935

SUPERINTENDENCIA Y COMERCIO
Radicación : 03036463 00010002 Folios: 95
Fecha (AMD): 2004-11-18 16:21:36
Tramite : 011 PCT-PATENT 379 FASE NACI 300 COMUNICAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

Industria y Comercio

FORMULARIO ÚNICO DE OPOSICI

SUPERINDUSTRIA Y COMERCIO(COPIA)
Radicacion : 03036463 00010002 Folios: 95
Fecha (AMD): 2004-11-18 16:21:36
Tramite : 011 PCT-PATENT 379 FASE NACI 400 OPOSICI
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

① OPOSICIÓN A :

- [X] Patente de Invencion.
- [ ] 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: 03-036463
Solicitante: ANDRX CORPORATION
Apoderado: JUANITA GOMEZ ACOSTA
Titulo de la nueva creación o denominación del signo: "COMPOSICIONES DE METFÓRMICA DE LIBERACIÓN CONTINUADA"
Gaceta: 544

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE

Nombre: PROCAPS S.A.
Dirección: CALLE 80 No. 78b-201
Nacionalidad o Domicilio: COLOMBIA
Lugar de Constitución: BARRANQUILLA
Teléfono: 371 99 00 Fax: 373 0815
E-mail:

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

REPRESENTANTE O APODERADO

Nombre: LUIS FERNANDO RINCÓN
Dirección: CALLE 119ª No. 53.99
Teléfono: 613 34 18 Fax: 24 47 87
E-mail: negocios@optimum-co.com

IDENTIFICACIÓN
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número 79.532.186 TP 113438

④ FUNDAMENTOS DE LA OPOSICIÓN:

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

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor:

Justificación:

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

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

⑥ **ANEXOS**

736

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

⑦

NOMBRE: LUÍS FERNANDO RINCÓN CUELLAR

FIRMA:

C.C. 79.532.186 **TP.** 113438

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

Optimum

Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

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

Referencia	: Expediente N° 03-036463
Asunto	: Oposición a la solicitud de patente de Invención titulada **"COMPOSICIONES DE METFÓRMICA DE LIBERACIÓN CONTINUADA".**
Solicitante:	**ANDRX CORPORATION**
Opositora:	**PROCAPS S.A.**

Publicada en la Gaceta de la Propiedad Industrial
N° 544 del 30 de Septiembre de 2004

Yo, Luis Fernando Rincón Cuellar, abogado con tarjeta profesional N° 113438 del consejo superior de la judicatura, en mi condición de apoderado de la sociedad PROCAPS S.A. conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la patente de Invención titulada **"COMPOSICIONES DE METFÓRMICA DE LIBERACIÓN CONTINUADA"**, solicitada por **ANDRX CORPORATION**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

2. 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 legitimo interés de nuestra representada debido a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida atentaría directamente a la comercialización que mi representada pretende con la presentación farmacéutica elaborada con base en la molécula de 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.

3. FUNDAMENTOS DE HECHOS

3.1. La solicitud objeto de la presente oposición fue presentada el 2 de Mayo de 2003, reivindicando prioridad bajo US09/705,630 del 03/11/2000 y US09/705,625 del 03/11/2000, cuya fecha de inicio en la fase nacional fue el 3 de Junio de 2003, con publicación internacional N° WO 02/36100 del 10 de Mayo de 2002 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 544, del 30 de Septiembre de 2004, bajo el N° de publicación NP. 348 (página 344).

3.2. La solicitud colombiana 03/036463 objeto de la presente oposición, comprende según sus cláusulas 1 a 42, una forma de dosis oral de liberación controlada para la reducción de los niveles de glucosa de suero en pacientes humanos con NIDDM, que comprende una dosis efectiva de al menos una droga hiperglicémica adecuada o una sal farmacéuticamente aceptable de esta y un portador de liberación controlada, dicha forma de dosis es adecuada para proporcionar una administración oral de una vez al día del agente o sal farmacéuticamente aceptable de esta, en donde a

forma de dosis proporciona un tiempo medio a concentración de plasma máximo (Tmax) del agente de 5,5 a 7,5 horas después de la administración. Adicionalmente, reivindica que la droga antihiperglicémica es metformina o una sal farmacéuticamente aceptable. Adicionalmente, reivindica que esta forma de dosis oral de liberación controlada exhibe los siguientes perfiles de disolución cuando son probados en un aparato tipo 2 USP a 75 rpm en 900 mL de fluido intestinal simulado (pH 7.5 en un buffer de fosfato) y a 37 C:
0-30% del fármaco es liberado después de 2 horas
10-45% del fármaco es liberado después de 4 horas
30-90% del fármaco es liberado después de 8 horas; no menos del 50% del fármaco es liberado después de 12 horas; no menos del 60% del fármaco es liberado después de 16 horas; y no menos del 70% del fármaco es liberado después de 20 horas. reivindican un método de tratamiento y el uso de esta forma de dosis oral de liberación controlada.

3.3. En primera instancia, se debe advertir que las reivindicaciones 1 a 44 caracterizan el arte general de la técnica, son generales y no definen las características propias para ser considerado como una invención. De dichas reivindicaciones no se puede establecer un avance inventivo, susceptible de estudio sobre los requisitos de patentabilidad. Adicionalmente, la reivindicación 44 se refiere al uso y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- "*Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*", los usos no están contemplados como patentables. Solo serán patentables los productos o procedimientos.

3.4. Así mismo, se está también tratando de reivindicar un método de tratamiento terapéutico en la reivindicación 43. La decisión 486 de la CAN establece claramente en su artículo número 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 animales"*. De aquí se deduce claramente que el objeto de la presente solicitud no puede ser objeto de patente en Colombia.

3.5. La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.* La presente solicitud carece de aplicación Industrial ya que como se demostró en el apartado anterior reclaman un método de tratamiento y estos no son aplicables industrialmente porque primero no se obtiene un resultado mediante el empleo de materias o fuerzas de la naturaleza; y segundo no es repetible ya que usados los medios previstos no se obtiene siempre el mismo resultado. Por lo tanto el objeto de la presente invención no cumple con el requisito de la aplicación industrial.

3.6. El artículo 14 de la Decisión 486 de la CAN, se refiere a que las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la novedad y el nivel inventivo de la presente solicitud:

- D1: US3174901 (23-03-65)
- D2: WO0028989 (25-05.00)

- D3: WO9947125 (23-09-99)
- D4: US5955106 (21-09-99)

3.7. El documento D1 afecta la NOVEDAD de la presente solicitud dado que revela con anterioridad una composición de dimetilbiguanida (Metformina). Para ello ver la pàgina 1, líneas 13 – 20. Este documento define un novedoso método de tratamiento de diabetes por administración oral, también la composición farmacéutica usada para ello, conteniendo una dimetilbiguanida (Metformina) como ingrediente activo. Según se revela en dicho documento anterior, tal composición farmacéutica contiene como ingrediente activo una dimetilbiguanida (Metformina) que puede ser preparada en varias formas farmacéuticas. De igual forma se define en la página 3, líneas 70 – 75 que los ingredientes de la composición pueden ser mezclados en proporciones propias y llenados en cápsulas de gelatina blanda o dura. Alternativamente, los compuestos pueden ser mezclados, granulados con lubricantes adecuados y tableteados; y que las tabletas convencionales o de liberación sostenida pueden ser preparadas por métodos conocidos en el arte de la formulación. A todas luces, este documento anterior revela la materia reivindicada en la solicitud objeto de remisión. Por lo tanto, la presente solicitud, a la luz del documento D1, carece del requisito de NOVEDAD, dado que lo que pretende se encuentra publicado mucho antes de la radicación de la prioridad de la solicitud Colombiana.

3.8. Por su parte, el documento D2 revela una composición novedosa, en particular una composición de liberación modificada de un sensibilizador de insulina y otro agente antidiabético, además un

transportador farmacéuticamente aceptable y su uso en medicina, especialmente su uso para el tratamiento de la Diabetes Mellitus. Este documento D2, revela que esta liberación modificada es una liberación sostenida, por ejemplo dando una liberación efectiva de los agentes activos por encima de un período de tiempo de 26 horas, típicamente en el rango de 4 a 24 horas según la página 3 líneas 3 a 5. A todas luces, este documento anterior revela la materia reivindicada en la solicitud objeto de remisión. Por lo tanto, la presente solicitud, a la luz del documento D2, carece del requisito de NOVEDAD, dado que lo que pretende se encuentra publicado antes de la radicación de la prioridad de la solicitud Colombiana.

3.9. De igual forma, cualquier persona versada en la materia, puede diseñar una forma de dosis oral de liberación controlada para conseguir los perfiles plasmáticos de concentración – tiempo adecuados. Por lo tanto, la presente solicitud, a la luz del documento D1 en combinación con el documento D2, carece del requisito de ALTURA INVENTIVA, dado que lo que pretende es derivable del arte anterior.

3.10. La referencia D3 claramente relaciona, según la página 1, líneas 3 a 7, una formulación de dosis unitaria de liberación controlada que contiene un fármaco antihiperglicémico. Mas específicamente, la referencia relaciona una forma de dosis oral que comprende una biguanida tal como Metformina o Buformina ò una sal farmacéuticamente aceptable. En la referencia D3 se revela una formulación de liberación controlada ò sostenida para un fármaco antihiperglicemiante que puede dar niveles terapéuticos continuos y no-pulsantes de un fármaco antihiperglicémico a un animal ò humano que necesita de tal tratamiento por encima de un período de doce horas a veinte y cuatro horas. De igual forma en las reivindicaciones 26 y 27

de la referencia D3 se revela un perfil de disolución similar al reivindicado en la solicitud del presente documento. Así las cosas, este documento D3, afecta la NOVEDAD de lo reivindicado en la presente solicitud objeto de oposición. En consecuencia, la solicitud colombiana objeto de oposición revela el mismo objeto indicado con anterioridad en el documento D3. Por lo tanto, esta forma de dosis oral de liberación controlada para la reducción de los niveles de glucosa no es NOVEDOSA a los ojos del documento D3.

3.11. Adicionalmente y como es de conocimiento general del arte, muchas técnicas se han usado para producir formas farmacéuticas de dosis de liberación controlada y extendida para mantener los niveles de sueros terapéuticos de los medicamentos (ver documento D2). Así las cosas, lo expuesto en las reivindicaciones de la solicitud Colombiana 03-036463, se deriva evidentemente del arte anterior de los documentos D1 y D2 en combinación con el documento D3 de manera que se demuestra que es obvio para cualquier persona versada en la materia. Por lo tanto, la combinación del conocimiento revelado en las solicitudes D1 y D2 en conjunto con el D3, afecta de manera directa el requisito de ALTURA INVENTIVA de la solicitud Colombiana que se pretende proteger.

3.12. Ahora bien, el documento D4 define composiciones farmacéuticas que contienen Metformina como sustancia activa y un agente formador de hidrocoloide como un retardante y opcionalmente sustancias auxiliares estándares farmacéuticas. En particular, el objeto de este documento D4 era el de diseñar una composición farmacéutica mejorada para la sustancia activa Metformina. En particular la forma de administración debería contener la sustancia activa Metformina con un posible alto contenido de la sustancia activa y un retardante, el retardante causa

una liberación controlada de la sustancia activa. Por lo tanto, se demuestra una forma de dosis oral de liberación controlada para la reducción de los niveles de glucosa utilizando Metformina, de manera que a la luz de este documento D4, la presente solicitud objeto de oposición pierde su estado de NOVEDAD.

3.13 De igual forma, una forma de dosis oral de liberación controlada puede dar una concentración plasmática máxima de metformina a un tiempo deseado después de su administración, esto se puede derivar de manera evidente de la combinación de los documentos D1, D2, D3 y D4. Ello es tan cierto que la misma solicitud objeto de oposición ha puntualizado en su página 1 que en el arte anterior muchas técnicas se han usado para producir formas farmacéuticas de dosis de liberación controlada ò extendida para mantener niveles de suero terapéutico de medicamentos. Así las cosas, lo expuesto en las reivindicaciones de la solicitud Colombiana 03-036463, se deriva evidentemente del arte anterior de los documentos D1 a D4 en combinación, de manera que se demuestra que es obvio para cualquier persona versada en la materia. Por lo tanto, la combinación del conocimiento revelado en las solicitudes D1 a D4 en conjunto, afecta de manera directa el requisito de ALTURA INVENTIVA de la solicitud Colombiana que se pretende proteger.

3.14 En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 03-036463 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con los TRES requisitos necesarios para su protección.

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

3.15.1. **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, 3 de noviembre de 2000, ya era conocido, pues como se demostró, era parte del arte anterior la materia sobre la cual busca protección en el capítulo reivindicatorio con base en los documentos D1, D2, D3 y D4.

3.14.2. **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 presentación, 2 de Mayo de 2003, los documentos D1 a D4 en combinación, es posible deducir una forma de dosis oral de liberación controlada para la reducción de niveles de glucosa, de suero, en pacientes humanos.

3.14.3. **CARENCIA DE APLICACIÓN INDUSTRIAL** La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.* La presente solicitud carece de aplicación Industrial ya que como se demostró lo que se está reclamando es un método de tratamiento. Éstos no son aplicables industrialmente porque primero no se obtiene un resultado mediante el empleo de materias o fuerzas de la

naturaleza; y segundo no es repetible ya que usados los medios previstos no se obtiene siempre el mismo resultado. Por lo tanto el objeto de la presente invención no cumple con el requisito de la aplicación industrial.

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

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

3.17. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"COMPOSICIONES DE METFÓRMICA DE LIBERACIÓN CONTINUADA"**, solicitada por **ANDRX CORPORATION**, solicitud Colombiana que apareció publicada en la Gaceta 544 de la Propiedad Industrial bajo el NP. 348 (página 344).

4. PRUEBAS

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

12

- D1: US3174901 (23-03-65)
- D2: WO0028989 (25-05.00)
- D3: WO9947125 (23-09-99)
- D4: US5955106 (21-09-99)

5. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

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

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

5.3. En las demás normas concordantes.

6. ANEXOS

Para los efectos correspondientes anexo al presente, aquellas referenciadas en el capítulo de pruebas así como los siguientes documentos:

6.1. Recibo de pago expedido por el Fondo Especial de esa Superintendencia, en el cual consta que se ha pagado el valor correspondiente a la tasa por tramitación de esta oposición.

6.2. Copia de la oposición para el traslado al solicitante.

6.3. Poder para actuar a nombre de mi representada.

7. 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 de abogado situadas en la calle 119ª Nº 53-99 de esta ciudad de Bogotá.

Señora Jefe,

LUÍS FERNANDO RINCÓN CUELLAR
C.C. 79'532.186 de Bogotá
T.P.A. 113.438 del C.S. de la J.

749

SUPERINDUSTRIA Y COMERCIO

Radicacion : 03836463 00010002 Folios: 95
Fecha (AMD): 2004-11-18 16:21:36
Tramite : 011 PCT-PATENT 379 FASE NACI 330 CORRECCION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINDUSTRIA Y COMERCIO(COPIA)

Radicacion : 03836463 00010002 Folios: 95
Fecha (AMD): 2004-11-18 16:21:36
Tramite : 011 PCT-PATENT 379 FASE NACI 400 OPOSICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 89,767
FECHA : NOVIEMBRE 18 DE 2004

***** 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	33942359	28/10/2004	224,000.00

***** 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	224,000.00
		TOTAL : $	224,000.

SON: DOSCIENTOS VEINTICUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

15

750

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 **LUIS FERNANDO RINCON CUELLAR**, abogado titulado, identificado como aparece al pie de su firma, con tarjeta profesional No. 113438 expedida por el Consejo Superior de la Judicatura, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **CO03036463**, de título: **"COMPOSICIONES DE METFORMICA DE LIBERACIÓN CONTINUADA"**, publicada en la Gaceta de la Propiedad Industrial N° 544, del 30 de Septiembre de 2004, bajo el N° de publicación NP. 348, y cuyo solicitante es la sociedad **ANDRX CORPORATION.**

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 11 días del mes de noviembre de 2004.

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

firma

Acepto,

LUIS FERNANDO RINCÓN CUELLAR
C.C. No. 79.532.186
T.P. 113438

DILIGENCIA DE PRESENTACION PERSONAL

DECRETO 960 DE 1970 - ART. 68

MARIA DEL S. ROMAN DE ARTETA - NOTARIA SEGUNDA DE BARRANQUILLA

CERTIFICA

En B/quilla a los 16 días del mes de Nov de 2004 Firmaron esta diligencia en su presencia: Walter Tonaka Tokavas

Portadores de las cedulas 16251923

Expedidas en Bogotá

y que declararon que es cierto el contenido del documento que antecede y esta autorizado con sus firmas

HUELLA

Comparecientes:

REPUBLICA DE COLOMBIA
NOTARIA SEGUNDA DEL CIRCULO DE BARRANQUILLA
LA NOTARIA

Maria del S. Roman De Arteta

2

DILIGENCIA DE RECONOCIMIENTO Y PRESENTACION PERSONAL

Ante el Notario Once del Circulo de Santafé de Bogotá, compareció:

Quién exhibió la C.C. No.

expedida en ______ T.P. 773438

y declaró que la firma y huella que aparecen en el presente memorial son suyas y que el contenido del mismo es cierto.

Memorial dirigido a ______

18 NOV 2004

Santafé de Bogotá D.C.

Firma del Declarante

HUELLA

Autorizó la anterior Diligencia

NOTARIA ONCE DEL CIRCULO DE SANTAFE DE BOGOTA

REPUBLICA DE COLOMBIA
NOTARIA ONCE DEL CIRCULO DE SANTAFE DE BOGOTA, D.C.
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE

03-818743 PROCAPS S.A.
Barranquilla, 21 de Octubre de 2,004 Hr:10:05:36

No. 8671161

CAMARA DE COMERCIO DE BARRANQUILLA

********** Pag.01

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

05**********

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

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

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

Que por Escritura Publica Nro. 1190 del 22 de Julio de 1,976, t rgada en la Notaria Tercera de Barranquilla, ----------
inscrita en esta Camara de Comercio, el 28 de Julio de 1,976 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 Publica Nro. 1307 del 28 de Junio de 1,979, ot rgada en la Notaria Tercera de Barranquilla, ----------
inscrita en esta Camara de Comercio, el 23 de Julio de 1,979 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 Publica Nro. 3810 del 31 de Dic/bre de 1,980, torgada en la Notaria Primera de Barranquilla, ----------
inscrita en esta Camara de Comercio, el 30 de Enero de 1,981 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 Publica Nro. 3755 del 10 de Nov/bre de 1,983, torgada en la Notaria Unica de Soledad, ----------
inscrita en esta Camara de Comercio, el 22 de Nov/bre de 1,983 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 Publica Nro. 3615 del 6 de Dic/bre de 1,996, t rgada en la Notaria 2a. de Barranquilla ----------
inscrita en esta Camara de Comercio, el 20 de Dic/bre de 1,996 bajo

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

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

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

el No. 67,218 del libro respectivo, la sociedad antes mencionada cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A . ----------

C E R T I F I C A

Que por Escritura Publica Nro. 3775 del 18 de Dic/bre de 1,996, otorgada en la Notaria 2a. de Barranquilla ----------
inscrita en esta Camara de Comercio, el 23 de Enero de 1,997 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	mm/dd/aaaa	Notaria	No.Ins o Reg	mm/dd/aaaa
39	1/18/1979	Notaria 3a. de Barranquilla	9,452	1/24/1979
992	4/30/1981	Notaria 1a. de Barranquilla	13,112	5/ 6/1981
1,464	8/27/1982	Notaria Unica de Soledad	15,533	9/ 8/1982
2,744	8/18/1983	Notaria Unica de Soledad	17,416	8/26/1983
3,826	7/16/1984	Notaria Unica de Soledad	19,554	7/27/1984
3,835	8/26/1985	Notaria Unica de Soledad	22,230	9/ 4/1985
2,260	9/10/1986	Notaria Unica de Soledad.	24,995	9/15/1986
1,849	7/11/1989	Notaria 2a. de Barranquilla	33,909	7/13/1989
444	2/21/1990	Notaria 2a. de Barranquilla	36,101	3/16/1990
3,090	12/17/1991	Notaria 2a. de Barranquilla	43,993	1/28/1992
269	2/ 1/1993	Notaria 2a. de Barranquilla	48,428	2/16/1993
2,342	7/28/1993	Notaria 2a. de Barranquilla	50,582	8/10/1993
3,652	11/ 9/1993	Notaria 2a. de Barranquilla	51,798	11/22/1993
3,615	12/ 6/1996	Notaria 2a. de Barranquilla	67,218	12/20/1996
89	1/16/1997	Notaria 2a. de Barranquilla	67,704	1/23/1997
2,070	7/17/1997	Notaria 2a. de Barranquilla	70,627	7/31/1997
2,281	8/ 4/1997	Notaria 2a. de Barranquilla	70,813	8/14/1997
765	4/22/1999	Notaria 3a. de Barranquilla	80,628	4/23/1999
459	2/21/2001	Notaria 2a. de Barranquilla	91,502	2/23/2001
2,608	10/ 5/2001	Notaria 2a. de Barranquilla	95,771	11/ 8/2001
1,730	7/29/2004	Notaria 2. de Barranquilla	112,999	8/26/2004

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

03-818743 PROCAPS S.A.
Barranquilla, 21 de Octubre de 2,004 Hr:10:05:38

No. 8671162

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

****

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

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

C E R T I F I C A

Direccion para notificaciones judiciales
CL 80 # 78B -201
de la ciudad de BARRANQUILLA

C E R T I F I C A

DURACION: El termino de duracion de la sociedad se fijo hasta el 18 de Agosto del ano 2,073. ----------

C E R T I F I C A

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

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

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

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

sarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuest s 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 Accion
AUTORIZADO:		
$******2,000,000,000.00	2,000,000.00	1,000.00
SUSCRITO:		
$******1,212,449,000.00	1,212,449.00	1,000.00
PAGADO:		
$******1,212,449,000.00	1,212,449.00	1,000.00

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 representaci n 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

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

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 s ciedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la socieda todo act o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le 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 s ciedad 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

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

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ello acreditar la ausencia del principal. La sociedad tendra un gerente general con su respectivo suplente, quienes tambien ejerceran la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el presidente y el vicepresidente. 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 superior al equivalente en pesos colom-+ bianos 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 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. Las demas funciones que les correspondan como representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El gerente lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades.-------

C E R T I F I C A

Que segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: ------
PROCAPS S.A. ----------
cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo,
y por Acta No. 127 del 22 de Marzo de 2,000, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: ------
PROCAPS S.A. ----------
cuya parte pertinente se inscribio en esta Camara de Comercio, el 29 de Mayo de 2,000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos: ----------

J U N T A D I R E C T I V A

Principales	Suplentes
1. Minski Gontovnik Ruben	Minski Zilberblum Elliot
2. Minski Gontovnik Meyer	Minski Deitel Daniel
3. Minski Gontovnik Jose	Minski Sharon

C E R T I F I C A

Que segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: ------
PROCAPS S.A. ----------
cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos: ----------

Cargo	Nombre	Identificacion

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

No. 8671164

754

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

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

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

C E R T I F I C A

Que segun Acta No. 124 del 29 de Marzo de 1,999, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: ------
PROCAPS S.A. ----------
cuya parte pertinente se inscribio en esta Camara de Comercio, el 4 de Agosto de 1,999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos: ----------

Cargo	Nombre	Identificacion
Revisor Fiscal Ppal.	Vargas Pertuz Ana Isabel	C.****32,696,645=

C E R T I F I C A

Que segun Acta No. 127 del 22 de Marzo de 2,000, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: ------
PROCAPS S.A. ----------
cuya parte pertinente se inscribio en esta Camara de Comercio, el 29 de Mayo de 2,000 bajo el No. 87,250 del libro respectivo, fueron hech s los siguientes nombramientos: ----------

Cargo	Nombre	Identificacion
Suplente del Revisor Fiscal.	Lozada Villareal Milena	C.****32,748,111=

C E R T I F I C A

Que segun Acta No. 11 del 1 de Febrero de 2,001, correspondiente a la Junta Directiva en Barranquilla de la sociedad: ----------
PROCAPS S.A. ----------
cuya parte pertinente se inscribio en esta Camara de Comercio, el 12 de Febrero de 2,001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos: ----------

Cargo	Nombre	Identificacion
Gerente General.	Uribe Ochoa Guillermo Luis	C.****70,073,754=

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. ----------

Que segun Acta No. 406 del 2 de Sep/bre de 2,004, correspondiente a la Junta Directiva en Barranquilla de la sociedad: ----------
PROCAPS S.A. ----------
cuya parte pertinente se inscribio en esta Camara de Comercio, el 9 de Sep/bre de 2,004 bajo el No.113,263 del libro respectivo, fueron hechos los siguientes nombramientos: ----------

Cargo	Nombre	Identificacion
Suplente del Gerente.	Tanaka Walter	C.****16,251,923=

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 cambiarias,en los ordenes Distrital, Departamental y Nacional. 2.-Se confiere Poder Especial,amplio y suficiente,a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancias y servicios con entidades oficiales, hasta por la suma de US$800.000.oo (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. GUPO A: GUILLERMO LUIS URIBE OCHO C.C. No. 70.073.754, LINO LAZALA SILVA VARGAS C.C. No. 19.260.410, JAIRO MOLINA MEJIA C.C. No. 8.706.380, CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.-293. BRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, HENRY CARO DIAZ C.C. No. 19.395.298, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZGRANADOS C.C. No. 22.377.540. Para el 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, com-

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

N. 8671165

755

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

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

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

parecer 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/ compensacion de impuestos y recibir los pagos por devoluciones de impuestos, firmar, notificarse y realizar todo acto necesario para cumplir con el mandato encomendado.----------

C E R T I F I C A

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

C E R T I F I C A

Que segun Documento Privado del 13 de diciembre del 2.002, inscrito en esta Camara de Comercio el 15 de enero del 2.003 bajo el No.2.290 del libro respectivo, el senor RUBEN MINSKI GONTOVNIK, C.C.No.7.463. 982, en calidad de REPRESENTANTE LEGAL, y en condicion de PRESIDENTE de PROCAPS S.A., mediante el presente documento otorgo PODER ESPECIAL al Sr. MARLON TATIS PAREDES, C.C.No.72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces. En consecuencia, el Sr. MARLON TATIS PAREDES, podra suscribir en representacion de PROCAPS S.A. declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces.----------

C E R T I F I C A

Que en esta Camara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolucion, liquidacion o nombramientos de representantes legales de la expresada sociedad.------

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

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

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

C E R T I F I C A

Que su ultima Renovacion fue el: 31 de Marzo de 2,004. ----------

La informacion sobre embargos de establecimientos se suministra en Certificados de Matricula, la de contratos sujetos a registro, en Certificados Especiales.

NO CAUSA IMPUESTO DE TIMBRE

EL SECRETARIO
MARIBEL REYES OVIEDO

ANEXO 1

United States Patent Office

3,174,901
Patented Mar. 23, 1965

3,174,901
PROCESS FOR THE ORAL TREATMENT OF DIABETES

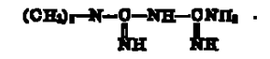
Jean J. Sterne, Suresnes, France, assignor to Jan Marcel Didier Aron-Sammel, Suresnes, France

No Drawing. Filed Jan. 31, 1963, Ser. No. 255,191
2 Claims. (Cl. 167—65)

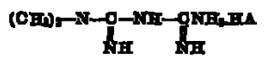
This is a continuation-in-part of U.S. application Serial No. 735,105, filed on May 14, 1958, which in turn is a continuation-in-part of U.S. application Serial No. 697,546, filed on November 20, 1957, both now abandoned.

The present invention relates to a novel method of treating diabetes by oral administration as well as to the pharmacentical compositions useful therefor.

The composition to be administered orally according to the present invention contains as active ingredient a dimethyl biguanide corresponding to the following formula



In a preferred embodiment, the dimethyl biguanide according to this invention is used in the form of its acid addition salts, primarily the hydrochloride, having the formula



in which A is the anion of a non-toxic acid.

While the preferred salt is the hydrochloride corresponding to the above structure when A represents a chloro atom, the acid addition salt with any nontoxic, stable, pharmacentically acceptable acid may be used, such as the following salts; the phosphate, sulfate, hydrobromide, salicylate, maleate, benzoate, succinate, ethanedisulfonate, fumarate or glycolate.

The classic means for controlling blood sugar and urine sugar in diabetics has been by injection of insulin. This method, although effective pharmacologically, has its obvious drawbacks since it requires that the material be injected by means of a hypodermic syringe.

Treatment by syringe has obvious drawbacks. Moreover the lowering of sugar content by insulin injections may produce hypoglycemic coma.

Another treatment has been by sulphonylureas taken orally. However, this composition has limited fields of use and many diabetics fail to respond to it.

Dimethyl biguanide has been experimented on animals. In 1929 Hesse and Tanhmann have found that the product could have a hypoglycemic action but that the dosages susceptible of reducing the blood sugar content were highly toxic. As a consequence they advised against any use of this product as an antidiabetic for human beings.

Another experimentor (Eusebio Y. Garcia) has attempted to use dimethyl biguanide as an analgesic and anti-flu drug. The dosages were of approximately 65 mg. by injection during a maximum period of two days.

The real problem of treating diabetes does not exclusively reside in the lowering of the sugar in the blood of any individuals. This can be done by many different compounds. But to control diabetes such an action must be exerted on diabetic individuals without any harmful action such as toxicity, lowering of the sugar content to the minimum physiological limit having as a consequence the hypoglycemic coma, etc. The ideal treatment will have to keep the sugar content as close as possible to the normal physiological range. This is the problem which has been solved by this present invention.

It has been observed that certain critical dosage limits

viduals in reducing the abnormal sugar content without being toxic and without decreasing the blood-sugar content to a dangerous limit to the point approaching the hypoglycemic coma.

It has also been observed that these critical range dosages exert no hypoglycemic action on normal human beings.

A normal daily regimen of the antidiabetic composition according to the invention, containing as an active ingredient dimethyl biguanide hydrochloride for oral administration, is from about 1–4 grams as an initial dosage per diem, which is then adjusted to a maintenance dosage, substantially in the said limits or at a lower dosage.

For children the dosages will have to be reduced according to age groups in a manner which is known in medical art.

As mentioned above, the novel drug is also very useful in such cases of diabetes in which preparations hitherto used for oral administration proved ineffective. One of these cases is for example oscillating diabetes.

The dimethyl biguanide constituent of the composition is prepared as follows:

Five hundred grams of cyanoguanide are melted with 475 g. of dimethylamine hydrochloride in a suitable vessel provided with an agitator and with a thermometer in an oil bath. The progressive melting is practically accomplished at about 120–130° C. The mixture is maintained for about three hours at about 135° C. and should not be overheated.

After this heating, this mixture is placed in boiling water and left for crystallization. This latter crystallization may be executed from alcohol.

The obtained crystals consist of pure dimethyl biguanide hydrochloride. The base is obtained by treatment with alkali. Other salts may be prepared by reacting the base with one equivalent or more of the acid in a suitable organic solvent such as ethanol or methanol. Alternatively, other salts are prepared by a double decomposition reaction of the soluble hydrochloride salt.

The exact assay of the product in aqueous or organic solutions is determined by the colorimetric system due to the reaction known as the Sakaguchi reaction proper to the guanidic group. The coloration of the guanide derivatives when operating at 0° and in a glycero-alcoholic medium is stable and can be measured by electrophotometric means.

In order to avoid any possible ambiguity, herebelow is a method of assaying this product.

The following four reagents are prepared:

(*a*) A solution of 1.0 g. of α naphtol in 100 cc. of alcohol at 95° C., this solution constituting a basic reagent to be diluted to ⅛ in distilled water when it is to be used;

(*b*) A solution of sodium hydroxide at 40%;

(*c*) A solution of sodium hypobromide obtained by the addition of 0.9 cc. of bromium to 100 cc. of a solution of sodium hydroxide at 40%;

(*d*) An aqueous solution of urea at 40 gr. per 100 cc.

When used, all the reagents are cooled at 0° C., for instance by means of an ice bath.

To execute the assay operation, a certain amount, for instance 50 to 400 g. of the guanide derivative contained in a fixed volume of 2 cc. is introduced into a tube. An amount of 0.25 cc. of the sodium hydroxide solution at 40% and 0.1 cc. of the solution of α naphthol upon dilution to ⅛ from the beforehand prepared solution is introduced thereafter. The mixture is agitated and the tube is allowed to stand during 15 minutes at the same temperature of 0° C. An amount of 0.5 cc. of the solution of sodium hypobromide is then added also under

agitation. The coloration attains its maximum intensity after 30 seconds. Immediately thereafter 10 cc. of alcohol at 95° C. and 1 cc. of the solution of urea at a concentration of 40 g. per 100 cc. are added. This new mixture is once again agitated and its contents poured into a vessel having a wall thickness of 1 cm. and adapted for the photocolorimetric method of Bonsy Maury executed with a green filter having a wave length of about 535 mμ.

Another tube is prepared in the same conditions but the guanide derivative is replaced by 2 cc. of distilled water. The difference between the optic densities of these two preparations gives the final result.

A normal daily maintenance regimen of the antidiabetic composition of this invention containing dimethyl biguanide hydrochloride for treating a human being is advantageously about 3.0 g. of the active ingredient corresponding, approximately to 15–20 mg./kg., when administered orally. Sometimes, 1.0 g. daily or even less is quite sufficient. Occasionally, doses amounting to 5.0 g. a day can be administered without untoward effects.

In general, the initial daily dosage regimen of this composition for beneficial antidiabetic effect can vary from about 1.0 g. to about 5.0 g. of active ingredient administered orally, usually in 3 or 4 divided doses. After this, maintenance treatment has to be continued.

The principle of this method of treatment of diabetes, in human beings, consists of rather high dosage of the active biguanide ingredient to lower the initial high sugar levels of the blood to normal as described hereabove. The maintenance doses may be at ranges lower than those initially required and are best determined by the attending physician who must take into account the case file of the patient.

No toxic effects whatsoever are observed interfering with the use of the new preparation of this invention even at the initial elevated doses.

Moreover, it has been observed that, the hereabove contemplated dosage regimens only affected the high sugar contents, i.e., those lying over the normal limit. In other words, these dosages are only effective with diabetic individuals. In these conditions hypoglycemic comas do not occur.

The compositions of this invention are dosage units comprised of from about 10 mg. to 1.0 g. of dimethyl biguanide or a salt thereof with a nontoxic acid and a pharmaceutical carrier or filler. The pharmaceutical filler may be, for example, a solid. Examples of the preferred solid carriers are talc, lactose, corn starch, ethyl cellulose, magnesium stearate, agar pectin, stearic acid, gelatin or acacia. Examples of liquid carriers are water, peanut oil, olive oil, and sesame oil. The amount of carrier may vary widely but will usually be from about 10 mg. to about 1.0 g. per unit dosage.

Preferable and advantageous dosage unit compositions are comprised of from about 250 mg. to about 750 mg. of dimethyl biguanide and a pharmaceutical carrier, preferably solid.

The compositions of this invention containing as active ingredient a dimethyl biguanide can be prepared in various pharmaceutical forms, such as tablets, pills, powders, troches, capsules, granules, solutions, etc. The granules or tablets can be covered if necessary by sugar, wax, lacquer, fat, shellac coatings or the like.

The best dose in the case of a tablet, capsule or pill is considered as being of about 500 mg., but it is obvious that this dose can vary as discussed above. The upper limit of active ingredient is limited only by the size of the final dosage unit.

The ingredients of the composition can be mixed in proper proportion and filled into hard or soft gelatin capsules. Alternatively, the components can be mixed, granulated with suitable lubricants and tableted. Conventional or sustained release tablets can be prepared by methods known to the formulation art.

Example 1

Dimethyl biguanide, 0.50 g., corresponding approximately to 80–90% and preferably 83% in weight.

Bicarbonate of sodium 0.085 g., corresponding approximately to 10–15%, preferably 14% in weight.

Stearate of magnesia 0.015 g. corresponding approximately to 2–5%, preferably 3% in weight.

The ingredients are mixed and filled into hard gelatin capsules.

Example 2

Dimethyl biguanide hydrochloride, about 0.50 g.
Sodium bicarbonate, about 0.072 g.
Arabic gum, about 0.04 g.
Stearate of magnesia, about 0.015 g.

A cementitious substance, for instance that known on the market under the trade name Rhodopas, about 0.012 g.

The ingredients are mixed, granulated and tableted on a standard tableting machine.

Example 3

Dimethyl biguanide hydrochloride, 0.10 g.
Lactose, 0.15 g.

The ingredients are mixed and filled into a hard gelatin capsule.

Example 4

Dimethyl biguanide, 0.60 g.
Talc, 0.025 g.

The ingredients are mixed and filled into a hard gelatin capsule.

To illustrate the above explanations, a limited number of clinical results will be given herebelow.

(1) A woman of 62, diabetic for 23 years. Fasting blood sugar varying between 180 and 300 mg.—Daily glycosuria was approximately 30 g./24 hrs.—Allergic to any other kind of antidiabetics.

The administration of the product of this invention at a daily dosage regimen varying after the initial treatment between .50 and 1.0 g. reduced the blood sugar to 100–130 mg.—Glycosuria disappeared completely. No allergy has been observed with dimethylbiguanide.

(2) A man of 54, diabetic for 10 years. Blood sugar of about 334 mg. Glycosuria of about 80 g. per 24 hours.

The administration of the product of this invention at a daily regimen of 3 g. gave the following results:

After 8 days: blood sugar 175 mg. Glycosuria—0
After 3 weeks: blood sugar 145 mg. Glycosuria—0
After 5 weeks: blood sugar 140 mg. Glycosuria—0

(3) A man of 50. Blood sugar of about 172 mg. and glycosuria of about 71 g. per 24 hours.

After an initial treatment with the product of this invention administered at a daily regimen of 1.25 g. per 24 hours:

After 8 days: blood sugar 140 mg. Glycosuria—0
After 15 days: blood sugar 115 mg. Glycosuria—0
After this initial treatment, a maintenance treatment is used at a daily dosage regimen of .75 g. per 24 hours.
After one month: blood sugar 120 mg.
After 3 months: blood sugar 95 mg.

What I claim is:

1. A method of continuously treating diabetes of human beings which comprises orally administering initially a daily dosage regimen of about 1 to 4 grams of a compound selected from the class consisting of

and its non-toxic acid addition salts, and thereafter orally administering a daily adjusted maintenance dose of said compound.

2. The method according to claim 1 wherein said compound is dimethyl biguanide hydrochloride.

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Chemical Abstracts 23: 4930–4932, 1929.
Chemical Abstracts 24, 2181–2182, 1930.

Chemical Abstracts 44: 6032(g), 1950.
Chemical Abstracts 49: 14186(c), 1955.
Chemical Abstracts 48: 13058(i), 13059(a), 1954.

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ANEXO 2

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(54) Title: PHARMACEUTICAL COMPOSITION FOR MODIFIED RELEASE OF AN INSULIN SENSITISER AND ANOTHER ANTIDIABETIC AGENT

(57) Abstract

A pharmaceutical composition, which composition comprises: an insulin sensitiser and another antidiabetic agent and a pharmaceutically acceptable carrier therefor, wherein the composition is arranged to provide a modified release of at least one of the insulin sensitiser and the other antidiabetes agent, and the use of such composition in medicine.

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PHARMACEUTICAL COMPOSITION FOR MODIFIED RELEASE OF AN INSULIN SENSITISER AND ANOTHER ANTIDIABETIC AGENT

This invention relates to a novel composition, in particular to a modified release composition and its use in medicine, especially its use for the treatment of diabetes mellitus, preferably Type 2 diabetes, and conditions associated with diabetes mellitus.

Alpha glucosidase inhibitor antihyperglycaemic agents (or alpha glucosidase inhibitors) and biguanide antihyperglycaemic agents (or biguanides) are commonly used in the treatment of Type 2 diabetes. Acarbose, voglibose, emiglitate and miglitol are examples of alpha glucosidase inhibitors.1,1 - Dimethylbiguanidine (or metformin) is a particular example of a biguanide.

Insulin secretagogues are compounds that promote increased secretion of insulin by the pancreatic beta cells. The sulphonylureas are well known examples of insulin secretagogues. The sulphonylureas act as hypoglycaemic agents and are used in the treatment of Type 2 diabetes. Examples of sulphonylureas include glibenclamide (or glyburide), glipizide, gliclazide, glimepiride, tolazamide and tolbutamide.

European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having antihyperglycaemic and hypolipidaemic activity. One particular thiazolidinedione disclosed in EP 0306228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter 'Compound (I)'). WO94/05659 discloses certain salts of Compound (I) including the maleate salt at example 1 thereof.

Compound (I) is an example of a class of anti-hyperglycaemic agents known as 'insulin sensitisers'. In particular Compound (I) is a thiazolidinedione insulin sensitiser.

European Patent Applications, Publication Numbers: 0008203, 0139421, 0032128, 0428312, 0489663, 0155845, 0257781, 0208420, 0177353, 0319189, 0332331, 0332332, 0528734, 0508740; International Patent Application, Publication Numbers 92/18501, 93/02079, 93/22445 and United States Patent Numbers 5104888 and 5478852, also disclose certain thiazolidinedione insulin sensitisers.

Another series of compounds generally recognised as having insulin sensitiser activity are those typified by the compounds disclosed in International Patent Applications, Publication Numbers WO93/21166 and WO94/01420. These compounds are herein referred to as 'acyclic insulin sensitisers'. Other examples of acyclic insulin sensitisers are those disclosed in United States Patent Number 5232945 and International Patent Applications, Publication Numbers WO92/03425 and WO91/19702.

Examples of other insulin sensitisers are those disclosed in European Patent Application, Publication Number 0533933, Japanese Patent Application Publication Number 05271204 and United States Patent Number 5264451.

The above mentioned publications are incorporated herein by reference.

It is now indicated that certain modified release pharmaceutical compositions allow administration of a single daily dose of Compound (I) and another antidiabetic agent, such as an alpha glucosidase inhibitor, a biguanide or an insulin secretagogue, to provide an advantageous delivery of drug for maintaining effective glycaemic control with no observed adverse side effects. Such modified release is therefore considered to be particularly useful for the delivery of insulin sensitisers in combination with other antidiabetic agents for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus.

Accordingly, the invention provides a pharmaceutical composition, suitable for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus in a mammal, such as a human, which composition comprises: an insulin sensitiser, such as Compound (I), and another antidiabetic agent, such as an alpha glucosidase inhibitor, a biguanide or an insulin secretagogue, and a pharmaceutically acceptable carrier therefor, wherein the composition is arranged to provide a modified release of at least one of the insulin sensitiser and the other antidiabetic agent.

In another aspect, the invention provides a modified release pharmaceutical composition, suitable for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus in a mammal, such as a human, which composition comprises: an insulin sensitiser, such as Compound (I), and another antidiabetic agent, such as an alpha glucosidase inhibitor, a biguanide or an insulin secretagogue, and a pharmaceutically acceptable carrier therefor, wherein the carrier is arranged to provide a modified release of at least one of the insulin sensitiser and the other antidiabetic agent

Suitably, the release of both the insulin sensitiser and the other antidiabetic agent is modified.

However, it is envisaged that the release of only the insulin sensitiser is modified. It is also envisaged that the release of only the other antidiabetic agent is modified. The remaining active agent would of course be subject to non-modified release.

Suitably, the modified release is delayed, pulsed or sustained release.

In one aspect the modified release is a delayed release.

Delayed release is conveniently obtained by use of a gastric resistant formulation such as an enteric formulation, such as a tablet coated with a gastric resistant polymer, for example Eudragit L100-55. Other gastric resistant polymers include methacrylates, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phtahlate, in particular, Aquateric, Sureteric, HPMCP-HP-55S.

The enteric coated tablet may be a single layer tablet, where the active agents are admixed prior to compression into tablet form, or a multi-layer tablet, such as a bi-or tri-layer tablet, wherein each active agent is present in a discrete layer within the compressed

tablet form. The discrete table layers can be arranged as required to provide modified or non-modified release of each active agent.

In a further aspect the modified release is a sustained release, for example providing effective release of active agents over a time period of up to 26 hours, typically in the range of 4 to 24 hours.

Sustained release is typically provided by use of a sustained release matrix, usually in tablet form, such as disintegrating, non-disintegrating or eroding matrices.

Sustained release is suitably obtained by use of a non disintegrating matrix tablet formulation, for example by incorporating Eudragit RS into the tablet. Alternative non disintegrating matrix tablet formulations are provided by incorporating methacrylates, cellulose acetates, hydroxypropyl methylcellulose phtahlate, in particular Eudragit L and RL , Carbopol 971P, HPMCP-HP-55S into the tablet.

Sustained release is further obtained by use of a disintegrating matrix tablet formulation, for example by incorporating methacrylates, methylcellulose, in particular Eudragit L, Methocel K4M into the tablet.

Sustained release can also be achieved by using a semi-permeable membrane coated tablet for example by applying methacrylates, ethylcellulose, cellulose acetate, in particular Eudragit RS, Surelease to the tablet.

Sustained release can also be achieved by using a multi layer tablet, where each active ingredient is formulated together or as a separate layer, for example as a matrix tablet, with the other layers providing further control for sustained release of either one or both active agents.

In yet a further aspect the modified release is a pulsed release, for example providing up to 4, for example 2, pulses of active agent per 24 hours.

One form of pulsed release is a combination of non-modified release of active agent and delayed release.

Suitable modified release includes controlled release. The composition of the invention also envisages a combination of pulsed, delayed and/or sustained release for each of the active agents, thereby enabling for example the release of the reagents at different times. For example, where the composition comprises an insulin sensitiser and a biguanide, such as metformin, the composition can be arranged to release the metformin overnight.

A suitable alpha glucosidase inhibitor is acarbose.

Other suitable alpha glucosidase inhibitors are emiglitate and miglitol. A further suitable alpha glucosidase inhibitor is voglibose.

Suitable biguanides include metformin, buformin or phenformin, especially metformin.

Suitable insulin secretagogues include sulphonylureas.

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Suitable sulphonylureas include glibenclamide, glipizide, gliclazide, glimepiride, tolazamide and tolbutamide. Further sulphonylureas include acetohexamide, carbutamide, chlorpropamide, glibornuride, gliquidone, glisentide, glisolamide, glisoxepide, glyclopyamide and glycylamide. Also included is the sulphonylurea glipentide.

Further suitable insulin secretagogues include repaglinide. An additional insulin secretagogue is nateglinide.

A preferred thiazolidinedione insulin sensitiser is Compound (I).

Other suitable thiazolidinedione insulin sensitisers include (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone) or 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl)thiazolidine-2,4-dione (or englitazone).

A particular thiazolidinedione insulin sensitiser is 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone).

A particular thiazolidinedione insulin sensitiser is (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (or troglitazone).

Suitable dosages, preferably unit dosages, of the insulin sensitiser and the other antidiabetic agent, such as the alpha glucosidase inhibitor, a biguanide or insulin secretagogue, include the known permissible doses for these compounds as described or referred to in reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) or the above mentioned publications.

The dosages of each particular active agent in any given composition can as required vary within a range of doses known to be required in respect of accepted dosage regimens for that compound. Dosages of each active agent can also be adapted as required to take into account advantageous effects of combining the agents as mentioned herein.

In one particular aspect, the composition comprises 2 to 12 mg of Compound (I).

Suitably the composition comprises 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound (I).

Particularly, the composition comprises 2 to 4 , 4 to 8 or 8 to 12 mg of Compound (I).

Particularly, the composition comprises 2 to 4mg of Compound (I).

Particularly, the composition comprises 4 to 8mg of Compound (I).

Particularly, the composition comprises 8 to 12 mg of Compound (I).

Preferably, the composition comprises 2 mg of Compound (I).

Preferably, the composition comprises 4 mg of Compound (I).

Preferably, the composition comprises 8 mg of Compound (I).

Suitable unit dosages of other insulin sensitisers include from 100 to 800mg of troglitazone such as 200, 400, 600 or 800mg or from 5 to 50mg, including 10 to 40mg, of pioglitazone, such as 20, 30 or 40 mg and also including 15, 30 and 45mg of pioglitazone.

As indicated above the unit doses of the additional antidiabetic agents including the alpha glucosidase inhibitor, the biguanide and the insulin secretagogue include those found in the reference texts mentioned herein and include the doses set out below.

For the alpha glucosidase inhibitor, a suitable amount of acarbose is in the range of from 25 to 600 mg, including 50 to 600 mg, for example 100mg or 200mg.

For the the biguanide, a suitable dosage of metformin is between 100 to 3000mg, for example 250, 500mg, 850mg or 1000mg.

For the insulin secretagogue, a suitable amount of glibenclamide is in the range of from 2.5 to 20 mg, for example 10mg or 20mg; a suitable amount of glipizide is in the range of from 2.5 to 40 mg; a suitable amount of gliclazide is in the range of from 40 to 320 mg; a suitable amount of tolazamide is in the range of from 100 to 1000 mg; a suitable amount of tolbutamide is in the range of from 1000 to 3000 mg; a suitable amount of chlorpropamide is in the range of from 100 to 500 mg; and a suitable amount of gliquidone is in the range of from 15 to 180 mg. Also a suitable amount of glimepiride is 1 to 6mg and a suitable amount of glipentide is 2.5 to 20mg.

A suitable amount of repaglinide is in the range of from 0.5mg to 20mg, for example 16mg. Also a suitable amount of nateglinide is 90 to 360mg, for example 270mg.

The compounds mentioned herein, in particular the thiazolidinediones such as Compound (I), may exist in one of several tautomeric forms, all of which are encompassed by the invention as individual tautomeric forms or as mixtures thereof. The compounds mentioned herein may contain one or more chiral carbon atoms and hence can exist in two or more stereoisomeric forms, all of which are encompassed by the invention either as individual isomers or as mixtures of isomers, including racemates.

It will be understood that the insulin sensitiser, such as Compound (I) and the other antidiabetic agent are in a pharmaceutically acceptable form, including pharmaceutically acceptable derivatives such as pharmaceutically acceptable salts, esters and solvates thereof, as appropriate to the relevant pharmaceutically active agent chosen. In certain instances herein the names used for the antidiabetic agent may relate to a particular pharmaceutical form of the relevant active agent: It will be understood that all

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pharmaceutically acceptable forms of the active agents per se are encompassed by this invention.

Suitable pharmaceutically acceptable forms of the insulin sensitiser and other antidiabetic agent depend upon the particular agent used but included are known pharmaceutically acceptable forms of the particular agent chosen. Such derivatives are found or are referred to in standard reference texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) and the above mentioned publications. For example, a particular form of metformin is metformin hydrochloride, a particular form of repaglinide is a benzoic acid salt form and a particular form of tolbutamide is a sodium salt form.

Suitable pharmaceutically acceptable forms of Compound (I) include those described in EP 0306228 and WO94/05659, especially pharmaceutically acceptable salted or solvated forms. A preferred pharmaceutically acceptable salt form of Compound (I) is a maleate. A preferred pharmaceutically acceptable solvated form of Compound (I) is a hydrate. A preferred form of pioglitazone is as the hydrochloride salt.

The insulin sensitiser or the alpha glucosidase inhibitor antihyperglycaemic agent of choice is prepared according to known methods, such methods are found or are referred to in standard reference texts, such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) or as described in the above mentioned publications.

Compound (I) or, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, may be prepared using known methods, for example those disclosed in EP 0306228 and WO94/05659. The disclosures of EP 0306228 and WO94/05659 are incorporated herein by reference.

When used herein the term 'conditions associated with diabetes' includes those conditions associated with the pre-diabetic state, conditions associated with diabetes mellitus itself and complications associated with diabetes mellitus.

When used herein the term 'conditions associated with the pre-diabetic state' includes conditions such as insulin resistance, including hereditary insulin resistance, impaired glucose tolerance and hyperinsulinaemia.

'Conditions associated with diabetes mellitus itself' include hyperglycaemia, insulin resistance, including acquired insulin resistance and obesity. Further conditions associated with diabetes mellitus itself include hypertension and cardiovascular disease, especially atherosclerosis and conditions associated with insulin resistance. Conditions

associated with insulin resistance include polycystic ovarian syndrome and steroid induced insulin resistance and gestational diabetes.

'Complications associated with diabetes mellitus' includes renal disease, especially renal disease associated with Type 2 diabetes, neuropathy and retinopathy.

Renal diseases associated with Type 2 diabetes include nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As used herein the term 'pharmaceutically acceptable' embraces both human and veterinary use: for example the term 'pharmaceutically acceptable' embraces a veterinarily acceptable compound.

For the avoidance of doubt, unless other wise stated, when reference is made herein to scalar amounts, including mg amounts, of the active compound such as Compound (I), in a pharmaceutically acceptable form, the scalar amount referred to is made in respect of the active compound *per se*: For example 2 mg of Compound (I) in the form of the maleate salt is that amount of maleate salt which provides 2 mg of Compound (I).

Diabetes mellitus is preferably Type 2 diabetes.

Glycaemic control may be characterised using conventional methods, for example by measurement of a typically used index of glycaemic control such as fasting plasma glucose or glycosylated haemoglobin (Hb A1c). Such indices are determined using standard methodology, for example those described in: Tuescher A, Richterich, P., Schweiz. med. Wschr. 101 (1971), 345 and 390 and Frank P., 'Monitoring the Diabetic Patent with Glycosolated Hemoglobin Measurements', Clinical Products 1988.

In a preferred aspect, the dosage level of each of the active agents when used in accordance with the treatment of the invention will be less than would have been required from a purely additive effect upon glycaemic control.

There is also an indication that the treatment of the invention will effect an improvement, relative to the non-modified release of the individual agents, in the levels of advanced glycosylation end products (AGEs), leptin and serum lipids including total cholesterol, HDL-cholesterol, LDL-cholesterol including improvements in the ratios thereof, in particular an improvement in serum lipids including total cholesterol, HDL-cholesterol, LDL-cholesterol including improvements in the ratios thereof.

Usually the compositions are adapted for oral administration. However, they may be adapted for other modes of administration, for example parenteral administration, sublingual or transdermal administration.

In a further aspect the invention also provides a process for preparing a pharmaceutical composition, suitably for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus in a mammal, such as a

human, which composition comprises an insulin sensitiser, such as Compound (I), and another antidiabetic agent, such as an alpha glucosidase inhibitor, a biguanide or an insulin secretagogue, and a pharmaceutically acceptable carrier therefor, which process comprises formulating the insulin sensitiser, the other antidiabetic agent and the pharmaceutically acceptable carrier so as to enable a modified release of at least one of the insulin sensitiser and the other antidiabetic agent.

In a further aspect, the invention provides a process for preparing a modified release pharmaceutical composition, suitably for the treatment of diabetes mellitus, especially Type 2 diabetes and conditions associated with diabetes mellitus in a mammal, such as a human, which composition comprises an insulin sensitiser, such as Compound (I) and another antidiabetic agent, such as an alpha glucosidase inhibitor, a biguanide or an insulin secretagogue and a pharmaceutically acceptable carrier therefor, which process comprises formulating the insulin sensitiser, the other antidiabetic agent and the pharmaceutically acceptable carrier so as to enable a modified release of at least one of the insulin sensitiser and the other antidiabetic agent.

The compositions are formulated to provide the modified release of active agents according to the appropriate methods required, for example those disclosed in Sustained and Controlled Release Drug Delivery Systems, Editor Joe R Robinson, Volume 7, published by Marcel Dekker under the title Drugs and the Pharmaceutical Sciences, Controlled Drug Delivery, 2nd Edition' edited by Joe Robinson and Vince Lee, Marcel Dekker, 1987 and 'Drug Delivery to the Gastrointestinal Tract' Editors: J G Hardy, S S. Davis and C G Wilson also with reference to texts such as the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Extra Pharmacopoeia (London, The Pharmaceutical Press) (for example see the 31st Edition page 341 and pages cited therein) and Harry's Cosmeticology (Leonard Hill Books).

Preferably, the compositions are in unit dosage form. Unit dosage presentation forms for oral administration may be in tablet or capsule form and may as necessary contain conventional excipients such as binding agents, fillers, lubricants, glidants, disintegrants and wetting agents.

Examples of binding agents include acacia, alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, dextrates, dextrin, dextrose, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium aluminium silicate, maltodextrin, methyl cellulose, polymethacrylates, polyvinylpyrrolidone, pregelatinised starch, sodium alginate, sorbitol, starch, syrup, tragacanth.

Examples of fillers include calcium carbonate, calcium phosphate, calcium sulphate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, compressible

sugar, confectioner's sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, dibasic calcium phosphate, fructose, glyceryl palmitostearate, glycine, hydrogenated vegetable oil-type 1, kaolin, lactose, maize starch, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, microcrystalline cellulose, polymethacrylates, potassium chloride, powdered cellulose, pregelatinised starch, sodium chloride, sorbitol, starch, sucrose, sugar spheres, talc, tribasic calcium phosphate, xylitol.

Examples of lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, microcrystalline cellulose, sodium benzoate, sodium chloride, sodium lauryl sulphate, stearic acid, sodium stearyl fumarate, talc, zinc stearate.

Examples of glidants include colloidal silicon dioxide, powdered cellulose, magnesium trisilicate, silicon dioxide, talc.

Examples of disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium, colloidal silicon dioxide, croscarmellose sodium, crospovidone, guar gum, magnesium aluminium silicate, microcrystalline cellulose, methyl cellulose, polyvinylpyrrolidone, polacrilin potassium, pregelatinised starch, sodium alginate, sodium lauryl sulphate, sodium starch glycollate.

An example of a pharmaceutically acceptable wetting agent is sodium lauryl sulphate.

As required the solid oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Compositions may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

No adverse toxicological effects are expected for the compositions of the invention in the above mentioned dosage ranges.

EXAMPLES COMPRISING AN INSULIN SENSITISER AND A BIGUANIDE

Example 1. Delayed Release Composition

Delayed release is achieved by coating single or bilayer tablets comprising 4mg or 8mg of Compound (I) as pure free base (pfb) and 500, preferably, or 1000 or 1500mg of metformin HCl with Eudragit L100-55, a gastric resistant polymer

The enteric coat consists of:

	%w/w
Eudragit L30 D-55 (30% aqueous dispersion)	76.8
Triethyl Citrate	7.7
Talc Alphafil 500	15.5

Example 2. Sustained release by use of a semi-permeable membrane

The semi-permeable membrane consists of:

	%w/w
Eudragit RS30D (30% aqueous dispersion)	90
Triethyl Citrate	1
Talc	9

This membrane is applied to a single or bilayer tablets each comprising 4mg or 8mg of Compound (I) and 500, preferably, or 1000 or 1500mg of metformin HCl

Example 3. Sustained Release by use of a non disintegrating matrix tablet

A matrix tablet is formed by tabletting the following mixture as:

(a) a single layer tablet:

	mg/tablet
Compound (I)	4 (pfb)
Metformin HCl	500
Eudragit L100-55	150
Lactose monohydrate	50
Eudragit RS powder to	1000

(b) a bilayer tablet to provide sustained release of Compound I and immediate (i.e non-modified) release of metformin HCl.

Layer A	mg/tablet
Compound (I)	4 (pfb)

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Eudragit L100-55	150
Lactose monohydrate	50
Eudragit RS powder to	500

Layer B	mg/tablet
Metformin HCl	500
Polyvinyl pyrollidone	15
Magnesium stearate to	520

Example 4. Sustained Release by use of a Mixed Eudragit matrix tablet

A matrix tablet is formed by tabletting the following mixture as:

(a) a single layer tablet:

	mg/tablet
Compound (I)	4 (pfb)
Metformin HCl	500
Eudragit L100-55	74
Eudragit RS powder	18.5
Colloidal Silicon dioxide	2.6
Magnesium stearate	3.25
Lactose monohydrate to	650

(b) a trilayer tablet:

Layer A	mg/tablet
Compound (I)	4 (pfb)
Eudragit L100-55	74
Eudragit RS powder	18.5
Colloidal Silicon dioxide	0.6
Magnesium stearate	1.5
Lactose monohydrate to	150

Layer B	mg/tablet
Metformin HCl	250
Eudragit L100-55	74
Eudragit RS powder to	345

Layer C	mg/tablet
Metformin HCl	250
Polyvinyl pyrrolidone	7.5
Magnesium stearate to	260

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Example 5. Sustained Release by use of a disintegrating matrix tablet

A matrix tablet is formed by tabletting the following mixture as a single layer tablet:

	mg/tablet
Compound (I)	4 (pfb)
Metformin HCl	500
Eudragit L100-55	74
Methocel K4M	18.5
Colloidal Silicon dioxide	2.6
Magnesium stearate	3.25
Lactose monohydrate to	650

Example 6. Sustained Release by use of a Mixed Carbopol matrix tablet

A matrix tablet is formed by tabletting the following mixture as single or bilayer tablet:

	mg/tablet
Compound (I)	4 (pfb)
Metformin HCl	500
Anhydrous dibasic calcium phosphate	35.7
Carbopol 971P	22.5
Carbopol 974P	7.5
Talc	0.75
Lactose monohydrate to	650

Example 7. Delayed Release Composition

A capsule containing multiple pellet cores is formed using the following mixture:

	mg/capsule
Compound (I)	4 (pfb)
Metformin HCl	500
Microcrystalline cellulose to	650

Delayed release can be achieved by coating the pellet cores with Eudragit L100-55, a gastric resistant polymer as in example 1.

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EXAMPLES COMPRISING AN INSULIN SENSITISER AND AN INSULIN SECRETAGOGUE

Example 1. Delayed Release Composition

Delayed release can be achieved by coating single or bilayer tablets comprising 4mg or 8mg of Compound (I) as pure free base (pfb) and 2.5, 10 or 20 mg of glibenclamide with Eudragit L100-55, a gastric resistant polymer

The enteric coat consists of:

	%w/w
Eudragit L30 D-55 (30% aqueous dispersion)	76.8
Triethyl Citrate	7.7
Talc Alphafil 500	15.5

Example 2. Sustained Release by use of a matrix tablet (single layer)

A matrix tablet is formed by tabletting the following mixture as a single layer tablet:

	mg/tablet
Compound (I)	8 (pfb)
glibenclamide	10
Eudragit L100-55	150
Lactose monohydrate	50
Eudragit RS powder to	500

Example 3. Sustained Release and Non-modifie Release by use of a matrix tablet (bilayer)

A matrix tablet is formed by tabletting the following mixture as a bilayer tablet to provide sustained release of Compound I and immediate (i.e non-modified) release of glibenclamide :

Layer A	mg/tablet
Compound (I)	8 (pfb)
Eudragit L100-55	150
Lactose monohydrate	50
Eudragit RS powder to:	500

Layer B	mg/tablet
Glibenclamide	10
Polyvinylpyrrolidone	12.5
Sodium starch glycolate	10

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Lactose monhydrate to	250

Example 4. Sustained release by use of a semi-permeable membrane

The semi-permeable membrane consists of:

	%w/w
Eudragit RS30D (30% aqueous dispersion)	90
Triethyl Citrate	1
Talc	9

This membrane is applied to a single or multi layer tablet each comprising 4mg or 8mg Compound (I) (pfb) and 2.5, 10 (preferably) or 20mg Glibenclamide.

Example 5. Sustained Release by use of a Mixed Eudragit matrix tablet

A matrix tablet is formed by tabletting the following mixture as:

(a) a single layer tablet:

	mg/tablet
Compound (I)	8 (pfb)
Glibenclamide	10
Eudragit L100-55	74
Eudragit RS powder	18.5
Colloidal Silicon dioxide	0.6
Magnesium stearate	1.5
Lactose monohydrate to	150

(b) a bilayer tablet:

Layer A	mg/tablet
Compound (I)	8 (pfb)
Eudragit L100-55	74
Eudragit RS powder	18.5
Colloidal Silicon dioxide	0.6
Magnesium stearate	1.5
Lactose monohydrate to	150

Layer B	mg/tablet
Glibenclamide	10
Eudragit L100-55	74
Eudragit RS powder	18.5

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Colloidal Silicon dioxide	0.6
Magnesium stearate	1.5
Lactose monohydrate to	150

Example 6. Sustained Release by use of a Mixed Carbopol matrix tablet

A matrix tablet is formed by tabletting the following mixture as single or bilayer tablet:

	mg/tablet
Compound (I)	8 (pfb)
Glibenclamide	10
Anhydrous dibasic calcium phosphate	35.7
Carbopol 971P	22.5
Carbopol 974P	7.5
Talc	0.75
Lactose monohydrate to	150

Example 7. Delayed Release Composition

A capsule containing multiple pellet cores is formed using the following mixture:

	mg/capsule
Compound (I)	8 (pfb)
Glibenclamide	10
Microcrystalline cellulose	133.5
Lactose monohydrate to	267

Delayed release can be achieved by coating the pellet cores with Eudragit L100-55, a gastric resistant polymer as in example 1.

EXAMPLES COMPRISING AN INSULIN SENSITISER AND AN ALPHA GLUCOSIDASE INHIBITOR.

Example 1. Delayed Release Composition

Delayed release can be achieved by coating single or bilayer tablets comprising 4mg or 8mg of Compound (I) as pure free base (pfb) and 100mg acarbose with Eudragit L100-55, a gastric resistant polymer

The enteric coat consists of:

	%w/w
Eudragit L30 D-55 (30% aqueous dispersion)	76.8
Triethyl Citrate	7.7
Talc Alphafil 500	15.5

Example 2. Sustained Release by use of a matrix tablet

A matrix tablet is formed by tabletting the following mixture as:

(a) a single layer tablet:

	mg/tablet
Compound (I)	8 (pfb)
Acarbose	100
Eudragit L100-55	150
Lactose monohydrate	50
Eudragit RS powder to	600

(b) a bilayer tablet to provide sustained release of Compound (I) and non modified (i.e immediate) release of acarbose :

Layer A	mg/tablet
Compound (I)	8 (pfb)
Eudragit L100-55	150
Lactose monohydrate	50
Eudragit RS powder to	500

Layer B	mg/tablet
Acarbose	100
Microcrystalline cellulose	134
Starch	12.5
Colloidal silicon dioxide	1.25
Magnesium stearate to	250

Example 3. Sustained release by use of a semi-permeable membrane

The semi-permeable membrane consists of:

	%w/w
Eudragit RS30D (30% aqueous dispersion)	90
Triethyl Citrate	1
Talc	9

This membrane is applied to a single or multi layer tablets each comprising 4mg or 8mg Compound (I) (pfb) and 100mg Acarbose

Example 4. Sustained Release by use of a Mixed Eudragit matrix tablet

A matrix tablet is formed by tabletting the following mixture as:

(a) a single layer tablet:

	mg/tablet
Compound (I)	8 (pfb)
Acarbose	100
Eudragit L100-55	74
Eudragit RS powder	18.5
Colloidal Silicon dioxide	1
Magnesium stearate	2.5
Lactose monohydrate to	250

(b) a bilayer tablet:

Layer A	mg/tablet
Compound (I)	8 (pfb)
Eudragit L100-55	74
Eudragit RS powder	18.5
Colloidal Silicon dioxide	0.6
Magnesium stearate	1.5
Lactose monohydrate to	150

Layer B	mg/tablet
Acarbose	100
Eudragit L100-55	74
Eudragit RS powder	18.5
Colloidal Silicon dioxide	0.6
Magnesium stearate	1.5
Lactose monohydrate to	250

Example 5. Sustained Release by use of a Disintegrating matrix tablet

A matrix tablet is formed by tabletting the following mixture as a single layer tablet:

	mg/tablet
Compound (I)	8 (pfb)
Acarbose	100
Eudragit L100-55	74
Methocel K4M	18.5

Colloidal Silicon dioxide	1
Magnesium stearate	2.5
Lactose monohydrate to	250

Example 6. Sustained Release by use of a Mixed Carbopol matrix tablet

A matrix tablet is formed by tabletting the following mixture as a single or bilayer tablet:

	mg/tablet
Compound (I)	8 (pfb)
Acarbose	100
Anhydrous dibasic calcium phosphate	35.7
Carbopol 971P	22.5
Carbopol 974P	7.5
Talc	0.75
Lactose monohydrate to	250

Example 7. Delayed Release Composition

A capsule containing multiple pellet cores is formed using the following mixture:

	mg/capsule
Compound (I)	8 (pfb)
Acarbose	100
Microcrystalline cellulose	133.5
Lactose monohydrate to	267

Delayed release can be achieved by coating the pellet cores with Eudragit L100-55, a gastric resistant polymer as in example 1.

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Claims:

1. A pharmaceutical composition, which composition comprises: an insulin sensitiser and another antidiabetic agent and a pharmaceutically acceptable carrier therefor, wherein the composition is arranged to provide a modified release of at least one of the insulin sensitiser and the other antidiabetic agent.

2. A modified release pharmaceutical composition, which composition comprises: an insulin sensitiser, such as Compound (I), and another antidiabetic agent and a pharmaceutically acceptable carrier therefor, wherein the carrier is arranged to provide a modified release of at least one of the insulin sensitiser and the other antidiabetes agent.

3. A composition according to claim 1 or claim 2, wherein the release of both the insulin sensitiser and the other antidiabetes agent is modified.

4. A composition according to any one of claims 1 to 3, wherein the modified release is a delayed release.

5. A composition according to claim 4, wherein the composition is in the form of an enteric tablet formulation.

6. A composition according to claim 5, wherein the enteric coated tablet is a single layer tablet.

7. A composition according to claim 7, wherein the enteric coated tablet is a multi-layer tablet.

8. A composition according to any one of claims 5 to 7, wherein the tablet is coated with a gastric resistant polymer.

9. A composition according to claim 8, wherein the gastric resistant polymer is selected from the list consisting of Eudragit L100-55, methacrylates, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phtahlate, in particular, Aquateric, Sureteric and HPMCP-HP-55S.

10. A composition according to any one of claims 1 to 3, wherein the modified release is a sustained release.

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11. A composition according to any one of claims 1 to 3, wherein the sustained release is provided by a sustained release matrix selected from disintegrating, non-disintegrating and eroding matrices.

13. A composition according to claim 11, wherein the non disintegrating matrix tablet formulation is provided by incorporating Eudragit RS, methacrylates, cellulose acetates, hydroxypropyl methylcellulose phthalate, Carbopol 971P or HPMCP-HP-55S into the matrix.

14. A composition according to claim 11, wherein the disintegrating matrix tablet formulation is provided by incorporating methacrylates, methylcellulose and Methocel K4M into the matrix.

15. A composition according to any one of claims 1 to 14, wherein the insulin sensitiser is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (pioglitazone) or (+) -5-[[4-[(3,4-dihydro-6-hydroxy-2, 5, 7, 8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione (troglitazone); or a derivative thereof.

16. A composition according to any one of claims 1 to 15, wherein the alpha glucosidase inhibitor is acarbose, emiglitate, miglitol or voglibose.

17. A composition according to any one of claims 1 to 15, wherein the biguanide is metformin, buformin or phenformin.

18. A composition according to any one of claims 1 to 15, wherein the insulin secretagogues is a sulphonylurea selected from glibenclamide, glipizide, gliclazide, glimepiride, tolazamide, tolbutamide, acetohexamide, carbutamide, chlorpropamide, glibornuride, gliquidone, glisentide, glisolamide, glisoxepide, glyclopyamide and glycylamide, glipentide.

19. A composition according to any one of claims 1 to 15, wherein the insulin secretagogue is repaglinide or nateglinide.

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ANEXO 3

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(54) Title: CONTROLLED RELEASE ORAL TABLET HAVING A UNITARY CORE

(57) Abstract

A controlled release antihyperglycemic tablet that does not contain an expanding polymer and comprising a core containing the antihyperglycemic drug, a semipermeable membrane coating the core and at least one passageway in the membrane.

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CONTROLLED RELEASE ORAL TABLET HAVING A UNITARY CORE

BACKGROUND OF THE INVENTION:

The present invention relates to controlled release unit dose formulations containing an antihyperglycemic drug. More specifically, the present invention relates to an oral dosage form comprising a biguanide such as metformin or buformin or a pharmaceutically acceptable salt thereof such as metformin hydrochloride or the metformin salts described in United States Patent Nos. 3,957,853 and 4,080,472 which are incorporated herein by reference.

In the prior art, many techniques have been used to provide controlled and extended-release pharmaceutical dosage forms in order to maintain therapeutic serum levels of medicaments and to minimize the effects of missed doses of drugs caused by a lack of patient compliance.

In the prior art are extended release tablets which have an osmotically active drug core surrounded by a semipermeable membrane. These tablets function by allowing a fluid such as gastric or intestinal fluid to permeate the coating membrane and dissolve the active ingredient so it can be released through a passageway in the coating membrane or if the active ingredient is insoluble in the permeating fluid, pushed through the passageway by an expanding agent such as a hydrogel. Some representative examples of these osmotic tablet systems can be found in United States Patent Nos. 3,845,770, 3,916,899, 4,034,758, 4,077,407 and 4,783,337. United States Patent No. 3,952,741 teaches an osmotic device wherein the active agent is released from a core surrounded by a semipermeable membrane only after sufficient pressure has developed within the membrane to burst or rupture the membrane at a weak portion of the membrane.

The basic osmotic device described in the above cited patents have been refined over time in an effort to provide greater control of the release of the active ingredient. For example United States Patent Nos. 4,777,049 and 4,851,229 describe an osmotic dosage form comprising a

semipermeable wall surrounding a core. The core contains an active ingredient and a modulating agent wherein the modulating agent causes the active ingredient to be released through a passageway in the semipermeable membrane in a pulsed manner. Further refinements have included modifications to the semipermeable membrane surrounding the active core such as varying the proportions of the components that form the membrane, i.e United States Patent Nos. 5,178,867, 4,587,117 and 4,522,625 or increasing the number of coatings surrounding the active core, i.e 5,650,170 and 4,892,739.

Although vast amounts of research has been performed on controlled or sustained release compositions and in particular on osmotic dosage forms, very little research has been performed in the area of controlled or sustained release compositions that employ antihyperglycemic drugs.

The limited work on controlled or sustained release formulations that employ antihyperglycemic drugs such as metformin hydrochloride has been limited to the combination of the antihyperglycemic drug and an expanding or gelling agent to control the release of the drug from the dosage form. This limited research is exemplified by the teachings of WO 96/08243 and by the GLUCOPHAGE® product which is a commercially available product from Bristol-Myers Squibb Co. containing metformin HCl.

It is reported in the 50th Edition of the Physicians' Desk Reference, copyright 1996, p. 753, that food decreases the extent and slightly delays the absorption of metformin delivered by the GLUCOPHAGE® dosage form. This decrease is shown by approximately a 40% lower peak concentration and a 25% lower AUC in plasma and a 35 minute prolongation of time to peak plasma concentration following administration of a single GLUCOPHAGE® tablet containing 850 mg of metformin HCl with food compared to the similar tablet administered under fasting conditions.

It is an object of the present invention to provide a controlled or sustained release formulation for an

antihyperglycemic drug wherein the bioavailability of the drug is not decreased by the presence of food.

It is a further object of the present invention to provide a controlled or sustained release formulation for an antihyperglycemic drug that does not employ an expanding polymer.

It is also a further object of the present invention to provide a controlled or sustained release formulation for an antihyperglycemic drug that can provide continuous and non-pulsating therapeutic levels of an antihyperglycemic drug to an animal or human in need of such treatment over a twelve hour to twenty-four hour period.

It is an additional object of the present invention to provide a controlled or sustained release formulation for an antihyperglycemic drug that obtains peak plasma levels approximately 8-12 hours after administration.

It is also an object of this invention to provide a controlled or sustained release pharmaceutical tablet having only a homogeneous osmotic core wherein the osmotic core component may be made using ordinary tablet compression techniques.

SUMMARY OF THE INVENTION

The foregoing objectives are met by a controlled release dosage form comprising:

(a) a core comprising:
  (i) an antihyperglycemic drug;
  (ii) optionally a binding agent; and
  (iii) optionally an absorption enhancer;
(b) a semipermeable membrane coating surrounding the core; and
(c) at least one passageway in the semipermeable membrane.

The dosage form of the present invention can provide therapeutic levels of the antihyperglycemic drug for twelve to twenty-four hour periods and does not exhibit a decrease in bioavailability if taken with food. In fact, a slight

increase in the bioavailability of the antihypoglycemic drug is observed when the controlled release dosage form of the present invention is administered with food. In a preferred embodiment, the dosage form will be administered once a day, ideally with or after a meal and most preferably with or after the evening meal, and provide therapeutic levels of the drug throughout the day with peak plasma levels being obtained between 8-12 hours after administration.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph which depicts the dissolution profile in simulated intestinal fluid (pH 7.5 phosphate buffer) and simulated gastric fluid (SGF) of the formulation described in Example 1 as tested according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm.

FIG. 2 is a graph which depicts the dissolution profile in simulated intestinal fluid (pH 7.5 phosphate buffer) and simulated gastric fluid (SGF) of the formulation described in Example 2 as tested according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm.

FIG. 3 is a graph which depicts the dissolution profile in simulated intestinal fluid (pH 7.5 phosphate buffer) and simulated gastric fluid (SGF) of the formulation described in Example 3 as tested according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm.

FIG. 4 is a graph depicting the in vivo metformin plasma profile of the formulation described in Example 1 and the in vivo metformin plasma profile of the commercially available metformin HCl product GLUCOPHAGE® under fasting conditions.

FIG. 5 is a graph depicting the in vivo metformin plasma profile of the formulation described in Example 2 and the in vivo metformin plasma profile of the

commercially available metformin HCl product GLUCOPHAGE® under fasting conditions.

FIG. 6 is a graph depicting the in vivo metformin plasma profile of the formulation described in Example 2 and the in vivo metformin plasma profile of the commercially available metformin HCl product GLUCOPHAGE® under fed conditions.

FIG. 7 is a graph depicting the in vivo metformin plasma profile of the formulation described in Example 3 and the in vivo metformin plasma profile of the commercially available metformin HCl product GLUCOPHAGE® under fed conditions (after breakfast).

FIG. 8 is a graph depicting the in vivo metformin plasma profile of the formulation described in Example 3 and the in vivo metformin plasma profile of the commercially available metformin HCl product GLUCOPHAGE® under fed conditions (after dinner).

DETAILED DESCRIPTION OF THE INVENTION

The term antihyperglycemic drugs as used in this specification refers to drugs that are useful in controlling or managing noninsulin-dependent diabetes mellitus (NIDDM). Preferably, the antihyperglycemic drug is a biguanide such as metformin or buformin or a pharmaceutically acceptable salt thereof such as metformin hydrochloride.

The binding agent may be any conventionally known pharmaceutically acceptable binder such as polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellulose, ethylcellulose, polymethacrylate, waxes and the like. Mixtures of the aforementioned binding agents may also be used. The preferred binding agents are water soluble such as polyvinyl pyrrolidone having a weight average molecular weight of 25,000 to 3,000,000. The binding agent comprises approximately about 0 to about 40% of the total weight of the core and preferably about 3% to about 15% of the total weight of the core.

The core may optionally comprise an absorption enhancer. The absorption enhancer can be any type of absorption enhancer commonly known in the art such as a fatty acid, a surfactant, a chelating agent, a bile salt or mixtures thereof. Examples of some preferred absorption enhancers are fatty acids such as capric acid, oleic acid and their monoglycerides, surfactants such as sodium lauryl sulfate, sodium taurocholate and polysorbate 80, chelating agents such as citric acid, phytic acid, ethylenediamine tetraacetic acid (EDTA) and ethylene glycol-bis(ß-aminoethyl ether)-N,N,N,N-tetraacetic acid (EGTA). The core comprises approximately 0 to about 20% of the absorption enhancer based on the total weight of the core and most preferably about 2% to about 10% of the total weight of the core.

The core of the present invention which comprises the antihyperglycemic drug, the binder which preferably is a pharmaceutically acceptable water soluble polymer and the absorption enhancer is preferably formed by wet granulating the core ingredients and compressing the granules with the addition of a lubricant into a tablet on a rotary press. The core may also be formed by dry granulating the core ingredients and compressing the granules with the addition of a lubricant into tablets or by direct compression.

Other commonly known excipients may also be included into the core such as lubricants, pigments or dyes.

The homogeneous core is coated with a semipermeable membrane, preferably a modified polymeric membrane to form the controlled release tablet of the invention. The semipermeable membrane is permeable to the passage of an external fluid such as water and biological fluids and is impermeable to the passage of the antihyperglycemic drug in the core. Materials that are useful in forming the semipermeable membrane are cellulose esters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose

diacetate, cellulose triacetate, cellulose acetate propionate, and cellulose acetate butyrate. Other suitable polymers are described in United States Patent Nos. 3,845,770, 3,916,899, 4,008,719, 4,036,228 and 4,11210 which are incorporated herein by reference. The most preferred semipermeable membrane material is cellulose acetate comprising an acetyl content of 39.3 to 40.3%, commercially available from Eastman Fine Chemicals.

In an alternative embodiment, the semipermeable membrane can be formed from the above-described polymers and a flux enhancing agent. The flux enhancing agent increases the volume of fluid imbibed into the core to enable the dosage form to dispense substantially all of the antihyperglycemic drug through the passageway and/or the porous membrane. The flux enhancing agent can be a water soluble material or an enteric material. Some examples of the preferred materials that are useful as flux enhancers are sodium chloride, potassium chloride, sucrose, sorbitol, mannitol, polyethylene glycol (PEG), propylene glycol, hydroxypropyl cellulose, hydroxypropyl methycellulose, hydroxypropyl methycellulose phthalate, cellulose acetate phthalate, polyvinyl alcohols, methacrylic acid copolymers and mixtures thereof. The preferred flux enhancer is PEG 400.

The flux enhancer may also be a drug that is water soluble such as metformin or its pharmaceutically acceptable salts or a drug that is soluble under intestinal conditions. If the flux enhancer is a drug, the present dosage form has the added advantage of providing an immediate release of the drug which is selected as the flux enhancer.

The flux enhancing agent comprises approximately 0 to about 40% of the total weight of the coating, most preferably about 2% to about 20% of the total weight of the coating. The flux enhancing agent dissolves or leaches from the semipermeable membrane to form paths in the

semipermeable membrane for the fluid to enter the core and dissolve the active ingredient.

The semipermeable membrane may also be formed with commonly known excipients such a plasticizer. Some commonly known plasticizers include adipate, azelate, enzoate, citrate, stearate, isoebucate, sebacate, triethyl citrate, tri-n-butyl citrate, acetyl tri-n-butyl citrate, citric acid esters, and those described in the Encyclopedia of Polymer Science and Technology, Vol. 10 (1969), published by John Wiley & Sons. The preferred plasticizers are triacetin, acetylated monoglyceride, grape seed oil, olive oil, sesame oil, acetyltributylcitrate, acetyltriethylcitrate, glycerin sorbitol, diethyloxalate, diethylmalate, diethylfumarate, dibutylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacate, triethylcitrate, tributylcitrate, glyceroltributyrate, and the like. Depending on the particular plasticizer, amounts of from 0 to about 25%, and preferably about 2% to about 15% of the plasticizer can be used based upon the total weight of the coating.

As used herein the term passageway includes an aperture, orifice, bore, hole, weaken area or an erodible element such as a gelatin plug that erodes to form an osmotic passageway for the release of the antihyperglycemic drug from the dosage form. A detailed description of the passageway can be found in United States Patents such as 3,845,770, 3,916,899, 4,034,758, 4,077,407, 4,783,337 and 5,071,607.

Generally, the membrane coating around the core will comprise from about 1% to about 5% and preferably about 2% to about 3% based on the total weight of the core and coating.

In an alternative embodiment, the dosage form of the present invention may also comprise an effective amount of the antihyperglycemic drug that is available for immediate release. The effective amount of antihyperglycemic drug for immediate release may be coated onto the semipermeable

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membrane of the dosage form or it may be incorporated into the semipermeable membrane.

In a preferred embodiment the dosage form will have the following composition:

	Preferred	Most Preferred
CORE:		
drug	50-98%	75-95%
binder	0-40%	3-15%
absorption enhancer	0-20%	2-10%
COATING:		
semipermeable polymer	50-99%	75-95%
flux enhancer	0-40%	2-20%
plasticizer	0-25%	2-15%

The dosage forms prepared according to the present invention should exhibit the following dissolution profile when tested in a USP type 2 apparatus at 75 rpms in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37°C:

	Preferred	Most Preferred
Time (hours)		
2	0-25%	0-15%
4	10-45%	20-40%
8	30-90%	45-90%
12	NTL 50%	NTL 60%
16	NTL 60%	NTL 70%
20	NTL 70%	NTL 80%

NTL = NOT LESS THAN

In the preparation of the tablets of the invention, various conventional well known solvents may be used to prepare the granules and apply the external coating to the tablets of the invention. In addition, various diluents, excipients, lubricants, dyes, pigments, dispersants etc. which are disclosed in Remington's Pharmaceutical Sciences, 1995 Edition may be used to optimize the formulations of the invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

EXAMPLE 1

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A controlled release tablet containing 850 mg of metformin HCl and having the following formula is prepared as follows:

I	Core	
	metformin HCl	90.54%
	povidone[1], USP	4.38%
	sodium tribasic phosphate	4.58%
	magnesium stearate	0.5 %

[1]approximate molecular weight = 50,000; dynamic viscosity (10%w/v solution at 20°C) = 5.5-8.5 m Pa s.

(a) Granulation

The metformin HCl is delumped by passing it through a 40 mesh screen and collecting it in a clean, polyethylene-lined container. The povidone, K-30, and sodium tribasic phosphate are dissolved in purified water. The delumped metformin HCl is then added to a top-spray fluidized bed granulator and granulated by spraying the binding solution of povidone and sodium tribasic phosphate under the following conditions: inlet air temperature of 50-70°C; atomization air pressure of 1-3 bars; and spray rate of 10-100 ml/min.

Once the binding solution is depleted, the granules are dried in the granulator until the loss on drying is less than 2%. The dried granules are passed through a Comil equipped with the equivalent of an 18 mesh screen.

(b) Tableting

The magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl granules for approximately five (5) minutes. After blending, the granules are compressed on a rotary press fitted with 15/32" round standard concave punches (plain lower punch, upper punch with an approximately 1 mm indentation pin).

(c) Seal Coating (optional)

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The core tablet is seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry Clear, in purified water. The Opadry solution is then sprayed onto the core tablet using a pan coater under the following conditions: exhaust air temperature of 38-42°C; atomization pressure of 28-40 psi; and spay rate of 10-15 ml/min. The core tablet is coated with the sealing solution until a theoretical coating level of approximately 2% is obtained.

II Sustained Release Coating	
cellulose acetate (398-10)[2]	85%
triacetin	5%
PEG 400	10%

[2]acetyl content 39.3 - 40.3%

(d) Sustained Release Coating

The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred until a clear solution is obtained. The clear coating solution is then sprayed onto the seal coated tablets in a fluidized bed coater employing the following conditions: product temperature of 16-22°C; atomization pressure of approximately 3 bars; and spray rate of 120-150 ml/min. The sealed core tablet is coated until a theoretical coating level of approximately 3% is obtained.

The resulting tablet is tested in simulated intestinal fluid (pH 7.5) and simulated gastric fluid (SGF) according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm and found to have the following release profile:

TIME (hours)	% Released (SGF)	% Released (pH 7.5)
2	9	12
4	27	32
8	62	82
12	82	100

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16	88	105
20	92	108

The release profile in pH 7.5 and SGF of the sustained release product prepared in this Example is shown in Figure 1.

Figure 4 depicts the in vivo metformin plasma profile of the sustained release product prepared in this Example. Also shown in Figure 4 is the in vivo metformin plasma profile of GLUCOPHAGE®, a commercially available pharmaceutical product containing the drug metformin HCl.

EXAMPLE 2

A controlled release tablet containing 850 mg of metformin HCl and having the following formula is prepared as follows:

I Core	
metformin HCl	88.555%
povidone[3], USP	6.368%
sodium lauryl sulfate	4.577%
magnesium stearate	0.5 %

[3]approximate molecular weight = 1,000,000, dynamic viscosity (10%w/v solution at 20°C) = 300-700 m Pa s.

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(a) **Granulation**

The metformin HCl and sodium lauryl sulfate are delumped by passing them through a 40 mesh screen and collecting them in a clean, polyethylene-lined container. The povidone, K-90F, is dissolved in purified water. The delumped metformin HCl and sodium lauryl sulfate are then added to a top-spray fluidized bed granulator and granulated by spraying with the binding solution of povidone under the following conditions: inlet air temperature of 50-70°C; atomization air pressure of 1-3 bars; and spray rate of 10-100 ml/min.

Once the binding solution is depleted, the granules are dried in the granulator until the loss on drying is less than 2%. The dried granules are passed through a Comil equipped with the equivalent of an 18 mesh screen.

(b) **Tableting**

The magnesium stearate is passed through a 40 mesh stainless steel screen and blended with the metformin HCl granules for approximately five (5) minutes. After blending, the coated granules are compressed on a rotary press fitted with 15/32" round standard concave punches (plain lower punch, upper punch with an approximately 1 mm indentation pin).

(c) **Seal Coating (optional)**

The core tablet is seal coated with an Opadry material or other suitable water-soluble material by first dissolving the Opadry material, preferably Opadry Clear in purified water. The Opadry solution is then sprayed onto the core tablet using a pan coater under the following conditions: exhaust air temperature of 38-42°C; atomization pressure of 28-40 psi; and spay rate of 10-15 ml/min. The core tablet is coated with the sealing solution until a theoretical coating level of approximately 2% is obtained.

II	Sustained Release Coating	
cellulose acetate (398-10)[4]		85%
triacetin		5%
PEG 400		10%

[4]acetyl content 39.3 - 40.3%

(d) Sustained Release Coating

The cellulose acetate is dissolved in acetone while stirring with a homogenizer. The polyethylene glycol 400 and triacetin are added to the cellulose acetate solution and stirred until a clear solution is obtained. The clear coating solution is then sprayed onto the seal coated tablets in a fluidized bed coater employing the following conditions: product temperature of 16-22°C; atomization pressure of approximately 3 bars; and spray rate of 120-150 ml/min. The sealed core tablet is coated until a theoretical coating level of approximately 3% is obtained.

The resulting tablet is tested in simulated intestinal fluid (pH 7.5) and simulated gastric fluid (SGF) according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm and found to have the following release profile:

TIME (hours)	% Released (SGF)	% Released (pH 7.5)
2	13	12
4	29	27
8	55	52
12	72	71
16	81	83
20	87	91

The release profile in pH 7.5 and SGF of the sustained release product prepared in this Example is shown in Figure 2.

Figure 5 depicts the in vivo metformin plasma profile of the sustained release product prepared in this Example under fasting conditions. Figure 5 also shows the in vivo metformin plasma profile of the GLUCOPHAGE® product under fasting conditions.

Figure 6 depicts the in vivo metformin plasma profile of the sustained release product prepared in this Example

under fed conditions. Figure 6 also shows the in vivo metformin plasma profile of the GLUCOPHAGE® product under fed conditions.

Figures 5 and 6 clearly show that the dosage forms prepared in accordance with the present invention exhibit consistent bioavailability under both fed and fasting conditions while the GLUOPHAGE® product's bioavailability decreases in the presence of food.

EXAMPLE 3

A controlled release tablet containing 850 mg of metformin HCl and having the same formula as in Example 2 is prepared as described in Example 2 except that an additional hole was drilled on the plain side of the coated tablet. The additional hole had a diameter of approximately 1 mm.

The resulting tablet is tested in simulated intestinal fluid (pH 7.5) and simulated gastric fluid (SGF) according to the procedure described in United States Pharmacopeia XXIII, Apparatus 2 @ 75 rpm and found to have the following release profile:

TIME (hours)	% Released (SGF)	% Released (pH 7.5)
2	13	14
4	27	28
8	50	63
12	67	84
16	84	95
20	97	102

The release profile in pH 7.5 and SGF of the sustained release product prepared in this Example is shown in Figure 3.

Figure 7 depicts the in vivo metformin plasma profile of the sustained release product prepared in this Example when administered shortly after breakfast. Figure 7 also shows the in vivo metformin plasma profile of the GLUCOPHAGE® product administered shortly after breakfast.

Figure 8 depicts the in vivo metformin plasma profile of the sustained release product prepared in this Example when administered shortly after dinner. Figure 8 also

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shows the in vivo metformin plasma profile of the GLUCOPHAGE® product administered shortly after dinner.

Table 1 is a summary of the bioavailability comparision data, test/reference ratio, shown in Figures 4-8 wherein the GLUCOPHAGE® product is the reference product in a two way crossover biostudy with n = 6.

TABLE 1

Formula	Figure	Study	AUC	Cmax	Tmax
Ex. 1	4	Fasting	0.202	0.12	2.15
Ex. 2	5	Fasting	0.369	0.214	1.73
Ex. 2	6	Fed (bkft)	0.628	0.305	1.94
Ex. 3	7	Fed (bkft)	0.797	0.528	1.82
Ex. 3	8	Fed (dinner)	0.850	0.751	2.00

bkft = breakfast

The results reported in Table 1 and Figures 4-8 show that dosage forms prepared in accordance with the present invention exhibit an increase in the bioavailability of the antihyperglycemic drug in the presence of food, especially when taken with or shortly after the evening meal.

While certain preferred and alternative embodiments of the invention have been set forth for purposes of disclosing the invention, modifications to the disclosed embodiments may occur to those who are skilled in the art. Accordingly, the appended claims are intended to cover all embodiments of the invention and modifications thereof which do not depart from the spirit and scope of the invention.

We claim:

1. A controlled release pharmaceutical tablet comprising:

(a) a core comprising:

(i) an antihyperglycemic drug;

(ii) optionally a binding agent; and

(iii) optionally an absorption enhancer; and

(b) a semipermeable membrane coating covering said core; and

(c) at least one passageway in the semipermeable membrane.

2. A controlled release pharmaceutical tablet as defined in claim 1 wherein the antihyperglycemic drug is a biguanide.

3. A controlled release pharmaceutical tablet as defined in claim 2 wherein the antihyperglycemic drug is metformin or a pharmaceutically acceptable salt thereof.

4. A controlled release pharmaceutical tablet as defined in claim 2 wherein the antihyperglycemic drug is buformin or a pharmaceutically acceptable salt thereof.

5. A controlled release pharmaceutical tablet as defined in claim 1 wherein the binding agent is water soluble.

6. A controlled release pharmaceutical tablet as defined in claim 1 wherein the water soluble binding agent is polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxyethyl cellulose, waxes or mixtures thereof.

7. A controlled release pharmaceutical tablet as defined in claim 6 wherein the water soluble binding agent is polyvinyl pyrrolidone.

8. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is selected from

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the group consisting of fatty acids, surfactants, chelating agents, bile salts or mixtures thereof.

9. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is a fatty acid selected from the group consisting of capric acid, oleic acid or their monoglycerides.

10. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is a surfactant selected from the group consisting of sodium lauryl sulfate, sodium taurocholate and polysorbate 80.

11. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is a chelating agent selected from the group consisting of citric acid, phytic acid, ethylene diamine tetraacetic acid and ethylene glycol-bis(ß-aminoethyl ether)-N,N,N,N-tetraacetic acid.

12. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is a bile salt.

13. A controlled release pharmaceutical tablet as defined in claim 1 wherein the absorption enhancer is sodium lauryl sulfate.

14. A controlled release pharmaceutical tablet as defined in claim 1 wherein the semipermeable membrane around the core is a water insoluble cellulose derivative.

15. A controlled release pharmaceutical tablet as defined in claim 14 wherein the water insoluble cellulose derivative in the membrane around the core is cellulose acetate.

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16. A controlled release pharmaceutical tablet as defined in claim 1 wherein semipermeable membrane comprises a flux enhancer.

17. A controlled release pharmaceutical tablet as defined in claim 16 wherein the flux enhancer is sodium chloride, potassium chloride, sucrose, sorbitol, mannitol, polyethylene glycol, propylene glycol, hydroxypropyl cellulose, hydroxypropyl methycellulose, hydroxypropyl methycellulose phthalate, cellulose acetate phthalate, polyvinyl alcohols, methacrylic acid copolymers or mixtures thereof.

18. A controlled release pharmaceutical tablet as defined in claim 17 wherein the flux enhancer is polyethylene glycol with an average molecular weight between 380 and 420.

19. A controlled release pharmaceutical tablet as defined in claim 1 wherein the semipermeable membrane comprises a plasticizer.

20. A controlled release pharmaceutical tablet as defined in claim 19 wherein the plasticizer is triacetin.

21. A controlled release pharmaceutical tablet as defined in claim 1 wherein at least two passageways are formed in the semipermeable membrane.

22. A controlled release pharmaceutical tablet as defined in claim 1 wherein the peak plasma level is obtained 8-12 hours after administration.

23. A controlled release pharmaceutical tablet as defined in claim 1 further comprising an effective amount of the antihyperglycemic drug coated onto the semipermeable membrane or mixed into the semipermeable membrane to

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provide an immediate release of an effective amount of the antihyperglycemic drug.

24. A controlled release pharmaceutical tablet as defined in claim 1 wherein the core comprises:

50-98% of the drug;

0-40% of the binding agent; and

0-20% of the absorption enhancer; and the coating comprises:

50-99% of the polymer;

0-40% of the flux enhancer; and

0-25% of the plasticizer.

25. A controlled release pharmaceutical tablet as defined in claim 1 wherein the core comprises:

75-95% of the drug;

3-15% of the binding agent; and

2-10% of the absorption enhancer; and the coating comprises:

75-95% of the polymer;

2-20% of the flux enhancer; and

2-15% of the plasticizer.

26. A controlled release pharmaceutical tablet as defined in claim 1 that exhibits the following dissolution profile when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37°C:

after 2 hours 0-25% of the drug is released;

after 4 hours 10-45% of the drug is released;

after 8 hours 30-90% of the drug is released;

after 12 hours not less than 50% of the drug is released;

after 16 hours not less than 60% of the drug is released; and after 20 hours not less than 70% of the drug is released.

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27. A controlled release pharmaceutical tablet as defined in claim 1 that exhibits the following dissolution profile when tested in a USP type 2 apparatus at 75 rpm in 900 ml of simulated intestinal fluid (pH 7.5 phosphate buffer) and at 37°C:
after 2 hours 0-15% of the drug is released;
after 4 hours 20-40% of the drug is released;
after 8 hours 45-90% of the drug is released;
after 12 hours not less than 60% of the drug is released;
after 16 hours not less than 70% of the drug is released; and after 20 hours not less than 80% of the drug is released.

28. A controlled release pharmaceutical tablet as defined in claim 1 that is administered with or shortly after the evening meal.

29. A controlled release antihyperglycemic tablet comprising:
(a) a core consisting essentially of:
(i) metformin or a pharmaceutically acceptable salt thereof;
(ii) a water soluble binding agent; and
(iii) an absorption enhancer; and
(b) a semipermeable membrane coating covering said core comprising:
(i) cellulose acetate;
(ii) a flux enhancer; and
(iii) a plasticizer; and
(c) at least one passageway in the semipermeable membrane.

30. A controlled release pharmaceutical tablet as defined in claim 29 wherein the peak plasma level is obtained 8-12 hours after administration.

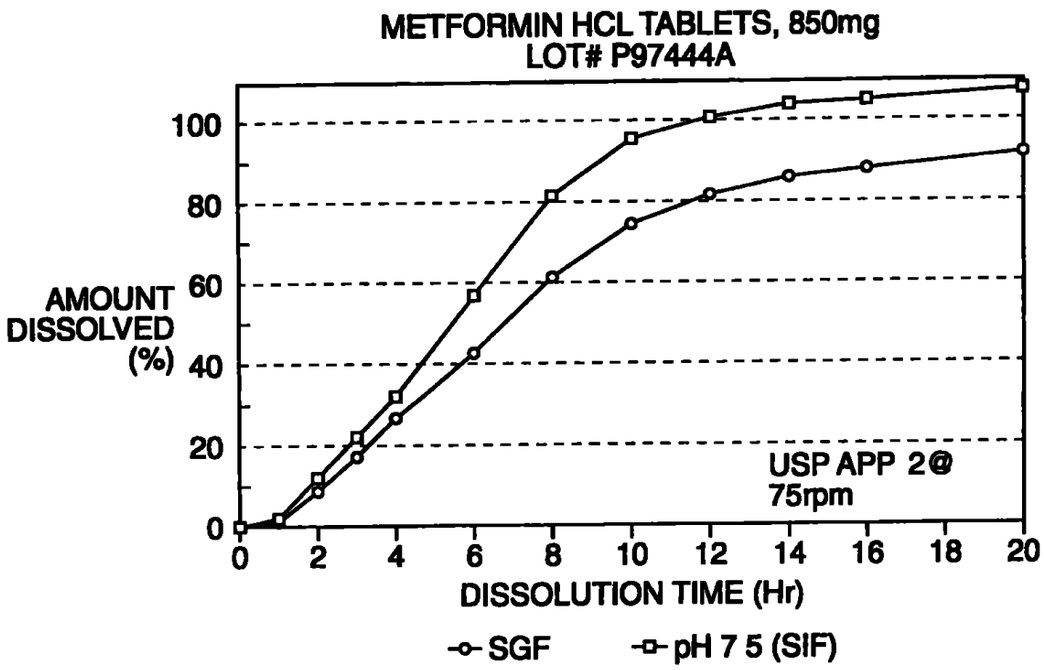
METFORMIN HCL TABLETS, 850mg
LOT# P97444A
AMOUNT DISSOLVED (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
18
20
USP APP 2@ 75rpm
DISSOLUTION TIME (Hr)
SGF
pH 7 5 (SIF)

FIG 1

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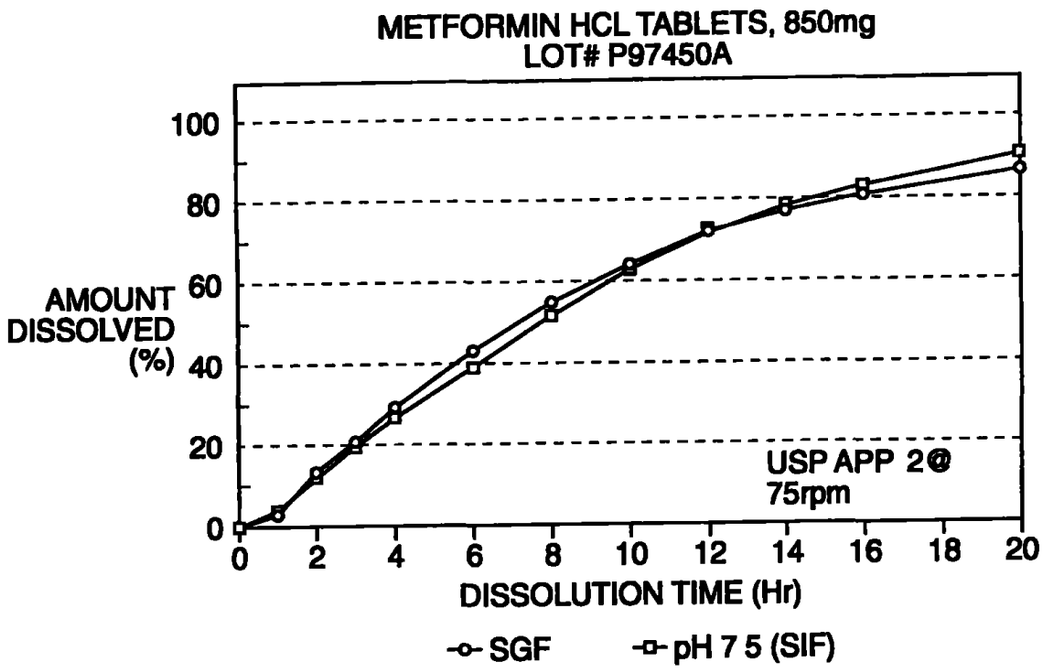
METFORMIN HCL TABLETS, 850mg
LOT# P97450A
AMOUNT DISSOLVED (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
18
20
DISSOLUTION TIME (Hr)
USP APP 2@ 75rpm
SGF
pH 7 5 (SIF)

FIG 2

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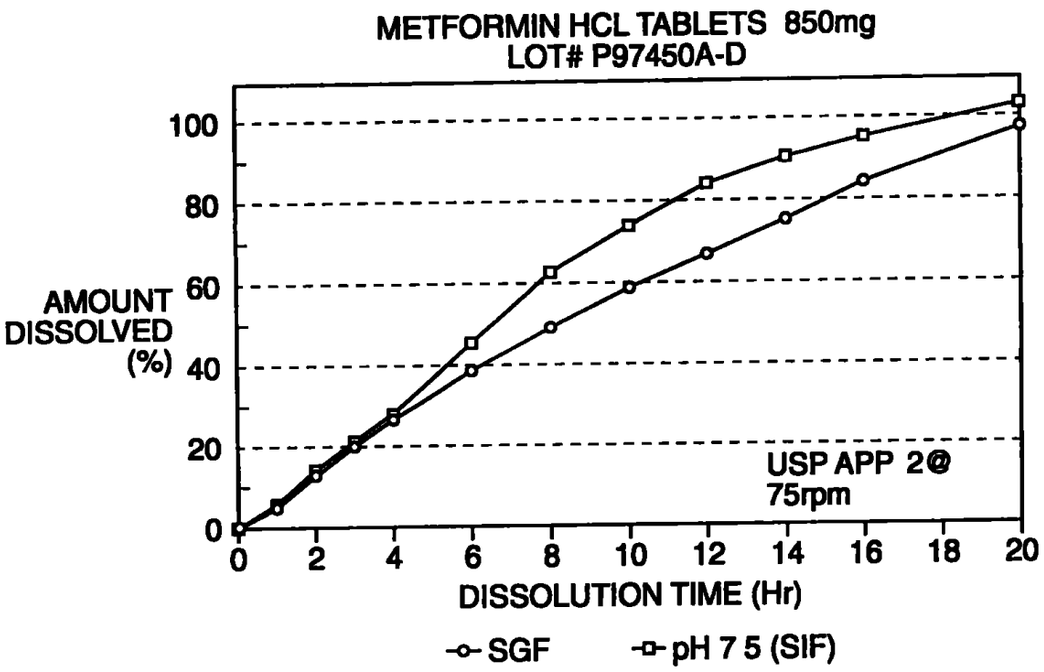
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LOT# P97450A-D
AMOUNT DISSOLVED (%)
100
80
60
40
20
0
0
2
4
6
8
10
12
14
16
18
20
DISSOLUTION TIME (Hr)
USP APP 2@
75rpm
SGF
pH 7 5 (SIF)

FIG 3

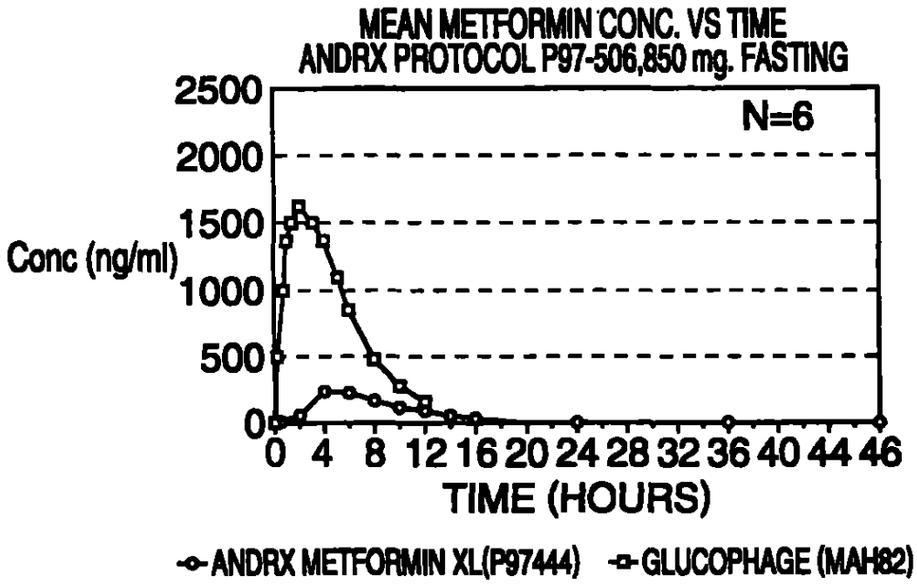
MEAN METFORMIN CONC. VS TIME
ANDRX PROTOCOL P97-506,850 mg. FASTING
N=6
Conc (ng/ml)
2500
2000
1500
1000
500
0
0 4 8 12 16 20 24 28 32 36 40 44 46
TIME (HOURS)
ANDRX METFORMIN XL(P97444)
GLUCOPHAGE (MAH82)

FIG. 4

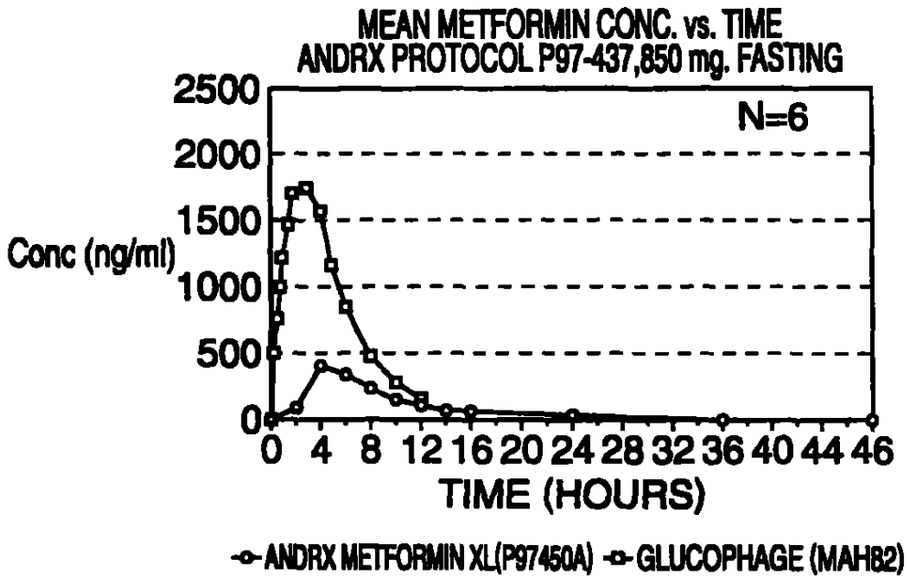
MEAN METFORMIN CONC. vs. TIME
ANDRX PROTOCOL P97-437,850 mg. FASTING
N=6
Conc (ng/ml)
2500
2000
1500
1000
500
0
0 4 8 12 16 20 24 28 32 36 40 44 46
TIME (HOURS)
ANDRX METFORMIN XL(P97450A)
GLUCOPHAGE (MAH82)

FIG. 5

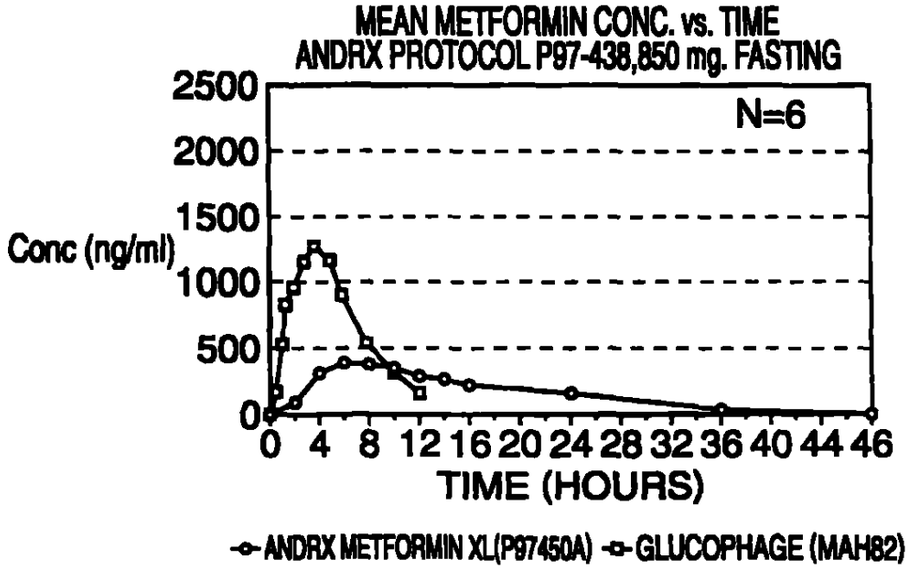
MEAN METFORMIN CONC. vs. TIME
ANDRX PROTOCOL P97-438,850 mg. FASTING
N=6
Conc (ng/ml)
2500
2000
1500
1000
500
0
0 4 8 12 16 20 24 28 32 36 40 44 46
TIME (HOURS)
ANDRX METFORMIN XL(P97450A)
GLUCOPHAGE (MAH82)

FIG. 6

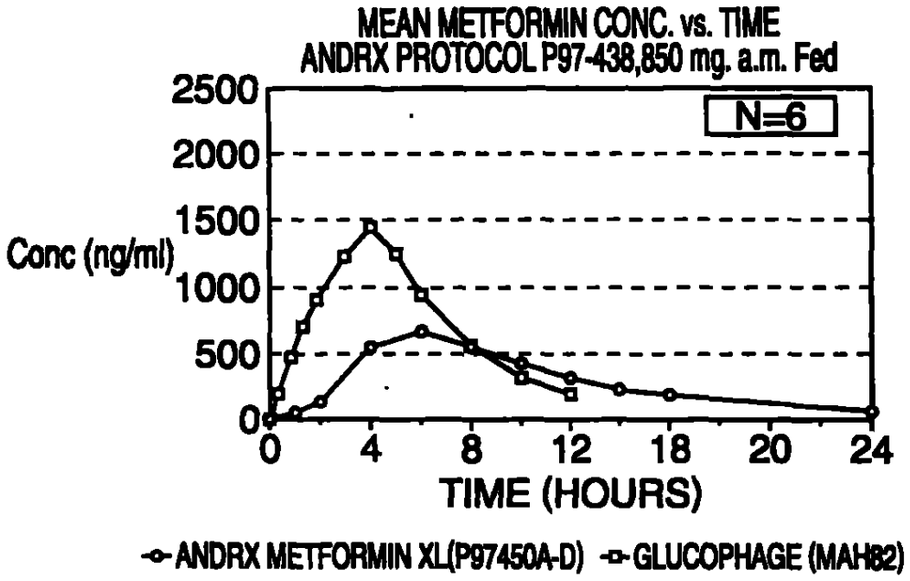
MEAN METFORMIN CONC. vs. TIME
ANDRX PROTOCOL P97-438,850 mg. a.m. Fed
N=6
Conc (ng/ml)
2500
2000
1500
1000
500
0
0
4
8
12
18
20
24
TIME (HOURS)
ANDRX METFORMIN XL(P97450A-D)
GLUCOPHAGE (MAH82)

FIG. 7

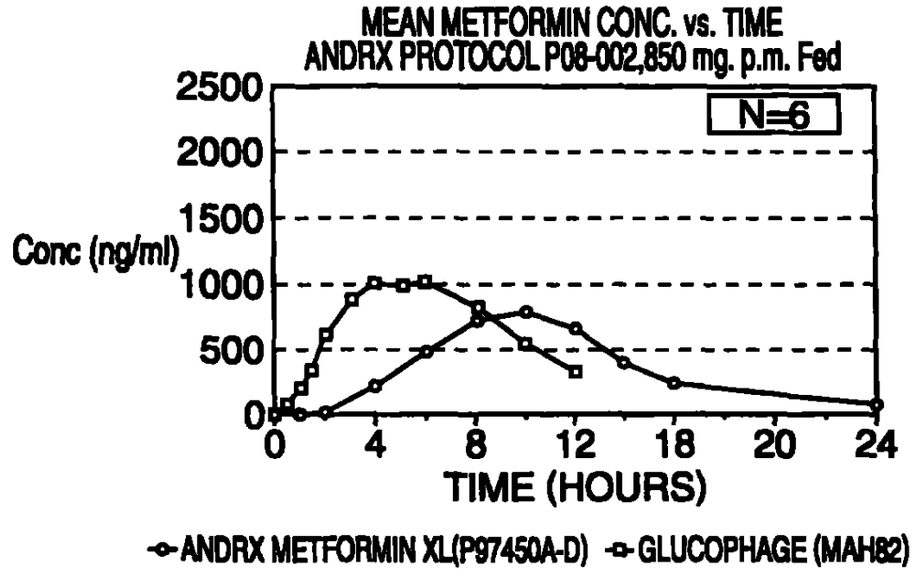
MEAN METFORMIN CONC. vs. TIME
ANDRX PROTOCOL P08-002,850 mg. p.m. Fed
N=6
Conc (ng/ml)
2500
2000
1500
1000
500
0
0
4
8
12
18
20
24
TIME (HOURS)
ANDRX METFORMIN XL(P97450A-D)
GLUCOPHAGE (MAH82)

FIG. 8

ANEXO 4

US005955106A

United States Patent [19]

Moeckel et al.

[11] Patent Number: 5,955,106

[45] Date of Patent: Sep. 21, 1999

[54] **PHARMACEUTICAL PREPARATION CONTAINING METFORMIN AND A PROCESS FOR PRODUCING IT**

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§ 371 Date: **Mar. 14, 1997**

§ 102(e) Date: **Mar. 14, 1997**

[87] PCT Pub. No.: **WO96/08243**

PCT Pub. Date: **Mar. 21, 1996**

[30] **Foreign Application Priority Data**

Sep. 14, 1994 [DE] Germany 44 32 757

[51] **Int. Cl.**[6] **A61K 9/20**

[52] **U.S. Cl.** **424/464**; 424/489; 424/461; 424/480; 424/451

[58] **Field of Search** 424/464, 482, 424/466, 480, 489

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,834,985	5/1989	Elger et al.	424/488
5,055,306	10/1991	Barry et al.	424/482

Primary Examiner—Thurman K. Page
Assistant Examiner—William E. Benston, Jr.

[57] **ABSTRACT**

The present invention concerns pharmaceutical compositions containing metformin as an active substance and a hydrocolloid-forming agent as a retardant and optionally standard pharmaceutical auxiliary substances, the residual moisture content in the pharmaceutical composition being 0.5–3% by weight. The invention also concerns a process for producing pharmaceutical compositions containing metformin as an active substance and a hydrocolloid-forming agent as a retardant and optionally standard pharmaceutical auxiliary substances characterized in that the active substance and retarding agent or a portion thereof are granulated with an aqueous solvent which can optionally contain a binder and where appropriate the other portion of the retardant or other standard pharmaceutical auxiliaries are admixed with the granulate which is then dried until the residual moisture content is reduced to 0.5–3% by weight.

19 Claims, No Drawings

PHARMACEUTICAL PREPARATION CONTAINING METFORMIN AND A PROCESS FOR PRODUCING IT

The invention concerns pharmaceutical preparations containing metformin hydrochloride (also called metformin in the following) as an active substance and a hydrocolloid-forming agent as a retardant and a process for their production.

It is known that metformin hydrochloride is a biguanide derivative (1,1-dimethylbiguanide monohydrochloride) which has an oral antidiabetic action. Metformin delayed release tablets containing 850 mg metformin hydrochloride per film tablet (Glucophage® retard) are on the market. Since metformin in contrast to other active substances cannot be pressed in its pure form (the mass disintegrates in an unchanged form after the compression) framework-forming auxiliary substances such as polyvinylacetate were used in these high-dose delayed release tablets as a retarding agent (Lipha, technical information Glucophage® August 1991, "Bundesverband der Pharmazeutischen Industrie e.V.", publ. Rote Liste 1993, Edition Cantor, Aulendorf 1993). The mechanism of action of such framework tablets is based on the fact that the readily water-soluble metformin diffuses out of the tablet independently of pH in the gastrointestinal tract whereas the tablet framework with the coating is excreted largely unchanged.

The disadvantage of using such framework-forming auxiliary substances such as polyvinylacetate is, however, that they have to be processed with organic solvents in particular during the granulation process, the organic solvent having to be removed again as completely as possible before the granulate is processed further to compressed pharmaceutical forms of administration and for example pressed into tablets.

The object of the invention was to provide an improved pharmaceutical composition for the active substance metformin. In particular the form of administration should contain the active substance metformin with a highest possible content of active substance and a retardant, the retardant causing a controlled release of the active substance. In particular the new pharmaceutical composition should not contain framework formers which have to be processed with organic solvents but should be composed on the basis of substances that can be processed aqueously. These pharmaceutical compositions should be readily or easily compressible so that they are suitable for the manufacture of solid pharmaceutical forms of administration such as e.g. tablets, dragées or comprimates for filling into capsules. In the case of the manufacture of tablets or other comprimates the maximum total weight should be about 1200–1300 mg in order not to jeopardize the therapeutic safety (patient compliance) since larger oral forms of administration are often not taken in the prescribed regularity.

Another object in the processing of the granulate for these high-dose forms of administration especially in the manufacture of tablets was to solve the problem of capping caused by the active substance which is particularly pronounced in the case of metformin in order to avoid losses of yield during the production and impairment of the pharmaceutical quality. Capping denotes the detachment of compressed mass in layers from the manufactured compact during the pressing or shortly afterwards (Schepky G. in: Bruchhausen, F. von et al.; publ. Hagers Handbuch der pharmazeutischen Praxis, Volume 2, Methoden, 5th ed. "Springer Verlag", Berlin 1991). In the case of metformin and especially when high doses of active substance are present in the granulate it has turned out that the tendency for capping is particularly high during the production of tablets.

The causes for these tabletting problems can be diverse and complex. Capping can be caused by an inadequate binding agent action, an inadequate or excessive moisture content of the granulate, unsuitable crystal forms, strongly aerophilic substances, excessive porosity, excessive proportion of powder, excessive interparticulate binding between the granulate particles and by unsuitable granulate forms. Machine factors which can lead to capping are an excessive pressing force, badly applied or worn tools, excessive pressing rates and poor deaeration of the matrix (fixed pressure). However, in the case of the active substance metformin it has turned out that the usual measures are not adequate to satisfactorily control the capping of the tabletting mass. A relatively high proportion of defective tablets was found during tablet production and the tabletting had to be discontinued due to high reject rates.

In the present case the object of the invention is achieved by providing high-dose pharmaceutical compositions containing metformin which contain a hydrocolloid-forming agent as a retardant and have a residual moisture content in the pharmaceutical composition of 0.5–3% by weight. These pharmaceutical compositions can be advantageously manufactured using aqueous solvents so that organic solvents are no longer required. In addition these compositions are surprisingly easy to compress. They are therefore particularly suitable for the manufacture of solid pharmaceutical forms of administration such as e.g. tablets, dragées or capsules and these can be manufactured with the aid of standard processing machines on a technical scale and in a good quality as well as in a high yield without large losses due to the undesired capping. Accordingly a subject matter of the invention is also a corresponding process for the production of these solid forms of administration in which the appropriate pharmaceutical compositions according to the invention are used in the form of granulates with a residual moisture content of 0.5–3% by weight. The residual moisture content is preferably 1–2.5% by weight in particular 1.5–2% by weight.

Surprisingly it was also found that in the case of the granulate according to the invention it was possible to omit the addition of humectants which are otherwise often necessary to set a constant residual moisture content until the granulate is compressed. This is particularly advantageous because it minimizes the addition of auxiliary substances and pharmaceutical compositions are obtained with a relatively high content of active substance. In addition these compositions have the advantage that they are stable on storage for a period of two days or more (starting from the production up to the use of the granulate for tabletting) with regard to the moisture content before they are compressed without there being a detectable disadvantageous change in the composition. This is particularly advantageous since it enables several partial batches of production lots of the pharmaceutical composition to be produced and these can then be mixed as a mass ready to be pressed at a later time in a common last process step and can be processed to solid pharmaceutical forms of administration.

In addition it surprisingly turned out that the use of a hydrocolloid-forming agent enabled for the first time the known poor compressibility of metformin to be brought under control in a technically satisfactory manner. In addition the solution according to the invention enables the desired retardation and compressibility to be ensured by the selection of the hydrocolloid-forming agent as the retardant and with a suitable control of the production process (adhering to the critical residual moisture content of 0.5–3% by weight in particular of 1–2.5% by weight and 1.5–2 by

weight) although the proportion of the hydrocolloid-forming agent in the formulation composition is unusually low. This is even more surprising since the active substance whose water absorbing capacity is very small (the pure active substances only binds 0.04% by weight water at a relative moisture content of 90%) forms the major proportion of the formulation (about 70–95% by weight).

The proportion by weight of the active substance in the high-dose pharmaceutical composition is in the range of at least 70% by weight, preferably 80–95% by weight relative to the pharmaceutical composition. The active substance can be used in the form of acid addition salts of inorganic or organic acids such as e.g. hydrochloric acid, formic acid, acetic acid, malic acid, tartaric acid or furmaric acid. The hydrochloride salt is preferably used.

The proportion of hydrocolloid-forming agent in the pharmaceutical composition is up to 15% by weight preferably 4–10% by weight and especially about 6–8% by weight.

Within the sense of the invention the standard hydrophilic gel forming agents are suitable as hydrocolloid-forming agents or as hydrophilic swelling substances such as for example cellulose derivatives, dextrins, starch, carbohydrate-based polymers, natural or hydrophilic gums, xanthanes, alginates, gelatin, polyacrylic acid, polyvinyl alcohol or polyvinylpyrrolidone. In the case of the cellulose derivatives the alkyl or hydroxyalkyl cellulose derivatives preferably come into consideration such as e.g. methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methylhydroxyethyl cellulose, methylhydroxypropyl cellulose or sodium carboxymethyl cellulose. In a preferred procedural variant of the invention methylhydroxypropyl cellulose (MHPC) is used. The hydrocolloid-forming agents can be used individually as well as in mixtures of two or several colloid-forming agents. The standard polymers suitable for pharmaceutical purposes with various degrees of substitution and/or different molecular weights corresponding to a different degree of viscosity of the aqueous solution can be used as suitable cellulose-based polymeric colloid-forming agents.

The use of hydrocolloid-forming agents as retardants is based on the property of the hydrocolloid-forming agents to swell and form a gel matrix when they are contacted with a release medium or digestive juices which erodes to release the active substance. The interaction between the amount of hydrocolloid-forming agent and the degree of viscosity determines the time course of the release. Thus for example a high proportion (70–95% relative to the core weight of the tablet) of polyvinyl alcohol of a lower or average viscosity level can for example retard riboflavin for several hours (M ōckel J. E., Lippold B. C., Pharm. Research, 1993, 10, 1066–1070).

The compressed forms of administration that are produced using the pharmaceutical composition according to the invention such as for example metformin delayed-release tablet cores can be additionally provided with a film envelope. The film envelope can on the one hand cause an additional retardation by using those film materials which represent a film-forming agent which is usually suitable for these purposes. On the other hand the film envelope used can be a taste-neutralizing film-forming agent to which dyes can optionally be added. In addition it is also possible to for example use films that are resistant to gastric juice. The proportion by weight of the film envelope relative to the final tablet is in the usual range of 0.3–3.0% by weight preferably of 0.8–1.2% by weight. Film formers such as for example ethyl cellulose; poly(methylmethacrylate) derivatives (Eudragit®) and also soluble cellulose derivatives such as methylhydroxypropyl cellulose and cellulose derivatives for forming films resistant to gastric juice such as cellulose acetate phthalate or methylhydroxypropyl cellulose phthalate come into consideration as film formers. Ethyl cellulose is preferably used. The dissolution of the active substance can be delayed by the film that is formed. Softeners, pore formers and pigments may be present in the film envelope as standard auxiliary substances.

The pharmaceutical composition according to the invention can also be used to produce compressed capsule filling materials. These comprimates or compacted granulates can then be filled into commercial capsules by means of suitable devices. In comparison to the other standard capsule filling materials containing metformin these compacted granulates have the advantage with the same content of active substance and the same dosage that smaller capsules can be used due to their smaller volume which can be more easily swallowed by the patient.

The pharmaceutical forms of administration according to the invention such as e.g. tablets contain—apart from the active substance whose proportion in the form of administration can be in the range of 70–95% by weight (for example 850 mg of the active substance is preferably used in the case of retarded tablets) and the retardant—preferably 2–10% by weight binder, up to 2% by weight preferably 0.1–0.3% by weight flow regulating agent and up to 2% by weight preferably 0.4–1.1% by weight lubricant each in relation to the total weight of the material ready to be tabletted or of the tablet core. The weight of a tablet core is usually between 200 and 1300 mg preferably in the range of less than 1200 mg especially of about 500–1000 mg. Flow regulating agents which come into consideration for the tablet according to the invention are standard agents such as for example colloidal silicon dioxide. Talcum or stearic acid or alkali or alkaline earth salts thereof in particular magnesium stearate are for example suitable as lubricants. Examples of binding agents that can be used are cellulose derivatives especially alkyl and hydroxyalkyl celluloses in particular methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methylhydroxyethyl cellulose, methylhydroxypropyl cellulose, sodium carboxymethyl cellulose etc., dextrins, starches, especially soluble starches, other polymers based on carbohydrates such as e.g. galactomannans, natural gums such as gum arabic, Traganth, Sterculia, Acacia and others, xanthane, alginates, polyacrylic acid, polyvinyl alcohol and polyvinylpyrrolidone. Polyvinylpyrrolidone is preferably used.

The pharmaceutical forms of administration according to the invention such as e.g. tablets are produced by dry mixing the active substance, the retardant or a portion of the retardant and optionally further auxiliary substances, wet-granulating with water or an aqueous solution of a binder, drying the material ready for tabletting to a desired residual moisture content and subsequently where appropriate the remaining portion of the retardant or other pharmaceutical auxiliary substances are admixed with the granulate so that in the last process step a residual moisture content of 0.5–3% by weight is achieved in the pharmaceutical composition. The determination of the residual moisture content is carried out by known analytical methods of aquametry for example by determining the water content with the aid of the Karl-Fischer reagent or other alternative methods of determination. In the wet granulation a portion of the active substance, the auxiliary substances used as well as the retardant may also be present dissolved or suspended completely or par-

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tially in water. Optionally it is also possible to add organic solvents that are miscible with water such as for example acetone or lower alcohols such as methanol or ethanol.

It is expedient to adjust the residual moisture content while drying in a fluid bed process in which the moist granulate is dried until the measured moisture content in the outlet air has reached the value previously determined when the residual moisture content in the drying material was calibrated. The composition produced in this manner is subsequently processed in the usual manner to form pharmaceutical forms of administration and for example pressed into tablets. The tablets can be coated with a film using the standard coating processes. It was found that the residual moisture content of 0.5–3% by weight that was set with the aid of the hydrocolloid-forming agent ensures that the material ready for tabletting can be compressed over the entire range of pressing force required to produce large tablets without capping.

The active substance can be processed completely or partially with the hydrocolloid-forming agent used for the retardation to form a granulate or the hydrocolloid-forming agent is mixed completely with a granulate free of hydrocolloid-forming agent after its production. However, an additional improvement in the tablet-forming properties is achieved when the hydrocolloid-forming agent or a portion thereof is granulated with the active substance.

The tablet is coated by standard methods such as e.g. the coating pan or fluid bed process.

The retarded tablets according to the invention release metformin in a controlled manner over a time period of 0.5–10 hours preferably over 4 hours (FIG. 1). Since due to the use of a hydrocolloid-forming agent large amounts of additional auxiliary substances and in particular no humectants such as for example glycerol or sorbitol are necessary, the maximum weight of the tablets is 1200 mg preferably below 1000 mg.

It is intended to elucidate the invention in the following by the procedural examples without limiting it thereto.

In the following examples 1–6 the residual moisture content was adjusted to the range according to the invention before the pharmaceutical composition in the form of a mass ready for pressing was pressed into tablets. In examples 7 and 8 the residual moisture content was set to a value of less than 0.5% by weight. In these two cases the tabletting had to be terminated due to high losses caused by capping.

EXAMPLE 1

Hydrocolloid-forming agent: methylhydroxypropyl cellulose (MHPC). The MHPC content can be varied e.g. from 40–95 mg.

residual moisture: 2.1%

Constituents	Tablet [mg]	Mass ready for pressing [kg/1 mio. pieces]
Core:		
metformin hydrochloride	850.00	850.00
methylhydroxypropyl cellulose	60.00	60.00
polyvidone	38.00	38.00
magnesium stearate	5.00	5.00
core total:	953.00	953.00
Film envelope:		
methylhydroxypropyl cellulose	20.00	20.00
ethyl cellulose	12.00	12.00
Macrogol	4.00	4.00
titanium dioxide	4.00	4.00
envelope total:	40.00	40.00
film tablet total:	993.00	993.00

Production

The production of granulate for an amount of about 1 million tablets is carried out in five partial batches. For each of the five partial batches 170 kg metformin hydrochloride and 12 kg methylhydroxypropyl cellulose were dry mixed together and wet-granulated in a mixer with a 10% aqueous binder solution of polyvidone. Subsequently the granulate is dried in a fluid bed granulator until it has an adequate residual moisture content. The five partial batches are combined and admixed with 5 kg magnesium stearate. The mass ready for pressing is tabletted. The tablet cores are coated in a coating pan with the film of the described composition.

In the stated formulation the residual moisture content is adjusted to 2.1%. The tabletting proceeds correspondingly without problems i.e. a capping of the manufactured tablet mass cannot be detected.

EXAMPLE 2

Hydrocolloid-forming agent: hydroxyethyl cellulose

Residual moisture: 2.0%

Constituents	Tablet [mg]	Mass ready for pressing [kg/1 mio. pieces]
Core:		
metformin hydrochloride	850.00	850.00
hydroxyethyl cellulose	70.00	70.00
polyvidone	40.00	40.00
magnesium stearate	5.00	5.00
core total:	965.00	965.00
Film envelope:		
methylhydroxypropyl cellulose	5.00	5.00
lactose	5.00	5.00
ethyl cellulose	10.00	10.00
Macrogol	3.00	3.00
titanium dioxide	3.00	3.00
envelope total:	26.00	26.00
film tablet total:	991.00	991.00

The granulate is produced and processed analogously to example 1; the tabletting proceeds correspondingly without problems.

EXAMPLE 3

Hydrocolloid-forming agent: sodium carboxymethyl cellulose

Residual moisture: 2.1%

Constituents	Tablet [mg]	Mass ready for pressing [kg/1 min. pieces]
Core:		
metformin hydrochloride	850.00	850.00
sodium carboxy methyl cellulose	80.00	80.00
polyvidone	35.00	35.00
magnesium stearate	5.00	5.00
core total:	970.00	970.00
Film envelope:		
methylhydroxypropyl cellulose	5.00	5.00
ethyl cellulose	10.00	10.00
Macrogol	4.00	4.00
titanium dioxide	3.00	3.00
envelope total:	22.00	22.00
film tablet total:	992.00	992.00

The granulate is produced and processed analogously to example 1; the tabletting proceeds correspondingly without problems.

EXAMPLE 4

Hydrocolloid-forming agent: polyacrylic acid

Residual moisture: 2.8%

Constituents	Tablet [mg]	Mass ready for pressing [kg/1 min. pieces]
Core:		
metformin hydrochloride	850.00	850.00
polyacrylic acid	60.00	60.00
methylhydroxypropyl cellulose	30.00	30.00
magnesium stearate	5.00	5.00
core total:	945.00	945.00
Film envelope:		
methylhydroxypropyl cellulose	10.00	10.00
ethyl cellulose	10.00	10.00
Macrogol	3.00	3.00
titanium dioxide	3.00	3.00
envelope total:	26.00	26.00
film tablet total:	971.00	971.00

The granulate is produced and processed analogously to example 1. As a variant methylhydroxypropyl cellulose in this case serves as a binder. The tabletting proceeds correspondingly without problems.

EXAMPLE 5

Hydrocolloid-forming agent: hydroxypropyl cellulose

Residual moisture: 1.95%

Constituents	Tablet [mg]	Mass ready for pressing [kg/1 min. pieces]
Core:		
metformin hydrochloride	850.00	850.00
hydroxypropyl cellulose	60.00	60.00
polyvidone	40.00	40.00
magnesium stearate	5.00	5.00
core total:	955.00	955.00
Film envelope:		
poly(ethylacrylate-methyl methacrylate) dispersion 30%	6.00*	6.00*
talcum	1.20	1.20
anti-foaming agent	0.07	0.07
envelope total:	7.27	7.27
film tablet total:	962.270	962.270

*Stated quantity refers to the dry substance.

The granulate is produced and processed analogously to example 1. As a variant the hydrocolloid-forming agent hydroxypropyl cellulose is in this case not granulated simultaneously but admixed dry with the completed granulate.

EXAMPLE 6

Hydrocolloid-forming agent: methylhydroxypropyl cellulose

Residual moisture: 2.0%

In the following example an additional binder is completely omitted, the methylhydroxypropyl cellulose used adopts the function of both binder and retardant.

Constituents	Tablet [mg]	Mass ready for pressing [kg/1 min. pieces]
Core:		
metformin hydrochloride	850.00	850.00
methylhydroxypropyl cellulose	100.00	100.00
magnesium stearate	5.00	5.00
core total:	955.00	955.00
Film envelope:		
methylhydroxypropyl cellulose	20.00	20.00
ethyl cellulose	12.00	12.00
Macrogol	4.00	4.00
titanium dioxide	4.00	4.00
envelope total:	40.00	40.00
film tablet total:	995.00	995.00

Production

The production of granulate is carried out in five partial batches. For each of the five partial batches 170 kg metformin hydrochloride and 18 kg methylhydroxypropyl cellulose are placed in a fluid bed granulator. 2 kg methylhydroxypropyl cellulose is dissolved in 50 l water. The dry mixture is granulated with the binder solution in a fluid bed granulator and subsequently dried. The five partial batches are combined and admixed with 5 kg magnesium stearate.

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The mass ready for pressing is tabletted. The tablet cores are coated in a coating pan with the film of the described composition.

EXAMPLE 7

Hydrocolloid-forming agent: methylhydroxypropyl cellulose

Residual moisture: 0.49%

A moisture content of 0.49% was obtained with the mixture below. The tabletting had to be stopped due to high losses by capping.

Constituents	Tablet [mg]
Core:	
metformin hydrochloride	850.00
methylhydroxypropyl cellulose	40.00
polyvidone	38.00
magnesium stearate	5.00
core total:	953.00
film envelope:	
methylhydroxypropyl cellulose	20.00
ethyl cellulose	12.00
Macrogol	4.00
titanium dioxide	4.00
envelope total:	40.00
film tablet total:	993.00

EXAMPLE 8

Hydrocolloid-forming agent: gelatin

Residual moisture: 0.48%

A moisture of 0.48% was obtained with the mixture below. The tabletting had to be stopped due to high losses by capping.

Constituents	[mg]
Core:	
metformin hydrochloride	850.00
lactose	70.00
gelatin	40.00
silicon dioxide, highly dispersed	2.00
magnesium stearate	2.50
core total:	964.50
film envelope:	
methylhydroxypropyl cellulose	10.00
ethyl cellulose	9.00
diethyl phthalate	3.00
titanium dioxide	3.00
envelope total:	25.00
film tablet total:	989.5

We claim:

1. Pharmaceutical composition comprising metformin as the active substance and a hydrocolloid forming retarding agent, wherein the pharmaceutical composition has a residual moisture content of about 0.5–3% by weight.

2. Composition of claim 1, wherein at least 70% by weight of the composition is metformin.

3. Composition of claim 1, wherein about 4–15% by weight of the composition is the hydrocolloid forming retarding agent.

4. Composition of claim 1, wherein the retarding agent is selected from the group consisting of cellulose derivatives, dextrins, starches, carbohydrate polymers, natural gums, xanthane, alginates, gelatin, polyacrylic acid, polyvinyl alcohol and polyvinyl pyrrolidone.

5. Composition of claim 4, wherein the retarding agent is a cellulose derivative.

6. Composition of claim 5, wherein the cellulose derivative is an alkyl or hydroxyalkyl cellulose.

7. Composition of claim 6, wherein the cellulose derivative is selected from the group consisting of methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, methylhydroxyethyl cellulose, methylhydroxypropyl cellulose or sodium carboxymethyl cellulose.

8. Composition of claim 1, further comprising about 3–5% by weight of binder, up to 2% by weight of flow regulating agent and up to 2% by weight of lubricant.

9. Composition of claim 1 in the form of a tablet or capsule.

10. Pharmaceutical tablets or compacted product for filling into capsules comprising metformin as the active substance and a hydrocolloid-forming retarding agent, the tablets having cores, wherein the cores or compacted product have a residual moisture content of about 0.5–3% by weight.

11. Product of claim 10, wherein the product is a tablet having a weight less than 1300 mg.

12. Process for producing a retarded metformin pharmaceutical composition which can be compressed, comprising

granulating metformin and a hydrocolloid-forming retarding agent with an aqueous solvent to form a granulated product,

and drying the granulated product to a residual moisture content of about 0.5 to 3% by weight.

13. Process of claim 12, including the further step of admixing further retarding agent with the granulated product prior to the drying step.

14. Process of claim 12, wherein the aqueous solvent used in the granulation step contains a binder.

15. Process of claim 12, including the further step of compressing the dried granulated product into tablets.

16. Process of claim 15, including the further step of coating the tablets with a film envelope.

17. Process of claim 12, including the further steps of compacting the dried granulated product to form a compacted product, and filling the compacted product into capsules.

18. Process of claim 12, wherein the retarding agent is methylhydroxypropyl cellulose.

19. Process of claim 12, wherein the compacted product further includes up to 2% by weight of lubricant, up to 2% by weight of flow regulating agent and up to 5% by weight of binder.

* * * * *

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Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Darío Cárdenas Navas
Apoderado

Oficio Nº: 11493

ASUNTO:

Radicación PCT Nº	03-36463
Trámite	011
Evento	379
Actuación	440
Folios	013

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 Luis Fernando Rincón, en su calidad de apoderado de Procaps S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única 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, 17 DIC. 2020.

202021

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Sede CAN: Tr. 40A No. 38-50 Conmutador: 3820840
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