Standard Sieve Series) mesh size of 300 μm. After a further mixing of the compressed mass, tablets are produced on a suitable pelleting machine, having a mass of 100 mg and a diameter of 6 mm, with a compression force of 8 kN being applied.

Example 4

Active Substances and Additives	Percent by Weight
ibuprofen	77.0
sodium caseinate	20.0
calcium chloride + $2H_2O$	1.0
Aerosil 200 TM	1.0
magnesium stearate	1.0

By spraying a suitable granulating liquid such as an ethanol/water mixture (v/v 3/2) or a colloid-containing granulating liquid such as gelatine/water (1/30), a crust granulate or an adhesive granulate is first produced from the ibuprofen.

The granulate is mixed with the remaining components in a suitable mixer and is compressed, using a compression force of 15 kN, into tablets having a mass of 520 mg and a diameter of 12 mm.

Example 5

Active Substances and Additives	Percent by Weight
memantine-HCl	20.0
sodium caseinate	48.0
calcium caseinate	32.0

All components are homogeneously distributed using a suitable mixer and, in a mixing kneader, are then intimately wetted with a suitable plasticizing liquid, such as purified water or an ethanol/water mixture (v/v 3/2) to an extent of about 60% v/v based on the solid portion. The resultant mass is lyo-extruded either on a screw extruder or on a distributing roll-type extruder with an apertured disk-diameter of 1.5 mm. The thus-obtained strands are divided and filleted on a spheronizer to form pellets of a diameter of 1.8 mm. Subsequently, the pellets are either loaded into capsules or are compressed into tablets after admixing with 1% Aerosil and 1% magnesium stearate.

II. Liberation or Release Tests

The media used in all dissolution tests is either simulated gastric fluid (pH 1.2) or simulated intestinal fluid (pH 7.5). To more closely approach in vivo conditions, pepsin (gastric fluid) and pancreatin (intestinal fluid) are added. In the chapter "Test Solutions" of the U.S. Pharmacopoea XXII, the compositions of the two media are exactly described as follows:

"Gastric Fluid, Simulated, TS—Dissolve 2.0 g of sodium chloride and 3.2 g of pepsin in 7.0 mL of hydrochloric acid and sufficient water to make 1000 mL. This test solution has a pH of about 1.2."

"Intestinal fluid, Simulated, TS—Dissolve 6.8 g of monobasic potassium phosphate in 250 mL of water, mix, and add 190 mL of 0.2N sodium hydroxide and 400 mL of water. Add 10.0 g of pancreatin, mix, and adjust the resulting solution with 0.2N sodiumhydroxide to a pH of 7.5±0.1. Dilute with water to 1000 mL."

1. Retarded Release of an Active Substance in Response to the Insoluble Caseinate Content

The following basic formula is compressed:

caffeine	20.0
Ca-caseinate	0-78.0% (based on the total casein content)
Aerosil 200	1.0
magnesium stearate	1.0
NaCaseinate	ad 100%

Eight different compressive masses of varying Na-caseinate and Ca-caseinate proportions (added as such) are formulated by using the tabletting auxiliaries Aerosil and magnesium stearate. As no other auxiliaries are added, a true picture of the release properties is obtained.

The total caseinate portion amounts to 78%. The pulverulent mixtures are compressed on an instrumentized Exacta 1 TM at an adjusted speed of 30 strokes/-min, using compressing tools of 6 mm, flat without facette, at a constant force of compression of 8 kN to form tablets having an individual weight of 100 mg.

Dosage form products are obtained having a Ca caseinate content of 0, 10, 20, 30, 40, 50, 70 and 100%, the liberation profile of which is determined at pH 1.2 (simulation of gastric environment).

FIG. 5 shows the dependence of drug release on the insoluble caseinate, i.e., calcium caseinate, content of the dosage form, and thus the extent of retardation. The tablet formulations employed in this study correspond to the basic formula of II. 1 just hereinabove provided.

The dissolution of 80% of total caffeine content occurs in the case of 20% Ca-caseinate (percentage related to total caseinate) at 160 min (vs. 127 min without Ca-caseinate—F=1.25), at 285 min with 50% Ca-caseinate (F=2.2), and at 350 min with a Ca-caseinate content of 100% (F=2.75). These data are the results of dissolution tests in gastric fluid (pH 1.2) without added enzyme.

It has thus been established that the release in this gastric environment can be inhibited by the combination of insoluble caseinate with soluble caseinate; depending on the relative proportions thereof, a varying retardation is obviously achieved. This permits the selection of a highly-desirable individual release profile, depending on the active substance and the type of indication to be treated.

2. Liberation or Release Profile of Caseinate Tablets Compressed at a Varying Force of Compression

The following formulation with a Ca-caseinate proportion of the total caseinate content of 40% is compressed in accordance with the aforementioned conditions at forces of compression of between 4 and 12 kN into tablets having an individual weight of 100 mg:

caffeine	20.0
Na-caseinate	46.8
Ca-caseinate	31.2
Aerosil 200	1.0
magnesium stearate	1.0

It has been found that varying forces of compression within these ranges have no bearing or effect on the release profile.

3. Addition of Polyvalent Salt to the Soluble Caseinate to Produce the Insoluble Caseinate In Situ

The following basic matrix formulation is produced in the foregoing manner with admixture and/or granulation and in accord with the foregoing conditions (see Examples 1–5):

caffeine	20.0
NaCaseinate	65.0
Ca-salt, optionally in aqueous solution	X
Aerosil	1.0
magnesium stearate	1.0
Avicel PH 102	ad 100%

When completely converting a soluble caseinate, for example the NaCaseinate, to an insoluble, e.g., calcium, salt, the insoluble cation content can be readily determined, e.g., the calcium content is normally 1.5% to 1.7% by weight, but can optionally be made even higher, so that an amount as suggested below according to the present invention can be readily determined and the desired amount of insoluble casein salt thereby calculated and thus-provided.

The following pharmaceutically-suitable calcium salts can, for example, be used in the foregoing formulation to provide an insoluble casein salt in situ in a formulation of the invention:

Amount X employed in the Formula:	
calcium chloride × $2H_2O$	3.6
calcium gluconate × H_2O	10.9
calcium carbonate	2.4
calcium hydrogen phosphate × $2H_2O$	4.2
calcium lactate × $5H_2O$	7.5
calcium citrate × $4H_2O$	5.8
calcium-D-saccharate	6.1
calcium levulinate	7.5

The compositions of the foregoing formulae are compressed under the aforementioned conditions at a constant force of compression of 8 kN into tablets having an individual weight of 100 mg and are found to have the same two-phase extended release profile as a unit dosage matrix containing the same proportions of soluble and insoluble casein salts in solid form but present as such in the beginning admixture.

It has been found that all calcium salts used in this manner produce insoluble casein salt-containing matrices having almost identical liberation profiles. The t_{50}-values vary within a narrow range of between 100 and 113 min, while the t_{90}-values vary between 262 and 295 min.

Identical results are also obtained with solutions of other polyvalent ions besides calcium, for example, magnesium, zinc, and aluminum salts.

4. Influence of the Incubation Medium

A variety of compressed dosage form products produced according to II.1 with varying proportions of insoluble caseinate, preferably calcium caseinate, are now examined as to their drug-liberation profile with changing media both with and without enzymes.

The results are shown in Studies 1 and 2 and their corresponding figures FIG. 1 and FIG. 2. The figures (FIGS. 1 and 2) resulting from these studies show the biphase profiles of the compositions produced according to the invention with a Ca-caseinate portion of 30, 40 and 50% by weight, the results being shown in the following TABLE 1 (medium change after 2 hours):

TABLE 1

	t_{50} (min)			t_{90} (min)		
pH Ca-caseinate (%)	30	40	50	30	40	50
1.2/7.5 without enzyme (Study 1) (FIG. 1).	111	138	143	232	300	376
1.2/7.5 with enzyme (Study 2) (FIG. 2).	112	123	132	195	220	239

Thus, FIG. 1 shows the dissolution curves of three tablet formulations (produced according to II.1) with varying Ca-caseinate contents: 30, 40 and 50%.

Dissolution media used are simulated gastric (phase 1) and intestinal (phase 2) fluids without enzymes.

In FIG. 2 the dissolution behavior of the abovementioned tablet formulations are graphically shown again, but in this case the dissolution media respectively contained pepsin (phase 1) and pancreatin (phase 2).

It can be clearly derived from FIGS. 1 and 2 that mainly in alkaline (intestinal) medium the rate of drug release can be controlled by the content of water-insoluble Ca-caseinate. The higher the Ca-caseinate concentration in the tablet formulation, the slower the drug release. In other words: Ca-caseinate is exhibiting a retarding effect.

A comparison between FIGS. 1 and 2 shows that control of drug release-rate by varying the Ca-caseinate content is not influenced by the presence of enzymes in the dissolution media, thus mimicking in vivo conditions. Only the time to attain complete drug release is reduced by a factor F=1.3.

Thus, surprisingly enough, it has been found that the desired liberation profile is relatively independent of the enzyme present. The low enzyme-induced acceleration virtually ensures a 100% release in the second phase after about five (5) hours.

5. Release of Memantine from Tablets According to the Invention (Study 3)

A formulation produced according to Example I.1. is tested, as above, at pH 1.2/pH 7.5 (without enzyme, medium change after 2 hours). The two-phase liberation profile is shown in FIG. 3.

6. Release of Caffeine from a Formulation According to the Invention (Study 4)

A formulation produced according to Example I.2 is tested, as above, at pH 1.2/pH 7.4 (without enzyme, medium change after 2 hours). Here, too, a two-phase liberation profile arises as shown in FIG. 4.

FIG. 3 graphically shows the release profile of a memantine formulation produced according to I.1, and FIG. 4 the dissolution curve of a caffeine formulation prepared according to I.2. In both cases, the dissolution media contained no enzymes.

Within the scope of simulated in vivo conditions, the change of dissolution media in each study represents the passage of a solid dosage form from the stomach into the intestine.

Especially the graphs of FIGS. 2 and 4, but also the plots of the other FIGS., clearly demonstrate that a change of pH results in a steeper slope of the dissolution curve, which means an accelerated drug release. Translating this into human use, the value of the extended-two-stage release is seen as a slower increase of drug concentration into the blood, thus reducing undesirable side effects. This is particularly true for gastric side effects because, according to FIGS. 1-4, only about 40-50% of the drug content is released in the stomach.

Beyond this, a reliable slow release, generally prolongs intervals between application or dosing and thus improves patient compliance considerably.

7. Study 5, which was productive of FIG. 5, showing the Direct Influence of Insoluble Casein on the Drug Release Profile, has already been fully discussed hereinbefore under the heading of II 1.

Accordingly, it is clear that formulations having an optimally-adapted release profile can be produced in simple manner by incorporation of physiologically-compatible components into two-phase extended-release compositions and dosage forms according to the present invention.

It is seen from the foregoing that the objects of the present invention have been accomplished and that novel, efficient, and economic solid pharmaceutical compositions in dosage form, which exhibit an extended matrix-controlled two-phase release profile and which are characterized by the presence in the matrix of both a water-soluble and a water-insoluble salt of casein, which water-insoluble salt of casein may be provided in situ therein, and a process for the production thereof have been thereby provided, whereby all of the previously-mentioned advantages have been attained and the shortcomings of the prior art have been obviated.

Although the preferred embodiments of the invention have been illustrated in the accompanying drawings and described in the foregoing Specification, it is to be understood that the invention is not limited to the embodiments disclosed or to the exact details of operation or exact compounds, compositions, methods, or procedures shown and described, inasmuch as the invention is capable of numerous modifications and substitutions of equivalents without departing from the spirit or scope thereof, as will readily be apparent to one skilled in the art, wherefore the present invention is to be understood as limited only by the full scope which can be legally accorded the appended claims.

We claim:

1. A solid pharmaceutical composition in a dosage form selected from a compressed tablet formed from (a) granules, (b) pellets, or (c) spheronized extruded strands, or in the form of small (a) through (c) themselves, optionally in a capsule filled therewith, having a matrix-controlled extended two-stage release profile having a matrix comprising an effective amount between 0.01 and 90% of the total weight of the pharmaceutical composition of (C) at least one pharmaceutically-active ingredient, wherein the matrix consists essentially of a combination of a water-soluble salt of casein (A) and a water-insoluble salt of casein (B), the total water-soluble casein salt (A) and water-insoluble casein salt (B) content comprising between 5% and 98% of the total weight of the pharmaceutical composition, the water-insoluble casein salt comprising between about 5% and 95% based upon the total casein salt content, all salts and cations being pharmacologically acceptable.

2. A pharmaceutical composition of claim 1, wherein the water-soluble and water-insoluble casein salts comprise between 10% and 90% by weight of the pharmaceutical composition.

3. A pharmaceutical composition of claim 2, wherein water-soluble and water-insoluble casein salts comprise between 30% and 80% by weight of the pharmaceutical composition.

4. A pharmaceutical composition of claim 1, wherein the percentage of water-insoluble casein salt to total casein salt content is between about 20% and 70% by weight.

5. A pharmaceutical composition of claim 1, wherein the water-insoluble casein salt is calcium caseinate.

6. A pharmaceutical composition of claim 1, wherein the water-soluble calcium salt is sodium caseinate.

7. A pharmaceutical composition of claim 1, wherein the pharmaceutical composition comprises an enzyme.

8. A pharmaceutical composition of claim 7, wherein the enzyme is pancreatin or pepsin or both.

9. A pharmaceutical composition of any of claims 1 through 3 and 4 through 8, wherein (A) is sodium caseinate and (B) is calcium caseinate and the active ingredient (C) is memantine.

10. A process for the preparation of a solid pharmaceutical composition in a dosage form selected from a compressed tablet formed from (a) granules, (b) pellets, or (c) spheronized extruded strands, or in the form of small (a) through (c) themselves, optionally in a capsule filled therewith, having a matrix-controlled two-stage release profile having a matrix comprising an effective amount between 0.01 and 90% of the total weight of the pharmaceutical composition of at least one pharmaceutically-active ingredient (C), wherein the matrix consists essentially of a combination of a water-soluble salt of casein (A) and a water-insoluble salt of casein (B), comprising the step of compressing, granulating, extruding, pelletizing, or tabletting, in dry or wet manner, of a mixture comprising the at least one pharmaceutically-active ingredient (C) in admixture with both a water-soluble salt of casein (A) and a water-insoluble salt of casein (B) or, alternatively, a water-soluble salt of casein (A) and a salt or solution of a polyvalent cation which is adapted to form a water-insoluble salt of casein (B) in situ, the total water-soluble and water-insoluble casein salt content of the admixture in the final composition comprising between 5% and 98% of the total weight of the pharmaceutical composition, the percentage of water-insoluble casein salt (B) to total casein salt content included in the mixture being between about 5% and 95% based upon the total casein salt content, all salts and cations being pharmacologically acceptable.

11. A process of claim 10, wherein the water-soluble and water-insoluble casein salts are included in the mixture to the extent of between 10% and 90% by weight of the pharmaceutical composition.

12. A process of claim 11, wherein the water-soluble and water-insoluble casein salts are included in the mixture to the extent of between 30% and 80% by weight of the pharmaceutical composition.

13. A process of claim 10, wherein the percentage of water-insoluble casein salt to total casein salt content included in the mixture is between about 20% and 70% by weight.

14. A process of claim 10, wherein the water-insoluble casein salt mixed into the composition is calcium caseinate and wherein the water-soluble casein salt is sodium caseinate.

15. A process of claim 10, wherein a water-soluble casein salt and a polyvalent cation salt is employed in the process, the percentage of the water-insoluble casein salt content to the final resultant casein salt content being between about 5% and 90%.

16. A process of claim 15, wherein the percentage is between 20% and 70%.

17. A process of claim 15, wherein the cation is the calcium ion.

18. A process of claim 15, wherein the water-soluble casein salt employed is sodium caseinate.

19. A process of claim 10, wherein an enzyme is also mixed into the pharmaceutical composition.

20. A process of claim 19, wherein the enzyme is pancreatin or pepsin or both.

21. A process according to any of claims 10 through 12 and 13 through 20, wherein (A) is sodium caseinate and (B) is calcium caseinate and the active ingredient (C) mixed into the composition is memantine.

22. A method of administering a pharmaceutically-active ingredient (C) consisting essentially of the step of administering the pharmaceutically-active ingredient (C) in the form of a two-phase extended-release pharmaceutically-effective solid dosage form of claim 1, or claim 5, or claim 6.

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Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Jerónimo Castillo Bonilla
Apoderado

Oficio Nº: 5057

ASUNTO:

Radicación PCT Nº	05-124706
Trámite	011
Evento	379
Actuación	440
Folios	009

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Laura Catalina Silva Barrera, 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 Nº 10 de 2001.

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

04 MAYO 2007

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

202021

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Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Jerónimo Castillo Bonilla
Apoderado

Oficio Nº: 5058

ASUNTO:

Radicación PCT Nº	05-124706
Trámite	011
Evento	379
Actuación	440
Folios	017

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Tecnoquímicas 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 Nº 10 de 2001.

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

El anterior requerimiento fue notificado por fijación en lista de fecha 04 MAYO 2007.

202021

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Sede CAN: Tr. 40A No. 38-50 Conmutador: 3820840
Fax: 382 28 95. Línea 9800-910 165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia