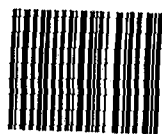


PETITORIO



01 21769

NICO DE SOLICITUD DE PATENTE
2000-3

SOLICITUD DE :

☒ Patente de Invención.

☐ Patente de Modelo de Utilidad

② SOLICITANTE
(71)

Nombre: PFIZER PRODUCTS INC. ✓
Dirección: Estern Point Road, Groton, Connecticut 06340 ✓
Teléfono: 570-0010 Fax: 285-6908
E-Mail: _____
Domicilio: Estado de Connecticut, Estados Unidos de América ✓

IDENTIFICACION

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Número _____

③ REPRESENTANTE
O APODERADO
(74)

Nombre: CARLOS R. OLARTE ✓
Dirección: CALLE 35 No. 7-25 Piso 4
Teléfono: 570-0010 Fax: 285-6908
E-Mail: patents.bogota@bakernet.com

IDENTIFICACION

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Número 79.782.747 TP 74.295

④ INVENTOR (ES)
(72)

Nombre: DENNIS JAY HOOVER, RAVI MYSORE SHANKER, DWAYNE THOMAS FRIESEN, DOUGLAS
Dirección: ALAN LORENZ, JAMES ALAN SCHRIEVER NIGHTINGALE.
Teléfono: _____ Fax: _____
E-Mail: _____
Domicilio: _____

IDENTIFICACION

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Número _____

⑤ Título (54)

COMPOSICIONES FARMACEUTICAS DE INHIBIDORES DE LA GLUCOGENOFOSFORILASA.

⑥ Clasificación Internacional (51)

A61K 31/4045

⑦ Prioridad

SI ☒ NO ☐

(33) País de Origen

US

(32) Fecha

Marzo 16, 2000 ✓

(31) Número de Solicitud

60/189,942 ✓

⑧

Para publicar a partir de la fecha de la presente solicitud a los:

6 meses ☐

12 meses ☐

18 meses ☒

Otro ☐

⑨

Comprobante de pago No. 15.719; 10.672

Fecha: Marzo 9, 2001; Febrero 21, 2001.

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

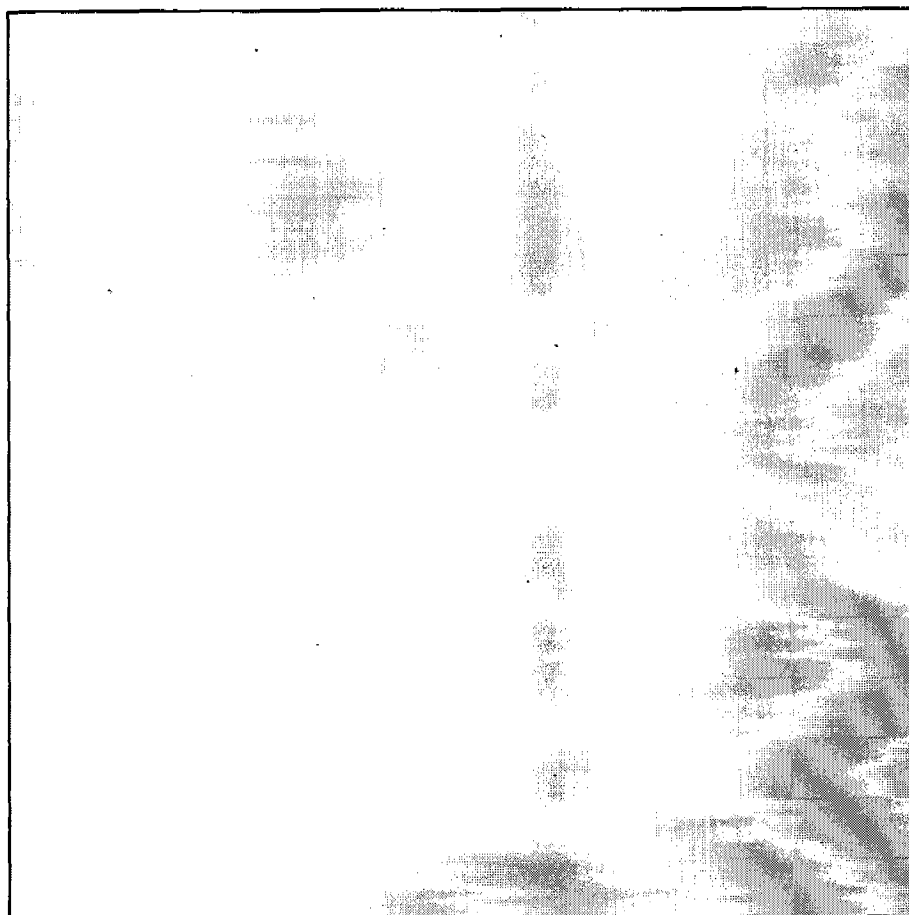
Anexos

⑩

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago de la tasa por concepto de excedente de palabras en la publicación
- ☒ Comprobante de pago por reivindicación de prioridad
- ☒ Certificado de existencia y representación legal cuando el solicitante sea persona jurídica
- ☒ Poderes, si fuere el caso
- ☒ Copia certificada de la primera solicitud si se reivindica prioridad
- ☒ Traducción simple de la primera solicitud, si se reivindica prioridad
- ☐ Documento de cesión del inventor al solicitante o as causante
- ☒ Descripción de la invención
- ☒ Una o más reivindicaciones.
- ☐ Dibujos y/o planos necesarios.
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12x12;

⑪

FIGURA CARACTERISTICA:



⑫

NOMBRE:

CARLOS R. OLARTE

FIRMA:

C.C. 79.782.747 de Btá T.P. 74.295



Industria y Comercio

SUPERINTENDENCIA

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 01 - 15,719
FECHA : MARZO 9 DE 2001

Radicación : 00000000000000000000
Fecha INDI : 2001-03-16 17:00:00
Trámite : 000 PATENTES D : 1 REGISTRO 411 PRESENTA
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
JORGE LUIS GOMEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	3292138	08/03/2001	18,563,400.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	356,640.00
TOTAL :			\$ 356,640.00

SON: TRESCIENTOS CINCUENTA Y SEIS MIL SEISCIENTOS CUARENTA PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Commutador: 382 0840
Fax: 350 5220
e-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

Industria y Comercio
SUPERINTENDENCIA

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 01 - 10,672
FECHA : FEBRERO 21 DE 2001

SUPERINTENDENCIA Y COMERCIO
Radicación : 10000703 10000003 Folios: 3/1
Fecha INNOV: 2001-02-21 10:10:00
Trámite : 002 PATENTES D 1 REGISTRAR/ 411 PRESENTAR
Dependencia: 8020 DIVISION DE NUEVAS CREACIONES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JORGE LUIS GOMEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	3303982	21/02/2001	14,672,800.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	82 INVOCACION DE UNA PRIORIDAD EN NU	100,000.00
	TOTAL :	100,000.00

SON: CIENTO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
Fax: 350 5220
e-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia



541 X

Traducción oficial del inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia.

PODER DE PFIZER PRODUCTS INC.

CONSULADO DE COLOMBIA EN LONDRES

Fechado el 22 enero, 2001 certifica que Kenneth Greenwood, ejerce funciones de notario de Egham, Surrey Inglaterra, cuya firma fue reconocida por J.M.A. Mason, de Legalizaciones del Ministerio de Relaciones de Gran Bretaña; Que J. Trevor Lumb es el asesor de patentes de Pfizer Products Inc. sociedad establecida en Nueva York, NY, Estados Unidos. Firma del cónsul: Jairo Berrio.

CERTIFICACION NOTARIAL

El 8 de enero del 2001 el Notario Público da fe:

1. compareció J. Trevor Lumb, domiciliado en Estados Unidos, quien suscribió el anterior documento. 2. Conozco al otorgante y tiene capacidad para el otorgamiento 3. ha suscrito el documento en su carácter de Asistente General Asesor de Patentes de Pfizer Inc, con sede en Nueva York, NY, 4. la compañía está legalmente constituida, con existencia legal actual y que el acto para el cual se otorgó el poder está dentro del objeto social. 5. El otorgante tiene la representación que ostenta y es legítima. 6. Baso las certificaciones 3, 4 y 5 en estos documentos.

Sello:

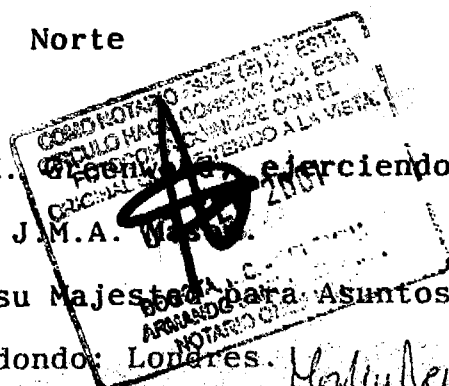
Certificado, verificado y autenticado en la localidad de Egham en Surrey el 8 enero, 2001, Kenneth Greenwood - Notario Público - Horne Engall & Freedom- sello notarial en alto relieve.

Al reverso:

Reino Unido de Gran Bretaña e Irlanda del Norte

No. D653464 - Fecha: 8 enero, 2001

Este documento lleva la firma/sello de K. Greenwood, ejerciendo funciones de Notario Público, firmado por J.M.A. Mason. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la Mancomunidad. Sello redondo: Londres.



Marlén Neira
MARLEN NEIRA CAST
Traductor e Intérprete
Londres, España

6
100
2

PODER DE REPRESENTACIÓN

Poder de representación otorgado por PFIZER PRODUCTS INC., compañía domiciliada en Eastern Point Road, Connecticut, Estados Unidos, a **CARLOS R. OLARTE.**

Dado y firmado en Nueva York, el 2 de enero de 2001 por:

J. Trevor Lumb

Vicepresidente

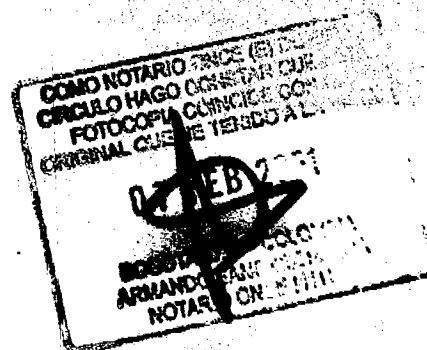
Sello en español:

Ministerio de Relaciones Exteriores No.407608_ certifica las funciones del J. Berrio a la fecha. Bogotá, febrero 2, 2001. Firma el Jefe de Legalizaciones.

--

Traducción certificada, con copia en archivo para confrontación, fechada el 6- 2-2001.

Marlen Neira C
MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1998



COPIA NOTARIO ONCE (1) DE ESTE
CIRCULO HAGO CONSTAR QUE ESTA
FOTOCOPIA COINCIDE CON EL
ORIGINAL QUE HE TENIDO A LA VISTA.
07 FEB 2001
BOGOTA, D.C. - COLOMBIA
ARMANDO SANCHEZ PARRA
NOTARIO ONCE (1) E

RECEIVED

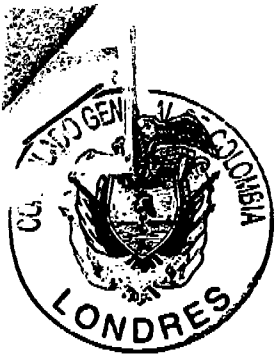
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SECRETARÍA DE DEFENSA
BOGOTÁ, D.C.

SECRETARÍA DE DEFENSA
BOGOTÁ, D.C.

217
Ing. *[Signature]*
CMA
BOGOTÁ, D.C.

[Handwritten mark]



CONSULADO GENERAL DE COLOMBIA

3RD FLOOR 15-19 GREAT TITCHFIELD STREET LONDON W1W 8HZ
TELEPHONE: 020 7637 9893 TELEFAX: 020 7637 5604
E-MAIL: CONSULCO@CONSULCO.DEMON.CO.UK

Handwritten notes in the top right corner: '7', '101', and '21'.

El suscrito Cónsul General de Colombia en Londres, vistos los documentos presentados ante este despacho,

CERTIFICA:

Que el Señor **KENNETH GREENWOOD**, quien autenticó el documento precedente, ejercía en la fecha las funciones de Notario Público de Egham, Surrey, Inglaterra, y que su firma fue debidamente reconocida por **J. M. A. MASON**, Funcionario del Departamento de Legalizaciones del Ministerio de Relaciones de la Gran Bretaña, cuya firma se encuentra registrada en este Consulado General.

Que **PFIZER PRODUCTS INC.** es una Sociedad debidamente constituida, organizada y existente en New York, N.Y., Estados Unidos de América, y que cumple con su objeto social de acuerdo con las leyes de ese país.

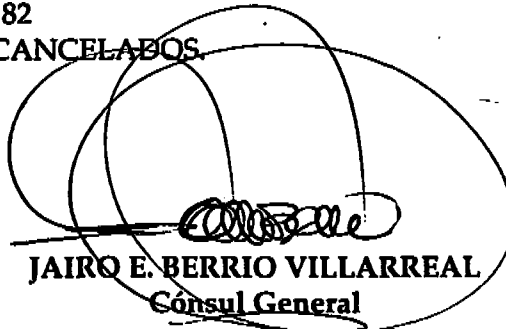
Que el Señor **J. TREVOR LUMB**, en su calidad de Vicepresidente de la mencionada Sociedad, otorga el Poder precedente y su firma ha sido autenticada por el Notario **KENNETH GREENWOOD**.

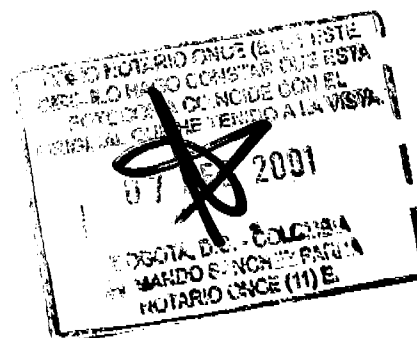
El Cónsul General no asume responsabilidad por el mencionado documento.

Dado en Londres, Reino Unido de la Gran Bretaña, a los veintidos (22) días del mes de enero del año dos mil uno (2001).

Certificación No. 01/0182

Derechos: US\$106.00, CANCELADOS.


JAIRO E. BERRIO VILLARREAL
Cónsul General





MINISTERIO DE RELACIONES
EXTERIORES

Lino Zamora
407608
CUYA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

2001 FEB -2 P 3:11

NIA
JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTÁ D.C.

RAISBECK, LARA, RODRIGUEZ & RUEDA

Members of the Firm

BAKER & MCKENZIE

ATTORNEYS AT LAW

APARTADO AEREO 3746

TELEFONO: 285-1400

SANTAFE DE BOGOTA, D.C.

COLOMBIA

NOTARIAL CERTIFICATION

On this 8th day of January

19 2001, the undersigned Notary

CERTIFIES

1. That J. Trevor Lumb

of legal age and domiciled in U.S.A.

set his hand on the foregoing document.

2. That the grantor is to me personally known and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as

Assistant General Patent Counsel

of the juridical person

Pfizer Inc

4. That the juridical person

Pfizer Inc

having its home office in

New York, NY.

is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact he referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:

Certified Verified And Authenticated
In The Town Of Egham In Surrey

This

Day Of

KENNETH GREENWOOD
NOTARY PUBLIC
HORNE ENGALL AND FREEMAN
Notary Public



CERTIFICACION NOTARIAL

A los dias del mes de

de 19, el suscrito Notario

DA FE

1. Que

mayor y domiciliado en

suscribio de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

3. Que el otorgante ha suscrito el referido documento en su carácter de

de la persona jurídica

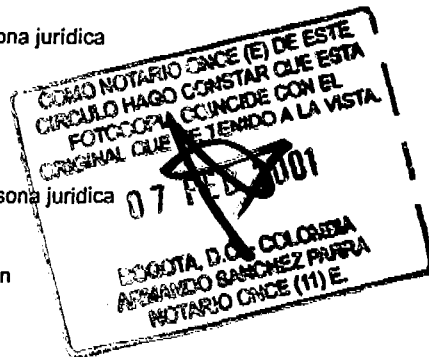
4. Que la persona jurídica

con sede en

está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se ha otorgado el poder está comprendido entre los que constituyen su objeto social.

5. Que el otorgante tiene efectivamente la representación que ostenta, y que esta es legitima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:



El Notario Público

9
Z

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

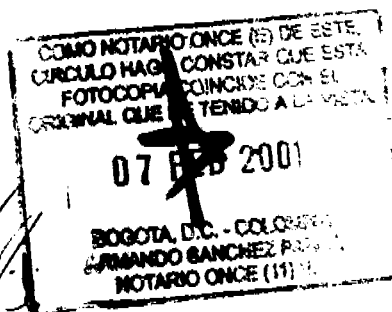
No. **D653464**

Date **8 January, 2001**

This document bears
the signature / seal of **K Greenwood**

Acting in the capacity of **Notary Public**

Signed by: **J. M. A. Mason**



*For Her Majesty's Principal Secretary of State
For Foreign and Commonwealth Affairs*

RAISBECK, LARA, RODRIGUEZ & RUEDA

Members of the Firm

BAKER & MCKENZIE

ATTORNEYS AT LAW

APARTADO AEREO 3746

TELEFONO: 285-1400

SANTAFE DE BOGOTA, D.C.

COLOMBIA



POWER OF ATTORNEY

The undersigned.

PFIZER PRODUCTS, INC.

located in
Eastern Point Road
Connecticut, United States of America

declares that it hereby grants to

CARLOS R. OLARTE

a full and sufficient power of attorney to apply to the proper national officers and authorities for the issue of:

Letters Patent, mergers, changes of name, assignments, filing and prosecution of oppositions, changes of address

to which end it empowers them to take all steps necessary before said authorities for the objects stated, to file petitions, prepare descriptions, make protests, declarations, appeals and objections, pay imposts, apply for certifications, receive documents and securities, abandon applications and collect refunds. To the said mandatories sufficient power is granted hereby to receive notifications for and on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the patents, and to do everything that may be required, before administrative or judicial officers of any class giving them likewise power to substitute these presents and revoke such substitutions if necessary.

Done and subscribed in New York, New York,
United States of America.

On the 2nd day of January 2001

XX

J. Trevor Lumb
J. Trevor Lumb
Vice President

PODER

La abajo firmada.

PFIZER PRODUCTS INC.

domiciliada en
Eastern Point Road
Connecticut, Estados Unidos de América

declara por el presente otorgar a

CARLOS R. OLARTE

poder especial amplio y bastante para recabar de las oficinas y autoridades nacionales que correspondan, la obtención de :

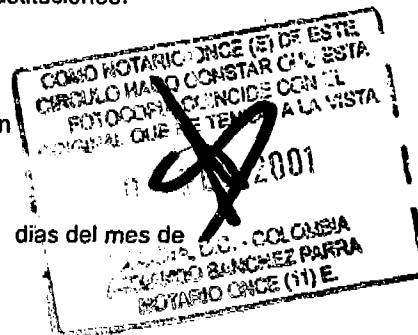
Solicitudes de Patentes de Invención, cambios de nombre, cesiones, presentación y tramitación de oposiciones, cambios de nombre

a cuyo efecto los faculta para dar ante dichas autoridades, todos los pasos necesarios al objeto indicado, elevar solicitudes, formular descripciones, protestas, declaraciones, apelaciones y reclamos, oblar impuestos, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede a los expresados mandatarios poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de las patentes se presentaren y hacer cuanto fuere necesario, ante las autoridades administrativas o judiciales de cualquier orden, dándoles asimismo facultad para sustituir el presente y en caso necesario revocar dichas sustituciones.

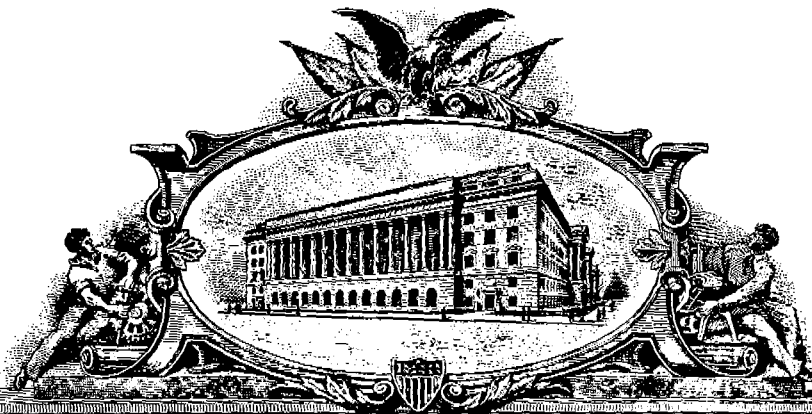
Dado y firmado en

A los

19



PA 354965



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

January 30, 2001

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/189,942

FILING DATE: *March 16, 2000*



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

P. R. Grant

P. R. GRANT

Certifying Officer

03-17-00

A/Prav 7

03/16/00
10713 U.S. PTO

Please type a plus sign (+) inside this box → ☒

Approved for use through 01/31/2001 OMB 0651-0037
Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

+

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

10713 U.S. PTO
60/169942
03/16/00

INVENTOR(S)					
Given Name (first and middle (if any))		Family Name or Surname		Residence (City and either State or Foreign Country)	
Dennis J.		HOOVER		Mystic, CT	
☒ Additional inventors are being named on the <u>1</u> separately numbered sheets attached hereto					
TITLE OF THE INVENTION (280 characters max)					
PHARMACEUTICAL COMPOSITIONS OF GLYCOGEN PHOSPHORYLASE INHIBITORS					
Direct all correspondence to: CORRESPONDENCE ADDRESS					
☐ Customer Number				Place Customer Number Bar Code Label here	
OR Type Customer Number here					
☒ Firm or Individual Name		Bruce W. DeKock, Chernoff Vilhauer McClung Stenzel			
Address		1600 ODS Tower			
Address		601 S.W. Second Avenue			
City		Portland		State	OR
Country		USA		ZIP	97204
		Telephone	503/227-5631	Fax	503/228-4373
ENCLOSED APPLICATION PARTS (check all that apply)					
☒ Specification Number of Pages		139		☐ Small Entity Statement	
☐ Drawing(s) Number of Sheets				☒ Other (specify) Postcard, express mail receipt	
METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)					
☒ A check or money order is enclosed to cover the filing fees				FILING FEE AMOUNT (\$)	
☒ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 03-1550				\$150.00	
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.					
☒ No.					
☐ Yes, the name of the U.S. Government agency and the Government contract number are:					

Respectfully submitted, Bruce W. DeKock Date **3 / 16 / 00**

SIGNATURE Bruce W. DeKock REGISTRATION NO. **40,585**

TYPED or PRINTED NAME Bruce W. DeKock (if appropriate)

TELEPHONE (503) 227-5631 Docket Number: **BWD:7783.011**

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C., 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C., 20231.

60169942-031500

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PROVISIONAL APPLICATION COVER SHEET Additional Page

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PTO/SB/16 (2-95)
Approved for use through 01/31/2001. OMB 0651-0037
Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Docket Number	BWD:7783011	Type a plus sign (+) inside this box	+
---------------	-------------	--------------------------------------	---

INVENTOR(S)/APPLICANT(S)		
Given Name (first and middle (if any))	Family or Surname	Residence (City and either State or Foreign Country)
Ravi M.	SHANKER	Groton, CT
James A.S.	NIGHTENGALE	Bend, OR
Dwayne T.	FRIESEN	Bend, OR
Douglas A.	LORENZ	Bend, OR

60189942-031500

Number 2 of 2

+

14
7

CERTIFICATE OF MAILING

BY "EXPRESS MAIL"

Express Mail No. EL472157445US

Date of Deposit: March 16, 2000

5013942-031500
I hereby certify that the provisional patent application attached hereto entitled PHARMACEUTICAL COMPOSITIONS OF GLYCOGEN PHOSPHORYLASE INHIBITORS ("GPI") (139 pages), together with Provisional Application cover sheet (in duplicate), Fee Transmittal cover sheet (in duplicate), a check for \$150.00, this Certificate of Mailing by Express Mail, and a return, acknowledgment postcard is being deposited with the United States Postal Service "Express Mail to Addressee" service on the date indicated above and is addressed to Box Provisional Application, Assistant Commissioner for Patents, Washington, DC 20231.


DWIGHT BERGQUIST-MOODY

PHARMACEUTICAL COMPOSITIONS OF GLYCOGEN
PHOSPHORYLASE INHIBITORS

BACKGROUND OF THE INVENTION

5 This invention relates to pharmaceutical compositions containing a glycogen phosphorylase inhibitor (GPI) and at least one concentration-enhancing polymer, and the use of such pharmaceutical compositions to treat diabetes, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemias, hyperlipidemia, atherosclerosis and myocardial ischemia in mammals.

10 In spite of the early discovery of insulin and its subsequent widespread use in the treatment of diabetes, and the later discovery of and use of sulfonylureas (e.g. Chlorpropamide (Pfizer), Glipizide (Pfizer), Tolbutamide (Upjohn), Acetohexamide (E.I. Lilly), Tolazimide (Upjohn)) and biguanides (e.g. Phenformin (Ciba Geigy), Metformin (G. D. Searle)) as oral hypoglycemic agents, the treatment of diabetes remains less than satisfactory. The use of insulin, necessary in about 10% of diabetic patients in which synthetic hypoglycemic agents are not effective (Type 1 diabetes, insulin dependent diabetes mellitus), requires multiple daily doses, usually by self-injection.

20 Determination of the proper dosage of insulin requires frequent estimations of the sugar in urine or blood. The administration of an excess dose of insulin causes hypoglycemia, with effects ranging from mild abnormalities in blood glucose to coma, or even death.

30 Treatment of non-insulin dependent diabetes mellitus (Type 2 diabetes, NIDDM) usually consists of a combination of diet, exercise, oral agents, e.g. sulfonylureas, and in more severe cases, insulin. However, the clinically available hypoglycemics can have other side effects which limit their use. In any event, where one of these agents may fail in an individual case, another may succeed. A continuing need for hypoglycemic

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agents, which may have fewer side effects or succeed where others fail, is clearly evident.

Hepatic glucose production is an important target for NIDDM therapy. The liver is the major regulator of plasma glucose levels in the post absorptive (fasted) state, and the rate of hepatic glucose production in NIDDM patients is significantly elevated relative to normal individuals. Likewise, in the postprandial (fed) state, where the liver has a proportionately smaller role in the total plasma glucose supply, hepatic glucose production is abnormally high in NIDDM patients.

Glycogenolysis is an important target for interruption of hepatic glucose production. The liver produces glucose by glycogenolysis (breakdown of the glucose polymer glycogen) and gluconeogenesis (synthesis of glucose from 2- and 3-carbon precursors). Several lines of evidence indicate that glycogenolysis may make an important contribution to hepatic glucose output in NIDDM. First, in normal post absorptive man, up to 75% of hepatic glucose production is estimated to result from glycogenolysis. Second, patients having liver glycogen storage diseases, including Hers' disease (glycogen phosphorylase deficiency), display episodic hypoglycemia. These observations suggest that glycogenolysis may be a significant process for hepatic glucose production.

Glycogenolysis is catalyzed in liver, muscle, and brain by tissue-specific isoforms of the enzyme glycogen phosphorylase (GP). This enzyme cleaves the glycogen macromolecule to release glucose-1-phosphate and a new shortened glycogen macromolecule. Several types of GPIs have been reported to date: glucose and glucose analogs [Martin, J. L. et al., *Biochemistry* 1991, 30, 10101] and caffeine and other purine analogs [Kasvinsky, P. J. et al., *J. Biol. Chem.* 1978, 253, 3343-3351 and 9102-9106]. These compounds, and GPIs in general, have been postulated to be of potential use for the treatment

of NIDDM by decreasing hepatic glucose production and lowering glycemia [Blundell, T. B. et al. *Diabetologia* 1992, 35, Suppl. 2, 569-576 and Martin et al. *Biochemistry* 1991, 30, 10101].

5 Sites at which GPIs have been reported to bind are the active site, the caffeine or purine binding site, and the ATP or nucleotide binding site. Enzyme activity is also controlled by phosphorylation at a single phosphorylation site, Ser 14. Phosphorylation normally
10 causes an increase in GP activity due to a conformational change in the GP enzyme. The features of this conformational change have been identified. See, Sprang et al., *Nature* 1988, 336, 215-21. The experimentally determined GP:GPI structures reveal that inhibitor
15 binding at any of the three binding sites named above reverses the conformational change in GP that normally occurs upon phosphorylation causing the GP enzyme to adopt the conformation of the "inactive," unphosphorylated protein.

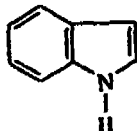
20 Several GPIs have been described. See, e.g., Kristiansen et al., U.S. Patent No. 5,952,363; Lundgren et al., EP 884 050 A1; Kristiansen et al., WO 98/50359; Bols, WO 97/31901; and Lundgren et al., WO 97/09040. Most of these compounds are cyclic amines with various
25 substituents that generally render them relatively hydrophilic with good water solubility and good potential for absorption. These GPIs, being water soluble, would thus be expected to not have solubility-limited absorption.

30 A new binding site has been recently discovered, together with new glycogen phosphorylase inhibitors which bind to this new site. See EP 0978279 A1. As used herein and in the claims, this new binding site shall be referred to as the "indole pocket
35 binding site." Four different types of GPIs have been identified so far that bind to the indole pocket binding

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site: See WO 96/39385, U.S. Patent No. 5,952,322, and EP 846464 A2 which disclose GPIs of the first type; WO 96/39384 and EP 832065 A1 which disclose GPIs of the second type; and U.S. Patent No. 5,998,463 which discloses GPIs of the third type. A fourth type is disclosed herein. In general, these compounds have in common the structural feature of one or more fused ring systems comprising a six-membered aromatic ring and a nitrogen-containing heterocycle. Such fused ring systems can be considered an "indole-like group," indole itself having the structure:



It is believed that GPIs which contain the indole-like group bind to the indole pocket binding site of the GP enzyme. GPIs that bind to this indole pocket binding site generally are relatively hydrophobic, have poor water solubility, and poor bioavailability.

Accordingly, what is therefore desired is a composition containing a poorly water soluble GPI that increases the GPI concentration in aqueous solution, does not adversely effect the ability of the GPI to bind to the GP enzyme, improves relative bioavailability, and is pharmaceutically acceptable.

BRIEF SUMMARY OF INVENTION

The present invention overcomes the aforesaid drawbacks by providing a pharmaceutical composition comprising a glycogen phosphorylase inhibitor and a concentration-enhancing polymer. The GPI binds to a portion or all portions of the following residues of a glycogen phosphorylase enzyme:

parent secondary

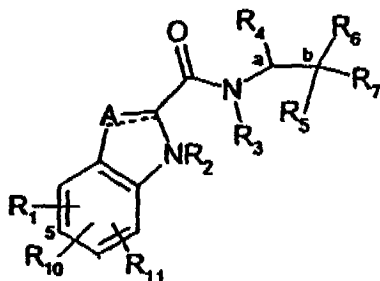
	<u>structure</u>	<u>residue number</u>
		13-23
	helix $\alpha 1$	24-37
5	turn	38-39, 43, 46-47
	helix $\alpha 2$	48-66, 69-70, 73-74, 76-78
		79-80
	strand $\beta 1$	81-86
		87-88
10	strand $\beta 2$	89-92
		93
	helix $\alpha 3$	94-102
		103
	helix $\alpha 4$	104-115
15		116-117
	helix $\alpha 5$	118-124
		125-128
	strand $\beta 3$	129-131
		132-133
20	helix $\alpha 6$	134-150
		151-152
	strand $\beta 4$	153-160
		161
	strand $\beta 4b$	162-163
25		164-166
	strand $\beta 5$	167-171
		172-173
	strand $\beta 6$	174-178
		179-190
30	strand $\beta 7$	191-192
		194, 197
	strand $\beta 8$	198-209
		210-211
	strand $\beta 9$	212-216
35	strand $\beta 10$	219-226, 228-232
		233-236

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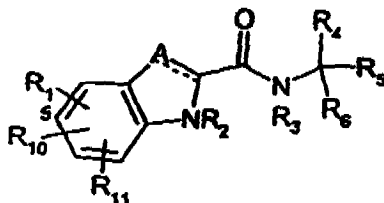
strand β 11	237-239, 241, 243-247
	248-260
helix α 7	261-276
strand β 11b	277-281
reverse turn	282-289
helix α 8	290-304.

In a second aspect of the invention, a pharmaceutical composition comprises a GPI and a concentration-enhancing polymer, the GPI having the general structure of Formula I:



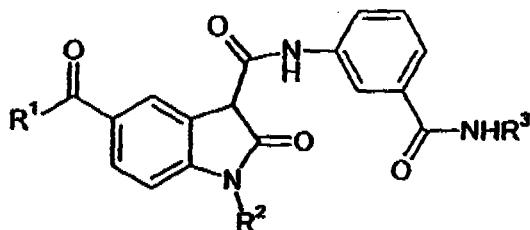
Formula I

In a third aspect of the invention, a pharmaceutical composition comprises a GPI and a concentration-enhancing polymer, the GPI having the general structure of Formula II:



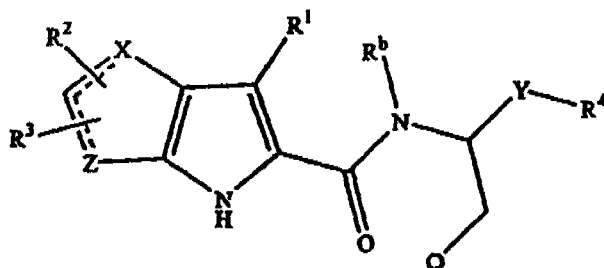
Formula II

In a fourth aspect of the invention, a pharmaceutical composition comprises a GPI and a concentration-enhancing polymer, the GPI having the general structure of Formula III:



Formula III

In a fifth aspect of the invention, a pharmaceutical composition comprises a GPI and a concentration-enhancing polymer, the GPI having the general structure of Formula IV:



Formula IV

In a sixth aspect of the invention, a pharmaceutical composition comprises a GPI and a concentration-enhancing polymer, the GPI having a solubility in aqueous solution, in the absence of the polymer, of less than 1.0 mg/mL at any pH of from 1 to 8.

In a seventh aspect of the invention, a pharmaceutical composition comprises a GPI and a concentration-enhancing polymer. The composition provides a maximum concentration of the GPI in a use environment that is 1.25-fold that of a control composition comprising an equivalent amount of the GPI and free from the polymer. As used herein, a "use environment" can be either the *in vivo* environment of the GI tract of a mammal, particularly a human, or the *in vitro* environment of a test solution, such as phosphate

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buffered saline (PBS) or a Model Fasted Duodenal (MFD) solution.

In an eighth aspect of the invention, a pharmaceutical composition comprises a GPI and a concentration-enhancing polymer. The composition provides a relative bioavailability that is at least 1.25 relative to a control composition comprising an equivalent amount of the GPI and free from the polymer.

In another aspect of the invention, a method of treatment of a mammal having an indication due to atherosclerosis, diabetes, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, cataracts, hypercholesterolemia, hypertriglycerdemia, hypertension, myocardial ischemia, hyperglycemia, hyperinsulinemia, hyperlipidemia, insulin resistance, bacterial infection, or tissue ischemia comprises the following steps. A composition of a GPI and a concentration-enhancing polymer is formed. The composition is then administered to the mammal.

The composition may be dosed in a variety of dosage forms, including both initial release and controlled release dosage forms, the latter including both delayed and sustained release forms. The composition may include blends of polymers, and may further include other polymers that improve the aqueous concentration of the GPI. The composition may further comprise other constituents that improve the stability, wetting, dissolution, tableting, or processing characteristics of the composition.

The various aspects of the present invention each have one or more of the following advantages. The compositions increase the concentration of GPI in aqueous solution relative to the crystalline form of the GPI. The compositions also improve relative bioavailability of the GPI. In addition, the compositions enable the use of poorly water soluble, hydrophobic GPIs without adversely affecting their binding characteristics.

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The foregoing and other objectives, features, and advantages of the invention will be more readily understood upon consideration of the following detailed description of the invention.

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DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compositions of GPIs and at least one concentration-enhancing polymer. As discussed above in the Background, a new class of
10 poorly water soluble, hydrophobic GPIs has been discovered that bind to the indole pocket binding site in the GP enzyme. It is believed that an important part of the binding of GPIs to this site is due to the indole-like group, which, being relatively hydrophobic, binds in
15 a hydrophobic pocket within the GP enzyme. In studying the GPI activity, binding mode, and GPI/GP complex structure of a wide variety of compounds, it has been found that compounds that have good GP inhibition activity at this indole pocket binding site often have a
20 number of features in common: (1) the presence of one or more indole-like groups in the structure; (2) extremely low solubilities in aqueous solution (*i.e.*, less than 1.0 mg/mL) at physiologically relevant pH (*e.g.*, any pH of from 1 through 8) measured at about 22°C; (3) a
25 relatively hydrophobic nature; and (4) a relatively low bioavailability when orally dosed in the crystalline state.

Accordingly, unlike other previously known GPIs, GPIs which bind to the indole pocket binding site
30 typically require some kind of modification or formulation to enhance their solubility and thereby achieve good bioavailability. However, the inventors have found that many of the conventional methods used to improve solubility, and in turn bioavailability, have
35 proved problematic. One method used generally to improve drug bioavailability is to form an ionic form of the drug, typically by incorporating an ionizable group into

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its structure, and particularly by forming a highly soluble salt form. However, the GPIs with the indole-like group having the best performance generally are neutral or nonionic and relatively hydrophobic.

5 The inventors have found that preparing GPIs having indole-like groups as compositions comprising a GPI and concentration-enhancing polymer, and preferably as a solid dispersion of the GPI and concentration-enhancing polymer, improves the aqueous concentration of
10 the GPIs as well as relative bioavailability, but does not adversely affect the binding characteristics of the GPIs. The compositions, GPIs, suitable polymers, and optional excipients are discussed in more detail as follows.

15 COMPOSITIONS OF GPIs AND CONCENTRATION-ENHANCING POLYMER

 The present invention finds utility with any low-solubility GPI, or any GPI which would benefit by improved bioavailability. The compositions of the
20 present invention are mixtures comprised of a GPI and at least one concentration-enhancing polymer. The mixtures are preferably solid dispersions, but simple physical mixtures of the GPI and polymer may also be suitable for some GPIs. The GPI in its pure state may be crystalline
25 or amorphous. Preferably, at least a major portion of the GPI in the composition is amorphous. By "amorphous" is meant simply that the GPI is in a non-crystalline state. As used herein, the term "a major portion" of the GPI means that at least 60% of the GPI in the composition
30 is in the amorphous form, rather than the crystalline form. Preferably, the GPI in the composition is substantially amorphous. As used herein, "substantially amorphous" means that the amount of the GPI in crystalline form does not exceed 25%. More preferably, the GPI in
35 the composition is "almost completely amorphous" meaning that the amount of GPI in the crystalline form does not exceed 10%. Amounts of crystalline GPI may be measured

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by powder X-ray diffraction, Scanning Electron Microscope (SEM) analysis, differential scanning calorimetry ("DSC"), or any other standard quantitative measurement. The composition may contain from about 1 to about 80 wt% GPI, depending on the dose of the GPI. Enhancement of aqueous GPI concentrations and relative bioavailability are typically best at low GPI levels, typically less than about 25 to 40 wt%. However, due to the practical limit of the dosage form size, higher GPI loadings are often preferred and perform well.

In a preferred aspect of the invention, GPI and concentration-enhancing polymer are present as a solid dispersion of the low-solubility GPI and polymer. Preferably, at least a major portion of the GPI in the dispersion is present in the amorphous, rather than the crystalline state. The amorphous GPI can exist as a pure phase, as a solid solution of GPI homogeneously distributed throughout the polymer or any combination of these states or those states that lie intermediate between them.

The dispersion is preferably substantially homogeneous so that the amorphous GPI is dispersed as homogeneously as possible throughout the polymer. As used herein, "substantially homogeneous" means that the GPI present in relatively pure amorphous domains within the solid dispersion is relatively small, on the order of less than 20%, and preferably less than 10% of the total amount of GPI. While the dispersion may have some GPI-rich domains, it is preferred that the dispersion itself have a single glass transition temperature (T_g) which demonstrates that the dispersion is substantially homogeneous. This contrasts with a simple physical mixture of pure amorphous GPI particles and pure amorphous polymer particles which generally display two distinct T_g s, one that of the GPI and one that of the polymer. T_g as used herein is the characteristic temperature where a glassy material, upon gradual

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heating, undergoes a relatively rapid (e.g., 10 to 100 seconds) physical change from a glass state to a rubber state. Dispersions of the present invention that are substantially homogeneous generally are more physically stable and have improved concentration-enhancing properties and, in turn improved bioavailability, relative to nonhomogeneous dispersions.

While the inventors have found that dispersions of the GPI and concentration-enhancing polymer yield good results, it has been found for at least one GPI that compositions of physical mixtures of amorphous GPI and concentration-enhancing polymer also yield improved aqueous GPI concentration. At least a major portion of the GPI in the mixture is amorphous. The composition may be in the form of a simple dry physical mixture wherein both the GPI and concentration-enhancing polymer are mixed in particulate form and wherein the particles of each, regardless of size, retain the same individual physical properties that they exhibit in bulk. Any conventional method used to mix the polymer and GPI together such as physical mixing and dry or wet granulation may be used. In this embodiment of the invention, the amorphous GPI and concentration-enhancing polymer need not be directly mixed, but only both present in the dosage form. For example, the amorphous GPI may be in the form of a tablet, bead, or capsule, and the concentration-enhancing polymer may be a coating, granulating material, or even the wall of the capsule.

The compositions comprising the GPI and concentration-enhancing polymer provide enhanced concentration of the GPI in *in vitro* dissolution tests. It has been determined that enhanced drug concentration in *in vitro* dissolution tests in Model Fasted Duodenal (MFD solution) or Phosphate Buffered Saline (PBS) is a good indicator of *in vivo* performance and bioavailability. An appropriate PBS solution is an aqueous solution comprising 20 mM sodium phosphate

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(Na_2HPO_4), 47 mM potassium phosphate (KH_2PO_4), 87 mM NaCl, and 0.2 mM KCl, adjusted to pH 6.5 with NaOH. An appropriate MFD solution is the same PBS solution wherein additionally is present 14.7 mM sodium taurocholic acid and 2.8 mM of 1-palmitoyl-2-oleyl-sn-glycero-3-phosphocholine. In particular, a composition of the present invention can be dissolution-tested by adding it to MFD or PBS solution and agitating to promote dissolution. Preferably, the composition of the present invention provides a Maximum Drug Concentration (MDC) that is at least 1.25-fold the equilibrium concentration of a control composition comprising an equivalent quantity of GPI but free from the polymer. In other words, if the equilibrium concentration provided by the control composition is 100 $\mu\text{g/mL}$, then a composition of the present invention provides an MDC of at least 125 $\mu\text{g/mL}$. The comparison composition is conventionally the undispersed GPI alone (e.g., typically, the crystalline GPI alone in its most thermodynamically stable crystalline form, or in cases where a crystalline form of the GPI is unknown, the control may be the amorphous GPI alone) or the GPI plus a weight of inert diluent equivalent to the weight of polymer in the test composition. More preferably, the MDC of GPI achieved with the compositions of the present invention are at least 2-fold, and even more preferably at least 3-fold, that of the control composition.

Alternatively, the compositions of the present invention provide in an aqueous use environment a concentration versus time Area Under The Curve (AUC), for any period of at least 90 minutes between the time of introduction into the use environment and about 270 minutes following introduction to the use environment that is at least 1.25-fold that of a control composition comprising an equivalent quantity of undispersed GPI.

Alternatively, the dispersion of the present invention, when dosed orally to a human or other animal,

provides an AUC in GPI concentration in the blood for any period of at least 90 minutes between the time of dosage and about 270 minutes following dosage that is at least 1.25-fold that observed when a control composition comprising an equivalent quantity of undispersed drug is dosed. Thus, the compositions of the present invention can be evaluated in either an *in vitro* or *in vivo* test, or both.

A typical test to evaluate enhanced drug concentration can be conducted by (1) dissolving a sufficient quantity of control composition, typically the GPI alone, in the *in vitro* test medium, typically MFD or PBS solution, to achieve equilibrium concentration of the GPI; (2) dissolving a sufficient quantity of test composition (e.g., the GPI and polymer) in an equivalent test medium, such that if all the GPI dissolved, the theoretical concentration of GPI would exceed the equilibrium concentration of the GPI by a factor of at least 2; and (3) determining whether the measured MDC of the test composition in the test medium is at least 1.25-fold that of the equilibrium concentration of the control composition. In conducting such a dissolution test, the amount of test composition or control composition used is an amount such that if all of the GPI dissolved the GPI concentration would be at least 2-fold to 100-fold that of the solubility of the GPI. The concentration of dissolved GPI is typically measured as a function of time by sampling the test medium and plotting GPI concentration in the test medium vs. time so that the MDC can be ascertained. To avoid GPI particulates which would give an erroneous determination, the test solution is either filtered or centrifuged. "Dissolved GPI" is typically taken as that material that either passes a 0.45 μm syringe filter or, alternatively, the material that remains in the supernatant following centrifugation. Filtration can be conducted using a 13 mm, 0.45 μm polyvinylidene difluoride syringe filter sold by

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Centrifugation is typically carried out in a polypropylene microcentrifuge tube by centrifuging at 13,000 G for 60 seconds. Other similar filtration or centrifugation methods can be employed and useful results obtained. For example, using other types of microfilters may yield values somewhat higher or lower ($\pm 10-40\%$) than that obtained with the filter specified above but will still allow identification of preferred dispersions. It is recognized that this definition of "dissolved GPI" encompasses not only monomeric solvated GPI molecules but also a wide range of species such as polymer/GPI assemblies that have submicron dimensions such as GPI aggregates, aggregates of mixtures of polymer and GPI, micelles, polymeric micelles, colloidal particles or nanocrystals, polymer/GPI complexes, and other such GPI-containing species that are present in the filtrate or supernatant in the specified dissolution test.

Relative bioavailability of GPIs in the dispersions of the present invention can be tested *in vivo* in animals or humans using conventional methods for making such a determination. An *in vivo* test, such as a crossover study, may be used to determine whether a composition of GPI and polymer provides an enhanced relative bioavailability compared with a control composition comprised of a GPI but no polymer as described above. In an *in vivo* crossover study a "test composition" of GPI and polymer is dosed to half a group of test subjects and, after an appropriate washout period (e.g., one week) the same subjects are dosed with a "control composition" that comprises an equivalent quantity of GPI as the "test composition". The other half of the group is dosed with the control composition first, followed by the test composition. The relative bioavailability is measured as the concentration in the blood (serum or plasma) versus time area under the curve

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(AUC) determined for the test group divided by the AUC in the blood provided by the control composition.

Preferably, this test/control ratio is determined for each subject, and then the ratios are averaged over all

5 subjects in the study. In vivo determinations of AUC can

be made by plotting the serum or plasma concentration of drug along the ordinate (y-axis) against time along the abscissa (x-axis). Generally, the values for AUC

represent a number of values taken from all of the

10 subjects in a patient test population averaged over the entire test population. A preferred embodiment of the

invention is one in which the relative bioavailability of the test composition is at least 1.25 relative to a

control composition comprised of a GPI but with no

15 polymer as described above. (That is, the AUC provided

by the test composition is at least 1.25-fold the AUC

provided by the control composition.) An even more

preferred embodiment of the invention is one in which the relative bioavailability of the test composition is at

20 least 2.0 relative to a control composition of the GPI

but with no polymer present, as described above. The

determination of AUCs is a well-known procedure and is

described, for example, in Welling, "Pharmacokinetics

Processes and Mathematics," ACS Monograph 185 (1986).

25

GLYCOGEN PHOSPHORYLASE INHIBITORS

The invention is useful for GPIs which have sufficiently low aqueous solubility that it is desirable to increase their water solubility. Therefore, anytime

30 one finds it desirable to raise the concentration of the

GPI in a use environment, the invention will find

utility. The GPI has "low-solubility," meaning that the

GPI may be either "substantially water-insoluble" (which means that the GPI has a minimum aqueous solubility at

35 any physiologically relevant pH (e.g., pH 1-8) and about

22°C of less than 0.01 mg/mL), or "sparingly water-

soluble" (that is, has a water solubility up to about 1

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mg/mL). (Unless otherwise specified, reference to aqueous solubility herein and in the claims is determined at about 22°C.) Compositions of the present invention find greater utility as the solubility of the GPI decreases, and thus are preferred for GPI solubilities less than 0.5 mg/mL, and even more preferred for GPI solubilities less than 0.1 mg/mL. In general, it may be said that the GPI has a dose-to-aqueous solubility ratio greater than about 10 mL, where the solubility (mg/mL) is the minimum value observed in any physiologically relevant aqueous solution (e.g., those with pH values from 1 to 8) including USP simulated gastric and intestinal buffers, and dose is in mg. Compositions of the present invention, as mentioned above, find greater utility as the solubility of the GPI decreases and the dose increases. Thus, the compositions are preferred as the dose-to-solubility ratio increases, and thus are preferred for dose-to-solubility ratios greater than 100 mL, and more preferred for dose-to-solubility ratios greater than 400 mL.

Preferably, the GPI binds to the GP enzyme at the indole pocket binding site. As used herein and in the claims, "bind" means a portion of the GPI binds to the GP enzyme in such a manner that a portion of the GPI is in van der Waals or hydrogen bonding contact with a portion or all portions of certain residues of the binding site. In a preferred embodiment, the GPI binds to the GP enzyme with a portion or all portions of the following residues of GP:

	parent secondary <u>structure</u>	<u>residue number</u>
		13-23
35	helix α 1	24-37
	turn	38-39, 43, 46-47
	helix α 2	48-66, 69-70, 73-74, 76-78
		79-80

18

	strand β 1	81-86
		87-88
	strand β 2	89-92
		93
5	helix α 3	94-102
		103
	helix α 4	104-115
		116-117
	helix α 5	118-124
10		125-128
	strand β 3	129-131
		132-133
	helix α 6	134-150
		151-152
15	strand β 4	153-160
		161
	strand β 4b	162-163
		164-166
	strand β 5	167-171
20		172-173
	strand β 6	174-178
		179-190
	strand β 7	191-192
		194, 197
25	strand β 8	198-209
		210-211
	strand β 9	212-216
	strand β 10	219-226, 228-232
		233-236
30	strand β 11	237-239, 241, 243-247
		248-260
	helix α 7	261-276
	strand β 11b	277-281
	reverse turn	282-289
35	helix α 8	290-304

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More preferably, the GPI binds with one or more of the following residues of GP in one or both subunits:

	parent secondary <u>structure</u>	<u>residue number</u>
5		13-23
	helix $\alpha 1$	24-37
	turn	38-39, 43, 46-47
10	helix $\alpha 2$	48-66, 69-70, 73-74, 76-78
		79-80
	strand $\beta 2$	91-92
		93
	helix $\alpha 3$	94-102
15		103
	helix $\alpha 4$	104-115
		116-117
	helix $\alpha 5$	118-124
		125-128
20	strand $\beta 3$	129-130
	strand $\beta 4$	159-160
		161
	strand $\beta 4b$	162-163
		164-166
25	strand $\beta 5$	167-168
	strand $\beta 6$	178
		179-190
	strand $\beta 7$	191-192
		194, 197
30	strand $\beta 9$	198-200
	strand $\beta 10$	220-226
		228-232
		233-236
	strand $\beta 11$	237-239, 241, 243-247
35		248-260
	helix $\alpha 7$	261-276
	strand $\beta 11b$	277-280

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Even more preferably, the GPI binds with one or more of the following residues of GP in one or both subunits:

5	<u>residue number</u>
	33-39
	49-66
	94
	98
10	102
	125-126
	160
	162
	182-192
15	197
	224-226
	228-231
	238-239
	241
20	245
	247

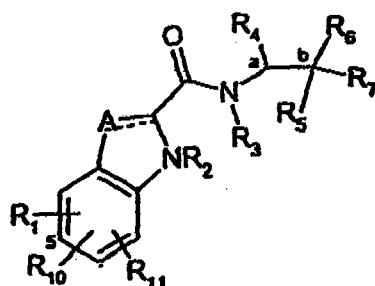
Most preferably, the GPI binds with one or more of the following residues of GP in one or both subunits:

25	<u>residue number</u>
	37-39
	53
	57
30	60
	63-64
	184-192
	226
	229

The indole pocket binding site is disclosed more fully in commonly assigned U.S. provisional patent application

Serial No. 95790 filed August 7, 1998 and corresponding published European Patent Application No. EP0978279 A1, the relevant disclosure of which is herein incorporated by reference.

It is believed that certain compounds are capable of binding at the indole pocket binding site. Accordingly, preferred GPIs of the present invention are those that are capable of binding at this site. One such set of compounds has the structure of Formula I:



Formula I

and the pharmaceutically acceptable salts and prodrugs thereof wherein the dotted line (---) is an optional bond, and the various substituents of Formula I are as follows;

A is $-C(H)=$, $-C((C_1-C_4)alkyl)=$ or $-C(halo)=$ when the dotted line (---) is a bond, or A is methylene or $-CH((C_1-C_4)alkyl)-$ when the dotted line (---) is not a bond;

R_1 , R_{10} or R_{11} are each independently H, halo, 4-, 6- or 7-nitro, cyano, $(C_1-C_4)alkyl$, $(C_1-C_4)alkoxy$, fluoromethyl, difluoromethyl or trifluoromethyl;

R_2 is H;

R_3 is H or $(C_1-C_5)alkyl$;

R_4 is methyl, ethyl, n-propyl,

hydroxy $(C_1-C_3)alkyl$, $(C_1-C_3)alkoxy(C_1-C_3)alkyl$, phenyl $(C_1-C_4)alkyl$, phenylhydroxy $(C_1-C_4)alkyl$, phenyl $(C_1-C_4)alkoxy(C_1-C_4)alkyl$, thien-2- or

-3-yl(C₁-C₄)alkyl or fur-2- or -3-yl(C₁-C₄)alkyl wherein said R₄ rings are mono-, di- or tri-substituted independently on carbon with H, halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, trifluoromethyl, hydroxy, amino or cyano;
5 or

R₄ is pyrid-2-, -3- or -4-yl(C₁-C₄)alkyl, thiazol-2-, -4- or -5-yl(C₁-C₄)alkyl, imidazol -1-, -2-, -4- or -5-yl(C₁-C₄)alkyl, pyrrol-2- or -3-yl(C₁-C₄)alkyl, oxazol-2-, -4- or -5-yl(C₁-C₄)alkyl, pyrazol-3-, -4- or
10 -5-yl(C₁-C₄)alkyl, isoxazol-3-, -4-, -5-yl(C₁-C₄)alkyl, isothiazol-3-, -4-, -5-yl(C₁-C₄)alkyl, pyridazin-3- or -4-yl-(C₁-C₄)alkyl, pyrimidin-2-, -4-, -5- or -6-yl(C₁-C₄)alkyl, pyrazin-2- or -3-yl(C₁-C₄)alkyl or 1,3,5-triazin-2-yl(C₁-C₄)alkyl, wherein said preceding R₄
15 heterocycles are optionally mono- or di-substituted independently with halo, trifluoromethyl, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, amino or hydroxy and said mono- or di-substituents are bonded to carbon;

R₅ is H, hydroxy, fluoro, (C₁-C₅)alkyl, (C₁-C₅)alkoxy, (C₁-C₆)alkanoyl, amino (C₁-C₄) alkoxy, mono-N- or di-N,N-(C₁-C₄)alkylamino(C₁-C₄)alkoxy, carboxy(C₁-C₄)alkoxy, (C₁-C₅)alkoxy-carbonyl(C₁-C₄)alkoxy, benzyloxycarbonyl(C₁-C₄)alkoxy, or carbonyloxy wherein
20 said carbonyloxy is carbon-carbon linked with phenyl, thiazolyl, imidazolyl, 1H-indolyl, furyl, pyrrolyl, oxazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazinyl and wherein said preceding R₅ rings are optionally mono-substituted with halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy,
25 hydroxy, amino or trifluoromethyl and said mono-substituents are bonded to carbon;

R₇ is H, fluoro or (C₁-C₅)alkyl; or

R₅ and R₇ can be taken together to be oxo;

R₆ is carboxy, (C₁-C₆)alkoxycarbonyl, C(O)NR₈R₉,
35 or C(O)R₁₂ wherein

R₈ is (C₁-C₃)alkyl, hydroxy or (C₁-C₃)alkoxy; and

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R_9 is H, (C_1-C_8) alkyl, hydroxy, (C_1-C_8) alkoxy, methylene-perfluorinated (C_1-C_8) alkyl, phenyl, pyridyl, thienyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl,

5 pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, piperidinyl, morpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl or 1,3,5-triazinyl wherein said preceding R_9 rings are carbon-nitrogen linked; or

R_9 is mono-, di- or tri-substituted

10 (C_1-C_5) alkyl, wherein said substituents are independently H, hydroxy, amino, mono-N- or di-N,N- (C_1-C_5) alkylamino; or

R_9 is mono- or di-substituted (C_1-C_5) alkyl,

wherein said substituents are independently phenyl,

pyridyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl,

15 thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl,

pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl,

pyridinyl, piperidinyl, morpholinyl, pyridazinyl,

pyrimidinyl, pyrazinyl, piperazinyl or 1,3,5-triazinyl

wherein the nonaromatic nitrogen-containing R_9

20 rings are optionally mono-substituted on nitrogen with

(C_1-C_6) alkyl, benzyl, benzoyl or (C_1-C_6) alkoxycarbonyl and

wherein the R_9 rings are optionally mono-substituted on

carbon with halo, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, hydroxy,

amino, or mono-N- and di-N,N (C_1-C_5) alkylamino provided

25 that no quaternized nitrogen is included and there are no nitrogen-oxygen, nitrogen-nitrogen or nitrogen-halo bonds;

R_{12} is piperazin-1-yl, 4- (C_1-C_4) alkylpiperazin-1-yl, 4-formylpiperazin-1-yl, morpholino, thiomorpholino,

30 1-oxothiomorpholino, 1,1-dioxo-thiomorpholino,

thiazolidin-3-yl, 1-oxo-thiazolidin-3-yl, 1,1-dioxo-

thiazolidin-3-yl, 2- (C_1-C_6) alkoxycarbonylpyrrolidin-1-yl,

oxazolidin-3-yl or 2(R)-hydroxymethylpyrrolidin-1-yl; or

R_{12} is 3- and/or 4-mono- or di-substituted

35 oxazetidin-2-yl, 2-, 4-, and/or 5- mono- or di-

substituted oxazolidin-3-yl, 2-, 4-, and/or 5- mono- or

di- substituted thiazolidin-3-yl, 2-, 4- and/or 5- mono-

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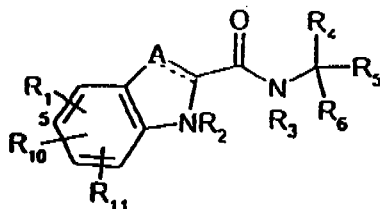
or di-substituted 1-oxothiazolidin-3-yl, 2-, 4-, and/or
 5- mono- or di-substituted 1,1-dioxothiazolidin-3-yl,
 3- and/or 4-, mono- or di-substituted pyrrolidin-1-yl,
 3-, 4- and/or 5-, mono-, di- or tri-substituted
 5 piperidin-1-yl, 3-, 4-, and/or 5- mono-, di-, or
 tri-substituted piperazin-1-yl, 3-substituted
 azetidin-1-yl, 4- and/or 5-, mono- or di-substituted
 1,2-oxazinan-2-yl, 3-and/or 4-mono- or di-substituted
 pyrazolidin-1-yl, 4- and/or 5-, mono- or di-substituted
 10 isothiazolidin-2-yl, 4- and/or 5-, mono- and/or
 di-substituted isothiazolidin-2-yl wherein said R₁₂,
 substituents are independently H, halo, (C₁-C₅)alkyl,
 hydroxy, amino, mono-N- or di-N,N-(C₁-C₅)alkylamino,
 formyl, oxo, hydroxyimino, (C₁-C₅)alkoxy, carboxy,
 15 carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl,
 (C₁-C₄)alkoxyimino, (C₁-C₄)alkoxymethoxy,
 (C₁-C₆)alkoxycarbonyl, carboxy(C₁-C₅)alkyl or
 hydroxy(C₁-C₅)alkyl;

with the proviso that if R₄ is H, methyl, ethyl
 20 or n-propyl, R₅ is OH;

with the proviso that if R₅ and R₇ are H, then
 R₄ is not H, methyl, ethyl, n-propyl, hydroxy(C₁-C₃)alkyl
 or (C₁-C₃)alkoxy(C₁-C₃)alkyl and R₆ is C(O)NR₈R₉, C(O)R₁₂ or
 (C₁-C₄)alkoxycarbonyl.

25 Compounds of Formula I are disclosed in
 published Patent Cooperation Treaty Application number
 WO 96/39385, the complete disclosure of which is hereby
 incorporated by reference.

In yet another preferred aspect of the
 30 invention, the GPI has the structure of Formula II, which
 is another class of compounds thought capable of binding
 to the indole pocket binding site:



Formula II

and the pharmaceutically acceptable salts and prodrugs thereof wherein the dotted line (---) is an optional bond and the substituents of Formula II are as follows:

A is -C(H)=, -C((C₁-C₄)alkyl)=, -C(halo)= or -N=, when the dotted line (---) is a bond, or A is methylene or -CH((C₁-C₄)alkyl)-, when the dotted line (---) is not a bond;

R₁, R₁₀ or R₁₁ are each independently H, halo, cyano, 4-, 6- or 7-nitro, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, fluoromethyl, difluoromethyl or trifluoromethyl;

R₂ is H;

R₃ is H or (C₁-C₃)alkyl;

R₄ is H, methyl, ethyl, n-propyl, hydroxy(C₁-C₃)alkyl, (C₁-C₃)alkoxy(C₁-C₃)alkyl, phenyl(C₁-C₄)alkyl, phenylhydroxy(C₁-C₄)alkyl, (phenyl)((C₁-C₄)-alkoxy)(C₁-C₄)alkyl, thien-2- or -3-yl(C₁-C₄)alkyl or fur-2- or -3-yl(C₁-C₄)alkyl wherein said R₄ rings are mono-, di- or tri-substituted independently on carbon with H, halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, trifluoromethyl, hydroxy, amino, cyano or 4,5-dihydro-1H-imidazol-2-yl; or

R₄ is pyrid-2-, -3- or -4-yl(C₁-C₄)alkyl, thiazol-2-, -4- or -5-yl(C₁-C₄)alkyl, imidazol-2-, -4-, or -5-yl(C₁-C₄)alkyl, pyrrol-2- or -3-yl(C₁-C₄)alkyl, oxazol-2-, -4- or -5-yl(C₁-C₄)alkyl, pyrazol-3-, -4- or -5-yl(C₁-C₄)alkyl, isoxazol-3-, -4- or -5-yl(C₁-C₄)alkyl, isothiazol-3-, -4- or -5-yl(C₁-C₄)alkyl, pyridazin-3- or -4-yl(C₁-C₄)alkyl, pyrimidin-2-, -4-, -5- or -6-yl(C₁-C₄)alkyl, pyrazin-2- or -3-yl(C₁-C₄)alkyl,

1,3,5-triazin-2-yl(C₁-C₄)alkyl or indol-2-(C₁-C₄)alkyl, wherein said preceding R₄ heterocycles are optionally mono- or di-substituted independently with halo, trifluoromethyl, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, amino, hydroxy or cyano and said substituents are bonded to carbon; or

R₄ is R₁₅-carbonyloxymethyl, wherein said R₁₅ is phenyl, thiazolyl, imidazolyl, 1H-indolyl, furyl, pyrrolyl, oxazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazinyl and wherein said preceding R₁₅ rings are optionally mono- or di-substituted independently with halo, amino, hydroxy, (C₁-C₄)alkyl, (C₁-C₄)alkoxy or trifluoromethyl and said mono- or di-substituents are bonded to carbon;

R₅ is H, methyl, ethyl, n-propyl, hydroxymethyl or hydroxyethyl;

R₆ is carboxy, (C₁-C₆)alkoxycarbonyl, benzyloxycarbonyl, C(O)NR₄R₅ or C(O)R₁₂

wherein R₇ is H, (C₁-C₆)alkyl, cyclo(C₃-C₆)alkyl, cyclo(C₃-C₆)alkyl(C₁-C₅)alkyl, hydroxy or (C₁-C₆)alkoxy; and

R₈ is H, cyclo(C₃-C₆)alkyl, cyclo(C₃-C₆)alkyl(C₁-C₅)alkyl, cyclo(C₄-C₇)alkenyl,

cyclo(C₃-C₆)alkyl(C₁-C₅)alkoxy, cyclo(C₃-C₇)alkyloxy, hydroxy, methylene-perfluorinated (C₁-C₆)alkyl, phenyl, or a heterocycle wherein said heterocycle is pyridyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, pyridinyl, piperidinyl, morpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, thiochromanyl or tetrahydrobenzothiazolyl wherein said heterocycle rings are carbon-nitrogen linked; or

R₉ is (C₁-C₆)alkyl or (C₁-C₆)alkoxy wherein said (C₁-C₆)alkyl or (C₁-C₆)alkoxy is optionally monosubstituted

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with cyclo(C₁-C₆)alken-1-yl, phenyl, thienyl, pyridyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, piperidinyl, morpholinyl, thiomorpholinyl, 1-oxothiomorpholinyl, 1,1-dioxothiomorpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl or indolyl and wherein said (C₁-C₆)alkyl or (C₁-C₆)alkoxy are optionally additionally independently mono- or di-substituted with halo, hydroxy, (C₁-C₃)alkoxy, amino, mono-N- or di-N,N-(C₁-C₃)alkylamino, cyano, carboxy, or (C₁-C₄)alkoxycarbonyl; and

wherein the R₂ rings are optionally mono- or di-substituted independently on carbon with halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, hydroxy, hydroxy(C₁-C₄)alkyl, amino(C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylamino (C₁-C₄)alkyl, (C₁-C₄)alkoxy(C₁-C₄)alkyl, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, cyano, carboxy, (C₁-C₃)alkoxycarbonyl, carbamoyl, formyl or trifluoromethyl and said R₂ rings may optionally be additionally mono- or di-substituted independently with (C₁-C₃)alkyl or halo;

with the proviso that no quaternized nitrogen on any R₂ heterocycle is included;

R₁₂ is morpholino, thiomorpholino, 1-oxothiomorpholino, 1,1-dioxothiomorpholino, thiazolidin-3-yl, 1-oxothiazolidin-3-yl, 1,1-dioxothiazolidin-3-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, piperazin-4-yl, azetidin-1-yl, 1,2-oxazinan-2-yl, pyrazolidin-1-yl, isoxazolidin-2-yl, isothiazolidin-2-yl, 1,2-oxazetidin-2-yl, oxazolidin-3-yl, 3,4-dihydroisoquinolin-2-yl, 1,3-dihydroisoindol-2-yl, 3,4-dihydro-2H-quinol-1-yl, 2,3-dihydro-benzo[1,4]oxazin-4-yl, 2,3-dihydro-benzo[1,4]-thiazine-4-yl, 3,4-dihydro-2H-quinoxalin-1-yl, 3,4-dihydro-benzo[c][1,2]oxazin-1-yl, 1,4-dihydro-

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benzo[d][1,2]oxazin-3-yl, 3,4-dihydro-benzo[e][1,2]-
oxazin-2-yl, 3H-benzo[d]isoxazol-2-yl,
3H-benzo[c]isoxazol-1-yl or azepan-1-yl,

wherein said R_{12} rings are optionally mono-, di-
5 or tri-substituted independently with halo, (C_1-C_5) alkyl,
 (C_1-C_5) alkoxy, hydroxy, amino, mono-N- or
di-N,N- (C_1-C_5) alkylamino, formyl, carboxy, carbamoyl,
mono-N- or di-N,N- (C_1-C_5) alkylcarbamoyl, (C_1-C_6) alkoxy
 (C_1-C_3) alkoxy, (C_1-C_3) alkoxycarbonyl, benzyloxycarbonyl,
10 (C_1-C_3) alkoxycarbonyl (C_1-C_3) alkyl,
 (C_1-C_4) alkoxycarbonylamino, carboxy (C_1-C_3) alkyl,
carbamoyl (C_1-C_3) alkyl, mono-N- or
di-N,N- (C_1-C_3) alkylcarbamoyl (C_1-C_5) alkyl,
hydroxy (C_1-C_3) alkyl, (C_1-C_4) alkoxy (C_1-C_4) alkyl,
15 amino (C_1-C_4) alkyl, mono-N- or
di-N,N- (C_1-C_4) alkylamino (C_1-C_4) alkyl, oxo, hydroxyimino or
 (C_1-C_6) alkoxyimino and wherein no more than two
substituents are selected from oxo, hydroxyimino or
 (C_1-C_6) alkoxyimino and oxo, hydroxyimino or
20 (C_1-C_6) alkoxyimino are on nonaromatic carbon; and
wherein said R_{12} rings are optionally
additionally mono- or di-substituted independently with
 (C_1-C_5) alkyl or halo;

with the proviso that when R_4 is
25 (C_1-C_3) alkoxycarbonyl or benzyloxycarbonyl then R_1 is
5-halo, 5- (C_1-C_4) alkyl or 5-cyano and R_4 is
(phenyl) (hydroxy) (C_1-C_4) alkyl,
(phenyl) $((C_1-C_4)$ alkoxy) (C_1-C_4) alkyl, hydroxymethyl or
 $Ar(C_1-C_2)$ alkyl, wherein Ar is thien-2- or -3-yl, fur-2- or
30 -3-yl or phenyl wherein said Ar is optionally mono- or
di-substituted independently with halo; with the provisos
that when R_4 is benzyl and R_3 is methyl, R_{12} is not
4-hydroxy-piperidin-1-yl or when R_4 is benzyl and R_3 is
methyl R_6 is not $C(O)N(CH_3)_2$;

35 with the proviso that when R_1 and R_{10} and R_{11} are
H, R_4 is not imidazol-4-ylmethyl, 2-phenylethyl or
2-hydroxy-2-phenylethyl;

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with the proviso that when R_4 and R_5 are n-pentyl, R_1 is 5-chloro, 5-bromo, 5-cyano, 5(C_1-C_3)alkyl, 5(C_1-C_3)alkoxy or trifluoromethyl;

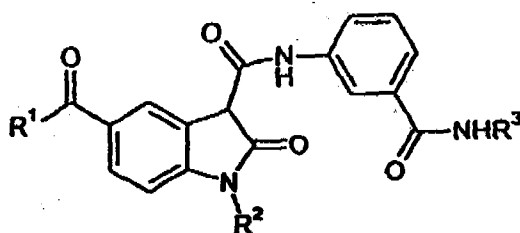
with the proviso that when R_{12} is 3,4-dihydroisoquinol-2-yl, said 3,4-dihydroisoquinol-2-yl is not substituted with carboxy((C_1-C_4) alkyl);

with the proviso that when R_6 is H and R_7 is (C_1-C_6)alkyl, R_9 is not substituted with carboxy or (C_1-C_4)alkoxycarbonyl on the carbon which is attached to the nitrogen atom N of NHR_9 ; and

with the proviso that when R_4 is carboxy and R_1 , R_{10} , R_{11} and R_5 are all H, then R_6 is not benzyl, H, (phenyl) (hydroxy)methyl, methyl, ethyl or n-propyl.

Compounds of Formula II are disclosed in published Patent Cooperation Treaty Publication number WO 96/39384, the complete disclosure of which is hereby incorporated by reference.

In yet another preferred aspect of the invention, the GPI has the structure of Formula III, which is another class of compounds believed to be capable of binding to the indole pocket binding site:



Formula III

a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein Formula III has the following substituents:

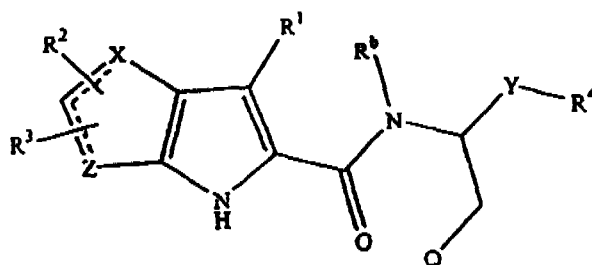
R^1 is (C_1-C_4)alkyl, (C_3-C_7)cycloalkyl, phenyl or phenyl substituted with up to three (C_1-C_4)alkyl, (C_1-C_4)alkoxy or halogen;

R^2 is (C_1-C_4)alkyl; and

R^3 is (C_3-C_7) cycloalkyl; phenyl; phenyl substituted at the para position with (C_1-C_4) alkyl, halo, hydroxy (C_1-C_4) alkyl or trifluoromethyl; phenyl substituted at the meta position with fluoro; or phenyl substituted at the ortho position with fluoro.

Compounds of formula III are disclosed more fully in commonly assigned U.S. patent No. 5,998,463, the relevant disclosure of which is incorporated by reference.

In yet another preferred aspect of the invention, the GPI has the structure of Formula IV, which is another class of compounds believed to be capable of binding to the indole pocket binding site:



Formula IV

a stereoisomer, pharmaceutically acceptable salt or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug, wherein Formula IV has the following substituents:

Q is aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

each Z and X are independently (C, CH or CH_2), N, O or S;

X^1 is NR^a , $-CH_2-$, O or S;

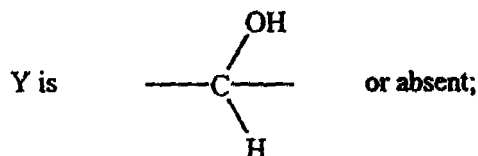
each - - - is independently a bond or is absent,

provided that both - - - are not simultaneously bonds;

R^1 is hydrogen, halogen, $-OC_1-C_6$ alkyl, $-SC_1-C_6$ alkyl,

-C₁-C₈alkyl, -CF₃, -NH₂, -NHC₁-C₈alkyl, -N(C₁-C₈alkyl)₂,
 -NO₂, -CN,
 -CO₂H, -CO₂C₁-C₈alkyl, -C₂-C₈alkenyl, or -C₂-C₈alkynyl;
 each R^a and R^b is independently hydrogen or -C₁-C₈alkyl;

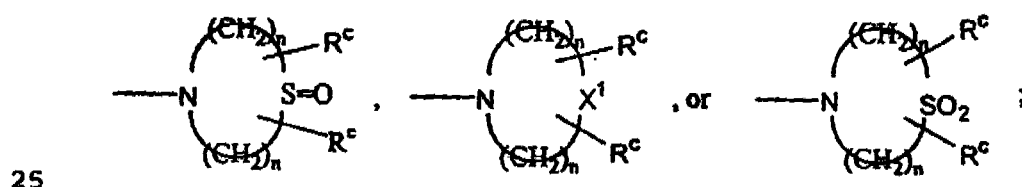
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- 10 R² and R³ are independently hydrogen, halogen,
 -C₁-C₈alkyl, -CN, -C≡C-Si(CH₃)₃,
 -OC₁-C₈alkyl, -SC₁-C₈alkyl, -CF₃, -NH₂, -NHC₁-C₈alkyl,
 -N(C₁-C₈alkyl)₂,
 -NO₂, -CO₂H, -CO₂C₁-C₈alkyl, -C₂-C₈alkenyl, or
 15 -C₂-C₈alkynyl, or R² and R³ together with the atoms on the
 ring to which they are attached form a five or six
 membered ring containing from 0 to 3 heteroatoms and from
 0 to 2 double bonds;

R⁴ is -C(=O)-A;

- 20 A is -NR^dR^c, -NR^dCH₂CH₂OR^a,



- each R^d is independently hydrogen, C₁-C₈alkyl, C₁-C₈alkoxy,
 aryl, substituted aryl, heteroaryl, or substituted
 heteroaryl;
 30 each R^c is independently hydrogen, -C(=O)OR^a, -OR^a, -SR^a,
 or -NR^aR^{a'} and
 each n is independently 1-3.

- Compounds of Formula IV are disclosed in commonly
 35 assigned U.S. Provisional Patent Application Serial
 No. 60/157,148, filed September 30, 1999, the relevant
 disclosure of which is incorporated by reference.

In an especially preferred embodiment, the GPI is selected from one of the following compounds of Formula I:

- 5 5-chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-dimethylcarbamoylmethyl)-2-phenyl-ethyl]-amide;
- 5-chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-methoxy-methylcarbamoylmethyl)-2-phenyl-ethyl]-amide;
- 10 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3S)-hydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide;
- 15 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide;
- 20 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3R,4R)-dihydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide; and
- 25 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-morpholin-4-yl-3-oxo-propyl]-amide.

In another especially preferred embodiment, the GPI is selected from one of the following compounds of Formula II:

- 30 5-chloro-1H-indole-2-carboxylic acid [2-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;
- 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-
- 35 amide;

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5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide;

5 5-chloro-1H-indole-2-carboxylic acid [(1S)-(4-fluorobenzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide;

5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide;

10 5-chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide; and

15 5-chloro-1H-indole-2-carboxylic acid [2-(1-oxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide.

In another especially preferred embodiment, the GPI is selected from one of the following compounds of Formula III:

20 5-acetyl-1-ethyl-2,3-dihydro-2-oxo-N-[3-[(phenylamino)carbonyl]phenyl]-1H-Indole-3-carboxamide;

25 5-acetyl-N-[3-[(cyclohexylamino)carbonyl]phenyl]-1-ethyl-2,3-dihydro-2-oxo-1H-Indole-3-carboxamide; and

5-acetyl-N-[3-[[4-bromophenyl]amino]carbonyl]phenyl]-2,3-dihydro-1-methyl-2-oxo-1H-Indole-3-carboxamide.

30 In another especially preferred embodiment, the GPI is selected from one of the following compounds of Formula IV:

35 2-Chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide; and

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Concentration-enhancing polymers suitable for use in the compositions of the present invention should be inert, in the sense that they do not chemically react with the GPI in an adverse manner, are pharmaceutically acceptable, and have at least some solubility in aqueous solution at physiologically relevant pHs (e.g. 1-8). The polymer can be neutral or ionizable, and should have an aqueous-solubility of at least 0.1 mg/mL over at least a portion of the pH range of 1-8. The polymer is a "concentration-enhancing polymer," meaning that it meets at least one, and more preferably both, of the following conditions. The first condition is that the concentration-enhancing polymer increases the MDC of the GPI in the environment of use relative to a control composition consisting of an equivalent amount of the GPI but no polymer. That is, once the composition is introduced into an environment of use, the polymer increases the aqueous concentration of GPI relative to the control composition. Preferably, the polymer increases the MDC of the GPI in aqueous solution by at least 1.25-fold relative to a control composition, and more preferably by at least 2-fold and most preferably by at least 3-fold. The second condition is that the concentration-enhancing polymer increases the AUC of the GPI in the environment of use relative to a control composition consisting of GPI but no polymer as described above. That is, in the environment of use, the composition comprising the GPI and the concentration-enhancing polymer provides an area under the concentration versus time curve (AUC) for any period of 90 minutes between the time of introduction into the use environment and about 270 minutes following introduction

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include the ionized functional groups. Such polymer/drug assemblies in solution may well resemble charged polymeric micellar-like structures. In any case, regardless of the mechanism of action, the inventors have
5 observed that such amphiphilic polymers, particularly ionizable cellulosic polymers, have been shown to improve the MDC and/or AUC of GPI in aqueous solution relative to control compositions free from such polymers.

Surprisingly, such amphiphilic polymers can
10 greatly enhance the maximum concentration of GPI obtained when an amorphous form of the GPI is dosed to a use environment. In addition, such amphiphilic polymers interact with the GPI to prevent the precipitation or crystallization of the GPI from solution despite its
15 concentration being substantially above its equilibrium concentration. In particular, when the preferred compositions are solid amorphous dispersions of the GPI and the concentration-enhancing polymer, the compositions provide a greatly enhanced drug concentration,
20 particularly when the dispersions are substantially homogeneous. The maximum drug concentration may be 2-fold and often up to 10-fold the equilibrium concentration of the crystalline GPI. Such enhanced GPI concentrations in turn lead to substantially enhanced
25 relative bioavailability for the GPI.

One class of polymers suitable for use with the present invention comprises neutral non-cellulosic polymers. Exemplary polymers include: vinyl polymers and copolymers having substituents of hydroxyl,
30 alkylacyloxy, and cyclicamido polyvinyl alcohols that have at least a portion of their repeat units in the unhydrolyzed (vinyl acetate) form; polyvinyl alcohol polyvinyl acetate copolymers; polyvinyl pyrrolidone; and polyethylene polyvinyl alcohol copolymers.

35 Another class of polymers suitable for use with the present invention comprises ionizable non-cellulosic polymers. Exemplary polymers include: carboxylic acid-

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functionalized vinyl polymers, such as the carboxylic acid functionalized polymethacrylates and carboxylic acid functionalized polyacrylates such as the EUDRAGITS[®] manufactured by Rohm Tech Inc., of Malden, Massachusetts; amine-functionalized polyacrylates and polymethacrylates; proteins; and carboxylic acid functionalized starches such as starch glycolate.

Non-cellulosic polymers that are amphiphilic are copolymers of a relatively hydrophilic and a relatively hydrophobic monomer. Examples include acrylate and methacrylate copolymers. Exemplary commercial grades of such copolymers include the EUDRAGITS, which are copolymers of methacrylates and acrylates.

A preferred class of polymers comprises ionizable and neutral cellulosic polymers with at least one ester- and/or ether- linked substituent in which the polymer has a degree of substitution of at least 0.1 for each substituent. It should be noted that in the polymer nomenclature used herein, ether-linked substituents are recited prior to "cellulose" as the moiety attached to the ether group; for example, "ethylbenzoic acid cellulose" has ethoxybenzoic acid substituents. Analogously, ester-linked substituents are recited after "cellulose" as the carboxylate; for example, "cellulose phthalate" has one carboxylic acid of each phthalate moiety ester-linked to the polymer and the other carboxylic acid unreacted.

It should also be noted that a polymer name such as "cellulose acetate phthalate" (CAP) refers to any of the family of cellulosic polymers that have acetate and phthalate groups attached via ester linkages to a significant fraction of the cellulosic polymer's hydroxyl groups. Generally, the degree of substitution of each substituent group can range from 0.1 to 2.9 as long as the other criteria of the polymer are met. "Degree of substitution" refers to the average number of the three hydroxyls per saccharide repeat unit on the cellulose

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chain that have been substituted. For example, if all of the hydroxyls on the cellulose chain have been phthalate substituted, the phthalate degree of substitution is 3.

Also included within each polymer family type are

- 5 cellululosic polymers that have additional substituents added in relatively small amounts that do not substantially alter the performance of the polymer.

Amphiphilic cellulosics may be prepared by substituting the cellulose at any or all of the 3

- 10 hydroxyl substituents present on each saccharide repeat unit with at least one relatively hydrophobic substituent. Hydrophobic substituents may be essentially any substituent that, if substituted to a high enough level or degree of substitution, can render the
- 15 cellululosic polymer essentially aqueous insoluble. Hydrophilic regions of the polymer can be either those portions that are relatively unsubstituted, since the unsubstituted hydroxyls are themselves relatively hydrophilic, or those regions that are substituted with
- 20 hydrophilic substituents. Examples of hydrophobic substituents include ether-linked alkyl groups such as methyl, ethyl, propyl, butyl, etc.; or ester-linked alkyl groups such as acetate, propionate, butyrate, etc.; and ether- and/or ester-linked aryl groups such as phenyl,
- 25 benzoate, or phenylate. Hydrophilic groups include ether- or ester-linked nonionizable groups such as the hydroxy alkyl substituents hydroxyethyl, hydroxypropyl, and the alkyl ether groups such as ethoxyethoxy or methoxyethoxy. Particularly preferred hydrophilic
- 30 substituents are those that are ether- or ester-linked ionizable groups such as carboxylic acids, thiocarboxylic acids, substituted phenoxy groups, amines, phosphates or sulfonates.

- One class of cellululosic polymers comprises
- 35 neutral polymers, meaning that the polymers are substantially non-ionizable in aqueous solution. Such polymers contain non-ionizable substituents, which may be

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either ether-linked or ester-linked. Exemplary ether-linked non-ionizable substituents include: alkyl groups, such as methyl, ethyl, propyl, butyl, etc.; hydroxy alkyl groups such as hydroxymethyl, hydroxyethyl,

- 5 hydroxypropyl, etc.; and aryl groups such as phenyl. Exemplary ester-linked non-ionizable groups include: alkyl groups, such as acetate, propionate, butyrate, etc.; and aryl groups such as phenylate. However, when
- 10 a sufficient amount of a hydrophilic substituent so that the polymer has at least some water solubility at any physiologically relevant pH of from 1 to 8.

- Exemplary non-ionizable polymers that may be used as the polymer include: hydroxypropyl methyl
- 15 cellulose acetate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, and hydroxyethyl ethyl cellulose.

- A preferred set of neutral cellulosic polymers
- 20 are those that are amphiphilic. Exemplary polymers include hydroxypropyl methyl cellulose and hydroxypropyl cellulose acetate, where cellulosic repeat units that have relatively high numbers of methyl or acetate substituents relative to the unsubstituted hydroxyl or
- 25 hydroxypropyl substituents constitute hydrophobic regions relative to other repeat units on the polymer.

- A preferred class of cellulosic polymers comprises polymers that are at least partially ionizable at physiologically relevant pH and include at least one
- 30 ionizable substituent, which may be either ether-linked or ester-linked. Exemplary ether-linked ionizable substituents include: carboxylic acids, such as acetic acid, propionic acid, benzoic acid, salicylic acid, alkoxybenzoic acids such as ethoxybenzoic acid or
- 35 propoxybenzoic acid, the various isomers of alkoxyphthalic acid such as ethoxyphthalic acid and ethoxyisophthalic acid, the various isomers of

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alkoxynicotinic acid such as ethoxynicotinic acid, and the various isomers of picolinic acid such as ethoxypicolinic acid, etc.; thiocarboxylic acids, such as thioacetic acid; substituted phenoxy groups, such as hydroxyphenoxy, etc.; amines, such as aminoethoxy, diethylaminoethoxy, trimethylaminoethoxy, etc.; phosphates, such as phosphate ethoxy; and sulfonates, such as sulphonate ethoxy. Exemplary ester linked ionizable substituents include: carboxylic acids, such as succinate, citrate, phthalate, terephthalate, isophthalate, trimellitate, and the various isomers of pyridinedicarboxylic acid, etc.; thiocarboxylic acids, such as thiosuccinate; substituted phenoxy groups, such as amino salicylic acid; amines, such as natural or synthetic amino acids, such as alanine or phenylalanine; phosphates, such as acetyl phosphate; and sulfonates, such as acetyl sulfonate. For aromatic-substituted polymers to also have the requisite aqueous solubility, it is also desirable that sufficient hydrophilic groups such as hydroxypropyl or carboxylic acid functional groups be attached to the polymer to render the polymer aqueous soluble at least at pH values where any ionizable groups are ionized. In some cases, the aromatic group may itself be ionizable, such as phthalate or trimellitate substituents.

Exemplary ionizable cellulosic polymers that are at least partially ionized at physiologically relevant pHs include: hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose succinate, hydroxypropyl cellulose acetate succinate, hydroxyethyl methyl cellulose succinate, hydroxyethyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, hydroxyethyl methyl cellulose acetate succinate, hydroxyethyl methyl cellulose acetate phthalate, carboxyethyl cellulose, carboxymethyl cellulose, cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate,

hydroxypropyl cellulose acetate phthalate, hydroxypropyl
methyl cellulose acetate phthalate, hydroxypropyl
cellulose acetate phthalate succinate, hydroxypropyl
methyl cellulose acetate succinate phthalate,
5 hydroxypropyl methyl cellulose succinate phthalate,
cellulose propionate phthalate, hydroxypropyl cellulose
butyrate phthalate, cellulose acetate trimellitate,
methyl cellulose acetate trimellitate, ethyl cellulose
acetate trimellitate, hydroxypropyl cellulose acetate
10 trimellitate, hydroxypropyl methyl cellulose acetate
trimellitate, hydroxypropyl cellulose acetate
trimellitate succinate, cellulose propionate
trimellitate, cellulose butyrate trimellitate, cellulose
acetate terephthalate, cellulose acetate isophthalate,
15 cellulose acetate pyridinedicarboxylate, salicylic acid
cellulose acetate, hydroxypropyl salicylic acid cellulose
acetate, ethylbenzoic acid cellulose acetate,
hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl
phthalic acid cellulose acetate, ethyl nicotinic acid
20 cellulose acetate, and ethyl picolinic acid cellulose
acetate.

Exemplary cellulosic polymers that meet the
definition of amphiphilic, having hydrophilic and
hydrophobic regions include polymers such as cellulose
25 acetate phthalate and cellulose acetate trimellitate
where the cellulosic repeat units that have one or more
acetate substituents are hydrophobic relative to those
that have no acetate substituents or have one or more
ionized phthalate or trimellitate substituents.

A particularly desirable subset of cellulosic
30 ionizable polymers are those that possess both a
carboxylic acid functional aromatic substituent and an
alkylate substituent and thus are amphiphilic. Exemplary
polymers include cellulose acetate phthalate, methyl
35 cellulose acetate phthalate, ethyl cellulose acetate
phthalate, hydroxypropyl cellulose acetate phthalate,
hydroxylpropyl methyl cellulose phthalate, hydroxypropyl

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5 methyl cellulose acetate phthalate, hydroxypropyl
cellulose acetate phthalate succinate, cellulose
propionate phthalate, hydroxypropyl cellulose butyrate
phthalate, cellulose acetate trimellitate, methyl
10 cellulose acetate trimellitate, ethyl cellulose acetate
trimellitate, hydroxypropyl cellulose acetate
trimellitate, hydroxypropyl methyl cellulose acetate
trimellitate, hydroxypropyl cellulose acetate
trimellitate succinate, cellulose propionate
15 trimellitate, cellulose butyrate trimellitate, cellulose
acetate terephthalate, cellulose acetate isophthalate,
cellulose acetate pyridinedicarboxylate, salicylic acid
cellulose acetate, hydroxypropyl salicylic acid cellulose
acetate, ethylbenzoic acid cellulose acetate,
20 hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl
phthalic acid cellulose acetate, ethyl nicotinic acid
cellulose acetate, and ethyl picolinic acid cellulose
acetate.

Another particularly desirable subset of
25 cellulosic ionizable polymers are those that possess a
non-aromatic carboxylate substituent. Exemplary polymers
include hydroxypropyl methyl cellulose acetate succinate,
hydroxypropyl methyl cellulose succinate, hydroxypropyl
cellulose acetate succinate, hydroxyethyl methyl
25 cellulose acetate succinate, hydroxyethyl methyl
cellulose succinate, and hydroxyethyl cellulose acetate
succinate.

Especially preferred polymers are hydroxypropyl
methyl cellulose acetate succinate (HPMCAS),
30 hydroxypropyl methyl cellulose phthalate (HPMCP),
cellulose acetate phthalate (CAP), cellulose acetate
trimellitate (CAT), methyl cellulose acetate phthalate,
hydroxypropyl cellulose acetate phthalate, cellulose
acetate terephthalate and cellulose acetate isophthalate.
35 The most preferred polymers are hydroxypropyl methyl
cellulose acetate succinate, hydroxypropyl methyl

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cellulose phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

While specific polymers have been discussed as being suitable for use in the mixtures of the present invention, blends of such polymers may also be suitable. Thus the term "polymer" is intended to include blends of polymers in addition to a single species of polymer.

To obtain the best performance, particularly upon storage for long times prior to use, it is preferred that the GPI remain, to the extent possible, in the amorphous state. The inventors have found that this is best achieved when the glass-transition temperature, T_g , of the amorphous GPI material is substantially above the storage temperature of the composition. In particular, it is preferable that the T_g of the amorphous state of the GPI be at least 40°C and preferably greater than 60°C. For those aspects of the invention in which the composition is a solid, substantially amorphous dispersion of GPI in the concentration-enhancing polymer and in which the GPI itself has a relatively low T_g (about 70°C or less) it is preferred that the concentration-enhancing polymer have a T_g of at least 40°C, preferably at least 70°C and more preferably greater than 100°C. Exemplary high T_g polymers include HPMCAS, HPMCP, CAP, CAT and other cellulose derivatives that have alkylate or aromatic substituents or both alkylate and aromatic substituents.

In addition, the preferred polymers listed above, that is amphiphilic cellulosic polymers, tend to have greater concentration-enhancing properties relative to the other polymers of the present invention. For any particular GPI, the amphiphilic cellulosic with the best concentration-enhancing properties may vary. However, the inventors have found that generally those that have ionizable substituents tend to perform best. *In vitro* tests of compositions with such polymers tend to have higher MDC and AUC values than compositions with other polymers of the invention. Often such compositions have

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MDC and AUC values that are more than 4-fold and in some cases more than 8-fold that of a control composition.

PREPARATION OF COMPOSITIONS

5 Compositions may comprise a physical mixture of
GPI and concentration-enhancing polymer or a dispersion
of GPI and polymer. Preferably, the compositions are
formed such that at least a major portion (at least 60%)
10 of the GPI is in the amorphous state. In cases where the
composition is a physical mixture of amorphous GPI and
polymer the amorphous GPI may be made by any known
process. Generally the amorphous form of the GPI is made
by (1) melting the drug followed by rapid cooling (e.g.,
15 melt-congeal process); (2) dissolution of the drug in a
solvent followed by precipitation or evaporation (e.g.,
spray drying, spray coating); or (3) mechanical
processing of the drug (e.g., extrusion, ball milling).
Various combinations of heat (as in melt processes),
solvent and mechanical force may be used to generate the
20 amorphous GPI.

Dispersions of the GPI and concentration-
enhancing polymer may be made according to any known
process which results in at least a major portion (at
least 60%) of the GPI being in the amorphous state.
25 Exemplary mechanical processes include milling and
extrusion; melt processes include high temperature
fusion, solvent modified fusion and melt-congeal
processes; and solvent processes include non-solvent
precipitation, spray coating and spray-drying. Although
30 the dispersions of the present invention may be made by
any of these processes, the dispersions generally have
their maximum bioavailability and stability when the GPI
is dispersed in the polymer such that it is substantially
amorphous and substantially homogeneously distributed
35 throughout the polymer. Although in some cases such
substantially amorphous and substantially homogeneous
dispersions may be made by any of these methods, it has

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been found that such dispersions are preferably formed by "solvent processing," which consists of dissolution of the GPI and one or more polymers in a common solvent.

"Common" here means that the solvent, which can be a
5 mixture of compounds, will simultaneously dissolve the drug and the polymer(s). After both the GPI and the polymer have been dissolved, the solvent is rapidly removed by evaporation or by mixing with a non-solvent. Exemplary processes are spray-drying, spray-coating (pan-coating, fluidized bed coating, etc.), and precipitation
10 by rapid mixing of the polymer and drug solution with CO₂, water, or some other non-solvent. Preferably, removal of the solvent results in a solid dispersion which is substantially homogeneous. As described previously, in
15 such substantially homogeneous dispersions, the GPI is dispersed as homogeneously as possible throughout the polymer and can be thought of as a solid solution of GPI dispersed in the polymer(s). When the resulting dispersion constitutes a solid solution of GPI in
20 polymer, the dispersion may be thermodynamically stable, meaning that the concentration of GPI in the polymer is at or below its equilibrium value, or it may be considered a supersaturated solid solution where the GPI concentration in the dispersion polymer(s) is above its
25 equilibrium value.

The solvent may be removed through the process of spray-drying. The term spray-drying is used conventionally and broadly refers to processes involving breaking up liquid mixtures into small droplets
30 (atomization) and rapidly removing solvent from the mixture in a container (spray-drying apparatus) where there is a strong driving force for evaporation of solvent from the droplets. The strong driving force for solvent evaporation is generally provided by maintaining
35 the partial pressure of solvent in the spray-drying apparatus well below the vapor pressure of the solvent at the temperature of the drying droplets. This is

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accomplished by either (1) maintaining the pressure in the spray-drying apparatus at a partial vacuum (e.g., 0.01 to 0.50 atm); (2) mixing the liquid droplets with a warm drying gas; or (3) both. In addition, at least a
5 portion of the heat required for evaporation of solvent may be provided by heating the spray solution.

Solvents suitable for spray-drying can be any organic compound in which the GPI and polymer are mutually soluble. Preferably, the solvent is also
10 volatile with a boiling point of 150°C or less. In addition, the solvent should have relatively low toxicity and be removed from the dispersion to a level that is acceptable according to The International Committee on Harmonization (ICH) guidelines. Removal of solvent to
15 this level may require a processing step such as tray-drying subsequent to the spray-drying or spray-coating process. Preferred solvents include alcohols such as methanol, ethanol, n-propanol, iso-propanol, and butanol; ketones such as acetone, methyl ethyl ketone and methyl
20 iso-butyl ketone; esters such as ethyl acetate and propylacetate; and various other solvents such as acetonitrile, methylene chloride, toluene, and 1,1,1-trichloroethane. Lower volatility solvents such as dimethyl acetamide or dimethylsulfoxide can also be used.
25 Mixtures of solvents, such as 50% methanol and 50% acetone, can also be used, as can mixtures with water as long as the polymer and GPI are sufficiently soluble to make the spray-drying process practicable. Generally, non-aqueous solvents are preferred meaning that the
30 solvent comprises less than about 40 wt% water. However, for certain GPIs, it has been found that addition of a small amount of water, typically about 5 wt% to about 35 wt%, to a solvent such as acetone may actually increase the solubility of the GPI in the solvent,
35 relative to that in the absence of water. In such cases, or to enhance the polymer solubility, addition of water may even be preferred.

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Generally, the temperature and flow rate of the drying gas is chosen so that the polymer/drug-solution droplets are dry enough by the time they reach the wall of the apparatus that they are essentially solid, and so that they form a fine powder and do not stick to the apparatus wall. The actual length of time to achieve this level of dryness depends on the size of the droplets. Droplet sizes generally range from 1 μm to 500 μm in diameter, with 5 to 100 μm being more typical. The large surface-to-volume ratio of the droplets and the large driving force for evaporation of solvent leads to actual drying times of a few seconds or less, and more typically less than 0.1 second. This rapid drying is often critical to the particles maintaining a uniform, homogeneous dispersion instead of separating into drug-rich and polymer-rich phases. Solidification times should be less than 100 seconds, preferably less than a few seconds, and more preferably less than 1 second. In general, to achieve this rapid solidification of the GPI/polymer solution, it is preferred that the size of droplets formed during the spray-drying process are less than 100 μm in diameter, preferably less than 50 μm in diameter, and more preferably less than 25 μm in diameter. The resultant solid particles thus formed are generally less than 100 μm in diameter, and preferably less than 50 μm in diameter, and more preferably less than 25 μm in diameter. Typically, particles are 1 to 20 μm in diameter.

Following solidification, the solid powder typically stays in the spray-drying chamber for about 5 to 60 seconds, further evaporating solvent from the solid powder. The final solvent content of the solid dispersion as it exits the dryer should be low, since this reduces the mobility of GPI molecules in the dispersion, thereby improving its stability. Generally, the solvent content of the dispersion as it leaves the spray-drying chamber should be less than 10 wt% and

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preferably less than 2 wt%. In some cases, it may be preferable to spray a solvent or a solution of a polymer or other excipient into the spray-drying chamber to form granules, so long as the dispersion is not adversely affected.

Spray-drying processes and spray-drying equipment are described generally in Perry's *Chemical Engineers' Handbook*, Sixth Edition (R. H. Perry, D. W. Green, J. O. Maloney, eds.) McGraw-Hill Book Co. 1984, pages 20-54 to 20-57. More details on spray-drying processes and equipment are reviewed by Marshall "Atomization and Spray-Drying," 50 *Chem. Eng. Prog. Monogr. Series 2* (1954).

Where the composition is a simple physical mixture, the composition may be prepared by dry- or wet-mixing the drug or drug mixture with the polymer to form the composition. Mixing processes include physical processing as well as wet-granulation and coating processes. Any conventional mixing method may be used, including those that substantially convert the drug and polymer to a molecular dispersion.

For example, mixing methods include convective mixing, shear mixing, or diffusive mixing. Convective mixing involves moving a relatively large mass of material from one part of a powder bed to another, by means of blades or paddles, revolving screw, or an inversion of the powder bed. Shear mixing occurs when slip planes are formed in the material to be mixed. Diffusive mixing involves an exchange of position by single particles. These mixing processes can be performed using equipment in batch or continuous mode. Tumbling mixers (e.g., twin-shell) are commonly used equipment for batch processing. Continuous mixing can be used to improve composition uniformity.

Milling may also be employed to prepare the compositions of the present invention. Milling is the

mechanical process of reducing the particle size of solids (comminution). The most common types of milling equipment are the rotary cutter, the hammer, the roller and fluid energy mills. Equipment choice depends on the characteristics of the ingredients in the drug form (e.g., soft, abrasive, or friable). Wet- or dry-milling techniques can be chosen for several of these processes, also depending on the characteristics of the ingredients (e.g., drug stability in solvent). The milling process may serve simultaneously as a mixing process if the feed materials are heterogeneous. Conventional mixing and milling processes suitable for use in the present invention are discussed more fully in Lachman, et al., *The Theory and Practice of Industrial Pharmacy* (3d Ed. 1986). The components of the compositions of this invention may also be combined by dry- or wet-granulating processes.

In addition to the physical mixtures described above, the compositions of the present invention may constitute any device or collection of devices that accomplishes the objective of delivering to the use environment both the GPI and the concentration-enhancing polymer. Thus, in the case of oral administration to a mammal, the dosage form may constitute a layered tablet wherein one or more layers comprise the amorphous GPI and one or more other layers comprise the polymer. Alternatively, the dosage form may be a coated tablet wherein the tablet core comprises the GPI and the coating comprises the concentration-enhancing polymer. In addition, the GPI and the polymer may even be present in different dosage forms such as tablets or beads and may be administered simultaneously or separately as long as both the GPI and polymer are administered in such a way that the GPI and polymer can come into contact in the use environment. When the GPI and the polymer are administered separately it is generally preferable to deliver the polymer prior to the GPI.

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The amount of concentration-enhancing polymer relative to the amount of GPI present in the mixtures of the present invention depends on the GPI and polymer and may vary widely from a GPI-to-polymer weight ratio of
5 from 0.01 to about 4 (e.g., 1 wt% GPI to 80 wt% GPI).

However, in most cases it is preferred that the GPI-to-polymer ratio is greater than about 0.05 (4.8 wt% GPI) and less than about 2.5 (71 wt% GPI). Often the enhancement in GPI concentration or relative

10 bioavailability that is observed increases as the GPI-to-polymer ratio decreases from a value of about 1 (50 wt% GPI) to a value of about 0.11 (10 wt% GPI). The maximum GPI:polymer ratio that yields satisfactory results varies from GPI to GPI and is best determined in in vitro

15 dissolution tests and/or in vivo bioavailability tests.

It should be noted that this level of concentration-enhancing polymer is usually substantially greater and often much greater than the amount of polymer conventionally included in dosage forms for other uses
20 such as binders or coatings. Thus, it is preferred in the compositions of this invention that there be included sufficient concentration-enhancing polymer that the compositions meet the in vitro MDC and AUC criteria and in vivo bioavailability criterion previously set forth.

25 In general, to maximize the GPI concentration or relative bioavailability of the GPI, lower GPI-to-polymer ratios are preferred. At low GPI-to-polymer ratios, there is sufficient polymer available in solution to ensure the inhibition of the precipitation or
30 crystallization of GPI from solution and, thus, the average concentration of GPI is much higher. For high GPI-to-polymer ratios, not enough polymer may be present in solution and GPI precipitation or crystallization of the GPI may occur more readily. In addition, the amount
35 of concentration-enhancing polymer that can be used in a dosage form is often limited by the total mass

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requirements of the dosage form. For example, when oral dosing to a human is desired, at low GPI-to-polymer ratios the total mass of drug and polymer may be unacceptably large for delivery of the desired dose in a single tablet or capsule. Thus, it is often necessary to use GPI-to-polymer ratios that are less than optimum in specific dosage forms to provide a sufficient GPI dose in a dosage form that is small enough to be easily delivered to a use environment.

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EXCIPIENTS AND DOSAGE FORMS

Although the key ingredients present in the compositions of the present invention are simply the GPI to be delivered and the concentration-enhancing polymer(s), the inclusion of other excipients in the composition may be useful. These excipients may be utilized with the GPI/polymer mixture in order to formulate the mixture into tablets, capsules, suspensions, powders for suspension, creams, transdermal patches, depots, and the like. The amorphous GPI and polymer can be added to other dosage form ingredients in essentially any manner that does not substantially alter the GPI. In addition, as described above, the GPI and the polymer may be mixed with excipients separately to form different beads, or layers, or coatings, or cores or even separate dosage forms.

One very useful class of excipients is surfactants. Suitable surfactants include fatty acid and alkyl sulfonates; commercial surfactants such as benzalkonium chloride (HYAMINE® 1622, available from Lonza, Inc., Fairlawn, New Jersey); dioctyl sodium sulfosuccinate, DOCUSATE SODIUM™ (available from Mallinckrodt Spec. Chem., St. Louis, Missouri); polyoxyethylene sorbitan fatty acid esters (TWEEN®, available from ICI Americas Inc., Wilmington, Delaware; LIPOSORB® P-20 available from Lipochem Inc., Patterson New Jersey; CAPMUL® POE-0 available from Abitec Corp.,

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Janesville, Wisconsin), and natural surfactants such as sodium taurocholic acid, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine, lecithin, and other phospholipids and mono- and diglycerides. Such materials can

5 advantageously be employed to increase the rate of dissolution by facilitating wetting, thereby increasing the maximum dissolved concentration, and also to inhibit crystallization or precipitation of drug by interacting with the dissolved drug by mechanisms such as
10 complexation, formation of inclusion complexes, formation of micelles or adsorbing to the surface of solid drug, crystalline or amorphous. These surfactants may comprise up to 5 wt% of the composition.

The addition of pH modifiers such as acids,
15 bases, or buffers may also be beneficial, retarding the dissolution of the composition (e.g., acids such as citric acid or succinic acid when the concentration-enhancing polymer is anionic) or, alternatively, enhancing the rate of dissolution of the composition
20 (e.g., bases such as sodium acetate or amines when the polymer is anionic).

Conventional matrix materials, complexing agents, solubilizers, fillers, disintegrating agents (disintegrants), or binders may also be added as part of
25 the composition itself or added by granulation via wet or mechanical or other means. These materials may comprise up to 90 wt% of the composition.

Examples of matrix materials, fillers, or diluents include lactose, mannitol, xylitol,
30 microcrystalline cellulose, calcium diphosphate, and starch.

Examples of disintegrants include sodium starch glycolate, sodium alginate, carboxy methyl cellulose sodium, methyl cellulose, and croscarmellose sodium.

35 Examples of binders include methyl cellulose, microcrystalline cellulose, starch, and gums such as guar gum, and tragacanth.

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and agitated to form the oral suspension. In yet another embodiment, the dosage form can be formulated as two powders which are reconstituted by first adding water to one powder to form a solution to which the second powder is combined with agitation to form the suspension.

Generally, it is preferred that the dispersion of GPI or amorphous form of GPI be formulated for long-term storage in the dry state as this promotes the chemical and physical stability of the GPI. Various excipients and additives are combined with the compositions of the present invention to form the dosage form. For example, it may be desirable to add some or all of the following: preservatives such as sulfites (an antioxidant), benzalkonium chloride, methyl paraben, propyl paraben, benzyl alcohol or sodium benzoate; suspending agents or thickeners such as xanthan gum, starch, guar gum, sodium alginate, carboxymethyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, hydroxypropyl methyl cellulose, polyacrylic acid, silica gel, aluminum silicate, magnesium silicate, or titanium dioxide; anticaking agents or fillers such as silicon oxide, or lactose; flavorants such as natural or artificial flavors; sweeteners such as sugars such as sucrose, lactose, or sorbitol as well as artificial sweeteners such as aspartame or saccharin; wetting agents or surfactants such as various grades of polysorbate, docusate sodium, or sodium lauryl sulfate; solubilizers such as ethanol propylene glycol or polyethylene glycol; coloring agents such as FD and C Red No. 3 or FD and C Blue No. 1; and pH modifiers or buffers such as carboxylic acids (including citric acid, ascorbic acid, lactic acid, and succinic acid), various salts of carboxylic acids, amino acids such as glycine or alanine, various phosphate, sulfate and carbonate salts such as trisodium phosphate, sodium bicarbonate or potassium bisulfate, and bases such as amino glucose or triethanol amine.

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A preferred additive to such formulations is additional concentration-enhancing polymer which may act as a thickener or suspending agent as well as to enhance the concentration of GPI in the environment of use and
5 may also act to prevent or retard precipitation or crystallization of GPI from solution. Such preferred additives are hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxypropyl methyl cellulose. In particular, the salts of carboxylic acid functional
10 polymers such as cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate succinate, and carboxymethyl cellulose are useful in this regard. Such polymers may be added in their salt forms or the salt form may be formed *in situ* during reconstitution by
15 adding a base such as trisodium phosphate and the acid form of such polymers.

In some cases, the overall dosage form or particles, granules or beads that make up the dosage form may have superior performance if coated with an enteric
20 polymer to prevent or retard dissolution until the dosage form leaves the stomach. Exemplary enteric coating materials include hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, cellulose acetate
25 trimellitate, carboxylic acid-functionalized polymethacrylates, and carboxylic acid-functionalized polyacrylate.

Compositions of this invention may be administered in a controlled release dosage form. In one
30 such dosage form, the composition of the GPI and polymer is incorporated into an erodible polymeric matrix device. By an erodible matrix is meant aqueous-erodible or water-swella-
ble or aqueous-soluble in the sense of being either erodible or swellable or dissolvable in pure water or
35 requiring the presence of an acid or base to ionize the polymeric matrix sufficiently to cause erosion or dissolution. When contacted with the aqueous environment

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of use, the erodible polymeric matrix imbibes water and forms an aqueous-swollen gel or "matrix" that entraps the mixture of GPI and polymer. The aqueous-swollen matrix gradually erodes, swells, disintegrates or dissolves in the environment of use, thereby controlling the release of the drug mixture to the environment of use. Examples of such dosage forms are disclosed more fully in commonly assigned pending U.S. Patent Application Serial No. 09/495,059 filed January 31, 2000 which claimed the benefit of priority of provisional patent application Serial No. 60/119,400 filed February 10, 1999, the relevant disclosure of which is herein incorporated by reference.

Alternatively, the compositions of the present invention may be administered by or incorporated into a non-erodible matrix device.

Alternatively, the drug mixture of the invention may be delivered using a coated osmotic controlled release dosage form. This dosage form has two components: (a) the core which contains an osmotic agent and the GPI and the concentration-enhancing polymer; and (b) a non-dissolving and non-eroding coating surrounding the core, the coating controlling the influx of water to the core from an aqueous environment of use so as to cause drug release by extrusion of some or all of the core to the environment of use. The GPI and the concentration-enhancing polymer may be homogeneously distributed throughout the core or they may be partially or completely segregated in separate regions of the core. The osmotic agent contained in the core of this device may be an aqueous-swellaable hydrophilic polymer, osmogen, or osmagent. The coating is preferably polymeric, aqueous-permeable, and has at least one delivery port. Examples of such dosage forms are disclosed more fully in commonly assigned pending U.S. Patent Application Serial No. 09/495,061 filed January 31, 2000 which claimed the benefit of priority of provisional Patent Application

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Serial No. 60/119,406 filed February 10, 1999, the relevant disclosure of which is herein incorporated by reference.

Alternatively, the drug mixture of the invention may be delivered via a coated hydrogel controlled release dosage form having at least three components: (a) a composition containing the GPI, (b) a water-swallowable composition wherein the water-swallowable composition is in a separate region within a core formed by the drug-containing composition and the water-swallowable composition, and (c) a coating around the core that is water-permeable, water-insoluble, and has at least one delivery port therethrough. In use, the core imbibes water through the coating, swelling the water-swallowable composition and increasing the pressure within the core, and fluidizing the GPI-containing composition. Because the coating remains intact, the GPI-containing composition is extruded out of the delivery port into an environment of use. The polymer may be delivered in a separate dosage form, may be included in the GPI-containing composition, may comprise a separate composition that occupies a separate region within the core, or may constitute all or part of a coating applied to the dosage form. Examples of such dosage forms are more fully disclosed in commonly assigned pending Provisional Application Serial No. 60/171,968 filed December 23, 1999, the relevant disclosure of which is herein incorporated by reference.

Alternatively, the compositions may be administered as multiparticulates. Multiparticulates generally refer to dosage forms that comprise a multiplicity of particles that may range in size from about 10 μm to about 2 mm, more typically about 100 μm to 1 mm in diameter. Such multiparticulates may be packaged, for example, in a capsule such as a gelatin capsule or a capsule formed from an aqueous-soluble polymer such as HPMCAS, HPMC or starch or they may be

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dosed as a suspension or slurry in a liquid. Such particulates may be made by any known process such as wet and dry granulation processes or melt congeal processes such as those previously described for forming amorphous GPI. For example, the GPI and a glyceride such as hydrogenated vegetable oil, a vegetable or synthetic fat or a wax such as paraffin may be blended and fed to a melt congeal process as a solid or liquid, followed by cooling to form beads comprised of amorphous GPI and the excipient.

The so-formed beads may then be blended with one or more concentration-enhancing polymers with or without additional excipients to form a multiparticulate dosage form. Alternatively, a high melting point concentration-enhancing polymer such as HPMCAS may be blended with the GPI and the fat or wax fed as a solid blend to a melt congeal process or the blend may be heated such that the GPI and the fat or wax melt to form a slurry of concentration-enhancing polymer particles in molten GPI and fat or wax. The resulting material comprises beads or particles consisting of an amorphous dispersion of GPI in the fat or wax with concentration-enhancing polymer particles trapped therein. Alternatively, a dispersion of the GPI in a concentration-enhancing polymer may be blended with a fat or wax and then fed to a melt congeal process as a solid or a slurry of the dispersion in the molten fat or wax. Such processing yields particles or beads consisting of particles of dispersion trapped in the solidified fat or wax matrix.

Similar multiparticulate dosage forms may be made with the various compositions of this invention but using excipients suited to the bead-forming or granule-forming process chosen. For example, when granules are formed by extrusion/spheronization processes the dispersion or other composition may be blended with, for

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example, microcrystalline cellulose or other cellulosic polymer to aid in processing.

In any case, the resulting particles may themselves constitute the multiparticulate dosage form or they may be coated by various film-forming materials such as enteric polymers or water-swellaable or water-soluble polymers, or they may be combined with other excipients or vehicles to aid in dosing to patients.

Alternatively, the compositions of the present invention may be co-administered, meaning that the GPI can be administered separately from, but within the same general time frame as, the polymer. Thus, amorphous GPI can, for example, be administered in its own dosage form which is taken at approximately the same time as the polymer which is in a separate dosage form. If administered separately, it is generally preferred to administer both the GPI and the polymer within 60 minutes, more preferably within 15 minutes, of each other, so that the two are present together in the environment of use. When not administered simultaneously, the polymer is preferably administered prior to the amorphous GPI.

In addition to the above additives or excipients, use of any conventional materials and procedures for preparation of suitable dosage forms using the compositions of this invention known by those skilled in the art are potentially useful.

In another aspect, the present invention concerns the treatment of diabetes, including impaired glucose tolerance, insulin resistance, insulin dependent diabetes mellitus (Type 1) and non-insulin dependent diabetes mellitus (NIDDM or Type 2). Also included in the treatment of diabetes are the treatment of the diabetic complications, such as neuropathy, nephropathy, retinopathy or cataracts. The compositions of the present invention can also be used for diabetes prevention.

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Diabetes can be treated by administering to a patient having diabetes (Type 1 or Type 2), insulin resistance, impaired glucose tolerance, or any of the diabetic complications such as neuropathy, nephropathy, retinopathy or cataracts, a therapeutically effective amount of a composition of the present invention. It is also contemplated that diabetes be treated by administering a composition of the present invention in combination with other agents that can be used to treat diabetes.

Representative agents that can be used to treat diabetes include insulin and insulin analogs (e.g. LysPro insulin); GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)-NH₂; sulfonylureas and analogs: chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide, glimepiride, repaglinide, meglitinide; biguanides: metformin, phenformin, buformin; α 2-antagonists and imidazolines: midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan; Other insulin secretagogues: linoglriride, A-4166; glitazones: ciglitazone, pioglitazone, englitazone, troglitazone, darglitazone, rosiglitazone; PPAR-gamma agonists; fatty acid oxidation inhibitors: clomoxir, etomoxir; α -glucosidase inhibitors: acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945; β -agonists: BRL 35135, BRL 37344, Ro 16-8714, ICI D7114, CL 316,243; phosphodiesterase inhibitors: L-386,398; lipid-lowering agents: benfluorex; antiobesity agents: fenfluramine; vanadate and vanadium complexes (e.g. Naglivan®) and peroxovanadium complexes; amylin antagonists; glucagon antagonists; gluconeogenesis inhibitors; somatostatin analogs and antagonists; antilipolytic agents: nicotinic acid, acipimox, WAG 994. Any combination of agents can be administered as described above.

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In addition to the categories and compounds mentioned above, the compositions of the present invention can be administered in combination with thyromimetic compounds, aldose reductase inhibitors, glucocorticoid receptor antagonists, NHE-1 inhibitors, or sorbitol dehydrogenase inhibitors, or combinations thereof, to treat or prevent diabetes, insulin resistance, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia, particularly myocardial ischemia.

It is generally accepted that thyroid hormones, specifically, biologically active iodothyronines, are critical to normal development and to maintaining metabolic homeostasis. Thyroid hormones stimulate the metabolism of cholesterol to bile acids and enhance the lipolytic responses of fat cells to other hormones. U.S. Patent Numbers 4,766,121; 4,826,876; 4,910,305; and 5,061,798 disclose certain thyroid hormone mimetics (thyromimetics), namely, 3,5-dibromo-3'-[6-oxo-3(1H)-pyridazinylmethyl]-thyronines. U.S. Patent Number 5,284,971 discloses certain thyromimetic cholesterol lowering agents, namely, 4-(3-cyclohexyl-4-hydroxy or -methoxy phenylsulfonyl)-3,5 dibromo-phenylacetic compounds. U.S. Patent Numbers 5,401,772; 5,654,468; and 5,569,674 disclose certain thyromimetics that are lipid lowering agents, namely, heteroacetic acid derivatives. In addition, certain oxamic acid derivatives of thyroid hormones are known in the art. For example, N. Yokoyama, et al. in an article published in the Journal of Medicinal Chemistry, 38 (4): 695-707 (1995) describe replacing a -CH₂ group in a naturally occurring metabolite of T₃ with an -NH group resulting in -HNCOCO₂H. Likewise, R.E. Steele et al. in an article published in International Congressional Service (Atherosclerosis X) 1066: 321-324 (1995) and Z.F. Stephan et al. in an

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article published in Atherosclerosis, 126: 53-63 (1996), describe certain oxamic acid derivatives useful as lipid-lowering thyromimetic agents, yet devoid of undesirable cardiac activities.

5 Each of the thyromimetic compounds referenced above and other thyromimetic compounds can be used in combination with the compositions of the present invention to treat or prevent diabetes, insulin resistance, diabetic neuropathy, diabetic nephropathy, 10 diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

 The compositions of the present invention can also be used in combination with aldose reductase 15 inhibitors. Aldose reductase inhibitors constitute a class of compounds that have become widely known for their utility in preventing and treating conditions arising from complications of diabetes, such as diabetic neuropathy and nephropathy. Such compounds are well 20 known to those skilled in the art and are readily identified by standard biological tests. For example, the aldose reductase inhibitors zopolrestat, 1-phthalazineacetic acid, 3,4-dihydro-4-oxo-3-[[5-(trifluoromethyl)-2-benzothiazolyl]methyl]-, and related 25 compounds are described in U.S. patent 4,939,140 to Larson et al.

 Aldose reductase inhibitors have been taught for use in lowering lipid levels in mammals. See, for example, U. S. patent 4,492,706 to Kallai-sanfacon and EP 30 0 310 931 A2 (Ethyl Corporation).

 U. S. patent 5,064,830 to Going discloses the use of certain oxophthalaziny l acetic acid aldose reductase inhibitors, including zopolrestat, for lowering of blood uric acid levels.

35 Commonly assigned U.S. patent 5,391,551 discloses the use of certain aldose reductase inhibitors, including zopolrestat, for lowering blood lipid levels in

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humans. The disclosure teaches that therapeutic utilities derive from the treatment of diseases caused by an increased level of triglycerides in the blood, such diseases include cardiovascular disorders such as

5 thrombosis, arteriosclerosis, myocardial infarction, and angina pectoris. A preferred aldose reductase inhibitor is 1-phthalazineacetic acid, 3,4-dihydro-4-oxo-3-[(5-trifluoromethyl)-2-benzothiazolyl]methyl]-, also known as zopolrestat.

10 The term aldose reductase inhibitor refers to compounds that inhibit the bioconversion of glucose to sorbitol, which is catalyzed by the enzyme aldose reductase.

Any aldose reductase inhibitor may be used in a

15 combination with a composition of the present invention. Aldose reductase inhibition is readily determined by those skilled in the art according to standard assays (J. Malone, Diabetes, 29:861-864 (1980). "Red Cell Sorbitol, an Indicator of Diabetic Control"). A variety of aldose

20 reductase inhibitors are described herein; however, other aldose reductase inhibitors useful in the compositions and methods of this invention will be known to those skilled in the art.

The activity of an aldose reductase inhibitor

25 in a tissue can be determined by testing the amount of aldose reductase inhibitor that is required to lower tissue sorbitol (i.e., by inhibiting the further production of sorbitol consequent to blocking aldose reductase) or lower tissue fructose (by inhibiting the

30 production of sorbitol consequent to blocking aldose reductase and consequently the production of fructose.

Accordingly, examples of aldose reductase inhibitors useful in the compositions, combinations and methods of the present invention include:

- 35 1. 3-(4-bromo-2-fluorobenzyl)-3,4-dihydro-4-oxo-1-phthalazineacetic acid (ponalrestat, US 4,251,528);

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2. N[[(5-trifluoromethyl)-6-methoxy-1-naphthalenyl]thioxomethyl]-N-methylglycine (tolrestat, US 4,600,724);
- 5 3. 5-[(Z,E)- β -methylcinnamylidene]-4-oxo-2-thioxo-3-thiazolideneacetic acid (epalrestat, US 4,464,382, US 4,791,126, US 4,831,045);
4. 3-(4-bromo-2-fluorobenzyl)-7-chloro-3,4-dihydro-2,4-dioxo-1(2H)-quinazolineacetic acid (zenarestat, US 4,734,419, and 4,883,800);
- 10 5. 2R,4R-6,7-dichloro-4-hydroxy-2-methylchroman-4-acetic acid (US 4,883,410);
6. 2R,4R-6,7-dichloro-6-fluoro-4-hydroxy-2-methylchroman-4-acetic acid (US 4,883,410);
7. 3,4-dihydro-2,8-diisopropyl-3-oxo-2H-1,4-benzoxazine-4-acetic acid (US 4,771,050);
- 15 8. 3,4-dihydro-3-oxo-4-[(4,5,7-trifluoro-2-benzothiazolyl)methyl]-2H-1,4-benzothiazine-2-acetic acid (SPR-210, U.S. 5,252,572);
9. N-[3,5-dimethyl-4-[(nitromethyl)sulfonyl]phenyl]-2-methyl-benzeneacetamide (ZD5522, U.S. 5,270,342 and U.S. 5,430,060);
- 20 10. (S)-6-fluorospiro[chroman-4,4'-imidazolidine]-2,5'-dione (sorbiniI, US 4,130,714);
11. d-2-methyl-6-fluoro-spiro(chroman-4',4'-imidazolidine)-2',5'-dione (US 4,540,704);
- 25 12. 2-fluoro-spiro(9H-fluorene-9,4'-imidazolidine)2',5'-dione (US 4,438,272);
13. 2,7-di-fluoro-spiro(9H-fluorene-9,4'-imidazolidine)2',5'-dione (US 4,436,745, US 4,438,272);
- 30 14. 2,7-di-fluoro-5-methoxy-spiro(9H-fluorene-9,4'-imidazolidine)2',5'-dione (US 4,436,745, US 4,438,272);
15. 7-fluoro-spiro(5H-indenol[1,2-b]pyridine-5,3'-pyrrolidine)2,5'-dione (US 4,436,745, US 4,438,272);
- 35 16. d-cis-6'-chloro-2',3'-dihydro-2'-methyl-spiro-(imidazolidine-4,4'-4'-H-pyrano(2,3-b)pyridine)-2,5-dione (US 4,980,357);

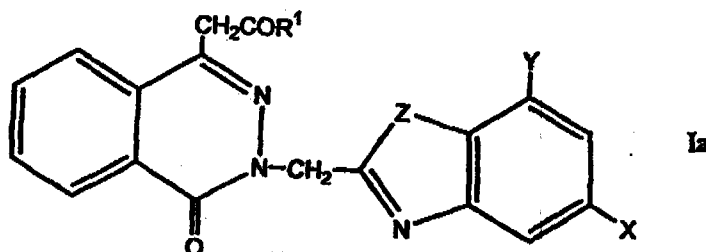
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17. spiro[imidazolidine-4,5'(6H)-quinoline]2,5-dione-3'-chloro-7,'8'-dihydro-7'-methyl-(5'-cis) (US 5,066,659);

18. (2S,4S)-6-fluoro-2',5'-dioxospiro(chroman-4,4'-imidazolidine)-2-carboxamide (US 5,447,946); and

19. 2-[(4-bromo-2-fluorophenyl)methyl]-6-fluorospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone (ARI-509, US 5,037,831).

Other aldose reductase inhibitors include compounds having Formula Ia below



or a pharmaceutically acceptable salt or prodrug thereof, wherein the substituents of Formula Ia are as follows:

Z is O or S;

R¹ is hydroxy or a group capable of being removed in vivo to produce a compound of Formula I

wherein R¹ is OH; and

X and Y are the same or different and are selected from hydrogen, trifluoromethyl, fluoro, and chloro.

A preferred subgroup within the above group of aldose reductase inhibitors includes numbered compounds 1, 2, 3, 4, 5, 6, 9, 10, and 17, and the following compounds of Formula Ia:

20. 3,4-dihydro-3-(5-fluorobenzothiazol-2-ylmethyl)-4-oxophthalazin-1-yl-acetic acid [R¹=hydroxy;

X=F; Y=H];

21. 3-(5,7-difluorobenzothiazol-2-ylmethyl)-
3,4-dihydro-4-oxophthalazin-1-ylacetic acid [R^1 =hydroxy;
X=Y=F];

22. 3-(5-chlorobenzothiazol-2-ylmethyl)-3,4-
5 dihydro-4-oxophthalazin-1-ylacetic acid [R^1 =hydroxy;
X=Cl; Y=H];

23. 3-(5,7-dichlorobenzothiazol-2-ylmethyl)-
3,4-dihydro-4-oxophthalazin-1-ylacetic acid [R^1 =hydroxy;
X=Y=Cl];

10 24. 3,4-dihydro-4-oxo-3-(5-
trifluoromethylbenzoxazol-2-ylmethyl)phthalazin-1-
ylacetic acid [R^1 =hydroxy; X=CF₃; Y=H];

25. 3,4-dihydro-3-(5-fluorobenzoxazol-2-
ylmethyl)-4-oxophthalazin-1-yl-acetic acid [R^1 =hydroxy;
15 X=F; Y=H];

26. 3-(5,7-difluorobenzoxazol-2-ylmethyl)-3,4-
dihydro-4-oxophthalazin-1-ylacetic acid [R^1 =hydroxy;
X=Y=F];

27. 3-(5-chlorobenzoxazol-2-ylmethyl)-3,4-
20 dihydro-4-oxophthalazin-1-ylacetic acid [R^1 =hydroxy; X=Cl;
Y=H];

28. 3-(5,7-dichlorobenzoxazol-2-ylmethyl)-3,4-
dihydro-4-oxophthalazin-1-ylacetic acid [R^1 =hydroxy;
X=Y=Cl]; and

25 29. zopolrestat; 1-phthalazineacetic acid,
3,4-dihydro-4-oxo-3-[[5-(trifluoromethyl)-2-
benzothiazolyl]methyl]- [R^1 =hydroxy; X=trifluoromethyl;
Y=H].

30 In compounds 20-23, and 29 Z is S. In compounds
24-28, Z is O.

Of the above subgroup, compounds 20-29 are more
preferred with 29 especially preferred. Procedures for
making the aldose reductase inhibitors of formula Ia can
be found in PCT publication number WO 99/26659.

35 Each of the aldose reductase inhibitors
referenced above and other aldose reductase inhibitors
can be used in combination with the compounds of the

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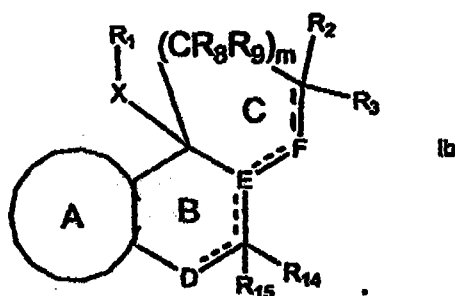
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present invention to treat diabetes, insulin resistance,
diabetic neuropathy, diabetic nephropathy, diabetic
retinopathy, cataracts, hyperglycemia,
hypercholesterolemia, hypertension, hyperinsulinemia,
5 hyperlipidemia, atherosclerosis, or tissue ischemia.

The compositions of the present invention can
also be used in combination with glucocorticoid receptor
antagonists. The glucocorticoid receptor (GR) is present
in glucocorticoid responsive cells where it resides in
10 the cytosol in an inactive state until it is stimulated
by an agonist. Upon stimulation the glucocorticoid
receptor translocates to the cell nucleus where it
specifically interacts with DNA and/or protein(s) and
regulates transcription in a glucocorticoid responsive
15 manner. Two examples of proteins that interact with the
glucocorticoid receptor are the transcription factors,
API and NFκ-B. Such interactions result in inhibition of
API- and NFκ-B- mediated transcription and are believed
to be responsible for the anti-inflammatory activity of
20 endogenously administered glucocorticoids. In addition,
glucocorticoids may also exert physiologic effects
independent of nuclear transcription. Biologically
relevant glucocorticoid receptor agonists include
cortisol and corticosterone. Many synthetic
25 glucocorticoid receptor agonists exist including
dexamethasone, prednisone and prednisilone. By
definition, glucocorticoid receptor antagonists bind to
the receptor and prevent glucocorticoid receptor agonists
from binding and eliciting GR mediated events, including
30 transcription. RU486 is an example of a non-selective
glucocorticoid receptor antagonist. GR antagonists can
be used in the treatment of diseases associated with an
excess or a deficiency of glucocorticoids in the body.
As such, they may be used to treat the following:
35 obesity, diabetes, cardiovascular disease, hypertension,
Syndrome X, depression, anxiety, glaucoma, human
immunodeficiency virus (HIV) or acquired immunodeficiency

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syndrome (AIDS), neurodegeneration (for example, Alzheimer's and Parkinson's), cognition enhancement, Cushing's Syndrome, Addison's Disease, osteoporosis, frailty, inflammatory diseases (such as osteoarthritis, rheumatoid arthritis, asthma and rhinitis), tests of adrenal function, viral infection, immunodeficiency, immunomodulation, autoimmune diseases, allergies, wound healing, compulsive behavior, multi-drug resistance, addiction, psychosis, anorexia, cachexia, post-traumatic stress syndrome, post-surgical bone fracture, medical catabolism and prevention of muscle frailty. Examples of GR antagonists that can be used in combination with a compound of the present invention include compounds of Formula Ib below:

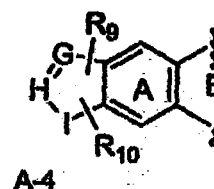
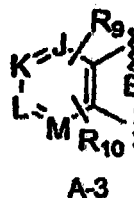
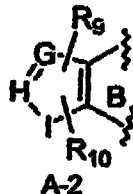
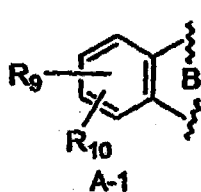


an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug wherein the substituents of Formula Ib are as follows:

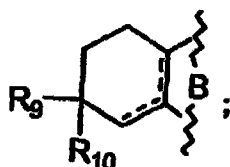
m is 1 or 2;

- - - represents an optional bond;

A is selected from the group consisting of



and



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D is CR₇, CR₇R₁₆, N, NR₇ or O;

E is C, CR₆ or N;

F is CR₄, CR₄R₅ or O;

G, H and I together with 2 carbon atoms from the A-ring or 2 carbon atoms from the B-ring form a 5-membered heterocyclic ring comprising one or more N, O or S atoms; provided that there is at most one of O and S per ring;

J, K, L and M together with 2 carbon atoms from the B-ring forms a 6-membered heterocyclic ring comprising 1 or more N atoms;

X is a) absent, b) -CH₂-, c) -CH(OH)- or d) -C(O)-;

R₁ is a) -H, b) -Z-CF₃, c) -(C₁-C₆)alkyl, d) -(C₂-C₆)alkenyl, e) -(C₂-C₆)alkynyl, f) -CHO, g) -CH=N-OR₁₂, h) -Z-C(O)OR₁₂, i) -Z-C(O)-NR₁₂R₁₃, j) -Z-C(O)-NR₁₂-Z-het, k) -Z-NR₁₂R₁₃, l) -Z-NR₁₂het, m) -Z-het, n) -Z-O-het, o) -Z-aryl', p) -Z-O-aryl', q) -CHOH-aryl' or r) -C(O)-aryl' wherein aryl' in substituents o) to r) is substituted independently with 0, 1 or 2 of the following: -Z-OH, -Z-NR₁₂R₁₃, -Z-NR₁₂-het, -C(O)NR₁₂R₁₃, -C(O)O(C₁-C₆)alkyl, -C(O)OH, -C(O)-het, -NR₁₂-C(O)-(C₁-C₆)alkyl, -NR₁₂-C(O)-(C₂-C₆)alkenyl, -NR₁₂-C(O)-(C₂-C₆)alkynyl, -NR₁₂-C(O)-Z-het, -CN, -Z-het, -O-(C₁-C₃)alkyl-C(O)-NR₁₂R₁₃, -O-(C₁-C₃)alkyl-C(O)O(C₁-C₆)alkyl, -NR₁₂-Z-C(O)O(C₁-C₆)alkyl, -N(Z-C(O)O(C₁-C₆)alkyl)₂, -NR₁₂-Z-C(O)-NR₁₂R₁₃, -Z-NR₁₂-SO₂-R₁₃, -NR₁₂-SO₂-het, -C(O)H, -Z-NR₁₂-Z-O(C₁-C₆)alkyl, -Z-NR₁₂-Z-NR₁₂R₁₃, -Z-NR₁₂-(C₃-C₆)cycloalkyl, -Z-N(Z-O(C₁-C₆)alkyl)₂, -SO₂R₁₂,

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-SOR₁₂, -SR₁₂, -SO₂NR₁₂R₁₃, -O-C(O)-(C₁-C₆)alkyl,
-O-SO₂-(C₁-C₆)alkyl, -halo or -CF₃;

Z for each occurrence is independently a)

-(C₀-C₆)alkyl, b) -(C₂-C₆)alkenyl or c) -(C₂-C₆)alkynyl;

5 R₂ is a) -H, b) -halo, c) -OH, d) -(C₁-C₆)alkyl
substituted with 0 or 1 -OH, e) -NR₁₂R₁₃, f)

-Z-C(O)O(C₁-C₆)alkyl, g) -Z-C(O)NR₁₂R₁₃, h) -O-(C₁-C₆)alkyl,
i) -Z-O-C(O)-(C₁-C₆)alkyl, j)

-Z-O-(C₁-C₃)alkyl-C(O)-NR₁₂R₁₃, k)

10 -Z-O-(C₁-C₃)alkyl-C(O)-O(C₁-C₆)alkyl, l) -O-(C₂-C₆)alkenyl,

m) -O-(C₂-C₆)alkynyl, n) -O-Z-het, o) -COOH, p) -C(OH)R₁₂R₁₃
or q) -Z-CN;

R₃ is a) -H, b) -(C₁-C₁₀)alkyl wherein 1 or 2

carbon atoms, other than the connecting carbon atom, may

15 optionally be replaced with 1 or 2 heteroatoms

independently selected from S, O and N and wherein each

carbon atom is substituted with 0, 1 or 2 R_y, c)

-(C₂-C₁₀)alkenyl substituted with 0, 1 or 2 R_y, d)

-(C₂-C₁₀)alkynyl wherein 1 carbon atom, other than the

20 connecting carbon atom, may optionally be replaced with 1

oxygen atom and wherein each carbon atom is substituted

with 0, 1 or 2 R_y, e) -CH=C-CH₂, f) -CN, g)

-(C₃-C₆)cycloalkyl, h) -Z-aryl, i) -Z-het, j)

-C(O)O(C₁-C₆)alkyl, k) -O(C₁-C₆)alkyl, l) -Z-S-R₁₂, m)

25 -Z-S(O)-R₁₂, n) -Z-S(O)₂-R₁₂, o) -CF₃, p) -NR₁₂O-(C₁-C₆)alkyl

or q) -CH₂OR_y;

provided that one of R₂ and R₃ is absent when

there is a double bond between CR₂R₃ (the 7 position) and

the F moiety (the 8 position) of the C-ring;

30 R_y for each occurrence is independently a) -OH,

b) -halo, c) -Z-CF₃, d) -Z-CF(C₁-C₃alkyl)₂, e) -CN, f)

-NR₁₂R₁₃, g) -(C₃-C₆)cycloalkyl, h) -(C₃-C₆)cycloalkenyl, i)

-(C₀-C₃)alkyl-aryl, j) -het or k) -N₃;

or R₂ and R₃ are taken together to form a)

35 =CHR₁₁, b) =NOR₁₁, c) =O, d) =N-NR₁₂, e) =N-NR₁₂-C(O)-R₁₂, f)

oxiranyl or g) 1,3-dioxolan-4-yl;

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R_4 and R_5 for each occurrence are independently

- a) -H, b) -CN, c) $-(C_1-C_6)$ alkyl substituted with 0 to 3 halo, d) $-(C_2-C_6)$ alkenyl substituted with 0 to 3 halo, e) $-(C_2-C_6)$ alkynyl substituted with 0 to 3 halo, f) $-O-(C_1-C_6)$ alkyl substituted with 0 to 3 halo, g) $-O-(C_2-C_6)$ alkenyl substituted with 0 to 3 halo, h) $-O-(C_2-C_6)$ alkynyl substituted with 0 to 3 halo, i) halo, j) -OH, k) (C_3-C_6) cycloalkyl or l) (C_3-C_6) cycloalkenyl;

or R_4 and R_5 are taken together to form =O;

- 10 R_6 is a) -H, b) -CN, c) $-(C_1-C_6)$ alkyl substituted with 0 to 3 halo, d) $-(C_2-C_6)$ alkenyl substituted with 0 to 3 halo, e) $-(C_2-C_6)$ alkynyl substituted with 0 to 3 halo or f) -OH;

R_7 and R_{16} for each occurrence are independently

- 15 a) -H, b) -halo, c) -CN, d) $-(C_1-C_6)$ alkyl substituted with 0 to 3 halo, e) $-(C_2-C_6)$ alkenyl substituted with 0 to 3 halo or f) $-(C_2-C_6)$ alkynyl substituted with 0 to 3 halo; provided that R_7 is other than -CN or -halo when D is NR_7 ;

or R_7 and R_{16} are taken together to form =O;

- 20 R_8 , R_9 , R_{14} and R_{15} for each occurrence are independently a) -H, b) -halo, c) (C_1-C_6) alkyl substituted with 0 to 3 halo, d) $-(C_2-C_6)$ alkenyl substituted with 0 to 3 halo, e) $-(C_2-C_6)$ alkynyl substituted with 0 to 3 halo, f) -CN, g) $-(C_3-C_6)$ cycloalkyl, h) $-(C_3-C_6)$ cycloalkenyl, i) -OH, j) $-O-(C_1-C_6)$ alkyl, k) $-O-(C_1-C_6)$ alkenyl, l) $-O-(C_1-C_6)$ alkynyl, m) $-NR_{12}R_{13}$, n) $-C(O)OR_{12}$ or o) $-C(O)NR_{12}R_{13}$;

or R_8 and R_9 are taken together on the C-ring to form =O; provided that when m is 2, only one set of R_8 and

- 30 R_9 are taken together to form =O;

or R_{14} and R_{15} are taken together to form =O; provided that when R_{14} and R_{15} are taken together to form =O, D is other than CR_7 and E is other than C;

- 35 R_{10} is a) $-(C_1-C_{10})$ alkyl substituted with 0 to 3 substituents independently selected from -halo, -OH and $-N_3$, b) $-(C_2-C_{10})$ alkenyl substituted with 0 to 3 substituents independently selected from -halo, -OH and

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- N₃, c) -(C₂-C₁₀)alkynyl substituted with 0 to 3 substituents independently selected from -halo, -OH and -N₃, d) -halo, e) -Z-CN, f) -OH, g) -Z-het, h) -Z-NR₁₂R₁₃, i) -Z-C(O)-het, j) -Z-C(O)-(C₁-C₆)alkyl, k) -Z-C(O)-NR₁₂R₁₃,
 5 l) -Z-C(O)-NR₁₂-Z-CN, m) -Z-C(O)-NR₁₂-Z-het, n) -Z-C(O)-NR₁₂-Z-aryl, o) -Z-C(O)-NR₁₂-Z-NR₁₂R₁₃, p) -Z-C(O)-NR₁₂-Z-O(C₁-C₆)alkyl, q) -(C₁-C₆)alkyl-C(O)OH, r) -Z-C(O)O(C₁-C₆)alkyl, s) -Z-O-(C₀-C₆)alkyl-het, t) -Z-O-(C₀-C₆)alkyl-aryl, u) -Z-O-(C₁-C₆)alkyl substituted
 10 with 0 to 2 R_x, v) -Z-O-(C₁-C₆)alkyl-CH(O), w) -Z-O-(C₁-C₆)alkyl-NR₁₂-het, x) -Z-O-Z-het-Z-het, y) -Z-O-Z-het-Z-NR₁₂R₁₃, z) -Z-O-Z-het-C(O)-het, a1) -Z-O-Z-C(O)-het, b1) -Z-O-Z-C(O)-het-het, c1) -Z-O-Z-C(O)-(C₁-C₆)alkyl, d1) -Z-O-Z-C(S)-NR₁₂R₁₃, e1)
 15 -Z-O-Z-C(O)-NR₁₂R₁₃, f1) -Z-O-Z-(C₁-C₃)alkyl-C(O)-NR₁₂R₁₃, g1) -Z-O-Z-C(O)-O(C₁-C₆)alkyl, h1) -Z-O-Z-C(O)-OH, i1) -Z-O-Z-C(O)-NR₁₂-O(C₁-C₆)alkyl, j1) -Z-O-Z-C(O)-NR₁₂-OH, k1) -Z-O-Z-C(O)-NR₁₂-Z-NR₁₂R₁₃, l1) -Z-O-Z-C(O)-NR₁₂-Z-het, m1) -Z-O-Z-C(O)-NR₁₂-SO₂-(C₁-C₆)alkyl, n1)
 20 -Z-O-Z-C(=NR₁₂)(NR₁₂R₁₃), o1) -Z-O-Z-C(=NOR₁₂)(NR₁₂R₁₃), p1) -Z-NR₁₂-C(O)-O-Z-NR₁₂R₁₃, q1) -Z-S-C(O)-NR₁₂R₁₃, r1) -Z-O-SO₂-(C₁-C₆)alkyl, s1) -Z-O-SO₂-aryl, t1) -Z-O-SO₂-NR₁₂R₁₃, u1) -Z-O-SO₂-CF₃, v1) -Z-NR₁₂C(O)OR₁₃ or w1) -Z-NR₁₂C(O)R₁₃;
 25 or R₉ and R₁₀ are taken together on the moiety of formula A-5 to form a) = O or b) = NOR₁₂;
 R₁₁ is a) -H, b) -(C₁-C₅)alkyl, c) -(C₃-C₆)cycloalkyl or d) -(C₀-C₃)alkyl-aryl;
 R₁₂ and R₁₃ for each occurrence are each
 30 independently a) -H, b) -(C₁-C₆)alkyl wherein 1 or 2 carbon atoms, other than the connecting carbon atom, may optionally be replaced with 1 or 2 heteroatoms independently selected from S, O and N and wherein each carbon atom is substituted with 0 to 6 halo, c)
 35 -(C₂-C₆)alkenyl substituted with 0 to 6 halo or d) -(C₁-C₆)alkynyl wherein 1 carbon atom, other than the connecting carbon atom, may optionally be replaced with 1

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oxygen atom and wherein each carbon atom is substituted with 0 to 6 halo;

or R_{12} and R_{13} are taken together with N to form het;

5 or R_6 and R_{14} or R_{15} are taken together to form 1,3-dioxolanyl;

aryl is a) phenyl substituted with 0 to 3 R_x , b) naphthyl substituted with 0 to 3 R_x or c) biphenyl substituted with 0 to 3 R_x ;

10 het is a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring containing from one (1) to three (3) heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the
15 above heterocyclic rings is fused to a benzene ring or another heterocycle; and the nitrogen may be in the oxidized state giving the N-oxide form; and substituted with 0 to 3 R_x ;

R_x for each occurrence is independently a)
20 -halo, b) -OH, c) $-(C_1-C_6)\text{alkyl}$, d) $-(C_2-C_6)\text{alkenyl}$, e) $-(C_2-C_6)\text{alkynyl}$, f) $-O(C_1-C_6)\text{alkyl}$, g) $-O(C_2-C_6)\text{alkenyl}$, h) $-O(C_2-C_6)\text{alkynyl}$, i) $-(C_0-C_6)\text{alkyl}-NR_{12}R_{13}$, j) $-C(O)-NR_{12}R_{13}$, k) $-Z-SO_2R_{12}$, l) $-Z-SOR_{12}$, m) $-Z-SR_{12}$, n) $-NR_{12}-SO_2R_{13}$, o) $-NR_{12}-C(O)-R_{13}$, p) $-NR_{12}-OR_{13}$, q) $-SO_2-NR_{12}R_{13}$, r) -CN, s)
25 $-CF_3$, t) $-C(O)(C_1-C_6)\text{alkyl}$, u) =O, v) $-Z-SO_2\text{-phenyl}$ or w) $-Z-SO_2\text{-het'}$;

aryl' is phenyl, naphthyl or biphenyl;

het' is a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring containing from
30 one (1) to three (3) heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle;

35 provided that:

(1) $X-R_1$ is other than hydrogen or methyl;

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(2) when R_9 and R_{10} are substituents on the A-ring, they are other than mono- or di-methoxy;

(3) when R_2 and R_3 are taken together to form $=CHR_{11}$ or $=O$ wherein R_{11} is $-O(C_1-C_6)alkyl$, then $-X-R_1$ is
5 other than $(C_1-C_4)alkyl$;

(4) when R_2 and R_3 taken together are $C=O$ and R_9 is hydrogen on the A-ring; or when R_2 is hydroxy, R_3 is hydrogen and R_9 is hydrogen on the A-ring, then R_{10} is other than $-O-(C_1-C_6)alkyl$ or $-O-CH_2-phenyl$ at the
10 2-position of the A-ring;

(5) when $X-R_1$ is $(C_1-C_4)alkyl$, $(C_2-C_4)alkenyl$ or $(C_2-C_4)alkynyl$, R_9 and R_{10} are other than mono-hydroxy or $=O$, including the diol form thereof, when taken together; and

(6) when X is absent, R_1 is other than a moiety
15 containing a heteroatom independently selected from N, O or S directly attached to the juncture of the B-ring and the C-ring. (See U.S. Provisional Patent Application number 60/132,130.)

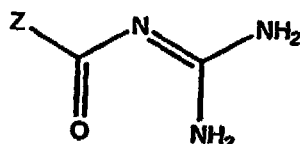
Each of the glucocorticoid receptor antagonists
20 referenced above and other glucocorticoid receptor antagonists can be used in combination with the compounds of the present invention to treat or prevent diabetes, hyperglycemia, hypercholesterolemia, hypertension,
25 hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

The compositions of the present invention can also be used in combination with sorbitol dehydrogenase inhibitors. Sorbitol dehydrogenase inhibitors lower
30 fructose levels and have been used to treat or prevent diabetic complications such as neuropathy, retinopathy, nephropathy, cardiomyopathy, microangiopathy, and macroangiopathy. U.S. patent numbers 5,728,704 and 5,866,578 disclose compounds and a method for treating or
35 preventing diabetic complications by inhibiting the enzyme sorbitol dehydrogenase.

Each of the sorbitol dehydrogenase inhibitors referenced above and other sorbitol dehydrogenase inhibitors can be used in combination with the compounds of the present invention to treat diabetes, insulin resistance, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

The compositions of the present invention can also be used in combination with sodium-hydrogen exchanger Type 1 (NHE-1) inhibitors. NHE-1 inhibitors can be used to reduce tissue damage resulting from ischemia. Of great concern is tissue damage that occurs as a result of ischemia in cardiac, brain, liver, kidney, lung, gut, skeletal muscle, spleen, pancreas, nerve, spinal cord, retina tissue, the vasculature, or intestinal tissue. NHE-1 inhibitors can also be administered to prevent perioperative myocardial ischemic injury.

Examples of NHE-1 inhibitors include a compound having the Formula Ic



Formula Ic

a prodrug thereof or a pharmaceutically acceptable salt of said compound or of said prodrug, wherein the substituents of Formula Ic are as follows:

Z is carbon connected and is a five-membered, diaza, diunsaturated ring having two contiguous nitrogens, said ring optionally mono-, di-, or tri-substituted with up to three substituents independently selected from R¹, R² and R³; or

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Z is carbon connected and is a five-membered, triaza, diunsaturated ring, said ring optionally mono- or di-substituted with up to two substituents independently selected from R⁴ and R⁵;

5 wherein R¹, R², R³, R⁴ and R⁵ are each independently hydrogen, hydroxy(C₁-C₄)alkyl, (C₁-C₄)alkyl, (C₁-C₄)alkylthio, (C₃-C₄)cycloalkyl, (C₃-C₇)cycloalkyl(C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₁-C₄)alkoxy(C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, M or M(C₁-C₄)alkyl, any of
10 said previous (C₁-C₄)alkyl moieties optionally having from one to nine fluorines; said (C₁-C₄)alkyl or (C₃-C₄)cycloalkyl optionally mono-or di-substituted independently with hydroxy, (C₁-C₄)alkoxy, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl,
15 (C₁-C₄)alkyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl; and said (C₃-C₄)cycloalkyl optionally having from one to seven fluorines;

20 wherein M is a partially saturated, fully saturated or fully unsaturated five to eight membered ring optionally having one to three heteroatoms selected independently from oxygen, sulfur and nitrogen, or, a bicyclic ring consisting of two fused partially saturated, fully saturated or fully unsaturated three to
25 six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen;

30 said M is optionally substituted, on one ring if the moiety is monocyclic, or one or both rings if the moiety is bicyclic, on carbon or nitrogen with up to three substituents independently selected from R⁶, R⁷ and R⁸, wherein one of R⁶, R⁷ and R⁸ is optionally a partially saturated, fully saturated, or fully unsaturated three to seven membered ring optionally having one to three
35 heteroatoms selected independently from oxygen, sulfur and nitrogen optionally substituted with (C₁-C₄)alkyl and additionally R⁶, R⁷ and R⁸ are optionally hydroxy, nitro,

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halo, (C₁-C₄)alkoxy, (C₁-C₄)alkoxycarbonyl, (C₁-C₄)alkyl, formyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkanoylamino, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl, mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl or (C₅-C₇)cycloalkenyl,

wherein said (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₇)alkanoyl, (C₁-C₄)alkylthio, mono-N- or di-N,N-(C₁-C₄)alkylamino or (C₃-C₇)cycloalkyl R⁶, R⁷ and R⁸ substituents are optionally mono- substituted independently with hydroxy, (C₁-C₄)alkoxycarbonyl, (C₃-C₇)cycloalkyl, (C₁-C₄)alkanoyl, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanoyloxy, (C₁-C₄)alkoxycarbonylamino, sulfonamido, (C₁-C₄)alkylsulfonamido, amino, mono-N- or di-N,N-(C₁-C₄)alkylamino, carbamoyl, mono-N- or di-N,N-(C₁-C₄)alkylcarbamoyl, cyano, thiol, nitro, (C₁-C₄)alkylthio, (C₁-C₄)alkylsulfinyl, (C₁-C₄)alkylsulfonyl or mono-N- or di-N,N-(C₁-C₄)alkylaminosulfonyl or optionally substituted with one to nine fluorines. (See PCT patent application number PCT/IB99/00206)

Each of the NHE-1 inhibitors referenced above and other NHE-1 inhibitors can be used in combination with the compositions of the present invention to treat or prevent diabetes, insulin resistance, diabetic neuropathy, diabetic nephropathy, diabetic retinopathy, cataracts, hyperglycemia, hypercholesterolemia, hypertension, hyperinsulinemia, hyperlipidemia, atherosclerosis, or tissue ischemia.

Other features and embodiments of the invention will become apparent from the following examples which are given for illustration of the invention rather than for limiting its intended scope.

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EXAMPLES

Example 1

This example discloses preparation of an amorphous solid dispersion of the GPI 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3R, 4S)-dihydroxy-pyrrolidin-1-yl)-3-oxy-propyl]-amide ("Drug 1"), which has a solubility in water of 60 to 80 $\mu\text{g/mL}$ and a solubility in MFD solution of 183 $\mu\text{g/mL}$. A dispersion of 25 wt% Drug 1 and 75 wt% polymer was made by mixing Drug 1 in the solvent acetone together with a "medium fine" (AQUOT-MF) grade of the cellulosic ester polymer HPMCAS (manufactured by Shin Etsu) to form a solution. The solution comprised 1.25 wt% Drug 1, 3.75 wt% HPMCAS, and 95 wt% acetone. This solution was then spray-dried by directing an atomizing spray using a two-fluid external-mix spray nozzle at 2.6 bar (37 psig) at a feed rate of 175 to 180 g/min into the stainless-steel chamber of a Niro XP spray-dryer, maintained at a temperature of 180°C at the inlet and 69°C at the outlet.

The resulting amorphous solid spray-dried dispersion (SDD) was collected via a cyclone and then dried in a Gruenberg solvent tray-dryer by spreading the spray-dried particles onto polyethylene-lined trays to a depth of not more than 1 cm and then drying them at 40°C for at least 8 hours.

Examples 2-7

Examples 2 through 7 were prepared using the same process as in Example 1, with the exception that different dispersion polymers and different amounts of drug and polymer were used. The variables are noted in Table 1. The SDD of Example 2 was prepared using the Niro PSD-1 spray-dryer. The SDDs of Examples 3-7 were prepared using a "mini" spray dryer, which consisted of an atomizer in the top cap of a vertically oriented stainless steel pipe. The atomizer was a two-fluid nozzle (Spraying Systems Co. 1650 fluid cap and 64 air

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cap) where the atomizing gas was nitrogen delivered to the nozzle at 100°C and a flux of 15 gm/min, and the spray-dried solution was delivered to the nozzle at room temperature and a flow rate of 1 gm/min using a syringe pump. Filter paper with a supporting screen was clamped to the bottom end of the pipe to collect the solid spray-dried material and to allow the nitrogen and evaporated solvent to escape.

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Table 1

Ex. No.	Drug	Drug Mass	Polymer*	Polymer Mass	Drug Conc. in the Dispersion (wt%)	Solv	Solv Mass	Spray Dryer
1	1	991g	HPMCAS-MF	3009g	25	acetone	101,670g	Niro XP
2	1	30g	HPMCAS-MF	30g	50	acetone	2,340g	Niro PSD-1
3	1	25mg	HPMC	75mg	25	acetone	10g	Mini
4	1	25mg	PVP	75mg	25	acetone	10g	Mini
5	1	25mg	CAP	75mg	25	acetone	10g	Mini
6	1	25mg	CAT	75mg	25	acetone	10g	Mini
7	1	25mg	HPMCP	75mg	25	acetone	10g	Mini

* Polymer designations: HPMCAS = hydroxypropyl methyl cellulose acetate succinate, HPMC = hydroxypropyl methyl cellulose, PVP = polyvinylpyrrolidone, CAP = cellulose acetate phthalate, CAT = cellulose acetate trimellitate, HPMCP = hydroxypropyl methyl cellulose phthalate.

Examples 8-9

Example 8 was prepared by rotoevaporating a polymer:drug solution to dryness. The solution consisted of 7.5 wt% Drug 1, 7.5 wt% HPMCAS-MF, 80.75 wt% acetone, and 4.25 wt% water. The solution was added to a round bottom flask. The flask was rotated at approximately 150 rpm in a 40°C water bath under a reduced pressure of about 0.1 atm. The resulting solid dispersion was removed from the flask as fine granules and used without further processing.

Example 9 was prepared by spraying a coating solution comprising 2.5 wt% Drug 1, 7.5 wt% HPMCAS-MF, and 90 wt% solvent (5 wt% water in acetone) onto Nu-Core beads (45/60 mesh) to produce a coating of an amorphous solid dispersion of the drug and polymer on the surface of the beads. An analysis showed that the coated beads contained 3.9 wt% Drug 1.

The drug, polymer and solvents for Examples 8 and 9 are shown in Table 2.

Table 2

Ex. No.	Drug	Drug Mass	Polymer	Polymer Mass	Drug Conc. in the Dispersion (wt%)	Solv	Solv Mass
8	1	1.875g	HMCAS-MF (rotovaporated)	1.875g	50	5 wt% water in acetone	21.25g
9	1	20g	HMCAS-MF (coated beads)	60g	25	5 wt% water in acetone	720g

CONTROLS 1-2

Comparative compositions Control 1 and Control 2 were simply 3.6 mg of crystalline Drug 1 and 3.6 mg of the amorphous form of Drug 1 respectively.

Example 10

In vitro dissolution tests were performed to evaluate the performance of the amorphous dispersions of Examples 1-9 relative to the performance of Controls 1 and 2. The dissolution performance of the SDD of Example 1 was evaluated in an in vitro dissolution test using a microcentrifuge method. In this test, 14.4 mg of the SDD of Example 1 was added to a microcentrifuge tube. The tube was placed in a 37°C sonicating bath, and 1.8 mL phosphate buffered saline (PBS) at pH 6.5 and 290 mOsm/kg was added. The samples were quickly mixed using a vortex mixer for about 60 seconds. The samples were centrifuged at 13,000 G at 37°C for 1 minute. The resulting supernatant solution was then sampled and diluted 1:6 (by volume) with methanol and then analyzed by high-performance liquid chromatography (HPLC). The contents of the tubes were mixed on the vortex mixer and allowed to stand undisturbed at 37°C until the next sample was taken. Samples were collected at 4, 10, 20, 40, 90, and 1200 minutes.

The performance of Example Nos. 2-8 was likewise evaluated in in vitro dissolution tests using the same microcentrifuge method described above. The

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dosage for each of these tests was 2000 $\mu\text{g/ml}$. The results of the dissolution tests are shown in Table 3.

5 The performance of the amorphous dispersions of Example 9 were tested using the same microcentrifuge method, except that 2.5 grams of the coated beads were added to 50 mL of PBS solution (resulting in a dosage of 2000 $\mu\text{g/mL}$).

10 For Controls 1 and 2, *in vitro* dissolution tests were also performed using the same microcentrifuge method except that 3.6 mg of either crystalline or amorphous Drug 1 was used.

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Table 3

Example	Time (mins)	Drug Concentration ($\mu\text{g/mL}$)	AUC ($\text{min} \cdot \mu\text{g/mL}$)
1	0	0	0
	4	635	1,300
	10	644	5,100
	20	711	11,900
	40	769	26,700
	90	844	67,000
	1200	1290	
2	0	0	0
	4	601	1,200
	10	625	4,900
	20	653	11,300
	40	624	24,000
	90	693	57,000
	1200	548	
3	0	0	0
	3	544	1,100
	10	558	4,400
	20	558	9,980
	40	552	21,100
	90	565	49,000
	1200	397	
4	0	0	0
	3	526	1,100
	10	637	4,500
	20	649	11,000
	40	651	24,000
	90	688	57,400
	1200	409	
5	0	0	0
	3	2066	4,100
	10	2035	16,400
	20	2075	37,000
	40	1965	77,400
	90	1845	173,600
	1200	255	
6	0	0	0
	3	2040	4,100
	10	1777	15,500
	20	1704	32,900
	40	1483	64,800
	90	427	112,600
	1200	257	
7	0	0	0
	3	1036	2,100
	10	1277	9,000
	20	1246	21,600
	40	1217	46,300
	90	503	89,300
	1200	350	

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Example	Time (mins)	Drug Concentration ($\mu\text{g/mL}$)	AUC ($\text{min} \cdot \mu\text{g/mL}$)
8	0	0	0
	4	134	270
	10	197	1,300
	20	248	3,500
	40	308	9,100
	90	378	26,200
	1200	591	
9	0	0	0
	4	412	820
	10	491	3,500
	20	523	8,600
	40	561	19,400
	90	617	48,900
	180	752	110,500
Control 1	0	0	0
	4	130	260
	10	149	1,100
	20	139	2,500
	40	149	5,400
	90	147	12,800
	1200	125	
Control 2	0	0	0
	4	586	1,200
	10	473	4,400
	20	220	7,800
	40	182	11,700
	90	167	20,600
	180	158	35,200
	1200	203	

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10 The results of the *in vitro* dissolution tests are summarized in Table 4, which shows the maximum concentration of Drug 1 in solution during the first 90 minutes of the test ($C_{\text{max},90}$), the area under the aqueous concentration versus time curve after 90 minutes (AUC_{90}), and the concentration at 1200 minutes (C_{1200}).

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Table 4

Example	Dosage ($\mu\text{g/mL}$)	$C_{\text{max}, 90}$ ($\mu\text{g/mL}$)	AUC_{90} ($\text{min} \cdot \mu\text{g}/\text{mL}$)	C_{1200} ($\mu\text{g/mL}$)
1	2000	844	67,000	1290
2	2000	693	57,000	548
3	2000	565	49,000	397
4	2000	688	57,400	409
5	2000	2075	172,600	255
6	2000	2040	112,600	257
7	2000	1277	89,300	350
8	2000	378	26,200	591
9	2000	617	48,900	967
Control 1	2000	149	12,800	125
Control 2	2000	586	20,600	203

The results, summarized in Table 4, show that the performance of the SDDs of Examples 1-9 was much better than that of the crystalline drug alone (Control 1), with $C_{\text{max}, 90}$ values ranging from 2.5- to 13.9-fold that of the crystalline drug, Control 1, and AUC_{90} values ranging from 2- to 13.4-fold that of the crystalline drug, Control 1. With respect to the amorphous drug alone, the dispersions of Examples 1-9 demonstrated an AUC_{90} that was 1.27- to 8.4-fold that of the amorphous drug alone, Control 2.

Example 11

This example shows improved *in vivo* performance of an amorphous dispersion of Drug 1 and concentration-enhancing polymer compared with the crystalline form of Drug 1. For Example 11, an SDD was prepared following the procedure described in Example 1. The SDD was then formulated as an oral powder for constitution (OPC) by suspending 1.2 gm of the SDD in 100 ml of a 0.5 wt% solution of Polysorbate 80 in sterile water. This OPC, which contained 300 mg of active Drug 1, was taken orally by healthy human subjects (n=4). The dosing bottle was rinsed twice with 100 ml of sterile water and administered orally to the subjects. As a control

(Control 3), an OPC was formed using an equivalent quantity of the crystalline form of Drug 1. The results of these *in vivo* tests are shown in Table 5, giving the maximum concentration of drug achieved in the blood plasma, the time to reach this maximum concentration, and the blood plasma drug AUC from 0 to 24 hours.

Table 5

Ex. No.	Dose (mg)	C _{max} (μg/mL)	Time to C _{max} (hr)	AUC ₀₋₂₄ (μg-hr/mL)
11	300	8.4±1.1	2.5±0.6	46±7.6
Control 3	300	1.3±0.3	2.3±1.3	7.4±3.3

As shown in Table 5, the OPC of Example 11 showed improved performance compared with the OPC of Control 3, thus demonstrating the advantage of using an amorphous dispersion of a GPI and concentration-enhancing polymer. Not only was the blood plasma C_{max} for Example 11 6.5-fold the blood plasma C_{max} for Control 3, but the blood plasma AUC₀₋₂₄ for Example 11 was 6.21-fold that of Control 3.

Examples 12-17

These examples demonstrate the utility of the GPI amorphous dispersions of the present invention with another GPI, 5-chloro-1H-indole-2-carboxylic acid [1S-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl] amide ("Drug 2"), which has a solubility in water of 14.6 μg/mL. For Example 12, a solution containing 0.5 wt% Drug 2 and 0.5 wt% HPMCAS-LF in acetone was prepared. This solution was pumped into a "mini" spray-dryer apparatus via a syringe pump at a rate of 1.3 mL/min. The polymer solution was atomized through a spray nozzle using a heated stream of nitrogen (100°C). The resulting solid SDD containing 50 wt% Drug 2 was collected on filter paper at a yield of about 80%.

Examples 13-17 were prepared using the same method used to prepare Example 12, but with different polymers and in some cases different solvents. The variations are noted in Table 6.

Table 6

Ex. No.	Drug	Drug Mass	Polymer*	Polymer Mass	Drug Conc. in the Dispersion (wt%)	Solv	Solv Mass	Spray Dryer
12	2	25mg	HPMCAS-LF	25mg	50	acetone	5g	mini
13	2	15mg	HPMCAS-LF	45mg	25	methanol	10g	mini
14	2	15mg	HPMCP-55	45mg	25	methanol	10g	mini
15	2	15mg	PVP	45mg	25	10 wt% water in methanol	11g	mini
16	2	150mg	CAP	150mg	50	50 wt% water in acetone	33.4 g	mini
17	2	150mg	CAT	150mg	50	50 wt% water in acetone	33.4 g	mini

* Polymer designations: HPMCAS = hydroxypropyl methyl cellulose acetate succinate, PVP = polyvinylpyrrolidone, CAP = cellulose acetate phthalate, CAT = cellulose acetate trimellitate, HPMCP = hydroxypropyl methyl cellulose phthalate.

CONTROLS 4-5

Comparative compositions Control 4 and Control 5 were simply 1.8 mg of crystalline Drug 2 and 1.8 mg of amorphous Drug 2, respectively.

Example 18

In vitro dissolution tests were performed to evaluate the performance of the amorphous dispersions of Examples 12-17 relative to the performance of Controls 4 and 5. The SDD of Example 12 was evaluated in an in vitro dissolution test using a microcentrifuge method. In this test, 3600 μ g of the SDD of Example 12 was added to a microcentrifuge tube. The tube was placed in a 37°C sonicating bath, and 1.8 mL of model fasted duodenal solution (MFDS), comprising phosphate buffered saline

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with 14.7 mM sodium taurocholic acid and 2.8 mM of 1-palmitoyl-2-oleyl-sn-glycero-3-phosphocholine, pH 6.5, 290 mOsm/kg, was added. This resulted in a dose of Drug 2 of 1000 µg/ml. The samples were quickly mixed using a vortex mixer for about 60 seconds. The samples were centrifuged at 13,000 G at 37°C for 1 minute. The resulting supernatant solution was then sampled and diluted 1:6 (by volume) with methanol and then analyzed by high-performance liquid chromatography (HPLC). The contents of the tubes were mixed on the vortex mixer and allowed to stand undisturbed at 37°C until the next sample was taken. Samples were collected at 4, 10, 20, 40, 90, and 1200 minutes.

For Controls 4 and 5, *in vitro* dissolution tests were performed using the procedures described above except that 1.8 mg of crystalline and amorphous Drug 2 was used, respectively.

Results of the dissolution tests are presented in Table 7.

Table 7

Example	Time (mins)	Drug Concentration (µg/mL)	AUC (min*µg/mL)
12	0	0	0
	4	850	1,700
	10	866	6,900
	20	895	15,700
	40	908	33,700
	90	923	79,500
	1200	933	
13	0	0	0
	4	958	1,900
	10	993	7,800
	20	997	17,700
	40	975	37,400
	90	992	86,600
	1200	961	
14	0	0	0
	4	860	1,700
	10	822	6,800
	20	804	14,900
	40	805	31,000
	90	778	70,600
	1200	732	

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Example	Time (mins)	Drug Concentration ($\mu\text{g/mL}$)	AUC ($\text{min} \cdot \mu\text{g/mL}$)
15	0	0	0
	4	467	930
	10	498	3,800
	20	505	8,800
	40	507	19,000
	90	495	44,000
	1200	545	
16	0	0	0
	4	696	1,400
	10	708	5,600
	20	708	12,700
	40	695	26,700
	90	701	61,600
	1200	735	
17	0	0	0
	4	768	1,500
	10	766	6,100
	20	746	13,700
	40	730	28,500
	90	744	65,300
	1200	722	
Control 4	0	0	0
	4	45	90
	10	44	357
	20	53	842
	40	72	2,100
	90	82	5,900
	1200	102	
Control 5	0	0	0
	4	151	302
	10	203	1,400
	20	225	3,500
	40	238	8,100
	90	268	20,800
	1200	370	

The results of these tests are summarized in Table 8, which shows the maximum concentration of Drug 2 in solution during the first 90 minutes of the test ($C_{\text{max},90}$), the aqueous area under the curve after 90 minutes (AUC_{90}), and the concentration at 1200 minutes (C_{1200}).

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Table 8

Example	Dosage ($\mu\text{g/mL}$)	$C_{\text{max},90}$ ($\mu\text{g/mL}$)	AUC_{90} ($\text{min} \cdot \mu\text{g/mL}$)	C_{1200} ($\mu\text{g/mL}$)
12	1000	923	79,500	933
13	1000	997	86,600	961
14	1000	860	70,600	732
15	1000	507	44,000	545
16	1000	708	61,600	735
17	1000	768	65,300	722
Control 4	1000	82	5,900	102
Control 5	1000	268	20,800	370

In general, the dispersions of Examples 12-17 showed much better performance than the crystalline drug alone, with $C_{\text{max},90}$ values ranging from 6.2- to 12.1-fold that of the crystalline drug, Control 4, and AUC_{90} values ranging from 7.5- to 14.7-fold that of the crystalline drug, Control 4. With respect to the amorphous drug alone, all of the dispersions of Examples 12-17 demonstrated a C_{max} and an AUC_{90} greater than that of the amorphous drug alone, with $C_{\text{max},90}$ values ranging from 1.9- to 3.7-fold that of the amorphous drug, Control 5, and AUC_{90} values ranging from 2.1- to 4.2-fold that of the amorphous drug, Control 5.

Example 19

This example demonstrates that the compositions of this invention, when orally dosed to beagle dogs, give a high systemic compound exposure (C_{max} and AUC). An amorphous solid dispersion of 50 wt% Drug 2 and 50 wt% polymer was made by mixing Drug 2 in the solvent acetone together with HPMCAS-LF to form a solution. The solution comprised 2.5 wt% Drug 2, 2.5 wt% HPMCAS-LF, and 95 wt% acetone. This solution was then spray-dried by directing an atomizing spray using a two-fluid external-mix spray nozzle at 2.2 bar at a feed rate of 200 g/min into the stainless-steel chamber of a Niro PSD-1 spray-dryer, maintained at a temperature of 180°C at the inlet and 68°C at the outlet.

The resulting amorphous solid SDD was collected via a cyclone and then dried in a Gruenberg solvent tray-dryer by spreading the spray-dried particles onto polyethylene-lined trays to a depth of not more than 1 cm and then drying them at 40°C for at least 8 hours.

The SDD was dosed as an oral powder for constitution (OPC) by suspending 200 mg of the SDD in approximately 20 ml of a 2 wt% solution of Polysorbate 80 in sterile water. This OPC, containing 100 mg of active Drug 2 was administered orally to beagle dogs using an oral gavage tube. As a control (Control 6), a similar OPC was formed using the crystalline form of the drug. Relative bioavailability was calculated by dividing the AUC in the blood of subjects receiving the test dose by the AUC in the blood of subjects receiving the control dose (Control 6).

Dogs that had fasted overnight were dosed with suspensions containing 100 mg of Drug 2, along with 20 mL of water. Blood was collected from the jugular vein of the dogs before dosing and at various time points after dosing. To 100 μ L of each plasma sample, 5 mL of methyl-tert-butyl ether (MTBE) and 1 mL of 500 mM sodium carbonate buffer (pH 9) were added; the sample was vortexed for 1 minute and then centrifuged for 5 minutes. The aqueous portion of the sample was frozen in a dry-ice/acetone bath, and the MTBE layer was decanted and evaporated in a vortex evaporator. Dried samples were reconstituted in 100 μ L of mobile phase (33% acetonitrile and 67% of 0.1% formic acid in water). Analysis was carried out by HPLC. The results of these tests are shown in Table 9, where C_{max} is the maximum concentration in the blood plasma, AUC_{0-24} is the area under the drug concentration in the blood curve in the first 24 hours, and Relative Bioavailability is the AUC in the blood of subjects receiving the test dose divided by the AUC of subjects receiving the Control 6.

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Table 9

Example No.	C _{max} (μg/mL)	AUC ₀₋₂₄ (μg-hr/mL)	Relative Bioavailability
19	9.8 ± 4.6	38 ± 6	6.2
Control 6	1.6 ± 0.7	6.1 ± 4.0	1

The results show the superior performance of the amorphous GPI and polymer dispersion of Example 19 relative to the crystalline GPI, Control 6, providing a C_{max} value that was 6.1-fold that of the control and a relative bioavailability of 6.2 relative to the control.

Examples 20-25

Examples 20-25 demonstrate the utility of the GPI amorphous dispersions of the present invention with another GPI, 5-chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-methoxy-methylcarbamoylmethyl)-2-phenylethyl]-amide ("Drug 3"), which has a solubility in water of 1 μg/mL and a solubility in MFD solution of 17 μg/mL. To prepare Example 20, a solution containing 0.5 wt% of Drug 3 and 0.5 wt% HPMCAS-MF in acetone was prepared. This solution was pumped into a "mini" spray-dryer apparatus via a syringe pump at a rate of 1.3 mL/min. The polymer solution was atomized through a spray nozzle using a heated stream of nitrogen (100°C). The resulting solid SDD containing 50 wt% Drug 3 was collected on a filter paper at a yield of about 62%.

Examples 21-25 were prepared using the same method used to prepare Example 20, but with different polymers and in some cases different solvents. The variations are note in Table 10.

Table 10

Ex. No.	Drug	Drug Mass	Polymer*	Polymer Mass	Drug Conc. in the Dispersion (wt%)	Solv	Solv Mass	Spray Driver
20	3	52 mg	HPMCAS-MF	52 mg	50.0	acetone	12 g	mini
21	3	50.5 mg	PVP	50.4 mg	50.0	acetone methanol	12 g 0.24 g	mini
22	3	49.7 mg	HPMCP	49.9 mg	49.9	acetone	12 g	mini
23	3	50.1 mg	CAP	50.3 mg	49.9	acetone	12 g	mini
24	3	50.9 mg	HPC	51.8 mg	49.6	acetone	12 g	mini
25	3	50 mg	PVAP	50 mg	50.0	acetone	12 g	mini

* Polymer designations: HPMCAS = hydroxypropyl methyl cellulose acetate succinate, HPMC = hydroxypropyl methyl cellulose, PVP = polyvinylpyrrolidone, CAP = cellulose acetate phthalate, HPC = hydroxypropyl cellulose, PVAP = polyvinyl acetate phthalate, HPMCP = hydroxypropyl methyl cellulose phthalate.

Control 8

Comparative composition Control 8 consisted of 5 mg of the crystalline form of Drug 3 alone.

Example 26

In vitro dissolution tests were performed to evaluate the performance of the amorphous dispersions of Examples 20-25 relative to the performance of Control 8. The SDD of Example 20 was evaluated in an in vitro dissolution test using a syringe/filter method. In this test, 10 mg of the SDD of Example 20 was added to 10 mL of MFD solution, comprising phosphate buffered saline with 14.7 mM sodium taurocholic acid and 2.8 mM of 1-palmitoyl-2-oleyl-sn-glycero-3-phosphocholine, pH 6.5, 290 mOsm/kg. The drug solution was added to a 10 mL polypropylene syringe fitted with a Titan PVDF 0.45 μ m filter. The syringe was attached to a vertical rotating wheel in a 37°C constant temperature chamber. At each sampling time, 13 drops were expelled from the syringe through the filter. The filtrate was then diluted 1:1 (by volume) with methanol and analyzed by high-performance liquid chromatography (HPLC). Between sampling times,

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the test solution was mixed as the syringe was rotated on the wheel at 37°C. Samples were collected at 0.5, 5, 30, 60, 180, and 1200 minutes.

In vitro dissolution tests for Examples 21-25
5 were performed using the same procedure described above for Example 20.

For Control 8, an in vitro dissolution test was performed using the procedure described above except that 5 mg of crystalline Drug 3 was used.

10 The concentrations of drug obtained in these samples are shown in Table 11 below.

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Table 11

Example	Time (mins)	Drug Concentration ($\mu\text{g}/\text{mL}$)	AUC ($\text{min} \cdot \mu\text{g}/\text{mL}$)
20	0	0	0
	0.5	25	6
	5	62	202
	30	112	2,400
	60	115	5,800
	180	120	19,900
	1200	14	
21	0	0	0
	0.5	8	2
	5	33	94
	30	121	2,000
	60	128	5,800
	180	114	20,300
	1200	13	
22	0	0	0
	0.5	12	3
	5	48	138
	30	112	2,100
	60	128	5,700
	180	106	19,800
	1200	13	
23	0	0	0
	0.5	14	4
	5	46	139
	30	106	2,000
	60	121	5,400
	180	127	20,300
	1200	13	
24	0	0	0
	0.5	24	6
	5	62	200
	30	94	2,200
	60	95	5,000
	180	91	16,100
	1200	11	
25	0	0	0
	0.5	6	2
	5	34	92
	30	89	1,600
	60	104	4,500
	180	17	11,800
	1200	9	
Control 8	0	0	0
	0.5	3	1
	5	8	26
	30	10	251
	60	10	551
	180	9	1,700
	1200	8	

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The results of these test are summarized in Table 12, which shows the maximum concentration of Drug 3 in solution after 180 minutes ($C_{\max 180}$), the aqueous area under the curve after 180 minutes (AUC_{180}), and the concentration at 1200 minutes (C_{1200}).

Table 12

Example	Dosage ($\mu\text{g/mL}$)	$C_{\max 180}$ ($\mu\text{g/mL}$)	AUC_{180} ($\text{min} \cdot \mu\text{g/mL}$)	C_{1200} ($\mu\text{g/mL}$)
20	500	120	19,900	14
21	500	133	20,300	13
22	500	127	19,800	13
23	500	127	20,300	13
24	500	97	16,100	11
25	500	104	11,800	9
Control 8	500	10	1,700	8

The results show that the performance of the SDD of Examples 20-25 was much better than that of the crystalline drug alone, with $C_{\max 180}$ values 9.7- to 13.3-fold that of Control 8, and AUC_{180} values 6.9- to 11.9-fold that of Control 8.

Examples 27-29

These examples disclose simple physical mixtures of a GPI and a concentration-enhancing polymer. Mixtures of Drug 1 and HPMCAS-MF were formed by dry mixing amorphous Drug 1 with HPMCAS-MF. For Example 27, the composition comprised 3.6 mg (75 wt%) Drug 1 and 1.2 mg (25 wt%) HPMCAS-MF; for Example 28, the composition comprised 3.6 mg (50 wt%) Drug 1 and 3.6 mg (50 wt%) HPMCAS-MF; for Example 29, the composition comprised 3.6 mg (25 wt%) Drug 1 and 10.8 mg (75 wt%) HPMCAS-MF.

These compositions were evaluated in in vitro dissolution tests using the procedures outlined in Example 10. The quantities of drug and polymer noted above were each added to a microcentrifuge tube, to which

was added 1.8 ml of PBS solution. The tube was vortexed immediately after adding the PBS solution. The results of these dissolution tests are given in Table 13, and summarized in Table 14.

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Table 13

Example	Time (mins)	Drug 1 Concentration ($\mu\text{g/mL}$)	AUC ($\text{min} \cdot \mu\text{g/mL}$)
27 75 wt% Drug 1/ 25 wt% HPMCAS-MF	0	0	0
	4	714	1,400
	10	737	5,800
	20	696	12,900
	40	690	26,800
	90	729	62,300
	180	684	125,800
28 50 wt% Drug 1/ 50 wt% HPMCAS-MF	1200	440	
	0	0	0
	4	377	755
	10	370	3,000
	20	836	9,000
	40	846	25,800
	90	898	69,500
29 25 wt% Drug 1/ 75 wt% HPMCAS-MF	180	918	151,200
	1200	627	
	0	0	0
	4	999	2,000
	10	1030	8,100
	20	1065	18,600
	40	1133	40,600
	90	1185	98,500
	180	1304	210,500
	1200	1379	

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Table 14

Example	Dosage ($\mu\text{g/mL}$)	$C_{\text{max},90}$ ($\mu\text{g/mL}$)	AUC_{90} ($\text{min} \cdot \mu\text{g/mL}$)	C_{1200} ($\mu\text{g/mL}$)
27	2000	729	62,300	440
28	2000	898	69,500	627
29	2000	1185	98,500	1379
Control 2	2000	586	20,600	203

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These simple physical mixtures of amorphous Drug 1 and HPMCAS-MF showed much better performance than the amorphous drug alone (Control 2, shown in Table 14 for comparison), with $C_{\text{max},90}$ values that were 1.24- to

2.0-fold that of Control 2, and AUC₉₀ values that were 3.0- to 4.8-fold that of Control 2.

Example 30

5 This example demonstrates another simple physical mixture of amorphous GPI and polymer. A coating solution comprising 7.5 wt% HPMCAS-MF dissolved in 92.5 wt% solvent (5 wt% water in acetone) was prepared and spray-coated onto Nu-Core Beads (45/60 mesh),
10 producing a thin coating of the polymer on the surface of the beads resulting in beads containing 12.2 wt% HPMCAS-MF. Samples of these beads (2.4 gm) were then mixed with 100 mg of amorphous Drug 1 (resulting in a drug:polymer ratio of 1:3 or 25 wt% Drug 1) and evaluated
15 in an in vitro dissolution test using the procedures outlined in Example 10. The results of the dissolution test are presented in Table 15.

Table 15

Example	Time (mins)	Drug 1 Concentration ($\mu\text{gA/mL}$)	AUC ($\text{min} \cdot \mu\text{g/mL}$)
30	0	0	0
	4	797	1,600
	10	1047	7,100
	20	1292	18,800
	40	1523	47,000
	90	1653	126,400
	180	1724	278,300
	1200	1885	

25 The physical mixture of HPMCAS-MF coated beads with amorphous Drug 1 showed improved performance over crystalline Drug 1 alone, with a $C_{\text{max}, 90}$ value that is
30 11-fold that of crystalline Drug 1 (Control 1) and an AUC₉₀ value that is 9.9-fold that of Control 1.

Example 31

A composition was formed by blending 50 wt% of
35 the SDD of Example 2 (containing 50 wt% Drug 1 and 50 wt%

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HPMCAS-MF) with 50 wt% HPMCAS-MF. This composition was evaluated in a dissolution test as described in Example 10. The results of this test are presented in Table 16, and show that the blend of the SDD with polymer performs well, with a $C_{max,90}$ value that is 6.6-fold that of the crystalline drug alone (Control 1) and an AUC_{90} value that is 6.2-fold that of Control 1.

Table 16

Example	Time (mins)	Drug 1 Concentration ($\mu\text{g/mL}$)	AUC ($\text{min} \cdot \mu\text{g/mL}$)
31	0	0	0
	4	766	1,500
	10	840	6,400
	20	874	14,900
	40	884	32,500
	90	979	79,100
	1200	1133	

Examples 32-35

An amorphous solid dispersion of 50 wt% Drug 1 and 50 wt% polymer was made by mixing Drug 1 in a solvent together with HPMCAS-MF to form a solution. The solution comprised 7.5 wt% Drug 1, 7.5 wt% HPMCAS, 80.75 wt% acetone and 4.25 wt% water. This solution was then spray-dried by directing an atomizing spray using a two-fluid external-mix spray nozzle at 2.7 bar (37 psig) at a feed rate of 175 g/min into the stainless-steel chamber of a Niro spray-dryer, maintained at a temperature of 175°C at the inlet and 70°C at the outlet.

The resulting amorphous solid spray-dried dispersion (SDD) was collected via a cyclone and then dried in a Gruenberg solvent tray-dryer by spreading the spray-dried particles onto polyethylene-lined trays to a depth of not more than 1 cm and then drying them at 40°C for 16 hours.

The SDD above was incorporated into tablets containing 25, 50, 100, and 200 mg. Tablets with a dose of 25 mg (Example 32) consisted of 7.14 wt% SDD, 40.0 wt%

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HPMCAS-MF, 49.11 wt% microcrystalline cellulose (Avicel® PH 102), 3.0 wt% croscarmellose sodium (Ac-Di-Sol®), and 0.75 wt% magnesium stearate. Tablets with a dose of 50 mg (Example 33) consisted of 14.29 wt% SDD, 40.0 wt% HPMCAS-MF, 41.96 wt% Avicel® PH 102, 3.0 wt% Ac-Di-Sol®, and 0.75 wt% magnesium stearate. Tablets with a dose of 100 mg (Example 34) consisted of 28.57 wt% SDD, 30.0 wt% HPMCAS-MF, 37.68 wt% Avicel® PH 102, 3.0 wt% Ac-Di-Sol®, and 0.75 wt% magnesium stearate. Tablets with a dose of 200 mg (Example 35) consisted of 57.14 wt% SDD, 39.11 wt% Avicel® PH 102, 3.0 wt% Ac-Di-Sol®, and 0.75 wt% magnesium stearate. In each case, the targeted tablet weight was 700 mg.

To form the tablets, the SDD was first granulated (roller compacted) on a Freund TF-mini roller compactor using an auger speed of 30 rpm, a roller speed of 4 rpm, and a roller pressure of 30 Kg_r/cm². The resulting compacted material was then reduced using a mini-Comil at a power setting of 4, with sieve 039R. The milled SDD was then blended in a V-blender with the HPMCAS-MF, Avicel®, and Ac-Di-Sol® for 20 minutes using the proportions noted above. Next, a portion of the magnesium stearate (about 20 wt% of the total magnesium stearate used) was added and the material was blended for 5 minutes. The blend was then granulated again using an auger speed of 20 rpm, a roller speed of 4 rpm, and a roller pressure of 30 Kg_r/cm². The resulting compacted material was then reduced using a Comill with a power setting of 3 and a sieve size of 032R. The remaining magnesium stearate was then added, and the material was blended for 5 minutes in a V-blender. This material was then formed into tablets using 0.3437 x 0.6875-inch oval tooling on a Kilian T-100 tablet press with precompression of 1 to 2 kN and a compression force of 10 kN.

To test *in vitro* drug dissolution, one of each of the tablets was each placed in 200 mL of a gastric

buffer solution (0.1 N HCl at pH 1.2) for 30 minutes at 37°C and stirred, after which 50 mL of a pH 13 buffer solution was added to produce a final pH of 7.5 and a final volume of 250 mL. The drug concentration was determined over time by periodically withdrawing samples, centrifuging the samples to remove any undissolved drug, diluting the supernatant in methanol, analyzing the samples by HPLC, and calculating drug concentrations. The concentrations of drug obtained in *in vitro* dissolution tests are shown in Table 17 below.

Table 17

Example	Time (mins)	Drug 1 Concentration ($\mu\text{g/mL}$)	AUC ($\text{min} \cdot \mu\text{g/mL}$)
32 25 mg	0	0	0
	5	6	16
	15	13	110
	20	15	178
	35	25	478
	45	30	755
	60	36	1,300
	75	43	1,800
	90	50	2,500
	120	58	4,200
	180	65	7,900
	1200	96	90,200
33 50 mg	0	0	0
	5	9	24
	15	19	166
	20	23	271
	35	42	755
	45	61	1,300
	60	82	2,300
	75	99	3,700
	90	111	5,300
	120	130	8,900
	180	152	17,400
	1200	202	197,800

Example	Time (mins)	Drug 1 Concentration ($\mu\text{g/mL}$)	AUC ($\text{min} \cdot \mu\text{g/mL}$)
34 100 mg	0	0	0
	5	20	49
	15	43	361
	20	50	594
	35	112	1,800
	45	150	3,100
	60	186	5,700
	75	199	8,500
	90	213	11,600
	120	236	18,300
	180	260	33,200
	1200	381	360,300
35 200 mg	0	0	0
	5	26	64
	15	64	514
	20	81	878
	35	168	2,800
	45	424	5,700
	60	470	12,400
	75	479	19,500
	90	502	26,900
	120	518	42,200
	180	522	73,400
	1200	298	491,000

The data demonstrate that approximately all of the drug had been released by 1200 minutes.

Example 36

An amorphous solid dispersion of 67 wt% Drug 3 and 33 wt% polymer was made by mixing Drug 3 in the solvent acetone together with HPMCAS-MF to form a solution. The solution comprised 3.33 wt% Drug 3, 1.67 wt% HPMCAS-MF, and 95 wt% acetone. This solution was then spray-dried by directing an atomizing spray using a two-fluid external-mix spray nozzle at 0.6 bar at a feed rate of 75 g/min into the stainless-steel chamber of a Niro PSD-1 spray-dryer, maintained at a temperature of 120°C at the inlet and 76°C at the outlet.

The resulting amorphous solid spray-dried dispersion (SDD) was collected via a cyclone and then dried in a Gruenberg solvent tray-dryer by spreading the spray-dried particles onto polyethylene-lined trays to a

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depth of not more than 1 cm and then drying them at 40°C for at least 8 hours.

Example 37

5 Capsules containing a total mass of 500 mg were prepared using the SDD of Drug 3 from Example 36. Each capsule contained 60 wt% of the SDD, 15 wt% Fast Flo lactose, 15 wt% Avicel PH-102, 7 wt% Explotab, 2 wt% sodium lauryl sulfate, and 1 wt% magnesium stearate,
10 resulting in capsules containing 200 mg of Drug 3.

Example 38

Tablets with a total mass of 600 mg were prepared containing 50 wt% SDD from Example 36, 32 wt%
15 Avicel PH-102, 11 wt% Fast Flo lactose, 5 wt% Explotab, 1 wt% sodium lauryl sulfate, and 1 wt% magnesium stearate, resulting in tablets containing 200 mg of Drug 3.

Examples 39-40

20 Capsules with a total mass of 600 mg were prepared, each capsule containing 50 wt% SDD from Example 36, 32 wt% Avicel PH-102, 11 wt% Fast Flo lactose, 5 wt% Explotab, 1 wt% sodium lauryl sulfate, and
25 1 wt% magnesium stearate (Example 39), resulting in capsules containing 200 mg of Drug 3. Example 40 was prepared by coating the capsules of Example 38 with cellulose acetate phthalate.

Example 41

30 The dosage forms of Examples 37 to 40 were tested in *in vivo* tests. Beagle dogs that had fasted overnight were dosed with capsules and tablets from Examples 37 to 40, along with 50 mL of water. Blood was
35 collected from the jugular vein of the dogs before dosing and at various time points after dosing. To 100 μ L of each plasma sample, 5 mL of methyl-tert-butyl ether

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(MTBE) and 1 mL of 500 mM sodium carbonate buffer (pH 9) were added; the sample was vortexed for 1 minute and then centrifuged for 5 minutes. The aqueous portion of the sample was frozen in a dry-ice/acetone bath, and the MTBE layer was decanted and evaporated in a vortex evaporator. Dried samples were reconstituted in 100 μ L of mobile phase (33% acetonitrile and 67% of 0.1% formic acid in water). Analysis was carried out by HPLC.

As a control (Control 9), an OPC was formed using the crystalline form of Drug 3 as follows. An aqueous suspension of 200 mg of crystalline drug was prepared in 2 wt% Polysorbate 80 in water. Oral administration of the aqueous drug suspensions was facilitated using an oral gavage equipped with a polyethylene tube insert. The polyethylene tube insert was used to accurately deliver the desired volume of dose by displacement, without the need for additional volume of water to rinse the tube.

The results of these tests are shown in Table 18, where C_{max} is the maximum concentration of Drug 3 in the blood plasma, AUC_{0-24} is the area under the curve in the first 24 hours, and Relative Bioavailability is the AUC in the blood of the test dose divided by the AUC in the blood of the reference dose (Control 9). The results show that the relative bioavailabilities obtained with the dosage forms of the present invention are 2.8 to 6.2 relative to Control 9. Furthermore, the C_{max} of the dosage forms of the present invention were 2.6-fold to 4.7-fold that of Control 9.

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Table 18

Example	Formulation	Dose (mg)	C _{max} (μg/mL)	AUC ₀₋₂₄ (μg-hr/mL)	Relative Bioavailability
Control	Crystalline suspension	200	1.03 ± 0.57	6.48 ± 3.60	—
37	Capsule	200	3.81 ± 2.39	31.75 ± 18.61	6.0
38	Tablet	200	2.84 ± 2.04	26.09 ± 21.43	4.2
39	Capsule	200	4.86 ± 2.30	40.55 ± 20.74	6.2
40	CAP coated Capsule	200	2.67 ± 2.45	18.08 ± 12.21	2.8

The terms and expressions which have been employed in the foregoing specification are used therein as terms of description and not of limitation, and there is no intention, in the use of such terms and expressions, of excluding equivalents of the features shown and described or portions thereof, it being recognized that the scope of the invention is defined and limited only by the claims which follow.

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CLAIMS

1. A pharmaceutical composition comprising a
glycogen phosphorylase inhibitor and a concentration-
5 enhancing polymer wherein a portion of said glycogen
phosphorylase inhibitor binds to a portion or all
portions of the following residues of a glycogen
phosphorylase enzyme:

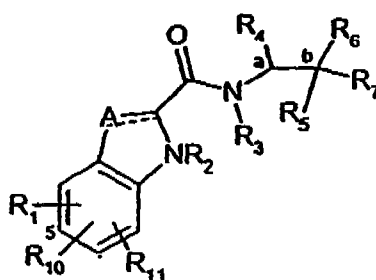
10	parent secondary	
	<u>structure</u>	<u>residue number</u>
		13-23
	helix α 1	24-37
15	turn	38-39, 43, 46-47
	helix α 2	48-66, 69-70, 73-74, 76-78
		79-80
	strand β 1	81-86
		87-88
20	strand β 2	89-92
		93
	helix α 3	94-102
		103
	helix α 4	104-115
25		116-117
	helix α 5	118-124
		125-128
	strand β 3	129-131
		132-133
30	helix α 6	134-150
		151-152
	strand β 4	153-160
		161

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	strand β 4b	162-163 164-166
	strand β 5	167-171 172-173
5	strand β 6	174-178 179-190
	strand β 7	191-192 194, 197
	strand β 8	198-209
10		210-211
	strand β 9	212-216
	strand β 10	219-226, 228-232 233-236
	strand β 11	237-239, 241, 243-247
15		248-260
	helix α 7	261-276
	strand β 11b	277-281
	reverse turn	282-289
	helix α 8	290-304.

2. A pharmaceutical composition comprising a glycogen phosphorylase inhibitor and a concentration-enhancing polymer, said glycogen phosphorylase inhibitor having the structure of Formula I:



Formula I

or the pharmaceutically acceptable salts or produrgs thereof wherein the dotted line (---) is an optional bond;

A is $-C(H)=$, $-C((C_1-C_4)alkyl)=$ or $-C(halo)=$ when the dotted line (---) is a bond, or A is methylene or $-CH((C_1-C_4)alkyl)-$ when the dotted line (---) is not a bond;

- 5 R_1 , R_{10} or R_{11} are each independently H, halo, 4-, 6- or 7-nitro, cyano, $(C_1-C_4)alkyl$, $(C_1-C_4)alkoxy$, fluoromethyl, difluoromethyl or trifluoromethyl;
- R_2 is H;
- R_3 is H or $(C_1-C_5)alkyl$;
- 10 R_4 is H, methyl, ethyl, n-propyl, hydroxy $(C_1-C_3)alkyl$, $(C_1-C_3)alkoxy(C_1-C_3)alkyl$, phenyl $(C_1-C_4)alkyl$, phenylhydroxy $(C_1-C_4)alkyl$, phenyl $(C_1-C_4)alkoxy(C_1-C_4)alkyl$, thien-2- or -3-yl $(C_1-C_4)alkyl$ or fur-2- or -3-yl $(C_1-C_4)alkyl$ wherein
- 15 said R_4 rings are mono-, di- or tri-substituted independently on carbon with H, halo, $(C_1-C_4)alkyl$, $(C_1-C_4)alkoxy$, trifluoromethyl, hydroxy, amino or cyano; or
- R_4 is pyrid-2-, -3- or -4-yl $(C_1-C_4)alkyl$,
- 20 thiazol-2-, -4- or -5-yl $(C_1-C_4)alkyl$, imidazol-1-, -2-, -4- or -5-yl $(C_1-C_4)alkyl$, pyrrol-2- or -3-yl $(C_1-C_4)alkyl$, oxazol-2-, -4- or -5-yl $(C_1-C_4)alkyl$, pyrazol-3-, -4- or -5-yl $(C_1-C_4)alkyl$, isoxazol-3-, -4-, -5-yl $(C_1-C_4)alkyl$, isothiazol-3-, -4-, -5-yl $(C_1-C_4)alkyl$, pyridazin-3- or
- 25 -4-yl $(C_1-C_4)alkyl$, pyrimidin-2-, -4-, -5- or -6-yl $(C_1-C_4)alkyl$, pyrazin-2- or -3-yl $(C_1-C_4)alkyl$ or 1,3,5-triazin-2-yl $(C_1-C_4)alkyl$, wherein said preceding R_4 heterocycles are optionally mono- or di-substituted independently with halo, trifluoromethyl, $(C_1-C_4)alkyl$,
- 30 $(C_1-C_4)alkoxy$, amino or hydroxy and said mono- or di-substituents are bonded to carbon;
- R_5 is H, hydroxy, fluoro, $(C_1-C_3)alkyl$, $(C_1-C_3)alkoxy$, $(C_1-C_6)alkanoyl$, amino $(C_1-C_4)alkoxy$, mono-N- or di-N,N- $(C_1-C_4)alkylamino(C_1-C_4)alkoxy$,
- 35 carboxy $(C_1-C_4)alkoxy$, $(C_1-C_3)alkoxy-carbonyl(C_1-C_4)alkoxy$, benzyloxycarbonyl $(C_1-C_4)alkoxy$, or carbonyloxy wherein said carbonyloxy is carbon-carbon linked with phenyl,

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thiazolyl, imidazolyl, 1H-indolyl, furyl, pyrrolyl, oxazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl or 1,3,5-triazinyl and wherein said preceding R₃ rings are optionally
 5 monosubstituted with halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, hydroxy, amino or trifluoromethyl and said mono-substituents are bonded to carbon;

R₇ is H, fluoro or (C₁-C₅)alkyl; or

R₅ and R₇ taken together are oxo;

10 R₆ is carboxy or (C₁-C₈)alkoxycarbonyl, C(O)NR₈R₉ or C(O)R₁₂ wherein

R₈ is H, (C₁-C₃)alkyl, hydroxy or (C₁-C₃)alkoxy;

and

15 R₉ is H, (C₁-C₈)alkyl, hydroxy, (C₁-C₈)alkoxy, methylene-perfluorinated(C₁-C₈)alkyl, phenyl, pyridyl, thienyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, piperidinyl, morpholinyl, pyridazinyl, pyrimidinyl,
 20 pyrazinyl, piperazinyl or 1,3,5-triazinyl wherein said preceding R₉ rings are carbon-nitrogen linked; or

R₉ is mono-, di- or tri-substituted

(C₁-C₅)alkyl, wherein said substituents are independently H, hydroxy, amino, mono-N- or di-N,N-(C₁-C₅)alkylamino; or

25 R₉ is mono- or di-substituted (C₁-C₅)alkyl,

wherein said substituents are independently phenyl, pyridyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl,

30 pyridinyl, piperidinyl, morpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl or 1,3,5-triazinyl

wherein the nonaromatic nitrogen-containing R₉ rings are optionally mono-substituted on nitrogen with (C₁-C₆)alkyl, benzyl, benzoyl or (C₁-C₆)alkoxycarbonyl and
 35 wherein the R₉ rings are optionally mono-substituted on carbon with halo, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, hydroxy, amino, or mono-N- and di-N,N (C₁-C₅)alkylamino provided

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that no quaternized nitrogen is included and there are no nitrogen-oxygen, nitrogen-nitrogen or nitrogen-halo bonds;

5 R_{12} is piperazin-1-yl, 4-(C_1-C_4)alkylpiperazin-1-yl, 4-formylpiperazin-1-yl, morpholino, thiomorpholino, 1-oxothiomorpholino, 1,1-dioxo-thiomorpholino, thiazolidin-3-yl, 1-oxo-thiazolidin-3-yl, 1,1-dioxo-thiazolidin-3-yl, 2-(C_1-C_6)alkoxycarbonylpyrrolidin-1-yl, oxazolidin-3-yl or 2(R)-hydroxymethylpyrrolidin-1-yl; or

10 R_{12} is 3- and/or 4-mono- or di-substituted oxazetidin-2-yl, 2-, 4-, and/or 5- mono- or di-substituted oxazolidin-3-yl, 2-, 4-, and/or 5- mono- or di-substituted thiazolidin-3-yl, 2-, 4- and/or 5- mono- or di-substituted 1-oxothiazolidin-3-yl, 2-, 4-,
15 and/or 5- mono- or di-substituted 1,1-dioxothiazolidin-3-yl, 3- and/or 4- mono- or di-substituted pyrrolidin-1-yl, 3-, 4- and/or 5-, mono-, di- or tri-substituted piperidin-1-yl, 3-, 4-, and/or 5- mono-, di-, or tri-substituted piperazin-1-yl, 3-substituted
20 azetidin-1-yl, 4- and/or 5-, mono- or di-substituted 1,2-oxazinan-2-yl, 3- and/or 4- mono- or di-substituted pyrazolidin-1-yl, 4- and/or 5-, mono- or di-substituted isoxazolidin-2-yl, 4- and/or 5-, mono- and/or di-substituted isothiazolidin-2-yl wherein said R_{12}
25 substituents are independently H, halo, (C_1-C_5)alkyl, hydroxy, amino, mono-N- or di-N,N-(C_1-C_5)alkylamino, formyl, oxo, hydroxyimino, (C_1-C_5)alkoxy, carboxy, carbamoyl, mono-N- or di-N,N-(C_1-C_5)alkylcarbamoyl, (C_1-C_4)alkoxyimino, (C_1-C_4)alkoxymethoxy,
30 (C_1-C_6)alkoxycarbonyl, carboxy(C_1-C_5)alkyl or hydroxy(C_1-C_5)alkyl;

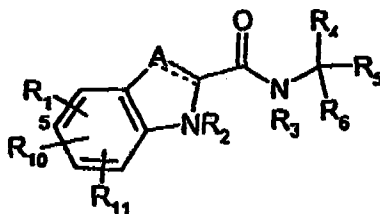
with the proviso that if R_4 is H, methyl, ethyl or n-propyl, R_5 is OH;

35 with the proviso that if R_5 and R_7 are H, then R_4 is not H, methyl, ethyl, n-propyl, hydroxy(C_1-C_3)alkyl or (C_1-C_3)alkoxy(C_1-C_3)alkyl and R_6 is $C(O)NR_8R_9$, $C(O)R_{12}$ or (C_1-C_4)alkoxycarbonyl.

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3. A pharmaceutical composition comprising a glycogen phosphorylase inhibitor and a concentration-enhancing polymer, wherein said glycogen phosphorylase inhibitor has the structure of Formula II:



Formula II

or the pharmaceutically acceptable salts or prodrugs thereof wherein the dotted line (---) is an optional bond:

A is $-C(H)=$, $-C((C_1-C_4)alkyl)=$, $-C(halo)=$ or $-N=$, when the dotted line (---) is a bond, or A is methylene or $-CH((C_1-C_4)alkyl)-$, when the dotted line (---) is not a bond;

R_1 , R_{10} or R_{11} are each independently H, halo, cyano, 4-, 6- or 7-nitro, $(C_1-C_4)alkyl$, $(C_1-C_4)alkoxy$, fluoromethyl, difluoromethyl or trifluoromethyl;

R_2 is H;

R_3 is H or $(C_1-C_3)alkyl$;

R_4 is H, methyl, ethyl, n-propyl, hydroxy $(C_1-C_3)alkyl$, $(C_1-C_3)alkoxy(C_1-C_3)alkyl$, phenyl $(C_1-C_4)alkyl$, phenylhydroxy $(C_1-C_4)alkyl$, (phenyl)((C_1-C_4)-alkoxy) $(C_1-C_4)alkyl$, thien-2- or -3-yl $(C_1-C_4)alkyl$ or fur-2- or -3-yl $(C_1-C_4)alkyl$ wherein said R_4 rings are mono-, di- or tri-substituted independently on carbon with H, halo, $(C_1-C_4)alkyl$, $(C_1-C_4)alkoxy$, trifluoromethyl, hydroxy, amino, cyano or 4,5-dihydro-1H-imidazol-2-yl; or

R_4 is pyrid-2-, -3- or -4-yl $(C_1-C_4)alkyl$, thiazol-2-, -4- or -5-yl $(C_1-C_4)alkyl$, imidazol-2-, -4-, or -5-yl $(C_1-C_4)alkyl$, pyrrol-2- or -3-yl $(C_1-C_4)alkyl$, oxazol-2-, -4- or -5-yl $(C_1-C_4)alkyl$, pyrazol-3-, -4- or

-5-yl (C₁-C₄)alkyl, isoxazol-3-, -4- or -5-yl (C₁-C₄)alkyl, isothiazol-3-, -4- or -5-yl (C₁-C₄)alkyl, pyridazin-3- or -4-yl (C₁-C₄)alkyl, pyrimidin-2-, -4-, -5- or -6-yl (C₁-C₄)alkyl, pyrazin-2- or -3-yl (C₁-C₄)alkyl,

- 5 1,3,5-triazin-2-yl (C₁-C₄)alkyl or indol-2-(C₁-C₄)alkyl, wherein said preceding R₄ heterocycles are optionally mono- or di-substituted independently with halo, trifluoromethyl, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, amino, hydroxy or cyano and said substituents are bonded to
- 10 carbon; or

- R₄ is R₁₅-carbonyloxymethyl, wherein said R₁₅ is phenyl, thiazolyl, imidazolyl, 1H-indolyl, furyl, pyrrolyl, oxazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl or
- 15 1,3,5-triazinyl and wherein said preceding R₁₅ rings are optionally mono- or di-substituted independently with halo, amino, hydroxy, (C₁-C₄)alkyl, (C₁-C₄)alkoxy or trifluoromethyl and said mono- or di-substituents are bonded to carbon;

- 20 R₅ is H, methyl, ethyl, n-propyl, hydroxymethyl or hydroxyethyl;

R₆ is carboxy, (C₁-C₈)alkoxycarbonyl, benzyloxycarbonyl, C(O)NR₈R₉ or C(O)R₁₂

- wherein R₈ is H, (C₁-C₆)alkyl, cyclo
- 25 (C₃-C₆)alkyl, cyclo(C₃-C₆)alkyl (C₁-C₃)alkyl, hydroxy or (C₁-C₈)alkoxy; and

- R₉ is H, cyclo(C₃-C₈)alkyl, cyclo(C₃-C₈)alkyl (C₁-C₃)alkyl, cyclo(C₄-C₇)alkenyl, cyclo(C₃-C₇)alkyl (C₁-C₃)alkoxy, cyclo(C₃-C₇)alkyloxy,
- 30 hydroxy, methylene-perfluorinated (C₁-C₈)alkyl, phenyl, or a heterocycle wherein said heterocycle is pyridyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, pyridinyl, piperidinyl,
- 35 morpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, thiochromanyl or

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tetrahydrobenzothiazolyl wherein said heterocycle rings are carbon-nitrogen linked; or

R_9 is (C_1-C_6) alkyl or (C_1-C_6) alkoxy wherein said (C_1-C_6) alkyl or (C_1-C_6) alkoxy is optionally monosubstituted
 5 with cyclo (C_4-C_7) alken-1-yl, phenyl, thienyl, pyridyl, furyl, pyrrolyl, pyrrolidinyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, pyranyl, piperidinyl, morpholinyl, thiomorpholinyl, 1-oxothiomorpholinyl,
 10 1,1-dioxothiomorpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl or indolyl and wherein said (C_1-C_6) alkyl or (C_1-C_6) alkoxy are optionally additionally independently mono- or di-substituted with
 15 halo, hydroxy, (C_1-C_5) alkoxy, amino, mono-N- or di-N,N- (C_1-C_5) alkylamino, cyano, carboxy, or (C_1-C_4) alkoxycarbonyl; and

wherein the R_9 rings are optionally mono- or di-substituted independently on carbon with halo, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, hydroxy, hydroxy (C_1-C_4) alkyl,
 20 amino (C_1-C_4) alkyl, mono-N- or di-N,N- (C_1-C_4) alkylamino (C_1-C_4) alkyl, (C_1-C_4) alkoxy (C_1-C_4) alkyl, amino, mono-N- or di-N,N- (C_1-C_4) alkylamino, cyano, carboxy, (C_1-C_5) alkoxycarbonyl, carbamoyl, formyl or trifluoromethyl and said R_9 rings may optionally be
 25 additionally mono- or di-substituted independently with (C_1-C_5) alkyl or halo;

with the proviso that no quaternized nitrogen on any R_9 heterocycle is included;

R_{12} is morpholino, thiomorpholino,
 30 1-oxothiomorpholino, 1,1-dioxothiomorpholino, thiazolidin-3-yl, 1-oxothiazolidin-3-yl, 1,1-dioxothiazolidin-3-yl, pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, piperazin-4-yl, azetidin-1-yl, 1,2-oxazinan-2-yl, pyrazolidin-1-yl,
 35 isoxazolidin-2-yl, isothiazolidin-2-yl, 1,2-oxazetidin-2-yl, oxazolidin-3-yl, 3,4-dihydroisoquinolin-2-yl, 1,3-dihydroisoindol-2-yl,

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3,4-dihydro-2H-quinol-1-yl, 2,3-dihydro-
benzo[1,4]oxazin-4-yl, 2,3-dihydro-benzo[1,4]-
thiazine-4-yl, 3,4-dihydro-2H-quinoxalin-1-yl,
3,4-dihydro-benzo[c][1,2]oxazin-1-yl, 1,4-dihydro-
5 benzo[d][1,2]oxazin-3-yl, 3,4-dihydro-benzo[e][1,2]-
oxazin-2-yl, 3H-benzo[d]isoxazol-2-yl,
3H-benzo[c]isoxazol-1-yl or azepan-1-yl,

wherein said R_{12} rings are optionally mono-, di-
or tri-substituted independently with halo, (C_1-C_5) alkyl,
10 (C_1-C_5) alkoxy, hydroxy, amino, mono-N- or
di-N,N- (C_1-C_5) alkylamino, formyl, carboxy, carbamoyl,
mono-N- or di-N,N- (C_1-C_5) alkylcarbamoyl, (C_1-C_6) alkoxy
 (C_1-C_3) alkoxy, (C_1-C_5) alkoxycarbonyl, benzyloxycarbonyl,
 (C_1-C_5) alkoxycarbonyl (C_1-C_5) alkyl,
15 (C_1-C_4) alkoxycarbonylamino, carboxy (C_1-C_5) alkyl,
carbamoyl (C_1-C_5) alkyl, mono-N- or
di-N,N- (C_1-C_5) alkylcarbamoyl (C_1-C_5) alkyl,
hydroxy (C_1-C_5) alkyl, (C_1-C_4) alkoxy (C_1-C_4) alkyl,
amino (C_1-C_4) alkyl, mono-N- or
20 di-N,N- (C_1-C_4) alkylamino (C_1-C_4) alkyl, oxo, hydroxyimino or
 (C_1-C_6) alkoxyimino and wherein no more than two
substituents are selected from oxo, hydroxyimino or
 (C_1-C_6) alkoxyimino and oxo, hydroxyimino or
 (C_1-C_6) alkoxyimino are on nonaromatic carbon; and
25 wherein said R_{12} rings are optionally
additionally mono- or di-substituted independently with
 (C_1-C_5) alkyl or halo;

with the proviso that when R_6 is
 (C_1-C_5) alkoxycarbonyl or benzyloxycarbonyl then R_1 is
30 5-halo, 5- (C_1-C_4) alkyl or 5-cyano and R_4 is
(phenyl) (hydroxy) (C_1-C_4) alkyl,
(phenyl) $((C_1-C_4)$ alkoxy) (C_1-C_4) alkyl, hydroxymethyl or
 $Ar(C_1-C_2)$ alkyl, wherein Ar is thien-2- or -3-yl, fur-2- or
-3-yl or phenyl wherein said Ar is optionally mono- or
35 di-substituted independently with halo; with the provisos
that when R_4 is benzyl and R_5 is methyl, R_{12} is not

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4-hydroxy-piperidin-1-yl or when R_4 is benzyl and R_5 is methyl R_6 is not $C(O)N(CH_3)_2$;

with the proviso that when R_1 and R_{10} and R_{11} are H, R_4 is not imidazol-4-ylmethyl, 2-phenylethyl or 2-hydroxy-2-phenylethyl;

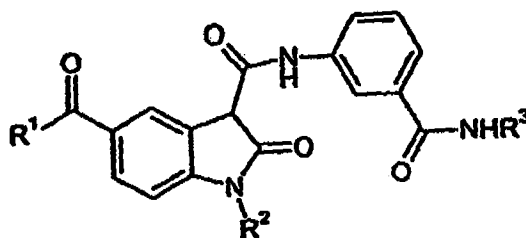
with the proviso that when R_8 and R_9 are n-pentyl, R_1 is 5-chloro, 5-bromo, 5-cyano, 5-(C_1-C_3)alkyl, 5-(C_1-C_3)alkoxy or trifluoromethyl;

with the proviso that when R_{12} is 3,4-dihydroisoquinol-2-yl, said 3,4-dihydroisoquinol-2-yl is not substituted with carboxy-(C_1-C_4)alkyl;

with the proviso that when R_8 is H and R_9 is (C_1-C_6)alkyl, R_9 is not substituted with carboxy or (C_1-C_4)alkoxycarbonyl on the carbon which is attached to the nitrogen atom N of NHR_9 ; and

with the proviso that when R_6 is carboxy and R_1 , R_{10} , R_{11} and R_5 are all H, then R_4 is not benzyl, H, (phenyl) (hydroxy)methyl, methyl, ethyl or n-propyl.

4. A pharmaceutical composition comprising a glycogen phosphorylase inhibitor and a concentration-enhancing polymer, wherein said glycogen phosphorylase inhibitor has the structure of Formula III:



Formula III

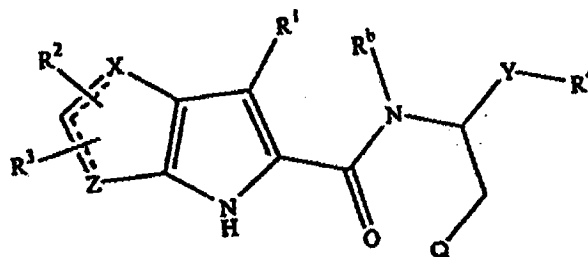
or a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug wherein:

R^1 is (C_1-C_4)alkyl, (C_1-C_7)cycloalkyl, phenyl or phenyl substituted with up to three (C_1-C_4)alkyl, (C_1-C_4)alkoxy or halogen;

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R^2 is (C_1-C_4) alkyl; and
 R^3 is (C_3-C_7) cycloalkyl; phenyl; phenyl
 substituted at the para position with (C_1-C_4) alkyl, halo,
 hydroxy (C_1-C_4) alkyl or trifluoromethyl; phenyl
 5 substituted at the meta position with fluoro; or phenyl
 substituted at the ortho position with fluoro.

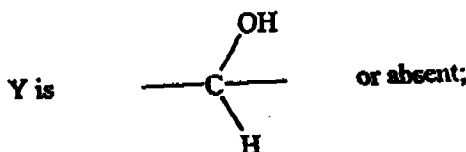
5. A pharmaceutical composition comprising a
 glycogen phosphorylase inhibitor and a concentration-
 10 enhancing polymer, wherein said glycogen phosphorylase
 inhibitor has the structure of Formula IV:



Formula IV

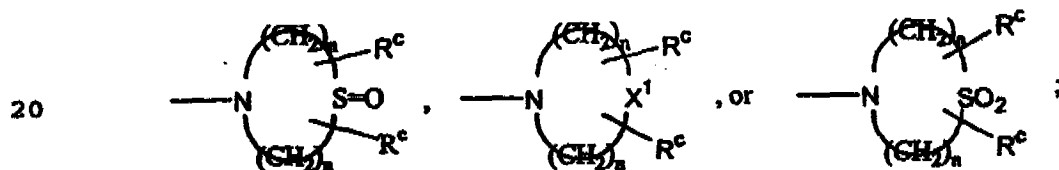
a stereoisomer, pharmaceutically acceptable salt or
 prodrug thereof, or a pharmaceutically acceptable salt of
 the prodrug,
 25 wherein
 Q is aryl, substituted aryl, heteroaryl, or substituted
 heteroaryl;
 each Z and X are independently (C, CH or CH_2), N, O or S;
 X^1 is NR^a , $-CH_2-$, O or S;
 30 each - - - - is independently a bond or is absent,
 provided that both - - - - are not simultaneously bonds;
 R^1 is hydrogen, halogen, $-OC_1-C_8$ alkyl, $-SC_1-C_8$ alkyl,
 $-C_1-C_8$ alkyl, $-CF_3$, $-NH_2$, $-NHC_1-C_8$ alkyl, $-N(C_1-C_8$ alkyl) $_2$, -
 NO_2 , $-CN$,
 35 $-CO_2H$, $-CO_2C_1-C_8$ alkyl, $-C_2-C_8$ alkenyl, or $-C_2-C_8$ alkynyl;
 each R^a and R^b is independently hydrogen or $-C_1-C_8$ alkyl;

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R² and R³ are independently hydrogen, halogen, -C₁-C₈alkyl, -CN, -C≡C-Si(CH₃)₃,
 -OC₁-C₈alkyl, -SC₁-C₈alkyl, -CF₃, -NH₂, -NHC₁-C₈alkyl, -
 10 N(C₁-C₈alkyl)₂,
 -NO₂, -CO₂H, -CO₂C₁-C₈alkyl, -C₂-C₈alkenyl, or -C₂-
 C₈alkynyl, or R² and R³ together with the atoms on the
 ring to which they are attached form a five or six
 15 membered ring containing from 0 to 3 heteroatoms and from
 0 to 2 double bonds;
 R⁴ is -C(=O)-A;
 A is -NR^aR^d, -NR^aCH₂CH₂OR^a,



each R^c is independently hydrogen, C₁-C₈alkyl, C₁-C₈alkoxy,
 aryl, substituted aryl, heteroaryl, or substituted
 25 heteroaryl;
 each R^c is independently hydrogen, -C(=O)OR^a, -OR^a, -SR^a,
 or -NR^aR^{a'} and
 each n is independently 1-3.

30 6. A pharmaceutical composition comprising a
 glycogen phosphorylase inhibitor and a concentration-
 enhancing polymer, said glycogen phosphorylase inhibitor
 having a solubility in aqueous solution, in the absence
 of said concentration-enhancing polymer, of less than
 35 1 mg/ml at any pH of from 1 to 8.

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7. A pharmaceutical composition comprising a glycogen phosphorylase inhibitor and a concentration-enhancing polymer, said composition providing a maximum concentration of said glycogen phosphorylase inhibitor in a use environment that is at least 1.25-fold the maximum concentration provided by a control composition comprising an equivalent amount of said glycogen phosphorylase inhibitor and free from said polymer.

10 8. A pharmaceutical composition comprising a glycogen phosphorylase inhibitor and a polymer, said composition providing a relative bioavailability that is at least 1.25 relative to a control composition comprising an equivalent amount of said glycogen phosphorylase inhibitor and free from said polymer.

9. The composition of any one of claims 1-8 wherein said composition is a solid amorphous dispersion.

20 10. The composition of claim 9 wherein said dispersion is substantially homogeneous.

25 11. The composition of claim 9 wherein a major portion of said glycogen phosphorylase inhibitor is amorphous.

30 12. The composition of claim 9 wherein said glycogen phosphorylase inhibitor is substantially amorphous.

13. The composition of claim 9 wherein said glycogen phosphorylase inhibitor is almost completely amorphous.

35 14. The composition of any one of claims 1-8 wherein said composition is a simple physical mixture.

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15. The composition of claim 14 wherein said mixture is substantially homogeneous.

16. The composition of claim 14 wherein a major portion of said glycogen phosphorylase inhibitor is amorphous.

17. The composition of claim 14 wherein said glycogen phosphorylase inhibitor is substantially amorphous.

18. The composition of claim 14 wherein said glycogen phosphorylase inhibitor is almost completely amorphous.

19. The composition of any one of claims 1-8 wherein said glycogen phosphorylase inhibitor is in a solid amorphous dispersion and only a portion of said concentration-enhancing polymer is present in said dispersion.

20. The composition of claim 1 wherein a portion of said glycogen phosphorylase inhibitor binds to one or more of the following residues of said glycogen phosphorylase enzyme in one or both subunits:

	parent secondary structure	residue number
		13-23
30	helix α 1	24-37
	turn	38-39, 43, 46-47
	helix α 2	48-66, 69-70, 73-74, 76-78
		79-80
	strand β 2	91-92
35		93
	helix α 3	94-102
		103

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	helix α 4	104-115
		116-117
	helix α 5	118-124
		125-128
5	strand β 3	129-130
	strand β 4	159-160
		161
	strand β 4b	162-163
		164-166
10	strand β 5	167-168
	strand β 6	178
		179-190
	strand β 7	191-192
		194, 197
15	strand β 9	198-200
	strand β 10	220-226
		228-232
		233-236
	strand β 11	237-239, 241, 243-247
20		248-260
	helix α 7	261-276
	strand β 11b	277-280

21. The composition of claim 1 wherein a
 25 portion of said glycogen phosphorylase inhibitor binds to
 a portion or all portions of the following residues of
 said glycogen phosphorylase enzyme in one or both
 subunits:

30	<u>residue number</u>
	33-39
	49-66
	94
	98
35	102
	125-126
	160

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162
182-192
197
224-226
5 228-231
238-239
241
245
247

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22. The composition of claim 1 wherein a portion of said glycogen phosphorylase inhibitor binds to a portion or all portions of the following residues of said glycogen phosphorylase enzyme in one or both
15 subunits:

residue number
37-39
53
20 57
60
63-64
184-192
226
25 229

23. The composition of any one of claims 2-8 wherein a portion of said glycogen phosphorylase inhibitor binds to a portion or all portions of the
30 following residues of a glycogen phosphorylase enzyme:

	<u>parent secondary structure</u>	<u>residue number</u>
		13-23
35	helix $\alpha 1$	24-37
	turn	38-39, 43, 46-47
	helix $\alpha 2$	48-66, 69-70, 73-74, 76-78
		79-80

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	strand β 1	81-86 87-88
	strand β 2	89-92 93
5	helix α 3	94-102 103
	helix α 4	104-115 116-117
	helix α 5	118-124 125-128
10	strand β 3	129-131 132-133
	helix α 6	134-150 151-152
15	strand β 4	153-160 161
	strand β 4b	162-163 164-166
	strand β 5	167-171 172-173
20	strand β 6	174-178 179-190
	strand β 7	191-192 194, 197
25	strand β 8	198-209 210-211
	strand β 9	212-216
	strand β 10	219-226, 228-232 233-236
30	strand β 11	237-239, 241, 243-247 248-260
	helix α 7	261-276
	strand β 11b	277-281
	reverse turn	282-289
35	helix α 8	290-304

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24. The composition of claim 23 wherein a portion of said glycogen phosphorylase inhibitor binds to a portion or all portions of the following residues of said glycogen phosphorylase enzyme in one or both subunits:

	parent secondary structure	residue number
		13-23
10	helix α 1	24-37
	turn	38-39, 43, 46-47
	helix α 2	48-66, 69-70, 73-74, 76-78
		79-80
	strand β 2	91-92
15		93
	helix α 3	94-102
		103
	helix α 4	104-115
		116-117
20	helix α 5	118-124
		125-128
	strand β 3	129-130
	strand β 4	159-160
		161
25	strand β 4b	162-163
		164-166
	strand β 5	167-168
	strand β 6	178
		179-190
30	strand β 7	191-192
		194, 197
	strand β 9	198-200
	strand β 10	220-226
		228-232
35		233-236

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strand β 11	237-239, 241, 243-247
	248-260
helix α 7	261-276
strand β 11b	277-280

5

25. The composition of claim 23 wherein a portion of said glycogen phosphorylase inhibitor binds to a portion or all portions of the following residues of said glycogen phosphorylase enzyme in one or both subunits:

10

residue number

33-39
49-66
94
98
102
125-126
160
162
182-192
197
224-226
228-231
238-239
241
245
247

15

20

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26. The composition of claim 23 wherein a portion of said glycogen phosphorylase inhibitor binds to a portion or all portions of the following residues of said glycogen phosphorylase enzyme in one or both subunits:

	<u>residue number</u>
	37-39
	53
10	57
	60
	63-64
	184-192
	226
15	229

27. The composition of any one of claims 1 and 6-8 wherein said glycogen phosphorylase inhibitor has the structure of Formula I defined in claim 2.

28. The composition of claim 2 wherein said glycogen phosphorylase inhibitor is selected from the group consisting of 5-chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-dimethylcarbamoylmethyl)-2-phenylethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-methoxy-methylcarbamoylmethyl)-2-phenylethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3S)-hydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3R,4R)-dihydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide, and 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-morpholin-4-yl-3-oxo-propyl]-amide.

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29. The composition of claim 27 wherein said glycogen phosphorylase inhibitor is selected from the group consisting of 5-chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-dimethylcarbamoylmethyl)-2-phenyl-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-((R)-hydroxy-methoxy-methylcarbamoylmethyl)-2-phenyl-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3S)-hydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3R,4R)-dihydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide, and 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-morpholin-4-yl-3-oxo-propyl]-amide.

30. The composition of any one of claims 1 and 6-8 wherein said glycogen phosphorylase inhibitor has the structure of Formula II defined in claim 3.

31. The composition of claim 3 wherein said glycogen phosphorylase inhibitor is selected from the group consisting of 5-chloro-1H-indole-2-carboxylic acid [2-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-(4-fluoro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide, and 5-chloro-1H-indole-2-carboxylic acid [2-(1-oxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide.

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32. The composition of claim 30 wherein said glycogen phosphorylase inhibitor is selected from the group consisting of 5-chloro-1H-indole-2-carboxylic acid [2-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3S,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-((3R,4S)-3,4-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-(4-fluoro-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [(1S)-benzyl-2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-amide, 5-chloro-1H-indole-2-carboxylic acid [2-(1,1-dioxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide, and 5-chloro-1H-indole-2-carboxylic acid [2-(1-oxo-thiazolidin-3-yl)-2-oxo-ethyl]-amide.

33. The composition of any one of claims 1 and 6-8 wherein said glycogen phosphorylase inhibitor has the structure of Formula III as defined in claim 4.

34. The composition of claim 4 wherein said glycogen phosphorylase inhibitor is selected from the group consisting of 5-acetyl-1-ethyl-2,3-dihydro-2-oxo-N-[3-[(phenylamino)carbonyl]phenyl]-1H-Indole-3-carboxamide, 5-acetyl-N-[3-[(cyclohexylamino)carbonyl]phenyl-1-ethyl-2,3-dihydro-2-oxo-1H-Indole-3-carboxamide, and 5-acetyl-N-[3-[(4-bromophenyl)amino]carbonyl]phenyl]-2,3-dihydro-1-methyl-2-oxo-1H-Indole-3-carboxamide.

35. The composition of claim 33 wherein said glycogen phosphorylase inhibitor is selected from the group consisting of 5-acetyl-1-ethyl-2,3-dihydro-2-oxo-N-[3-[(phenylamino)carbonyl]phenyl]-1H-Indole-3-carboxamide, 5-acetyl-N-[3-[(cyclohexylamino)carbonyl]phenyl-1-ethyl-2,3-dihydro-2-

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oxo-1H-Indole-3-carboxamide, and 5-acetyl-N-[3-[[[4-bromophenyl)amino]carbonyl]phenyl]-2,3-dihydro-1-methyl-2-oxo-1H-Indole-3-carboxamide.

5 36. The composition of any one of claims 1 and 6-8 wherein said glycogen phosphorylase inhibitor has the structure of Formula IV as defined in claim 5.

10 37. The composition of claim 5 wherein said glycogen phosphorylase inhibitor is selected from the group consisting of 2-Chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, and 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide.

20 38. The composition of claim 36 wherein said glycogen phosphorylase inhibitor is selected from the group consisting of 2-Chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-2-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-amide, and 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid [(1S)-benzyl-(2R)-hydroxy-3-((3R,4S)-dihydroxy-pyrrolidin-1-yl)-3-oxo-propyl]-amide.

30 39. The composition of any one of claims 1-5 and 7-8 wherein said glycogen phosphorylase inhibitor has a solubility in aqueous solution in the absence of said concentration-enhancing polymer of less than 1 mg/ml at any pH of from 1 to 8.

35 40. The composition of claim 39 wherein said glycogen phosphorylase inhibitor has an aqueous solubility of less than 0.5 mg/ml.

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41. The composition of claim 6 wherein said glycogen phosphorylase inhibitor has an aqueous solubility of less than 0.5 mg/ml.

5 42. The composition of claim 40 wherein said solubility is less than 0.1 mg/mL.

43. The composition of claim 41 wherein said solubility is less than 0.1 mg/mL.

10

44. The composition of any one of claims 1-8 wherein said glycogen phosphorylase inhibitor has a dose-to-aqueous-solubility ratio of at least 10 ml.

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45. The composition of claim 44 wherein said dose-to-aqueous solubility ratio is at least 100 ml.

46. The composition of claim 45 wherein said dose-to-aqueous solubility ratio is at least 400 ml.

20

47. The composition of any one of claims 1-8 wherein said concentration-enhancing polymer comprises a blend of polymers.

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48. The composition of any one of claims 1-8 wherein said concentration-enhancing polymer has at least one hydrophobic portion and at least one hydrophilic portion.

30

49. The composition of any one of claims 1-8 wherein said concentration-enhancing polymer is an ionizable polymer.

35 50. The composition of any one of claims 1-8 wherein said concentration-enhancing polymer is selected from the group consisting of ionizable cellulosic polymers, nonionizable cellulosic polymers, and vinyl

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polymers and copolymers having substituents selected from the group consisting of hydroxyl, alkylacyloxy, and cyclicamido.

5 51. The composition of any one of claims 1-8 wherein said concentration-enhancing polymer is a cellulosic polymer.

10 52. The composition of claim 51 wherein said concentration-enhancing polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, and
15 hydroxyethyl ethyl cellulose.

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20 53. The composition of claim 51 wherein said concentration-enhancing polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose succinate, hydroxypropyl cellulose acetate succinate, hydroxyethyl methyl cellulose succinate, hydroxyethyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, hydroxyethyl methyl cellulose
25 acetate succinate, hydroxyethyl methyl cellulose acetate phthalate, carboxyethyl cellulose, carboxymethyl cellulose, cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl
30 methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, hydroxypropyl methyl cellulose acetate succinate phthalate, hydroxypropyl methyl cellulose succinate phthalate, cellulose propionate phthalate, hydroxypropyl cellulose
35 butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate

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trimellitate, hydroxypropyl methyl cellulose acetate
trimellitate, hydroxypropyl cellulose acetate
trimellitate succinate, cellulose propionate
trimellitate, cellulose butyrate trimellitate, cellulose
5 acetate terephthalate, cellulose acetate isophthalate,
cellulose acetate pyridinedicarboxylate, salicylic acid
cellulose acetate, hydroxypropyl salicylic acid cellulose
acetate, ethylbenzoic acid cellulose acetate,
hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl
10 phthalic acid cellulose acetate, ethyl nicotinic acid
cellulose acetate, and ethyl picolinic acid cellulose
acetate.

54. The composition of claim 51 wherein said
15 concentration-enhancing polymer is selected from the
group consisting of cellulose acetate phthalate, methyl
cellulose acetate phthalate, ethyl cellulose acetate
phthalate, hydroxypropyl cellulose acetate phthalate,
hydroxypropyl methyl cellulose phthalate, hydroxypropyl
20 methyl cellulose acetate phthalate, hydroxypropyl
cellulose acetate phthalate succinate, cellulose
propionate phthalate, hydroxypropyl cellulose butyrate
phthalate, cellulose acetate trimellitate, methyl
cellulose acetate trimellitate, ethyl cellulose acetate
25 trimellitate, hydroxypropyl cellulose acetate
trimellitate, hydroxypropyl methyl cellulose acetate
trimellitate, hydroxypropyl cellulose acetate
trimellitate succinate, cellulose propionate
trimellitate, cellulose butyrate trimellitate, cellulose
30 acetate terephthalate, cellulose acetate isophthalate,
cellulose acetate pyridinedicarboxylate, salicylic acid
cellulose acetate, hydroxypropyl salicylic acid cellulose
acetate, ethylbenzoic acid cellulose acetate,
hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl
35 phthalic acid cellulose acetate, ethyl nicotinic acid
cellulose acetate, and ethyl picolinic acid cellulose
acetate.

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55. The composition of claim 51 wherein said concentration-enhancing polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, methyl cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl cellulose acetate phthalate, cellulose acetate terephthalate and cellulose acetate isophthalate.

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56. The composition of claim 55 wherein said concentration-enhancing polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, cellulose acetate phthalate, and cellulose acetate trimellitate.

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57. The composition of any one of claims 1-6 and 8 wherein said concentration-enhancing polymer is present in an amount sufficient to permit said composition to provide a maximum concentration of said glycogen phosphorylase inhibitor in a use environment that is at least 1.25-fold that of a control composition comprising an equivalent quantity of said glycogen phosphorylase inhibitor and free from said concentration-enhancing polymer.

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58. The composition of claim 57 wherein said maximum concentration of said glycogen phosphorylase inhibitor in said use environment is at least 2-fold that of said control composition.

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59. The composition of claim 7 wherein said maximum concentration of said glycogen phosphorylase inhibitor in said use environment is at least 2-fold that of said control composition.

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60. The composition of any one of claims 1-8 wherein said composition provides in an aqueous use environment an area under the concentration versus time curve for any period of at least 90 minutes between the time of introduction into the use environment and about 270 minutes following introduction to the use environment that is at least 1.25-fold that of a control composition comprising an equivalent quantity of said glycogen phosphorylase inhibitor and free from said concentration-enhancing polymer.

61. The composition of any one of claims 1-7 wherein said composition provides a relative bioavailability that is at least 1.25 relative to a control composition comprising an equivalent quantity of said glycogen phosphorylase inhibitor and free from said concentration-enhancing polymer.

62. The composition of claim 7 wherein said use environment is *in vitro*.

63. The composition of claim 7 wherein said use environment is *in vivo*.

64. The composition of claim 63 wherein said use environment is the gastrointestinal tract of an animal.

65. The composition of claim 64 wherein said animal is a human.

66. The composition of claim 57 wherein said use environment is *in vitro*.

67. The composition of claim 57 wherein said use environment is *in vivo*.

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68. The composition of claim 67 wherein said use environment is the gastrointestinal tract of an animal.

5 69. The composition of claim 68 wherein said animal is a human.

70. The composition of claim 60 wherein said use environment is in vitro.

10 71. The composition of claim 60 wherein said use environment is in vivo.

15 72. The composition of claim 71 wherein said use environment is the gastrointestinal tract of an animal.

20 73. The composition of claim 72 wherein said animal is a human.

74. The composition of claim 9 wherein said dispersion is formed by solvent processing.

25 75. The composition of claim 74 wherein said solvent processing is spray-drying.

30 76. A method of treating or preventing atherosclerosis, the method comprising the step of administering to a patient having atherosclerosis or at risk of having atherosclerosis a therapeutically effective amount of a composition of any one of claims 1-8.

35 77. A method of treating diabetes, the method comprising the step of administering to a patient having diabetes a therapeutically effective amount of a composition of any one of claims 1-8.

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78. The method of claim 77 wherein the diabetes is non-insulin dependent diabetes mellitus (Type 2).

5 79. The method of claim 77 wherein the diabetes is insulin dependent diabetes mellitus (Type 1).

10 80. A method of treating insulin resistance, the method comprising the step of administering to a patient having insulin resistance a therapeutically effective amount of a composition of any one of claims 1-8.

15 81. A method of treating diabetic neuropathy, the method comprising the step of administering to a patient having diabetic neuropathy a therapeutically effective amount of a composition of any one of claims 1-8.

20 82. A method of treating diabetic nephropathy, the method comprising the step of administering to a patient having diabetic nephropathy a therapeutically effective amount of a composition of any one of claims 1-8.

25 83. A method of treating diabetic retinopathy, the method comprising the step of administering to a patient having diabetic retinopathy a therapeutically effective amount of a composition of any one of claims 1-8.

30 84. A method of treating cataracts, the method comprising the step of administering to a patient having cataracts a therapeutically effective amount of a composition of any one of claims 1-8.

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85. A method of treating or preventing hypercholesterolemia, the method comprising the step of administering to a patient having hypercholesterolemia or at risk of having hypercholesterolemia a therapeutically effective amount of a composition of any one of claims 1-8.

86. A method of treating or preventing hypertriglyceridemia, the method comprising the step of administering to a patient having hypertriglyceridemia or at risk of having hypertriglyceridemia a therapeutically effective amount of a composition of any one of claims 1-8.

87. A method of treating or preventing hyperlipidemia, the method comprising the step of administering to a patient having hyperlipidemia or at risk of having hyperlipidemia a therapeutically effective amount of a composition of any one of claims 1-8.

88. A method of treating hyperglycemia, the method comprising the step of administering to a patient having hyperglycemia or at risk of having hyperglycemia a therapeutically effective amount of a composition of any one of claims 1-8.

89. A method of treating hypertension, the method comprising the step of administering to a patient having hypertension or at risk of having hypertension a therapeutically effective amount of a composition of any one of claims 1-8.

90. A method of treating or preventing tissue ischemia, the method comprising the step of administering to a patient having tissue ischemia or at risk of having tissue ischemia a therapeutically effective amount of a composition of any one of claims 1-8.

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91. A method of treating or preventing myocardial ischemia, the method comprising the step of administering to a patient having myocardial ischemia or at risk of having myocardial ischemia a therapeutically effective amount of a composition of any one of claims 1-8.

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92. A method of inhibiting glycogen phosphorylase, the method comprising the step of administering to a patient in need of glycogen phosphorylase inhibition, a glycogen phosphorylase
5 inhibiting amount of a composition of any one of claims 1-8.

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PHARMACEUTICAL COMPOSITIONS OF GLYCOGEN
PHOSPHORYLASE INHIBITORS

ABSTRACT OF THE DISCLOSURE

5 Pharmaceutical compositions comprise a glycogen
phosphorylase inhibitor and at least one concentration-
enhancing polymer. The composition may be a simple
physical mixture of glycogen phosphorylase inhibitor and
concentration-enhancing polymer or a dispersion of
10 glycogen phosphorylase inhibitor and polymer.

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Intérprete Jurado de los idiomas
francés e inglés

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LOS ESTADOS UNIDOS DE AMÉRICA

A TODO AQUEL A QUIEN CONCIERNA LO PRESENTE:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Patentes y Marcas de los Estados Unidos

30 de Enero de 2001

LA PRESENTE ES PARA CERTIFICAR QUE ADJUNTA A LA MISMA HAY UNA COPIA FIEL DE LOS REGISTROS DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA EN LO QUE SIGUE, QUE CUMPLEN LOS REQUISITOS PARA OTORGARLE UNA FECHA DE PRESENTACIÓN BAJO 35 USC 111.

NÚMERO DE SOLICITUD: 60/189.942

FECHA DE PRESENTACIÓN: 16 de Marzo de 2000



Por la Autoridad del
COMISARIO DE PATENTES Y MARCAS

P. R. GRANT

Oficial certificador

Por favor, escribir a máquina un signo (+) dentro de esta casilla

PTO/SB/16 (12-97)
Aprobado para uso a través 1/31/98. OMB 0551-0037

Oficina de Patentes y Marcas: DEPARTAMENTO DE COMERCIO DE LOS EE.UU.
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HOJA PORTADA DE SOLICITUD PROVISIONAL DE PATENTE

Esta es una petición para presentar una SOLICITUD PROVISIONAL DE PATENTE bajo 37 CFR 1.53 (c).

INVENTOR(ES)					
Nombre pautsmal (primero y central (si lo hay))	Apellido o sobrenombre	Residencia (Ciudad y estado o país extranjero)			
Dennis J.	HOOVER	Mystic, CT			
☒ Los inventores adicionales son nombrados en <u>1</u> hojas numeradas por separado anejas al presente					
TÍTULO DE LA INVENCIÓN (máximo 280 caracteres)					
COMPOSICIONES FARMACÉUTICAS DE INHIBIDORES DE LA GLUCOGENOFOSFORILASA					
DIRECCIÓN DE CORRESPONDENCIA					
Dirijan toda la correspondencia a:					
☐ Número de cliente					
☐ Macanografien aquí el número de cliente					
☒ Empresa o Nombre particular		Bruce W. DeKock, Chernoff Vilhauer McClung Stenzel			
Dirección		1600 ODS Tower			
Dirección		601 S.W. Second Avenue			
Ciudad		Portland	Estado	OR	Código Postal 97204
País		EE.UU.	Teléfono	503/227-5631	Fax 503/228-4373
PARTES DE LA SOLICITUD ANEJAS (márquese todo lo que sea pertinente)					
☒ Memoria descriptiva	Número de páginas	102	☐ Declaración de pequeña entidad		
☐ Dibujo(s)	Número de hojas		☒ Otros (especificar) Carta postal de correo expres con recibo		
MÉTODO DE PAGO DE TASAS DE PRESENTACIÓN PARA ESTA SOLICITUD PROVISIONAL DE PATENTE					
☒ Se adjunta un cheque o transferencia para cubrir las tasas de presentación			CANTIDAD DE LA TASA DE PRESENTACIÓN (\$)		
☒ El Comisionado está autorizado con la presente para cargar las tasas de presentación o abonar cualquier pago al Número de Cuenta de Depósito:			03-1550 150,00		
La invención se efectuó mediante una Agencia del Gobierno de los Estados Unidos o bajo un contrato con una Agencia del Gobierno de los Estados Unidos.					
☒ No.					
☐ Sí, el nombre de la Agencia del Gobierno de EE.UU. y el número de contrato con el Gobierno son _____					

Respetuosamente sometido,

FIRMA Bruce W. DeKock
NOMBRE ESCRITO A Bruce W. DeKock
MÁQUINA O IMPRESO
TELÉFONO (503) 227-5631

Fecha 3/16/00

Nº DE REGISTRO 40.585
(si procede)
Número de expediente: BWD:7783,011

PRESENTACIÓN DE SOLICITUD PROVISIONAL DE PATENTE ÚNICAMENTE

Este compendio de información es requerido por 37 CFR 1.51. La información es utilizada por el público para presentar (y por la PTO para procesar) una solicitud provisional. La confidencialidad está gobernada por 35 U.S.C. y 37 CFR 1.14. Se estima que este compendio tarda 8 horas en completarse, incluyendo recopilación, preparación y remisión de la solicitud provisional completa a la PTO. El tiempo variará en función de las necesidades del caso particular. Cualquier comentario sobre la cantidad de tiempo que requiera Vd. para completar este formulario y/o sugerencias para reducir esta carga, deberá enviarse a la Oficina de Información y Gestión, Oficina de Patentes y Marcas, Washington, DC 20231. NO ENVIAR TASAS NI FORMULARIOS COMPLETADOS A ESTA DIRECCIÓN. ENVIAR A: Departamento de Solicitudes Provisionales, Comisionado de Patentes, Washington, DC 20231.

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PTO 5B/1A (12-97)

Oficina de Patentes y Marcas: DEPARTAMENTO DE COMERCIO DE LOS EE.UU.

Según la Ley de Reducción del Papeleo de 1995, no se requiere a las personas a responder a la recogida de información a menos que exista un número de control válido de OMB-

Número de expediente

BWD:7783011

Mecanografiar un signo (+) dentro de esta casilla

✱

Número 2 de 2

+

Número 2 de 2

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CERTIFICADO DE ENVÍO POR CORREO
MEDIANTE "CORREO EXPRES"

Correo exprés N° EL4721574745US

Fecha de depósito: 16 de marzo de 2000.

Yo, por la presente, certifico que la solicitud de patente provisional unida a este documento, titulada COMPOSICIONES FARMACÉUTICAS DE INHIBIDORES DE LA GLUCÓGENOFOSFORILASA (102 páginas), junto con una hoja cubierta de Solicitud Provisional (por duplicado), hoja cubierta de Transmisión de Honorarios (por duplicado), un cheque de 150.00\$, este Certificado de Envío por Correo mediante Correo Exprés, y una carta postal de acuse por retorno, son depositados en el servicio "Correo Exprés a Destinatario" del Servicio Postal de los Estados Unidos en la fecha indicada anteriormente y son dirigidos al Buzón de Solicitud Provisional, Delegado Adjunto para Patentes, Washington, DC 20231.


DWIGHT BERGQUIST-MOODY

COMPOSICIONES FARMACÉUTICAS DE INHIBIDORES DE LA GLUCÓGENO-FOSFORILASA

ANTECEDENTES DE LA INVENCION

Esta invención se refiere a composiciones farmacéuticas que contienen un
5 inhibidor de la glucógeno-fosforilasa (GPI) y al menos un polímero que aumenta la
concentración, y al uso de tales composiciones farmacéuticas para tratar la diabetes,
hiperglucemia, hipercolesterolemia, hipertensión, hiperinsulinemias, hiperlipidemia,
aterosclerosis e isquemia miocárdica en los mamíferos.

A pesar del temprano descubrimiento de la insulina y la subsiguiente amplia
10 difusión de su uso en el tratamiento de la diabetes, y el descubrimiento posterior y uso
de las sulfonilureas (por ejemplo, clorpropamida (Pfizer), glipizida (Pfizer), tolbutamida
(Upjohn), acetohexamida (E. I. Lilly), tolazimida (Upjohn), y biguanidas (por ejemplo
fenformina (Ciba Geigy), metformina (G. D. Searle)) como agentes hipoglucémicos
orales, el tratamiento de la diabetes no ha llegado a ser satisfactorio. El uso de la insu-
15 lina, necesario en aproximadamente el 10 % de los pacientes diabéticos en los que los
agentes hipoglucémicos sintéticos no son efectivos (diabetes tipo 1, diabetes mellitus
insulino-dependiente) requiere múltiples dosis diarias, usualmente por autoinyección.
La determinación de la dosificación apropiada de insulina requiere frecuentes estima-
ciones del azúcar en orina o sangre. La administración de un exceso de dosis de insu-
20 lina causa hipoglucemia, con efectos que varían desde anomalías suaves en la
glucosa sanguínea hasta el coma, o incluso la muerte. El tratamiento de la diabetes
mellitus no insulino-dependiente (diabetes tipo 2, NIDDM) usualmente consiste en una
combinación de dieta, ejercicio, agentes orales, por ejemplo, sulfonilureas, y en los
casos más graves, insulina. Sin embargo, los agentes hipoglucémicos clínicamente
25 disponibles pueden tener otros efectos secundarios que limitan su uso. En cualquier
caso, cuando uno de estos agentes puede fallar en un caso individual, otro puede te-
ner éxito. Es claramente evidente que continúa la necesidad de agentes hipoglucémi-
cos que puedan tener menos efectos secundarios o que puedan ser satisfactorios
cuando otros fallan.

La producción de glucosa hepática es un importante objetivo para la terapia de
30 la NIDDM. El hígado es el principal regulador de los niveles de glucosa plasmática en
el estado de post-absorción (en ayunas), y la velocidad de producción de glucosa he-
pática en pacientes con NIDDM es significativamente elevada en comparación con los
individuos normales. Asimismo, en el estado posprandial (con alimentos), cuando el
35 hígado tiene un papel proporcionalmente más pequeño en el suministro total de gluco-

sa plasmática, la producción de glucosa hepática es anormalmente alta en pacientes con NIDDM.

La glucogenolisis es un objetivo importante para la interrupción de la producción de glucosa hepática. El hígado produce glucosa por glucogenolisis (ruptura del glucógeno, polímero de glucosa) y gluconeogénesis (síntesis de la glucosa a partir de precursores con 2-carbono y 3-carbono). Varias pruebas indican que la glucogenolisis puede realizar una importante contribución a la producción de glucosa hepática en la NIDDM. En primer lugar, en el hombre normal en estado de post-absorción, se estima que hasta un 75 % de la producción de glucosa hepática resulta de la glucogenolisis. En segundo lugar, los pacientes que tienen enfermedades con acumulación de glucógeno en el hígado, incluyendo la enfermedad de Hers (deficiencia de glucógeno-fosforilasa), presentan hipoglucemia episódica. Estas observaciones indican que la glucogenolisis puede ser un procedimiento significativo para la producción de glucosa hepática.

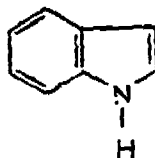
La glucogenolisis es catalizada en el hígado, músculo, y cerebro por isoformas de la enzima glucógeno-fosforilasa (GP) específicas del tejido. Esta enzima escinde la macromolécula de glucógeno para liberar glucosa-1-fosfato y una nueva macromolécula de glucógeno acortada. Se han descrito hasta la fecha varios tipos de GPI: glucosa y análogos de glucosa [Martin, J.L. *et al.*, *Biochemistry* 1991, 30, 10101] y cafeína y otros análogos de purina [Kasvinsky, P.J. *et al.*, *J. Biol. Chem.* 1978, 253, 3343-3351 y 9102-9106]. Estos compuestos, y los GPI en general, se supone que son de uso potencial para el tratamiento de la NIDDM, por disminuir la producción de glucosa hepática y reducir la glucemia [Blundell, T. B. *et al.* *Diabetologia* 1992, 35, Suppl. 2, 569-576 y Martin *et al.* *Biochemistry* 1991, 30, 10101].

Los sitios a los que se ha descrito que se unen los GPI son el sitio activo, el sitio de unión de la cafeína o purina y el sitio de unión del ATP o nucleótidos. La actividad enzimática se controla también por la fosforilación en un único sitio de fosforilación, Ser 14. La fosforilación normalmente produce un aumento en la actividad de la GP debido a un cambio conformacional de la enzima GP. Se han identificado las características de este cambio conformacional. Véase, Sprang *et al.*, *Nature* 1988, 336, 215-21. Las estructuras de GP:GPI determinadas experimentalmente revelan que la unión del inhibidor a cualquiera de los tres sitios de unión citados antes invierte el cambio conformacional de la GP que normalmente tiene lugar después de la fosforilación, haciendo que la enzima GP adopte la conformación "inactiva" de la proteína no fosforilada.

Se han descrito varios GPI. Véanse, por ejemplo, Kristiansen *et al.*, patente de

Estados Unidos 5.952.363; Lundgren *et al.*, EP 884 050 A1; Kristiansen *et al.*, WO 98/50359; Bols, WO 97/31901; y Lundgren *et al.*, WO 97/09040. La mayor parte de estos compuestos son aminas cíclicas con diferentes sustituyentes que generalmente las hacen relativamente hidrófilas con buena solubilidad en agua y buen potencial para absorción. Se debe esperar, por tanto, que estos GPI, al ser solubles en agua, no tengan absorción limitada por la solubilidad.

Un nuevo sitio de unión ha sido descubierto recientemente, junto con nuevos inhibidores de la glucógeno-fosforilasa que se unen a este nuevo sitio. Véase EP 0978279 A1. Como se usa aquí y en las reivindicaciones, este nuevo sitio de unión será denominado como el "sitio de unión del núcleo de indol". Se han identificado hasta ahora cuatro tipos diferentes de GPI que se unen al sitio de unión del núcleo de indol: Véanse, WO 96/39385, patente de Estados Unidos 5.952.322, y EP 846464 A2 que describen los GPI del primer tipo; WO 96/39384 y EP 832065 A1 que describen los GPI del segundo tipo; y la patente de Estados Unidos 5.998.463 que describe los GPI del tercer tipo. Aquí se describe un cuarto tipo. En general, estos compuestos tienen en común la característica estructural de uno o más sistemas de anillos condensados que comprenden un anillo aromático de seis miembros y un heterociclo que contiene nitrógeno. Tales sistemas de anillos condensados, se pueden considerar un "grupo semejante al indol", teniendo el propio indol la estructura:



Se cree que los GPI que contienen el grupo semejante al indol se unen al sitio de unión del núcleo de indol de la enzima GP. Los GPI que se unen a este sitio de unión del núcleo de indol generalmente son relativamente hidrófobos, tienen mala solubilidad en agua y pobre biodisponibilidad.

Por consiguiente, lo que se desea por tanto es una composición conteniendo un GPI poco soluble en agua, que aumenta la concentración del GPI en solución acuosa, que no afecta de modo adverso la capacidad del GPI para unirse a la enzima GP, que mejora la biodisponibilidad relativa y que es farmacéuticamente aceptable.

BREVE SUMARIO DE LA INVENCION

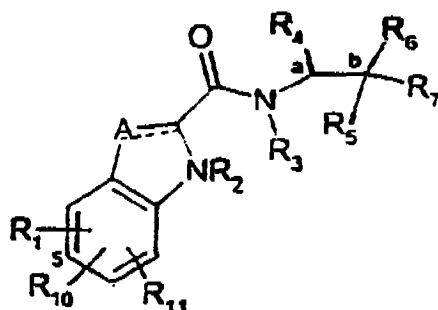
La presente invención evita los inconvenientes mencionados proporcionando una composición farmacéutica que comprende un inhibidor de la glucógeno-fosforilasa y un polímero que aumenta la concentración. El GPI se une a una porción o a todas las porciones de los siguientes residuos de una enzima glucógeno-fosforilasa:

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<u>Estructura secundaria original</u>	<u>Número de residuo</u>
	13-23
hélice $\alpha 1$	24-37
vuelta	38-39, 43, 46-47
hélice $\alpha 2$	48-66, 69-70, 73-74, 76-78
	79-80
cadena $\beta 1$	81-86
	87-88
cadena $\beta 2$	89-92
	93
hélice $\alpha 3$	94-102
	103
hélice $\alpha 4$	104-115
	116-117
hélice $\alpha 5$	118-124
	125-128
cadena $\beta 3$	129-131
	132-133
hélice $\alpha 6$	134-150
	151-152
cadena $\beta 4$	153-160
	161
cadena $\beta 4b$	162-163
	164-166
cadena $\beta 5$	167-171
	172-173
cadena $\beta 6$	174-178
	179-190
cadena $\beta 7$	191-192
	194, 197
cadena $\beta 8$	198-209
	210 -211
cadena $\beta 9$	212 - 216
cadena $\beta 10$	219-226, 228-232
	233-236

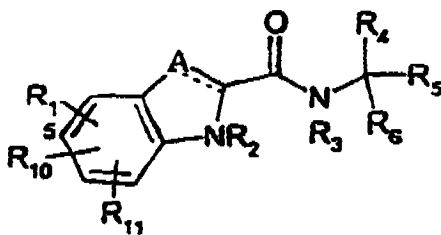
cadena $\beta 11$	237-239, 241, 243-247
	248-260
hélice $\alpha 7$	261-276
cadena $\beta 11b$	277-281
vuelta inversa	282-289
hélice $\alpha 8$	290-304.

En un segundo aspecto de la invención, una composición farmacéutica comprende un GPI y un polímero que aumenta la concentración, teniendo el GPI la estructura general de la fórmula I:



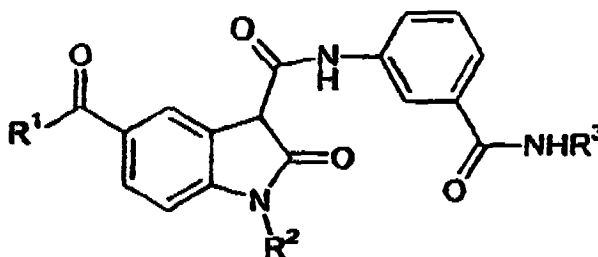
Fórmula I

En un tercer aspecto de la invención, una composición farmacéutica comprende un GPI y un polímero que aumenta la concentración, teniendo el GPI la estructura general de la fórmula II:



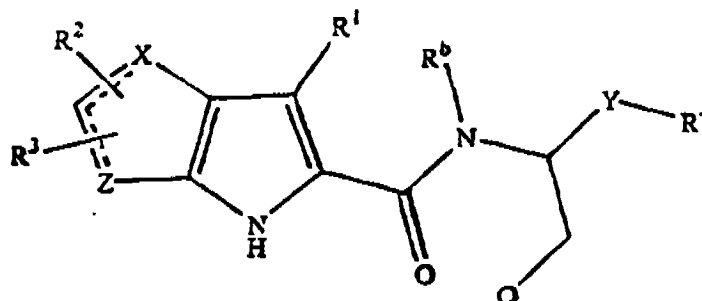
Fórmula II

En un cuarto aspecto de la invención, una composición farmacéutica comprende un GPI y un polímero que aumenta la concentración, teniendo el GPI la estructura general de la fórmula III:



Fórmula III

En un quinto aspecto de la invención, una composición farmacéutica comprende un GPI y un polímero que aumenta la concentración, teniendo el GPI la estructura general de la fórmula IV:



Fórmula IV

En un sexto aspecto de la invención, una composición farmacéutica comprende un GPI y un polímero que aumenta la concentración, teniendo el GPI una solubilidad en solución acuosa, en ausencia del polímero, de menos de 1,0 mg/ml a cualquier pH de 1 a 8.

En un séptimo aspecto de la invención, una composición farmacéutica comprende un GPI y un polímero que aumenta la concentración. La composición proporciona una concentración máxima del GPI en un medio de uso que es 1,25 veces la de una composición de referencia que comprende una cantidad equivalente del GPI y está libre del polímero. Como se usa aquí, un "medio de uso" puede ser o el medio *in vivo* del tracto gastrointestinal de un mamífero, particularmente un humano, o el medio *in vitro* de una solución de ensayo, tal como solución salina tamponada de fosfato (PBS) o una solución *Model Fasten Duodenal* (MFD).

En un octavo aspecto de la invención, una composición farmacéutica comprende un GPI y un polímero que aumenta la concentración. La composición proporciona una biodisponibilidad relativa que es al menos 1,25 en relación a una composición de referencia que comprende una cantidad equivalente del GPI y está libre del polímero.

En otro aspecto de la invención, un método de tratamiento de un mamífero que tiene una indicación debida a aterosclerosis, diabetes, neuropatía diabética, nefropatía diabética, retinopatía diabética, cataratas, hipercolesterolemia, hipertrigliceridemia, hipertensión, isquemia miocárdica, hiperglucemia, hiperinsulinemia, hiperlipidemia, resistencia a la insulina, infección bacteriana, o isquemia tisular comprende las siguientes etapas. Se forma una composición de un GPI y un polímero que aumenta la concentración. La composición se administra entonces al mamífero.

La composición se puede dosificar en una variedad de formas farmacéuticas, incluyendo tanto las formas farmacéuticas de liberación inicial como las de liberación controlada, incluyendo las últimas tanto las formas de liberación retardada como las de

liberación sostenida. La composición puede incluir mezclas de polímeros, y puede incluir además otros polímeros que mejoran la concentración acuosa del GPI. La composición puede comprender también otros constituyentes que mejoran la estabilidad, humectación, disolución, compresión o características de elaboración de la composición.

Los diferentes aspectos de la presente invención tienen cada uno de ellos una o más de las siguientes ventajas. Las composiciones aumentan la concentración del GPI en solución acuosa en relación a la forma cristalina del GPI. Las composiciones también mejoran la biodisponibilidad relativa del GPI. Además, las composiciones hacen posible el uso de los GPI hidrófobos, poco solubles en agua, sin afectar adversamente a sus características de unión.

Los anteriores y otros objetivos, características y ventajas de la invención se entenderán más fácilmente tras la consideración de la siguiente descripción detallada de la invención.

15 DESCRIPCIÓN DETALLADA DE LA INVENCION

La presente invención proporciona composiciones de los GPI y al menos un polímero que aumenta la concentración. Como se ha expuesto antes en los antecedentes, se ha descubierto una nueva clase de los GPI hidrófobos poco solubles en agua, que se unen al sitio de unión del núcleo de indol en la enzima GP. Se cree que una parte importante de la unión de los GPI a este sitio se debe al grupo semejante al indol, que siendo relativamente hidrófobo, se une en una bolsa hidrófoba dentro de la enzima GP. Al estudiar la actividad del GPI, el modo de unión, y la estructura del complejo GPI/GP de una amplia variedad de compuestos, se ha encontrado que los compuestos que tienen buena actividad de inhibición de la GP en este sitio de unión del núcleo de indol tienen a menudo una serie de características en común: (1) la presencia de uno o más grupos semejantes al indol en su estructura; (2) solubilidades extremadamente bajas en solución acuosa (esto es, menos de 1,0 mg/ml) a un pH fisiológicamente apropiado (por ejemplo cualquier pH de 1 a 8) medidas a aproximadamente 22 °C; (3) una naturaleza relativamente hidrófoba; y (4) una biodisponibilidad relativamente baja cuando se administran oralmente en el estado cristalino.

Por tanto, a diferencia de otros GPI conocidos previamente, los GPI que se unen al sitio de unión del núcleo de indol requieren típicamente algún tipo de modificación o formulación para aumentar su solubilidad y con ello alcanzar una buena biodisponibilidad. Sin embargo, se ha encontrado en la invención que muchos de los métodos convencionales usados para mejorar la solubilidad, y a su vez la biodisponibilidad, han demostrado ser problemáticos. Un método usado generalmente para mejorar la

biodisponibilidad de un fármaco es preparar una forma iónica del fármaco, típicamente incorporando un grupo ionizable a su estructura, y particularmente preparando una forma de sal muy soluble. Sin embargo, los GPI con el grupo semejante al indol que tienen el mejor comportamiento, generalmente son neutros o no iónicos y relativamente hidrófobos.

Se ha encontrado en la invención que preparando los GPI que tienen grupos semejantes al indol como composiciones que comprenden un GPI y un polímero que aumenta la concentración, y preferiblemente como una dispersión sólida del GPI y el polímero que aumenta la concentración, se aumenta la concentración acuosa de los GPI así como la biodisponibilidad relativa, pero no se afecta adversamente a las características de unión de los GPI. Las composiciones, los GPI, los polímeros adecuados, y los excipientes opcionales, se exponen en más detalle a continuación.

COMPOSICIONES DE LOS GPI Y POLÍMERO QUE AUMENTA LA CONCENTRACIÓN

La presente invención tiene utilidad con cualquier GPI de baja solubilidad, o con cualquier GPI que se pueda beneficiar por una mejor biodisponibilidad. Las composiciones de la presente invención son mezclas que constan de un GPI y al menos de un polímero que aumenta la concentración. Las mezclas son preferiblemente dispersiones sólidas, pero también pueden ser adecuadas para algunos GPI las mezclas físicas simples del GPI y el polímero. El GPI en su estado puro puede ser cristalino o amorfo. Preferiblemente, al menos una porción importante del GPI de la composición es amorfa. Por "amorfo" se entiende simplemente que el GPI no está en estado cristalino. Como se usa aquí, el término "una porción importante" del GPI significa que al menos el 60 % del GPI de la composición está en la forma amorfa, en lugar de la forma cristalina. Preferiblemente, el GPI de la composición es sustancialmente amorfo. Como se usa aquí "sustancialmente amorfo" significa que la cantidad del GPI en forma cristalina no excede del 25 %. Más preferiblemente, el GPI de la composición es "casi completamente amorfo" lo que significa que la cantidad de GPI en forma cristalina no excede del 10 %. Las cantidades de GPI cristalino se pueden medir por difracción de rayos X en polvo, análisis con microscopio electrónico de barrido (SEM), calorimetría diferencial de barrido ("DSC"), y cualquier otra medida cuantitativa estándar. La composición puede contener desde aproximadamente 1 hasta aproximadamente 80 % en peso de GPI, dependiendo de la dosis del GPI. El aumento de las concentraciones acuosas de GPI y de la biodisponibilidad relativa son típicamente mejores a niveles bajos de GPI, típicamente menos de aproximadamente 25 a 40 % en peso. Sin embargo, debido al límite práctico del tamaño de la forma farmacéutica, se prefieren a

menudo mayores cargas de GPI y dan buenos resultados.

En un aspecto preferido de la invención, el GPI y el polímero que aumenta la concentración están presentes como una dispersión sólida del GPI de baja solubilidad y el polímero. Preferiblemente, al menos una porción importante del GPI en la dispersión está presente en estado amorfo, en lugar de en estado cristalino. El GPI amorfo puede existir como una fase pura, como una solución sólida del GPI distribuido homogéneamente por todo el polímero o cualquier combinación de estos estados o aquellos estados que sean intermedios entre ellos.

La dispersión es preferiblemente sustancialmente homogénea de forma que el GPI amorfo se dispersa tan homogéneamente como sea posible por todo el polímero. Como se usa aquí "sustancialmente homogénea" significa que el GPI presente en los dominios amorfos relativamente puros dentro de la dispersión sólida es relativamente poco, del orden de menos del 20 %, y preferiblemente menos del 10 % de la cantidad total de GPI. Aunque la dispersión puede tener algunos dominios ricos en GPI, se prefiere que la propia dispersión tenga una única temperatura de transición vítrea (T_g) lo que demuestra que la dispersión es sustancialmente homogénea. Esto contrasta con una mezcla física simple de partículas de GPI amorfo puro y partículas de polímero amorfo puro que generalmente presenta dos T_g distintas, una la del GPI y otra la del polímero. La T_g como se usa aquí es la temperatura característica en la que un material vítreo, después de calentamiento gradual, sufre un cambio físico relativamente rápido (por ejemplo, de 10 a 100 segundos) desde un estado vítreo a un estado tipo elastómero. Las dispersiones de la presente invención que son sustancialmente homogéneas generalmente son más estables físicamente y tienen mejores propiedades para aumentar la concentración, y a su vez mejor biodisponibilidad, en relación con las dispersiones no homogéneas.

Aunque en la invención se ha encontrado que las dispersiones del GPI y el polímero que aumenta la concentración dan buenos resultados, se ha visto, para un GPI al menos, que las composiciones de mezclas físicas de GPI amorfo y polímero que aumenta la concentración también proporcionan un aumento de la concentración acuosa del GPI. Al menos una porción importante del GPI en la mezcla es amorfa. La composición puede estar en forma de una mezcla física simple seca donde ambos, el GPI y el polímero que aumenta la concentración están mezclados en la forma de partículas y donde las partículas de cada uno de ellos, sin importar el tamaño, conservan las mismas propiedades físicas individuales que presentan a granel. Se puede usar cualquier método convencional de los utilizados para mezclar el polímero y el GPI juntos, tal como el mezclado físico y la granulación seca o húmeda. En esta realización

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de la invención, no es necesario que el GPI amorfo y el polímero que aumenta la concentración se mezclen directamente, sino sólo que ambos estén presentes en la forma farmacéutica. Por ejemplo, el GPI amorfo puede estar en forma de un comprimido, perla o cápsula, y el polímero que aumenta la concentración puede ser un recubrimiento, material de granulación o incluso la pared de la cápsula.

Las composiciones que comprenden el GPI y el polímero que aumenta la concentración, proporcionan un aumento de la concentración del GPI en los ensayos de disolución *in vitro*. Se ha determinado que el aumento de la concentración del fármaco en los ensayos de disolución *in vitro* en *Model Fasted Duodenal* (solución MFD) o en solución salina tamponada de fosfato (PBS) es un buen indicador del comportamiento y biodisponibilidad *in vivo*. Una solución PBS apropiada es una solución acuosa que comprende fosfato de sodio (Na_2HPO_4) 20 mM, fosfato de potasio (KH_2PO_4) 47 mM, NaCl 87 mM, y KCl 0.2 mM, ajustada a pH 6,5 con NaOH. Una solución MFD apropiada es la misma solución PBS en la que adicionalmente están presentes sal de sodio de ácido taurocólico 14,7 mM y 1-palmitoil-2-oleil-sn-glicero-3-fosfocolina 2,8 mM. En particular, una composición de la presente invención se puede ensayar en cuanto a disolución añadiéndola a una solución MFD o PBS y agitando para facilitar la disolución. Preferiblemente, la composición de la presente invención proporciona una concentración máxima de fármaco (MDC) que es al menos 1,25 veces la concentración de equilibrio de una composición de referencia que comprende una cantidad equivalente de GPI pero está libre del polímero. En otras palabras, si la concentración de equilibrio proporcionada por la composición de referencia es 100 $\mu\text{g/ml}$, entonces una composición de la presente invención proporciona una MDC de al menos 125 $\mu\text{g/ml}$. La composición de comparación es convencionalmente el GPI solo, no dispersado (por ejemplo, típicamente, el GPI cristalino solo en su forma cristalina más termodinámicamente estable, o en los casos en que no se conoce una forma cristalina del GPI, la referencia puede ser el GPI amorfo solo) o el GPI más un peso de diluyente inerte equivalente al peso del polímero en la composición de ensayo. Más preferiblemente, la MDC del GPI conseguida con las composiciones de la presente invención es al menos 2 veces, e incluso más preferiblemente al menos 3 veces, la de la composición de referencia.

Alternativamente, las composiciones de la presente invención proporcionan en un medio de uso acuoso un área bajo la curva (AUC) de concentración frente al tiempo, para cualquier periodo de al menos 90 minutos entre el tiempo de introducción en el medio de uso y aproximadamente 270 minutos después de la introducción en el medio de uso, que es al menos 1,25 veces la de una composición de referencia que comprende una cantidad equivalente del GPI no dispersado.

Alternativamente, la dispersión de la presente invención, cuando se administra oralmente a un humano o a un animal, proporciona una AUC de la concentración del GPI en la sangre para cualquier periodo de al menos 90 minutos entre el tiempo de administración y aproximadamente 270 minutos después de la administración, que es al menos 1,25 veces la observada cuando se administra una composición de referencia que comprende una cantidad equivalente del fármaco no dispersado. Por ello, las composiciones de la presente invención se pueden evaluar en ensayos o bien *in vitro* o bien *in vivo*, o en ambos.

Un ensayo típico para evaluar el aumento de la concentración del fármaco se puede realizar por medio de (1) disolver una cantidad suficiente de la composición de referencia, típicamente el GPI solo, en el medio de ensayo *in vitro*, típicamente solución MFD o PBS, para alcanzar la concentración de equilibrio del GPI; (2) disolver una cantidad suficiente de la composición de ensayo (por ejemplo, el GPI y el polímero), en un medio de ensayo equivalente, de tal forma que si todo el GPI estuviera disuelto, la concentración teórica de GPI excedería la concentración de equilibrio del GPI por un factor de 2 como mínimo; y (3) determinar si la MDC de la composición de ensayo medida en el medio de ensayo es al menos 1,25 veces la de la concentración de equilibrio de la composición de referencia. Al realizar tal ensayo de disolución, la cantidad de la composición de ensayo o de la composición de referencia usada, es una cantidad tal que si todo el GPI estuviera disuelto, la concentración de GPI sería al menos de 2 veces a 100 veces la de la solubilidad del GPI. La concentración del GPI disuelto se mide típicamente como una función del tiempo tomando muestras del medio de ensayo y representando gráficamente la concentración del GPI en el medio de ensayo frente al tiempo de forma que se puede determinar la MDC. Para evitar las partículas de GPI que podrían dar una determinación errónea, la solución de ensayo se filtra o se centrifuga. El "GPI disuelto" se considera típicamente como aquel material que o bien pasa por un filtro de jeringa de 0,45 μm , o alternativamente, el material que queda en el sobrenadante después de la centrifugación. La filtración se puede realizar usando un filtro de jeringa de 13 mm, de poli(difluoruro de vinilideno) de 0,45 μm comercializado por Scientific Resources con la marca comercial de TITAN®. La centrifugación se realiza típicamente en un tubo de microcentrifuga de polipropileno centrifugando a 13.000 g durante 60 segundos. Se pueden emplear otros métodos similares de filtración o centrifugación y se obtienen resultados útiles. Por ejemplo, usando otros tipos de microfiltros se pueden obtener valores algo más altos o más bajos ($\pm$ 10-40 %) que los obtenidos con el filtro especificado antes pero, sin embargo, permiten la identificación de las dispersiones preferidas. Se reconoce que esta definición de "GPI disuelto"

engloba no sólo las moléculas monoméricas del GPI solvatado sino también una amplia serie de formas tales como conjuntos de polímero/GPI que tienen dimensiones inferiores a la micra tales como los agregados de GPI, agregados de mezclas de polímero y GPI, micelas, micelas poliméricas, partículas coloidales o nanocristales, complejos de polímero/GPI, y otras formas similares que contienen GPI que están presentes en el filtrado o sobrenadante del especificado ensayo de disolución.

La biodisponibilidad relativa de los GPI en las dispersiones de la presente invención se puede ensayar *in vivo* en animales o humanos usando métodos convencionales para realizar tal determinación. Un ensayo *in vivo*, tal como un estudio cruzado, se puede usar para determinar si una composición de GPI y polímero proporciona un aumento de la biodisponibilidad relativa en comparación con una composición de referencia que comprende un GPI pero ningún polímero como se ha descrito antes. En un estudio cruzado *in vivo*, una "composición de ensayo" de GPI y polímero se administra a la mitad de los sujetos de un grupo de ensayo y después de un periodo apropiado de eliminación (por ejemplo una semana), los mismos sujetos recibieron una "composición de referencia" que comprende una cantidad del GPI equivalente a la de la "composición de ensayo". A la otra mitad del grupo se le administra primero la composición de referencia seguida por la composición de ensayo. La biodisponibilidad relativa se mide como el área bajo la curva (AUC) de la concentración en sangre (suero o plasma) frente al tiempo, determinada para el grupo de ensayo dividida por el AUC en sangre proporcionada por la composición de referencia. Preferiblemente esta relación ensayo/referencia se determina para cada sujeto, y después se calcula la media de estas relaciones en todos los sujetos del estudio. Las determinaciones *in vivo* del AUC se pueden hacer representando gráficamente la concentración sérica o plasmática del fármaco en el eje de ordenadas (eje de las y) frente al tiempo en el eje de abscisas (eje de las x). Generalmente, los valores de AUC representan una serie de valores tomados de todos los sujetos en una población de pacientes de ensayo que son la media de toda la población del ensayo. Una realización preferida de la invención es aquella en que la biodisponibilidad relativa de la composición de ensayo es al menos 1,25 en relación a una composición de referencia que consta de un GPI pero sin ningún polímero como se ha descrito antes. (Esto es, el AUC proporcionada por la composición de ensayo es al menos 1,25 veces el AUC proporcionada por la composición de referencia). Una realización de la invención aún más preferida es aquella en la que la biodisponibilidad relativa de la composición de ensayo es al menos 2,0 en relación a una composición de referencia del GPI pero sin ningún polímero presente como se ha descrito antes. La determinación de las AUC es un procedimiento bien conocido y está

descrito por ejemplo, en Welling, "Pharmacokinetics Processes and Mathematics", ACS Monograph 185 (1986).

INHIBIDORES DE LA GLUCÓGENO-FOSFORILASA

La invención es útil para los GPI que tienen una solubilidad acuosa suficiente-
5 mente baja para que sea deseable aumentar su solubilidad en agua. Por tanto, la invención tendrá utilidad siempre que se encuentre deseable aumentar la concentración del GPI en un medio de uso. Que el GPI tiene "baja solubilidad" significa que el GPI puede ser o bien "sustancialmente insoluble en agua" (lo que significa que el GPI tiene una solubilidad acuosa mínima a cualquier pH fisiológicamente apropiado (por ejem-
10 plo, pH 1-8) y aproximadamente 22 °C, de menos de 0,01 mg/ml), o bien "escasamente soluble en agua" (esto es, tiene una solubilidad en agua de hasta aproximadamente 1 mg/ml). (A menos que se especifique otra cosa, la referencia a la solubilidad acuosa aquí y en las reivindicaciones se determina a 22 °C aproximadamente). Las composiciones de la presente invención encuentran mayor utilidad cuando la solubili-
15 dad del GPI disminuye, y por ello son preferidas para las solubilidades de los GPI inferiores a 0,5 mg/ml y aún más preferidas para las solubilidades de los GPI inferiores a 0,1 mg/ml. En general, se puede decir que el GPI tiene una relación dosis a solubilidad acuosa mayor de aproximadamente 10 ml, donde la solubilidad (mg/ml) es el valor mínimo observado en cualquier solución acuosa fisiológicamente apropiada (por ejem-
20 plo aquellas con valores de pH de 1 a 8) incluyendo las soluciones tampones gástricas e intestinales simuladas de la Farmacopea de los Estados Unidos (USP), y la dosis está en mg. Las composiciones de la presente invención, como se ha mencionado antes, encuentran mayor utilidad cuando la solubilidad del GPI disminuye, y la dosis aumenta. Por ello, se prefieren las composiciones en las que la relación dosis a solubi-
25 lidad aumenta, y por tanto se prefieren las relaciones dosis a solubilidad mayores de 100 ml, y son más preferidas las relaciones dosis a solubilidad mayores de 400 ml.

Preferiblemente, el GPI se une a la enzima GP en el sitio de unión del núcleo del indol. Como se usa aquí y en las reivindicaciones, "unión" significa que una porción del GPI se une a la enzima GP de tal manera que una porción del GPI está en con-
30 tacto por medio de un enlace de van der Waals o de hidrógeno con una porción o todas las porciones de ciertos residuos del sitio de unión. En una realización preferida, el GPI se une a la enzima GP con una porción o todas las porciones de los siguientes residuos de GP:

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Estructura secundaria original	<u>Número de residuo</u>
	13-23
hélice $\alpha 1$	24-37
vuelta	38-39, 43, 46-47
hélice $\alpha 2$	48-66, 69-70, 73-74, 76-78
	79-80
cadena $\beta 1$	81-86
	87-88
cadena $\beta 2$	89-92
	93
hélice $\alpha 3$	94-102
	103
hélice $\alpha 4$	104-115
	116-117
hélice $\alpha 5$	118-124
	125-128
cadena $\beta 3$	129-131
	132-133
hélice $\alpha 6$	134-150
	151-152
cadena $\beta 4$	153-160
	161
cadena $\beta 4b$	162-163
	164-166
cadena $\beta 5$	167-171
	172-173
cadena $\beta 6$	174-178
	179-190
cadena $\beta 7$	191-192
	194, 197
cadena $\beta 8$	198-209
	210-211
cadena $\beta 9$	212-216
cadena $\beta 10$	219-226, 228-232

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	233-236
cadena β 11	237-239, 241. 243-247
	248-260
hélice α 7	261-276
cadena β 11b	277-281
vuelta inversa	282-289
hélice α 8	290-304

Más preferiblemente, el GPI se une con uno o más de los siguientes residuos de GP en una o ambas subunidades:

<u>Estructura secundaria original</u>	<u>Número de residuo</u>
	13-23
hélice α 1	24-37
vuelta	38-39, 43, 46-47
hélice α 2	48-66, 69-70, 73-74, 76-78
	79-80
cadena β 2	91-92
	93
hélice α 3	94-102
	103
hélice α 4	104-115
	116-117
hélice α 5	118-124
	125-128
cadena β 3	129-130
cadena β 4	159-160
	161
cadena β 4b	162-163
	164-166
cadena β 5	167-168
cadena β 6	178
	179-190
cadena β 7	191-192
	194, 197

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cadena β 9	198-200
cadena β 10	220-226
	228-232
	233-236
cadena β 11	237-239, 241, 243-247
	248-260
hélice α 7	261-276
cadena β 11b	277-280

Aún más preferiblemente, el GPI se une con uno o más de los siguientes residuos de GP en una o ambas subunidades:

Número de residuo

33-39
49-66
94
98
102
125-126
160
162
182-192
197
224-226
228-231
238-239
241
245
247

5 Más preferiblemente, el GPI se une con uno o más de los siguientes residuos de GP en una o ambas subunidades:

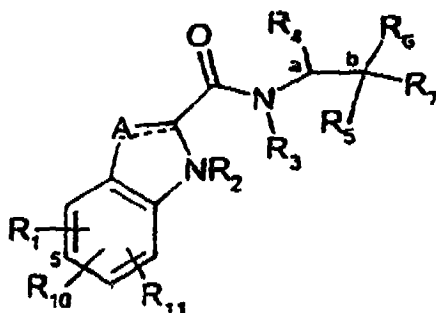
Número de residuo

37-39
53

57
60
63-64
184-192
226
229

El sitio de unión del núcleo de indol está descrito de forma más completa en la solicitud provisional de patente de Estados Unidos comúnmente cedida, número de serie 95790 presentada el 7 de agosto de 1998, y la correspondiente solicitud publicada de patente europea número EP0978279 A1, cuya descripción pertinente se incorpora aquí como referencia.

Se cree que ciertos compuestos son capaces de unirse al sitio de unión del núcleo del indol. Por tanto, los GPI preferidos de la presente invención son aquellos que son capaces de unirse a este sitio. Un grupo de tales compuestos tiene la estructura de la fórmula I:



Fórmula I

y sus sales y profármacos farmacéuticamente aceptables donde la línea de trazos (- -) es un enlace opcional, y los diferentes sustituyentes de la fórmula I son como sigue; A es -C(H)=, -C(alquil (C₁-C₄))= o -C(halo)= cuando la línea de trazos (- -) es un enlace, o A es metileno o -CH(alquil (C₁-C₄))- cuando la línea de trazos (- -) no es un enlace;

R₁, R₁₀ o R₁₁ son cada uno independientemente H, halo, 4-, 6- o 7-nitro, ciano, alquilo (C₁-C₄), alcoxi (C₁-C₄), fluorometilo, difluorometilo o trifluorometilo;

R₂ es H;

R₃ es H o alquilo (C₁-C₅);

R₄ es metilo, etilo, *n*-propilo, hidroxialquilo (C₁-C₃), alcoxi (C₁-C₃)-alquilo (C₁-C₃), fenilalquilo (C₁-C₄), fenilhidroxialquilo (C₁-C₄), fenilalcoxi (C₁-C₄)-alquilo (C₁-C₄), tien-2-ilalquilo (C₁-C₄) o tien-3-ilalquilo (C₁-C₄) o fur-2-ilalquilo (C₁-C₄) o fur-3-ilalquilo (C₁-C₄)

donde dichos anillos R₄ están mono-, di- o tri-sustituídos independientemente sobre

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carbono con H, halo, alquilo (C_1-C_4), alcoxi (C_1-C_4), trifluorometilo, hidroxilo, amino o ciano; o

R_4 es pirid-2-il-alquilo (C_1-C_4), pirid-3-il-alquilo (C_1-C_4) o pirid-4-il-alquilo (C_1-C_4), tiazol-2-il-alquilo (C_1-C_4), tiazol-4-il-alquilo (C_1-C_4) o tiazol-5-il-alquilo (C_1-C_4), imidazol-1-il-alquilo (C_1-C_4), imidazol-2-il-alquilo (C_1-C_4), imidazol-4-il-alquilo (C_1-C_4) o imidazol-5-il-alquilo (C_1-C_4), pirrol-2-il-alquilo (C_1-C_4) o pirrol-3-il-alquilo (C_1-C_4), oxazol-2-il-alquilo (C_1-C_4), oxazol-4-il-alquilo (C_1-C_4) u oxazol-5-il-alquilo (C_1-C_4), pirazol-3-il-alquilo (C_1-C_4), pirazol-4-il-alquilo (C_1-C_4) o pirazol-5-il-alquilo (C_1-C_4), isoxazol-3-il-alquilo (C_1-C_4), isoxazol-4-il-alquilo (C_1-C_4), isoxazol-5-il-alquilo (C_1-C_4), isotiazol-3-il-alquilo (C_1-C_4), isotiazol-4-il-alquilo (C_1-C_4), isotiazol-5-il-alquilo (C_1-C_4), piridazin-3-il-alquilo (C_1-C_4) o piridazin-4-il-alquilo (C_1-C_4), pirimidin-2-il-alquilo (C_1-C_4), pirimidin-4-il-alquilo (C_1-C_4), pirimidin-5-il-alquilo (C_1-C_4) o pirimidin-6-il-alquilo (C_1-C_4), pirazin-2-il-alquilo (C_1-C_4) o pirazin-3-il-alquilo (C_1-C_4) o 1,3,5-triazin-2-il-alquilo (C_1-C_4), donde dichos heterociclos R_4 precedentes están opcionalmente mono- o di-sustituídos independientemente con halo, trifluorometilo, alquilo (C_1-C_4), alcoxi (C_1-C_4), amino o hidroxilo y dichos mono- o di-sustituyentes están unidos a carbono;

R_5 es H, hidroxilo, flúor, alquilo (C_1-C_5), alcoxi (C_1-C_5), alcanilo (C_1-C_6), amino-alcoxi (C_1-C_4), mono-N-alquilamino (C_1-C_4)-alcoxi (C_1-C_4) o di-N,N-alquilamino (C_1-C_4)-alcoxi (C_1-C_4), carboxi-alcoxi (C_1-C_4), alcoxi (C_1-C_5)-carbonil-alcoxi (C_1-C_4), benciloxicarbonil-alcoxi (C_1-C_4), o carbonilo donde dicho carbonilo está unido carbono-carbono con fenilo, tiazolilo, imidazolilo, 1H-indolilo, furilo, pirrolilo, oxazolilo, pirazolilo, isoxazolilo, isotiazolilo, piridazinilo, pirimidinilo, pirazinilo o 1,3,5-triazinilo y donde dichos anillos R_5 precedentes están opcionalmente mono-sustituídos con halo, alquilo (C_1-C_4), alcoxi (C_1-C_4), hidroxilo, amino o trifluorometilo y dichos monosustituyentes están unidos a carbono;

R_7 es H, flúor o alquilo (C_1-C_5); o

R_5 y R_7 considerados juntos son oxo;

R_8 es carboxi, alcoxi (C_1-C_6)-carbonilo, $C(O)NR_8R_9$ o $C(O)R_{12}$, donde

R_8 es alquilo (C_1-C_3), hidroxilo o alcoxi (C_1-C_3); y

R_9 es H, alquilo (C_1-C_6), hidroxilo, alcoxi (C_1-C_6), metilen-alquilo (C_1-C_6) perfluorado, fenilo, piridilo, tienilo, furilo, pirrolilo, pirrolidinilo, oxazolilo, tiazolilo, imidazolilo, pirazolilo, pirazolinilo, pirazolidinilo, isoxazolilo, isotiazolilo, piranilo, piperidinilo, morfolinilo, piridazinilo, pirimidinilo, pirazinilo, piperazinilo o 1,3,5-triazinilo donde dichos anillos R_9 precedentes están ligados por carbono-nitrógeno; o

R_9 es alquilo (C_1-C_6) mono-, di- o tri-sustituído, donde dichos sustituyentes son independientemente H, hidroxilo, amino, mono-N-alquilamino (C_1-C_5) o di-N,N-alquilamino

(C₁-C₅); o

R₉ es alquilo (C₁-C₅) mono- o di-sustituido, donde dichos sustituyentes son independientemente fenilo, piridilo, furilo, pirrolilo, pirrolidinilo, oxazolilo, tiazolilo, imidazolilo, pirazolilo, pirazolinilo, pirazolidinilo, isoxazolilo, isotiazolilo, piranilo, piridinilo, piperidinilo, morfolinilo, piridazinilo, pirimidinilo, pirazinilo, piperazinilo o 1,3,5-triazinilo,

donde los anillos no aromáticos R₉ que contienen nitrógeno están opcionalmente mono-sustituídos sobre el nitrógeno con alquilo (C₁-C₆), bencilo, benzoilo o alcoxi (C₁-C₆)-carbonilo y donde los anillos R₉ están opcionalmente mono-sustituídos sobre carbono con halo, alquilo (C₁-C₄), alcoxi (C₁-C₄), hidroxilo, amino o mono-N-alquilamino (C₁-C₅) y di-N,N-alquilamino (C₁-C₅) con la condición de que no está incluido ningún nitrógeno cuaternizado y no hay enlaces nitrógeno-oxígeno, nitrógeno-nitrógeno o nitrógeno-halo;

R₁₂ es piperazin-1-ilo, 4-alquil (C₁-C₄)-piperazin-1-ilo, 4-formilpiperazin-1-ilo, morfolino, tiomorfolino, 1-oxotiomorfolino, 1,1-dioxo-tiomorfolino, tiazolidin-3-ilo, 1-oxo-tiazolidin-3-ilo, 1,1-dioxo-tiazolidin-3-ilo, 2-alcoxi (C₁-C₆)-carbonilpirrolidin-1-ilo, oxazolidin-3-ilo o 2(R)-hidroximetilpirrolidin-1-ilo; o

R₁₂ es oxazetidin-2-ilo mono- o di-sustituido en 3- y/o 4-, oxazolidin-3-ilo mono- o di-sustituido en 2-, 4-, y/o 5-, tiazolidin-3-ilo mono- o di-sustituido en 2-, 4-, y/o 5-, 1-oxotiazolidin-3-ilo mono- o di-sustituido en 2-, 4-, y/o 5-, 1,1-dioxotiazolidin-3-ilo mono- o di-sustituido en 2-, 4-, y/o 5-, pirrolidin-1-ilo mono- o di-sustituido en 3-, y/o 4-, piperidin-1-ilo mono- di- o tri-sustituido en 3-, 4-, y/o 5-, piperazin-1-ilo mono- di- o tri-sustituido en 3-, 4-, y/o 5-, azetidin-1-ilo sustituido en 3-, 1,2-oxazinan-2-ilo mono- o di-sustituido en 4-, y/o 5-, pirazolidin-1-ilo mono- o di-sustituido en 3-, y/o 4-, isotiazolidin-2-ilo mono- o di-sustituido en 4-, y/o 5-, isotiazolidin-2-ilo mono- y/o di-sustituido en 4-, y/o 5-, donde dichos sustituyentes de R₁₂ son independientemente H, halo, alquilo (C₁-C₅), hidroxilo, amino, mono-N-alquilamino (C₁-C₅) o di-N,N-alquilamino (C₁-C₅), formilo, oxo, hidroximino, alcoxi (C₁-C₅), carboxi, carbamoilo, mono-N-alquil (C₁-C₄)-carbamoilo o di-N,N-alquil (C₁-C₄)-carbamoilo, alcoxi (C₁-C₄)-imino, alcoxi (C₁-C₄)-metoxi, alcoxi (C₁-C₆)-carbonilo, carboxi-alquilo (C₁-C₅) o hidroxil-alquilo (C₁-C₅);

con la condición de que si R₄ es H, metilo, etilo o *n*-propilo, R₅ es OH;

con la condición de que si R₆ y R₇ son H, entonces R₄ no es H, metilo, etilo, *n*-propilo, hidroxil-alquilo (C₁-C₃) o alcoxi (C₁-C₃)-alquilo (C₁-C₃) y R₈ es C(O)NR₈R₉, C(O)R₁₂ o alcoxi (C₁-C₄)-carbonilo.

Los compuestos de la fórmula I están descritos en la solicitud de tratado de cooperación de patente publicada, número WO 96/39385, cuya descripción completa se incorpora aquí como referencia.

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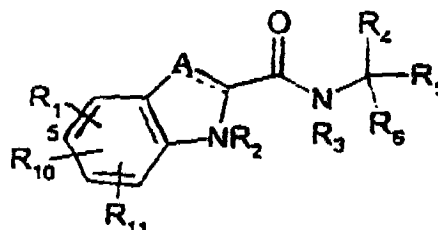
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También en otro aspecto preferido de la invención, el GPI tiene la estructura de la fórmula II, que es otra clase de compuestos que se consideran capaces de unirse al sitio de unión del núcleo del indol:



Fórmula II

y sus sales y profármacos farmacéuticamente aceptables donde la línea de trazos (- -) es un enlace opcional, y los sustituyentes de la fórmula II son como sigue;

A es $-C(H)=$, $-C(\text{alquil } (C_1-C_4))=$ o $-C(\text{halo})=$ o $-N=$, cuando la línea de trazos (- -) es un enlace, o A es metileno o $-CH(\text{alquil } (C_1-C_4))-$ cuando la línea de trazos (- -) no es un enlace;

R_1 , R_{10} o R_{11} son cada uno independientemente H, halo, ciano, 4-, 6- o 7-nitro, alquilo (C_1-C_4), alcoxi (C_1-C_4), fluorometilo, difluorometilo o trifluorometilo;

R_2 es H;

R_3 es H o alquilo (C_1-C_5);

R_4 es H, metilo, etilo, *n*-propilo, hidroxialquilo (C_1-C_3), alcoxi (C_1-C_3)-alquilo (C_1-C_3), fenilalquilo (C_1-C_4), fenilhidroxialquilo (C_1-C_4), fenilalcoxi (C_1-C_4)-alquilo (C_1-C_4), tien-2-ilalquilo (C_1-C_4) o tien-3-ilalquilo (C_1-C_4) o fur-2-ilalquilo (C_1-C_4) o fur-3-ilalquilo (C_1-C_4) donde dichos anillos R_4 están mono-, di- o tri-sustituídos independientemente sobre carbono con H, halo, alquilo (C_1-C_4), alcoxi (C_1-C_4), trifluorometilo, hidroxilo, amino, ciano o 4,5-dihidro-1H-imidazol-2-ilo; o

R_4 es pirid-2-ilalquilo (C_1-C_4), pirid-3-ilalquilo (C_1-C_4) o pirid-4-ilalquilo (C_1-C_4), tiazol-2-ilalquilo (C_1-C_4), tiazol-4-ilalquilo (C_1-C_4) o tiazol-5-ilalquilo (C_1-C_4), imidazol-2-ilalquilo (C_1-C_4), imidazol-4-ilalquilo (C_1-C_4) o imidazol-5-ilalquilo (C_1-C_4), pirrol-2-ilalquilo (C_1-C_4) o pirrol-3-ilalquilo (C_1-C_4), oxazol-2-ilalquilo (C_1-C_4), oxazol-4-ilalquilo (C_1-C_4) u oxazol-5-ilalquilo (C_1-C_4), pirazol-3-ilalquilo (C_1-C_4), pirazol-4-ilalquilo (C_1-C_4) o pirazol-5-ilalquilo (C_1-C_4), isoxazol-3-ilalquilo (C_1-C_4), isoxazol-4-ilalquilo (C_1-C_4) o isoxazol-5-ilalquilo (C_1-C_4), isotiazol-3-ilalquilo (C_1-C_4), isotiazol-4-ilalquilo (C_1-C_4) o isotiazol-5-ilalquilo (C_1-C_4), piridazin-3-ilalquilo (C_1-C_4) o piridazin-4-ilalquilo (C_1-C_4), pirimidin-2-ilalquilo (C_1-C_4), pirimidin-4-ilalquilo (C_1-C_4), pirimidin-5-ilalquilo (C_1-C_4) o pirimidin-6-ilalquilo (C_1-C_4), pirazin-2-ilalquilo (C_1-C_4) o pirazin-3-ilalquilo (C_1-C_4), 1,3,5-triazin-2-ilalquilo (C_1-C_4) o indol-2-ilalquilo (C_1-C_4), donde dichos heterociclos R_4 precedentes están opcionalmente mono- o di-sustituídos independientemente

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con halo, trifluorometilo, alquilo (C₁-C₄), alcoxi (C₁-C₄), amino, hidroxilo o ciano y dichos sustituyentes están unidos a carbono; o

R₄ es R₁₅-carboniloximetilo, donde dicho R₁₅ es fenilo, tiazolilo, imidazolilo, 1H-indolilo, furilo, pirrolilo, oxazolilo, pirazolilo, isoxazolilo, isotiazolilo, piridilo, piridazinilo, pirimidinilo, pirazinilo o 1,3,5-triazinilo y donde dichos anillos R₁₅ precedentes están opcionalmente mono- o di-sustituidos independientemente con halo, amino, hidroxilo, alquilo (C₁-C₄), alcoxi (C₁-C₄) o trifluorometilo y dichos mono- o di-sustituyentes están unidos a carbono;

R₅ es H, metilo, etilo, *n*-propilo, hidroximetilo o hidroxietilo;

10 R₆ es carboxi, alcoxi (C₁-C₈)-carbonilo, benciloxycarbonilo, C(O)NR₈R₉ o C(O)R₁₂, donde R₈ es H, alquilo (C₁-C₈), cicloalquilo (C₃-C₈), cicloalquil (C₃-C₈)-alquilo (C₁-C₅), hidroxilo o alcoxi (C₁-C₈); y

R₉ es H, cicloalquilo (C₃-C₈), cicloalquil (C₃-C₈)-alquilo (C₁-C₅), cicloalquenilo (C₄-C₇), cicloalquil (C₃-C₇)-alcoxi (C₁-C₅), cicloalquilo (C₃-C₇), hidroxilo, metilen-alquilo (C₁-C₈)
15 perfluorado, fenilo o un heterociclo donde dicho heterociclo es piridilo, furilo, pirrolilo, pirrolidinilo, oxazolilo, tiazolilo, imidazolilo, pirazolilo, pirazolinilo, pirazolidinilo, isoxazolilo, isotiazolilo, piranilo, piridinilo, piperidinilo, morfolinilo, piridazinilo, pirimidinilo, pirazinilo, piperazinilo, 1,3,5-triazinilo, benzotiazolilo, benzoxazolilo, bencimidazolilo, tioromanilo o tetrahydrobenzotiazolilo donde dichos anillos heterociclos están ligados por carbono-nitrógeno; o

R₉ es alquilo (C₁-C₈) o alcoxi (C₁-C₈) donde dichos alquilo (C₁-C₈) o alcoxi (C₁-C₈) están opcionalmente monosustituidos con cicloalquen-1-ilo (C₄-C₇), fenilo, tienilo, piridilo, furilo, pirrolilo, pirrolidinilo, oxazolilo, tiazolilo, imidazolilo, pirazolilo, pirazolinilo, pirazolidinilo, isoxazolilo, isotiazolilo, piranilo, piperidinilo, morfolinilo, tiomorfolinilo, 1-oxotiomorfolinilo, 1,1-dioxotiomorfolinilo, piridazinilo, pirimidinilo, pirazinilo, piperazinilo,
25 1,3,5-triazinilo o indolilo y donde dichos alquilo (C₁-C₈) o alcoxi (C₁-C₈) están además opcionalmente mono- o di-sustituidos independientemente con halo, hidroxilo, alcoxi (C₁-C₅), amino, mono-N-alquilamino (C₁-C₅) o di-N,N-alquilamino (C₁-C₅), ciano, carboxi, o alcoxi (C₁-C₄)-carbonilo; y

30 donde los anillos R₉ están opcionalmente mono- o di-sustituidos independientemente sobre carbono con halo, alquilo (C₁-C₄), alcoxi (C₁-C₄), hidroxilo, hidroxilo-alquilo (C₁-C₄), amino-alquilo (C₁-C₄), mono-N-alquilamino (C₁-C₄) o di-N,N-alquilamino (C₁-C₄), alquilo (C₁-C₄), alcoxi (C₁-C₄)-alquilo (C₁-C₄), amino, mono-N-alquilamino (C₁-C₄) o di-N,N-alquilamino (C₁-C₄), ciano, carboxi, alcoxi (C₁-C₅)-carbonilo, carbamoilo, formilo o trifluorometilo y dichos anillos R₉ pueden estar además opcionalmente mono- o di-sustituidos independientemente con alquilo (C₁-C₅) o halo;

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con la condición de que no está incluido ningún nitrógeno cuaternizado sobre ningún heterociclo R_9 ;

R_{12} es morfolino, tiomorfolino, 1-oxotiomorfolino, 1,1-dioxotiomorfolino, tiazolidin-3-ilo, 1-oxotiazolidin-3-ilo, 1,1-dioxotiazolidin-3-ilo, pirrolidin-1-ilo, piperidin-1-ilo, piperazin-1-ilo, piperazin-4-ilo, azetidin-1-ilo, 1,2-oxazinan-2-ilo, pirazolidin-1-ilo, isoxazolidin-2-ilo, isotiazolidin-2-ilo, 1,2-oxazetidin-2-ilo, oxazolidin-3-ilo, 3,4-dihidroisoquinolin-2-ilo, 1,3-dihidroisoindol-2-ilo, 3,4-dihidro-2H-quinol-1-ilo, 2,3-dihidrobenczo[1,4]oxazin-4-ilo, 2,3-dihidro-benczo[1,4]tiazin-4-ilo, 3,4-dihidro-2H-quinoxalin-1-ilo, 3,4-dihidro-benczo[c][1,2]-oxazin-1-ilo, 1,4-dihidro-benczo[d][1,2]oxazin-3-ilo, 3,4-dihidro-benczo[e][1,2]oxazin-2-ilo, 3H-benczo[d]isoxazol-2-ilo, 3H-benczo[c]isoxazol-2-ilo o azepan-1-ilo,

donde dichos anillos R_{12} están opcionalmente mono-, di- o tri-sustituídos independientemente con halo, alquilo (C_1-C_5), alcoxi (C_1-C_5), hidroxilo, amino, mono-N-alquilamino (C_1-C_5) o di-N,N-alquilamino (C_1-C_5), formilo, carboxi, carbamoilo, mono-N-alquil (C_1-C_5)-carbamoilo o di-N,N-alquil (C_1-C_5)-carbamoilo, alcoxi (C_1-C_6), alcoxi (C_1-C_3), alcoxi (C_1-C_4)-carbonilo, benciloxicarbonilo, alcoxi (C_1-C_5)-carbonil-alquilo (C_1-C_5), alcoxi (C_1-C_5)-carbonilamino, carboxi-alquilo (C_1-C_5), carbamoil-alquilo (C_1-C_5), mono-N-alquil (C_1-C_5)-carbamoil-alquilo (C_1-C_5) o di-N,N-alquil (C_1-C_5)-carbamoil-alquilo (C_1-C_5), hidroxilo-alquilo (C_1-C_5), alcoxi (C_1-C_4)-alquilo (C_1-C_4), amino-alquilo (C_1-C_4), mono-N-alquilamino (C_1-C_4)-alquilo (C_1-C_4) o di-N,N-alquilamino (C_1-C_4)-alquilo (C_1-C_4), oxo, hidroximiino o alcoxi (C_1-C_6)-imino y donde no más de dos sustituyentes se seleccionan entre oxo, hidroximiino o alcoxi (C_1-C_6)-imino y los oxo, hidroximiino o alcoxi (C_1-C_6)-imino están sobre un carbono no aromático; y

donde dichos anillos R_{12} están además opcionalmente mono-, o di-sustituídos independientemente con alquilo (C_1-C_5) o halo;

con la condición de que cuando R_8 es alcoxi (C_1-C_5)-carbonilo o benciloxicarbonilo, entonces R_1 es 5-halo, 5-alquilo (C_1-C_4) o 5-ciano y R_4 es (fenil)(hidroxilo)alquilo (C_1-C_4), (fenil)(alcoxi (C_1-C_4))-alquilo (C_1-C_4), hidroximetilo o Ar-alquilo (C_1-C_2), donde Ar es tien-2-ilo o tien-3-ilo, fur-2-ilo o fur-3-ilo o fenilo donde dicho Ar está opcionalmente mono-, o di-sustituído independientemente con halo; con las condiciones de que cuando R_4 es bencilo y R_5 es metilo, R_{12} no es 4-hidroxipiperidin-1-ilo o cuando R_4 es bencilo y R_5 es metilo, R_8 no es $C(O)N(CH_3)_2$;

con la condición de que cuando R_1 y R_{10} y R_{11} son H, R_4 no es imidazol-4-ilmetilo, 2-feniletilo o 2-hidroxil-2-feniletilo;

con la condición de que cuando R_8 y R_9 son *n*-pentilo, R_1 es 5-cloro, 5-bromo, 5-ciano, 5-alquilo (C_1-C_5), 5-alcoxi (C_1-C_5) o trifluorometilo;

con la condición de que cuando R_{12} es 3,4-dihidroisoquinol-2-ilo, dicho 3,4-

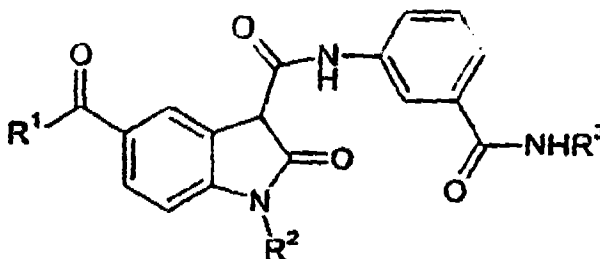
dihidroisoquinol-2-ilo no está sustituido con carboxi-alquilo (C_1-C_4);

con la condición de que cuando R_8 es H y R_9 es alquilo (C_1-C_6), R_9 no está sustituido con carboxi o alcoxi (C_1-C_4)-carbonilo sobre el carbono que está unido al átomo de nitrógeno N de NHR_9 ; y

- 5 con la condición de que cuando R_6 es carboxi y R_1 , R_{10} , R_{11} y R_5 son todos H, entonces R_4 no es bencilo, H, (fenil)(hidroxi)metilo, metilo, etilo o *n*-propilo.

Los compuestos de la fórmula II están descritos en la solicitud de tratado de cooperación de patente publicada, número WO 96/39384, cuya descripción completa se incorpora aquí como referencia.

- 10 También en otro aspecto preferido de la invención, el GPI tiene la estructura de la fórmula III, que es otra clase de compuestos que se consideran capaces de unirse al sitio de unión del núcleo del indol:



Fórmula III

- 15 uno de sus profármacos o una sal farmacéuticamente aceptable de dicho compuesto o de dicho profármaco, donde la fórmula III tiene los siguientes sustituyentes:

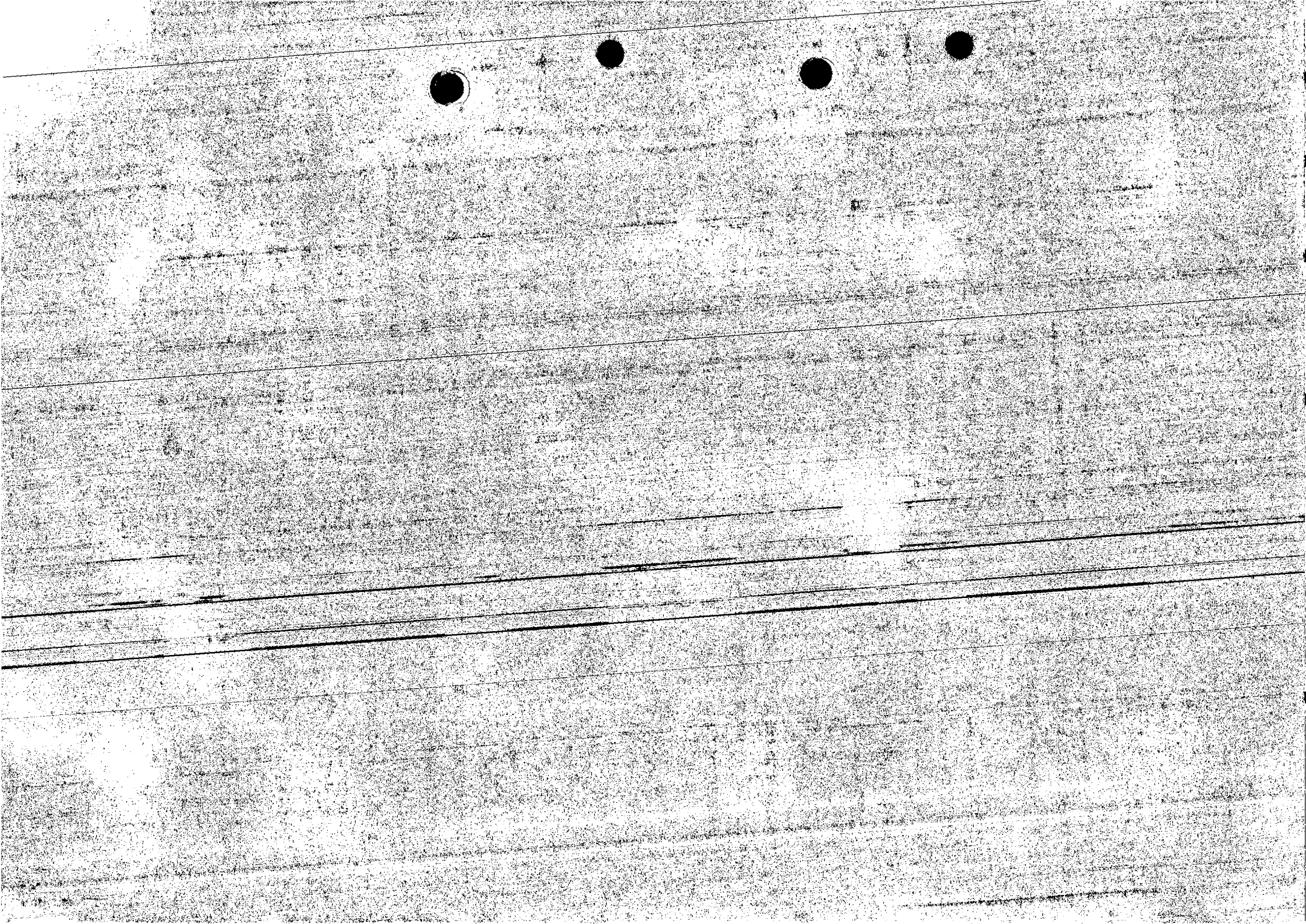
R^1 es alquilo (C_1-C_4), cicloalquilo (C_3-C_7), fenilo o fenilo sustituido con hasta tres alquilo (C_1-C_4), alcoxi (C_1-C_4) o halógeno;

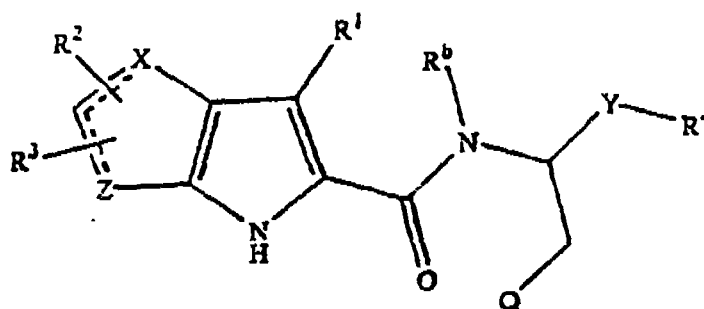
R^2 es alquilo (C_1-C_4); y

- 20 R^3 es cicloalquilo (C_3-C_7); fenilo; fenilo sustituido en la posición *para* con alquilo (C_1-C_4), halo, hidroxialquilo (C_1-C_4) o trifluorometilo; fenilo sustituido en la posición *meta* con flúor; o fenilo sustituido en la posición *orto* con flúor.

- Los compuestos de la fórmula III están descritos más completamente en la patente de Estados Unidos comúnmente cedida número 5.998.463, cuya descripción relevante se incorpora aquí como referencia.

También en otro aspecto preferido de la invención, el GPI tiene la estructura de la fórmula IV, que es otra clase de compuestos a los que se considera capaces de unirse al sitio de unión del núcleo del indol:





Fórmula IV

uno de sus estereoisómeros, sales o profármacos farmacéuticamente aceptables, o una sal farmacéuticamente aceptable del profármaco, donde la fórmula IV tiene los siguientes sustituyentes:

Q es arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

cada uno de Z y X son independientemente (C, CH o CH₂), N, O o S;

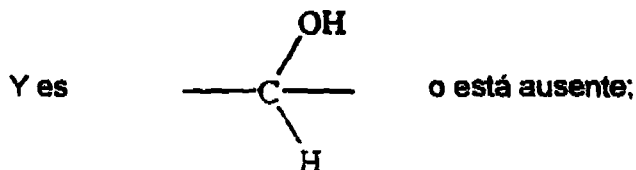
X¹ es NR^a, -CH₂-, O o S;

cada - - - es independientemente un enlace o está ausente,

con la condición de que ambos - - - no son simultáneamente enlaces;

R¹ es hidrógeno, halógeno, -O-alquilo C₁-C₈, -S-alquilo C₁-C₈, -alquilo C₁-C₈, -CF₃, -NH₂, -NH-alquilo C₁-C₈, -N(alquilo C₁-C₈)₂, -NO₂, -CN, -CO₂H, -CO₂-alquilo C₁-C₈, -alquenilo C₂-C₈ o -alquinilo C₂-C₈;

cada uno de R^a y R^b es independientemente hidrógeno o -alquilo C₁-C₈;



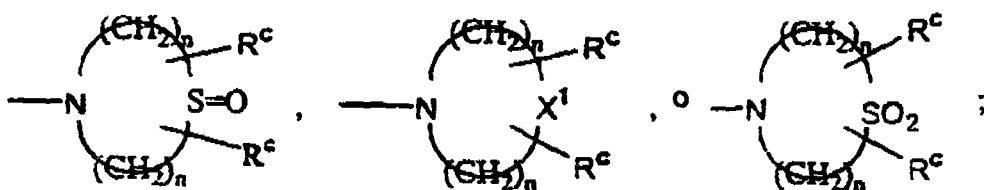
R² y R³ son independientemente hidrógeno, halógeno, -alquilo C₁-C₈, -CN, -C≡C-Si(CH₃)₃, -O-alquilo C₁-C₈, -S-alquilo C₁-C₈, -CF₃, -NH₂, -NH-alquilo C₁-C₈, -N(alquilo C₁-C₈)₂, -NO₂, -CO₂H, -CO₂-alquilo C₁-C₈, -alquenilo C₂-C₈ o -alquinilo C₂-C₈, o R² y R³ junto con los átomos del anillo al que están unidos forman un anillo de cinco o seis

miembros que contiene de 0 a 3 heteroátomos y de 0 a 2 dobles enlaces;

R⁴ es -C(=O)-A;

A es -NR^dR^d, NR^aCH₂CH₂OR^a,

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/f



cada R^d es independientemente hidrógeno, alquilo C_1-C_8 , alcoxi C_1-C_8 , arilo, arilo sustituido, heteroarilo, o heteroarilo sustituido;

cada R^e es independientemente hidrógeno, $-C(=O)OR^a$, $-OR^a$, $-SR^a$, o $-NR^aR^a$; y

cada n es independientemente 1-3.

5 Los compuestos de la fórmula IV están descritos en la solicitud provisional de patente de Estados Unidos comúnmente cedida, número de serie 60/157.148, presentada el 30 de septiembre de 1999, cuya descripción relevante se incorpora como referencia.

En una realización especialmente preferida, el GPI se selecciona de uno de los siguientes compuestos de la fórmula I:

[(1S)-((R)-hidroxi-dimetilcarbamoilmetil)-2-fenil-etil]-amida del ácido 5-cloro-1H-indol-2-carboxílico;

[(1S)-((R)-hidroxi-metoxi-metilcarbamoilmetil)-2-fenil-etil]-amida del ácido 5-cloro-1H-indol-2-carboxílico;

15 [(1S)-bencil-(2R)-hidroxi-3-((3S)-hidroxi-pirrolidin-1-il)-3-oxo-propil]-amida del ácido 5-cloro-1H-indol-2-carboxílico;

[(1S)-bencil-(2R)-hidroxi-3-((3R,4S)-dihidroxi-pirrolidin-1-il)-3-oxo-propil]-amida del ácido 5-cloro-1H-indol-2-carboxílico;

20 [(1S)-bencil-(2R)-hidroxi-3-((3R,4R)-dihidroxi-pirrolidin-1-il)-3-oxo-propil]-amida del ácido 5-cloro-1H-indol-2-carboxílico; y

[(1S)-bencil-(2R)-hidroxi-3-morfolin-4-il-3-oxo-propil]-amida del ácido 5-cloro-1H-indol-2-carboxílico.

En otra realización especialmente preferida, el GPI se selecciona de uno de los siguientes compuestos de la fórmula II:

25 [2-((3R,4S)-3,4-dihidroxi-pirrolidin-1-il)-2-oxo-etil]-amida del ácido 5-cloro-1H-indol-2-carboxílico;

[(1S)-bencil-2-((3R,4S)-3,4-dihidroxi-pirrolidin-1-il)-2-oxo-etil]-amida del ácido 5-cloro-1H-indol-2-carboxílico;

30 [(1S)-bencil-2-((3R,4S)-3,4-dihidroxi-pirrolidin-1-il)-2-oxo-etil]-amida del ácido 5-cloro-1H-indol-2-carboxílico;

[(1S)-(4-fluorobencil)-2-(4-hidroxi-piperidin-1-il)-2-oxo-etil]-amida del ácido 5-cloro-1H-

indol-2-carboxílico;

[(1S)-bencil-2-(3-hidroxi-azetidín-1-il)-2-oxo-etil]-amida del ácido 5-cloro-1H-indol-2-carboxílico;

[2-(1,1-dioxo-tiazolidín-3-il)-2-oxo-etil]-amida del ácido 5-cloro-1H-indol-2-carboxílico; y

5 [2-(1-oxo-tiazolidín-3-il)-2-oxo-etil]-amida del ácido 5-cloro-1H-indol-2-carboxílico.

En otra realización especialmente preferida, el GPI se selecciona de uno de los siguientes compuestos de la fórmula III:

5-acetil-1-etil-2,3-dihidro-2-oxo-N-[3-[(fenilamino)carbonil]fenil]-1H-indol-3-carboxamida:

10 5-acetil-N-[3-[(ciclohexilamino)carbonil]fenil]-1-etil-2,3-dihidro-2-oxo-1H-indol-3-carboxamida; y

5-acetil-N-[3-[(4-bromofenil)amino]carbonil]fenil]-2,3-dihidro-1-metil-2-oxo-1H-indol-3-carboxamida.

15 En otra realización especialmente preferida, el GPI se selecciona de uno de los siguientes compuestos de la fórmula IV:

[(1S)-bencil-2-((3R,4S)-dihidroxi-pirrolidin-1-il)-2-oxo-etil]-amida del ácido 2-cloro-6H-tieno[2,3-b]pirrol-5-carboxílico; y

[(1S)-bencil-(2R)-hidroxi-3-((3R,4S)-dihidroxi-pirrolidin-1-il)-3-oxo-propil]-amida del ácido 2-cloro-6H-tieno[2,3-b]pirrol-5-carboxílico.

20 POLÍMEROS QUE AUMENTAN LA CONCENTRACIÓN

Los polímeros que aumentan la concentración adecuados para uso en las composiciones de la presente invención deben ser inertes, en el sentido de que no reaccionan químicamente con el GPI de forma adversa, son farmacéuticamente aceptables, y tienen al menos algo de solubilidad en solución acuosa a los pH fisiológicamente apropiados (por ejemplo, 1-8). El polímero puede ser neutro o ionizable, y debe tener una solubilidad acuosa de al menos 0,1 mg/ml durante al menos una parte del intervalo de pH de 1-8. El polímero es un "polímero que aumenta la concentración", lo que significa que cumple al menos una, y más preferiblemente ambas, de las siguientes condiciones. La primera condición es que el polímero que aumenta la concentración aumenta la MDC del GPI en el medio de uso en relación con una composición de referencia que consta de una cantidad equivalente del GPI pero sin polímero. Esto es, una vez que la composición se introduce en un medio de uso, el polímero aumenta la concentración acuosa del GPI en relación con la composición de referencia. Preferiblemente, el polímero aumenta la MDC del GPI en la solución acuosa al menos 1,25 veces en relación con una composición de referencia, y más preferiblemente al menos 2 veces y más preferiblemente al menos 3 veces. La segunda condi-

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ción es que el polímero que aumenta la concentración aumenta el AUC del GPI en el medio de uso en relación con una composición de referencia que consta de GPI pero sin polímero como se ha descrito antes. Esto es, en el medio de uso, la composición que comprende el GPI y el polímero que aumenta la concentración, proporciona un
5 área bajo la curva (AUC) de concentración frente al tiempo durante un periodo de 90 minutos entre el tiempo de introducción en el medio de uso y aproximadamente 270 minutos después de la introducción en el medio de uso que es al menos 1,25 veces la de una composición de referencia que comprende una cantidad equivalente del GPI pero ningún polímero.

10 Los polímeros que aumentan la concentración adecuados para uso con la presente invención pueden ser celulósicos o no celulósicos. Los polímeros pueden ser neutros o ionizables en solución acuosa. De ellos, se prefieren los polímeros ionizables y celulósicos, siendo los más preferidos los polímeros celulósicos ionizables.

Una clase preferida de polímeros comprende los polímeros que son de naturaleza "anfifila", lo que significa que el polímero tiene porciones hidrófobas e hidrófilas.
15 Los grupos hidrófobos pueden comprender grupos tales como grupos hidrocarbonados alifáticos o aromáticos. Los grupos hidrófilos pueden comprender grupos ionizables o no ionizables que son capaces de formar enlaces de hidrógeno tales como hidroxilos, ácidos carboxílicos, ésteres, aminas o amidas.

20 Los polímeros anfifilos y/o ionizables son preferidos porque se cree que tales polímeros pueden contribuir a tener interacciones relativamente fuertes con el GPI y pueden facilitar la formación de los diferentes tipos de conjuntos polímero/fármaco en el medio de uso como se ha descrito previamente. Adicionalmente, la repulsión de cargas semejantes de los grupos ionizados de tales polímeros puede servir para limitar
25 el tamaño de los conjuntos polímero/fármaco a la escala de los nanómetros o submicras. Por ejemplo, aunque no se desea ligarlos a una teoría particular, tales conjuntos polímero/fármaco pueden comprender conglomerados hidrófobos de GPI rodeados por el polímero con las regiones hidrófobas del polímero vueltas interiormente hacia el GPI y las regiones hidrófilas del polímero vueltas exteriormente hacia el medio acuoso.
30 Alternativamente, dependiendo de la naturaleza química específica del GPI, los grupos funcionales ionizados del polímero se pueden asociar, por ejemplo, por medio de apareamiento de iones o enlaces de hidrógeno, con los grupos iónicos o polares del GPI. En el caso de polímeros ionizables, las regiones hidrófilas del polímero incluirán los grupos funcionales ionizados. Tales conjuntos polímero/fármaco en solución pueden
35 semejar favorablemente a estructuras poliméricas similares a las micelas con carga. En cualquier caso, prescindiendo del mecanismo de acción, se ha observado en la

invención que tales polímeros anfífilos, particularmente los polímeros celulósicos ionizables, han demostrado que mejoran la MDC y/o AUC del GPI en solución acuosa en relación con las composiciones de referencia libres de tales polímeros.

Sorprendentemente, tales polímeros anfífilos pueden aumentar notablemente la concentración máxima de GPI obtenida cuando se administra a un medio de uso una forma amorfa del GPI. En adición, tales polímeros anfífilos interactúan con el GPI para evitar la precipitación o cristalización del GPI de la solución a pesar de que su concentración está sustancialmente por encima de su concentración de equilibrio. En particular, cuando las composiciones preferidas son dispersiones sólidas amorfas del GPI y el polímero que aumenta la concentración, las composiciones proporcionan un gran aumento de la concentración del fármaco, particularmente cuando las dispersiones son sustancialmente homogéneas. La concentración máxima del fármaco puede ser 2 veces y a menudo hasta 10 veces la concentración de equilibrio del GPI cristalino. Tal aumento de las concentraciones del GPI hace a su vez que aumente sustancialmente la biodisponibilidad relativa del GPI.

Una clase adecuada de polímeros para uso con la presente invención comprende polímeros neutros no celulósicos. Ejemplos de estos polímeros incluyen: polímeros y copolímeros de vinilo que tienen sustituyentes de hidroxilo, alquilaciloxi, y ciclo-amido; poli(alcoholes vinílicos) que tienen al menos una porción de sus unidades repetidas en forma no hidrolizada (acetato de vinilo); copolímeros de poli(alcohol vinílico) y poli(acetato de vinilo); poli(vinil-pirrolidona); y copolímeros de polietileno y poli(alcohol vinílico).

Otra clase adecuada de polímeros para uso con la presente invención comprende polímeros ionizables no celulósicos. Ejemplos de estos polímeros incluyen: polímeros de vinilo con grupo funcional de ácido carboxílico, tales como los polimetacrilatos con grupo funcional de ácido carboxílico y los poliacrilatos con grupo funcional de ácido carboxílico tales como los EUDRAGITS® fabricados por Rohm Tech Inc., of Malden, Massachusetts; poliacrilatos y polimetacrilatos con grupo funcional amina; proteínas; y almidones con grupo funcional de ácido carboxílico tales como el glicolato de almidón.

Los polímeros no celulósicos que son anfífilos son copolímeros de un monómero relativamente hidrófilo y un monómero relativamente hidrófobo. Los ejemplos incluyen copolímeros de acrilato y metacrilato. Ejemplos de grados comerciales de tales copolímeros incluyen los EUDRAGITS que son copolímeros de metacrilatos y acrilatos.

Una clase preferida de polímeros comprende polímeros celulósicos ionizables y

neutros con al menos un sustituyente con unión éster- y/o éter en la cual el polímero tiene un grado de sustitución de al menos 0,1 para cada sustituyente. Se debe observar que en la nomenclatura de polímeros usada aquí, los sustituyentes con unión éter se indican antes de la "celulosa" como el resto unido al grupo éter; por ejemplo, el "ácido etilbenzoico-celulosa" tiene sustituyentes de ácido etoxibenzoico. Análogamente, los sustituyentes con unión éster se indican en inglés después de la "celulosa" como el carboxilato, aunque en español se nombran antes de la "celulosa" pero añadiendo la preposición de; por ejemplo, el "ftalato de celulosa" tiene un ácido carboxílico de cada resto ftalato ligado con unión éster al polímero y el otro ácido carboxílico sin reaccionar.

Se debe notar también que el nombre de un polímero tal como "acetato ftalato de celulosa" (CAP) se refiere a cualquiera de la familia de polímeros celulósicos que tiene grupos acetato y ftalato unidos por medio de uniones éster a una fracción significativa de los grupos hidroxilo del polímero celulósico. Generalmente, el grado de sustitución de cada grupo sustituyente puede variar de 0,1 a 2,9 siempre que se cumplan los otros criterios del polímero. "Grado de sustitución" se refiere al número medio de los tres hidroxilos por unidad repetida de sacárido que han sido sustituidos en la cadena de celulosa. Por ejemplo, si todos los hidroxilos de la cadena de celulosa han sido sustituidos con ftalato, el grado de sustitución con ftalato es 3. También están incluidos dentro de cada tipo de familia de polímeros los polímeros celulósicos que tienen sustituyentes adicionales añadidos en cantidades relativamente pequeñas que no alteran sustancialmente el comportamiento del polímero.

Los polímeros celulósicos anfífilos se pueden preparar sustituyendo los polímeros celulósicos en alguno o en todos los sustituyentes de los 3 hidroxilos presentes sobre cada unidad repetida de sacárido, con al menos un sustituyente relativamente hidrófobo. Los sustituyentes hidrófobos pueden ser esencialmente cualquier sustituyente que, si se sustituye hasta un nivel o grado de sustitución bastante alto, puede hacer que el polímero celulósico sea esencialmente insoluble en agua. Las regiones hidrófilas del polímero pueden ser cualquiera de aquellas porciones que están relativamente sin sustituir, puesto que los hidroxilos sin sustituir son por sí mismos relativamente hidrófilos, o aquellas regiones que están sustituidas con sustituyentes hidrófilos. Ejemplos de sustituyentes hidrófobos incluyen los grupos alquilo con unión éter tales como metilo, etilo, propilo, butilo, etc.; o grupos alquilo con unión éster tales como acetato, propionato, butirato, etc.; y los grupos arilo con unión éter y/o éster tales como fenilo, benzoato, o fenilato. Los grupos hidrófilos incluyen grupos no ionizables con unión éter o éster tales como los sustituyentes hidroxialquilo, hidroxietilo, hidroxial-

propilo, y los grupos alquil-éter tales como etoxietoxi o metoxietoxi. Los sustituyentes hidrófilos particularmente preferidos son aquellos que son grupos ionizables con unión éter o éster tales como los ácidos carboxílicos, ácidos tiocarboxílicos, grupos fenoxi sustituidos, aminas, fosfatos o sulfonatos.

5 Una clase de polímeros celulósicos comprende polímeros neutros, lo que significa que los polímeros son sustancialmente no ionizables en solución acuosa. Tales polímeros contienen sustituyentes no ionizables, que pueden estar unidos con unión éter o unión éster. Ejemplos de sustituyentes no ionizables con unión éter incluyen: grupos alquilo, tales como metilo, etilo, propilo, butilo, etc; grupos hidroxi-alquilo tales
10 como hidroximetilo, hidroxietilo, hidroxipropilo, etc; y grupos arilo tales como fenilo. Ejemplos de sustituyentes no ionizables con unión éster incluyen: grupos alquilo, tales como acetato, propionato, butirato, etc; y grupos arilo tales como fenilato. Sin embargo, cuando se incluyen los grupos arilo, puede ser necesario que el polímero incluya una cantidad suficiente de un sustituyente hidrófilo de forma que el polímero tenga al
15 menos algo de solubilidad en agua a cualquier pH fisiológicamente apropiado de 1 a 8.

Ejemplos de polímeros no ionizables que se pueden usar como el polímero incluyen: acetato de hidroxipropil-metil-celulosa, hidroxipropil-metil-celulosa, hidroxipropil-celulosa, metil-celulosa, hidroxietil-metil-celulosa, acetato de hidroxietil-celulosa, e hidroxietil-etil-celulosa.

20 Un grupo preferido de polímeros celulósicos neutros son aquellos que son anfífilos. Ejemplos de estos polímeros incluyen hidroxipropil-metil-celulosa y acetato de hidroxipropil-celulosa, donde las unidades celulósicas repetidas que tienen relativamente gran número de sustituyentes metilo o acetato en relación a los hidroxilo sin sustituir o los sustituyentes hidroxipropilo constituyen las regiones hidrófobas en relación a otras unidades repetidas del polímero.
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Una clase preferida de polímeros celulósicos comprende polímeros que son al menos parcialmente ionizables a pH fisiológicamente apropiado e incluyen al menos un sustituyente ionizable, que puede tener o unión éter o unión éster. Ejemplos de sustituyentes ionizables con unión éter incluyen: ácidos carboxílicos, tales como acético
30 ácido, ácido propiónico, ácido benzoico, ácido salicílico, ácidos alcoxibenzoicos tales como ácido etoxibenzoico o ácido propoxibenzoico, los diferentes isómeros del ácido alcoxifálico tales como ácido etoxifálico y ácido etoxisofálico, los diferentes isómeros del ácido alcoxinicotínico tales como ácido etoxinicotínico, y los diferentes isómeros del ácido picolínico tales como ácido etoxipicolínico, etc; ácidos tiocarboxílicos, tales como ácido tioacético; grupos fenoxi sustituidos, tales como hidroxifenoxi,
35 etc; aminas, tales como aminoetoxi, dietilaminoetoxi, trimetilaminoetoxi, etc; fosfatos,

tales como etoxi-fosfato; y sulfonatos, tales como etoxi-sulfonato. Ejemplos de sustituyentes ionizables con unión éster incluyen: ácidos carboxílicos, tales como succinato, citrato, ftalato, tereftalato, isoftalato, trimelitato, y los diferentes isómeros del ácido piridindicarboxílico, etc; ácidos tiocarboxílicos, tales como tiosuccinato; grupos fenoxi sustituidos, tales como ácido amino-salicílico; aminas, tales como los aminoácidos naturales o sintéticos, tales como alanina o fenilalanina; fosfatos, tales como acetil-fosfato; y sulfonatos, tales como acetil-sulfonato. Para que los polímeros aromático-sustituidos tengan también el requisito de la solubilidad acuosa, es también deseable que se unan al polímero suficientes grupos hidrófilos tales como grupos hidroxipropilo o grupos funcionales de ácido carboxílico para hacer que el polímero sea soluble en agua al menos a los valores de pH en que cualquier grupo ionizable se ioniza. En algunos casos, el grupo aromático puede ser ionizable por sí mismo, tal como los sustituyentes de ftalato o trimelitato.

Ejemplos de polímeros celulósicos ionizables que se ionizan al menos parcialmente a pH fisiológicamente apropiado incluyen: acetato succinato de hidroxipropil-metil-celulosa, succinato de hidroxipropil-metil-celulosa, acetato succinato de hidroxipropil-celulosa, succinato de hidroxietil-metil-celulosa, acetato succinato de hidroxietil-celulosa, ftalato de hidroxipropil-metil-celulosa, acetato succinato de hidroxietil-metil-celulosa, acetato ftalato de hidroxietil-metil-celulosa, carboxietil-celulosa, carboximetil-celulosa, acetato ftalato de celulosa, acetato ftalato de metil-celulosa, acetato ftalato de etil-celulosa, acetato ftalato de hidroxipropil-celulosa, acetato ftalato de hidroxipropil-metil-celulosa, acetato ftalato succinato de hidroxipropil-celulosa, acetato succinato ftalato de hidroxipropil-metil-celulosa, succinato ftalato de hidroxipropil-metil-celulosa, propionato ftalato de celulosa, butirato ftalato de hidroxipropil-celulosa, acetato trimelitato de celulosa, acetato trimelitato de metil-celulosa, acetato trimelitato de etil-celulosa, acetato trimelitato de hidroxipropil-celulosa, acetato trimelitato de hidroxipropil-metil-celulosa, acetato trimelitato succinato de hidroxipropil-celulosa, propionato trimelitato de celulosa, butirato trimelitato de celulosa, acetato tereftalato de celulosa, acetato isoftalato de celulosa, acetato piridindicarboxilato de celulosa, acetato de ácido salicílico-celulosa, acetato de hidroxipropil-ácido salicílico-celulosa, acetato de ácido etilbenzoico-celulosa, acetato de hidroxipropil-ácido etilbenzoico-celulosa, acetato de ácido etil-ftálico-celulosa, acetato de ácido etil-nicotínico-celulosa, y acetato de ácido etil-picolínico-celulosa.

Ejemplos de polímeros celulósicos que cumplen la definición de anfífilos, que tienen regiones hidrófilas e hidrófobas incluyen los polímeros tales como acetato ftalato de celulosa y acetato trimelitato de celulosa donde las unidades repetidas celuló-

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sicas que tienen uno o más sustituyentes acetato son hidrófobas en relación con las que no tienen sustituyentes acetato o tienen uno o más sustituyentes ftalato o trimelitato ionizados.

Un subconjunto de polímeros celulósicos ionizables particularmente deseables son aquellos que tienen tanto un sustituyente aromático con ácido carboxílico funcional como un sustituyente alquilato y por tanto son anfífilos. Ejemplos de estos polímeros incluyen acetato ftalato de celulosa, acetato ftalato de metil-celulosa, acetato ftalato de etil-celulosa, acetato ftalato de hidroxipropil-celulosa, ftalato de hidroxipropil-metil-celulosa, acetato ftalato de hidroxipropil-metil-celulosa, acetato ftalato succinato de hidroxipropil-celulosa, propionato ftalato de celulosa, butirato ftalato de hidroxipropil-celulosa, acetato trimelitato de celulosa, acetato trimelitato de metil-celulosa, acetato trimelitato de etil-celulosa, acetato trimelitato de hidroxipropil-celulosa, acetato trimelitato de hidroxipropil-metil-celulosa, acetato trimelitato succinato de hidroxipropil-celulosa, propionato trimelitato de celulosa, butirato trimelitato de celulosa, acetato tereftalato de celulosa, acetato isoftalato de celulosa, acetato piridindicarboxilato de celulosa, acetato de ácido salicílico-celulosa, acetato de hidroxipropil-ácido salicílico-celulosa, acetato de ácido etilbenzoico-celulosa, acetato de hidroxipropil-ácido etilbenzoico-celulosa, acetato de ácido etil-ftálico-celulosa, acetato de ácido etil-nicotínico-celulosa, y acetato de ácido etil-picolínico-celulosa.

Otro subconjunto de polímeros celulósicos ionizables particularmente deseables son aquellos que tienen un sustituyente carboxilato no aromático. Ejemplos de estos polímeros incluyen acetato succinato de hidroxipropil-metil-celulosa, succinato de hidroxipropil-metil-celulosa, acetato succinato de hidroxipropil-celulosa, acetato succinato de hidroxietil-metil-celulosa, succinato de hidroxietil-metil-celulosa y acetato succinato de hidroxietil-celulosa.

Los polímeros especialmente preferidos son acetato succinato de hidroxipropil-metil-celulosa (HPMCAS), ftalato de hidroxipropil-metil-celulosa (HPMCP), acetato ftalato de celulosa (CAP), acetato trimelitato de celulosa (CAT), acetato ftalato de metil-celulosa, acetato ftalato de hidroxipropil-celulosa, acetato tereftalato de celulosa y acetato isoftalato de celulosa. Los polímeros más preferidos son acetato succinato de hidroxipropil-metil-celulosa, ftalato de hidroxipropil-metil-celulosa, acetato ftalato de celulosa y acetato trimelitato de celulosa.

Aunque se han descrito polímeros específicos como adecuados para uso en las mezclas de la presente invención, las mezclas de tales polímeros también pueden ser adecuadas. Por ello el término "polímero" se pretende que incluya las mezclas de polímeros además de una única especie de polímero.

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Para conseguir el mejor comportamiento, particularmente después de almacenamiento durante largo tiempo antes de su uso, se prefiere que el GPI esté, hasta donde sea posible, en el estado amorfo. Se ha encontrado en la invención que esto se consigue mejor cuando la temperatura de transición vítrea, T_g , del material de GPI amorfo está sustancialmente por encima de la temperatura de almacenamiento de la composición. En particular, es preferible que la T_g del estado amorfo del GPI sea al menos de 40 °C y preferiblemente superior a 60 °C. Para aquellos aspectos de la invención en los que la composición es un sólido, la dispersión sustancialmente amorfa de GPI en el polímero que aumenta la concentración y en la que el propio GPI tiene una T_g relativamente baja (aproximadamente 70 °C o menos), se prefiere que el polímero que aumenta la concentración tenga una T_g de al menos 40 °C, preferiblemente al menos 70 °C y más preferiblemente superior a 100 °C. Ejemplos de polímeros con alta T_g incluyen HPMCAS, HPMCP, CAP, CAT y otros polímeros celulósicos que tienen sustituyentes alquilatos o aromáticos o ambos sustituyentes, alquilatos y aromáticos.

Adicionalmente, los polímeros preferidos listados antes, es decir los polímeros celulósicos anfífilos, tienden a tener mayores propiedades de aumentar la concentración en relación con los otros polímeros de la presente invención. Para cualquier GPI particular, el polímero celulósico anfífilo con las mejores propiedades de aumentar la concentración puede variar. Sin embargo, se ha encontrado en la invención que generalmente aquellos que tienen sustituyentes ionizables tienden a comportarse mejor. Los ensayos *in vitro* de las composiciones con tales polímeros suelen tener valores más altos de MDC y AUC que las composiciones con otros polímeros de la invención. A menudo tales composiciones tienen valores de MDC y AUC que son más de 4 veces y en algunos casos más de 8 veces los de una composición de referencia.

PREPARACIÓN DE COMPOSICIONES

Las composiciones pueden comprender una mezcla física del GPI y el polímero que aumenta la concentración o una dispersión del GPI y el polímero. Preferiblemente, las composiciones se forman de tal manera que al menos una porción importante (al menos 60 %) del GPI está en estado amorfo. En los casos en que la composición es una mezcla física del GPI amorfo y el polímero, el GPI amorfo se puede preparar por cualquier procedimiento conocido. Generalmente, la forma amorfa del GPI se prepara por (1) fusión del fármaco seguida por rápido enfriamiento (por ejemplo, procedimiento de fusión-congelación); (2) disolución del fármaco en un disolvente seguida por precipitación o evaporación (por ejemplo, secado por pulverización, recubrimiento por pulverización); o (3) tratamiento mecánico del fármaco (por ejemplo, extrusión, molienda

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con bolas). Para generar el GPI amorfo se pueden usar diferentes combinaciones de calor (como en los procedimientos de fusión), disolvente y fuerza mecánica.

Las dispersiones del GPI y el polímero que aumenta la concentración se pueden preparar de acuerdo con cualquier procedimiento conocido que da como resultado que al menos una porción importante (al menos 60 %) del GPI esté en estado amorfo. Ejemplos de procedimientos mecánicos incluyen molienda y extrusión; los procedimientos de fusión incluyen fusión a alta temperatura, fusión modificada con disolventes y procedimientos de fusión-congelación; y los procedimientos con disolvente incluyen precipitación con un no-disolvente, recubrimiento por pulverización y secado por pulverización. Aunque las dispersiones de la presente invención se pueden preparar por cualquiera de estos procedimientos, generalmente las dispersiones tienen su máxima biodisponibilidad y estabilidad cuando el GPI está dispersado en el polímero de tal forma que es sustancialmente amorfo y está distribuido sustancialmente de forma homogénea por todo el polímero. Aunque en algunos casos tales dispersiones sustancialmente amorfas y sustancialmente homogéneas se pueden preparar por cualquiera de estos métodos, se ha encontrado que tales dispersiones se forman preferiblemente por el "procedimiento con disolvente" que consiste en la disolución del GPI y uno o más polímeros en un disolvente común. "Común" significa aquí que el disolvente, que puede ser una mezcla de compuestos, disolverá simultáneamente el fármaco y el polímero(s). Una vez que se han disuelto ambos, el GPI y el polímero, se separa rápidamente el disolvente por evaporación o por mezcla con un no-disolvente. Ejemplos de estos procedimientos son secado por pulverización, recubrimiento por pulverización (recubrimiento en bombo, recubrimiento en lecho fluido, etc), y precipitación por mezcla rápida de la solución de polímero y fármaco con CO₂, agua, o algún otro no-disolvente. Preferiblemente, la separación del disolvente da como resultado una dispersión sólida que es sustancialmente homogénea. Como se ha descrito previamente, en tales dispersiones sustancialmente homogéneas, el GPI se dispersa tan homogéneamente como sea posible por todo el polímero y se puede considerar como una solución sólida del GPI dispersado en el polímero(s). Cuando la dispersión resultante constituye una solución sólida del GPI en el polímero, la dispersión puede ser termodinámicamente estable, lo que significa que la concentración de GPI en el polímero está en su valor de equilibrio o por debajo de éste, o se puede considerar una solución sólida supersaturada en la que la concentración del GPI en el polímero(s) de dispersión está por encima de su valor de equilibrio.

Se puede eliminar el disolvente por medio del procedimiento de secado por pulverización. El término secado por pulverización se usa convencionalmente y se

refiere en general a procedimientos que implican la ruptura de mezclas líquidas en pequeñas gotitas (atomización) y la separación rápida del disolvente de la mezcla en un recipiente (aparato de secado por pulverización) donde hay una fuerte fuerza motriz para la evaporación del disolvente desde las gotitas. La fuerte fuerza motriz para la evaporación del disolvente generalmente se proporciona manteniendo la presión parcial del disolvente en el aparato de secado por pulverización marcadamente por debajo de la presión de vapor del disolvente a la temperatura de secado de las gotitas. Esto se consigue por cualquiera de estos procedimientos (1) manteniendo la presión en el aparato de secado por pulverización a un vacío parcial (por ejemplo de 0,01 a 0,50 atm); (2) mezclando las gotitas líquidas con un gas de secado caliente; o (3) por ambos procedimientos. Adicionalmente, al menos una porción del calor requerido para la evaporación del disolvente se puede proporcionar calentando la solución de pulverización.

Los disolventes adecuados para el secado por pulverización pueden ser cualquier compuesto orgánico en el que el GPI y el polímero son mutuamente solubles. Preferiblemente, el disolvente es también volátil con un punto de ebullición de 150 °C o menos. Adicionalmente, el disolvente debe tener una toxicidad relativamente baja y ser eliminado de la dispersión hasta un nivel que es aceptable de acuerdo con la guía del Comité Internacional de Armonización (ICH). La eliminación del disolvente hasta este nivel puede requerir una etapa de procedimiento tal como el secado en bandejas subsiguiente al procedimiento del secado por pulverización o recubrimiento por pulverización. Los disolventes preferidos incluyen alcoholes tales como metanol, etanol, *n*-propanol, *iso*-propanol, y butanol; cetonas tales como acetona, metil-etil-cetona y metil-isobutil-cetona; ésteres tales como acetato de etilo y acetato de propilo; y otros disolventes diferentes tales como acetonitrilo, cloruro de metileno, tolueno, y 1,1,1-tricloroetano. También se pueden usar disolventes de más baja volatilidad tales como dimetilacetamida o dimetilsulfóxido. Se pueden usar también mezclas de disolventes, tales como 50 % de metanol y 50 % de acetona, como se pueden usar las mezclas con agua siempre que el polímero y el GPI sean suficientemente solubles para hacer practicable el procedimiento de secado por pulverización. Generalmente, se prefieren los disolventes no acuosos lo que significa que el disolvente lleva menos de aproximadamente el 40 % en peso de agua. Sin embargo, para ciertos GPI, se ha encontrado que la adición de una pequeña cantidad de agua, típicamente aproximadamente de 5 % en peso a aproximadamente 35 % en peso, a un disolvente tal como la acetona puede realmente aumentar la solubilidad del GPI en el disolvente, en relación con la que tiene en ausencia de agua. En tales casos, o para aumentar la solubilidad del po-

límero, incluso se puede preferir la adición de agua.

Generalmente la temperatura y el caudal del gas de secado se eligen de tal forma que las gotitas de la solución de polímero/fármaco están suficientemente secas al tiempo de alcanzar la pared del aparato como para ser esencialmente sólidas, y formar así un polvo fino que no se pega a la pared del aparato. La duración real de tiempo para conseguir este nivel de sequedad depende del tamaño de las gotitas. El tamaño de las gotitas generalmente varía desde 1 μm a 500 μm de diámetro, siendo más típico de 5 a 100 μm . La gran relación superficie a volumen de las gotitas y la gran fuerza motriz para la evaporación del disolvente lleva a tiempos reales de secado de unos segundos o menos, y más típicamente de menos de 0,1 segundos. Este rápido secado es a menudo crítico para que las partículas mantengan una dispersión uniforme homogénea en lugar de separarse en fases ricas en fármaco y ricas en polímero. Los tiempos de solidificación deben ser inferiores a 100 segundos, preferiblemente menos de unos segundos y más preferiblemente menos de 1 segundo. En general, para conseguir esta rápida solidificación de la solución de GPI/polímero, se prefiere que el tamaño de las gotitas formadas durante el procedimiento de secado por pulverización sea menos de 100 μm de diámetro, preferiblemente menos de 50 μm de diámetro, y más preferiblemente menos de 25 μm de diámetro. Las partículas sólidas resultantes así formadas tienen generalmente menos de 100 μm de diámetro, y preferiblemente menos de 50 μm de diámetro, y más preferiblemente menos de 25 μm de diámetro. Típicamente, las partículas tienen de 1 a 20 μm de diámetro.

Después de la solidificación, el polvo sólido permanece típicamente en la cámara de secado por pulverización durante aproximadamente 5 a 60 segundos, evaporándose después el disolvente desde el polvo sólido. El contenido final de disolvente de la dispersión sólida cuando sale del secador debe ser bajo, puesto que esto reduce la movilidad de las moléculas de GPI en la dispersión, con lo que se aumenta su estabilidad. Generalmente, el contenido en disolvente de la dispersión sólida cuando ésta deja la cámara de secado por pulverización debe ser menos del 10 % en peso y preferiblemente menos del 2 % en peso. En algunos casos, puede ser preferible rociar un disolvente o una solución de un polímero u otro excipiente dentro de la cámara de secado por pulverización para formar gránulos, siempre que la dispersión no sea afectada de modo adverso.

Los procedimientos de secado por pulverización y el equipo de secado por pulverización están descritos de forma general en *Perry's Chemical Engineers' Handbook*, Sixth Edition (R. H. Perry, D. W. Green, J. O. Maloney, eds) McGraw-Hill Book Co. 1984, páginas 20-54 a 20-57. Mas detalles sobre los procedimientos y equipo de se-

cado por pulverización son examinados por Marshall "Atomization and Spray-Drying", 50 *Chem. Eng. Prog. Monogr. Series 2* (1954).

5 Cuando la composición es una mezcla física simple, la composición se puede preparar por medio de mezclado en seco o en húmedo del fármaco o de la mezcla del fármaco con el polímero para formar la composición. Los procedimientos de mezclado incluyen procedimientos físicos así como procedimientos de granulación húmeda y de recubrimiento. Se puede usar cualquier método convencional de mezclado, incluyendo aquellos que convierten sustancialmente el fármaco y el polímero en una dispersión molecular.

10 Por ejemplo, los métodos de mezclado incluyen mezclado por convección, mezclado por cizallamiento, o mezclado por difusión. El mezclado por convección comprende mover una masa relativamente grande de material de una parte a otra de un lecho de polvo, por medio de álabes o paletas, tornillo giratorio, o una inversión del lecho de polvo. El mezclado por cizallamiento tiene lugar cuando se forman planos de
15 deslizamiento en el material a ser mezclado. El mezclado por difusión comprende un cambio de posición de las partículas individuales. Estos procedimientos de mezclado se pueden realizar usando equipo en lotes o en forma continua. Para el procedimiento en lotes se usan comúnmente los mezcladores de volteo (por ejemplo, los de doble cubierta). El mezclado continuo se puede usar para mejorar la uniformidad de la com-
20 posición.

Para preparar las composiciones de la presente invención se puede emplear también la molienda. La molienda es el procedimiento mecánico para reducir el tama-
ño de partícula de los sólidos (conminución). Los tipos más comunes de equipos para moler son los molinos de corte giratorio, los de martillos, de rodillos y los de energía
25 fluida. La elección del equipo depende de las características de los ingredientes de la forma farmacéutica (por ejemplo, suaves, abrasivos o friables). Las técnicas de mo- lienda en húmedo o en seco se pueden elegir para varios de estos procedimientos, dependiendo también de las características de los ingredientes (por ejemplo, estabili- dad del fármaco en el disolvente). El procedimiento de molienda puede servir a la vez
30 como un procedimiento de mezclado si los materiales de alimentación son heterogé- neos. Los procedimientos convencionales de mezclado y molienda adecuados para uso en la presente invención se exponen más completamente en Lachman *et al.*, *The Theory and Practice of Industrial Pharmacy* (3d Ed. 1986). Los componentes de las composiciones de esta invención se pueden combinar también por procedimientos de
35 granulación seca o húmeda.

En adición a las mezclas físicas descritas antes, las composiciones de la pre-

sente invención pueden estar constituidas por cualquier dispositivo o conjunto de dispositivos que cumplen el objetivo de administrar al medio de uso tanto el GPI como el polímero que aumenta la concentración. Por ello, en el caso de administración oral a un mamífero, la forma farmacéutica puede ser un comprimido en capas en el que una o más capas comprenden el GPI amorfo y una o más del resto de las capas comprenden el polímero. Alternativamente la forma farmacéutica puede ser un comprimido recubierto en el que el núcleo del comprimido comprende el GPI y el recubrimiento comprende el polímero que aumenta la concentración. Adicionalmente, el GPI y el polímero pueden incluso estar presentes en diferentes formas farmacéuticas tales como comprimidos o perlas y se pueden administrar simultáneamente o separadamente siempre que tanto el GPI como el polímero se administren de tal forma que el GPI y el polímero se puedan poner en contacto en el medio de uso. Cuando el GPI y el polímero se administran por separado generalmente es preferible administrar el polímero antes que el GPI.

La cantidad de polímero que aumenta la concentración en relación a la cantidad de GPI presente en las mezclas de la presente invención depende del GPI y el polímero y puede variar ampliamente desde una relación en peso GPI a polímero de 0,01 hasta aproximadamente 4 (por ejemplo, 1 % en peso de GPI a 80 % en peso de GPI). Sin embargo, en la mayor parte de los casos se prefiere que la relación GPI a polímero sea mayor que aproximadamente 0,05 (4,8 % en peso de GPI) y menor de aproximadamente 2,5 (71 % en peso de GPI). A menudo el aumento que se observa de la concentración del GPI o de la biodisponibilidad relativa aumenta cuando la relación GPI a polímero disminuye desde un valor de aproximadamente 1 (50 % en peso de GPI) hasta un valor de aproximadamente 0,11 (10 % en peso de GPI). La relación máxima GPI:polímero que da resultados satisfactorios varía de GPI a GPI y se determina mejor en los ensayos de disolución *in vitro* y/o en los ensayos de biodisponibilidad *in vivo*. Se debe observar que este nivel del polímero que aumenta la concentración es usualmente sustantivamente mayor y a menudo mucho mayor que la cantidad de polímeros convencionalmente incluidos en las formas farmacéuticas para otros usos, tales como los aglutinantes o los materiales de recubrimiento. Por tanto, se prefiere en las composiciones de esta invención que se incluya suficiente polímero que aumenta la concentración para que las composiciones cumplan los criterios de MDC y AUC *in vitro* y los criterios de biodisponibilidad *in vivo* previamente establecidos.

En general, para maximizar la concentración del GPI o la biodisponibilidad relativa del GPI, se prefiere reducir las relaciones de GPI a polímero. A bajas relaciones de GPI a polímero, hay suficiente polímero disponible en solución para asegurar la

inhibición de la precipitación o cristalización del GPI desde la solución y, con ello, la concentración media de GPI es mucho más alta. Para altas relaciones de GPI a polímero, puede no haber presente bastante polímero en solución y la precipitación o cristalización del GPI pueden ocurrir más fácilmente. Además, la cantidad de polímero que aumenta la concentración que se puede usar en una forma farmacéutica está limitada a menudo por los requerimientos de la masa total de la forma farmacéutica. Por ejemplo, cuando se desea la administración oral a un humano, a bajas relaciones de GPI a polímero, la masa total de fármaco y polímero puede ser inaceptablemente grande para la administración de la dosis deseada en un único comprimido o cápsula. Por ello, a menudo es necesario usar relaciones de GPI a polímero que son inferiores a las óptimas en formas farmacéuticas específicas para proporcionar una dosis suficiente de GPI en una forma farmacéutica que es bastante pequeña para que sea administrada fácilmente a un medio de uso.

EXCIPIENTES Y FORMAS FARMACÉUTICAS

Aunque los ingredientes clave presentes en las composiciones de la presente invención son simplemente el GPI a ser administrado y el polímero(s) que aumenta la concentración, puede ser útil la inclusión de otros excipientes en la composición. Estos excipientes se pueden utilizar con la mezcla de GPI/polímero para formular la mezcla en comprimidos, cápsulas, suspensiones, polvos para suspensión, cremas, parches transdérmicos, depósitos, y similares. El GPI amorfo y el polímero se pueden añadir a otros ingredientes de las formas farmacéuticas esencialmente de cualquier forma que no altere sustancialmente al GPI. Adicionalmente, como se ha descrito antes, el GPI y el polímero se pueden mezclar con excipientes por separado para formar diferentes perlas, o capas o recubrimientos, o núcleos o incluso formas farmacéuticas separadas.

Una clase muy útil de excipientes son los tensioactivos. Los tensioactivos adecuados incluyen ácidos grasos y sulfonatos de alquilo; tensioactivos comerciales tales como cloruro de benzalconio (HYAMINE® 1622, disponible de Lonza, Inc. Fairlawn, New Jersey); dioctil-sulfosuccinato de sodio, DOCUSATE SODIUM™ (disponible de Mallinckrodt Spec. Chem., St. Louis, Missouri); ésteres de ácidos grasos y polioxietilén-sorbitano (TWEEN®, disponible de ICI Americas Inc., Wilmington, Delaware; LIPOSORB® P-20 disponible de Lipochem Inc., Patterson New Jersey; CAPMUL® POE-0 disponible de Abitec Corp., Janesville, Wisconsin), y tensioactivos naturales tales como sal de sodio de ácido taurocólico, 1-palmitoil-2-oleil-sn-glicero-3-fosfocolina, lecitina, y otros fosfolípidos y mono- y di-glicéridos. Tales materiales se pueden emplear ventajosamente para aumentar la velocidad de disolución facilitando la humectación, con lo que aumentan la concentración máxima disuelta, y también para inhibir la cris-

5 talización o precipitación del fármaco interactuando con el fármaco disuelto por mecanismos tales como formación de complejos, formación de complejos de inclusión, formación de micelas o por adsorción a la superficie del fármaco sólido, cristalino o amorfo. Estos tensioactivos pueden comprender hasta el 5 % en peso de la composición.

10 La adición de modificadores del pH tales como ácidos, bases, o tampones, puede ser también beneficiosa, retardando la disolución de la composición (por ejemplo ácidos tales como ácido cítrico o ácido succínico cuando el polímero que aumenta la concentración es aniónico) o, alternativamente, aumentando la velocidad de disolu-
ción de la composición (por ejemplo, bases tales como acetato de sodio o aminas cuando el polímero es aniónico).

15 Se pueden añadir también materiales matriciales convencionales, agentes complejantes, solubilizantes, de carga, agentes de desintegración (desintegrantes), o aglutinantes, como parte de la propia composición o añadidos por granulación por vía húmeda o mecánica o por otros medios. Estos materiales pueden constituir hasta el 90 % en peso de la composición.

Ejemplos de materiales matriciales, agentes de carga, o diluyentes incluyen lactosa, manitol, xilitol, celulosa microcristalina, difosfato de calcio y almidón.

20 Ejemplos de desintegrantes incluyen glicolato sódico de almidón, alginato de sodio, carboximetilcelulosa sódica, metilcelulosa, y croscarmelosa sódica.

Ejemplos de aglutinantes incluyen metilcelulosa, celulosa microcristalina, almidón y gomas tales como goma guar, y tragacanto.

Ejemplos de lubricantes incluyen estearato de magnesio y estearato de calcio.

25 En las composiciones de esta invención se pueden emplear otros excipientes convencionales, incluyendo aquellos excipientes bien conocidos en la técnica. Generalmente, se pueden usar excipientes tales como pigmentos, lubricantes, aromatizantes, y demás, para los propósitos habituales y en cantidades típicas sin afectar adversamente las propiedades de las composiciones. Estos excipientes se pueden utilizar para formular la composición en comprimidos, cápsulas, suspensiones, polvos
30 para suspensión, cremas, parches transdérmicos, y similares.

Las composiciones de esta invención se pueden usar en una amplia variedad de formas farmacéuticas para administración de los GPI. Ejemplos de formas farmacéuticas son los polvos o gránulos que se pueden tomar oralmente ya sea secos o reconstituidos por la adición de agua u otros líquidos para formar una pasta, mezcla,
35 suspensión o solución; comprimidos; cápsulas; multipartículas; y píldoras. Se pueden mezclar, moler o granular con las composiciones de esta invención diferentes aditivos

para formar un material adecuado para las formas farmacéuticas anteriores.

Las composiciones de la presente invención se pueden formular en diferentes formas de tal modo que se administren como una suspensión de partículas en un vehículo líquido. Tales suspensiones se pueden formular como un líquido o una pasta en el tiempo de la fabricación o se pueden formular como un polvo seco con un líquido, típicamente agua, añadido más tarde pero antes de la administración oral. Tales polvos que se reconstituyen en una suspensión se denominan a menudo formulaciones en sobres o en polvo oral para reconstitución. (OPC). Tales formas farmacéuticas se pueden formular y reconstituir por cualquier procedimiento conocido. El método más simple es formular la forma farmacéutica como un polvo seco que se reconstituye por simple adición de agua y agitación. Alternativamente, la forma farmacéutica puede ser formulada como un líquido y un polvo seco que se reúnen y agitan para formar la suspensión oral. En otra realización más, la forma farmacéutica puede ser formulada como dos polvos que se reconstituyen añadiendo primero agua a uno de los polvos para formar una solución a la cual se añade el segundo polvo con agitación para formar la suspensión.

Generalmente, se prefiere que la dispersión de GPI o de la forma amorfa de GPI se formule para almacenamiento a largo plazo en estado sólido ya que esto favorece la estabilidad física y química del GPI. Diferentes excipientes y aditivos se combinan con las composiciones de la presente invención para formar la forma farmacéutica. Por ejemplo, puede ser deseable añadir alguno o todos de los siguientes: conservantes tales como sulfitos (un antioxidante), cloruro de benzalconio, metilparabeno, propilparabeno, alcohol bencílico o benzoato de sodio; agentes de suspensión o espesantes tales como goma xantano, almidón, goma guar, alginato de sodio, carboximetilcelulosa, carboximetilcelulosa sódica, metilcelulosa, hidroxipropilmetilcelulosa, ácido poliacrílico, gel de sílice, silicato de aluminio, silicato de magnesio, o dióxido de titanio; agentes antiaglutinantes o agentes de carga tales como óxido de silicio, o lactosa; aromatizantes tales como aromas naturales o artificiales; edulcorantes tales como azúcares tales como sacarosa, lactosa, o sorbitol así como edulcorantes artificiales tales como aspartamo o sacarina; agentes humectantes o tensioactivos tales como diferentes grados de polisorbato, docusato de sodio, o laurilsulfato de sodio; solubilizantes tales como etanol, propilenglicol o polietilenglicol; agentes colorantes tales como rojo FDC N° 3 o azul FDC N° 1; y modificadores del pH o tampones tales como ácidos carboxílicos (incluyendo ácido cítrico, ácido ascórbico, ácido láctico, y ácido succínico), diferentes sales de ácidos carboxílicos, aminoácidos tales como glicina o alanina, diferentes sales fosfatos, sulfatos y carbonatos tales como fosfato de trisodio,

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bicarbonato de sodio o bisulfato de potasio, y bases tales como aminoglucosa o trietanolamina.

Un aditivo preferido para tales formulaciones es un polímero adicional que aumenta la concentración que puede actuar como un agente espesante o de suspensión así como aumentar la concentración del GPI en el medio de uso y puede actuar también para evitar o retrasar la precipitación o cristalización del GPI desde la solución. Tales aditivos preferidos son hidroxietil-celulosa, hidroxipropil-celulosa e hidroxipropil-metil-celulosa. En particular, las sales de polímeros con ácido carboxílico funcional tales como acetato ftalato de celulosa, acetato succinato de hidroxipropil-metil-celulosa y carboximetil-celulosa, son útiles a este respecto. Tales polímeros pueden ser añadidos en sus formas de sales o se puede formar *in situ* la forma de sal durante la reconstitución añadiendo una base tal como fosfato de trisodio y la forma ácida de tales polímeros.

En algunos casos, la forma farmacéutica global o las partículas, gránulos o perlas que constituyen la forma farmacéutica pueden tener un comportamiento superior si se recubren con un polímero entérico para evitar o retrasar la disolución hasta que la forma farmacéutica deja el estómago. Ejemplos de materiales de recubrimiento entérico incluyen acetato succinato de hidroxipropil-metil-celulosa, ftalato de hidroxipropil-metil-celulosa, acetato ftalato de celulosa, acetato trimelitato de celulosa, polimetacrilatos con ácido carboxílico funcional, y poliacrilato con ácido carboxílico funcional.

Las composiciones de esta invención se pueden administrar en una forma farmacéutica de liberación controlada. En tal forma farmacéutica, la composición del GPI y polímero se incorpora dentro de un dispositivo de matriz polimérica erosionable. Por una matriz erosionable se quiere indicar erosionable por el agua, o hinchable por el agua o soluble en agua en el sentido de ser o erosionable o hinchable o soluble en agua pura o requiriendo la presencia de un ácido o una base para ionizar suficientemente la matriz polimérica para causar la erosión o disolución. Cuando se pone en contacto con el medio acuoso de uso, la matriz polimérica erosionable embebe agua y forma un gel hinchado por el agua o "matriz" que atrapa la mezcla de GPI y polímero. La matriz hinchada por el agua se erosiona gradualmente, se hincha, se disgrega o se disuelve en el medio de uso, con lo que se controla la liberación de la mezcla del fármaco al medio de uso. Ejemplos de tales formas farmacéuticas están descritos más completamente en la solicitud de patente de Estados Unidos comúnmente cedida, en tramitación, número de serie 09/495.059 presentada el 31 de enero de 2000, que reivindica el beneficio de prioridad de la solicitud provisional de patente número de serie