



No. 06-090492- -00002-0000

Fecha: 2008-06-27 13:04:08 Dep. 2020 NUECREACIONE
Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 400 OPOSIOBSERVTER Folios: 29

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A :

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

②

SOLICITUD
PUBLICADA

Número del expediente: 06-90492

Solicitante: LABORATORIOS SILANES, S.A DE C.V

Apoderado: EMILIO FERRERO

Título de la nueva creación o denominación del signo: "COMPOSICION
FARMACEUTICA ESTABLE DE METFORMINA CON LIBERACION PROLONGADA".

Gaceta: 590

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: GYNOPHARM S.A	IDENTIFICACIÓN	
	Dirección: CALLE 80 No. 78B -201	C.C. ☐	NIT ☒
	Nacionalidad o Domicilio: COLOMBIA	C.E. ☐	Otro ☐
	Lugar de Constitución: BARRANQUILLA	Cual <u> </u>	
	Teléfono: (571)3719900 Fax: (571)3730818	Número <u>802.006.279-4</u>	
	E-mail: <u> </u>		
REPRESENTANTE O APODERADO	Nombre: ELIANA ISAURA MORENO BOHORQUEZ	IDENTIFICACIÓN	
	Dirección: CARRERA 13 No. 119-95 104	C.C. ☒	NIT ☐
	Teléfono: (571) 2131213 Fax: (571) 6121979	C.E. ☐	Otro ☐
	E-mail: <u>negocios@optimum-co.com</u>	Cual <u> </u>	
		Número <u>51'975.664</u> TP <u>83823</u>	

④ FUNDAMENTOS DE LA OPOSICIÓN:

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

No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo
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".

98 2
38

⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

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

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA: _____

C.C. 51.975.664

TP. 83823

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

Referencia : Expediente N° 06-90492
Asunto : Oposición a la solicitud de patente de Invención titulada
"COMPOSICIÓN FARMACÉUTICA ESTABLE DE
GLIMEPIRIDA CON LIBERACIÓN INMEDIATA Y
METFORMINA CON LIBERACIÓN PROLONGADA"
Solicitante : LABORATORIOS SILANES, S.A. DE C.V.
Opositora : GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 590 del 31 de marzo de 2008

Yo, *ELIANA ISAURA MORENO BOHORQUEZ*, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad *GYNOPHARM 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 "COMPOSICIÓN FARMACÉUTICA ESTABLE DE GLIMEPIRIDA CON LIBERACIÓN INMEDIATA Y METFORMINA CON LIBERACIÓN PROLONGADA", cuyo titular es LABORATORIOS SILANES, S.A. DE C.V., y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular glimepirida y metformina. 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 8 de septiembre de 2006, reivindicando prioridad bajo la solicitud MX2005PA09633 del 2005-09-08; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 590 del 31 de marzo de 2008.

2.2. La solicitud colombiana 06-90492 objeto de la presente oposición, se refiere a una composición farmacéutica estable en forma de tableta caracterizada por que comprende un núcleo o matriz que contiene una biguanida de liberación prolongada; una capa o recubrimiento aislante de un polímero hidrofóbico; y un recubrimiento que contiene una sulfonilurea de liberación inmediata, donde el núcleo o matriz está compuesto por una cantidad equivalente de 250 a 1,500 mg una biguanida, donde el recubrimiento contiene una cantidad equivalente a 0.2 a 10 mg de una sulfonilurea, donde el recubrimiento aislante intermedio entre el núcleo y el recubrimiento comprende de 5 a 50 mg de etilcelulosa, en la cual la biguanida puede ser cualquiera del grupo seleccionado de la metformina, la

fenformina y la buformina; donde comprende clorhidrato de metformina equivalente a una cantidad de 250 a 1,000 mg de metformina, donde la sulfonilurea puede cualquiera del grupo que comprende la glimepirida, glipizida o gliburida, glibornurida, glisoxepida, gliclazida, acetohexamida, clopropamida, tolazamida o tolbutamida, donde la glimepirida equivalente a una cantidad de 0.2 a 10.0 mg de glimepirida.

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

- D1: US2003147952 publicada el 7 de marzo de 2003.
- D2: US6303146 publicada el 16 de octubre de 2001.

2.4. Ahora bien, el documento D1 particularmente en la descripción y reivindicaciones revela un método para fabricar una pastilla farmacéutica para la administración oral, que combina tanto liberación inmediata como los modos de liberación prolongada. El método implica el empleo de las partículas de medicina de liberación inmediata que son iguales a, o menos de, 10 micras en el diámetro, aplicado como una capa de recubrimiento sobre un núcleo de medicina de liberación prolongada. Según la reivindicación 1 de esta anterioridad D1, se revela que el método comprende la fabricación de una pastilla farmacéutica de ingestión oral que entrega una primera medicina por liberación inmediata y una segunda medicina por liberación sostenida definida como una tarifa de liberación en el fluido gástrico que es bastante lento para dejar al menos aproximadamente el 40 % de la segunda medicina dentro de una hora después de la ingestión, y en el cual

dicha primera medicina es en la mayoría con moderación soluble en el agua y la proporción de peso de la primera medicina a la segunda medicina es igual o menor que aproximadamente 0.01:1. Así las cosas, este documento anterior D1, afectaría directamente la novedad de la presente solicitud, toda vez que revela una solución similar que implica una forma oral para suministrar dos medicinas donde el núcleo comprenda una primera medicina de liberación prolongada y un recubrimiento que comprenda una segunda medicina de liberación inmediata. Por lo tanto, este documento D1, afecta la novedad de la presente solicitud.

2.5. Por su parte, el documento D2, revela con base en la descripción, resumen y reivindicaciones, una forma de dosificación sólida oral que comprende una combinación de metformina y glibenclamida en el cual el tamaño de la glibenclamida es tal que en la mayor parte del 10 % de las partículas son menos de 2 μm y en la mayor parte del 10 % de las partículas es mayor que 60 μm , de modo que la biodisponibilidad de la glibenclamida sea comparable con la biodisponibilidad de la glibenclamida obtenido como una administración separada de cada una. Como lo ilustra esta anterioridad D2, dicha combinación entre una biguanida y una sulfonilurea y el hecho de obtener una administración separada en una misma dosis no implica altura inventiva con base en este documento D2 y la forma de liberación de estas dos con base en lo que ilustra el documento D1, donde cualquier persona versada en la materia, a partir de estos dos documentos puede llegar de manera evidente y obvia a conformar una forma farmacéutica oral que comprenda un núcleo de biguanida de liberación prolongada y un recubrimiento que contiene una sulfonilurea de liberación inmediata, tal y como se define en el documento D1 en combinación con la materia definida en el documento D2. Por lo tanto, visto dicho documento D2 en combinación con el documento D1, la presente solicitud carece evidentemente de altura inventiva.

2.6. Por lo tanto, este documento objeto de oposición a la luz del documento D1 carece evidentemente de NOVEDAD y con base en el documento D2, carece de ALTURA INVENTIVA.

9537

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 06-90492 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

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

2.8.1. **CARECE DE NOVEDAD:** Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”* A la fecha de prioridad, 8 de septiembre de 2005 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, un método para fabricar una pastilla farmacéutica para la administración oral, que combina tanto liberación inmediata como los modos de liberación prolongada, sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. **CARENCIA DE ALTURA INVENTIVA.** Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”* A la fecha de prioridad, 8 de septiembre de 2005, a partir del documento D2 en combinación con D1, puede llegar de manera evidente a una forma farmacéutica oral que comprenda un núcleo de biguanida de liberación prolongada y un recubrimiento que contiene una sulfonilurea de liberación inmediata, sobre el cual busca protección en el capítulo reivindicatorio.

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

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **“COMPOSICIÓN FARMACÉUTICA ESTABLE DE GLIMEPIRIDA CON LIBERACIÓN INMEDIATA Y METFORMINA CON LIBERACIÓN PROLONGADA”**, cuyo titular es **LABORATORIOS SILANES, S.A. DE C.V.**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 590 del 31 de marzo de 2008.

3. PRUEBAS

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

- D1: US2003147952 publicada el 7 de marzo de 2003.
- D2: US6303146 publicada el 16 de octubre de 2001.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

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

5. ANEXOS

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

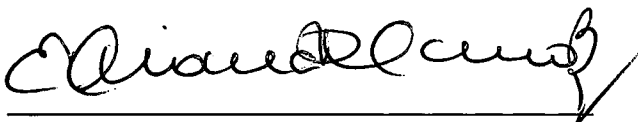
1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **GYNOPHARM S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:

- D1: US2003147952 publicada el 7 de marzo de 2003.
- D2: US6303146 publicada el 16 de octubre de 2001.

6. NOTIFICACIONES

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

Señor Superintendente,



ELIANA ISAURA MORENO BOHÓRQUEZ

C.C. 51'975.664 de Bogotá

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

91
794

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-090492-00002-0000

Fecha: 2008-06-27 13:04:08 Dep. 2020 NUECREACIONE
Tra. 2 PATENTES Eve: 1 REGDEPOSITO
Act. 400 OPOSIOBSERVTER Folios: 29

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO ORIGINAL DE PAGO : 98 - 51.748
FECHA : JUNIO 27 DE 2008

***** CONSIGNACION *****

DEBITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ZUPRA E U LTDA.	CONSIGNACION	BANCO DE BOGOTA	062754387	4638625	11/06/2008	266,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-03-04	PRESENTACION DE OBSERVACIONES	
12		MARCAS Y LENAS COMERCIALES	266,000.00
		TOTAL :	\$ 266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

12
10543

PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGON**, 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 **GYNOPHARM S.A** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 06. 90492, titulada "**COMPOSICION FARMACEUTICA ESTABLE DE GLIMEPIRIDA CON LIBERACION INMEDIATA Y METFORMINA CON LIBERACION PROLONGADA**", cuyo titular es **LABORATORIOS SILANES, S.A. DE C.V.**, publicada en la gaceta No. 590 del 31 de marzo de 2008.

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

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

Dado y Firmado en Barranquilla (Colombia) a los 19 días del mes de mayo de 2008.

GYNOPHARM S.A

C.Ext. N° 319788

NIT: 802006279

Representante Legal

Acepto:

Elia Isaura Moreno Bohorquez

ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

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

RECONOCIMIENTO DE DOCUMENTO PRIVADO
Ante mí, **NIBARDO AGUSTIN FUERTES MORALES**,
Notario Veinticinco del Circuito de Bogotá (E),
comparece *Luis Palacios Aragon*
Palacios Aragon
identificado con cédula de ciudadanía
DC 319788
y declara que la firma puesta en el presente
instrumento privado es suya y que el contenido
del mismo es cierto.
Bogotá D.C. **03 JUN 2008**
FIRMA *Luis Palacios Aragon*
NIBARDO AGUSTIN FUERTES MORALES
NOTARIO VEINTICINCO (E)



01



* 7 0 9 5 2 3 8 9 *



13
18
99

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080529

Hora Certificado 11:49:33

Operacion : 02CP20529010

PAGINA No. 1

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

EN JUNIO DE ESTE AÑO SE ELEGIR? JUNTA DIRECTIVA DE LA C?MARA DE COMERCIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA QUINCENA DE MAYO. PARA INFORMACI?N DETALLADA DIRIGIRSE A LA SEDE PRINCIPAL O COMUNICARSE AL SIGUIENTE TELEFONO: 3303911.

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

C E R T I F I C A

Que por Escritura P?blica No. 3,551 del 17 de Dic/bre de 1997, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta C?mara de Comercio, el 18 de Dic/bre de 1997 bajo el No. 72,965 del libro respectivo, fue constituida la sociedad-----
anonima denominada GYNOPHARM 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
532	1999/03/25	Notaria 3a. de Barranquilla	80,373	1999/04/13

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:

GYNOPHARM S.A.-----

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 802.006.279-4.

MATRICULA MERCANTIL: 245,470.

C E R T I F I C A

Direccion para notificaciones judiciales:

CL 80 No 78 B - 201.

De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El t?rmino de duraci?n de la sociedad se fij? hasta el 16 de Dic/bre de 2047.

C E R T I F I C A

*** CONTINUA ***



01



* 7 0 9 5 2 3 9 0 *



JA
100

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080529

Hora Certificado 11:49:33

Operacion : 02CP20529010

PAGINA No. 3

Suscrito

\$*****2,672,646,000 *****2,672,646 *****1,000

Pagado

\$*****2,672,646,000 *****2,672,646 *****1,000

C E R T I F I C A

ADMINISTRACION: Seran funciones de la junta directiva, entre otras:
Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion y para enajenar o gravar bienes inmuebles y demas activos fijos de la sociedad, cualquiera que sea la cuantia de la transaccion. Las demas que le sean propias y no esten atribuidas a otro organo social y las que le correspondan en virtud de la ley. la sociedad tendra un Gerente General, quien ejercera la administracion y representacion legal de la sociedad y tendra las siguientes atribuciones, 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\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto. Para enajenar, a cualquier titulo, bienes inmuebles de la sociedad o constituir gravámenes sobre los mismos, debera obtener la aprobacion de la junta directiva, cualquiera que sea la cuantia de la transaccion; o las demas funciones que le correspondan como representante legal por disposicion de la ley, de estos estatutos o de la junta directiva. El Gerente General tendra un suplente, designado por la junta directiva, quien lo reemplazara con identicas facultades en sus faltas temporales, absolutas o meramente accidentales, sin que sea necesario para ello acreditar la ausencia del principal.-----

C E R T I F I C A

Que segun Acta No. 15 del 18 de Febrero de 2008 correspondiente a la Asamblea de Accionistas en Bogota, de la sociedad:
GYNOPHARM S.A.-----
cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 25 de Febrero de 2008 bajo el No. 137,919 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE:

JUNTA DIRECTIVA

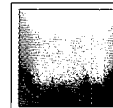
*** CONTINUA ***



01



* 7 0 9 5 2 3 9 1 *



15
103
101

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080529

Hora Certificado 11:49:33

Operacion : 02CP20529010

PAGINA No. 5

crito en esta Camara de Comercio el 23 de Noviembre del 2.000 bajo el No. 1.872 del libro repectivo, consta que el senor RUBEN MINSKI GONTOVNIK C.C. No. 7.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficiente a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombre y representacion de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM 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 de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 12 de junio del 2.002, bajo el 2.164 del libro respectivo, consta que el senor JORGE CASTELLANOS MARTINEZ, identificado con C.C.No.19.460.089, actuando como representante legal de la sociedad GYNOPHARM S.A, otorga Poder Especial Amplio y Suficiente a KAREN FIGUEROA GARCIA, identificada con la cedula de ciudadania No.32.732.070 de Barranquilla, mediante documento privado de octubre 10/2000, inscrito en la Camara de Comercio de Barranquilla bajo el No.1.872 del libro respectivo, para que en representacion de GYNOFARM S.A, suscriba las declaraciones cambiarias a los que esta obligada GYNOFARM S.A. en el giro ordinario de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que en esta Camara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disoluci?n, liquidaci?n o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su ?ltima Renovaci?n fue el: 23 de Abril de 2008.

La informaci?n sobre embargos de establecimiento se suministra en Certificados de Matr?cula, la de contratos sujetos a registro, en Certificados Especiales.

C E R T I F I C A

Que los actos de registro aqu? certificados quedan en firme cinco d?as h?biles despues de la correspondiente inscripci?n, siempre que, dentro de dicho t?rmino, no sean objeto de los recursos de reposici?n ante esta entidad, y/o de apelaci?n para ante la Superintendencia de Industria y Comercio.

100
102

ANEXO 1



US 20030147952A1

26
EDT
103(19) **United States**(12) **Patent Application Publication**
Lim et al.(10) **Pub. No.: US 2003/0147952 A1**(43) **Pub. Date: Aug. 7, 2003**(54) **MANUFACTURE OF ORAL DOSAGE FORMS
DELIVERING BOTH IMMEDIATE-RELEASE
AND SUSTAINED-RELEASE DRUGS**(75) **Inventors: Jong C. Lim, San Jose, CA (US); John
N. Shell, Rocklin, CA (US)**

Correspondence Address:

**TOWNSEND AND TOWNSEND AND CREW,
LLP****TWO EMBARCADERO CENTER
EIGHTH FLOOR****SAN FRANCISCO, CA 94111-3834 (US)**(73) **Assignee: DepoMed, Inc., Menlo Park, CA (US)**(21) **Appl. No.: 10/066,146**(22) **Filed: Feb. 1, 2002****Publication Classification**(51) **Int. Cl.⁷ A61K 9/20; A61K 9/22;
D04H 1/00**(52) **U.S. Cl. 424/468; 264/109**(57) **ABSTRACT**

A method is disclosed for manufacturing a pharmaceutical tablet for oral administration, the tablet combining both immediate-release and prolonged-release modes of drug delivery and using an immediate-release drug that is either insoluble in water or only sparingly soluble and is present in a very small amount compared to the prolonged-release drug. The method involves the use of particles of the immediate-release drug that are equal to or less than 10 microns in diameter, applied as a layer or coating over a core of the prolonged-release drug, the layer or coating being either the drug particles themselves, applied as an aqueous suspension, or a solid mixture containing the drug in admixture with a material that disintegrates rapidly in gastric fluid. The result in both cases is a high degree of uniformity in the proportions of the immediate-release and prolonged-release drugs, uniformity that is otherwise difficult to achieve in view of the insolubility of the immediate-release drug and its relatively small amount compared to the prolonged-released drug.

MANUFACTURE OF ORAL DOSAGE FORMS DELIVERING BOTH IMMEDIATE-RELEASE AND SUSTAINED-RELEASE DRUGS

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

[0002] This invention is in the field of pharmacology, and relates to drug dosage forms that are designed to deliver the drugs to human patients at particular rates.

[0003] 2. Description of the Prior Art

[0004] Certain pharmacological therapies either require or benefit from the administration of drugs in a sequential manner. This can be done by a regimen in which the patient follows a prescribed time schedule, but because of patient non-compliance, scrupulous adherence to a schedule often requires the assistance of a medical professional. Even those therapies that involve only two dosages, such as an immediate but rapidly declining high-level dosage combined with a prolonged low-level or moderate-level dosage, either of the same drug or of two different drugs, can be a nuisance to the individual or troublesome to maintain if the individual is required to take separate unitary dosage forms. Certain pharmaceutical formulations have therefore been developed that combine both functions into a single dosage form. This simplifies the therapy and reduces or eliminates the chances of improper administration.

[0005] Many unitary dosage forms that have been proposed for combining immediate release with prolonged release do so by the placement of the drugs in different layers of a tablet or by placing one drug in a quickly-dissolving or quickly-dispersing coating over the surface of a slowly dissolving or swellable core that contains the other drug. With its high initial release concentration and rapid rate of decline, the immediate-release drug is often provided in a much lower amount than the prolonged-release drug. The immediate-release portion of the dosage form is therefore either a very thin layer or coating or a layer or coating with a very low concentration of the drug relative to the drug in the prolonged-released portion. It is common, for example, to design the dosage form such that the amount of drug intended for immediate release is 1/100th or less of the amount intended for prolonged release.

[0006] This large imbalance in the amounts of immediate-release and controlled-release drug creates problems in manufacturing, particularly in achieving uniformity from one tablet to the next. It is difficult to achieve uniform immediate-release coatings or layers of uniform drug content when the drug is so low in quantity or concentration. The problem is exacerbated when the drug in the immediate-release portion is one that has little or no solubility in water.

SUMMARY OF THE INVENTION

[0007] It has now been discovered that a dosage form that includes a core from which drug is released on a prolonged basis and a coating or layer from which drug is released on an immediate-release basis can be made in a manner that provides a high degree of uniformity in the immediate-release portion, even when the drug in the immediate-release portion is either insoluble or only sparingly soluble in water. This is achieved by limiting the drug particle diameter in the immediate-release coating or layer to 10 microns or less.

The coating or layer is either the particles themselves, applied as an aqueous suspension, or a solid composition that contains the drug particles incorporated in a solid material that disintegrates rapidly in gastric fluid. Either mixture can be applied as a coating or layer over a core or coherent mass of the prolonged-release drug. When an aqueous suspension is used and applied as a coating, a suspending agent, binder, or both can be included to improve the procedure, and in either case, other excipients can be included to facilitate the manufacturing process.

[0008] Details on these and other features, advantages, and embodiments of the invention will be apparent from the description that follows.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

[0009] The dosage forms of this invention are designed for oral ingestion, and the prolonged-release portion of the dosage form is one that delivers its drug to the digestive system continuously over a period of time of at least an hour and preferably several hours. The drug is retained in a matrix or supporting body of pharmaceutically inert solid, and the controlled delivery rate can be achieved by using a matrix that allows the gastric fluid to permeate the matrix and leach out the drug (i.e., allow the drug to diffuse out from the matrix as the drug slowly dissolves in the permeating fluid), or a matrix that slowly dissolves or erodes to expose the drug to the gastric fluid, or one that does both of these at once. The delivery rate is preferably slow enough that at least about 40% of the drug remains unreleased one hour after ingestion, more preferably at least about 60% and most preferably at least about 80%. In general, the drug will be substantially all released within about ten hours and preferably within about eight hours, and in most cases, the matrix supporting the drug will remain substantially intact until all of the drug is released. "Substantially intact" in this sense means that the matrix retains its size and shape without dissolving or disintegrating into fragments.

[0010] The immediate-release portion of the dosage form is either a coating applied or deposited over the entire surface of a unitary prolonged-release core, or a single layer of a tablet constructed in two or more layers, one of the other layers of which is the prolonged-released portion. Immediate release of the drug from the immediate-release layer is achieved by any of various methods known in the art. One example is the use of a very thin layer or coating which by virtue of its thinness is quickly penetrated by gastric fluid allowing fast leaching of the drug. Another example is by incorporating the drug in a mixture that includes a supporting binder or other inert material that dissolves readily in gastric fluid, releasing the drug as the material dissolves. A third is the use of a supporting binder or other inert material that rapidly disintegrates upon contact with gastric fluid, with both the material and the drug quickly dispersing into the fluid as small particles. Examples of materials that rapidly disintegrate and disperse are lactose and microcrystalline cellulose. An example of a suspending agent and binder is hydroxypropyl methyl cellulose.

[0011] The dosage forms of this invention include those in which the same drug is used in both the immediate-release and the prolonged-release portions as well as those in which

one drug is formulated for immediate release and another drug, different from the first, for prolonged release. This invention is particularly directed to dosage forms in which the immediate-release drug is at most sparingly soluble in water, i.e., either sparingly soluble or insoluble in water, while the prolonged-release drug can be of any level of solubility. The immediate-release drug is of sufficiently low solubility that it remains a solid particle during the preparation of the dosage form when the dosage form is prepared without the use of organic solvents. The only dispersing medium, when one is used, is water or an aqueous solution that may contain other components. The term "at most sparingly soluble" as used herein denotes a drug having a solubility in water at 37° C. that is generally less than 2% by weight, preferably less than 0.5% by weight. The particle size of the drug as it is used in the practice of this invention is equal to or less than about 10 microns in diameter, preferably within the range of from about 0.3 micron to about 10 microns in diameter, and most preferably with the range of from about 1 micron to about 5 microns in diameter.

[0012] The immediate-release drug can thus be deposited as a suspension over a unitary core of the controlled-release drug, with deposition being achieved by coating techniques known in the pharmaceutical formulation art such as spraying, pan coating, and the like, or the drug can be combined with particles of a binding matrix and compressed over a preformed layer of the controlled-release drug to form a layered tablet. In either case, the immediate-release coating or layer separates relatively quickly from the remainder of the tablet after ingestion, leaving the remainder intact. The weight ratio of the immediate-release drug to the prolonged-release drug is about 0.01:1 or less, preferably from about 0.001:1 to about 0.01:1.

[0013] In certain preferred embodiments of the invention, the supporting matrix in controlled-release portion of the tablet is a material that swells upon contact with gastric fluid to a size that is large enough to promote retention in the stomach while the subject is in the digestive state, which is also referred to as the postprandial or "fed" mode. This is one of two modes of activity of the stomach that differ by their distinctive patterns of gastroduodenal motor activity. The "fed" mode is induced by food ingestion and begins with a rapid and profound change in the motor pattern of the upper gastrointestinal (GI) tract. The change consists of a reduction in the amplitude of the contractions that the stomach undergoes and a reduction in the pyloric opening to a partially closed state. The result is a sieving process that allows liquids and small particles to pass through the partially open pylorus while indigestible particles that are larger than the pylorus are retropelled and retained in the stomach. This process causes the stomach to retain particles that are greater than about 1 cm in size for about 4 to 6 hours. The controlled-release matrix in these embodiments of the invention is therefore selected as one that swells to a size large enough to be retropelled and thereby retained in the stomach, causing the prolonged release of the drug to occur in the stomach rather than in the intestines.

[0014] Disclosures of oral dosage forms that swell to sizes that will prolong the residence time in the stomach are found in U.S. Pat. No. 5,007,790 ("Sustained-Release Oral Drug Dosage Form," Shell, inventor; Apr. 16, 1991), U.S. Pat. No. 5,582,837 ("Alkyl-Substituted Cellulose-Based Sustained-Release Oral Drug Dosage Forms," Shell, inventor; Dec. 10,

1996); U.S. Pat. No. 5,972,389 ("Gastric-Retentive Oral Drug Dosage Forms for the Controlled Release of Sparingly Soluble Drugs and Insoluble Matter," Shell et al., inventors; Oct. 26, 1999); International (PCT) Patent Application WO 98/55107 ("Gastric-Retentive Oral Drug Dosage Forms for Controlled Release of Highly Soluble Drugs," Shell et al., inventors; publication date Dec. 10, 1998); United States Patent Application Publication No. US 2001/0018707 A1 ("Extending the Duration of Drug Release Within the Stomach During the Fed Mode," Shell et al., inventors, publication date Aug. 30, 2001); and International (PCT) Patent Application WO 96/26718 ("Controlled Release Tablet," Kim, inventor; publication date Sep. 6, 1996). Each of the documents cited in this paragraph is incorporated herein in its entirety.

[0015] In general, swellable matrices contain binders that are water-swellable polymers, and suitable polymers are those that are non-toxic, that swell in a dimensionally unrestricted manner upon imbibition of water, and that release the drug gradually over time. Examples of polymers meeting this description are:

- [0016] cellulose polymers and their derivatives including, but not limited to, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethylcellulose, and microcrystalline cellulose
- [0017] polysaccharides and their derivatives
- [0018] polyalkylene oxides
- [0019] polyethylene glycols
- [0020] chitosan
- [0021] poly(vinyl alcohol)
- [0022] xanthan gum
- [0023] maleic anhydride copolymers
- [0024] poly(vinyl pyrrolidone)
- [0025] starch and starch-based polymers
- [0026] maltodextrins
- [0027] poly (2-ethyl-2-oxazoline)
- [0028] poly(ethylencimine)
- [0029] polyurethane hydrogels
- [0030] crosslinked polyacrylic acids and their derivatives

[0031] Further examples are copolymers of the polymers listed above, including block copolymers and graft polymers. Specific examples of copolymers are PLURONIC® and TECTONIC®, which are polyethylene oxide-polypropylene oxide block copolymers available from BASF Corporation, Chemicals Div., Wyandotte, Mich., USA. Further examples are hydrolyzed starch polyacrylonitrile graft copolymers, commonly known as "Super Slurper" and available from Illinois Corn Growers Association, Bloomington, Ill., USA.

[0032] Particularly preferred polymers are poly(ethylene oxide), hydroxypropyl methyl cellulose, and combinations of poly(ethylene oxide) and hydroxypropyl methyl cellulose.

24
108
100

[0033] As indicated above, the dosage forms of the present invention find utility when administered to subjects who are either in the fed mode or the fasting mode. Administration during the fed mode is preferred, since the narrowing of the pyloric opening that occurs in the fed mode serves as a further means of promoting gastric retention by retaining a broader range of smaller dosage form sizes.

[0034] The fed mode is normally induced by food ingestion, but can also be induced pharmacologically by the administration of pharmacological agents that have an effect in this regard that is the same or similar to that of a meal. These fed-mode inducing agents may be administered separately or they may be included in the dosage form as an ingredient dispersed in the dosage form or in an outer immediate-release coating. Examples of pharmacological fed-mode inducing agents are disclosed in co-pending U.S. patent application Ser. No. 09/432,881, filed Nov. 2, 1999, entitled "Pharmacological Inducement of the Fed Mode for Enhanced Drug Administration to the Stomach," inventors Markey, Shell, and Berner, the contents of which are incorporated herein by reference.

[0035] The size, shape, and dimensions of the tablet are not critical to the invention, provided that in embodiments where a swellable matrix is used, the tablet is sufficiently sized that upon swelling it reaches the dimensions that will be retained in the stomach during the fed mode. The tablet may be circular or elongated. An elongated tablet may be 18 to 22 mm in length, 6.5 to 10 mm in width, and 6.2 to 7.5 mm in height. A specific example is one that is 20 mm in length, 6.7 mm in width, and 6.4 mm in height. Again, these are merely examples; the shapes and sizes can be varied considerably.

[0036] Tablets in accordance with this invention can be prepared by conventional mixing, comminution, and tabletting techniques that are well known in the pharmaceutical formulations industry. The controlled-release portion can for example be fabricated by direct compression by punches and dies fitted to a rotary tabletting press, ejection or compression molding, granulation followed by compression, or forming a paste and extruding the paste into a mold or cutting the extrudate into short lengths. The immediate-release portion can be applied as a coating over the controlled-release portion by spraying, dipping, or pan-coating, or as an additional layer by tabletting or compression in the same manner as the controlled-release portion.

[0037] When tablets are made by direct compression, the addition of lubricants may be helpful and is sometimes important to promote powder flow and to prevent capping of the tablet (the breaking off of a portion of the tablet) when the pressure is relieved. Useful lubricants are magnesium stearate (in a concentration of from 0.25% to 3% by weight, preferably about 1% or less by weight, in the powder mix), and hydrogenated vegetable oil (preferably hydrogenated and refined triglycerides of stearic and palmitic acids at about 1% to 5% by weight, most preferably about 2% by weight). Additional excipients may be added to enhance powder flowability, tablet hardness, and tablet friability and to reduce adherence to the die wall.

[0038] The drug that is contained in the controlled release portion of the tablet may be any chemical compound, complex or composition that is suitable for oral administration and that has a beneficial biological effect, preferably a

therapeutic effect in the treatment of a disease or an abnormal physiological condition. The drug can be either a high-solubility drug or a sparingly soluble or insoluble drug, all referring to solubility in water or aqueous media.

[0039] Examples of high solubility drugs are metformin hydrochloride, vancomycin hydrochloride, captopril, lisinopril, erythromycin lactobionate, ranitidine hydrochloride, sertraline hydrochloride, ticlopidine hydrochloride, baclofen, amoxicillin, cefuroxime axetil, cefaclor, clindamycin, levodopa, doxifluridine, tramadol, fluoxetine hydrochloride, bupropion, potassium chloride, and esters of ampicillin. Examples low solubility drugs are saquinavir, ritonavir, nelfinavir, thiamphenicol, ciprofloxacin, calcium carbonate, clarithromycin, azithromycin, ceftazidime, acyclovir, ganciclovir, cyclosporin, digoxin, paclitaxel, iron salts, topiramate, ketoconazole, and sulfonyleureas such as glimepiride, glyburide, and glipizide. Other drugs suitable for use will be apparent to those skilled in the art. This invention is of particular interest for antibiotics and angiotensin converting inhibitors, particularly lisinopril, enalapril, captopril, and benazepril. A particularly preferred group of drugs is lisinopril, acyclovir, metformin hydrochloride, baclofen, ciprofloxacin, furosemide, cyclosporin, sertraline hydrochloride, and calcium carbonate. The drug that is contained in the immediate-release portion of the tablet is a sparingly soluble or insoluble drug, such as those listed above. Combinations of particular interest are metformin hydrochloride in the controlled-released portion and a sulfonyleurea such as glimepiride, glyburide, or glipizide in the immediate-release portion. Metformin hydrochloride and glimepiride are particularly preferred.

[0040] The following examples are offered for purposes of illustration only and are not intended to limit the scope of the invention.

EXAMPLES

[0041] Tablets containing 500 mg of metformin hydrochloride and 2.10 mg of glimepiride were made by the following procedure.

[0042] Preformed Metformin hydrochloride tablets were used that included 500 mg of metformin hydrochloride and a matrix containing approximately equal proportions by weight of hydroxypropyl methylcellulose and poly(ethylene oxide) to form a 1000 mg tablet. A solution was then prepared by dissolving four parts of Polysorbate 80 (polyethylene sorbitan monooleate) in 715 parts of deionized water, all by weight. Glimepiride in particulate form (1.60 parts by weight, 2-4 micron diameter particle size) was then dispersed in the Polysorbate 80 solution, and Opadry YS-1-19025-A Clear (hydroxypropyl methyl cellulose, available from Colorcon, West Point, Pa., USA) was added in an amount of 80 parts by weight. The resulting suspension was sprayed onto the metformin hydrochloride tablets at a rate of 5 g/min until the tablet weight increased by 11.2%.

[0043] The foregoing is offered primarily for purposes of illustration. It will be readily apparent to those skilled in the art that further drugs can be included, and that the shapes, components, additives, proportions, methods of formulation, and other parameters described herein can be modified further or substituted in various ways without departing from the spirit and scope of the invention.

26
104
107

What is claimed is:

1. A method for the manufacture of a pharmaceutical tablet which upon oral ingestion delivers a first drug by substantially immediate release and a second drug by sustained release defined as a release rate into gastric fluid that is slow enough to leave at least about 40% of said second drug unreleased one hour after ingestion, and in which said first drug is at most sparingly soluble in water and the weight ratio of said first drug to said second drug is equal to or less than about 0.01:1, said method comprising:

dispersing said second drug in a solid matrix to form a unitary core which upon immersion in gastric fluid releases said second drug by sustained release while retaining at least a portion of the mass of said solid matrix as a coherent body until said second drug is fully released therefrom;

depositing on the surface of said unitary core an aqueous suspension of particles of said first drug that are equal to or less than about 10 microns in diameter, using an amount of said first drug selected to achieve said weight ratio relative to said second drug; and

evaporating water from said aqueous suspension thus deposited to leave a solid shell encasing said unitary core and containing said first drug.

2. A method for the manufacture of a pharmaceutical tablet which upon oral ingestion delivers a first drug by substantially immediate release and a second drug by sustained release defined as a release rate into gastric fluid that is slow enough to leave at least about 40% of said second drug unreleased one hour after ingestion, and in which said first drug is at most sparingly soluble in water and the weight ratio of said first drug to said second drug is equal to or less than about 0.01:1, said method comprising:

combining said second drug with a first solid matrix to form a sustained-release layer, said first solid matrix being of a substance which when formed into a coherent body and immersed in gastric fluid releases said second drug by sustained release while retaining at least a portion of the mass of said first solid matrix as a coherent body until said second drug is fully released therefrom; and

combining particles of said first drug that are equal to or less than about 10 microns in diameter with particles of a second solid matrix to form an immediate-release layer adjoined to said sustained-release layer as a layered tablet, said second solid matrix being of a substance that separates into discrete matrix particles immediately upon immersion in gastric fluid, using amounts of said first and second drugs selected to achieve said weight ratio.

3. A method in accordance with claims 1 or 2 in which said weight ratio is from about 0.001:1 to about 0.01:1.

4. A method in accordance with claims 1 or 2 in which said particles of said first drug are from about 0.3 micron to about 10 microns in diameter.

5. A method in accordance with claims 1 or 2 which said particles of said first drug are from about 1 micron to about 5 microns in diameter.

6. A method in accordance with claims 1 or 2 in which said first drug has a solubility in water at 37° C. of less than 2% by weight.

7. A method in accordance with claims 1 or 2 in which said first drug has a solubility in water at 37° C. of less than 0.5% by weight.

8. A method in accordance with claims 1 or 2 in which said first drug is a sulfonylurea and said second drug is a member selected from the group consisting of metformin hydrochloride, vancomycin hydrochloride, captopril, erythromycin lactobionate, ranitidine hydrochloride, sertraline hydrochloride, ticlopidine hydrochloride, amoxicillin, cefuroxime axetil, cefaclor, clindamycin, doxifluridine, tramadol, fluoxetine hydrochloride, ciprofloxacin, gancyclovir, bupropion, lisinopril, cefaclor, ciprofloxacin, saquinavir, ritonavir, nelfinavir, clarithromycin, azithromycin, ceftazidime, cyclosporin, digoxin, paclitaxel, iron salts, topiramate, and ketoconazole.

9. A method in accordance with claims 1 or 2 in which said first drug is a sulfonylurea selected from the group consisting of glimepiride, glyburide, and glipizide, and said second drug is metformin hydrochloride.

10. A method in accordance with claims 1 or 2 in which said first drug is glimepiride and said second drug is metformin hydrochloride.

11. A method in accordance with claims 1 or 2 in which said solid matrix is a member selected from the group consisting of poly(ethylene oxide), hydroxypropyl methyl cellulose, and combinations of poly(ethylene oxide) and hydroxypropyl methyl cellulose.

12. A method in accordance with claim 1 in which said aqueous suspension has a suspending agent dissolved therein.

13. A method in accordance with claim 12 in which said suspending agent is hydroxypropyl methyl cellulose.

14. A method in accordance with claim 2 in which said second solid matrix is a member selected from the group consisting of lactose, microcrystalline cellulose, and combinations of lactose and microcrystalline cellulose.

* * * * *

110
108

ANEXO 2



US006303146B1

(12) **United States Patent**
Bonhomme et al.

(10) **Patent No.:** **US 6,303,146 B1**
(45) **Date of Patent:** **Oct. 16, 2001**

(54) **SOLID ORAL DOSAGE FORM COMPRISING
A COMBINATION OF METFORMIN AND
GLIBENCLAMIDE**

5,922,769 7/1999 Barelli et al. .
5,965,584 10/1999 Ikeda et al. .

FOREIGN PATENT DOCUMENTS

(75) **Inventors:** **Yves Bonhomme**, Charbonnieres les
Bains (FR); **Geoffrey Nicholson**,
Aylesbury (GB); **Gillian Cave**,
Ellesmere Port (GB); **Sarah J.**
Nicholson, Helsby (GB)

0 362 704 4/1990 (DE) .
A-42302/89 4/1990 (AU) .
WO 97/17975 5/1997 (WO) .
WO 98/57634 12/1998 (WO) .

OTHER PUBLICATIONS

(73) **Assignee:** **LIPHA**, Lyons (FR)

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

(21) **Appl. No.:** **09/353,141**

(22) **Filed:** **Jul. 14, 1999**

(30) **Foreign Application Priority Data**

Jul. 15, 1998 (EP) 98401781

(51) **Int. Cl.⁷** **A61K 9/20**; **A61K 9/14**;
A61K 9/16

(52) **U.S. Cl.** **424/465**; **424/464**; **424/489**;
424/494

(58) **Field of Search** **424/464**, **465**,
424/489, 494

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,174,901 3/1965 Sterne .
3,979,520 9/1976 Rothe et al. .
4,060,634 11/1977 Rothe et al. .
4,916,163 4/1990 Ni .
5,631,224 5/1997 Efendic et al. .
5,663,198 9/1997 Reul et al. .

R. Vigneri, et al., *Diabete & Metabolisme*, vol. 17, pp. 232-234, "Treatment of NIDDM Patients With Secondary Failure to Glyburide: Comparison of the Addition of Either Metformin or Bed-Time NPH Insulin to Glyburide", 1991. Linda Higginbotham, et al., *The Medical Journal of Australia*, pp. 154-156, "Double-Blind Trial of Metformin in the Therapy of Non-Ketotic Diabetics", Aug. 11, 1979. Iris J. Edwards, et al., *Diabetes*, vol. 46, No. 5, Suppl. 1, pp. 45A, "Combination Glipizide Gits/Metformin Treatment Reduces Low Density Lipoprotein Binding To Arterial Proteoglycans In NIDDM", 1997.

(List continued on next page.)

Primary Examiner—Thurman K. Page

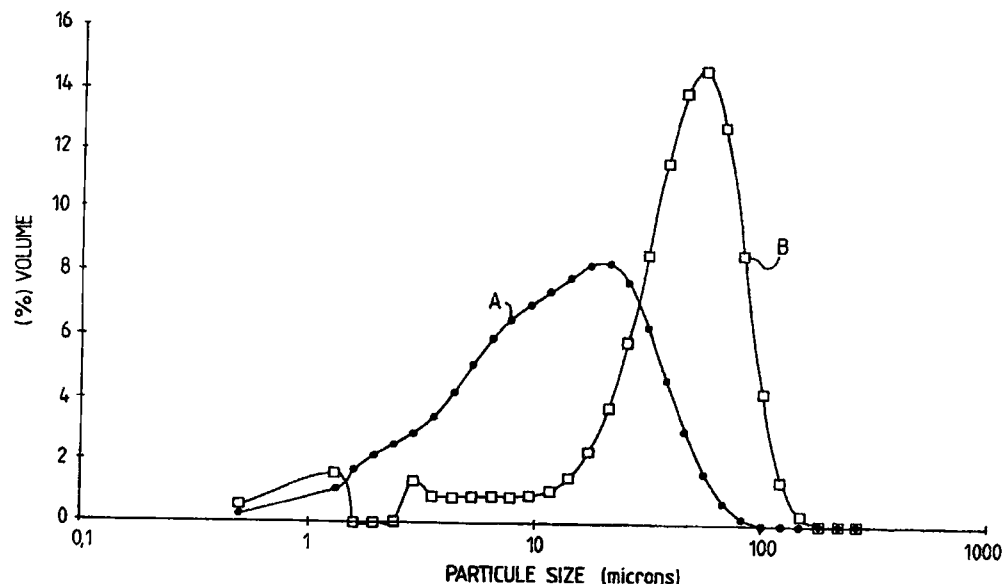
Assistant Examiner—S. Tran

(74) *Attorney, Agent, or Firm*—Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

(57) **ABSTRACT**

The present invention relates to a solid oral dosage form comprising a combination of metformin and glibenclamide in which the size of glibenclamide is such that the glibenclamide bioavailability is comparable to the glibenclamide bioavailability obtained with a separate administration of metformin and glibenclamide.

10 Claims, 3 Drawing Sheets



22
11/0

OTHER PUBLICATIONS

William T. Cefalu, et al., Diabetes, vol. 45, Suppl. 2, pp. 201A, "Combination Glipizide Gits/Metformin Normalizes Glucose And Improves Insulin Sensitivity In Hyperinsulinemic Moderately Well Controlled NIDDM", 1996.

John R. Crouse, et al., Circulation, vol. 94, No. 8, Suppl. 1508, Effects Of Combination Glipizide Gits/Metformin Treatment On Oxidizability Of LDL In Non-Insulin Dependent Diabetes Mellitus, 1996.

W. T. Cefalu, et al., Diabetologia, vol. 39, Suppl. 1, pp. A231, "Insulin Sensitivity Is Improved After Glipizide Monotherapy And Combination With Metformin", 1996.

Gerald M. Reaven, et al., Journal of Clinical Endocrinology and Metabolism, vol. 74, No. 5, pp. 1020-1026, Combined Metformin-Sulfonylurea Treatment Of Patients With Non-insulin-Dependent Diabetes In Fair To Poor Glycemic Control, 1992.

CB Hollenbeck, et al., Diabetes, vol. 39, Suppl. 1, pp. 108A, "Combination Glipizide/Metformin Treatment In Non-Insulin Dependent Diabetes (NIDDM)", 1990.

Press Release Sep. 30, 1999: Bristol-Myers Squibb Files New Drug Application for Novel Oral Antidiabetic Drug, 2 pp., 1999.

Glucomide—Italian Package Insert, Repertorio Farmaceutico Italiano, 1 p., 1999 (with English translation pp. 1-6).

Glibomet—Italian Package Insert, Repertorio Farmaceutico Italiano, 1 p., 1999 (with English translation pp. 1-7).

Suguan M—Italian Package Insert, Repertorio Farmaceutico Italiano, 1 p., 1999 (with English translation pp. 1-9).

Bi-Euglucon M13 Italian Package Insert, Repertorio Farmaceutico Italiano, 1 p., (with English translation pp. 1-9).

2/3
W3
111

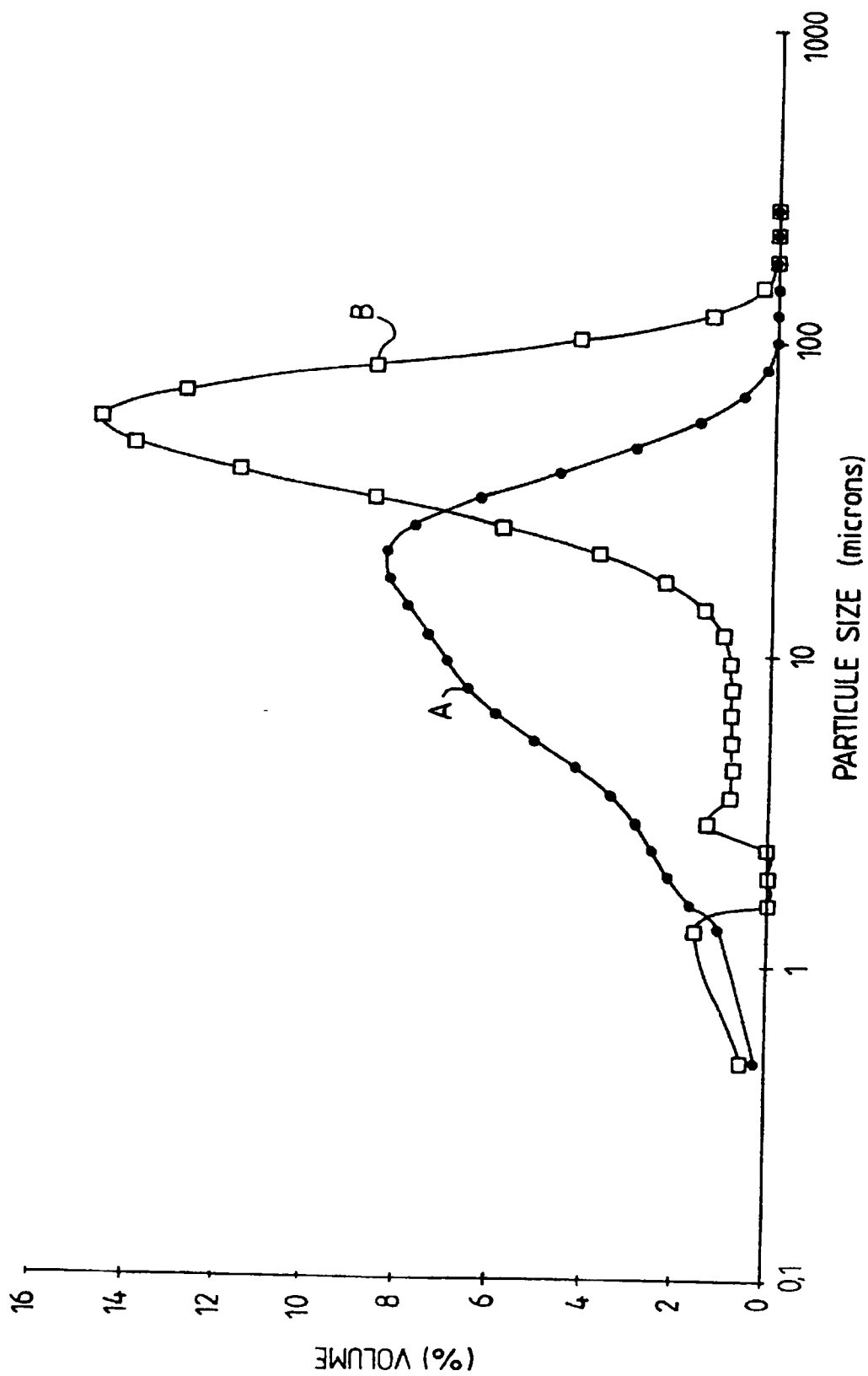
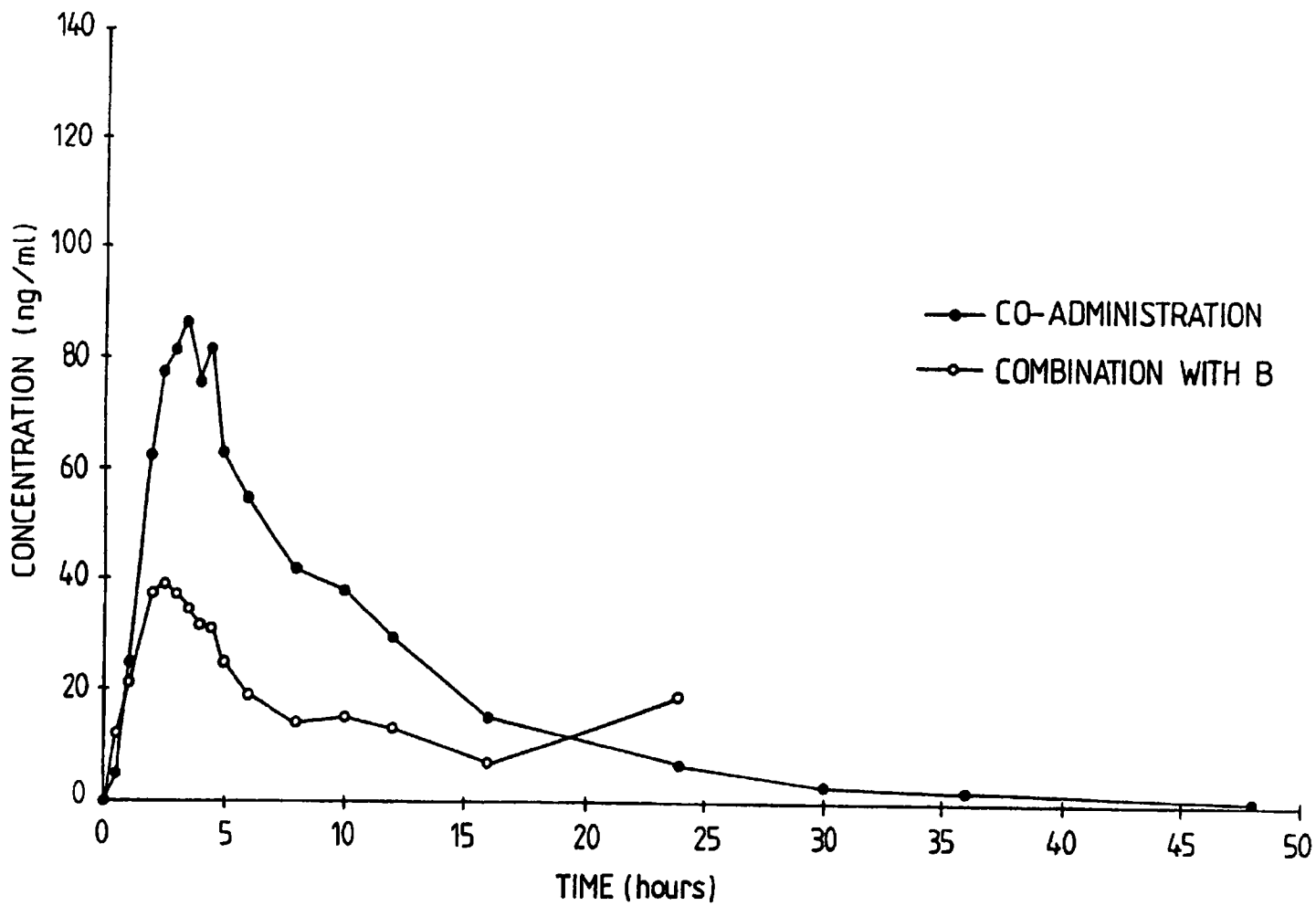
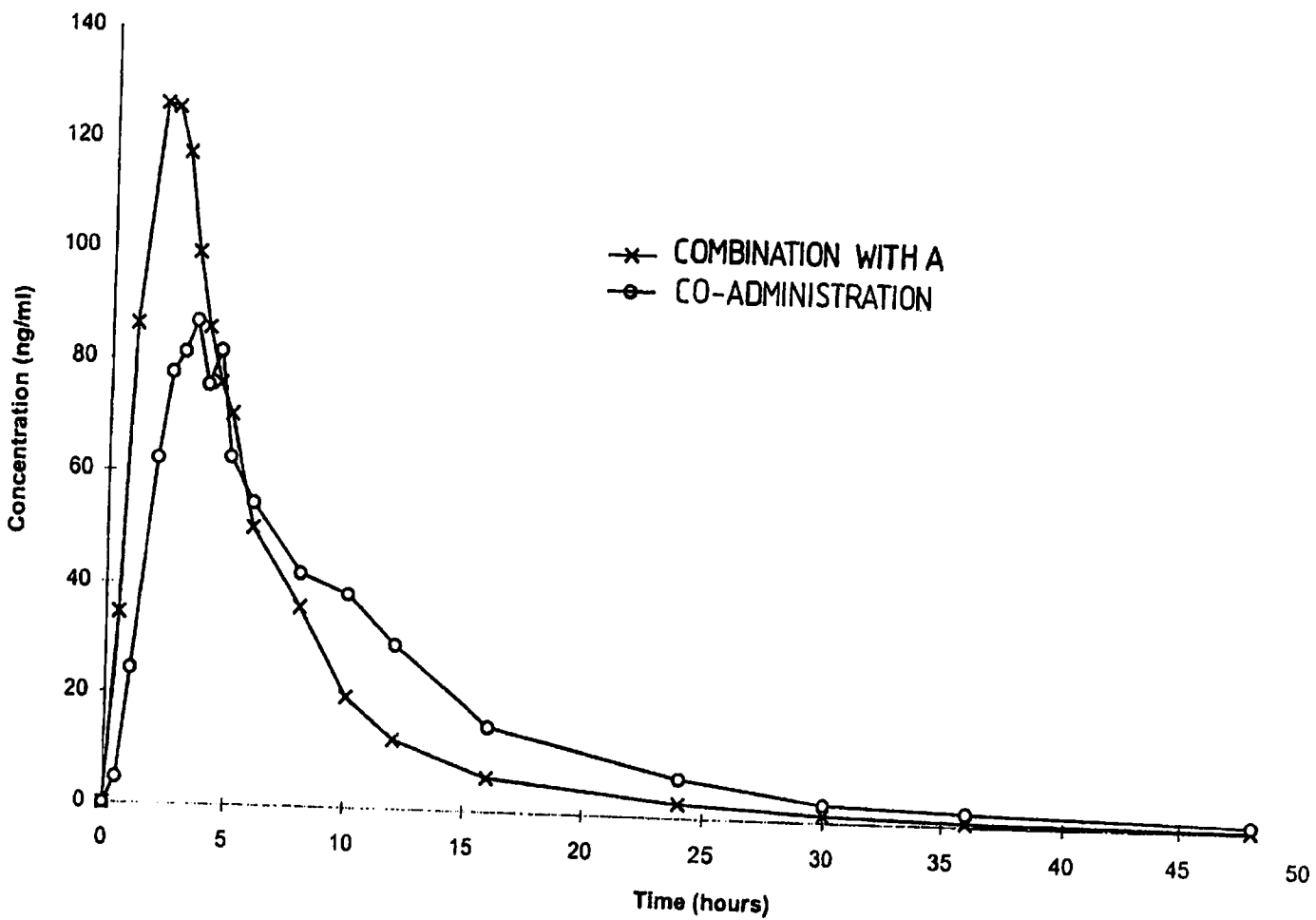


FIG. 1

FIG. 224
11/2

FIG. 3

10/16/01
11/3

**SOLID ORAL DOSAGE FORM COMPRISING
A COMBINATION OF METFORMIN AND
GLIBENCLAMIDE**

The present invention relates to solid oral dosage forms for the treatment of non-insulin dependent diabetes.

Non-insulin dependent diabetes is a metabolic disorder characterized by hyperglycaemia, which occurs due to insulin deficiency, insulin resistance and reduced glucose tolerance.

There are two main groups of oral antidiabetic drugs available: these are the sulphonylureas and the biguanidines. Sulphonylureas act by stimulating insulin release and are thus only effective with some residual pancreatic beta-cell activity, examples of sulphonylureas available are glibenclamide, gliclazide, tolbutamide, glipizide, tolazamide, gliquidone and chlorpropamide. The biguanidines, such as metformin, act by decreasing gluconeogenesis and by increasing peripheral utilisation of glucose, and as they require endogenous insulin they are only effective with some residual pancreatic islet cell activity.

The initial treatment of non-insulin dependent diabetes involves diet control and exercise. Only after this has been shown to be inadequate are oral antidiabetic drugs used, and then only to complement the effect of diet and not replace it. Monotherapy with an oral antidiabetic can be an effective treatment for many years. However the efficiency can decrease with time. Due to sulphonylureas and biguanidines having complementary modes of action, combined therapy is now an established form of treatment for non-insulin dependent diabetes.

To improve patient compliance a combined tablet would be an advantage. The present invention relates to solid oral dosage forms comprising a combination of metformin and glibenclamide (also named glyburide).

A combination of metformin with glibenclamide has been disclosed in WO 97/17975 for the treatment of type II diabetes with a defined ratio of the two active ingredients, which is a requirement in order to obtain an optimum therapeutic effect. This prior art defines an optimum therapeutic ratio of metformin hydrochloride to glibenclamide of 100:1, for example 500 mg of metformin hydrochloride with 5 mg glibenclamide in a single dosage unit. This ratio allows a range of daily doses, based on increasing the number of tablets taken per day, that avoid poor disease control through underdosing of either ingredient when there is a requirement for co-administration, and avoids hypoglycaemia by overdosing of either component when so co-administered. Assurance of performance in clinical use, which will derive from having a product exhibiting appropriate bioavailability of the glibenclamide component, is a key requirement for physicians wishing to treat patients with a combination formulation. Appropriate bioavailability implies that 5 mg of glibenclamide formulated into a combination tablet with metformin is absorbed to an acceptably similar extent, and at a comparable rate, to glibenclamide dosed as a single entity formulation of the same strength when dosed concurrently with a single entity formulation of metformin.

This prior art does not teach how to formulate a combination product of metformin with glibenclamide so as to assure appropriate bioavailability of the glibenclamide component. There is no issue in this respect in the case of metformin hydrochloride on account of its high water solubility and therefore the bioavailability of metformin from combination formulations will not be discussed further. It is however a very important aspect to consider for glibenclamide

as this is a poorly soluble drug substance (solubility is 0.1 mg/ml in water at 25° C.—practically insoluble as defined by the USP).

As such, its rate of solution after administration of a dosage form will influence the rate and extent of entry of the drug into the bloodstream (bioavailability). The control of the rate and extent of entry into the bloodstream is important for appropriate therapeutic effect.

Hence, the reference discloses a suitable ratio of the two active ingredients in a single dosage form, in order to model how the two individual ingredients might be desirably co-administered (based on how they would be dosed according to usual practice associated with currently available single entity formulations), it does not teach how to assure that such a combination formulation will perform in terms of bioavailability of glibenclamide. This bioavailability should be as similar as possible to when the relevant doses of the two single entity formulations are co-administered.

In addition, when a combination tablet using standard galenic procedures is proceeded with standard generic glibenclamide in the combination tablet, a reduced bioavailability in comparison to the co-prescribed situation was apparent.

It has now been found using in-vitro and in-vivo testing that the reduced bioavailability is related to the particle size and the particle size distribution of the glibenclamide. It has been found that particles which are too small result in high glibenclamide blood levels with consequent risk of hypoglycaemia and particles which are too large cannot dissolve sufficiently rapidly to give comparable bioavailability with the co-prescribed situation. It is therefore necessary to have a closely defined particle size distribution of the glibenclamide in the combination form.

The selection of a specific size fraction of glibenclamide enables the production of a solid oral dosage form comprising a combination of metformin and glibenclamide, and in particular a tablet, exhibiting glibenclamide bioavailability comparable to the bioavailability obtained with the separated administration of metformin and glibenclamide, when judged by the area under the curve of the in-vivo analysis.

The present invention provides in particular a tablet comprising a combination of metformin and glibenclamide, exhibiting a comparable glibenclamide bioavailability to the co-administered tablets.

In a first embodiment, the solid oral form such as a tablet, according to the invention, contains a combination of glibenclamide and metformin in which the size of the glibenclamide is such that at most 10% of the particles are less than 2 μ m and at most 10% of the particles are greater than 60 μ m. Preferably, the size of the glibenclamide is such that at most 10% of the particles are less than 3 μ m and at most 10% of the particles are greater than 40 μ m. This specific particle size range of glibenclamide may be obtained by sieving or air jet milling.

In a second embodiment, the solid oral dosage form comprises a combination of metformin and glibenclamide in which the size of glibenclamide is such that at most 25% of the particles are less than 11 μ m and at most 25% of the particles are greater than 46 μ m.

Preferably, 50% of particles are less than 23 μ m.

Metformin may be used as a salt of metformin, such as hydrochloride, fumarate, hydrobromide, p-chlorophenoxy acetate or embonate. The weight ratio of metformin salt to glibenclamide should preferably be between 50/1 to 250/1.

The preferred compositions for the oral dosage form is provided in the table below, with ranges on components being provided:

Ingredient	Amount of ingredient, mg per tablet		
	Product identity		
	500/5	500/2.5	250/1.25
Metformin hydrochloride	500.0	500.0	250.0
Glibenclamide	5.00	2.50	1.25
Croscarmellose sodium	6.0-30.0	6.0-30.0	3.0-15.0
Microcrystalline cellulose	30.0-120.0	30.0-120.0	15.0-60.0
Polyvinyl pyrrolidone	6.0-36.0	6.0-36.0	3.0-18.0
Magnesium stearate	0.6-15.0	0.6-15.0	0.3-7.5
Film coat*	9.0-24.0	9.0-24.0	4.5-12.0

*a commercially-available film coat composition is used, such as Opadry (Colorcon, UK).

The especially preferred compositions are as follows:

Ingredient	Amount of ingredient, mg per tablet		
	Product identity		
	500/5	500/2.5	250/1.25
Metformin hydrochloride	500.0	500.0	250.0
Glibenclamide	5.00	2.50	1.25
Croscarmellose sodium	14.0	14.0	7.0
Microcrystalline cellulose	54.0	56.5	28.25
Polyvinyl pyrrolidone	20.0	20.0	10.0
Magnesium stearate	1.2-12.0	1.2-12.0	0.6-6.0
Film coat*	9.0-24.0	9.0-24.0	4.5-12.0

*a commercially-available film coat composition is used, such as Opadry (Colorcon, UK).

The tablet according to the present invention may be obtained by a process comprising:

- forming granules by wet granulation of a mixture of metformin and glibenclamide;
- blending the granules with a tableting aid and diluent, and
- tableting the blend thus obtained into tablets.

Advantageously the mixture used for forming the granules comprises a granulating binder. This granulating binder is in particular a polyvinylpyrrolidone such as for example, a polyvinylpyrrolidone having a molecular weight of 45000. The polyvinylpyrrolidone may be used in a proportion of 2 to 4% by weight with respect to the final tablet.

After the granulating step the granules may be sieved and dried.

The granules are then blended with a diluent and tableting aid. The diluent may be any material usually used for making tablets, such as microcrystalline cellulose. The tableting aid may be any material usually for making tablets, such as magnesium stearate.

The tablets thus obtained may then be coated with a hydrophilic cellulose polymer and talc. The hydrophilic cellulose polymer may be 2-hydroxypropyl methylcellulose.

The following examples and tests illustrate the present invention.

EXAMPLE 1

A tablet of metformin/glibenclamide has been prepared as follows:

66.6 g of polyvinylpyrrolidone are mixed with 246 g of purified water with a stirrer. 1500 g metformin hydrochloride, 7.5 g of glibenclamide (with a 10 to 90% size range between 2 to 60 μ m), 42 g croscarmellose sodium and 284.4 g of microcrystalline cellulose are mixed in a granulator. The polyvinylpyrrolidone solution is added to the

granulator and the wet mass is granulated. The granules are extruded through a 1 mm mesh. The granules are emptied into a preheated fluidised bed dryer and the granules are dried. 97.5 g of microcrystalline cellulose is mixed into the granules using a tumbling mixer. 12 g of magnesium stearate is added to the tumbling mixer and mix. The granule mix is tableted using a suitable tablet press. The tablets are coated with a 2% hydroxypropyl methylcellulose coat in a coating machine.

EXAMPLE 2

A tablet of metformin/glibenclamide has been prepared as follows:

5.83 g of glibenclamide (with a 10 to 90% size range between 2 to 60 μ m), are preblended with 32.67 g of croscarmellose sodium. 46.67 g of polyvinylpyrrolidone are mixed with 93.33 g of purified water with a stirrer. The glibenclamide-croscarmellose sodium blend is mixed with 1166.6 g of metformin hydrochloride in a granulator. The polyvinylpyrrolidone solution is added to the granulator and the wet mass is granulated. The granules are emptied into a preheated fluidised bed dryer and the granules are dried. The particle size of the granules is reduced by passing through a 1 mm mesh. 131.83 g of microcrystalline cellulose are mixed into the granules in the granulator. 16.3 g of magnesium stearate are added to the granulator and mixed. The granule mix is tableted using a suitable tablet press. The tablets are coated with a 2% hydroxypropyl methylcellulose coat in a coating machine.

Test 1

In-vivo bioavailability tests were performed with tablets prepared as disclosed in example 2, using two batches of glibenclamide. The two batches have the following 10 to 90% particle size range:

batch A: 3.47-38.08 μ m

batch B: 15.63-91.6 μ m;

The distribution of the particle size of batches A and B are illustrated in FIG. 1.

The two batches of tablets were administered to healthy patients in comparison to co-administered glibenclamide (marketed under the trade name Daonil) and metformin hydrochloride (16 patients for each group).

The comparative concentrations of glibenclamide in a tablet comprising a combination of metformin and respectively the batch A and the batch B of glibenclamide and with the co-administration are shown respectively in FIGS. 2 and 3.

The area under the curve (AUC) are the following:

	AUC (ng/ml/h)
combination with batch A	790.5
combination with batch B	353.0
co-administration	869.3

It appears that with the combination according to the invention with batch A the AUC is substantially the same as in the case of co-administration, whereas with the combination with batch B the AUC is more clearly different.

Test 2

Careful examination of blood levels of glibenclamide in humans following administration of a series of tablet formulations of metformin hydrochloride combined with glibenclamide (identified as formulations Combo 1, 2, 3 and 4), where the formulation are identical save for the particle size

characteristics of the glibenclamide used, compared with commercially available reference formulations of metformin hydrochloride (Glucophage™, Bristol-Myers Squibb) and glibenclamide (Micronase™, Upjohn) dosed together, allowed definition of particle characteristics for glibenclamide that would assure appropriate bioavailability of the glibenclamide component from the combination formulation. This means that disease control when patients are first treated with such a combination formulation will be predictable, based on prior physician knowledge of treatments employing either single drug.

Alternatively, if patients have undergone prior stabilization of their disease by adding treatment with a commercial product like Micronase™ to existing treatment with Glucophage™ (or vice versa), then the switch over to a more convenient treatment employing the combination in a single tablet (and where the appropriate bioavailability of the glyburide component is assured) will result in the desired level of disease control being maintained.

Data from the studies with metformin hydrochloride/glibenclamide tablets formulated with glibenclamide of different particle size characteristics allowed the development of a correlation between drug particle size and the in vivo performance. The properties of the lots of glyburide used in the series of combination tablets employed are shown in the table below:

Tablet batch	glibenclamide particle size (microns)		
	25% undersize	50% undersize	75% undersize
Combo 1	15	33	62
Combo 2	28	58	88
Combo 3	10	25	52
Combo 4	6	11	19

When four compositionally-identical individual batches of tablets of metformin hydrochloride-glyburide 500/2.5 mg were prepared using each of these lots of glibenclamide and dosed to humans, the following pharmacokinetic parameters were found on analysis of the glibenclamide plasma concentration-time curves:

Tablet batch	Pharmacokinetic parameters glibenclamide			
	C _{max} (ng/ml, geo. mean)	AUC (ng/ml/hr, geo. mean)	C _{max} (ng/ ml, arith. mean)	AUC (ng/ml/hr, arith. mean)
Combo 1	71	478	76	493
Combo 2	52	345	54	339
Combo 3	64	513	67	531
Combo 4	88	642	93	716

A reasonable correlation can be obtained between particle size and the maximum attained geometric mean glibenclamide plasma concentration, C_{max}, and also with the geometric mean area under the glibenclamide plasma concentration-time curve, AUC.

From these correlations, projected limits on particle size for glyburide that would give predicted C_{max} and AUC values $\pm 25\%$ of a mean value for batches of the reference glibenclamide formulation, Micronase™ utilised in the in vivo studies become:

	25% undersize limits	50% undersize limits	75% undersize limits
C _{max}	<0-18 microns	<0-37 microns	<0-63 microns
AUC	<0-11 microns	<0-25 microns	<0-46 microns

Accommodating both C_{max} and AUC requirements, the projected limits then become:

25% undersize limits	50% undersize limits	75% undersize limits
≤ 11 microns	≤ 23 microns	≤ 46 microns

Glibenclamide having these particle size characteristics have powder surface area values in the range 1.7 to 2.2 m² g⁻¹ as determined by nitrogen adsorption. Therefore material of these properties when formulated as described in this work is distinct from the material disclosed in U.S. Pat. No. 3,979,520 which required glibenclamide of powder surface area in excess of 3 m² g⁻¹ (preferably 5 to 10 m² g⁻¹) to yield appropriate glibenclamide bioavailability. The glibenclamide of particle size properties detailed in this work, when formulated as described here produces appropriate glibenclamide bioavailability in humans as described in the next test.

Test 3

A batch of metformin hydrochloride-glibenclamide tablets 500/5 mg was prepared as follows. Glibenclamide (1.0 kg) with the above defined size was tumble mixed with 2.8 kg of croscarmellose sodium and this mixture was then blended in a high shear mixer with metformin hydrochloride (100 kg) to which 0.5% by weight of magnesium stearate had been added.

This dry mix was wet granulated in a high shear mixer with 12.1 kg of an aqueous solution of povidone (containing 4 kg of povidone). The wet granules were dried in a fluid bed drier at 60° C. to a defined moisture content. The dried (loss on drying 2-3% w/w) granules were size reduced in a oscillator (1.0 mm screen aperture) then tumble mixed with 10.8 kg of microcrystalline cellulose, followed by mixing with 0.9 kg of the tablet lubricant magnesium stearate. The lubricated granules were compressed using 16 mm×8 mm capsule shaped tooling and the tablet cores were film coated (weight gain approximately 2% w/w) with the proprietary film coat material Opadry 32920 to yield the final yellow, capsule-shaped tablets. In a human pharmacokinetic study volunteer either were dosed with one of these tablets or with a treatment being one 500 mg Glucophage tablet plus one 5 mg Micronase™ tablet co-administered. Glibenclamide plasma levels following dosing were analysed and the following pharmacokinetic were found for this component:

Treatment	Parameter	Mean	Adjusted geometric mean	Ratio of means (Point estimate)
Combination	C _{max}	122	116	1.14
Tablet 500/5	AUC (O-T)	859	831	1.07
Glucophage +	C _{max}	113	101	—
Micronase	AUC (O-T)	842	780	—

Glibenclamide bioavailability from the combination tablet is comparable to that from the reference glibenclamide formulation, Micronase™. This would thus allow patients to

conveniently take one tablet of the combination product instead of two tablets of existing therapies together, without concern that low glibenclamide blood levels would result, which might occur with prior art formulations and lead to loss of control of disease.

EXAMPLE 3

Instead of compressing into tablet granulation as prepared for test 3 was filled into size 00 capsules to either provide for metformin hydrochloride/glibenclamide 500 mg/5 mg product or the 500 mg/2.5 mg product. Granulation was filled into size 1 capsules to provide the 250 mg/2.5 mg product.

These capsule exhibited acceptable physical properties and provide an alternative to the tablets. Formulations as described in WO 97/17975 could not be filled in capsules of a size acceptable to most patients because of the larger amount of excipients employed the formulations they described.

What is claimed is:

1. A solid oral dosage form comprising a combination of metformin and glibenclamide in which the size of the glibenclamide is such that at most 10% of the particles are less than $2\ \mu\text{m}$ and at most 10% of the particles are greater than $60\ \mu\text{m}$, so that the glibenclamide bioavailability is comparable to the glibenclamide bioavailability obtained with a separate administration of metformin and glibenclamide.

2. A solid pharmaceutical composition comprising metformin and glibenclamide in particulate form, wherein the size of the glibenclamide particles is such that at most 10% of the particles are less than $2\ \mu\text{m}$ and at most 10% of the particles are greater than $60\ \mu\text{m}$.

3. A solid oral dosage form as claimed in claim 1 in which the size of the glibenclamide is such that at most 10% of the particles are less than $3\ \mu\text{m}$ and at most 10% of the particles are greater than $60\ \mu\text{m}$.

4. A solid oral dosage form comprising a combination of metformin and glibenclamide in which the size of glibenclamide is such that at most 25% of the particles are less than $11\ \mu\text{m}$ and at most 25% of the particles are greater than $46\ \mu\text{m}$.

5. A solid oral dosage form in which 50% of particles are less than $23\ \mu\text{m}$.

6. A solid oral dosage form as claimed in claim 1 in which metformin is present as metformin salt and the weight ratio of metformin salt to glibenclamide is 50/1 to 250/1.

7. A solid oral dosage form as claimed in claim 1 which is a tablet.

8. A tablet as claimed in claim 7 which is obtained by a process comprising:

- a) forming granules by wet granulation of a mixture of metformin and glibenclamide;
- b) blending the granules with a tableting aid
- c) tableting the blend thus obtained into tablets.

9. A method for treating non-insulin dependent diabetes or hyperglycaemia, comprising administering to a subject in need thereof, the composition of claim 1.

10. A method for treating non-insulin dependent diabetes or hyperglycemia, comprising administering to a subject in need thereof, the composition of claim 2.

* * * * *

21
49
119

110
118

2020
Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado

Oficio N°:
11149

ASUNTO:	Radicación N°	06-90492
	Trámite	002
	Evento	001
	Actuación	440
	Folios	009

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Eliana Isaura Moreno Bohórquez, en su calidad de apoderada de Gynopharm S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

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

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


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

04 SET. 2008

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

202021