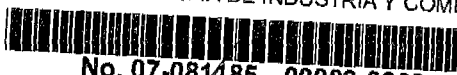


No. 07-081185-00003-0000



No. 07-081185-00003-0000

Fecha: 2008-08-28 14:13:28 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 79

①

OPOSICIÓN A:

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

②

SOLICITUD
PUBLICADA

Numero del expediente: 07-81185
Solicitante: EURO.CELTIQUE S.A
Apoderado: LUIS FELIPE CASTILLO GIBSONE
Titulo de la nueva creación o denominación del signo: "FORMAS DE
DOSIS RESISTENTES AL ALCOHOL".
Gaceta: 592

③ OPOSICIÓN PRESENTADA POR:

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

④ FUNDAMENTOS DE LA OPOSICIÓN:

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

Signo opositor:

Justificación:

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

⑤ Comprobante de pago No. _____

Fecha _____

⑥ ANEXOS

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

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA: _____

C.C. 51.975.664

TP. 83823



Optimum

36 3
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° 07 081185

Asunto : Oposición a la solicitud de patente de Invención titulada
"FORMAS DE DOSIS RESISTENTES AL ALCOHOL"

Solicitante : EURO CELTIQUE S.A..

Opositora : GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 592 del 30 de mayo de 2008

Yo, **ELIANA ISaura MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **GYNOPHARM S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "**FORMAS DE DOSIS RESISTENTES AL ALCOHOL**", cuyo titular es **EURO CELTIQUE S.A.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.



1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular naloxona, naltrexona, nalorfina, hidromorfona, y/o oxicodona. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

- 2.1. La solicitud objeto de la presente fue presentada el 9 de agosto de 2007, reivindicando prioridad bajo la solicitud US20050670506P del 2005-04-12; US20050730339P del 2005-10-26; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 592 del 30 de mayo de 2008, cuya publicación internacional corresponde a la WO2006079550 del 2006-08-03.
- 2.2. La solicitud colombiana 07 081185 objeto de la presente oposición, se refiere al uso de un polímero termoplástico escasamente permeable al agua o un polímero hidrofóbico como material matriz de liberación controlada en la manufacturación de una formulación matriz opioide de liberación controlada para otorgar resistencia a la extracción de alcohol del opioide, caracterizado porque dicha formulación que tiene un polímero termoplástico escasamente permeable al agua o polímero hidrofóbico como material matriz de liberación controlada libera una menor



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Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

cantidad de opioide en un análisis de extracción de alcohol en comparación con la misma formulación pero con el polímero termoplástico escasamente permeable al agua o polímero hidrofóbico sustituido totalmente o en parte por otros materiales matrices.; un material hidrofóbico como material matriz de liberación controlada en la manufacturación de una formulación matriz de sal opioide de liberación controlada para otorgar resistencia a la extracción de alcohol de la sal opioide, caracterizado porque menos de un 25 % de la sal opioide es liberada luego de 1 hora de disolución in-vitro de una forma de dosis que comprende dicha formulación en 900 ml de Fluido Gástrico Simulado con un 20 % etanol utilizando un Aparato USP I (cesta) funcionando a 100 rpm a 37°C; y, una forma de dosis de liberación controlada caracterizada porque comprende: una matriz que comprende una sal farmacéuticamente aceptable de un analgésico opioide en un material de liberación controlada; en donde menos de un 25% de la sal opioide es liberada luego de 1 hora de disolución in-vitro de la forma de dosis en 900 ml de Fluido Gástrico Simulado con un 20% etanol utilizando un Aparato USP I (cesta) a 100 rpm a 37 grados C°.

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

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

- D1: EP1348429 publicada el 10 de octubre de 2003.
- D2: WO03004009 publicada el 16 de enero de 2003.

2.5. Igualmente, además que la presente define un uso y un método terapéutico que no es objeto de patente, también la forma de dosificación sostenida revelada es obvia y derivable de manera evidente del estado de la técnica. Así lo evidencia por un lado el documento D1, particularmente en la descripción que revela formas biodisponibles de liberación sostenida en formas de dosificación orales que incluyen opioide analgésicos, comprendiendo una pluralidad de multiparticulados producidos por técnicas de derretido. Según esta anterioridad se revela Una sostener-liberación formulación farmacéutica, comprendiendo un derretir particularmente en la reivindicación 1 una mezcla expulsada de un agente terapéuticamente activo, uno o varios materiales hidrófobos seleccionados del grupo que consiste en alquilcelulosas, polímeros acrílicos y ácidos metacrílicos y copolímeros, laca, zein, aceite de castor hidrogenado, aceite de verduras hidrogenado y mezclas de ellos así como uno o varios portadores hidrófobos fusibles que proporcionan un remoto efecto de retardante y seleccionado del grupo que consiste en ceras naturales o sintéticas, ácidos grasos, alcoholes grasos, y



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Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

mezclas de ellos y dicho portador fusible hidrófobo. Ahora bien, igualmente el documento D2 define un proceso para preparar formas de dosificación en pastilla de agentes farmacéuticos de metformina HCl. Según las reivindicaciones de la anterioridad D2, se revela un proceso para preparar una formulación de pastilla farmacéutica de un agente farmacéutico de difícil compresión, que comprende los pasos de preparar una mezcla por combinando del agente farmacéutico de difícil compresión, un componente hidrófilo erodible y un componente hidrófobo; se comprime la mezcla en una pastilla. Por lo tanto, visto dicho documento D2 en combinación con el documento D1, la presente solicitud carece evidentemente de altura inventiva, pues a partir de estas una persona del medio puede de manera obvia llegar a definir un polímero termoplástico escasamente permeable al agua o un polímero hidrofóbico como material matriz de liberación controlada en la manufacturación de una formulación matriz opioide de liberación controlada para otorgar resistencia a la extracción de alcohol del opioide, caracterizado porque dicha formulación que tiene un polímero termoplástico escasamente permeable al agua o polímero hidrofóbico como material matriz de liberación controlada libera una menor cantidad de opioide en un análisis de extracción de alcohol en comparación con la misma formulación pero con el polímero termoplástico escasamente permeable al agua o polímero hidrofóbico sustituido totalmente o en parte por otros materiales matrices.

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

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 07 081185 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

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

2.8.1. **CARENCIA DE ALTURA INVENTIVA.** Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."* A la fecha de prioridad, 12 de abril de 2005, a partir del documento D2 en combinación con D1, puede llegar de manera evidente a un polímero termoplástico escasamente permeable al agua o un polímero hidrofóbico como material matriz de liberación controlada en la manufacturación de una formulación matriz opioide de liberación controlada para otorgar resistencia a la extracción de alcohol del opioide, sobre el cual busca protección en el capítulo reivindicatorio.

2.8.2. **CARENCIA DE APLICACIÓN INDUSTRIAL** La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman el método terapéutico y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a los usos y métodos terapéuticos, no cumplen con el requisito de la aplicación industrial.

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

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"FORMAS DE DOSIS RESISTENTES AL ALCOHOL"**, cuyo titular es **EURO CELTIQUE S.A.,** solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 592 del 30 de mayo de 2008

3. PRUEBAS

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

- D1: EP1348429 publicada el 10 de octubre de 2003.
- D2: WO03004009 publicada el 16 de enero de 2003.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

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

5. ANEXOS

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

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de GYNOPHARM S.A.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: EP1348429 publicada el 10 de octubre de 2003.
 - D2: WO03004009 publicada el 16 de enero de 2003.

6. NOTIFICACIONES

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

Señor Superintendente,



ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

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

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 68,587
FECHA : AGOSTO 28 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO


No. 07-081185- 00003-0000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO


No. 07-081185- 00003-0000

Fecha: 2008-08-28 14:13:26 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 79

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

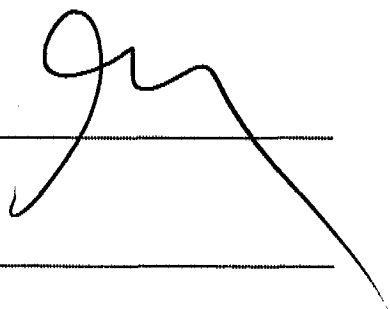
DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GYNOFARM S A	CONSIGNACION	BANCO DE BOGOTA	062754387	4638222	17/07/2008	1,330,000.00

***** 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	266,000.00
	TOTAL :	\$ 266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE :



RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

PODER ESPECIAL

Yo, **LUIS PALACIOS ARAGÓN**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **GYNOPHARM S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 07-81185, titulada "**FORMAS DE DOSIS RESISTENTES AL ALCOHOL**", cuyo titular es **EURO CELTIQUE S.A.**, publicada en la gaceta No. 592 del 30 de mayo de 2008.

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

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

Dado y Firmado en Barranquilla (Colombia) a los 26 días del mes de 08 de 2008.

GYNOPHARM S.A.

Cédula de Extranjería: No. 319788.

NIT: 802.006.279-4

Representante Legal

Acepto:

ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

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

RECONOCIMIENTO DE DOCUMENTO PRIVADO
 Ante mí, **NIBARDO AGUSTIN FUERTES MORALES**,
 Notario Veinticinco del Circuito de Bogotá (E),
 comparece **Luis Palacios**
Arcadio
 identificado con cédula de ciudadanía
CE 319788 Btc
 y declara que la firma puesta en el presente
 instrumento privado es suya y que el contenido
 el mismo es cierto. **26 AGO. 2008**
 Bogotá D.C.
 FIRMA: 
NIBARDO AGUSTIN FUERTES MORALES
 NOTARIO VEINTICINCO(E)

PRESENTACION PERSONAL
 El anterior escrito fue presentado ante la
 NOTARIA DIECIOCHO DEL CIRCULO DE BOGOTA, D.C.
 personalmente por **Elvira Rueda**
Norma Bohorquez
 quien exhibió la c.c. **51 775664** de **RJ**
 y Tarjeta Profesional No. **83863** C.O.J.
 Fecha **20 AGO 2008**
Victory B
Victoria Bana Tanguito
 NOTARIA



Elvira Rueda



01



* 7 2 9 3 8 4 3 3 *



14

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080814

Hora Certificado 16:59:44

Operacion : 02NUK0814067

PAGINA No. 1

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

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

C E R T I F I C A

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

C E R T I F I C A

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

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
532	1999/03/25	Notaria 3a. de Barranquilla	80,373	1999/04/13

C E R T I F I C A

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

DENOMINACION O RAZON SOCIAL:

GYNOPHARM S.A.-----

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 802.006.279-4.

MATRICULA MERCANTIL: 245,470.

C E R T I F I C A

Direccion para notificaciones judiciales:

CR 49 C No 80 - 125 OF 512.

De la ciudad de Barranquilla.

Correo electr?nico:

C E R T I F I C A

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

C E R T I F I C A

OBJETO SOCIAL: a) La fabricacion de capsulas y otro 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

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080814 Hora Certificado 16:59:44

Operacion : 02NJK0814067 PAGINA No. 2

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 y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos, medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. e) Actuar como representante o agente de personas naturales y juridicas nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualesquiera de las actividades descritas en los literales a), b), c) y d) antes transcritos. f) Prestar los servicios de asesoria y consultoria en las areas administrativa, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de GYNOPHARM S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial. g) Adquirir, operar, administrar y explotar, a cualquier titulo, empresas o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto; comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o lo de sus socios.-----

C E R T I F I C A

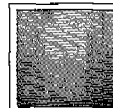
CAPITAL Nro Acciones Valor Acci?n

Autorizado \$*****4,000,000,000 *****4,000,000 *****1,000

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

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

*** CONTINUA ***



CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080814

Hora Certificado 16:59:44

Operacion : 02NJK0814067

PAGINA No. 3

C E R T I F I C A

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

C E R T I F I C A

Que segun Acta No. 15 del 18 de Febrero de 2008 correspondiente a la Asamblea de Accionistas en Bogota, de la sociedad:

GYNOPHARM S.A.

cuya parte pertinente se inscribi? en esta Cámara de Comercio, el 25 de Febrero de 2008 bajo el No. 137,919 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Llobet Poal Manuel	CC.*****14,670,196
2. Zanatta Reheman Leonardo Andres	CC.*****2,760,271
3. Munoz Marroquin Diego	CC.*****7,688,292

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080814 Hora Certificado 16:59:44

Operacion : 02NJK0814067

PAGINA No. 4

4. Montealegre Gonzalez Andres Leonardo CC.*****79,950,262

Suplentes

1. Agudelo Pelaez Luis Hernando CC.*****14,238,997

2. Aroca Almanza Arleth Ayelina CC.*****36,718,415

3. Penaranda Urbina Adriana Paola CC.*****53,120,683

4. tovar Vasquez Ruth CC.*****52,175,756

CERTIFICA

Que segun Acta No. 13 del 30 de Octubre de 2003 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 06 de Nov/bre de 2003 bajo el No. 107,783 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificaci?n
Gerente General	
Palacios Aragon Luis Alberto	CE.*****319,788

CERTIFICA

Que segun Acta No. 49 del 03 de Marzo de 2008 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificaci?n
Suplente del Gerente	
Mollajoli Centurion Andres Fernando	CE.*****351,283

CERTIFICA

Que segun Acta No. 16 del 08 de Mayo de 2008 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribi? en esta C?mara de Comercio, el 22 de Mayo de 2008 bajo el No. 140,053 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificaci?n
Revisor Fiscal	
Marroquin Sepulveda Edgar	CC *****17,147,542

CERTIFICA

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 23 de Noviembre del 2.000 bajo el No. 1.872 del libro repectivo, consta que el senor RUBEN MINSKI GONTOVNIK C.C. No. 7.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial,

*** CONTINUA ***



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* 7 2 9 3 8 4 3 5 *



CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

Fecha : 20080814

Hora Certificado 16:59:44

Operacion : 02NJK0814067

PAGINA No. 5

Amplio y Suficiente a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.-732.070, para que en nombre y representacion de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM S.A., en el giro normal de sus negocios y operaciones sociales.-----

C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 12 de junio del 2.002, bajo el 2.164 del libro respectivo, consta que el senor JORGE CASTELLANOS MARTINEZ, identificado con C.C.No.19.460.089, actuando como representante legal de la sociedad GYNOPHARM S.A, otorga Poder Especial Amplio y Suficiente a KAREN FIGUEROA GARCIA, identificada con la cedula de ciudadanía No.32.732.070 de Barranquilla, mediante documento privado de octubre 10/2000, inscrito en la Camara de Comercio de Barranquilla bajo el No.1.872 del libro respectivo, para que en representacion de GYNOPHARM S.A, suscriba las declaraciones cambiarias a los que esta obligada GYNOPHARM S.A. en el giro ordinario de sus negocios y operaciones sociales.-----

C E R T I F I C A

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

C E R T I F I C A

Que su ultima Renovacion fue el: 23 de Abril de 2008.

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

C E R T I F I C A

Que los actos de registro aqui certificados quedan en firme cinco dias hábiles despues de la correspondiente inscripcion, siempre que, dentro de dicho termino, no sean objeto de los recursos de reposicion ante esta entidad, y/o de apelacion para ante la Superintendencia de Industria y Comercio.

mkajoa

(19)  **Europäisches Patentamt**
European Patent Office
Office européen des brevets



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(71) Applicant: **Euro-Celtique S.A.**
2330 Luxembourg (LU)

(72) Inventors:
• **Oshlack, Benjamin**
New York 10028, New York (US)

• **Chasin, Mark**
Manalapan 07726, New Jersey (US)
• **Huang, Hua-Pin**
Englewood Cliffs 07632, New Jersey (US)
• **Sackler, David**
Greenwich 06830, Connecticut (US)

(74) Representative: **Ruffles, Graham Keith**
MARKS & CLERK,
57-60 Lincoln's Inn Fields
London WC2A 3LS (GB)

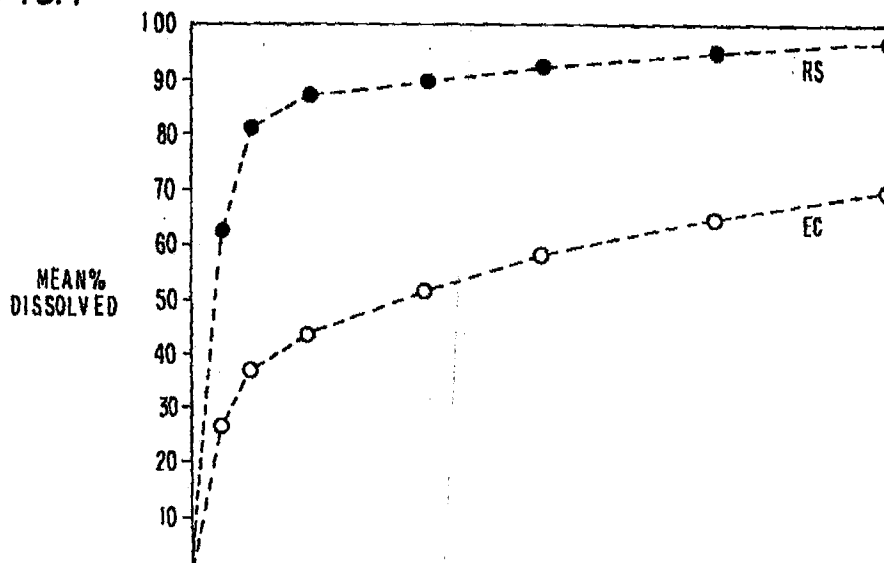
Remarks:

This application was filed on 07 - 07 - 2003 as a
divisional application to the application mentioned
under INID code 62.

(54) **Melt-extruded orally administrable opioid formulations**

(57) Bioavailable sustained release oral opioid analgesic dosage forms, comprising a plurality of multiparticulates
produced via melt extrusion techniques are disclosed.

FIG. 1



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Description

BACKGROUND OF THE INVENTION

5 [0001] The present invention relates to the use of melt extrusion technology in the production of bioavailable sustained-release matrix pharmaceutical formulations. Previously, melt extrusion has been used in the production of immediate release formulations.

10 [0002] It is known in the pharmaceutical art to prepare compositions which provide for controlled release of pharmacologically active substances contained in the compositions after oral administration to humans and animals. Such slow release compositions are used to delay absorption of a medicament until it has reached certain portions of the alimentary tract. Such sustained-release of a medicament in the alimentary tract further maintains a desired concentration of said medicament in the blood stream for a longer duration than would occur if conventional rapid release dosage forms are administered.

15 [0003] Different methods of preparing controlled release pharmaceutical dosage forms have been suggested. For example, direct compression techniques, wet granulation techniques, encapsulation techniques and the like have been proposed to deliver pharmaceutically active ingredients to the alimentary tract over extended periods.

20 [0004] Additionally, various types of sustained release formulations are known in the art, including specially coated pellets, coated tablets and capsules wherein the slow release of the active medicament is brought about through selective breakdown of the coating of the preparation or through compounding with a special matrix to affect the release of a drug. Some sustained release formulations provide for related sequential release of a single dose of an active compound at predetermined periods after administration.

25 [0005] It is the intent of all sustained-release preparations to provide a longer period of pharmacologic response after the administration of the drug and is ordinarily experienced after the administration of the rapid release dosage forms. Such longer periods of response provide for many inherent therapeutic benefits that are not achieved with corresponding short acting, immediate release preparations. This is especially true in the treatment of cancer patients or other patients in need of treatment for the alleviation of moderate to severe pain, where blood levels of an opioid analgesic medicament must be maintained at a therapeutically effective level to provide pain relief. Unless conventional rapid acting drug therapy is carefully administered at frequent intervals to maintain effective steady state blood levels of the drug, peaks and valleys in the blood level of the active drug occur because of the rapid absorption, systemic excretion of the compound and through metabolic inactivation, thereby producing special problems in maintenance of analgesic efficacy

30 [0006] The prior art teaching of the preparation and use of compositions providing the sustained-release of an active compound from a carrier is basically concerned with the release of the active substance into the physiologic fluid of the alimentary tract. However, it is generally recognized that the mere presence of an active substance in the gastrointestinal fluids does not, by itself, insure bioavailability.

35 [0007] In order to be absorbed, the active drug substance must be in solution. The time required for a given proportion of an active substance from a unit dosage form is determined as the proportion of the amount of active drug substance released from a unit dosage form over a specified time base by a test method conducted under standardized conditions. The physiologic fluids of the gastrointestinal tract are the media for determining dissolution time. The present state of the art recognizes many satisfactory test procedures to measure dissolution time for pharmaceutical compositions, and these test procedures are described in official compendia world wide.

40 [0008] Although there are many diverse factors which influence the dissolution of drug substance from its carrier, the dissolution time determined for a pharmacologically active substance from the specific composition is relatively constant and reproducible. Among the different factors affecting the dissolution time are the surface area of the drug substance presented to the dissolution solvent medium, the pH of the solution, the solubility of the substance in the specific solvent medium, and the driving forces of the saturation concentration of dissolved materials in the solvent medium. Thus, the dissolution concentration of an active drug substance is dynamically modified in its steady state as components are removed from the dissolution medium through absorption across the tissue site. Under physiologic conditions, the saturation level of the dissolved materials is replenished from the dosage form reserve to maintain a relatively uniform and constant dissolution concentration in the solvent medium providing for a steady state absorption.

45 [0009] The transport across a tissue absorption site of the gastrointestinal tract is influenced by the Donnan osmotic equilibrium forces on both sides of the membrane since the direction of the driving force is the difference between the concentrations of active substance on either side of the membrane, i.e., the amount dissolved in the gastrointestinal fluids and the amount present in the blood. Since the blood levels are constantly being modified by dilution, circulatory changes, tissue storage, metabolic conversion and systemic excretion, the flow of active materials is directed from the

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bioavailability. The dissolution time and the bioavailability determined for a composition are two of the most significant fundamental characteristics for consideration when evaluating sustained-release compositions.

[0011] Melt granulation techniques have also been suggested to provide controlled release formulations. Generally, melt granulation involves mechanically working an active ingredient in particulate form with one or more suitable binders and/or pharmaceutically acceptable excipients in a mixer until one or more of the binders melts and adheres to the surface of the particulate, eventually building up granules.

[0012] U.S. Patent No. 4,957,681 (Klimesch, et. al.) discloses a continuous process for preparing pharmaceutical mixtures having at least two components which are continuously metered. The process includes continuously metering the individual components of the pharmaceutical mixture at a rate of at least 50 g/h on electronic differential metering balances having a metering accuracy of at least $\pm 5\%$ within time intervals of less than one minute and, additionally, having screw conveyors, thereby obtaining a substantially uniformly metered mixture; and shaping the mixture. Example 1 of the '681 patent is representative of the process. The requisite amounts of a copolymer having a K value of 30 and obtained from 60% of N-vinylpyrrolid-2-one (NVP), stearyl alcohol and theophylline are metered via three metering balances into the hopper of an extruder and extruded. The temperatures of the extruder cylinder consisting of six shots ranged from 30-60°C and the die is heated to 100°C. The resultant extrudate is then pressed into tablets of the required shape. The '681 patent does not disclose preparation of sustained release opioid pharmaceutical formulations.

[0013] N. Follonier, et al., Hot-Melt Extruded Pellets for the Sustained Release of Highly Dosed Freely Soluble Drugs, Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 18 (1991) describes certain diltiazem hydrochloride formulations prepared using hot-melt screw-extrusion to obtain sustained-release pellets to be filled into hard gelatin capsules. The polymers used were ethylcellulose, a copolymer of ethyl acrylate and methyl methacrylate containing quaternary ammonium groups, cellulose acetate butyrate, poly(vinyl chloride-co-vinyl acetate) and a copolymer of ethylene and vinyl acetate. In order to lower the extrusion temperature, some plasticizers were used.

[0014] WO 93/07859 describes drug loaded pellets produced through melt spheronization wherein the therapeutically active agent is blended with various excipients and binders; the formulation is fed to an extruder where it is heated and extruded at a speed of about 0.05 to 10 mm/sec. at approximately 60-180° C. The extrudate is then cut into pieces in a pelletizer and subsequently fed to a spheronizer for uniform pellet formulation.

[0015] Despite the foregoing advances and the various techniques for preparing sustained release formulations available in the pharmaceutical art, there is a need in the art for an orally administrable opioid formulation which would provide an extended duration of effect which is also easy to prepare, e.g. via melt-granulation techniques.

OBJECTS AND SUMMARY OF THE INVENTION

[0016] It is therefore an object of the present invention to provide sustained-release pharmaceutical formulations suitable for oral administration and methods for preparing the same utilizing melt-extrusion techniques.

[0017] It is also an object of the present invention to provide improved methods for producing pharmaceutical extrudates containing opioid analgesics and pharmaceutically acceptable hydrophobic materials via melt extrusion techniques.

[0018] It is a further object of the present invention to provide a sustained-release melt extruded multi-particulate formulation which need not be spheronized in order to obtain a final dosage form.

[0019] It is also an object of the present invention to provide methods of treatment for human patients in need of opioid analgesic therapy using dosage forms prepared in accordance with the methods disclosed herein.

[0020] In accordance with the above objects and others which will be apparent from the further reading of the specification and of the appended claims, the present invention is related in part to the surprising discovery that sustained-release oral opioid analgesic formulations may be prepared utilizing melt extrusion techniques to provide bioavailable unit dose products which provide analgesia in a patient for, e.g., 8 - 24 hours..

[0021] The invention is also related in part to a new melt-extruded oral sustained-release dosage forms which comprise a pharmaceutically acceptable hydrophobic material, a retardant selected from waxes, fatty alcohols, and fatty acids, and a drug.

[0022] More particularly, one aspect of the present invention is related to a pharmaceutical extrudate including an opioid analgesic dispersed in a matrix. Preferably, the extrudate is strand or spaghetti-shaped and has a diameter from about 0.1 to about 5 mm. The extrudate is divided into unit doses of the opioid analgesic for oral administration to a patient, and provides a sustained analgesic effect for 8-24 hours or more.

[0023] The matrices preferably include a hydrophobic material and a second retardant material (preferably a hydrophobic fusible carrier) which acts to further slow or control the release of the therapeutically active agent when the formulation is exposed to aqueous solutions in-vitro, or exposed to gastric and/or intestinal fluids.

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[0025] The retardant material (hydrophobic fusible carrier) is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols and mixtures of the same. Examples include beeswax and carnauba wax, stearic acid, and stearyl alcohol. This list is of course not meant to be exclusive.

[0026] The extrudate may be cut into multiparticulates by any cutting means known in the art. Preferably, the multiparticulates have a length of from about 0.1 to 5 mm in length. The multiparticulates may then be divided into unit doses such that each individual unit dose includes a dose of opioid analgesic sufficient to provide analgesia to a mammal, preferably a human patient.

[0027] The unit doses of multiparticulates may then be incorporated into a solid pharmaceutical dosage formulation, e.g. via compression or shaping into tablets, by placing a requisite amount inside a gelatin capsule, or by forming the extruded product into the form of a suppository.

[0028] The pharmaceutical extrudates of the present invention may be prepared by blending the drug together with all matrix ingredients (hydrophobic material, binder and any additional (optional) excipients), feeding the resultant mixture into an extruder heated to the requisite temperature necessary to soften the mixture sufficiently to render the mixture extrudable; extruding the viscous, heated mass as a spaghetti-like strand; allowing the extrudate to congeal and harden, and then dividing the strand into desired pieces. This may be accomplished, e.g., by cutting the strands into pellets of 1.5 mm in diameter and 1.5 mm in length. Preferably, the extrudate has a diameter of from about 0.1 to about 5 mm and provides sustained release of said opioid analgesic for a time period of from about 8 to about 24 hours.

[0029] Another aspect of the invention is directed to pharmaceutical dosage forms including the extrudate prepared as outlined above. The extrudate is cut into multiparticulates using any cutting means known in the art, e.g. a blade. The multiparticulates are then divided into unit doses containing an effective amount of opioid analgesic to provide analgesia or pain relief in a human patient over the desired dosing interval. The unit dose of multiparticulates may then be incorporated into tablets, e.g. via direct compression, formed into suppositories, or encapsulated by any means known in the art.

[0030] In yet a further aspect of the invention, there is provided a method of treating a patient with sustained-release formulations prepared as described above. This method includes administering a dosage form containing the novel extrudate to a patient in need of opioid analgesic therapy. For purposes of the present invention, a unit dose is understood to contain an effective amount of the therapeutically active agent to produce pain relief and/or analgesia to the patient. One skilled in the art will recognize that the dose of opioid analgesic administered to a patient will vary due to numerous factors; e.g. the specific opioid analgesic(s) being administered, the weight and tolerance of the patient, other therapeutic agents concomitantly being administered, etc.

[0031] As mentioned above, in order for a dosage form to be effective for its intended purpose, the dosage form must be bioavailable. For purposes of the present invention, the term "bioavailable" is defined as the total amount of a drug substance that is absorbed and available to provide the desired therapeutic effect after administration of a unit dosage form. Generally, the bioavailability of a given dosage form is determined by comparison to a known reference drug product, as commonly determined and accepted by Governmental Regulatory Agencies, such as the United States FDA.

[0032] The term "bioavailability" is defined for purposes of the present invention as the extent to which the drug (e.g., opioid analgesic) is absorbed from the unit dosage form and is available at the site of drug action.

[0033] The terms "sustained release", "extended duration", and "controlled release" are defined for purposes of the present invention as the release of the drug (e.g., opioid analgesic) at such a rate that blood (e.g., plasma) levels are maintained within the therapeutic range but below toxic levels over a period of time greater than 8 hours, more preferably for about 12 to about 24 hours, or longer.

[0034] The term "unit dose" is defined for purposes of the present invention as the total amount of multiparticulates needed to administer a desired dose of therapeutically active agent (e.g., opioid analgesic) to a patient.

[0035] The extrudates of the present invention preferably permit release of the opioid (or salts thereof) over a sustained period of time in an aqueous medium. The term "aqueous medium" is defined for purposes of the present invention as any water-containing medium, e.g. water, pharmaceutically acceptable dissolution medium, gastric fluid and/or intestinal fluid and the like.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] The following drawing is illustrative of an embodiment of the invention and is not meant to limit the scope of the invention as encompassed by the claims.

Figure 1 is a graph displaying the dissolution results of Examples 1 and 2:

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Figure 5 is a graph displaying the dissolution results of Examples 7 and 8 vs. Example 6;
 Figure 6 is a graph displaying the dissolution results of Examples 9 and 10;
 Figure 7 is a graph displaying the dissolution results of Examples 11 and 12;
 Figure 8 is a graph displaying the dissolution results of Examples 15 and 16;
 Figure 9 is a schematic representation of a system for carrying out the present invention;
 Figure 10 is a graph displaying the fed/fast bioavailability results for Example 20;
 Figure 11 is a graph displaying the plasma morphine concentrations of Example 21 obtained from administration of the capsules from Example 6 vs. MS Contin®;
 Figure 12 is a graph displaying the plasma oxycodone concentrations of Example 22 obtained from administering the capsules from Examples 11 and 13 vs. OxyContin®;
 Figure 13 is a graphical representation of the plasma oxycodone concentrations of Example 14;
 Figure 14 is a graphical representation of the hydromorphone concentrations of Example 24 using the capsules from Example 17 vs. Dilaudid®;
 Figure 15 is a graph displaying the plasma hydromorphone concentrations of Example 24 using capsules from Example 18 vs. Dilaudid®;
 Figure 16 is a graph of the steady-state plasma hydromorphone concentrations of Example 25 using the capsules of Example 17; and
 Figure 17 is a graph of the plasma hydromorphone concentrations of Example 26 using the capsules of Example 19.

DETAILED DESCRIPTION

[0037] In one aspect of the invention, the sustained-release dosage forms comprise an opioid analgesic as the therapeutically active agent. In such formulations, the drug is incorporated into a melt-extruded strand which includes a pharmaceutically acceptable hydrophobic material such as an alkylcellulose or an acrylic polymer or copolymer. In certain embodiments, it is preferable to further add to the blend a plasticizer for the hydrophobic material in order to reduce the extrusion temperature. The choice of the most suitable plasticizer is made based on its ability to lower the glass transition temperature (T_g) of the polymer. In preferred alternative embodiments, a hydrophobic fusible carrier (which may also act as a binder) is utilized instead of a plasticizer. The hydrophobic fusible carrier preferably imparts a slower release of the therapeutically active agent from the melt extruded formulation. Any further pharmaceutical excipients known to those skilled in the art may be added as deemed necessary.

[0038] Another aspect of the invention is directed to improved melt extruded matrices which comprise a hydrophobic material and a fatty binder such as previously specified. In accordance therewith, a therapeutically active agent is combined with one or more suitable hydrophobic materials and a hydrophobic fusible carrier is extruded to form an extrudate. The extrudate may then be cut into multiparticulates which are subsequently incorporated into sustained release dosage forms.

Therapeutically Active Agents

[0039] Therapeutically active agents which may be used in accordance with the present invention include both water soluble and water insoluble drugs. Examples of such therapeutically active agents include antihistamines (e.g., dimenhydrinate, diphenhydramine, chlorpheniramine and dexchlorpheniramine maleate), analgesics (e.g., aspirin, codeine, morphine, dihydromorphone, oxycodone, etc.), non-steroidal anti-inflammatory agents (e.g., naproxen, diclofenac, indomethacin, ibuprofen, sulindac), anti-emetics (e.g., metoclopramide, methylaltrexone), anti-epileptics (e.g., phenytoin, meprobamate and nitrazepam), vasodilators (e.g., nifedipine, papaverine, diltiazem and nicardipine), anti-tussive agents and expectorants (e.g., codeine phosphate), anti-asthmatics (e.g. theophylline), antacids, anti-spasmodics (e.g. atropine, scopolamine), antidiabetics (e.g., insulin), diuretics (e.g., ethacrynic acid, bendrofluthiazide), anti-hypotensives (e.g., propranolol, clonidine), antihypertensives (e.g. clonidine, methyl dopa), bronchodilators (e.g., albuterol), steroids (e.g., hydrocortisone, triamcinolone, prednisone), antibiotics (e.g., tetracycline), antihemorrhoidals, hypnotics, psychotropics, antiarrhythmics, mucolytics, sedatives, decongestants, laxatives, vitamins, stimulants (including appetite suppressants such as phenylpropanolamine), as well as salts, hydrates, and solvates of the same.

[0040] In embodiments of the invention directed to opioid analgesics, the opioid analgesics used in accordance with the present invention include alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphone, dimenoxadol, dimpheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydroco-

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ymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, pir-
itramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, salts thereof,
mixtures of any of the foregoing, mixed mu-agonists/antagonists, mu-antagonist combinations, and the like. The opioid
analgesic may be in the form of the free base, or in the form of a pharmaceutically acceptable salt, or in the form of a
pharmaceutically acceptable complex.

[0041] In certain preferred embodiments, the opioid analgesic is selected from morphine, codeine, hydromorphone,
hydrocodone, oxycodone, dihydrocodeine, dihydromorphine, oxymorphone, tramadol or mixtures thereof.

[0042] In one preferred embodiment the sustained-release opioid oral dosage form of the present invention includes
hydromorphone as the therapeutically active ingredient in an amount from about 4 to about 64 mg hydromorphone
hydrochloride. Alternatively, the dosage form may contain molar equivalent amounts of other hydromorphone salts or
of the hydromorphone base. In other preferred embodiments where the opioid analgesic is other than hydromorphone,
the dosage form contains an appropriate amount to provide a substantially equivalent therapeutic effect. For example,
when the opioid analgesic comprises morphine, the sustained-release oral dosage forms of the present invention
include from about 5 mg to about 800 mg morphine, by weight (based on morphine sulfate). When the opioid analgesic
comprises oxycodone, the sustained-release oral dosage forms of the present invention include from about 5 mg to
about 400 mg oxycodone. When the opioid analgesic is tramadol, the sustained-release oral dosage forms of the
invention include from about 50 mg to about 800 mg tramadol by weight, based on the hydrochloride salt.

[0043] The sustained-release dosage forms of the present invention generally achieve and maintain therapeutic
levels substantially without significant increases in the intensity and/or degree of concurrent side effects, such as nau-
sea, vomiting or drowsiness, which are often associated with high blood levels of opioid analgesics. There is also
evidence to suggest that the use of the present dosage forms leads to a reduced risk of drug addiction.

[0044] In the present invention, the oral opioid analgesics have been formulated to provide for an increased duration
of analgesic. Surprisingly, these formulations, at comparable daily dosages of conventional immediate-release drug,
are associated with a lower incidence in severity of adverse drug reactions and can also be administered at a lower
daily dose than conventional oral medication while maintaining pain control.

[0045] When the therapeutically active agent included in the dosage forms of the present invention is an opioid
analgesic, the dosage form may further include one or more additional which may or may not act synergistically with
the opioid analgesics of the present invention. Examples of such additional therapeutically active agents include non-
steroidal anti-inflammatory agents, including ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen,
flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muprofen, trioxaprofen, suprofen,
aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidomet-
acin, acetmetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid
tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam or isoxicam, and the like. Other suitable additional drugs
which may be included in the dosage forms of the present invention include acetaminophen, aspirin, salicylate-derived
analgesics and antipyretics or salts thereof, and other non-opioid analgesics.

[0046] The additional (non-opioid) therapeutically active agent may be included in controlled release form or in im-
mediate release form. The additional drug may be incorporated into the controlled release matrix along with the opioid;
incorporated as a separated controlled release layer or immediate release layer; or may be incorporated as a powder,
granulation, etc., in a gelatin capsule with the extrudates of the present invention.

Matrix Ingredients

[0047] The extrudates of the present invention include at least one hydrophobic material. The hydrophobic material
will preferably impart sustained release of the opioid analgesic to the final formulation. Preferred hydrophobic materials
which may be used in accordance with the present invention include alkylcelluloses such as natural or synthetic cel-
luloses derivatives (e.g. ethylcellulose), acrylic and methacrylic acid polymers and copolymers, shellac, zein, wax-type
substances including hydrogenated castor oil or hydrogenated vegetable oil, or mixtures thereof. This list is not meant
to be exclusive, and any pharmaceutically acceptable hydrophobic material which is capable of imparting sustained
release of the active agent and which melts (or softens to the extent necessary to be extruded) may be used in ac-
cordance with the present invention.

[0048] In certain preferred embodiments of the present invention, the hydrophobic material is a pharmaceutically
acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacr-
ylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate
copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacr-
ylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and the

insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve constant release, the individual wax-like substances in the binder material should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial release phases.

[0050] Useful water-insoluble wax-like substances may be those with a water-solubility that is lower than about 1: 5,00 (w/w)

[0051] Such hydrophobic fusible carrier materials are preferably water-insoluble with more or less pronounced hydrophilic and/or hydrophobic stend. Preferably, the retardant materials useful in the invention have a melting point from about 30 to about 200°C, preferably from about 45 to about 90°C. Specifically, the hydrophobic fusible carrier may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic acid, stearyl alcohol and hydrophobic and hydrophilic polymers having hydrocarbon backbones. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax. For purposes of the present invention, a wax-like substance is defined as any material which is normally solid at room temperature and has a melting point of from about 30 to about 100°C.

[0052] Suitable hydrophobic fusible carrier materials which may be used in accordance with the present invention include digestible, long chain (C_8 - C_{50} , especially C_{12} - C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and natural and synthetic waxes. Hydrocarbons having a melting point of between 25° and 90°C are preferred. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred in certain embodiments.. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

[0053] In addition to the above ingredients, a sustained-release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation. In addition to the above ingredients, a sustained-release matrix incorporating melt-extruded multiparticulates may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art in amounts up to about 50% by weight of the particulate if desired. Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986), incorporated by reference herein.

[0054] In order to facilitate the preparation of a solid, sustained-release oral dosage form according to this invention there is provided, in a further aspect of the present invention, a process for the preparation of a solid, sustained-release oral dosage form according to the present invention comprising incorporating opioids or a salt thereof in a sustained-release melt-extruded matrix. Incorporation in the matrix may be effected, for example, blending the opioid analgesic, together with at least one hydrophobic material and preferably the additional retardant material (hydrophobic fusible carrier) to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded, e.g., using a twin-screw extruder, to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The strands are cooled and cut into multiparticulates. The multiparticulates are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 to about 5 mm and provides sustained release of the therapeutically active agent for a time period of from about 8 to about 24 hours.

[0055] An optional process for preparing the melt extrusions, multiparticulates and unit doses of the present invention includes directly metering into an extruder a water-insoluble retardant, a therapeutically active agent, and an optional binder; heating said homogenous mixture, extruding said homogenous mixture to thereby form strands; cooling said strands containing said homogeneous mixture; and cutting said strands into particles having a size from about 0.1 mm to about 12 mm; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

[0056] The diameter of the extruder aperture or exit port can also be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

[0057] The melt extruded multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit orifice. For purposes of the present invention, the terms "melt-extruded multiparticulate(s)" and "melt-extruded multiparticulate system(s)" and "melt-extruded particles" shall refer to a plurality of units, preferably within a range of similar size and/or shape and containing one or more active agents and one or more excipients, preferably including a retardant as described herein. In this regard, the melt-extruded multiparticulates will

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[0058] A particular advantage provided by the invention is the preparation of sustained-release melt-extruded multiparticulate formulations which do not require further processing, e.g., the extrudate may simply be cut into desired lengths and divided into unit doses of the therapeutically active agent without the need of a spheronization step.

[0059] In one preferred embodiment, oral dosage forms are prepared to include an effective amount of melt-extruded multiparticulates within a capsule. For example, a plurality of the melt-extruded multiparticulates may be placed in a gelatin capsule in an amount sufficient to provide an effective sustained-release dose when ingested and contacted by gastric fluid.

[0060] In another preferred embodiment, a suitable amount of the multiparticulate extrudate is compressed into an oral tablet using conventional tableting equipment using standard techniques. Techniques and compositions for making tablets (compressed and molded), capsules (hard and soft gelatin) and pills are also described in Remington's Pharmaceutical Sciences, (Arthur Osol, editor), 1553-1593 (1980), incorporated by reference herein.

[0061] In yet another preferred embodiment, the extrudate can be shaped into tablets as set forth in U.S. Patent No. 4,957,681 (Klimesch, et. al.), described in additional detail above and hereby incorporated by reference.

[0062] In yet a further embodiment, the extrudate can be shaped into suppositories containing a unit dose of the therapeutically active agent. This may be accomplished using techniques and equipment well known to those skilled in the art.

[0063] Optionally, the sustained-release melt-extruded multiparticulate systems or tablets can be coated, or the gelatin capsule can be further coated, with a sustained-release coating comprising one of the hydrophobic materials described above. Such coatings preferably include a sufficient amount of hydrophobic material to obtain a weight gain level from about 2 to about 30 percent, although the overcoat may be greater depending upon the physical properties of the particular opioid analgesic compound utilized and the desired release rate, among other things. In certain preferred embodiments of the present invention, the hydrophobic polymer comprising the sustained-release coating is a pharmaceutically acceptable acrylic polymer, such as those described hereinabove. The solvent which is used for the hydrophobic material in the coating may be any pharmaceutically acceptable solvent, including water, methanol, ethanol, methylene chloride and mixtures thereof.

[0064] The unit dosage forms of the present invention may further include combinations of melt-extruded multiparticulates containing one or more of the therapeutically active agents disclosed above before being encapsulated. Furthermore, the unit dosage forms can also include an amount of an immediate release therapeutically active agent for prompt therapeutic effect. The immediate release therapeutically active agent may be incorporated, e.g., as separate pellets within a gelatin capsule, or may be coated on the surface of the compressed tablet which has been prepared from the multiparticulate extrudate as set forth above.

[0065] The controlled-release formulations of the present invention slowly release the therapeutically active agent, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The controlled-release profile of the melt-extruded formulations of the invention can be altered, for example, by varying the amount of retardant, i.e., hydrophobic polymer, by varying the amount of plasticizer relative to hydrophobic polymer, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. In certain embodiments of the invention, the sustained-release dosage forms of the present invention preferably release the therapeutically active agent at a rate that is independent of pH, e.g., between pH 1.6 and 7.2. In other embodiments, the formulations can be designed to provide a pH-dependent release of the therapeutically active agent.

[0066] In other embodiments of the invention, the melt extruded material is prepared without the inclusion of the therapeutically active agent, which is added thereafter to the extrudate. Such formulations typically will have the therapeutically active agent blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release formulation. Such formulations may be advantageous, for example, when the therapeutically active agent included in the formulation is sensitive to temperatures needed for softening the material and/or the retardant material.

Opioid Analgesic Formulations

[0067] In certain preferred embodiments, the invention is directed to sustained-release oral opioid formulations which are administrable on a once-a-day basis, and which are prepared from the melt extrudates described herein. Such dosage forms will provide an in-vitro release (when assessed by the USP Paddle or Basket Method at 100 rpm at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37°C from about 1 to about 42.5% opioid released after one hour, from about 5 to about 65% opioid released after 2 hours, from about 15 to about 85% opioid released after 4 hours, from about 20 to about 90% opioid released after 6 hours, from about 35 to about 95% opioid released after 12 hours, from about 45 to about 100% opioid released after 18 hours, and from about 55 to about 100% opioid released after 24

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[0068] In certain preferred embodiments, the oral 24 hour sustained-release opioid dosage form provides a rapid rate of initial rise in the plasma concentration of the opioid after oral administration, such that the peak plasma level obtained in-vivo occurs from about 2 to about 8 hours after oral administration, and/or the absorption half-life is from about 1 to about 8 hours after oral administration (in the fasted state). More preferably in this embodiment the absorption half-life is 1-6 hours and possibly 1-3 hours after oral administration (in the fasted state). Such formulations provide an in-vitro dissolution under the conditions specified above, from about 12.5 to about 42.5% opioid released after one hour, from about 25 to about 65% opioid released after 2 hours, from about 45 to about 85% opioid released after 4 hours, and greater than about 60% opioid released after 8 hours, by weight.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0069] The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

MELT-EXTRUSION TECHNIQUES

[0070] Typical melt extrusion systems capable of carrying-out the present invention include a suitable extruder drive motor having variable speed and constant torque control, start-stop controls, and ammeter. In addition, the system will include a temperature control console which includes temperature sensors, cooling means and temperature indicators throughout the length of the extruder. In addition, the system will include an extruder such as twin-screw extruder which consists of two counterrotating intermeshing screws enclosed within a cylinder or barrel having an aperture or die at the exit thereof. The feed materials enter through a feed hopper and is moved through the barrel by the screws and is forced through the die into strands which are thereafter conveyed such as by a continuous movable belt to allow for cooling and being directed to a pelletizer or other suitable device to render the extruded ropes into the multiparticulate system. The pelletizer can consist of rollers, fixed knife, rotating cutter and the like. Suitable instruments and systems are available from distributors such as C.W. Brabender Instruments, Inc. of South Hackensack, New Jersey. Other suitable apparatus will be apparent to those of ordinary skill in the art.

[0071] A further aspect of the invention is related to the preparation of melt extruded multiparticulates as set forth above in a manner which controls the amount of air included in the extruded product. By controlling the amount of air included in the extrudate, it has been surprisingly found that the release rate of the therapeutically active agent from the, e.g., multiparticulate extrudate, can be altered significantly. In certain embodiments, it has been surprisingly found that the pH dependency of the extruded product can be altered as well.

[0072] Thus, in a further aspect of the invention, the melt extruded product is prepared in a manner which substantially excludes air during the extrusion phase of the process. This may be accomplished, for example, by using a Leistritz extruder having a vacuum attachment. It has been surprisingly found that extruded multiparticulates prepared according to the invention using the Leistritz extruder under vacuum provides a melt-extruded product having different physical characteristics. In particular, the extrudate is substantially non-porous when magnified, e.g., using a scanning electron microscope which provides an SEM (scanning electron micrograph). Contrary to conventional thought, it has been found that such substantially non-porous formulations provide a faster release of the therapeutically active agent, relative to the same formulation prepared without vacuum. SEMs of the multiparticulates prepared using an extruder under vacuum appear very smooth, and the multiparticulates tend to be more robust than those multiparticulates prepared without vacuum. It has been observed that in at least certain formulations, the use of extrusion under vacuum provides an extruded multiparticulate product which is more pH-dependent than its counterpart formulation prepared without vacuum.

General Pellet Manufacturing Procedure

[0073] The following technique was used to manufacture the extrudate and multiparticulates for Examples 1-26:

Blend the required amount of drug, hydrophobic material and binder along with any additional excipients.
 Charge a powder feeder with proper amount of drug/ excipient blend.
 Set temperatures of extruder heating zones to the required temperature, depending on the formulation. Typically, the temperature should be set at about 83 ° C. Wait until the corresponding heating zones reach steady temperatures. Set the extruder screw rotation speed to 20 rpm. Start the feeder, the conveyor and the pelletizer. After the excipients are melted and the drug is embedded in the molten mixture, the resultant viscous mass is extruded as

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to be congealed and/or hardened while transported to the pelletizer on the conveyor belt. Additional cooling devices may be needed to ensure proper congealing. (The conveyor belt may not be needed to cool the strand, if the material congeals rapidly enough.)

Set the roller knife to an appropriate speed (e.g., to 3-100 ft/min and 100-800 rpm). Cut the congealed strands to desired size (e.g., 3-5 mm in diameter, 0.3-5 mm in length).

Collect the pellet product.

Fill a desired weight of pellets into hard gelatin capsules to obtain an appropriate doses of the drug.

Dissolution Method

[0074] The following dissolution method was used to obtain dissolution profiles for the dosage forms of Examples 1-25:

(USP II Paddle at 100 rpm at 37°C)

[0075] Media - 1st hour in 700 ml simulated gastric fluid (SGF), pH 1.2 without enzyme thereafter, 900 ml simulated intestinal fluid (SIF), pH 7.5 without enzyme

Using HPLC procedures for assay

[0076] The following examples illustrate various aspects of the present invention. They are not meant to be construed to limit the claims in any manner whatsoever.

EXAMPLES 1-2

CONTROLLED RELEASE CHLORPHENIRAMINE FORMULATIONS

[0077] In these examples, chlorpheniramine maleate controlled release pellets were prepared according to the above manufacturing procedure using ethylcellulose and an acrylic polymer (Eudragit RSPO), respectively as the retardant. The formulations are set forth in Tables 1 and 2 below. The dissolution of these formulations is set forth in Figure 1. Drug release rate from ethylcellulose pellets (prepared at 105°C) is significantly slower than that from Eudragit RSPO pellets (prepared at 85°C).

TABLE 1

EX. 1	
Composition	Amt. (mg) per Capsule
Chlorpheniramine Maleate	60
Ethyl Cellulose	84
Stearic Acid	36
Total	180

TABLE 2

EX. 2	
Composition	Amt. (mg) per Capsule
Chlorpheniramine Maleate	60
Eudragit RSPO	84
Stearic Acid	36
Total	180

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EXAMPLES 3-6

CONTROLLED RELEASE MORPHINE FORMULATIONS

[0078] Ex. 3 The excipients used in Ex. 2 were employed to make morphine sulfate controlled release pellets.

TABLE 3

EX. 3	
Composition	Amt. (mg per Capsule)
Morphine Sulfate	60
Eudragit RSPO	42
Stearic Acid	18
Total	120

[0079] The drug release rate of Example 3 was slower than expected especially during later hours of the dissolution.

[0080] Ex. 4-5 Examples 4-5 were prepared in accordance with Example 3 above. To increase the drug dissolution rate during later hours, varying amounts of Eudragit L-100 were incorporated in the formulation. The drug dissolution rate increases with increasing amount of Eudragit L-100 in the formulation. The morphine sulfate capsule formulation are set forth in tables 4-6 below:

TABLE 4

EX. 4	
Composition	Amt. (mg) per Capsule
Morphine Sulfate	60
Eudragit RSPO	38.4
Eudragit L-100	3.6
Stearic Acid	18
Total	120

TABLE 5

EX. 5	
Composition	Amt. (mg) per Capsule
Morphine Sulfate	60
Eudragit RSPO	33.6
Eudragit L-100	8.4
Stearic Acid	18
Total	120

[0081] Ex. 6. A sustained release morphine sulfate formulation was prepared having the ingredients listed in Table 6 below:

TABLE 6

Ingredients	Amt(mg)/Capsule	Percentage in Formula
Morphine Sulfate	60	50
Eudragit RSPO	26	22

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TABLE 6 (continued)

Ingredients	Amt(mg)/Capsule	Percentage in Formula
Stearic Acid	18	15
Total	120	100

The formulation of Example 6 was prepared as follows:

Pellet Manufacture

[0082]

a. Extruder system description- The twin screw extruder is consisted of a pair of counterrotating screws and a barrel block equipped with heating/cooling zones. The extrudate is delivered to a pelletizer through a conveyor belt and cut into pellets of the desirable size.

b. Manufacturing procedure-

1. Blend the drug and all the excipients in a proper mixer.
2. Place the mixture in a powder feeder.
3. Set temperatures of the extruder heating zones to approximately 83°C.
4. Set the extruder screw rotation speed to 20 rpm.
5. Start the feeder, the conveyor and the pelletizer.
6. After the excipients are melted and the drug embedded in the molten mixture, the viscous mass is extruded as spaghetti-like strands.
7. The extrudate is congealed and hardened while being delivered to the pelletizer on the conveyor belt.
8. The roller knife of the pelletizer cuts the strands into pellets of 1.5 mm in diameter and 1.5 mm in length.

Encapsulation

[0083] After the pellets were manufactured, 120 mg of pellets are encapsulated in size #2 hard gelatin capsules, rendering capsules containing 60 mg of morphine sulfate. These capsules were then tested using the following dissolution methodology:

[0084] The capsules of Example 6 were found to have the following dissolution results:

Time (hr)	1	2	4	8	12	18	24
Mean % dissolved	16	33	52	72	84	95	102

[0085] As seen in Figure 3, the drug dissolution rate obtained from the product of Ex. 3 showed a significant pH dependency. The release rate was slower in SIF (simulated intestinal fluid) than in SGF (simulated gastric fluid).

[0086] In Figure 4, it can be seen that due to the addition of Eudragit L-100, the drug dissolution rate obtained from Ex. 6 was less pH dependent. The drug release rate was faster in SIF during later hours of dissolution which is desirable for complete bioavailability.

EXAMPLES 7-8

[0087] As demonstrated in Fig. 5, with proper choice of plasticizers, the drug release rate from the formula containing Eudragit L-100 can be reduced. This may be necessary to achieve desirable plasma drug concentration profiles after oral administration of the pellets.

TABLE 7

EX.7	
Composition	Amt. (mg) per Capsule

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EXAMPLES 11-14**CONTROLLED RELEASE OXYCODONE FORMULATIONS**

[0089] The formula used in Ex. 6 was applied to oxycodone hydrochloride. Due to the higher potency of oxycodone, only 20 mg of drug was used. The missing 40 mg was replaced by 40 mg of talc (Ex. 12). No replacement was used in Ex. 11. When tested in only SGF or SIF, the use of Eudragit L causes the formulation to become less pH dependent. The results are shown in Figure 7.

TABLE 11

Ingredients	Amt(mg)/Capsule	Percentage in Formula
Oxycodone HCL	20	25
Eudragit RSPO	36	45
Eudragit L-100	6	7.5
Stearic Acid	18	22.5
Total	80	100

[0090] The pellet manufacturing procedure and the dissolution method are the same as described in Example 6.

[0091] The above capsules were found to have the dissolution results set forth in Table 11a below:

TABLE 11a

Time (hr)	1	2	4	8	12	18	24
Mean % dissolved	14	26	45	66	81	94	101

TABLE 12

EX. 12	
Composition	Amt. (mg) per Capsule
Oxycodone Hydrochloride	20
Eudragit RSPO	36
Eudragit L-100	6
Stearic Acid	18
Talc	40
Total	120

[0092] Ex. 13 Oxycodone HCl once-a-day capsules were produced with the following formula using the technology described in Example 6. The formulation is set forth in Table 13 below.

TABLE 13

Ingredients	Amt(mg)/Capsule	Percentage in Formula
Oxycodone HCl	20	25
Eudragit RSPO	39	48.75
Eudragit L-100	3	3.75
Stearic Acid	18	22.5
Total	80	100

[0093] The pellet manufacturing procedure is the same as described in Example 6. However, 80 mg of pellets were

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1. Apparatus-USP type II (paddle), 100rpm at 37°C
2. Media- Either 900 ml simulated gastric fluid (SGF), pH 1.2 without enzyme. or 900 ml simulated intestinal fluid (SIF), pH 7.5 without enzyme.
3. Analytical method- High performance liquid chromatography.

[0095] The dissolution results are set forth in Table 13a below:

TABLE 13a

Time(hr)	1	2	4	8	12	18	24
Mean % dissolved (SGF)	13	20	29	41	51	62	71
Mean % dissolved (SIF)	14	21	31	44	57	68	80

[0096] Ex. 14 To prepare an oxycodone HCl controlled release tablet which would dissolve preferentially in a lower pH, the following formula is used:

TABLE 14

Ingredients	Amt(mg)/Tablet	Percentage in Formula
Oxycodone HCl	40	30.8
Eudragit RS30D (solid)	14	10.8
Spray Dried Lactose	35.25	27.1
PVP	5	3.9
Triacetin	2	1.5
Stearyl Alcohol	25	19.2
Talc	2.5	1.9
Magnesium Stearate	1.25	0.9
Film Coat	5	3.9
Total	130	100

Total Manufacture

[0097]

1. Mix Eudragit RS30D (suspension) and Triacelin for 5 minutes.
2. Place spray dried lactose, oxycodone HCl, PVP, in a fluid bed drier.
3. Spray the suspension onto the powders under fluidization.
4. Pass the granulation through a Comil to reduce lumps.
5. Melt stearyl alcohol at 70°C.
6. Incorporate the molten stearyl alcohol into the dry granulation in a Collete Mixer.
7. Transfer the waxed granulation to a cooling tray and allow the granulation to congeal.
8. Pass the granulation through a Comil.
9. Mix the waxed granulation with talc and magnesium stearate in a Collete Mixer.
10. Compress the lubricated granulation into tablets using a rotary tablet press.
11. Film coat the tablets.

[0098] These tablets were then tested using the following dissolution methodology described in Example 13.

[0099] The above tablets were found to have the following dissolution results:

TABLE 14a

Time (hr)	1	2	4	8	12
Mean % dissolved SGF	39	53	70	90	99
Mean % dissolved SIF	35	48	65	83	93

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EXAMPLES 15-19**CONTROLLED RELEASE HYDROMORPHONE FORMULATIONS**

[0100] Ex. 15-16 The formula used in Ex. 6 was applied to hydromorphone hydrochloride. Due to the higher potency of hydromorphone, only 8 mg of drug was used. The missing 52 mg was replaced by 52 mg of talc (Ex. 16) or 52 mg of excipients (Ex. 15). The results are shown in Figure 8.

TABLE 15

EX. 15	
Composition	Amt. (mg) per Capsule
Hydromorphone Hydrochloride	8
Eudragit RSPO	67.2
Eudragit L-100	11.2
Stearic Acid	33.6
Total	120

TABLE 16

EX. 16	
Composition	Amt. (mg) per Capsule
Hydromorphone Hydrochloride	8
Eudragit RSPO	36
Eudragit L-100	6
Stearic Acid	18
Talc	52
Total	120

[0101] Ex. 17 Hydromorphone HCl once-a-day capsules were produced with the formula set forth in Table 17 below using the technology described in Example 6.

TABLE 17

Ingredients	Amt(mg)/Capsule	Percentage in Formula
Hydromorphone HCL	8	10
Eudragit RSPO	53	66.25
Stearyl Alcohol	19	23.75
Total	80	100

[0102] The pellet manufacturing procedure is the same as described in Example 6. However, pellets of 1.0 mm in diameter and 1.0 mm in length were prepared. Each capsule holds 80 mg of pellets and contains 8 mg of hydromorphone HCL.

[0103] The above capsules were tested using the dissolution methodology described in Example 6.

[0104] The above capsules were found to have the dissolution results set forth in Table 17a below:

TABLE 17a

Time (hr)	1	2	4	8	12	18	24
Mg. Released	17	33	45	53	60	66	73

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as the second example of the technology described in Example 6.

TABLE 18

Ingredients	Amt(mg)/Capsule	Percentage in Formula
Hydromorphone HCl	8	10
Eudragit RSPO	48	60
Stearyl Alcohol	24	30
Total	80	100

[0106] The pellet manufacturing procedure and the dissolution method are the same as described in Example 6.

[0107] The above capsules were found to have the dissolution results set forth in Table 18a below:

TABLE 18a

Time (hr)	1	2	4	8	12	18	24
Mean % dissolved	23	29	40	56	69	84	96

[0108] Ex. 19 Hydromorphone HCl once-a-day capsules were produced with the following formula according to the method described Example 6.

TABLE 19

Ingredients	Amt(mg)/Capsule	Percentage in Formula
Hydromorphone HCL	8	10
Eudragit RSPO	41.5	51.9
Eudragit L-100	8.5	10.6
Stearic Acid	22	27.5
Total	80	100

[0109] The manufacturing procedure of the pellets and the dissolution method are the same as described in Example 6.

[0110] The above capsules were found to have the following dissolution results:

TABLE 19a

Time (hr)	1	2	4	8	12	18	24
Mean % dissolved	4	14	36	52	64	75	84

EXAMPLE 20

[0111] In this Example, a bioavailability study was undertaken. Fourteen subjects were given the morphine sulfate formulations of Example 3. The results are provided in Table 20 below in Figure 10.

TABLE 20

Group	AUC	Cmax	Tmax
Example 3 Fasted	230	15.7	2.1
Example 3 Fed	213	14.0	3.2

[0112] From the above data, it can be seen that the formulation is an ideal candidate for an extended release or once-a-day product without a food effect.

EXAMPLE 21

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[0114] A bioavailability study of morphine capsules of Example 6 was conducted in 12 normal male volunteers. Capsules of 60 mg in strength were administered either with or without food in a single dose, two-way crossover study. Blood samples were taken periodically and assayed for morphine concentrations using gas chromatography with mass detection (G/MS). From the data, the following pharmacokinetic parameters were calculated and are indicated in Table 21 below.

TABLE 21

Treatment	AUC, n. hr/ml	Cmax, n/ml	Tmax, hr
Fasted	228	15.7	2.1
Fed	210	14.0	3.2

[0115] When compared to the typical blood levels of MS Contin®, a single dose twice-a-day marketed morphine sulfate 30 mg tablets, in the fasted state, it can be seen that the capsules of Example 6 are suitable for once daily administration. At the 24th hour the blood levels are well above MS-Contin and within the therapeutic range (Figure 11).

EXAMPLE 22

Bioavailability of OXY-MEM 20 mg capsules.

[0116] A bioavailability study of oxycodone capsules of examples 11 and 13 was conducted in 10 normal male volunteers. Capsules of example 13 were administered either with or without food. Capsules of example 11 were administered without food. The study was conducted in a single dose, four-way crossover design. Blood samples were taken periodically and assayed for oxycodone concentrations using gas chromatography with mass detection (G/MS).

[0117] From the data, the following pharmacokinetic parameters were calculated as set forth in Table 22 below:

TABLE 22

Treatment	AUC, n. hr/ml	Cmax, n/ml	Tmax, hr
Example 13, fasted	207	9.7	5.3
Example 13, fed	261	14.8	6.4
Example 11, fasted	244	12.9	6.0
Oxycontin, fasted	249	20.8	3.2

[0118] From the above data, it can be concluded that both Examples 11 and 13, but particularly Example 13, are suitable for once daily administration. This is shown graphically in Figure 12.

EXAMPLE 23

Bioavailability of Example 14 Tablets.

[0119] A bioavailability study of oxycodone controlled release tablets of example 14 was conducted in 25 normal volunteers. These tablets were administered either with or without food. The study was conducted in a single dose, randomized crossover design. Blood samples were taken periodically and assayed for oxycodone concentrations using gas chromatography with mass detection (GC/MS). The plasma oxycodone concentration versus time curves are shown in Figure 13.

[0120] From the data, the following pharmacokinetic parameters were calculated.

TABLE 23

Treatment	AUC, ng.hr/ml	Cmax, ng/ml	Tmax, hr
Example 14, fasted	422	39.3	3.1
Example 14, fed	416	35.3	4.8

[0121] Surprisingly, it was found that the controlled release oxycodone HCl preparation, which dissolved preferen-

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AUC (area under the curve) data, it appears that the amount of drug absorbed with or without food is similar ($416/422=0.986$).

EXAMPLE 24

Bioavailability of HH-MEM 8 mg capsules.

[0122] A bioavailability study of hydromorphone capsules of Examples 17 and 18 was conducted using a single dose, five-way crossover study in 12 normal male volunteers. The subjects received either 8 mg of Dilaudid tablet (immediate release) or 8 mg of HH-MEM capsules. Dilaudid tablets were administered after an overnight fast. MEM capsules were administered with or without food. Blood samples were taken periodically and assayed for hydromorphone concentrations using gas chromatography with mass detection (G/MS). From the data, the following pharmacokinetic parameters were calculated.

TABLE 24

Treatment	AUC, n. hr/ml	Cmax, n/ml	Tmax, hr
Example 17, fasted	19.23	0.76	3.9
Example 17, fed	21.47	0.93	1.9
Example 18, fasted	19.00	0.72	6.8
Example 18, fed	20.10	0.75	2.4
Dilaudid, fasted	14.55	3.69	0.7

[0123] From the above data, both formulations 17 and 18 would be suitable for once-a-day administration both not having a food effect, and in fact Example 17 looks ideal. The data of Example 17 is shown graphically in Figure 14 and the data of Example 18 is shown graphically in Figure 15.

EXAMPLE 25

Steady State Bioavailability of HH-MEM 8 mg capsules.

[0124] To assess steady state plasma levels and the effect of food on hydromorphone, a single dose, two-way cross-over study was conducted in 12 normal male volunteers. The subjects received either 4 mg of Dilaudid (immediate release) every 6 hours or 16 mg of the capsules according to Example 17 every 24 hours. Venous blood samples were taken at predetermined time points. The plasma hydromorphone concentrations were quantitated using gas chromatography with mass detection (G/MS).

[0125] From the data from day 4, the following pharmacokinetic parameters were calculated and are set forth in Table 25 below.

TABLE 25

Treatment	AUC, n. hr/ml	Cmax, n/ml	Cmin, n/ml	Tmax, hr
Example 16	36.08	2.15	1.49	5.8
Dilaudid	33.53	3.44	0.94	1.6

[0126] The results are shown graphically in Figure 16. From this data it can be seen that Example 17 is an ideal product for once-a-day administration for either single dose or multiple dose administration.

EXAMPLE 26

Bioavailability of HH-MEM 8 mg capsules.

[0127] To assess bioavailability and effect of food on hydromorphone MEM capsules, a single dose, three-way cross-over study was conducted in 12 normal male volunteers. The subjects received either 8 mg of Dilaudid tablet (immediate release) or 8 mg of HH-MEM (Example 19). Dilaudid tablets were administered after an overnight fast. MEM capsules

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[0128] From the data, the following pharmacokinetic parameters were calculated and are set forth in Table 26 below.

TABLE 26

Treatment	AUC, n. hr/ml	Cmax, n/ml	Tmax, hr
Example 18, fasted	15.83	0.52	5.6
Example 18, fed	16.55	0.65	4.1
Dilaudid, fasted	16.54	3.15	0.8

[0129] From the above data it can be concluded that a once-a-day Hydromorphone product can be produced using other ingredients than are used for Examples 17 and 18. This data is shown graphically in Figure 17.

EXAMPLE 27

Tramadol HCl 200 mg SR Tablet

[0130] The following formula is used to prepare melt extrusion granulation and tablet.

TABLE 27

Ingredients	Amt(mg)/Tablet	Percentage in Formula
Tramadol HCl	200	53.4
Eudragit RSPO	74	19.8
Tributyl Citrate	14.8	4.0
Stearyl Alcohol	74	19.8
Talc	7.4	2.0
Magnesium Stearate	38	10.0
Total	374	100

Granulation Manufacture

[0131]

a. Extruder system description- The twin screw extruder is consisted of a pair of counterrotating screws and a barrel block equipped with heating/cooling zones. The stranded extrudate is congealed on a conveyor belt and cut into pellets of the desirable size.

b. Manufacturing procedure-

1. Blend the drug and all the excipients in a proper mixer.
2. Place the mixture in a powder feeder.
3. Set temperatures of the extruder heating zones to approximately 65 °C.
4. Set the extruder screw rotation speed to 40 rpm.
5. Start the feeder and the conveyor.
6. After the excipients are melted and the drug embedded in the molten mixture, the viscous mass is extruded as spaghetti-like strands.
7. The extrudate is congealed and hardened while being carried away on a conveyor belt.
8. The stranded extrudate was cut into pellets of 2 mm in diameter and 2-8 cm in length.

Tabletting

[0132] The pellets were milled into granules through a suitable screen. The granulation was blended with talc and magnesium stearate. The mixture was then compressed into capsule-shaped tablets.

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Dissolution Method

[0133]

1. Apparatus- USP Type II (paddle), 100 rpm at 37°C.
2. The tablet was placed in a tablet sinker clip and immersed in each vessel.
3. Media- 900 ml pH 6.5 phosphate buffer.
4. Analytical method- High performance liquid chromatography.

[0134] The above tablets were found to have the following dissolution results:

TABLE 27a

Time(hr)	1	2	4	8	12	18	24
Mean% dissolved	24	33	45	61	71	82	88

EXAMPLE 28

Tramadol HCl 200 mg SR Tablet

[0135] The following formula is used to prepare melt extrusion granulation and tablet with a slower dissolution profile than example 27.

TABLE 28

Ingredients	Amt(mg)/Tablet	Percentage in Formula
Tramadol HCl	200	44.1
Ethyl cellulose	110	24.3
Tributyl Citrate	22	4.9
Stearyl Alcohol	110	24.3
Talc	7.4	1.6
Magnesium Stearate	3.8	0.8
Total	453.2	100

[0136] The manufacturing procedure and dissolution method are the same as described in example 27. Additional dissolution media used include pH 1.2 simulated gastric fluid (SGF) without enzyme, pH 7.5 simulated intestinal fluid (SIF) without enzyme, and pH 4 phosphate buffer.

[0137] The above tablets were found to have the following dissolution results:

TABLE 28a

Time(hr)		1 2 4			8	12	18	24
Mean % dissolved	SGF	18	26	35	49	59	70	80
	pH4	17	25	34	49	60	73	83
	pH6.5	17	23	33	46	57	70	81
	SIF	17	23	32	45	56	68	78

[0138] The results show that the dissolution profiles of Tramadol SR tablets in media of different pH values are similar. Based on our experience with similar formulae of other opiates, a formula which demonstrates pH independent dissolution profile would provide a consistent drug release profile in vivo without food effect.

[0139] The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

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agent, one or more hydrophobic materials selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, and mixtures thereof; and one or more hydrophobic fusible carriers which provide a further retardant effect and selected from the group consisting of natural or synthetic waxes, fatty acids, fatty alcohols, and mixtures thereof, said hydrophobic fusible carrier having a melting point from 30 to 200°C, said melt-extruded blend divided into a unit dose containing an effective amount of said therapeutically active agent to render a desired therapeutic effect and providing a sustained-release of said therapeutically active agent for a time period of from about 8 to about 24 hours.

2. The formulation of claim 1, wherein said extrudate comprises a strand-shaped matrix cut into multi-particulates having a length of from about 0.1 to about 5 mm in length.
3. The formulation of claim 1, wherein said extrudate has a diameter of from about 0.1 to about 5 mm.
4. The formulation of claim 1, wherein said therapeutically active agent is an opioid analgesic.
5. The formulation of claim 4, wherein said opioid analgesic is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacetyl morphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, naltorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, proph-eptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, salts thereof and mixtures thereof.
6. The extrudate of claim 1, wherein said opioid analgesic is selected from the group consisting of morphine, codeine, hydromorphone, hydrocodone, oxycodone, oxymorphone, dihydrocodeine, dihydromorphine, tramadol and mixtures thereof.
7. The formulation of claim 2, wherein a unit dose comprising an effective amount of said multiparticulates to render a therapeutic effect is contained within a gelatin capsule.
8. The formulation of claim 2, wherein a unit an effective amount of said multiparticulates to render a therapeutic effect is compressed into a tablet.
9. The formulation of claim 8, wherein said therapeutically active agent is tramadol.
10. The formulation of claim 7 wherein said therapeutically active agent is an opioid analgesic selected from the group consisting of morphine, codeine, hydromorphone, hydrocodone, oxycodone, oxymorphone, dihydrocodeine, dihydromorphine, tramadol and mixtures thereof.
11. The formulation of claim 10, which provides an in-vitro release (when assessed by the USP Paddle or Basket Method at 100 rpm at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37°C from about 1 to about 42.5% opioid released after one hour, from about 5 to about 65% opioid released after 2 hours, from about 15 to about 85% opioid released after 4 hours, from about 20 to about 90% opioid released after 6 hours, from about 35 to about 95% opioid released after 12 hours, from about 45 to about 100% opioid released after 18 hours, and from about 55 to about 100% opioid released after 24 hours, by weight.
12. The formulation of claim 10, which provides a peak plasma level at from about 2 to about 8 hours after oral administration, and preferably from about 4 to about 6 hours after administration.
13. The formulation of claim 10, which provides a W_{50} from about 4 to about 12 hours.

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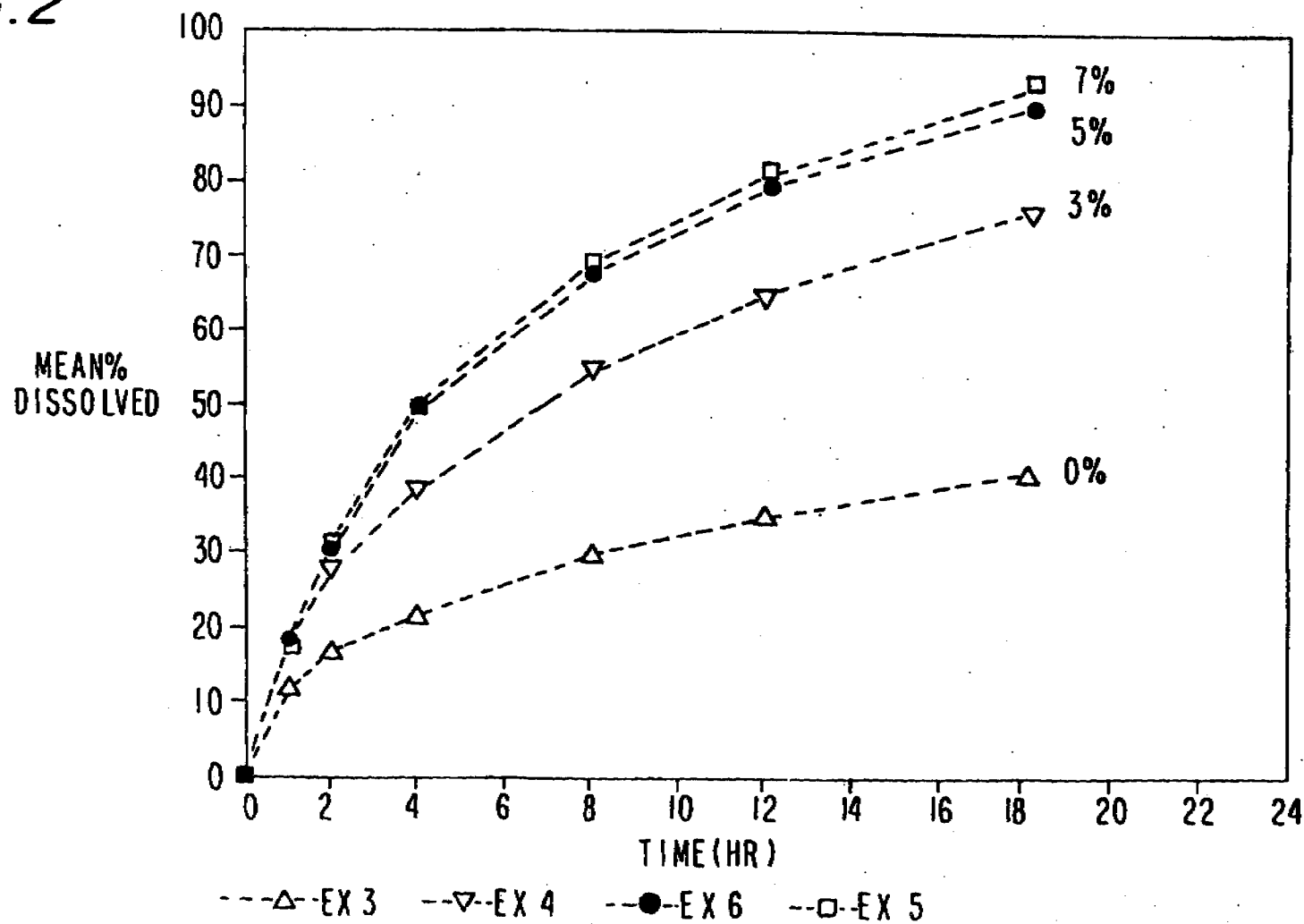
15. The formulation of claim 10, which provides a rapid rate of initial rise in the plasma concentration of the opioid after oral administration, such that the absorption half-life is from about 1 to about 8 hours after oral administration (in the fasted state).
16. The formulation of claim 10, which provides an in-vitro release (when assessed by the USP Paddle or Basket Method at 100 μ m at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37°C from about 12.5 to about 42.5% opioid released after one hour, from about 25 to about 65% opioid released after 2 hours, from about 45 to about 85% opioid released after 4 hours, and greater than about 60% opioid released after 8 hours, by weight).
17. The formulation of claim 1, wherein said extruded blend is substantially non-porous.
18. A method of preparing a sustained-release pharmaceutical extrudate suitable for oral administration, comprising:
- blending a therapeutically active agent together with (1) a hydrophobic material selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, and mixtures thereof and (2) a hydrophobic fusible carrier selected from the group consisting of natural or synthetic waxes, fatty acids, fatty alcohols, and mixtures thereof; said retardant material having a melting point between 30-200°C and being included in an amount sufficient to further slow the release of the therapeutically active agent,
- heating said blend to a temperature sufficient to soften the mixture sufficiently to extrude the same;
- extruding said heated mixture as a strand having a diameter of from 0.1 - 3 mm;
- cooling said strand; and
- dividing said strand to form non-spheroidal multi-pariculates of said extrudate having a length from 0.1 - 5 mm; and
- dividing said non-spheroidal multi-pariculates into unit doses containing an effective amount of said therapeutically active agent, said unit dose providing a sustained-release of said therapeutically active agent for a time period of from about 8 to about 24 hours.
19. The method of claim 18, wherein said therapeutically active agent is an opioid analgesic is selected from the group consisting of alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, fentanyl, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levallorphan, levorphanol, levophenacyl morphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicomorphine, norlevorphanol, normethadone, naltorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tramadol, tilidine, salts thereof and mixtures thereof.
20. The method of claim 18, further comprising containing said unit dose of said multiparticulates within a gelatin capsule.
21. The method of claim 18, further comprising compressing said unit dose of multi-particulates into a tablet.
22. The method of claim 18, further comprising extruding said heated mixture under vacuum conditions to provide a substantially non-porous extrudate.
23. A sustained-release pharmaceutical formulation, comprising a melt-extruded blend of an opioid analgesic and one or more hydrophobic materials selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, and mixtures thereof; said melt-extruded blend divided into a unit dose containing an effective amount of said therapeutically active agent to render a desired therapeutic effect and providing a sustained-release of said therapeutically active agent for a time period of from about 8 to about 24 hours.

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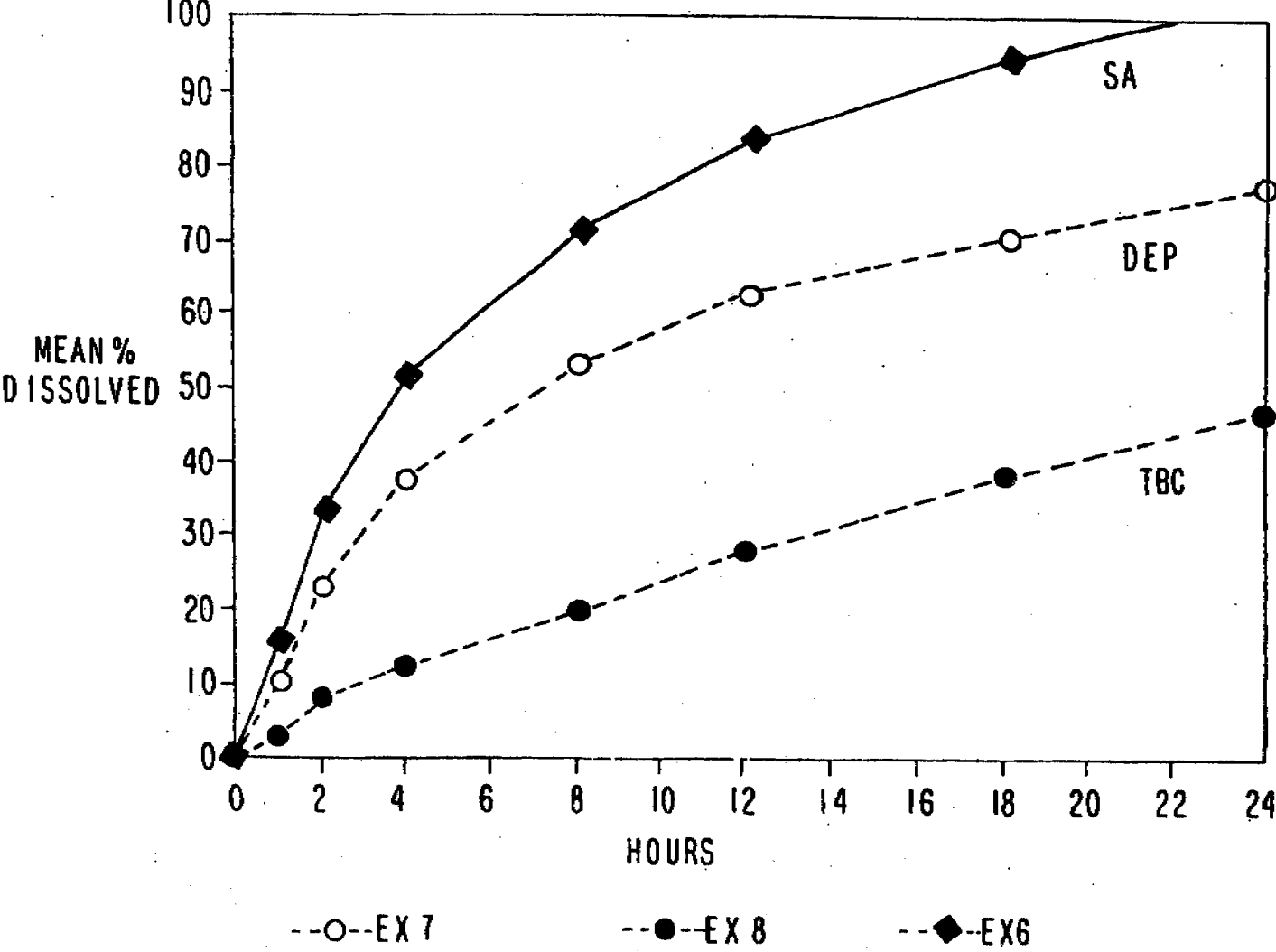
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- 10
- 15
- 20
- 25
- 30
- 35
- 40
- 45
- 50
- 55
25. A method of controlling the release characteristics of a therapeutically active agent from sustained-release pharmaceutical extrudate suitable for oral administration, the sustained-release pharmaceutical extrudate being prepared by blending a therapeutically active agent together with (1) a hydrophobic material selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, and mixtures thereof and (2) an optional hydrophobic fusible carrier retardant material selected from the group consisting of natural or synthetic waxes, fatty acids, fatty alcohols, and mixtures thereof; said optional hydrophobic fusible carrier having a melting point between 30-200°C; heating said blend to a temperature sufficient to soften the mixture sufficiently to extrude the same; extruding said heated mixture as a strand having a diameter of from 0.1 - 3 mm; cooling said strand; and optionally dividing said strand to form multiparticulates of said extrudate; the method comprising controlling the amount of air present during said extrusion phase and thereby controlling the porosity of the extrudate thereby obtained.

FIG. 2



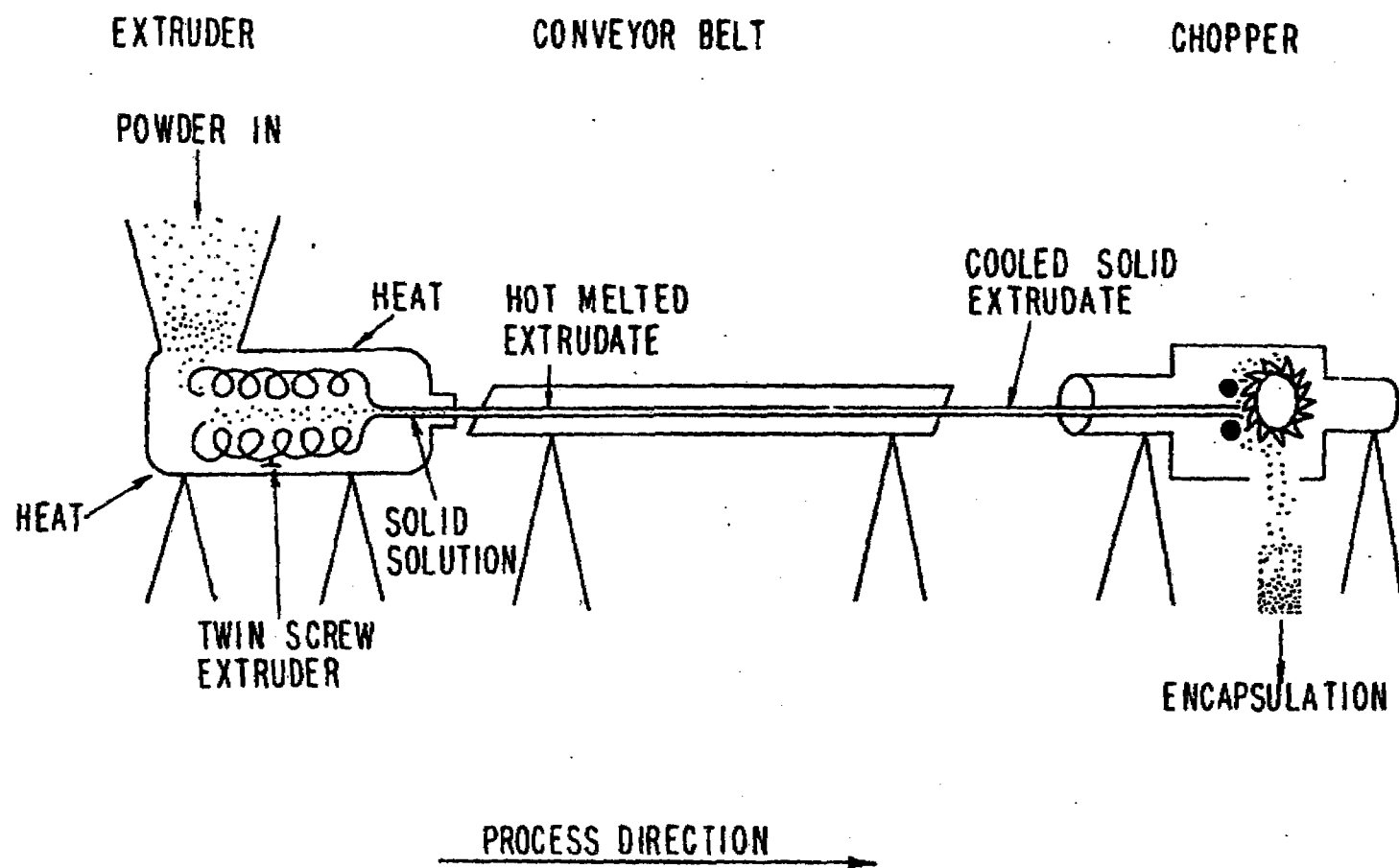
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FIG.5



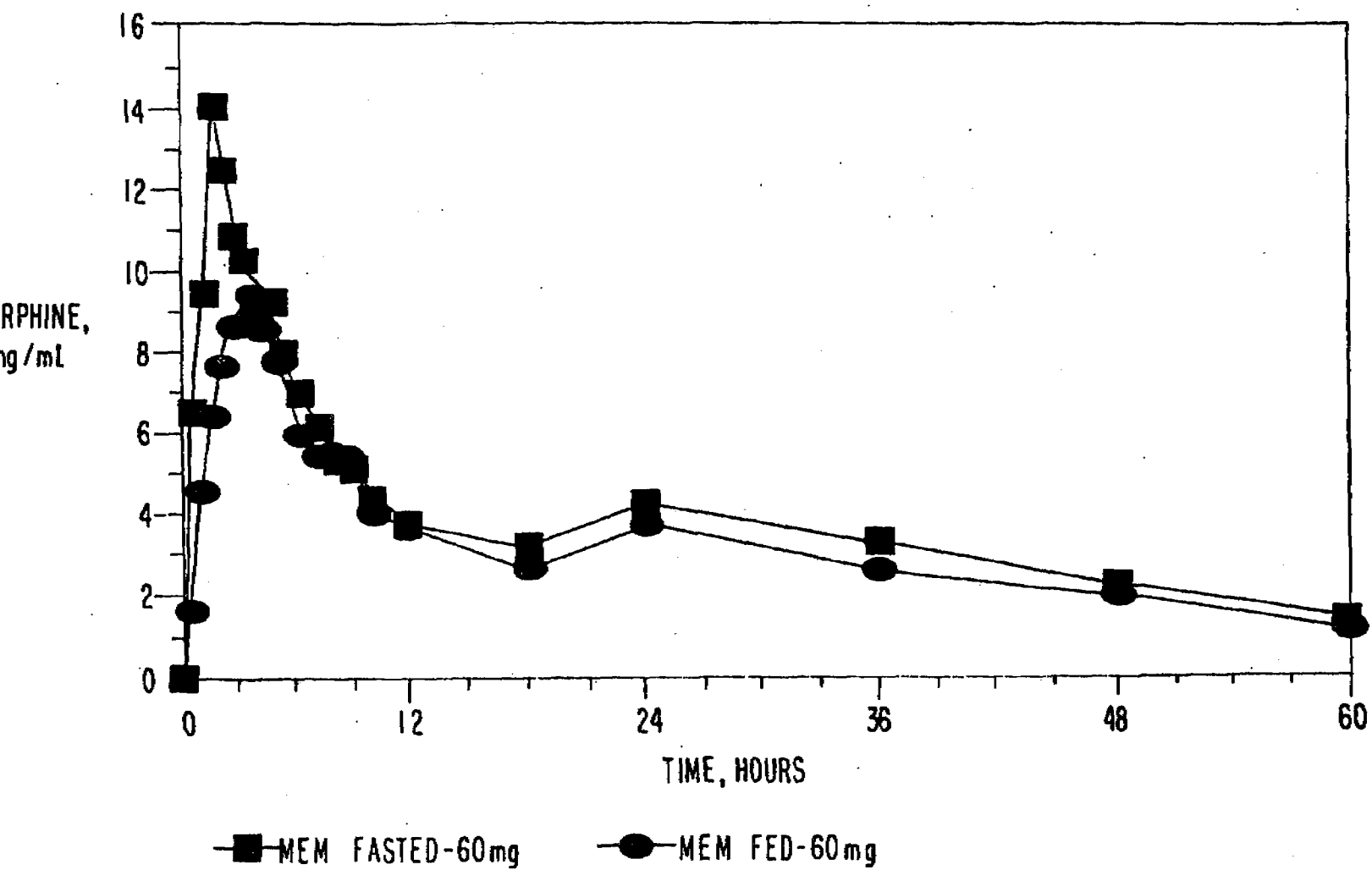
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FIG. 9



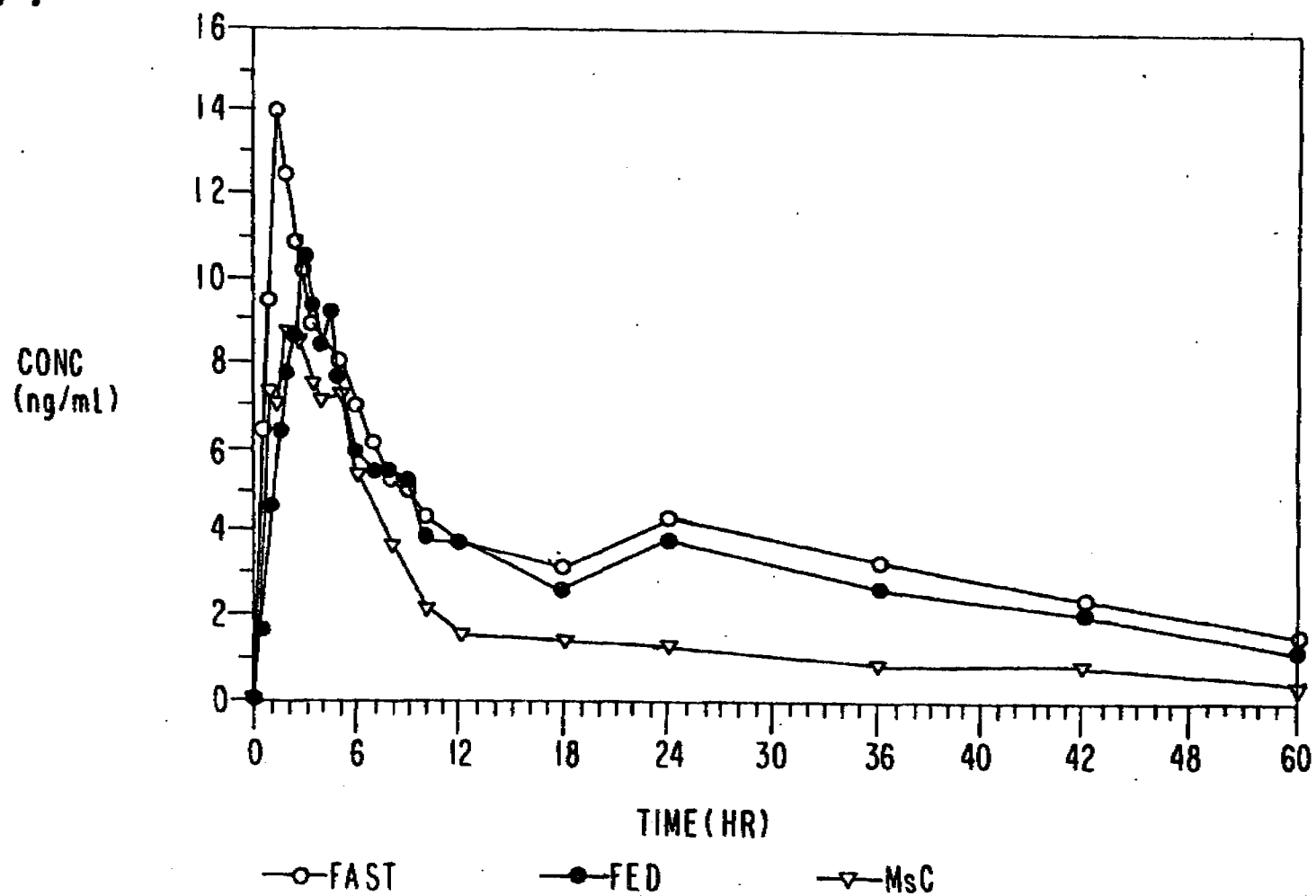
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FIG. 10



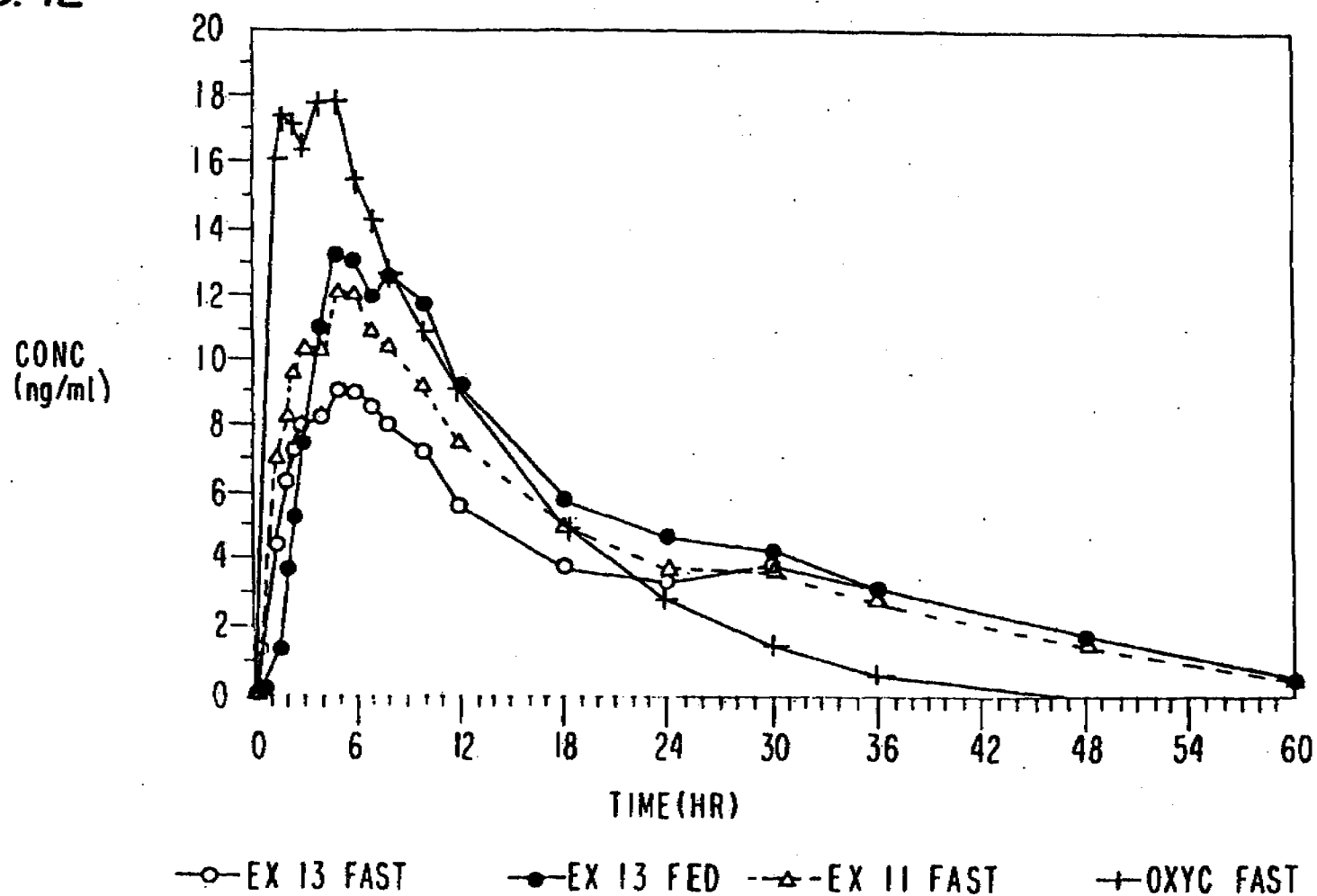
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FIG. 11



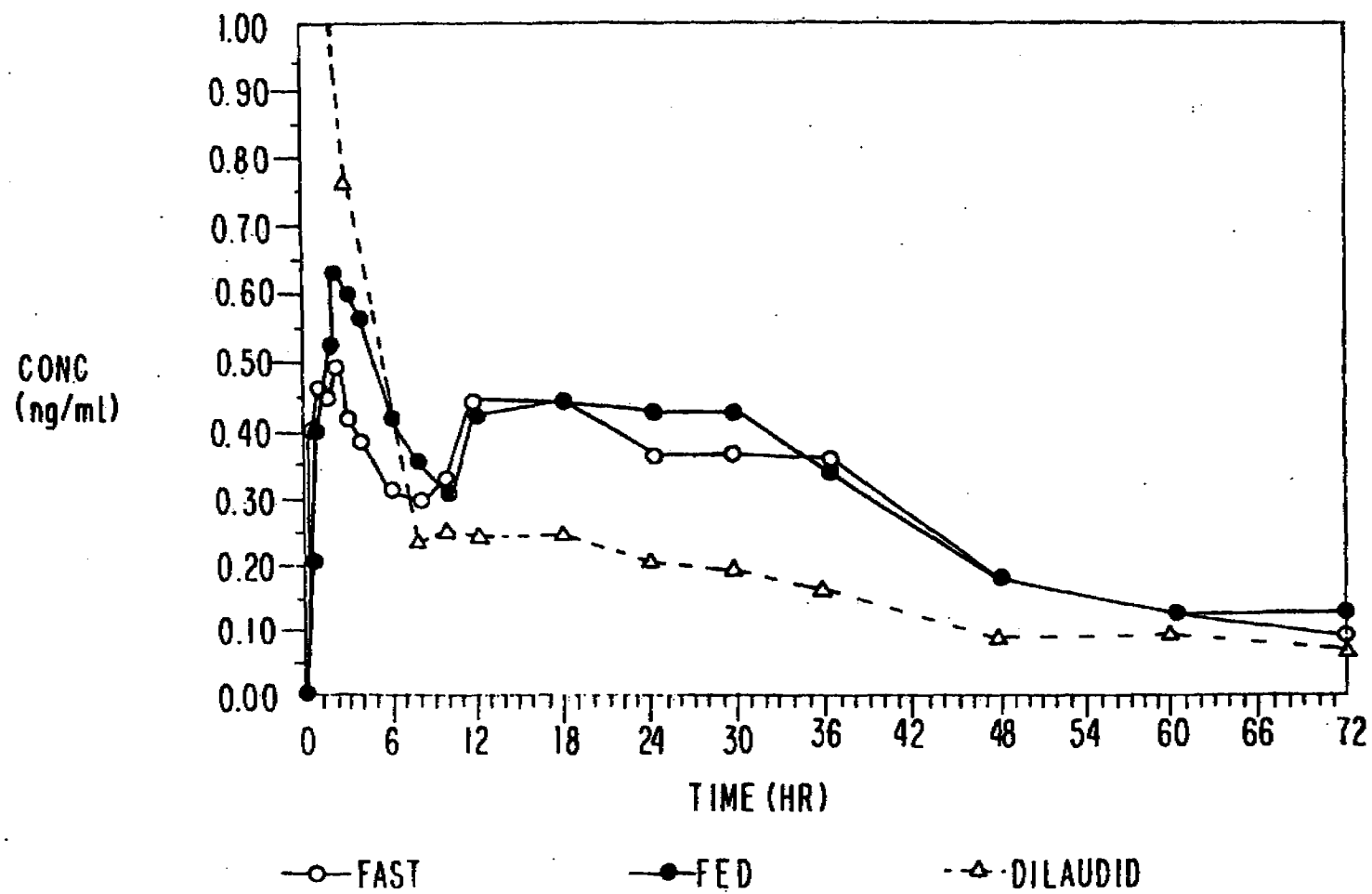
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FIG. 12



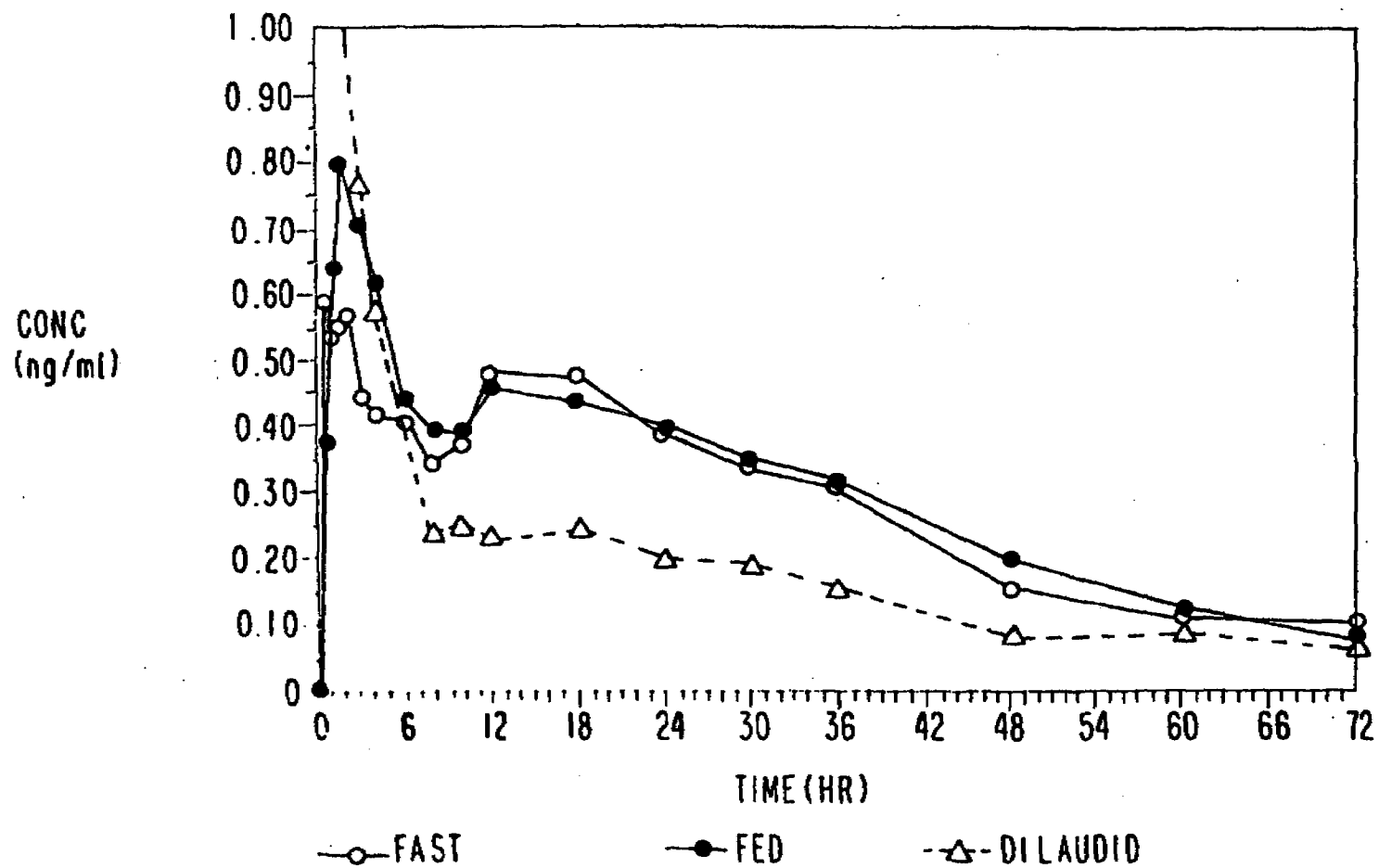
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FIG. 14



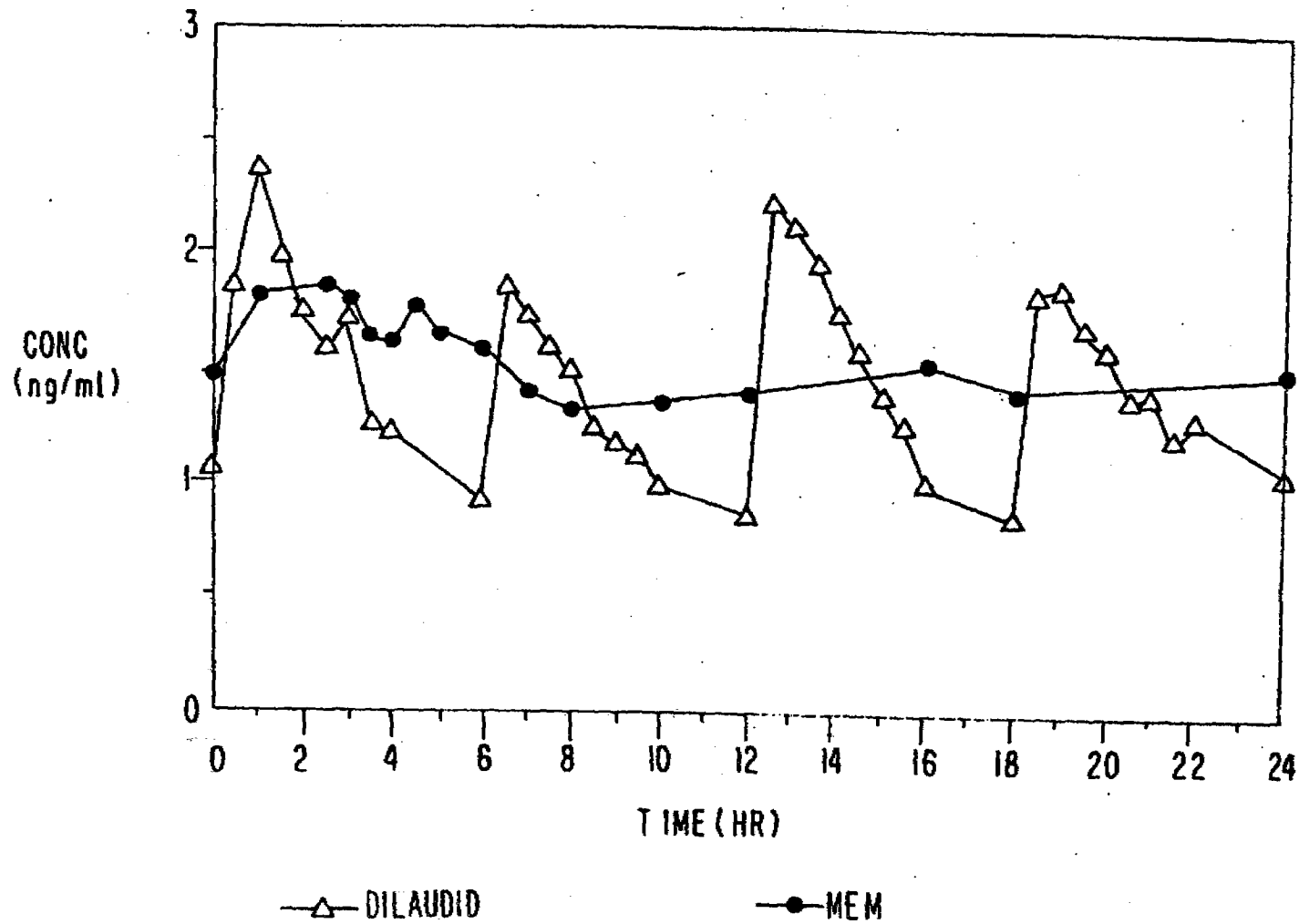
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FIG. 15



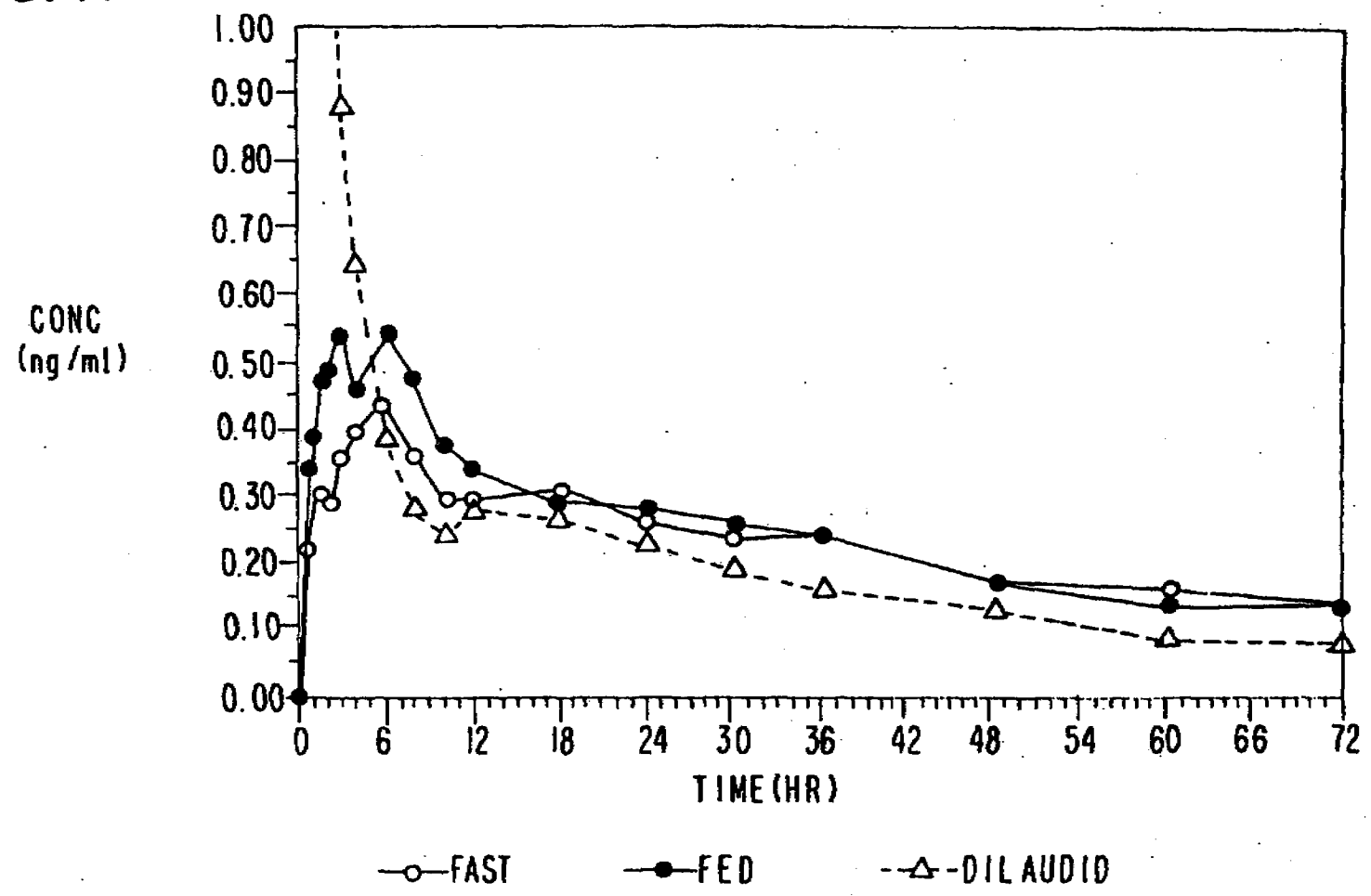
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FIG. 16



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FIG. 17



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- (71) Applicant (for all designated States except US): **GENEVA PHARMACEUTICALS, INC.** [US/US]; 2655 West Midway Boulevard, Broomfield, CO 80038 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **MATHARU, Amol, Singh** [US/US]; Princeton Arms, 193 N2, Cranbury, NJ 08512 (US). **PATEL, Mahendra, R.** [US/US]; 18 Timothy Lane, East Brunswick, NJ 08816 (US).
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PHARMACEUTICAL COMPOSITION

Summary

The present invention relates to a process for preparing a pharmaceutical tablet formulation of a poorly-compressible pharmaceutical agent, for example, the drug metformin HCl formulated as a monolithic or single phase homogenous system.

Background

Some pharmaceutical agents are difficult to formulate into a tablet dosage form due to agent's poor compressibility. Conventional tablet formulations of such poorly-compressible pharmaceutical agents lack adequate hardness and are often friable. Thus, special formulation techniques are required to formulate poorly-compressible pharmaceutical agents into a commercially viable tablet dosage form.

One way to overcome the poor compressibility of pharmaceutical agents is to utilize wet granulation techniques to prepare the tablet formulation. This involves additional unit operations of wet milling, drying and milling of dried granulation. However, tablets prepared by wet methods often show incremental hardness as a function of time and storage temperature. Therefore, tablets prepared by wet methods are more likely to show variable product performance.

The object of the present invention is to prepare pharmaceutical tablets of poorly-compressible drugs that have adequate and stable hardness and good reproducibility, by a process that avoids wet granulation during processing. This object is achieved by formulating the poorly-compressible pharmaceutical agent according to a process whereby the active ingredient, an erodible hydrophilic component, a hydrophobic component and optionally other excipients, are blended, and the resulting blend is sized and/or lubricated, if necessary, and compressed into tablets as a monolithic or single-phase homogenous system.

The present invention is applicable to non-compressible drugs and drugs susceptible to hydrolysis and degradation due to water or a solvent.

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Detailed Description

The present invention relates to a process for preparing a pharmaceutical tablet formulation of a poorly-compressible pharmaceutical agent, which comprises:

- (a) preparing a blend by combining the poorly-compressible pharmaceutical agent, a hydrophilic erodible component and a hydrophobic component as a monolithic or single phase homogenous system; and
- (b) compressing the blend into a tablet.

The blend may optionally comprise other pharmaceutically acceptable excipients and the blend may optionally be lubricated prior to being compressed into tablets. The present invention is applicable to non-compressible drugs and drugs susceptible to hydrolysis and degradation due to water or a solvent.

A poorly compressible substance is one that does not bond to form a tablet upon application of compression force. Therefore, such substances may require additional processing and special formulating before it can be compressed into a tablet. With such substances, the additional processing necessary is usually a wet granulation step; direct compression would not be effective. These substances may also be formulated with binders or other materials having high binding capacity (or act as an aid to compressibility) such that the non-bonding properties of the non-compressible material is overcome. Other techniques to assist compression include having residual moisture in the blend prior to compression or having the non-compressible material in very low amounts in the tablet formulation. High-dose drugs do not lend themselves to direct compression because of poor flowability and poor compressibility.

The hydrophilic erodible component of the present invention is a pharmaceutically acceptable excipient which is a water-loving soluble/gellable agent. These components possess properties, such as the ability to imbibe external fluid and dissolve/erode over a period of time. Typical hydrophilic erodible components include hydroxypropylmethyl cellulose; soluble fillers, such as lactose; tablet disintegrants, such as croscarmellose sodium; binders, such as polyvinylpyrrolidone; gums, such as guar and xanthan gums. Examples of water soluble and/or swellable hydrophilic polymers include solid polyethylene glycol with molecular weights greater than 400 (MW >400), celluloses (hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, carboxymethyl cellulose,

carboxyethyl cellulose, sodium carboxymethyl cellulose, sodium alginate, methyl cellulose, hydroxypropyl methyl cellulose), carboxypolymethylene, gums (acacia gum, guar gum, tragacanth gum and xanthan gum), polyethylene oxide and the like. High molecular weight cellulose derivatives are preferred as the hydrophilic erodible component.

The hydrophobic component is a pharmaceutically acceptable excipient which is water insoluble and does not dissolve in water over a period of time. Typical hydrophobic components include ethyl cellulose, methacrylic acid polymers and copolymers, such as EUDRAGIT NE 30 D from Rohm and Haas, fatty acids and esters thereof, such as stearic acid, behenic acid, glyceryl monostearate, glyceryl palmitostearate, glyceryl behenate and other waxes, such as carbuna wax. Also included are high molecular weight fatty alcohols, such as cetyl alcohol and the like. Cetyl alcohol and stearyl alcohol are preferred as the hydrophobic component.

The poorly-compressible pharmaceutical agent typically represents from about 10% to about 90% by weight of the formulation. Preferably, the poorly-compressible pharmaceutical agent is present in the formulation in amount of from about 30% to about 70% by weight.

The hydrophilic erodible component typically represents from about 10% to about 90% by weight of the formulation. Preferably, the hydrophilic erodible component is present in the formulation in amount of from about 30% to about 70% by weight.

The hydrophobic component typically represents from about 1% to about 30% by weight of the formulation. Preferably, the hydrophobic component is present in the formulation in amount of from about 15% to about 25% by weight.

Typically, the ratio of hydrophilic erodible component to hydrophobic component is in the range from about 9:1 to 1:1. Preferably the ratio is in the range from about 2:1 to 3:1.

Preferred formulations comprise from about 40% to about 60% by weight of the poorly-compressible pharmaceutical agent and comprise the hydrophilic erodible component and hydrophobic component in a ratio of from about 2:1 to 3:1.

The poorly-compressible pharmaceutical agent, hydrophilic erodible component and hydrophobic component are blended by standard techniques. Typically, the components are added to a standard blending apparatus and blended. Hydrophobic components which are

solid at room temperature, such as waxes, are often liquefied before and/or during the blending operation.

In another embodiment, the poorly-compressible pharmaceutical agent and hydrophilic erodible component are pre-mixed by standard techniques and then combined with the hydrophobic component. The pre-mixed components are combined with the hydrophobic component by a variety of techniques, such as adding the hydrophobic component to the blending apparatus containing the pre-mixed components. The fluidized bed technique may also be used and is especially appropriate when the hydrophobic component is ethyl cellulose or a polymethacrylic acid polymer or co-polymer.

The blend produced by combining the poorly-compressible pharmaceutical agent, hydrophilic erodible component and hydrophobic component is typically a monolithic or single phase homogenous free flowing powder. As is typical when formulating tablets, the free flowing powder blend is often milled or sieved in order to control the particle size of the blend and to remove large agglomerates.

If needed, the blend may optionally be lubricated prior to compression into tablets. Typical lubricants include magnesium stearate and stearic acid. However, the presence of the hydrophobic component often renders additional lubrication unnecessary. Additional lubricants will generally represent 0% to about 6% by weight of the tablet formulation.

In addition to the poorly-compressible pharmaceutical agent, hydrophilic erodible component, hydrophobic component and optional lubricant, the tablet formulations of the present invention may contain additional pharmaceutical excipients, such as flavoring agents, binders and/or fillers.

Since an objective of the present invention is to form a compressible formulation by a process other than wet granulation, the granulation process will be conducted without solvent or water. It is preferred for the process to be carried out under substantially anhydrous conditions.

The process of the present invention is useful for preparing both immediate-release and sustained-release tablet dosage forms of poorly-compressible pharmaceutical agents. The release rate of the pharmaceutical agent is controlled by the hydrophilic erodible agent and hydrophobic agent. Thus, an immediate-release formulation will typically contain the

2:8. Increasing the amount of hydrophilic erodible component will extend the release rate of the pharmaceutical agent. Thus, sustained-release tablet dosage forms typically contain the hydrophilic erodible component and hydrophobic components in a ratio of from about 3:1 to 2:1.

The dissolution profile obtained in phosphate buffer (pH 6.8), USP Apparatus II, for tablets prepared according to the present invention are:

Time (hrs)	% Dissolved
1	20 – 40
4	50 – 70
7	75 – 90

Examples of poorly-compressible pharmaceutical agents that are formulated into tablets in accordance with the inventive process include metformin HCl, naproxen or naproxen sodium. High-dose drugs do not lend themselves to direct compression because of poor flowability and poor compressibility. Representative active medicaments include antacids, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, anti-infectives, psychotropics, antimanics, stimulants, antihistamines, laxatives, decongestants, vitamins, gastrointestinal sedatives, antidiarrheal preparations, anti-anginal drugs, vasodilators, antiarrhythmics, anti-hypertensive drugs, vasoconstrictors and migraine treatments, anticoagulants and antithrombotic drugs, analgesics, anti-pyretics, hypnotics, sedatives, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypoglycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, uterine relaxants, mineral and nutritional additives, anti-obesity drugs, anabolic drugs, erythropoietic drugs, anti-asthmatics, expectorants, cough suppressants, mucolytics, anti-uricemic drugs, and drugs or substances acting locally in the mouth.

Typical active medicaments include gastrointestinal sedatives, such as metoclopramide and propantheline bromide; antacids, such as aluminum trisilicate, aluminum hydroxide and cimetidine; anti-inflammatory drugs, such as phenylbutazone, indomethacin, naproxen, ibuprofen, flurbiprofen, diclofenac, dexamethasone, prednisone and prednisolone; coronary vasodilator drugs, such as glyceryl trinitrate, isosorbide dinitrate

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vincamine, naftidrofuryl oxalate, co-dergocrine mesylate, cyclandelate, papaverine and nicotinic acid; anti-infective substances, such as erythromycin stearate, cephalexin, nalidixic acid, tetracycline hydrochloride, ampicillin, flucloxacillin sodium, hexamine mandelate and hexamine hippurate; neuroleptic drugs, such as fluazepam, diazepam, temazepam, amitriptyline, doxepin, lithium carbonate, lithium sulfate, chlorpromazine, thioridazine, trifluoperazine, fluphenazine, piperothiazine, haloperidol, maprotiline hydrochloride, imipramine and desmethylinipramine; central nervous stimulants, such as methylphenidate, ephedrine, epinephrine, isoproterenol, amphetamine sulfate and amphetamine hydrochloride; anti-histamic drugs such as diphenhydramine, diphenylpyraline, chlorpheniramine and brompheniramine; anti-diarrheal drugs, such as bisacodyl and magnesium hydroxide; the laxative drugs, such as dioctyl sodium sulfosuccinate; nutritional supplements, such as ascorbic acid, alpha tocopherol, thiamine and pyridoxine; anti-spasmodic drugs, such as dicyclomine and diphenoxylate; drugs effecting the rhythm of the heart, such as verapamil, nifedepine, diltiazem, procainamide, disopyramide, bretylium tosylate, quinidine sulfate and quinidine gluconate; drugs used in the treatment of hypertension, such as propranolol hydrochloride, guanethidine monosulphate, methyldopa, oxprenolol hydrochloride, captopril and hydralazine; drugs used in the treatment of migraine, such as ergotamine; drugs effecting coagulability of blood, such as epsilon aminocaproic acid and protamine sulfate; analgesic drugs, such as acetylsalicylic acid, acetaminophen, codeine phosphate, codeine sulfate, oxycodone, dihydrocodeine tartrate, oxycodone, morphine, heroin, nalbuphine, butorphanol tartrate, pentazocine hydrochloride, cyclazacine, pethidine, buprenorphine, scopolamine and mefenamic acid; anti-epileptic drugs, such as phenytoin sodium and sodium valproate; neuromuscular drugs, such as dantrolene sodium; substances used in the treatment of diabetes, such as tolbutamide, diabenase glucagon and insulin; drugs used in the treatment of thyroid gland disfunction, such as triiodothyronine, thyroxine and propylthiouracil; diuretic drugs, such as furosemide, chlorthalidone, hydrochlorthiazide, spironolactone and triamterene; uterine relaxant drugs, such as ritodrine; appetite suppressants, such as fenfluramine hydrochloride, phentermine and diethylpropion hydrochloride; anti-asthmatic drugs, such as aminophylline, theophylline, salbutamol, orciprenaline sulphate and terbutaline sulphate, expectorant drugs, such as guaiphenesin; cough suppressants, such as dextromethorphan and noscapine; mucolytic drugs, such as carbocisteine; anti-septics, such as cetylpyridinium chloride, tyrothricin and chlorhexidine; decongestant drugs, such as phenylpropanolamine and pseudoephedrine; hypnotic drugs, such as dichloralphenazone and nitrazepam; anti-nauseant drugs, such as

gluconate, uricosuric drugs, such as sulphinpyrazone, allopurinol and probenecid and the like.

The invention is applicable to sublingual lozenges, buccal tablets, oral lozenges, suppositories and compressed tablets, the latter being intended to be swallowed in unit dosage form and which upon ingestion according to a prescribed regimen give slow and regular release of active medicaments of a fixed percentage in the intestinal tract. It is further understood that the invention is not restricted to the above listed medications.

The process of the present invention is especially useful for formulating metformin HCl into tablets. Thus, the present invention especially relates to a process wherein the poorly-compressible pharmaceutical agent is selected from the group consisting of metformin HCl.

In a preferred embodiment, the poorly-compressible pharmaceutical agent is metformin HCl, the hydrophilic erodible component is hydroxypropyl methylcellulose and the hydrophobic component is stearyl alcohol, wherein the hydrophilic agent and hydrophobic agent are in a ratio of from about 3:1 to about 2:1.

Preferably, the tablet comprises from about 40-60% by weight of metformin HCl.

Most preferably, the tablet comprises from about 45-50% by weight of metformin HCl, a hydrophilic erodible component which is hydroxypropyl methylcellulose and a hydrophobic component which is stearyl alcohol and a weight ratio of hydrophilic erodible component to hydrophobic component in the range from 3:1 to about 2:1.

In one embodiment, the tablet may comprise 250 mg, 500 mg, 850 mg or 1 g of metformin HCl. Most preferably, the tablet comprises about 500 mg of metformin HCl.

The present invention further relates to pharmaceutical tablet dosage form which comprises a poorly-compressible pharmaceutical agent, a hydrophilic erodible component and a hydrophobic component. All of the preferences discussed above for the process also apply to the tablet dosage form, if applicable to a tablet dosage form.

The present invention further relates to a pharmaceutical tablet dosage form of metformin HCl with the preferences discussed above applying to the dosage form.

EXAMPLE 1

Item no.	Ingredient	%	mg/unit	Amount per batch
1	Metformin HCl	48.54	500	55 kg
2	Hydroxypropyl methylcellulose	31.06	320	39.05 kg
3	Stearyl alcohol	19.41	200	18.15 kg
4	Magnesium stearate	0.97	10	1.1 kg
Total		100	1030	113.3 kg

Metformin HCl is first de-lumped using Fitz-mill equipped with 0.050" screen at medium speed. De-lumped metformin HCl and hydroxypropyl methyl cellulose (available as Methocel K100 M Premium CR, Dow Chemical Company, MI) are mixed in a 340 Qt. AMF Planetary Mixer and mixed for 10 minutes to form a pre-mix blend. The pre-mix blend is transferred to drums. To a pre-heated jacketed bowl of 340 Qt. AMF Planetary Mixer, stearyl alcohol is added and allowed to melt to form a clear liquid at the jacket temperature of not less than 65°C. To the melted wax, pre-mix is added and mixed until a uniform granulation is obtained while heating at the jacket temperature of not less than 65°C. The granulation is transferred to trays lined with Kraft paper and cooled down to a temperature of 25°C-30°C. The cooled granulation is sized using a low energy screening/milling device such as a Glatt Quick sieve equipped with 1.5 mM screen. The lubrication is performed using magnesium stearate in a 30 cu. ft. Gemco Blender. The final-mix obtained is compressed into tablets using Manesty Unipress Diamond using modified oval tools. The hardness of the tablets obtained was 10-18 SCU. The dissolution profile of the tablets matched that of Glucophage® XR 500 mg (Bristol-Myers Squibb, NJ).

The dissolution profile (average, n=6) obtained in phosphate buffer (pH 6.8), USP Apparatus II, is:

Time (hours)	% dissolved
1	31.7
4	64.2
7	80.1

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EXAMPLE 2

Item no.	Ingredient	%	mg/unit	Amount per batch
1	Metformin HCl with 0.5% magnesium stearate	48.8	502.5	40.0 kg
2	Hydroxypropyl methylcellulose	28.8	297	23.76 kg
3	Stearyl alcohol	21.4	220	17.6 kg
4	Colloidal silicon dioxide	0.3	3	0.24 kg
5	Magnesium stearate	0.7	7.5	0.6 kg
TOTAL		100	1030	82.4 kg

Metformin HCl with 0.5% magnesium stearate and hydroxypropyl methyl cellulose (available as Methocel K100 M Premium CR, Dow Chemical Company, MI) are mixed in a PMA 300 Fielder High Shear to form a pre-mix blend. The pre-mix blend is transferred to drums. To a pre-heated jacketed bowl of 340 Qt. AMF Planetary Mixer, stearyl alcohol is added and allowed to melt to form a clear liquid at the jacket temperature of not less than 65°C. To the melted wax, pre-mix is added and mixed until a uniform granulation is obtained while heating at the jacket temperature of not less than 65°C. The granulation is transferred to trays lined with Kraft paper and cooled down to a temperature of 25°C-30°C. The cooled granulation is sized using a low energy screening/milling device such as a Quadro Co-Mill equipped with 93 screen. The Pre-lubrication and Lubrication is performed using colloidal silicon dioxide and magnesium stearate, respectively, in a Patterson-Kelley Blender. The final-mix obtained is compressed into tablets using Manesty Unipress Diamond using modified oval tools. The hardness of the tablets obtained was 10-18 SCU. The dissolution profile of the tablets matched that of Glucophage® XR 500 mg (Bristol-Myers Squibb, NJ).

The dissolution profile (average, n=6) obtained in phosphate buffer (pH 6.8), USP Apparatus II, is:

Time (hours)	% dissolved
1	31.5
4	63.5
7	80.9

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EXAMPLE 3 (Immediate-Release formulation)

Item no.	Ingredient	%	mg/unit
1	Metformin HCl	71.4	500
2	Hydroxypropyl methylcellulose	10.6	74
3	Stearyl alcohol	17.0	119
4	Colloidal silicon dioxide	0.2	1.4
5	Magnesium stearate	0.8	5.6
TOTAL		100	700

Metformin HCl and hydroxypropyl methyl cellulose (available as Pharmacoat 606, Shin-Etsu Chemical Co. Ltd., Japan) are mixed in a 500 mL glass beaker with the help of a stainless steel spatula. Stearyl alcohol is melted in a glass beaker. To the melted wax, pre-mix is added and mixed until a uniform granulation is obtained while heating at temperature of not less than 65°C. The granulation is transferred to Kraft paper and cooled down to a temperature of 25°C-30°C. The cooled granulation is sized using screen # 20. The Pre-lubrication and Lubrication is performed using colloidal silicon dioxide and magnesium stearate, respectively, in a glass beaker using a stainless steel spatula. The final-mix obtained is compressed into tablets using Carver hydraulic press. The hardness of the tablets obtained was 8 SCU.

The dissolution profile (average, n=3) obtained in phosphate buffer (pH 6.8), USP Apparatus II, is:

Time (minutes)	% dissolved
15	43.9
30	76.1
45	97.1
60	100.2

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EXAMPLE 4 (Immediate-Release formulation)

Item no.	Ingredient	%	mg/unit
1	Metformin HCl	50.0	500
2	Microcrystalline cellulose	32.0	320
3	Stearyl alcohol	17.0	170
4	Colloidal silicon dioxide	0.2	2
5	Magnesium stearate	0.8	8
TOTAL		100	1000

Metformin HCl and microcrystalline cellulose are mixed in a 500 mL glass beaker with the help of a stainless steel spatula. Stearyl alcohol is melted in a glass beaker. To the melted wax, pre-mix is added and mixed until a uniform granulation is obtained while heating at temperature of not less than 65°C. The granulation is transferred to Kraft paper and cooled down to a temperature of 25°C-30°C. The cooled granulation is sized using screen No. 20. The pre-lubrication and lubrication is performed using colloidal silicon dioxide and magnesium stearate, respectively, in a glass beaker using a stainless steel spatula. The final-mix obtained is compressed into tablets using Carver hydraulic press. The hardness of the tablets obtained was 8 SCU.

The dissolution profile (average, n=3) obtained in phosphate buffer (pH 6.8), USP Apparatus II, is:

Time (minutes)	% dissolved
5	75.6
15	100.4

We claim:

1. A process for preparing a pharmaceutical tablet formulation of a poorly-compressible pharmaceutical agent, which comprises the steps of
 - (a) preparing a blend by combining the poorly-compressible pharmaceutical agent, a hydrophilic erodible component and a hydrophobic component; and
 - (b) compressing the blend into a tablet.
2. A process accordingly to Claim 1 further comprising mixing an optional lubricant with the blend prior to compressing the blend into a tablet.
3. A process accordingly to Claim 1 further comprising mixing optional pharmaceutically acceptable excipients with the blend prior to compressing the blend into a tablet.
4. A process according to Claim 1, wherein the process is carried out under substantially anhydrous conditions.
5. A process according to Claim 1, wherein the poorly-compressible pharmaceutical agent is selected from the group consisting of metformin HCl, metoclopramide, propantheline bromide, aluminum trisilicate, aluminum hydroxide, cimetidine, phenylbutazone, indomethacin, naproxen, ibuprofen, flurbiprofen, diclofenac, dexamethasone, prednisone and prednisolone, glyceryl trinitrate, isosorbide dinitrate, pentaerythritol tetranitrate, soloctidilum, vincamine, naftidrofuryl oxalate, co-dergocrine mesylate, cyclandelate, papaverine, nicotinic acid, clarithromycin, azithromycin, erythromycin stearate, cephalexin, nalidixic acid, tetracycline hydrochloride, ampicillin, fluocolaxacillin sodium, hexamine mandelate, hexamine hippurate, fluazepam, diazepam, temazepam, amitriptyline, doxepin, lithium carbonate, lithium sulfate, chlorpromazine, thioridazine, trifluoperazine, fluphenazine, piperothiazine, haloperidol, maprotiline hydrochloride, imipramine and desmethylinipramine, methylphenidate, ephedrine, epinephrine, isoproterenol, amphetamine sulfate and amphetamine hydrochloride, diphenhydramine, diphenylpyraline, chlorpheniramine and brompheniramine, bisacodyl, magnesium hydroxide, dioctyl sodium sulfosuccinate, ascorbic acid, alpha tocopherol, thiamine, pyridoxine, dicyclomine, diphenoxylate, verapamil, nifedepine, diltiazem, procainamide, disopyramide, bretylium tosylate, quinidine sulfate, quinidine gluconate,

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hydrochloride, captopril and hydralazine, ergotamine, epsilon aminocaproic acid, warfarin, sodium, ticlopidine, protamine sulfate, acetylsalicylic acid, acetaminophen, codeine phosphate, codeine sulfate, oxycodone, dihydrocodeine tartrate, oxycodone, morphine, heroin, nalbuphine, butorphanol tartrate, pentazocine hydrochloride, cyclazacine, pethidine, buprenorphine, scopolamine and mefenamic acid, phenytoin sodium and sodium valproate, dantrolene sodium, tolbutamide, diabenase glucagons, glipizide, glyburide, insulin, triiodothyronine, thyroxine and propylthiouracil, furosemide, chlorthalidone, hydrochlorothiazide, spironolactone, triamterene, ritodrine, fenfluramine hydrochloride, phentermine and diethylpropion hydrochloride, aminophylline, theophylline, salbutamol, orciprenaline sulphate, terbutaline sulphate, guaiphenesin, dextromethorphan, noscapine, carbocysteine, cetylpyridinium chloride, tyrothricin and chlorhexidine, phenylpropanolamine and pseudoephedrine; hypnotic drugs, such as dichloralphenazone, nitrazepam, promethazine theoclate, ferrous sulphate, folic acid and calcium gluconate, sulphinpyrazone, allopurinol and probenecid and the like.

6. A process according to Claim 1, wherein the poorly-compressible pharmaceutical agent is selected from the group consisting of metformin HCl.

7. A process according to Claim 1, wherein the hydrophilic erodible component is selected from the group consisting of hydroxypropyl methylcellulose, lactose, croscarmellose sodium, polyvinylpyrrolidone, guar and xanthan gums, polyethylene glycol (MW >400), celluloses, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, carboxymethyl cellulose, carboxyethyl cellulose, sodium carboxymethyl cellulose, sodium alginate, methyl cellulose, carboxypolymethylene, acacia gum, tragacanth gum and polyethylene oxide.

8. A process according to Claim 7, wherein the hydrophilic erodible component is hydroxypropyl methylcellulose.

9. A process according to Claim 1, wherein the hydrophobic component is selected from the group consisting of ethyl cellulose, methacrylic acid polymers and copolymers, fatty acids and esters thereof, waxes and high molecular weight fatty alcohols.

10. A process according to Claim 1, wherein the hydrophobic component is selected from the group consisting of EUDRAGIT NE 30 D from Rohm and Haas, stearic acid, behenic acid, glyceryl monostearate, glyceryl palmitostearate, glyceryl behenate, carbuna wax and cetyl alcohol.
11. A process according to Claim 9, wherein the hydrophobic component is selected from the group consisting of cetyl alcohol and stearyl alcohol.
12. A process according to Claim 1, wherein the poorly-compressible pharmaceutical agent comprises from about 10% to about 90% by weight of the formulation.
13. A process according to Claim 1, wherein the hydrophilic erodible component comprises from about 10% to about 90% by weight of the formulation.
14. A process according to Claim 1, wherein the hydrophobic component comprises from about 10% to about 30% by weight of the formulation.
15. A process according to Claim 1, wherein the ratio of hydrophilic erodible component to hydrophobic component is 9:1 to 1:1.
16. A process according to Claim 1, wherein the blend of step (a) comprises from about 40% to about 60% by weight of the poorly-compressible pharmaceutical agent and the hydrophilic erodible component and hydrophobic component are in a ratio of from 2:1 to 3:1.
17. A process according to Claim 2, wherein the lubricant comprises about 0% to about 6% by weight of the blend.
18. A process for preparing an immediate-release pharmaceutical tablet formulation of a poorly-compressible pharmaceutical agent, which comprises the steps of:
 - (a) preparing a blend by combining the poorly-compressible pharmaceutical agent, a hydrophilic erodible component and a hydrophobic component, wherein the hydrophilic erodible component and the hydrophobic component are present in a ratio of 1:9 to 2:8; and
 - (b) compressing the blend into a tablet.

19. A process for preparing an sustained-release pharmaceutical tablet formulation of a poorly-compressible pharmaceutical agent, which comprises the steps of:
- (a) preparing a blend by combining the poorly-compressible pharmaceutical agent, a hydrophilic erodible component and a hydrophobic component, wherein the hydrophilic erodible component and hydrophobic component are present in a ratio of 3:1 to 2:1; and
 - (b) compressing the blend into a tablet.
20. A process according to Claim 1, wherein the tablet comprises about 500 mg of metformin HCl.
21. A process according to Claim 1, wherein the tablet comprises about 40-60 weight percent of metformin HCl.
22. A pharmaceutical tablet prepared according to the process of Claim 1.
23. A pharmaceutical tablet comprising 10% to about 90% by weight of a poorly-compressible pharmaceutical agent; from about 10% to about 90% by weight of hydrophilic erodible component; from about 10% to about 30% by weight of a hydrophobic component.
24. A pharmaceutical tablet comprising a poorly-compressible pharmaceutical agent, a hydrophilic erodible component and a hydrophobic component, wherein the ratio of hydrophilic erodible component to hydrophobic component is 9:1 to 1:1.
25. A pharmaceutical tablet comprising from about 40% to about 60% by weight of a poorly-compressible pharmaceutical agent, and a hydrophilic erodible component and a hydrophobic component, wherein the hydrophilic erodible component and hydrophobic component are present in a ratio of from 2:1 to 3:1.
26. An immediate-release pharmaceutical tablet formulation of a poorly-compressible pharmaceutical agent comprising a poorly-compressible pharmaceutical agent, a hydrophilic erodible component and a hydrophobic component, wherein the hydrophilic erodible component and hydrophobic component are present in a ratio of 1:9 to 2:8.

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27. A sustained-release pharmaceutical tablet formulation of a poorly-compressible pharmaceutical agent comprising a poorly-compressible pharmaceutical agent, a hydrophilic erodible component and a hydrophobic component, wherein the hydrophilic erodible component and hydrophobic component are present in a ratio of 3:1 to 2:1.

28. A process for preparing a pharmaceutical tablet formulation of a pharmaceutical agent susceptible to hydrolysis and degradation due to water or a solvent, which comprises the steps of:

- (a) preparing a blend by combining the poorly-compressible pharmaceutical agent, a hydrophilic erodible component and a hydrophobic component; and
- (b) compressing the blend into a tablet.

drugs susceptible to hydrolysis and degradation due to water or a solvent.

29. A pharmaceutical tablet prepared according to the process of Claim 28.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/20323

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/155 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, PHARMAPROJECTS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; ABDALLAH, O. Y. ET AL: "Preparation and evaluation of metformin hydrochloride controlled-release tablets" retrieved from STN Database accession no. 108:156419 XP002216063	1,5-7,9, 22,28,29
Y	abstract & S.T.P. PHARMA (1988), 4(1), 15-20 , --- -/--	1-29

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

9 October 2002

24/10/2002

INTERNATIONAL SEARCH REPORT

In International Application No
PCT/US 02/20323

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 117 451 A (KUMAR VIJAI) 12 September 2000 (2000-09-12)	1,3-8, 12,13, 15,20, 22-24, 28,29
Y	column 4, line 55 - line 62 column 9, line 34 - line 45 examples 1-9 claims 1-9	1-29
X	WO 98 55107 A (DEPOMED INC ;SHELL JOHN W (US); LOUIE HELM JENNY (US)) 10 December 1998 (1998-12-10)	1-9, 12-29
Y	page 4, line 17 page 4, line 23 - line 29 page 4, line 30 -page 6, line 5 page 6, line 32 -page 7, line 2 page 7, line 3 page 7, line 28 - line 33 page 7, line 37 -page 8, line 6 example 4 claims 1-5,9-16,20	1-29
A	WO 99 47128 A (SQUIBB BRISTOL MYERS CO) 23 September 1999 (1999-09-23) example 4	1-29
P,A	WO 02 28181 A (TEWARI PRASHANT KUMAR ;USV LTD (IN); GIDWANI SURESH KUMAR (IN); SI) 11 April 2002 (2002-04-11) examples 1-6	1-29

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6117451	A	12-09-2000	NONE	
WO 9855107	A	10-12-1998	AU 729529 B2	01-02-2001
			AU 8138698 A	21-12-1998
			EP 0998271 A1	10-05-2000
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WO 9947128	A	23-09-1999	AU 736951 B2	09-08-2001
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			AU 7308500 A	15-04-2002

**Industria y Comercio**
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Luis Felipe Castillo Gibsone
Apoderado

Oficio N°: **Nº 14505**

ASUNTO:

Radicación PCT N°	07-81185
Trámite	011
Evento	379
Actuación	440
Folios	010

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

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

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



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

El anterior oficio fue notificado por fijación en lista de fecha, 14 NOV. 2008.

202021

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Señora Jefe
DIVISIÓN DE NUEVAS CREACIONES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Bogotá, D.C.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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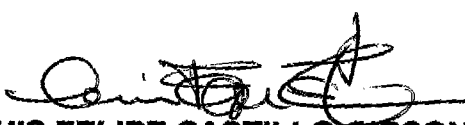
Acto 2008-30-24-15-23-50 Dep. 2020 NULCREACIONE
Trib. 11 PATENTABILIDAD Lva 378 FASENACIONAL
Act 536 PETICION Folios 2

Re.: Expediente No. 07 81.185
Fase Nacional Solicitud de Patente PCT
a nombre de
EURO-CELTIQUE S.A.
Código 011 - 378 - 538

En relación con la solicitud contenida en el Expediente de la referencia y, en particular, con la publicación del extracto de la misma en la Gaceta de la Propiedad Industrial No. 592 de 30 de Mayo de 2008, por medio del presente escrito muy respetuosamente me permito solicitarle se sirva proceder a efectuar el **EXAMEN DE PATENTABILIDAD** de la solicitud aquí contenida.

Para tal efecto, acompaño el comprobante de pago por concepto de la tasa respectiva, Recibo No. **841287**

De Usted Atentamente,


LUIS-FELIPE CASTILLO GIBSONE
T.P. # 68.995 del C.S.J.