Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-068963- -00006-0000
Fecha: 2010-11-17 15:48:19 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 QPOSIOBSERVTER Folios: 66

FORMULARIO ÚNICO DE OPOSICIÓN

① OPOSICIÓN A :

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

② SOLICITUD PUBLICADA

Número del expediente: 09.068.963
Solicitante: SCOLR PHARMA, INC.
Apoderado: MAURICIO JARAMILLO CAMPUZANO
Título de la nueva creación o denominación del signo: "FORMA DE DOSIS DE IBUPROFENO MODIFICADA"
Gaceta: 619

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE

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

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

REPRESENTANTE O APODERADO

Nombre: ELIANA ISAURA MORENO BOHORQUEZ
Dirección: CARRERA 13 No. 119-95
Teléfono: (571)213 12 13 Fax: (571)612 19 79
E-mail: negocios@optimum-co.com

IDENTIFICACIÓN
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número 51'975.664 TP 83823

④ FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN
Causal: No cumple con los requisitos de patentabilidad.
Signo opositor:
Justificación:
La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

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

⑥ **ANEXOS**

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

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA:

C.C. 51'975.664 **TP.** 83823

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

Optimum

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia	: Expediente N° 09 068.963
Asunto	: Oposición a la solicitud de patente de Invención titulada "FORMA DE DOSIS DE IBUPROFENO DE LIBERACION MODIFICADA"
Solicitante	: SCOLR PHARMA, INC..
Opositora	: PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 619 del 20 de agosto de 2010

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

1. INTERÉS PARA ACTUAR

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

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 3 de julio de 2009, reivindicando prioridad bajo la solicitud US20060633322 del 2006-12-04; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial **N° 619 del 20 de agosto de 2010**, cuya publicación internacional corresponde a la WO2008069941 del 2008-06-12.

2.2. La solicitud colombiana **09 068.963** objeto de la presente oposición, se refiere una forma de dosis sólida para liberación modificada después de la administración oral de ibuprofeno, que comprende: un polímero hidrofílico que tiene dos diferentes viscosidades, que comprende un primer polímero hidrofílico que tiene una primera viscosidad baja y un segundo polímero hidrofílico que tiene una segunda mayor viscosidad de al menos 4000 cps, en la cual dicho primer polímero hidrofílico se

encuentra presente en una concentración en el intervalo de 5% a 15% por peso de ibuprofeno, y dicho segundo polímero hidrofílico se encuentra presente en una concentración mayor en el intervalo de aproximadamente 15% a aproximadamente 30% por peso de ibuprofeno; de 300 a 800 mg de ibuprofeno en la forma de dosis sólida uniformemente disperso en dicho polímero hidrofílico; un aditivo de disolución disperso en dicho polímero hidrofílico en una cantidad en el intervalo de 10% a 35% por peso de ibuprofeno, en donde dicho aditivo de disolución es carbonato de sodio, glicina, arginina, croscarmelosa sódica o una combinación de los mismos; y un aditivo de formulación inerte disperso en la hidroxipropil metilcelulosa en una cantidad en el intervalo de 15% a 75% por peso de ibuprofeno, en donde dicho aditivo de formulación comprende celulosa microcristalina; en donde al menos 20% del ibuprofeno se libera dentro de las dos hora.

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

- D1: WO2006039692 publicada el 13 de abril de 2006.

2.4.Ahora bien, el documento D1, particularmente en la descripción revela una forma de dosificación sólida para la administración oral de ibuprofeno que comprende una formulación de liberación modificada de ibuprofeno que proporciona un efecto de explosión inmediata y, posteriormente, una liberación sostenida de

ibuprofeno suficiente para mantener los niveles de sangre por lo menos 6,4 g [mu] / ml durante un período prolongado período de al menos 8 horas tras la administración de una dosis única. Según D1, se revela que la forma de dosificación libera ibuprofeno a un ritmo suficiente para ofrecer inicialmente una cantidad eficaz de ibuprofeno dentro de aproximadamente 2,0 horas tras la administración. Igualmente, se define que la forma de dosificación, posteriormente, entrega la cantidad restante de ibuprofeno a un ritmo relativamente constante, suficiente para mantener un nivel de ibuprofeno durante un período de entrega predeterminado de por lo menos 8 horas. Según las reivindicaciones y la descripción, este documento anterior D1 una dosis orla solida en forma tal como un tableta de matriz homogénea que comprende dos polímeros hidrófilos HPMC que tiene diferentes viscosidades, un HPMC con baja viscosidad y un HPMC con alta viscosidad mayor a 4000 cps; donde D1 define carbonato de sodio y glicina disueltos con aditivos y MCC como aditivo inerte en cantidades definidas. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica.

2.5. Por lo tanto, este documento objeto de oposición a la luz del documento D1 carece evidentemente de NOVEDAD.

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana **09 068.963** no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con uno de los tres requisitos necesarios para su protección.

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

2.7.1. CARECE DE NOVEDAD: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."*. A la fecha de prioridad, 4 de diciembre de 2006 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, un compuesto farmacéutico que combine una vitamina D con alendronato para tratar la osteoporosis posmenopáusica, sobre el cual busca protección en el capítulo reivindicatorio.

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

2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada **"FORMA DE DOSIS DE IBUPROFENO DE LIBERACION MODIFICADA"**, cuyo titular es **SCOLR PHARMA, INC.**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial **N° 619 del 20 de agosto de 2010.**

3. PRUEBAS

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

- D1: WO2006039692 publicada el 13 de abril de 2006.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

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

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

4.3. En las demás normas concordantes.

5. ANEXOS

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

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

- D1: WO2006039692 publicada el 13 de abril de 2006.

Optimum

Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 Nº 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,

ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

10

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-068963- -00006-0000

Fecha: 2010-11-17 15:48:19 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 66

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 97,371
FECHA : NOVIEMPRE 17 DE 2010

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	392197421	17/11/2010	2,360,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	295,000.00
		TOTAL : $	295,000.00

SON: DOSCIENTOS NOVENTA Y CINCO MIL PESOS

RESPONSABLE _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

PROCAPS

PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 **del C.S. de la J.**, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **09 068.963**, titulada "**FORMA DE DOSIS DE IBUPROFENO DE LIBERACION MODIFICADA**", cuyo titular es **SCOLR PHARMA, INC.,** publicada en la gaceta No. 619 del 20 de agosto de 2010.

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

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

Dado y Firmado en Barranquilla (Colombia) a los 3 días del mes de Noviembre de 2010.

PROCAPS S.A.

C.C. N° 16'251.923
NIT: 890.106.527-5
Representante Legal

APROBADO
3 - NOV. 2010
JURIDICA

Acepto:

ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

CIRCULO DE BARRANQUI
RECONOCIMIENTO

ante el Notario tercero de Barranquilla se presentó:

WALTER TANAKA TOKEKAWA

identificado con: CC 16 251-923 PALMIRA

Y declaro que el contenido del anterior Documento es cierto y suya la firma que lo refrenda.

Barranquilla: 05 NOV. 2010

NOTARIA TERCERA DEL CIRCULO DE BARRANQUILLA
ALFONSO LUIS AVILA FADUL
NOTARIO

03-07027333,024802 PROCAPS S.A.
Barranquilla, 21 de Octubre de 2010 Hr:13:55:49

No.15159676

CAMARA DE COMERCIO DE BARRANQUILLA

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
05**********

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

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

C E R T I F I C A

Que por Escritura Pública No. 1,190 del 22 de Julio de 1976, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 28 de Julio de 1976 bajo el No. 6,070 del libro respectivo, fue constituida la sociedad----------
limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA "PROCAPS LIMITADA".----------

C E R T I F I C A

Que por Escritura Pública No. 1,307 del 28 de Junio de 1979, otorgada en la Notaria Tercera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Julio de 1979 bajo el No. 10,039 del libro respectivo, la sociedad antes mencionada----------
se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".----------

C E R T I F I C A

Que por Escritura Pública No. 3,810 del 31 de Dic/bre de 1980, otorgada en la Notaria Primera de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 30 de Enero de 1981 bajo el No. 12,705 del libro respectivo, la sociedad antes mencionada----------
se transformo en sociedad de responsabilidad limitada bajo al razon social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI - MITADA".----------

C E R T I F I C A

Que por Escritura Pública No. 3,755 del 10 de Nov/bre de 1983, otorgada en la Notaria Unica de Soledad, inscrito(as) en esta Cámara de Comercio, el 22 de Nov/bre de 1983 bajo el No. 17,922 del libro respectivo, la sociedad antes mencionada----------
se transformo en sociedad anonima bajo la denominacion social de "PRODUCTORA DE CAPSULAS DE GELATINA S.A. "PROCAPS S.A.".----------

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del

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

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

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

libro respectivo, la sociedad antes mencionada----------
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A
. ----------

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del libro respectivo, la sociedad antes mencionada----------
cambio de razon social, por la denominacion PROCAPS S.A. ----------

C E R T I F I C A

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

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16
2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18
710	2009/05/05	Notaria 3 a. de Barranquilla	150,130	2009/06/30
1,054	2009/06/25	Notaria 3 a. de Barranquilla	150,130	2009/06/30

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:
DENOMINACION O RAZON SOCIAL:
PROCAPS S.A.----------
SIGLA: PROCAPS.
DOMICILIO PRINCIPAL: Barranquilla.
NIT No: 890.106.527-5.
MATRICULA MERCANTIL: 24,802.

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

03-07027333 024802 PROCAPS S.A.
Barranquilla, 21 de Octubre de 2010 Hr:13:55:49

No.15159677

CAMARA DE COMERCIO DE BARRANQUILLA

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
05**********

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

C E R T I F I C A

Direccion para notificaciones judiciales:
CL 80 No 78 B - 201.
De la ciudad de Barranquilla.

C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a) La fabicacion, importacion y comercializacion de alimentos procesados y suplementos dietarios. b)La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, para uso y consumo humano y veterinario. c) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas para uso y consumo humano, animal y vegetal. d) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimen ticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. e) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. f) La compra, venta, exportacion, fabricacion, importacion, distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. g) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos. h) Prestar los servicios de asesorias y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, alimenticios, cosmeticos y

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

farmaceuticos para uso humano, animal o industrial. i) Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, alimenticios, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables, comprar, vender y constituir gravamenes sobre bienes muebles e inmuebles, designar representantes apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de sus obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravamenes reales sobre sus bienes de cualquier naturaleza.----------

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
$**********2,000,000,000	**********2,000,000	**********1,000
Suscrito		
$**********1,234,071,000	**********1,234,071	**********1,000
Pagado		
$**********1,234,071,000	**********1,234,071	**********1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponderа a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva.
La sociedad tendra un Presidente , quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se

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

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

requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la socieda todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguentes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes inversiones y todo tipo de derechos de la sociedad, o de constituir gravamenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junra Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para

ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad, en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravamenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente. ----------

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:
PROCAPS S.A.----------
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, y según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad:
PROCAPS S.A.----------
cuya parte pertinente se inscribió en esta Cámara de Comercio, el 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE: JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben	CC.*******7,463,982
2. Minski Gontovnik Meyer	CC.*******7,461,324
3. Minski Gontovnik Jose	CC.*******8,671,834

Suplentes

1. Minski Zirberblum Elliot	CC.******72,219,541
2. Minski Deitel Daniel	.****************
3. Minski Sharon	PA.*990,212,082,805

C E R T I F I C A

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

CAMARA DE COMERCIO DE BARRANQUILLA

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
05**********

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

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Presidente.	
Minski Gontovnik Ruben	CC.*******7,463,982
Suplente del Presidente	
Minski Minski Abraham	CC.*********802,575
Vicepresidente	
Minski Gontovnik Meyer	CC.*******7,461,324
Suplente del vicepresidente	
Minski Gontovnik Jose	CC.*******8,671,834

C E R T I F I C A

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

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

C E R T I F I C A

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

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

C E R T I F I C A

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

Cargo/Nombre	Identificación

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

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

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

Revisor Fiscal Ppal.
Vargas Pertuz Ana Isabel CC.******32,696,645

C E R T I F I C A

Que según Acta No. 151 del 31 de Marzo de 2009 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 30 de Julio de 2009 bajo el No. 151,129 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre Identificación

Suplente del Revisor Fiscal.
Duarte Diaz David CC.******73,115,965

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo,---------- y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, ---- 3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, ----- 3.507, Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, ------ obrando como Presidente y Representante Legal de la sociedad C.I. NATURMEGA S.A., que obrando en su condicion de Presidente y ------- Representante Legaql de la sociedad PROCAPS S.A., el presidente ---- debidamente facultado por los Estatutos Sociales y por el Maximo Organo Social, otorga los siguientes poderes: Otorgar poder -------- general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN ---- MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO ------ CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con las facultades que se transcriben a continuacion: a.- Para que ----- representen a la sociedad PROCAPS S.A, ante todo tipo de ---------- autoridades administrativas y jurisdiccionales, en asuntos de ------ naturaleza civil, laboral, comercial, penal, aduanera, cambiaria, tributaria, policiva, administrativa y fiscal. b.- Contestar y ----- presentar demandas, requerimientos, recursos, pedir y aportar ------ pruebas, recibir, notificarse, ejercer la accion de tutela, -------- tramitar incidente de desacato, comparecer en los procesos que ----- cursen contra la sociedad, allanarse en nombre de la sociedad en los asuntos que sean necesarios, transigir, desistir, sustituir, renunciar y reasumir el poder. c.- La facultad expresa de ---------- conciliar, por tanto pueden llegar a acuerdos conciliatorios, ------ transaccionales, judiciales o extrajudiciales o extrajudiciales, cualquiera que sea su cuantia, para lo cual las apoderadas deben aportar la autorizacion simple y escrita del Representante legal de la sociedad. d.- Podran presentar solicitudes de devolucion y/o compensacion de impuestos, ventas y rentas, recibir los pagos por las devoluciones y adelantar todo tramite o proceso administrativo ante la DIAN, de tal forma que en ningun momento quede sin --------- representacion legal de la sociedad. PODERES ESPECIALES: a.- Se ---- confiere poder especial amplio y suficiente a las personas que se determinan seguidamente, que conforman el grupo A y B, para, para

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

CAMARA DE COMERCIO DE BARRANQUILLA

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
05**********

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

que conjuntamente suscriban contratos de suministros de mercancias y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), ------- liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. Grupo A. WALTER NANAKA TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO ---------- CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN ------ VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA ---------- DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO ------- CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial ----- amplio y suficiente al senor WILLIAM ALBERTO BARROS CERRA ---------- CC.No.8.715.941, para que en nombre y representacion de PROCAPS ---- S.A., suscriban declaraciones cambiarias, aduaneras y tributarias a que este obligada la sociedad, en el giro normal de sus negocios y operaciones sociales, por tanto quedan facultados para firmarlas, como tambien los demas documentos relacionados con ellas, ---------- notificarse, aportar y solicitar las pruebas que sean necesarias. c.-Otorgar poder especial amplio y suficiente al senor MARLON ----- TATIS PAREDES CC.No.72.176.874 y al senor WILLIAM ALBERTO BARROS CERRA CC.No.8.715.941, para que en nombre y representacion de ------ PROCANPS S.A., suscriban las declaraciones, reportes y cualquier documento relacionado con los tramites o registros de Comercio ----- Exterior y o cualquier entidad del Estado que haga sus veces: d) Otorgar poder especial amplio y suficiente a la doctora CARMEN ----- ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y ---------- representacion de PROCAPS S.A.; endosen los titulos valores de la sociedad hasta por la suma de UN MIL MILLONES DE PESOS ---------- (1.000.000.000.00) M.L. CUARTO: EI representante legal de la ------- sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta que la presente reforma fue aprobada por la Asamblea General ------- Extraordinaria de Accionista de PROCAPS S.A., con observancia de las disposiciones legales y estatutarias.----------

C E R T I F I C A

Que por Escritura Pública No. 1,933 del 16 de Sep/bre de 2008, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Octubre de 2008 bajo el No. 3,748 del libro respectivo,----------
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, que comparece en su condicion de Presidente y Representante Legal de la Sociedad PROCAPS S.A., confiere por medio de este instrumento ------ publico Poder especial Amplio y Suficiente a la doctora MILENA -----

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

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

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

ESCAFFI PARDO, C.C. No. 32.758.420, para que en nombre y ----------
representacion de PROCAPS S.A., suscriba declaraciones cambiarias, aduaneras y tributarias a que este obligada la sociedad en el giro normal de sus negocios y operaciones sociales, por tanto queda -----
facultada para firmar, como tambien los demas documentos ----------
relacionados con ellas, notificarse, aportar y solicitar las -------
pruebas que sean necesarias.----------

C E R T I F I C A

Que por Documento Privado del 09 de Abril de 2010, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 20 de Abril de 2010 bajo el Nro 4,201 del libro respectivo,----------
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, ----
quien obra en el caracter de Presidente y/o Representante legal de la sociedad PROCAPS S.A., que por medio de este instrumento --------
publico, otorga Poder Especial Amplio y Suficiente a la Doctora ----
MONICA DE HART DE OCHOA, identificada con C.C. No. 32.676.025, para que en nombre y representacion de la sociedad, Endose las Facturas Nacionales e Internacionales hasta por la suma de UN MIL MILLONES DE PESOS ($1.000.000.000.00)M.L. La doctora Monica de Hart de Ochoa, queda facultada para realizar todo acto o tramite necesario para el cabal cumplimiento del presente mandato.----------

C E R T I F I C A

Que por Documento Privado del 10 de Junio de 2010, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 13 de Julio de 2010 bajo el Nro 4,228 del libro respectivo,----------
consta que el señor RUBEN MISNKI GONTOVNIK, cc. No. 7.463.982 en su condicion de Presidente y representante legal de PROCAPS S.A., -----
confiere poder especial, amplio y suficiente al señor RICARDO DORADO HURTADO cc. No. 79.715.772 para que represente a la sociedad, ante el INVIMA, Fondo Nnacional de estupefacientes e ICA, con el fin que gestione, tramite o presente las diferentes solicitudes y ----------
peticiones de la empresa, segun la competencia de estas entidades.
Por lo anterior, el Señor RICARDO DORADO HURTADO, queda facultado para presentar, gestionar, tramitar y firmar las diferentes --------
solicitudes y peticiones de la empresa, segun la competencia de ----
estas entidades, como tambien presentar y firmar todo los ----------
documentos relacionados con estas solicitudes, notificarse de ------
cualquier acto administrativo que expidan, aportar y solicitar las pruebas que sean necesarias, desistir, y en general a realizar todo tramite o acto necesario de tal forma que la sociedad en ningun ----
momento quede sin representacion legal ante estas entidades, en ----
cumplimiento fiel al mandato otorgado.----------

C E R T I F I C A

Que por Documento Privado del 03 de Agosto de 2010, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 24 de Agosto de 2010 bajo el Nro 4,258 del libro respectivo,----------
consta que RUBEN MINSKI GONTOVNIK, varón, mayor de edad, de ésta

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

CAMARA DE COMERCIO DE BARRANQUILLA

C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
05**********

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

vecindad, identificado con la cédula de ciudadanía No.7.463.982, expedida en Barranquilla, en mi condición de Representante legal y/o Presidente de la sociedad PROCAPS S. A., conforme a las -------- facultades otorgadas por los Estatutos Sociales, todo lo cual ------ demuestro con el certificado de existencia y representación legal expedido por la Cámara de Comercio de Barranquilla, que adjunto a este escrito, me permito manifestarles que confiero poder especial, amplio y suficiente al señor MARIO LÓPEZ LEON, varón, mayor de ----- edad, de esta vecindad, identificado con la cédula de ciudadanía No.72.311.558, expedida en Puerto Colombia (Atlántico), para que en nombre y representación de la sociedad, realice los siguientes ----- actos: 1. Endosar las Facturas Nacionales e Internacionales de esas compañías hasta por la suma de UN MIL MILLONES DE PESOS ---------- ($1.000.000.000.00) Moneda Legal. 2. Suscribir Declaraciones ------- Cambiarias, Aduaneras y Tributarias a las que esta obligada la ----- sociedad en el giro ordinario de sus negocios, quedando facultado para notificarse, aportar y solicitar pruebas relacionados con las declaraciones Cambiarias. El señor MARIO LÓPEZ LEÓN, queda --------- facultado para notificarse, aportar y solicitar pruebas, presentar escritos en caso que resulte necesario en general a realizar todo acto, diligencia o tramite que considere indispensable para el ----- cabal cumplimiento del presente mandato.----------

C E R T I F I C A

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.

C E R T I F I C A

Que su última Renovación fue el: 30 de Marzo de 2010.

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

C E R T I F I C A

Que los actos de registro aquí certificados quedan en firme cinco días hábiles despues de la correspondiente inscripción, siempre que, dentro de dicho término, no sean objeto de los recursos de reposición ante esta entidad, y/o de apelación para ante la Superintendencia de Industria y Comercio.

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

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

NIT: 890.106.527-5.

ANEXO 1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 April 2006 (13.04.2006)

PCT

(10) International Publication Number
WO 2006/039692 A2

(51) International Patent Classification:
A61K 9/22 (2006.01)

(21) International Application Number:
PCT/US2005/035630

(22) International Filing Date:
30 September 2005 (30.09.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/614,932	30 September 2004 (30.09.2004)	US
60/689,631	10 June 2005 (10.06.2005)	US
11/238,802	29 September 2005 (29.09.2005)	US

(71) Applicant *(for all designated States except US)*: **SCOLR PHARMA, INC.** [US/US]; 3625 132nd Avenue, SE# 300, Bellevue, WA 98006 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HITE, Michael** [US/US]; 9324 57th Avenue South, Seattle, WA 98118 (US). **FEDERICI, Cathy** [US/US]; 2312 E. Pike, Seattle, WA 98122 (US). **BRUNELLE, Alan** [US/US]; 14104 194th Avenue NE, Woodinville, WA 98077 (US). **TURNER, Stephen** [US/US]; 34620 SE Curtis Drive, Snoqualmie, WA 98065 (US).

(74) Agent: **ANDERSEN, Robert, L.**; RatnerPrestia, P.O. Box 980, Valley Forge, PA 19482 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

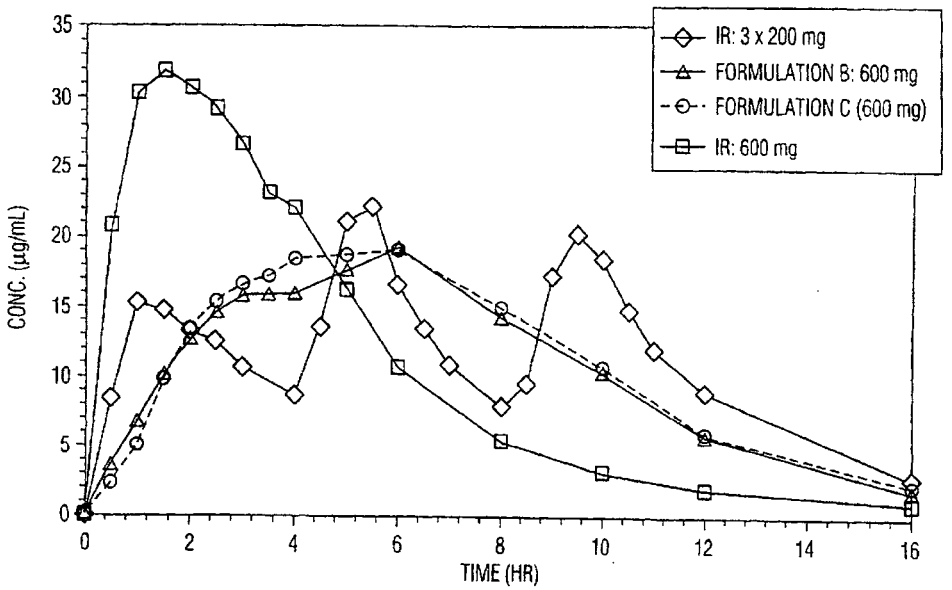
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

[Continued on next page]

(54) Title: MODIFIED RELEASE IBUPROFEN DOSAGE FORM



(57) **Abstract:** The present invention is a solid dosage form for oral administration of ibuprofen comprising a modified release formulation of ibuprofen which provides an immediate burst effect and thereafter a sustained release of sufficient ibuprofen to maintain blood levels at least 6.4 µg/ml over an extended period of at least 8 hours following administration of a single dose. The dosage form releases ibuprofen at a rate sufficient to initially deliver a effective amount of ibuprofen within about 2.0 hours following administration. The dosage form then subsequently delivers the remaining amount of ibuprofen at a relatively constant rate sufficient to maintain a level of ibuprofen over a predetermined delivery period of for at least 8 hours.

WO 2006/039692 A2

WO 2006/039692 A2

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

MODIFIED RELEASE IBUPROFEN DOSAGE FORM

CROSS REFERENCE TO RELATED APPLICATIONS

The present invention claims the benefit of U.S. Provisional Applications Nos. 60/614,932, filed September 30, 2004 and 60/689,631, filed June 10, 2005, and U.S. Non-Provisional Application No. (TO BE ASSIGNED), filed September 29, 2005.

BACKGROUND OF THE INVENTION

Ibuprofen is 2-(4-isobutylphenyl)propionic acid and is a non-steroidal anti-inflammatory compound (NSAID), which exhibits high levels of anti-inflammatory, analgesic and antipyretic activities necessary for the effective treatment of rheumatoid arthritis and osteo-arthritis and other inflammatory conditions. Most dosage forms of ibuprofen are immediate release dosage forms that provide rapid onset of therapeutic action, then rapidly declining levels of active ingredient, necessitating repeated dosing. They do not maintain therapeutic levels from one treatment over an extended period of time. Repeat dosing is thus required at intervals of four to six hours. Formulations that claim extended release fail to have an initial burst of the drug and thus exhibit substantial delay between administration and the achievement of an effective therapeutic blood level. Therefore, a need exists for a solid dosage form, for example a compressed tablet, which provides an initial burst of released ibuprofen, leading to prompt onset of action, then thereafter provides a sustained release of sufficient ibuprofen to maintain beneficial blood levels of ibuprofen over an extended period of 8 or more hours.

SUMMARY OF THE INVENTION

In accordance with the foregoing, we have provided a solid dosage form for oral administration of ibuprofen comprising a modified release formulation of ibuprofen which provides an immediate burst effect and thereafter a sustained release of sufficient ibuprofen to maintain blood levels at least 6.4 μg/ml over an extended period of at least 8 hours following administration of a single dose.

More particularly, the invention comprises a solid dosage form for oral administration comprising a hydrophilic polymer, a pharmaceutically effective amount of ibuprofen in the range of 300 mg to 800 mg uniformly dispersed in the polymer, a dissolution additive dispersed in the polymer in an amount in the range of 10% to 35% by weight of the ibuprofen, and a formulation additive dispersed in the polymer in an amount of 15% to 75% by weight of the ibuprofen. The dosage form releases ibuprofen at a rate sufficient to initially deliver a effective amount of ibuprofen within about 2.0 hours following administration. The dosage form then subsequently delivers the

remaining amount of ibuprofen at a relatively constant rate sufficient to maintain a level of ibuprofen over a predetermined delivery period of for at least 8 hours.

As used herein, a relative constant rate refers to a substantially linear relationship shown in the examples following the initial burst (up to about 2 hours) between percentage released and elapsed time.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: *In-vitro* dissolution of Example 1

Figure 2: *In-vitro* dissolution of Example 2

Figure 3: *In-vitro* dissolution of Example 3

Figure 4: *In-vitro* dissolution of Example 4

Figure 5: *In-vitro* dissolution of Example 5

Figure 6: *In-vitro* dissolution of Example 6

Figure 7: *In-vitro* dissolution of Example 7

Figure 8: *In-vitro* dissolution of Example 8

Figure 9: *In-vitro* dissolution of Example 9

Figure 10: *In-vitro* dissolution of Example 10

Figure 11: *In-vitro* dissolution of Example 11

Figure 12: *In-vitro* dissolution of Example 12

Figure 13: *In-vitro* dissolution of Example 13

Figure 14: *In-vitro* dissolution of Example 14

Figure 15: *In-vitro* dissolution of Example 15

Figure 16: *In-vitro* dissolution of Example 16

Figure 17: *In-vitro* dissolution of Examples 17 and 18

Figure 18: *In-vitro* dissolution of BRUFEN RETARD, an extended release form of Ibuprofen available for sale in Europe.

Figure 19: *In-vivo* data from comparison of present invention versus Motrin®

DETAILED DESCRIPTION OF THE INVENTION

The present invention is further illustrated and described by reference to the following disclosure, examples and discussion below. In the examples and discussion which follow, the use of particular polymers, electrolytes, additives, fillers and tableting aids are provided by way of example only and are not intended to limit the scope of this invention. Although the invention is illustrated and described herein with reference to specific embodiments, the invention is not intended to be limited to the details shown. Rather, various modifications may be made in the details within the scope and range of equivalents of the claims and without departing from the invention.

The ibuprofen content of the dosage form may be between in the range about 300 mg and about 800 mg per dosage unit, preferably about 300, 400 or 600 mg

per unit dosage form. Also contemplated is using prodrugs of ibuprofen such as ibuprofen-lysine and ibuprofen-arginine. If a smaller dosage form is desired, a single dose of ibuprofen may be divided between multiple, for example two to three, dosage units, such as tablets, which may be administered at substantially the same time. The dosage form may comprise from about 25% to about 75% by weight ibuprofen.

The hydrophilic polymer used in the dosage form may be selected from a wide variety of hydrophilic polymers. Hydrophilic polymers suitable for use in the sustained release formulation include: one or more natural or partially or totally synthetic hydrophilic gums such as acacia, gum tragacanth, locust bean gum, guar gum, or karaya gum; modified cellulosic substances such as methylcellulose, hydroxy methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose, or carboxyethylcellulose; proteinaceous substances such as agar, pectin, carrageenan, and alginates; and other hydrophilic polymers such as carboxypolymethylene, gelatin, casein, zein, bentonite, magnesium aluminum silicate, polysaccharides, modified starch derivatives, and other hydrophilic polymers known to those of skill in the art, or a combination of such polymers.

These hydrophilic polymers gel and dissolve slowly in aqueous acidic media thereby allowing the ibuprofen to diffuse from the gel in the stomach and gastrointestinal tract. Hydroxypropyl methylcellulose (HPMC) and other hydrophilic polymers mentioned above may be available in forms that have varying viscosity ratings. In general these polymers, or the combination of them, may be present in the dosage form alone or in combination in an amount or at a concentration in the range of 10% to 70% by weight of the ibuprofen present in the formulation, for example 15% to 50% or 15% to 33%, depending on the release pattern which is sought to be achieved with the particular dosage form.

One hydrophilic polymer useful in the present invention is HPMC K4M. This is a nonionic swellable hydrophilic polymer manufactured by "The Dow Chemical Company" under the tradename "Methocel." HPMC K4M is also referred to as HPMC K4MP, in which the "P" refers to premium cellulose ether designed for controlled release formulations. The "4" in the abbreviation suggests that the polymer has a nominal viscosity (2% in water) of 4000. The percent of methoxyl and hydroxypropyl groups are 19-24 and 7-12, respectively. In its physical form, HPMC K4M is a free-flowing, off-white powder with a particle size limitation of 90%<100 mesh screen. A more complete list of HPMC is K100LVP, K15MP, K100MP, E4MP and E10MP CR with nominal viscosities of 100, 15000, 100000, 4000, and 10000 respectively.

The solid dosage form also includes at least one formulation additive such as one or more of a filler, a diluent or a compression aid. These are additives which aid

in preparation or manufacture of the dosage form and for a tableted solid dosage form a tableting aid such as microcrystalline cellulose (MCC), such MCC 105 (particle size of about 20 μm), MCC 200 (particle size of about 180 μm) and MCC 302 (particle size of about 90 μm), silicified microcrystalline cellulose (MCC bonded to SiO_2), such as Prosolv90 (particle size of about 90 μm) and Prosolv50 (paricle size of about 50 μm), lactose, such as spray dried lactose (Lactopress®), dicalcium phosphate, silica or pregelatinized starch and combinations thereof may be incorporated into the formulation in an amount or at a concentration in the range of about 15% to about 75% by weight of the ibuprofen present in the dosage form. It is contemplated that various particle sizes of microcrystalline cellulose may be used if desired, for example two different particle sizes in which each of them are present in individual amounts in the range of 17% to 33% by weight of the ibuprofen present in the formulation. In one embodiment, one can pre-blend silica with ibuprofen or pre-blend silica and/or formulation additive MCC with ibuprofen.

In addition to formulation additives, the dosage form also contains at least one dissolution additive. Such additives which generally comprise a pore-forming, wetting or disintegration agent which facilitates dissolution of the dosage form. Such dissolution additives may be present in the dosage form at an amount or concentration in the range of about 10% to about 35% by weight of the ibuprofen, for example, at 10% to about 15%. The additive may suitably be selected from alkali metal salts, such as sodium and potassium carbonate; sodium carbonate, monohydrate; sodium bicarbonate; amino acids with neutral-to-basic side chains, such as glycine, alanine, valine, leucine, iso-leucine, cysteine, methionine, phenylalanine, proline, lysine, arginine, histidine, serine, threonine, asparagine, tryptophan, tyrosine and glutamine; conventional pharmaceutical disintegrants and combinations or mixtures thereof. Examples of such additives are sodium carbonate, glycine, arginine and croscarmellose sodium.

In addition to ibuprofen, multiple active ingredients are contemplated and may be present in the present dosage form. Combinations of ibuprofen with actives such as caffeine, psuedophedrine, aspirin, phenylephrine and/or sympathomemetics, analgesics, such as hydrocodone, and antihistamines are within the scope of the invention.

Favorable *in vitro* characteristics that lead to an acceptable *in vivo* efficacy are contemplated as 20% or greater release within 2.0 hour after oral administration or contact with an aqueous environment, followed by more gradual release over several hours, leading to release of at least 70% release in 8 to 12 hours following administration or contact with an aqueous environment. The method of determining *in*

vitro release is using an agitated aqueous medium, such as stirring at 50 rpm in pH 7.2 KH_2PO_4 media; or surrogate methods using alternate pH media, such as 0.1N HCl or SGF @ pH 1.2 for an initial (30min-2hr period or using alternate hydrodynamic conditions such as 100 to 150rpm for a period of 1-2hrs).

The accepted range for minimal efficacy *in vivo* is from about 6.4 μg/ml to about 10 μg/ml mean ibuprofen blood concentration.

Examples

The formulations of the invention are illustrated by the following examples. The use of particular polymers, electrolytes, additives, fillers and compression aids are not intended to limit the scope of this invention but are exemplary only.

The solid dosage comprising a modified release formulation of the present invention was prepared and tested for both *in vitro* release and *in vivo* blood levels as described in Examples 1-20 below. In the *in vivo* testing, the dissolution rates of the subject dosage forms were compared against two commercially available tablets, one being an immediate release formulation of 200 mg of ibuprofen and the other being an immediate release 600 mg ibuprofen formulation. The solid dosage forms comprising the modified release formulation of the present invention demonstrated an initial burst similar to an immediate release tablet and a slower, more controlled release of ibuprofen over a eight hour period, as best seen in Fig. 19.

Unless otherwise noted, all *in vitro* release performance was evaluated in a type II dissolution apparatus in 900mL KH_2PO_4 buffer, pH 7.2, at 50rpm paddle speed.

Example 1

In one embodiment, the formulation comprised ibuprofen, hydroxypropyl methylcellulose (HPMC K15M and HPMC K100LV), glycine and sodium carbonate, in which HPMC K15M was present at a concentration of 18% by weight of ibuprofen, HPMC K100LV was present at a concentration of 17% by weight of ibuprofen, glycine was present at a concentration of 2.5% by weight of ibuprofen, and sodium carbonate was present at a concentration of 17% by weight of ibuprofen within a monolithic compressed tablet. The specific formulations are as follows:

Ex. 1a	**mg**
Ibuprofen 90 grade	600
HPMC K15M	110
HPMC K100LV	100
MCC PH102	100

Ex. 1b	**mg**
Ibuprofen 90 grade	600
HPMC K15M	125
HPMC K100LV	100
MCC PH102	100

Na_2CO_3, anhydrous	150	Na_2CO_3, anhydrous	150
Glycine	15	Glycine	15
Silica, Syloid 244	20	Silica, Syloid 244	20
Mg Stearate	10	Mg Stearate	10
Total: A	1105	Total:	1120

II

Ingredients were passed through a 30-mesh screen and blended with the remaining formulation components in a V-blender. The resulting powder was compressed into tablets using conventional compression techniques.

As shown in **Fig. 1**, the results of this Example demonstrate that the invention is capable of an *in vitro* release profile comprising a burst effect, followed by the sustained release of the remaining material, leading to in excess of 90% release in approximately 12 hours. This formulation thus overcomes one of the principle problems with many ibuprofen formulations which exhibit substantially less than complete release over an extended period of time.

Example 2

In another embodiment, the formulation comprised ibuprofen, hydroxypropyl methylcellulose (HPMC K100M and HPMC K100LV), sodium carbonate, flow agents and tableting aids, in which HPMC K100M was present at a concentration of 17% by weight of ibuprofen, HPMC K100LV was present at a concentration of 17% by weight of ibuprofen and sodium carbonate was present at a concentration of 25% by weight of ibuprofen within a compressed monolithic tablet. The specific formula is as follows:

Ex. 2	**mg**
Ibuprofen	600
HPMC K100M	100
HPMC K100LV	100
Na_2CO_3, anhydrous	150
MCC PH102	150
Silica, Syloid 244	20
Mg Stearate	10
Total:	1130

The formulation components were mixed in a V-blender. The resulting powder was compressed into tablets using conventional technologies. In this Example a combination of a medium to high viscosity HPMC and a low viscosity HPMC was used.

As shown in **Fig. 2**, the results of this Example demonstrate an *in vitro* release profile comprising a burst effect, followed by the sustained release of the remaining material. The burst effect provides release of 20% of ibuprofen within 2 hours, and the release of approximately 90% of the available ibuprofen over a period of 12 to 14 hours.

Example 3

In another embodiment, the formulation comprised ibuprofen, hydroxypropyl methylcellulose (HPMC K15M and HPMC K100LV), sodium carbonate, flow agents and tableting aids, in which HPMC K100M was present at a concentration of 17% by weight of ibuprofen, HPMC K100LV was present at a concentration of 17% by weight of ibuprofen and sodium carbonate was present at a concentration of 25% by weight of ibuprofen within a compressed monolithic tablet.

Ex. 3	**mg**
Ibuprofen	600
HPMC K15M	100
HPMC K100LV	100
MCC PH102	100
Na_2CO_3, anhydrous	150
Glycine	15
Silica, Syloid 244	20
Mg Stearate	10
Total:	1095

The formulation components were mixed in a V-blender. The resulting powder was compressed into tablets using conventional compression technology. In this Example a combination of a medium to high viscosity HPMC and a low viscosity HPMC was used.

As shown in **Fig. 3**, the results of this Example demonstrate an *in vitro* release profile comprising a burst effect providing release of 20% of ibuprofen within 2 hours, followed by the sustained release of the remaining material evidencing release of 100% of the ibuprofen present in about 11 hours and greater than 90% in approximately 8 hours.

Example 4

In another embodiment, the formulation comprised ibuprofen, hydroxypropyl methylcellulose (HPMC K100M and HPMC K100LV), sodium carbonate, flow agents and tableting aids, in which HPMC K100M was present at a concentration of

17% by weight of ibuprofen, HPMC K100LV was present at a concentration of 17% by weight of ibuprofen, and sodium carbonate was present at a concentration of 25% by weight of ibuprofen within a compressed monolithic tablet.

Ex. 4	**mg**
Ibuprofen	600
HPMC K100M	100
HPMC K100LV	100
MCC PH102	100
Na_2CO_3, anhydrous	150
Silica, Syloid 244	20
Mg Stearate	10
Total:	1080

The formulation components were mixed in a V-blender. The resulting powder was compressed into tablets using conventional technologies. In this Example a combination of a medium to high viscosity HPMC and a low viscosity HPMC was used.

As shown in **Fig. 4**, the results of this Example demonstrate an *in vitro* release profile comprising a burst effect, followed by the sustained release of the remaining material. 20% of ibuprofen was released within 2 hours, followed by gradual sustained release, resulting in approximately 95% release after 12 hours.

Example 5

In another embodiment, the formulation comprised ibuprofen, hydroxypropyl methylcellulose (HPMC K100M), polyethylene oxide (PEO WSRN 301), sodium carbonate, glycine, flow agents and tableting aids, in which HPMC was present at a concentration of 33% by weight of ibuprofen, glycine was present at a concentration of 8.25% by weight of ibuprofen and sodium carbonate was present at a concentration of 25% by weight of ibuprofen within a compressed monolithic tablet.

Ex. 5	**mg**
Ibuprofen	600
PEO 301	50
HPMC K100M	100
MCC PH102	100
Na_2CO_3, anhydrous	150
Glycine	20
Silica, Syloid 244	20

Mg Stearate	10
Total:	1050

The formulation components were mixed in a V-blender. The resulting powder was compressed into tablets using conventional compression technology.

As shown in **Fig. 5**, the results of this Example demonstrate an *in vitro* release profile comprising a burst effect, followed by the sustained release of the remaining material. For this formulation 20% of ibuprofen was released within 2 hours, but incomplete release was evidenced after 12 hours.

Example 6

In another embodiment, the formulation comprised ibuprofen, hydroxypropyl methylcellulose (HPMC K15M), potassium carbonate, flow agents and tableting aids, in which HPMC was present at a concentration of 33% by weight of ibuprofen, and potassium carbonate was present at a concentration of 17% by weight of ibuprofen within a compressed monolithic tablet.

Ex. 6	**mg**
Ibuprofen 90 grade	600
MCC PH 105	210
HPMC K15M Prem	190
MCC PH 200	100
K_2CO_3 anhydrous	100
	1200

The formulation components were mixed in a V-blender. The resulting powder was compressed into tablets using conventional compression technology.

As shown in **Fig. 6**, the results of this Example demonstrate an *in vitro* release profile comprising a burst effect, followed by the sustained release of the remaining material. 20% of ibuprofen was released in under 2 hours, and release was thereafter sustained over a period of 15 hours. However, incomplete release was exhibited by the dosage form.

Example 7

In this embodiment, the formulation comprised ibuprofen, hydroxypropyl methylcellulose (HPMC K15M), sodium carbonate, microcrystalline cellulose (MCC PH105 and MCC PH200), in which HPMC was present at a concentration of 33% by weight of ibuprofen, sodium carbonate was present at a concentration of 17% by weight of ibuprofen, MCC PH105 was present at a concentration of 33%, and MCC PH200 was present at a concentration of 17% within a compressed monolithic tablet.

Ex. 7	Mg
Ibuprofen 90 grade	600
HPMC K15M Prem	190
MCC PH 105	210
MCC PH 200	100
Na_2CO_3 anhydrous	100
	1200

All ingredients were passed through a 30-mesh screen. The ibuprofen and the MCC 105 were blended in a V-blender. The resulting homogenous pre-blend was granulated with water, dried and subsequently blended with the remaining formulation components in a V-blender. The resulting powder was compressed into tablets using conventional compression technology.

As shown in **Fig. 7**, this Example demonstrates an *in vitro* release profile comprising a burst effect, followed by the sustained release of the remaining material. The burst effect releases 20% of ibuprofen in under 2 hour, followed by relatively constant release over the next 10 -12 hours and resulting in approximately 90% release after 12 hours.

Example 8

In the embodiment of Example 1, the tablet resulting from the formulation was split into two equal parts, and both sections were placed into a dissolution vessel.

Ex. 8	mg
Ibuprofen 90 grade	600
HPMC K15M	110
HPMC K100LV	100
MCC PH102	100
Na_2CO_3, anhydrous	150
Glycine	15
Silica, Syloid 244	20
Mg Stearate	10
Total:	1105

As shown in **Fig. 8**, the results of this Example demonstrates an *in vitro* release profile comprising a burst effect, followed by the sustained release of the remaining material, even when split into sections after tableting. In each case 20% of

ibuprofen was released in less than one hour and substantially all the ibuprofen had been released at about 12 hours.

Example 9

In one embodiment, the formulation comprised ibuprofen, hydroxypropyl methylcellulose (HPMC K15M), sodium carbonate, microcrystalline cellulose (MCC PH 302), in which HPMC was present at a concentration of 33% by weight of ibuprofen, sodium carbonate was present at a concentration of 18% by weight of ibuprofen, and MCC PH 302 was present at a concentration of 33% within a compressed monolithic tablet.

Ex. 9	**mg**
Ibuprofen 90 grade	300
HPMC K15M Prem	100
MCC PH 302	100
Na_2CO_3 anhydrous	50
Glycine	7.5
Silica	5.5
Total:	563

All ingredients were passed through a 30-mesh screen and blended in a V-blender. The resulting homogenous pre-blend was granulated with water, dried and subsequently blended with the remaining formulation components in a V-blender. The resulting powder was compressed into tablets using conventional technologies.

As shown in **Fig. 9**, the results of this Example demonstrate an *in vitro* release profile comprising a burst effect, followed by the sustained release of the remaining material. 20% of ibuprofen was released within 2 hours, about 90% release was obtained in about 9 hours followed by 100% release in under 16 hours.

Example 10

In another embodiment, the formulation comprised ibuprofen, hydroxypropyl methylcellulose (HPMC K4M), flow agents and tableting aids, in which HPMC K4M was present at a concentration of 32% by weight of ibuprofen, and arginine was present at a concentration of 17% by weight of ibuprofen within a compressed monolithic tablet.

Ex. 10	**mg**
Ibuprofen 90 grade	600
Silica	5.5
MCC PH 105	210

HPMC K4M Prem	190
Arginine	100
Silica	5.5
Total:	1111

The formulation components were mixed in a V-blender. The resulting powder was compressed into tablets using conventional technologies.

As shown in **Fig. 10**, the results of this Example demonstrate an *in vitro* release profile comprising a slight burst effect, followed by the sustained release of the remaining material. While the burst effect in this formulation produces somewhat delayed achievement of the percentage released, this formulation demonstrates in excess of 90% release over a period of 8 hours.

Example 11

In another embodiment, the formulation comprised ibuprofen, hydroxypropyl methylcellulose (HPMC K4M), sodium carbonate, arginine, flow agents and tableting aids, in which HPMC K4M was present at a concentration of 32% by weight of ibuprofen, sodium carbonate was present at concentration of 17% by weight of the ibuprofen, and arginine was present at a concentration of 17% by weight of ibuprofen within a compressed monolithic tablet.

Ex. 11	**mg**
Ibuprofen 90 grade	600
Silica	5.5
MCC PH 105	210
HPMC K4M Prem	190
Na_2CO_3 anhydrous	100
MCC PH 200	100
Arginine	100
Silica	5.5
Stearic Acid	12
Total:	1323

The formulation components are mixed in a V-blender. The resulting powder was compressed into tablets using conventional technologies.

As shown in **Fig. 11**, the results of this Example demonstrate the *in vitro* release profile comprising a burst effect, followed by the sustained release of the

remaining material. The initial release is greater than 20% of ibuprofen in less than two hours, and approximately 90% release over a period of 14 hours.

Example 12

In another embodiment, the formulation comprised ibuprofen, hydroxypropyl methylcellulose (HPMC K4M), microcrystalline cellulose (MCC 105), sodium carbonate, flow agents and various tableting aids, in which HPMC K4M was present at a concentration of 32% by weight of ibuprofen, sodium carbonate was present at concentration of 17% by weight of the ibuprofen, and tableting aid, either Lactopress (12a), dicalcium phosphate (12b), or pregelatinized starch (12c), was present at a concentration of 17% by weight of ibuprofen within a monolithic tablet.

Ex. 12a	mg
Ibuprofen 90 grade	600
Silica	5.5
MCC PH 105	210
HPMC K4M Prem	190
Na_2CO_3 anhydrous	100
Lactopress	100
Silica	5.5
Stearic acid	12
Total:	1223

Ex. 12b	mg
Ibuprofen 90 grade	600
Silica	5.5
MCC PH 105	210
HPMC K4M Prem	190
Na_2CO_3 anhydrous	100
Dicalcium phosphate	100
Silica	5.5
Stearic acid	12
Total:	1223

Ex. 12c	mg
Ibuprofen 90 grade	600
Silica	5.5
MCC PH 105	210
HPMC K4M Prem	190
Na_2CO_3 anhydrous	100
Starch 1500	100
Silica	5.5
Stearic acid	12
Total:	1223

All ingredients were passed through a 30-mesh screen. The ibuprofen and the MCC 105 were blended in a V-blender. The resulting homogenous pre-blend was granulated with water, dried and subsequently blended with the remaining formulation

components in a V-blender. The resulting powder was compressed into tablets using conventional technologies.

As shown in **Fig. 12**, the results of this Example demonstrate the invention is capable of an *in vitro* release profile comprising a burst effect, followed by the sustained release of the remaining material, with little or no alteration in release profile when the tableting aid selection is varied. The *in vitro* profile shows greater than 20 % release before 2.0 hours with a constant rate release and at least 70% release by 14 hours.

Example 13

In another embodiment, the formulation comprised ibuprofen, hydroxypropyl methylcellulose (HPMC K4M), microcrystalline cellulose (MCC 105), sodium carbonate, flow agents and various tableting aids, in which HPMC K4M was present at a concentration of 32% by weight of ibuprofen, sodium carbonate was present at concentration of 17% by weight of the ibuprofen, and croscarmellose sodium was present at a concentration of 3% by weight of ibuprofen within a monolithic tablet.

Ex. 13	**mg**
Ibuprofen 90 grade	600
Silica	5.5
MCC PH 105	210
HPMC K4M Prem	190
Na_2CO_3 anhydrous	100
MCC PH 200	100
Croscarmellose sodium	18
Silica	5.5
Stearic acid ~ 1%	12
Total:	1241

All ingredients were passed through a 30-mesh screen. The ibuprofen, silica and the MCC 105 were blended in a V-blender. The resulting homogenous pre-blend was granulated with water, dried and subsequently blended with the remaining formulation components in a V-blender. The resulting powder was compressed into tablets using conventional technologies.

As shown in **Fig. 13**, the results of this Example demonstrates an *in vitro* release profile comprising a burst effect, followed by the sustained release of the remaining material. The *in vitro* profile shows greater than 20% release before 2.0

hours followed by a relatively constant rate release and at least 80% release by 14 hours.

Example 14

In another embodiment, the formulation comprised ibuprofen, hydroxypropyl methylcellulose (HPMC K4M), microcrystalline cellulose (MCC 105), glycine, sodium carbonate, flow agents and various tableting aids, in which HPMC K4M was present at a concentration of 32% by weight of ibuprofen, sodium carbonate was present at concentration of 17% by weight of the ibuprofen, glycine was present at a concentration of 8% by weight of ibuprofen and croscarmellose sodium was present at a concentration of 6% by weight of ibuprofen within a monolithic tablet.

Ex. 14	**mg**
Ibuprofen 90 grade	600
MCC PH 105	200
Silica	5.5
HPMC K4M Prem	190
MCC PH 200	100
Glycine	50
Croscarmellose sodium	35
Silica	5.5
Stearic acid ~ 1%	12
Total:	1198

All ingredients were passed through a 30-mesh screen. The ibuprofen, silica and the MCC 105 were blended in a V-blender. The resulting homogenous pre-blend was granulated with water, dried and subsequently blended with the remaining formulation components in a V-blender. The resulting powder was compressed into tablets using conventional technologies.

As shown in **Fig. 14**, the results of this Example demonstrate the invention is capable of an *in vitro* release profile comprising a burst effect, followed by the sustained release of the remaining material. The *in vitro* profile shows greater than 20% release before 2.0 hours with a constant rate release and at least 70% release by 14 hours.

Example 15

In another embodiment, the formulation comprised ibuprofen, polyethylene oxide (PEO 301), PEO 60K, glycine, sodium carbonate, flow agents and various tableting aids, in which PEO was present at a concentration of 32% by weight of

ibuprofen, sodium carbonate was present at concentration of 25% by weight of the ibuprofen, and glycine was present at a concentration of 37% by weight of ibuprofen within a monolithic tablet.

Ex. 15	**mg**
Ibuprofen	400
PEO 301	50
PEO 60K	75
Na2CO3	100
Glycine	150
Maltodextrin M-580	100
Stearic acid	10
Silica	10
Total:	**895**

All ingredients were passed through a 30-mesh screen. The ibuprofen was blended with the formulation components in a V-blender. The resulting powder was compressed into tablets using conventional technologies.

As shown in **Fig. 15**, the results of this Example demonstrate the invention is capable of an *in vitro* release profile comprising a burst effect, followed by the sustained release of the remaining material. The *in vitro* profile shows greater than 20% release before 2.0 hours with a constant rate release and at least 80% release by 8 hours.

Example 16

In another embodiment, the formulation comprised ibuprofen, polyethylene oxide (PEO 301), PEO 60K, glycine, sodium carbonate, flow agents and various tableting aids, in which PEO was present at a concentration of 32% by weight of ibuprofen, sodium carbonate was present at concentration of 25% by weight of the ibuprofen, and glycine was present at a concentration of 37% by weight of ibuprofen within a monolithic tablet.

Ex. 16	**mg**
Ibuprofen	400
PEO 301	50
PEO 60K	50
Na2CO3	100
Glycine	100
Maltodextrin M-580	100

Stearic acid	10
Silica	10
Total:	**820**

All ingredients were passed through a 30-mesh screen. The ibuprofen was blended with the formulation components in a V-blender. The resulting powder was compressed into tablets using conventional technologies.

As shown in **Fig. 16**, the results of this Example demonstrate the invention is capable of an *in vitro* release profile comprising a burst effect, followed by the sustained release of the remaining material. The *in vitro* profile shows greater than 20 % release before 2.0 hours with a constant rate release and at least 90% release by 8 hours.

Example 17

In another embodiment, the formulation comprised ibuprofen, polyethylene oxide (PEO 301), glycine, sodium carbonate, flow agents and various tableting aids, in which PEO was present at a concentration of 25% by weight of ibuprofen, sodium carbonate was present at concentration of 25% by weight of the ibuprofen, and glycine was present at a concentration of 25% by weight of ibuprofen within a monolithic tablet.

Ex. 17	**mg**
Ibuprofen	400
PEO 301	100
Na2CO3	100
Glycine	100
Stearic acid	10
Total:	**710**

All ingredients were passed through a 30-mesh screen. The ibuprofen was blended with the formulation components in a V-blender. The resulting powder was compressed into tablets using conventional technologies.

As shown in **Fig. 17**, the results of this Example demonstrate the invention is capable of an *in vitro* release profile comprising a burst effect, followed by the sustained release of the remaining material. The *in vitro* profile shows greater than 20 % release before 2.0 hours with a constant rate release and at least 80% release by 8 hours.

Example 18

In another embodiment, the formulation comprised ibuprofen, polyethylene oxide (PEO 301), glycine, sodium carbonate, croscarmellose sodium, flow agents and various tableting aids, in which PEO was present at a concentration of 25% by weight of ibuprofen, sodium carbonate was present at concentration of 25% by weight of the ibuprofen, and glycine was present at a concentration of 25% by weight of ibuprofen within a monolithic tablet.

Ex. 18	**mg**
Ibuprofen	400
PEO 301	100
Na2CO3	100
Glycine	100
Croscarmellose Sodium	50
DCP	150
Stearic acid	10
Total:	**910**

All ingredients were passed through a 30-mesh screen. The ibuprofen was blended with the formulation components in a V-blender. The resulting powder was compressed into tablets using conventional technologies.

As shown in **Fig. 17**, the results of this Example demonstrate the invention is capable of an *in vitro* release profile comprising a burst effect, followed by the sustained release of the remaining material. The *in vitro* profile shows greater than 20% release before 2.0 hours with a constant rate release and at least 90% release by 8 hours.

Comparative *in vitro* data

BRUFEN RETARD is a commercially available in Europe as a sustained release formulation of ibuprofen. BRUFEN RETARD tablets are specially formulated to allow the gradual release of active substance giving stable levels and a prolonged duration of effect over the dosage interval. BRUFEN RETARD is a film coated tablet with 800mg of ibuprofen. BRUFEN RETARD is indicated for its analgesic and anti-inflammatory effect in the treatment of rheumatoid arthritis (including juvenile rheumatoid arthritis or Still's disease), ankylosing spondylitis, and osteo-arthritis. BRUFEN RETARD is indicated in the treatment of non-articular rheumatism including

fibrositis. BRUFEN RETARD is indicated in periarticular conditions such as frozen shoulder (capsulitis), bursitis, tendinitis, tenosynovitis and low-back pain. BRUFEN RETARD can also be used in soft-tissue injuries such as sprains and strains. BRUFEN RETARD is also indicated for its analgesic effect in the relief of mild to moderate pain such as dysmenorrhoea, dental, post-episiotomy pain and post-partum pain.

Example 19 (Figure 18)

BRUFEN RETARD tablet *in vitro* release performance was evaluated in a type II dissolution apparatus in 900mL KH_2PO_4 buffer, pH 7.2, at 50rpm paddle speed.

As shown in **Fig. 18**, the results of this Example demonstrate the *in vitro* data results of BRUFEN RETARD. The figure shows that BRUFEN RETARD is incapable of an *in vitro* release profile comprising a burst effect, followed by the sustained release of the remaining material. BRUFEN RETARD fails to deliver to release at least 20% of ibuprofen by 2.0 hours with a constant rate of release with at least 70% release at 14 hours.

Example 20 - In Vivo Trial

In the *in vivo* testing, serum concentrations of subjects taking tablets comprising the modified release formulation of the present invention were compared with serum concentrations of subjects taking immediate release ibuprofen tablets (Motrin® IB 200 mg and Motrin® 600 mg). Tablets comprising the modified release formulation of the present invention demonstrated a burst effect followed by sustained release and therapeutic concentration at extended time periods that the other two immediate release formulations did not. The minimum mean serum plasma ibuprofen concentration in the blood of the subject was between 8 and 10μg/ml for Motrin® IB..

The *in vivo* behavior of modified release solid dosages of 1a and 1b from Example 1 were compared to the *in vivo* behavior of an immediate release formulation (MOTRIN®). The open-label study involved 10 healthy male volunteers over the age of 18. Following an overnight fast of at least ten hours, each subject received either one 600 mg dose of one of the two above described modified release tablets or 200 mg every four hours for 3 doses of the immediate release formulation of MOTRIN® IB or one 600 mg tablet of MOTRIN®. 88 blood samples were taken prior to dosing and at specific intervals up to 12 hours after dosing.

The blood samples were kept in ice bath prior to centrifugation and were centrifuge as soon as possible under refrigerated condition at 35000 rpm for seven minutes. The collected plasma from each blood collection tube was aliquotted into pre-cooled labeled polypropylene tubes. The samples were kept in an ice bath, then stored frozen at minus 25 °C ±10 °C until assayed.

The plasma samples were analyzed by a fully validated HPLC method. The analytes were separated by reverse phase chromatography. Evaluation of the assay was carried out by the construction of an eight point calibration curve (excluding zero concentration) covering the range of 0.400 μg/ml to 51.200 μg/ml (in human plasma) for ibuprofen. The slope and intercept of the calibration curves were determined through weighted linear regression analysis (1/conc.^{2}). The results are depicted in FIGURE 19.

Table 1. Summary of 90% CI

Formulation	Reference: D (1 x 600 mg)			Reference: E (3 x 200 mg)		
	C_{max}	$AUC_{0\text{-last}}$	$AUC0_{-\infty}$	C_{max}	$AUC_{0\text{-last}}$	$AUC_{0-\infty}$
B (1a)	42.4-53.8	96.2-115	97.0-116	67.0-85.0	86.9-104	86.3-103
C (1b)	44.7-57.0	96.9-116	98.7-119	70.7-90.3	87.5-105	87.7-106
D	-	-	-	140-179	82.3-99.2	80.9-97.7
E	55.9-71.5	101-122	102-124	-	-	-

D is a 3 x 200mg MOTRIN® IB

E is a 1 x 600mg MOTRIN®

Treatments (B & C) versus Treatment E

The systematic exposure to ibuprofen after the administration of the one 600 mg ibuprofen tablet 1a or 1b (Treatments B & C) was similar to that obtained when compared to the administration of one MOTRIN® 600mg tablet. The peak exposure to ibuprofen from one 600 mg ibuprofen tablet 1a or 1b (Treatments A-C) was significantly lower than that from the MOTRIN® 600mg tablet. The absorption time was modified comparing one 600 mg ibuprofen tablet 1a or 1b (Treatments B & C) with median T_{max} value of 5.0h to a 1.5h T_{max} of one MOTRIN® 600mg tablet.

Treatments (B & C) versus Treatment D

The systematic exposure to ibuprofen after the administration of the one 600 mg ibuprofen tablet 1a or 1b (Treatments B & C) was similar to that obtained when compared to the administration of three MOTRIN® IB 200mg tablets. The peak exposure to ibuprofen from one 600 mg ibuprofen tablet 1a or 1b (Treatments B & C) was significantly lower than that from three MOTRIN® IB 200mg tablets. The absorption time was modified comparing one 600 mg ibuprofen tablet 1a or 1b (Treatments B & C) with median T_{max} value of 5.0h to a 1.0h T_{max} of three MOTRIN® IB 200mg tablet.

Figure 19 depicts the results discussed above. Treatment D shows an initial burst that falls to a valley at four hours and the second tablet is administered. This valley again happens at the eighth hour. This valley constitutes the minimum plasma concentration for ibuprofen to be considered therapeutic. A mean ibuprofen plasma concentration of about 6.4-10 μg/ml is considered the concentration of ibuprofen needed in the blood to be considered clinically effective. Treatment E shows an extreme initial burst of ibuprofen followed by a steady decline that falls below therapeutic threshold at about 6 hours.

Treatments B and C have an initial burst of ibuprofen that reaches the level of 6.4 μg/ml at about 0.5 to 1 hour and maintains the level until about hour 12. The present invention provides for a single dosage of ibuprofen that provides an initial burst similar to an immediate release formulation of ibuprofen and then provides a mean ibuprofen plasma concentration of above 6.4 μg/ml for about 12 hours.

What is Claimed:

1. A solid dosage form for modified oral administration of ibuprofen comprising:

a hydrophilic polymer;

300 to 800 mg of ibuprofen in the solid dosage form uniformly dispersed in said polymer;

a dissolution additive dispersed in said hydrophilic polymer in an amount in the range of 10% to 35% by weight of the ibuprofen, said dissolution additive comprising an alkali metal salt, an amino acid having a neutral to alkaline side chain, croscarmellose or a salt thereof, or a combination of any two of such dissolution additives; and

an inert formulation additive dispersed in said hydrophilic polymer in an amount in the range of 15% to 75% by weight of the ibuprofen, said formulation additive comprising microcrystalline cellulose, silica, magnesium stearate, stearic acid, lactose, pre-gelatinized starch, dicalcium phosphate or a combination of any of them,

wherein at least 20% of the ibuprofen is released within 2 hours following oral administration or exposure to an agitated aqueous medium of a single dosage unit, then thereafter releases ibuprofen at a relatively constant rate over a period of at least 8 hours, and wherein at least 70% of the ibuprofen is released over a period of not more than 14 hours following such administration or exposure.

2. The solid dosage form of claim 1, wherein ibuprofen is present in each dosage form in an amount of about 300 mg, 400 mg or 600 mg.

3. The solid dosage form of claim 1, wherein said polymer comprises polyethylene oxide, hydroxypropyl methylcellulose or a combination thereof.

4. The solid dosage form of claim 1, wherein said polymer comprises hydroxypropyl methylcellulose with a viscosity of at least 100 cps.

5. The solid dosage form of claim 4, wherein said hydrophilic polymer comprises a first hydroxypropyl methylcellulose having a viscosity of greater than 100 cps and a second HPMC having a viscosity of about 100 cps, each at a concentration of 17% to 42% by weight of ibuprofen.

6. The solid dosage form of claim 1, wherein said dissolution additive is sodium carbonate, glycine, arginine, croscarmellose sodium or a combination thereof.

7. The solid dosage form of claim 1, where said inert formulation additive comprises microcrystalline cellulose present at a concentration at 17% to about 33% by weight of the ibuprofen.

8. The solid dosage form of claim 7, wherein said inert formulation additive comprises a first microcrystalline cellulose having particle size of about 20 μm and a second MCC having a particles size of about 180 μm, each of which is present at a concentration at 17% to about 33% by weight of the ibuprofen.

9. The solid dosage form of claim 1, wherein said solid dosage form demonstrates a mean serum ibuprofen concentration in a subject greater than or equal to 6.4 μg/ml within two hours of administration, and wherein said solid dosage form also demonstrates a mean serum ibuprofen concentration in a subject greater than or equal to 6.4 μg/ml for at least 8 hours after administration.

10. A modified release tablet, comprising:

ibuprofen in an amount in the range of 300 mg to 800 mg per tablet;

a hydrophilic polymer;

a dissolution additive at a concentration of from 10% to 35% by weight of the ibuprofen comprising alkali metal salts, an amino acid possessing neutral-to-alkaline side chain, croscarmellose or a salt thereof or a combination thereof; and

an inert formulation additive comprising microcrystalline cellulose, silicified microcrystalline cellulose, dicalcium phosphate, lactose, pre-gelatinized starch or mixtures thereof, said inert formulation additive being present in said dosage in an amount of 15% to about 75% by weight of the ibuprofen,

wherein said tablet demonstrates a mean serum ibuprofen concentration in a subject greater than or equal to 6.4 μg/ml within two hours of administration, and wherein said tablet also demonstrates a mean serum ibuprofen concentration in a subject greater than or equal to 6.4 μg/ml for at least 8 hours after administration.

11. The tablet of claim 10,

wherein the hydrophilic polymer comprises hydroxypropyl methylcellulose at a concentration of 17% to 42% by weight of ibuprofen;

wherein ibuprofen is present in an amount of about 600 mg and dispersed uniformly in said polymer;

wherein said dissolution additive is sodium carbonate uniformly dispersed in said polymer; and

wherein said formulation additive is two differing particle sizes of microcrystalline cellulose dispersed in said polymer, each at 15% to 50% by weight of the ibuprofen.

12. The tablet of claim 10,

wherein the hydrophilic polymer comprises hydroxypropyl methylcellulose at a concentration of 17% to 42% by weight of ibuprofen;

wherein ibuprofen is present in an amount of about 600 mg and is dispersed uniformly in said polymer;

wherein said dissolution additive is glycine uniformly dispersed in said polymer at a concentration of 10% to 15% by weight of the ibuprofen.

13. The tablet of claim 10,

wherein the hydrophilic polymer comprises hydroxypropyl methylcellulose at a concentration of 17% to 42% by weight of ibuprofen;

wherein ibuprofen is present in an amount of about 600 mg and is dispersed uniformly in said polymer;

wherein said dissolution additive is glycine uniformly dispersed in said polymer at a concentration of 10% to 15% by weight of the ibuprofen;

wherein said formulation additive is two differing particle sizes of microcrystalline cellulose dispersed in said polymer, each at 15% to 50% by weight of the ibuprofen.

14. The tablet of claim 10,

wherein said hydrophilic polymer comprises hydroxypropyl methylcellulose having two differing viscosities, selected from the group consisting of HPMC 100 cps, HPMC 4000 cps, HPMC 15000 cps, and HPMC 100000 cps, each at a concentration of 17% to 42% by weight of ibuprofen;

wherein the dissolution additive is glycine uniformly dispersed in said polymer at a concentration of 5% to 35% by weight of the ibuprofen;

wherein the formulation additive is two differing particle sizes of microcrystalline cellulose dispersed in said polymer, each at 15% to 50% by weight of the ibuprofen.

15. The tablet of claim 10,

wherein said hydrophilic polymer comprises hydroxypropyl methylcellulose having two differing viscosities, selected from the group consisting of HPMC 100 cps, HPMC 4000 cps, HPMC 15000 cps, and HPMC 100000 cps, each at a concentration of 17% to 42% by weight of ibuprofen;

wherein 300mg to 800mg ibuprofen dispersed uniformly in said polymer;

wherein the dissolution additive is glycine uniformly dispersed in said polymer at a concentration of 5% to 35% by weight of the ibuprofen and croscarmellose sodium uniformly dispersed in said polymer at a concentration of 1% to 15% by weight of the ibuprofen.

16. The tablet of claim 10,

wherein said hydrophilic polymer comprises hydroxypropyl methylcellulose having two differing viscosities, selected from the group consisting of HPMC 100 cps, HPMC 4000 cps, HPMC 15000 cps, and HPMC 100000 cps, each at a concentration of 17% to 42% by weight of ibuprofen;

wherein 300mg to 800mg ibuprofen dispersed uniformly in said polymer;

wherein the dissolution additive is glycine uniformly dispersed in said polymer at a concentration of 5% to 35% by weight of the ibuprofen and croscarmellose sodium uniformly dispersed in said polymer at a concentration of 1% to 15% by weight of the ibuprofen;

wherein the formulation additive is two differing particle sizes of microcrystalline cellulose dispersed in said polymer, each at 15% to 50% by weight of the ibuprofen.

17. The tablet of claim 10,

wherein said hydrophilic polymer comprises hydroxypropyl methylcellulose having two differing viscosities, selected from the group consisting of HPMC 100 cps, HPMC 4000 cps, HPMC 15000 cps, and HPMC 100000 cps, each at a concentration of 17% to 42% by weight of ibuprofen;

wherein 300mg to 800mg ibuprofen dispersed uniformly in said polymer;

wherein the dissolution additive is sodium carbonate uniformly dispersed in said polymer at a concentration of 5% to 35% by weight of the ibuprofen;

wherein the formulation additive is two differing particle sizes of microcrystalline cellulose dispersed in said polymer, each at 15% to 50% by weight of the ibuprofen.

18. The tablet of claim 10,

wherein said hydrophilic polymer comprises hydroxypropyl methylcellulose having two differing viscosities, selected from the group consisting of HPMC 100 cps, HPMC 4000 cps, HPMC 15000 cps, and HPMC 100000 cps, each at a concentration of 17% to 42% by weight of ibuprofen;

wherein 300mg to 800mg ibuprofen dispersed uniformly in said polymer;

wherein the dissolution additive is sodium carbonate uniformly dispersed in said polymer at a concentration of 5% to 35% by weight of the ibuprofen, and croscarmellose sodium uniformly dispersed in said polymer at a concentration of 1% to 15% by weight of the ibuprofen;

wherein the formulation additive is two differing particle sizes of microcrystalline cellulose dispersed in said polymer, each at 15% to 50% by weight of the ibuprofen.

19. The tablet of claim 10,

wherein said hydrophilic polymer comprises hydroxypropyl methylcellulose having two differing viscosities, selected from the group consisting of HPMC 100 cps, HPMC 4000 cps, HPMC 15000 cps, and HPMC 100000 cps, each at a concentration of 17% to 42% by weight of ibuprofen;

wherein 300mg to 800mg ibuprofen dispersed uniformly in said polymer;

wherein the dissolution additives are sodium carbonate uniformly dispersed in said polymer at a concentration of 5% to 35% by weight of the ibuprofen, glycine uniformly dispersed in said polymer at a concentration of 5% to 35% by weight of the ibuprofen, and croscarmellose sodium uniformly dispersed in said polymer at a concentration of 1% to 15% by weight of the ibuprofen;

wherein the formulation additive is two differing particle sizes of microcrystalline cellulose dispersed in said polymer, each at 15% to 50% by weight of the ibuprofen.

20. A method of maintaining a mean plasma ibuprofen concentration of at least 6.4 μg/ml over a time period of 2 to 8 hours in a patient, comprising:

administering a single dosage of the solid dosage form according to claim 1.

21. The method for providing immediate and extended release of ibuprofen to a subject, comprising:

administering to a subject in a single dose of a modified release tablet comprising,

ibuprofen in an amount in the range of 300 mg to 800 mg per tablet;

a hydrophilic polymer;

a dissolution additive at a concentration of from 10% to 35% by weight of the ibuprofen comprising alkali metal salts, an amino acid possessing neutral-to-alkaline side chain, croscarmellose or a salt thereof or a combination thereof; and

an inert formulation additive comprising microcrystalline cellulose, silicified microcrystalline cellulose, dicalcium phosphate, lactose, pre-gelatinized starch or mixtures thereof, said inert formulation additive being present in said dosage in an amount of 15% to about 75% by weight of the ibuprofen,

wherein said tablet demonstrates a mean serum ibuprofen concentration in a subject greater than or equal to 6.4 μg/ml within two hours of administration, and wherein said tablet also demonstrates a mean serum ibuprofen concentration in a subject greater than or equal to 6.4 μg/ml for at least 8 hours after administration.

22. The method according to claim 21,

wherein said hydrophilic polymer comprises hydroxypropyl methylcellulose having two differing viscosities, selected from the group consisting of HPMC 100 cps, HPMC 4000 cps, HPMC 15000 cps, and HPMC 100000 cps, each at a concentration of 17% to 42% by weight of ibuprofen;

wherein 300mg to 800mg ibuprofen dispersed uniformly in said polymer;

wherein the dissolution additives are sodium carbonate uniformly dispersed in said polymer at a concentration of 5% to 35% by weight of the ibuprofen, glycine uniformly dispersed in said polymer at a concentration of 5% to 35% by weight of the ibuprofen, and croscarmellose sodium uniformly dispersed in said polymer at a concentration of 1% to 15% by weight of the ibuprofen;

wherein the formulation additive is two differing particle sizes of microcrystalline cellulose dispersed in said polymer, each at 15% to 50% by weight of the ibuprofen.

23. The method according to claim 21,

wherein said hydrophilic polymer comprises hydroxypropyl methylcellulose having two differing viscosities, selected from the group consisting of HPMC 100 cps, HPMC

4000 cps, HPMC 15000 cps, and HPMC 100000 cps, each at a concentration of 17% to 42% by weight of ibuprofen;

wherein 300mg to 800mg ibuprofen dispersed uniformly in said polymer;

wherein the dissolution additive is sodium carbonate uniformly dispersed in said polymer at a concentration of 5% to 35% by weight of the ibuprofen, and croscarmellose sodium uniformly dispersed in said polymer at a concentration of 1% to 15% by weight of the ibuprofen;

wherein the formulation additive is two differing particle sizes of microcrystalline cellulose dispersed in said polymer, each at 15% to 50% by weight of the ibuprofen.

24. The method according claim 21,

wherein said hydrophilic polymer comprises hydroxypropyl methylcellulose having two differing viscosities, selected from the group consisting of HPMC 100 cps, HPMC 4000 cps, HPMC 15000 cps, and HPMC 100000 cps, each at a concentration of 17% to 42% by weight of ibuprofen;

wherein 600mg ibuprofen is dispersed uniformly in said polymer; and

wherein the dissolution additive is sodium carbonate uniformly dispersed in said polymer at a concentration of 10% to 35% by weight of the ibuprofen, and glycine uniformly dispersed in said polymer at a concentration of 1% to 15% by weight of the ibuprofen.

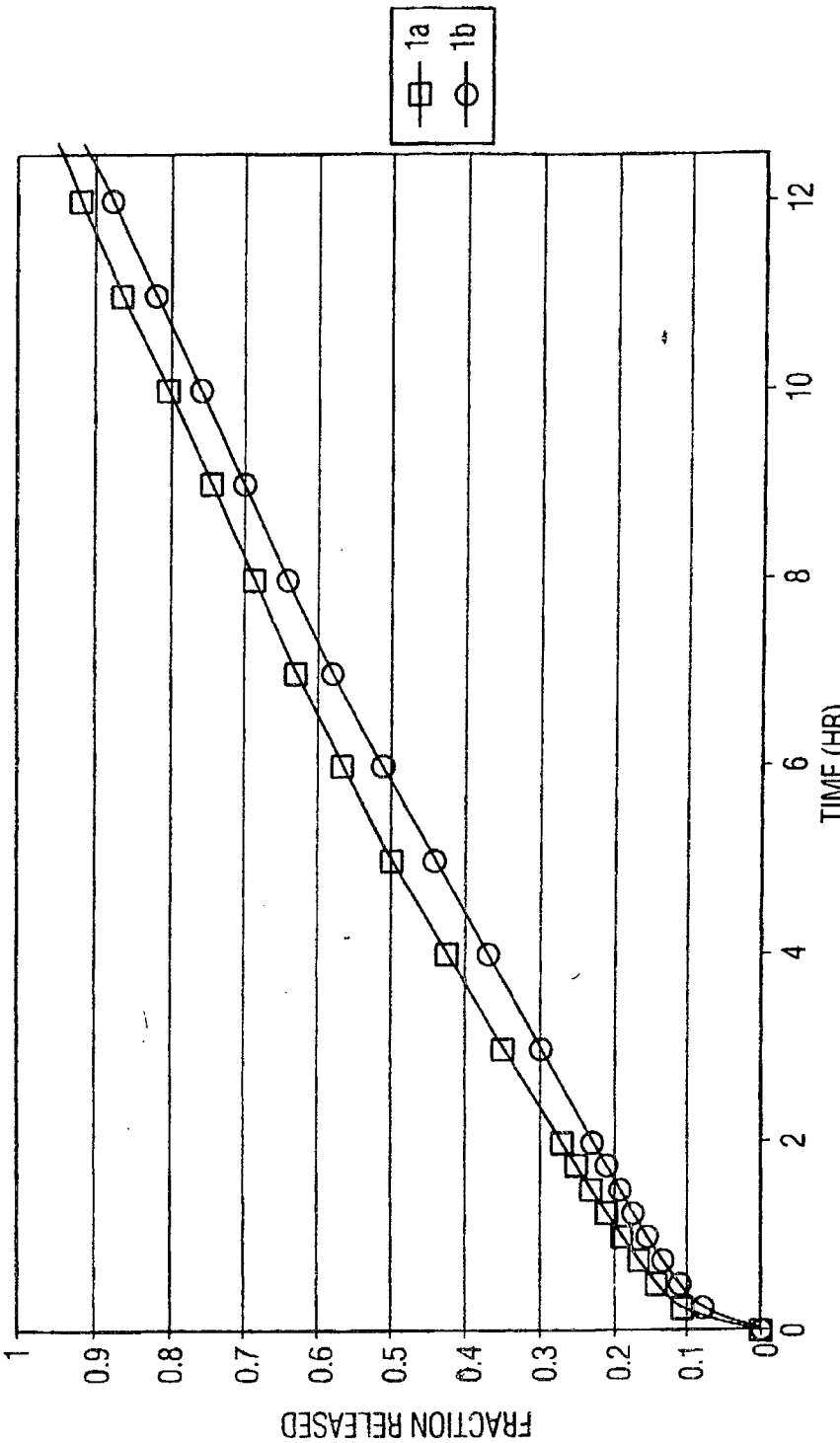

1a
1b
FRACTION RELEASED
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
TIME (HR)

FIG. 1

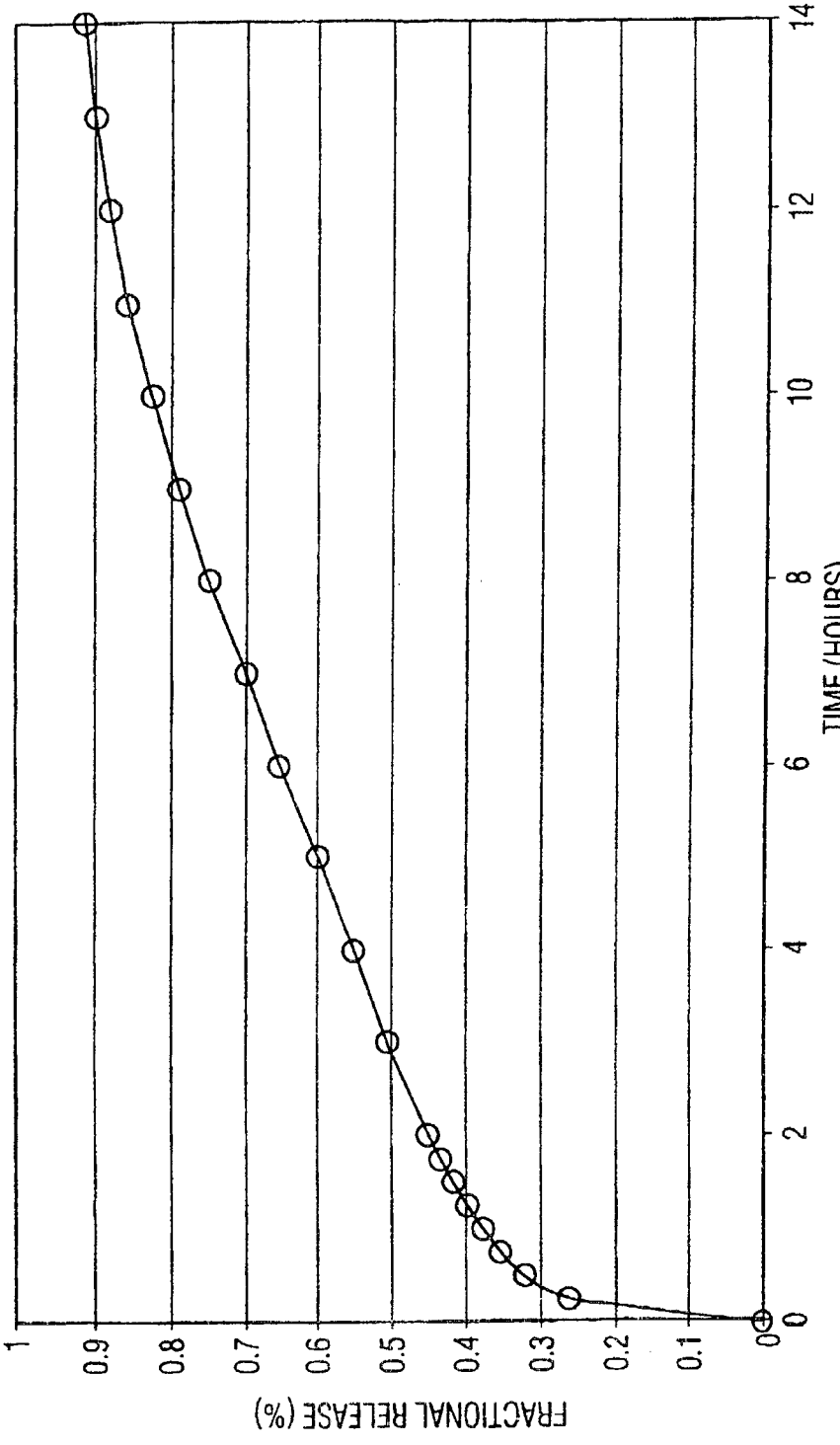

FRACTIONAL RELEASE (%)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
TIME (HOURS)
0
2
4
6
8
10
12
14

FIG. 2

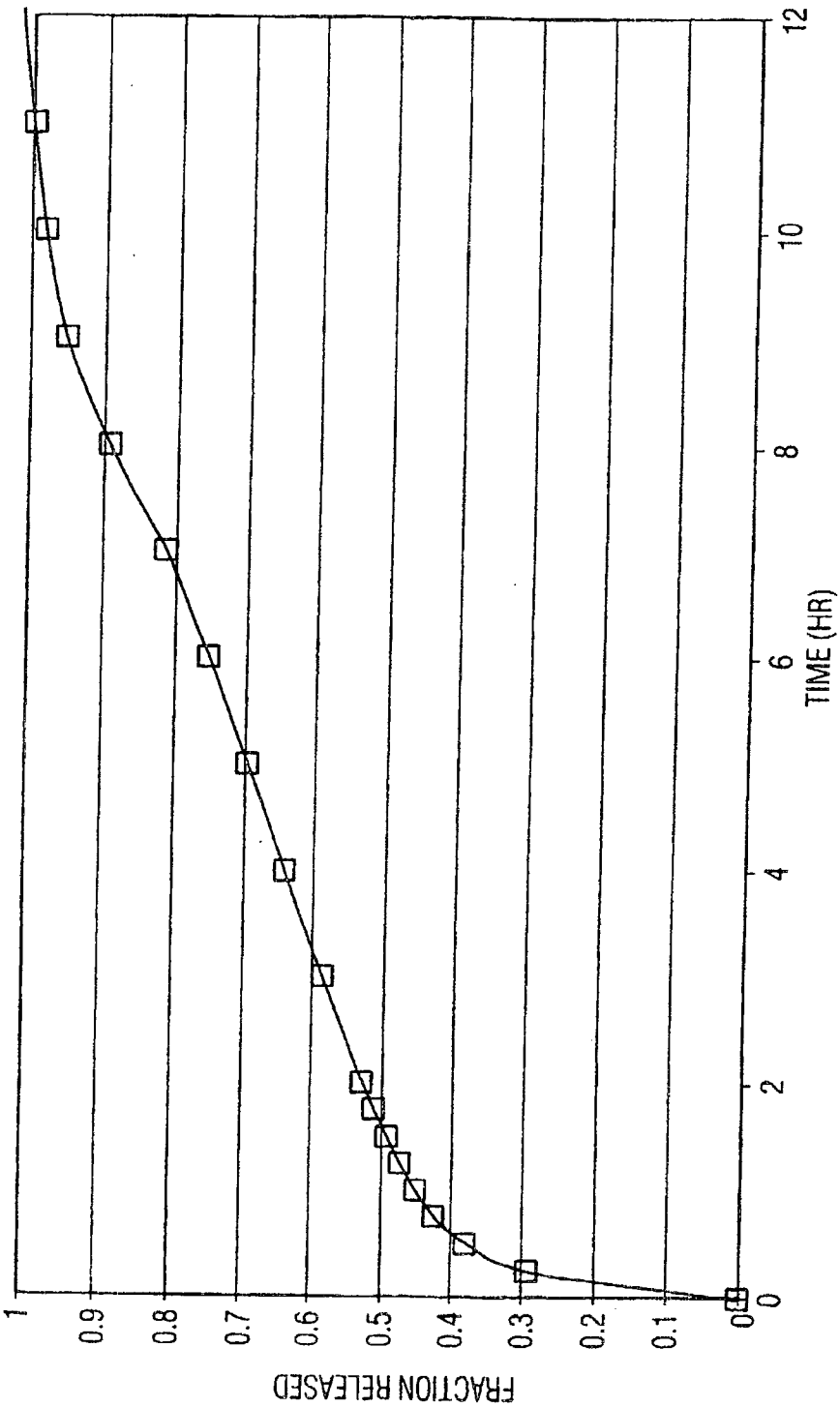

FRACTION RELEASED
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
TIME (HR)

FIG. 3

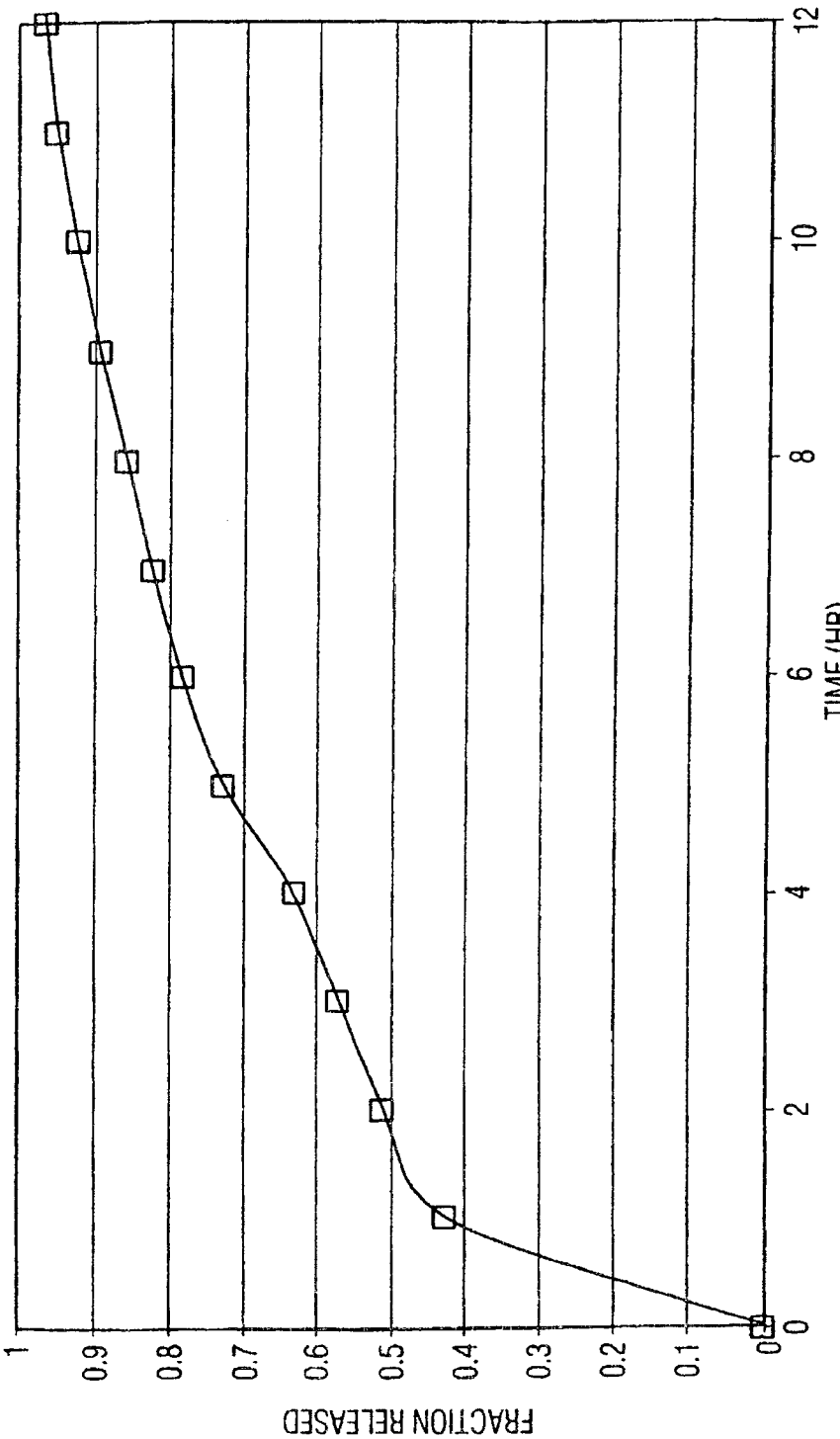

FRACTION RELEASED
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
TIME (HR)

FIG. 4

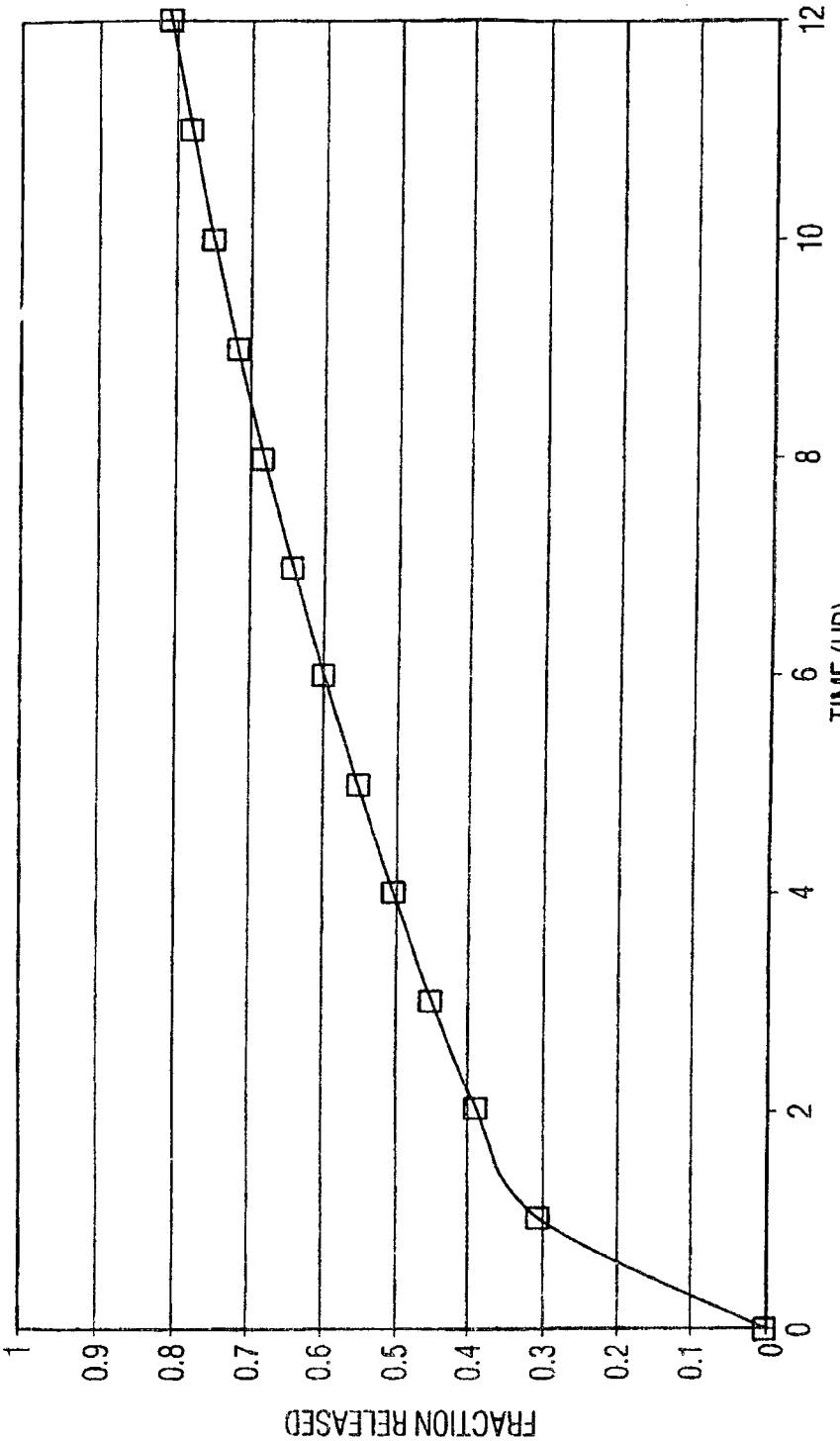

FRACTION RELEASED
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
TIME (HR)

FIG. 5

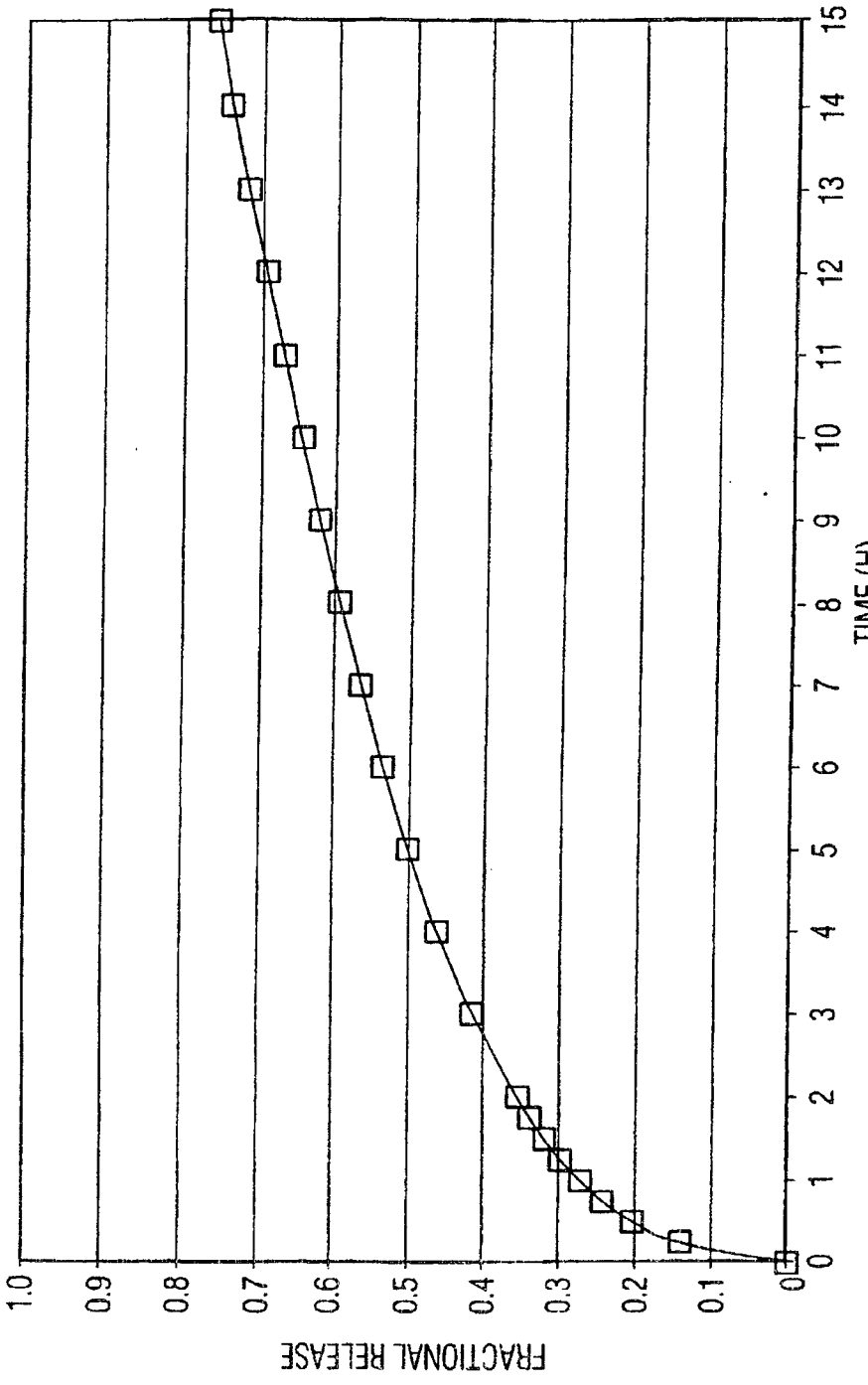

FRACTIONAL RELEASE
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
TIME (H)
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15

FIG. 6

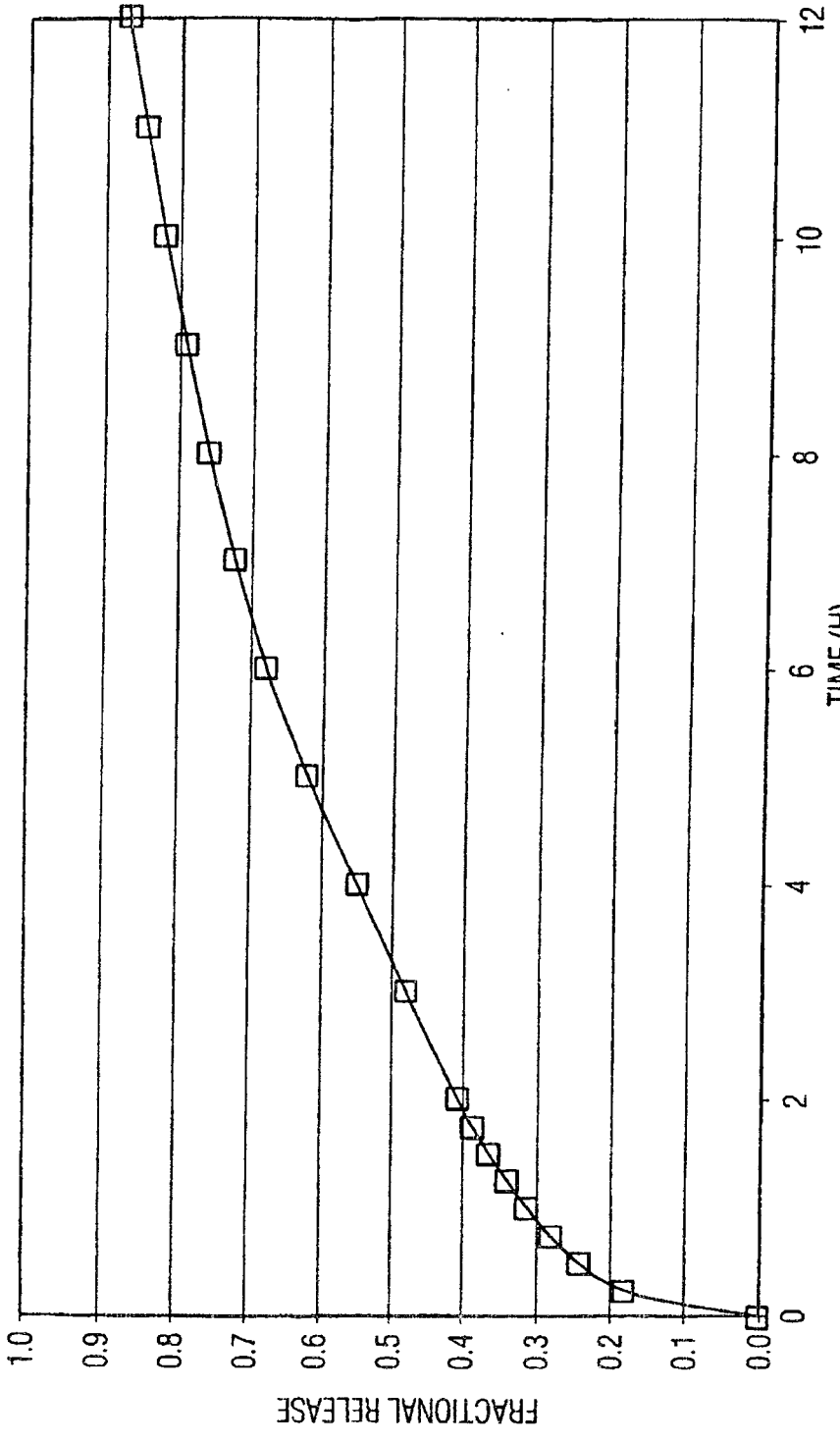

FRACTIONAL RELEASE
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
2
4
6
8
10
12
TIME (H)

FIG. 7

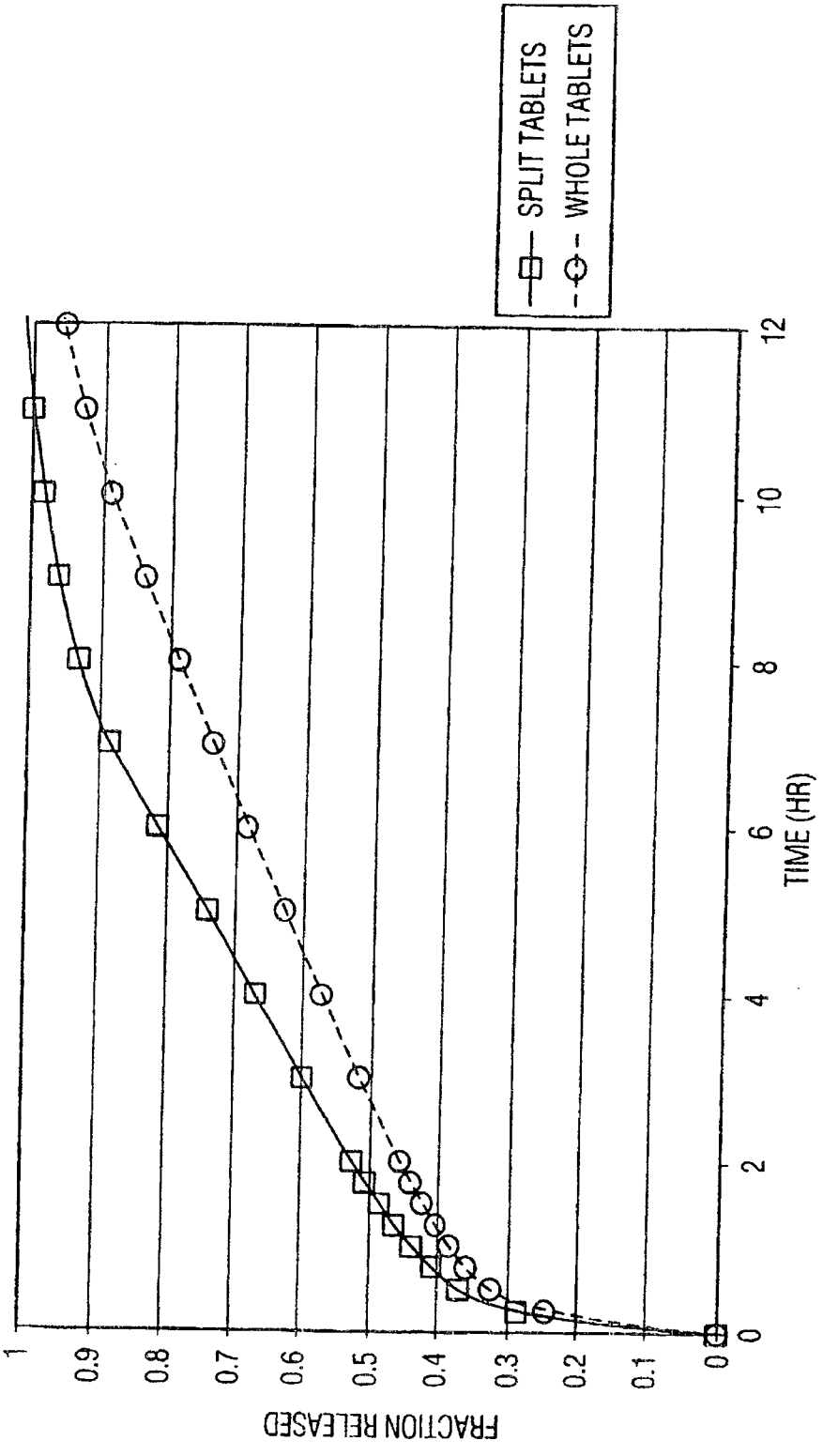

SPLIT TABLETS
WHOLE TABLETS
FRACTION RELEASED
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
TIME (HR)

FIG. 8

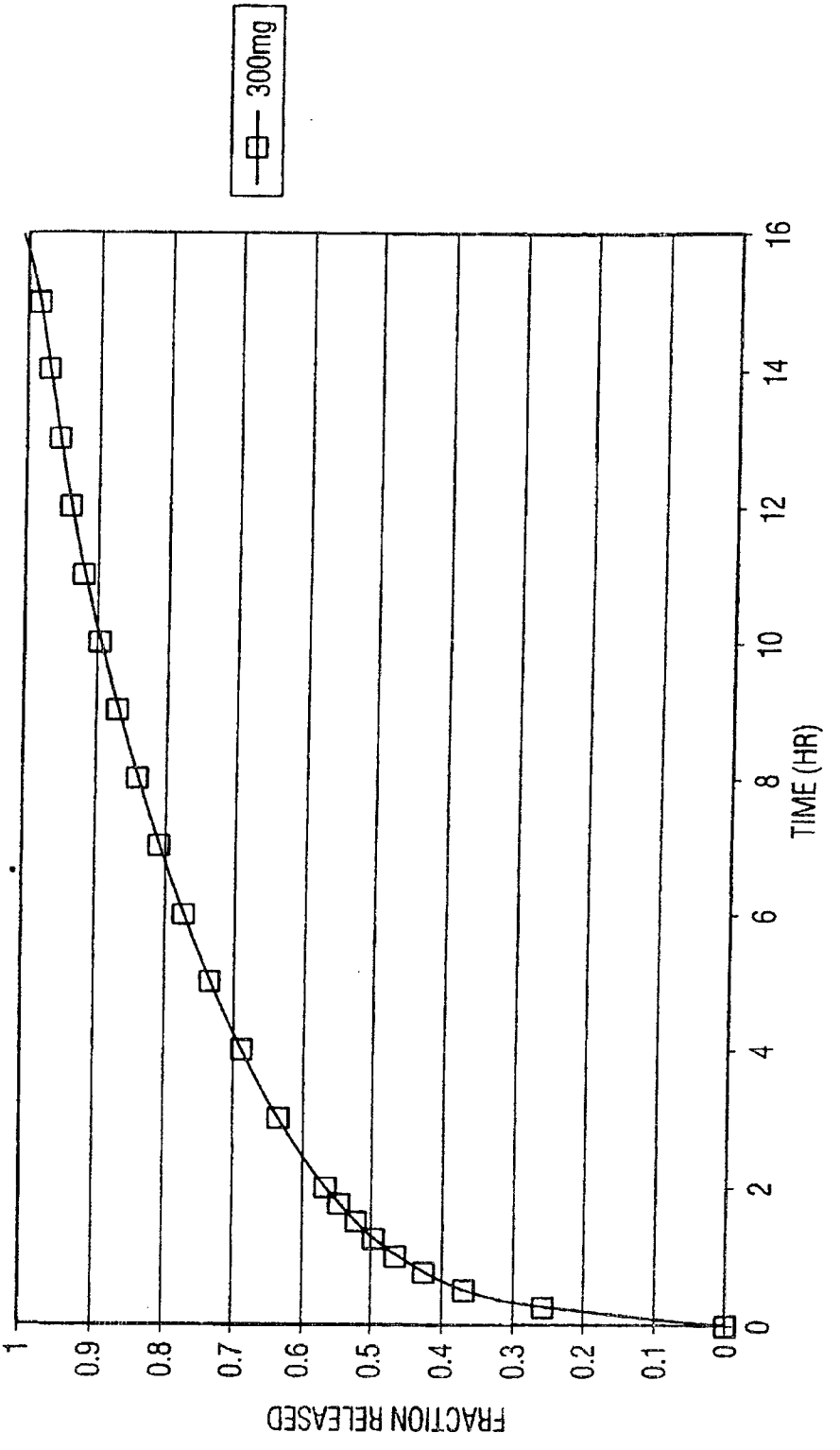

300mg
FRACTION RELEASED
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
14
16
TIME (HR)

FIG. 9

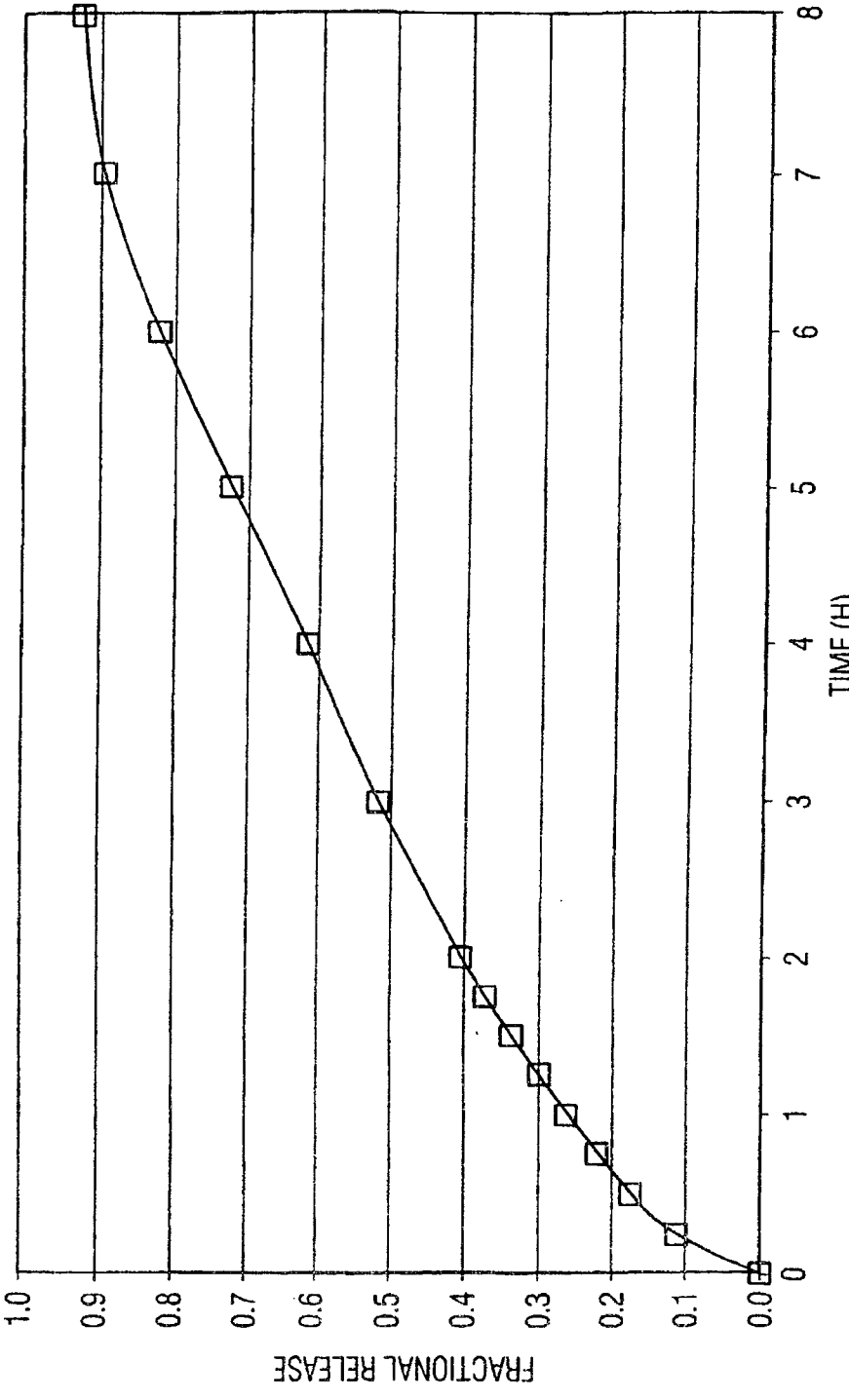

FRACTIONAL RELEASE
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
TIME (H)
0
1
2
3
4
5
6
7
8

FIG. 10

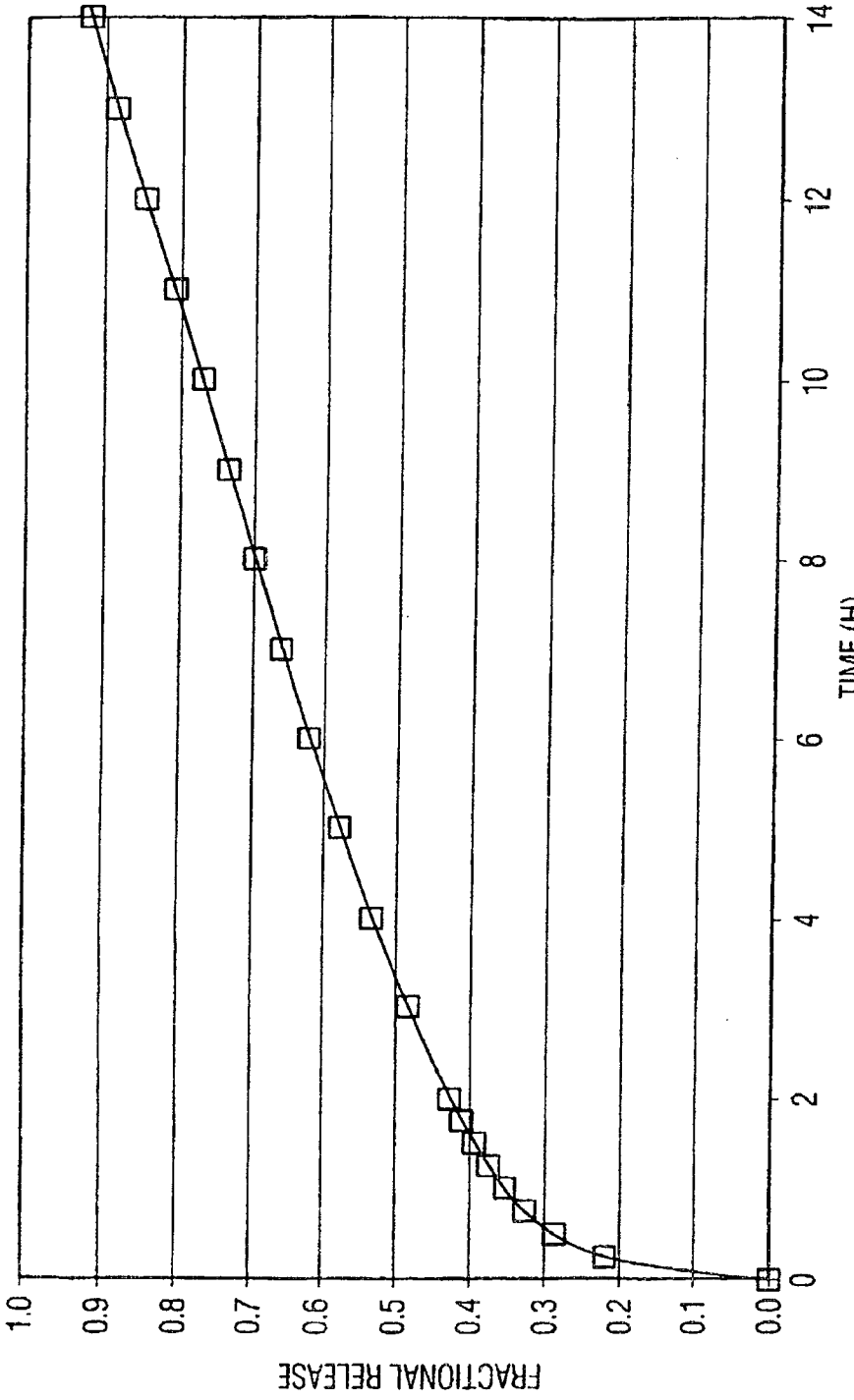

FRACTIONAL RELEASE
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
TIME (H)
0
2
4
6
8
10
12
14

FIG. 11

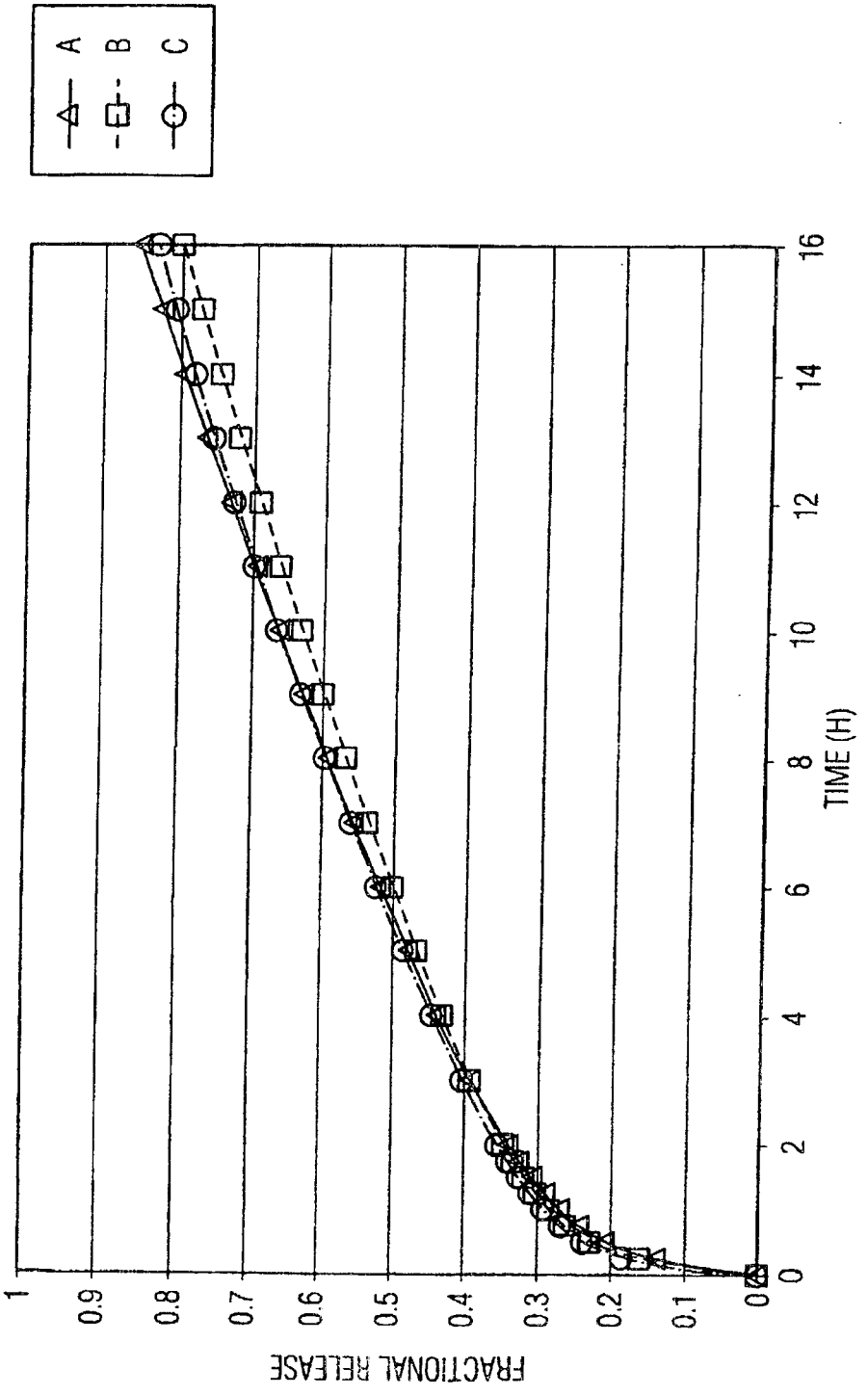

A
B
C
FRACTIONAL RELEASE
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
14
16
TIME (H)

FIG. 12

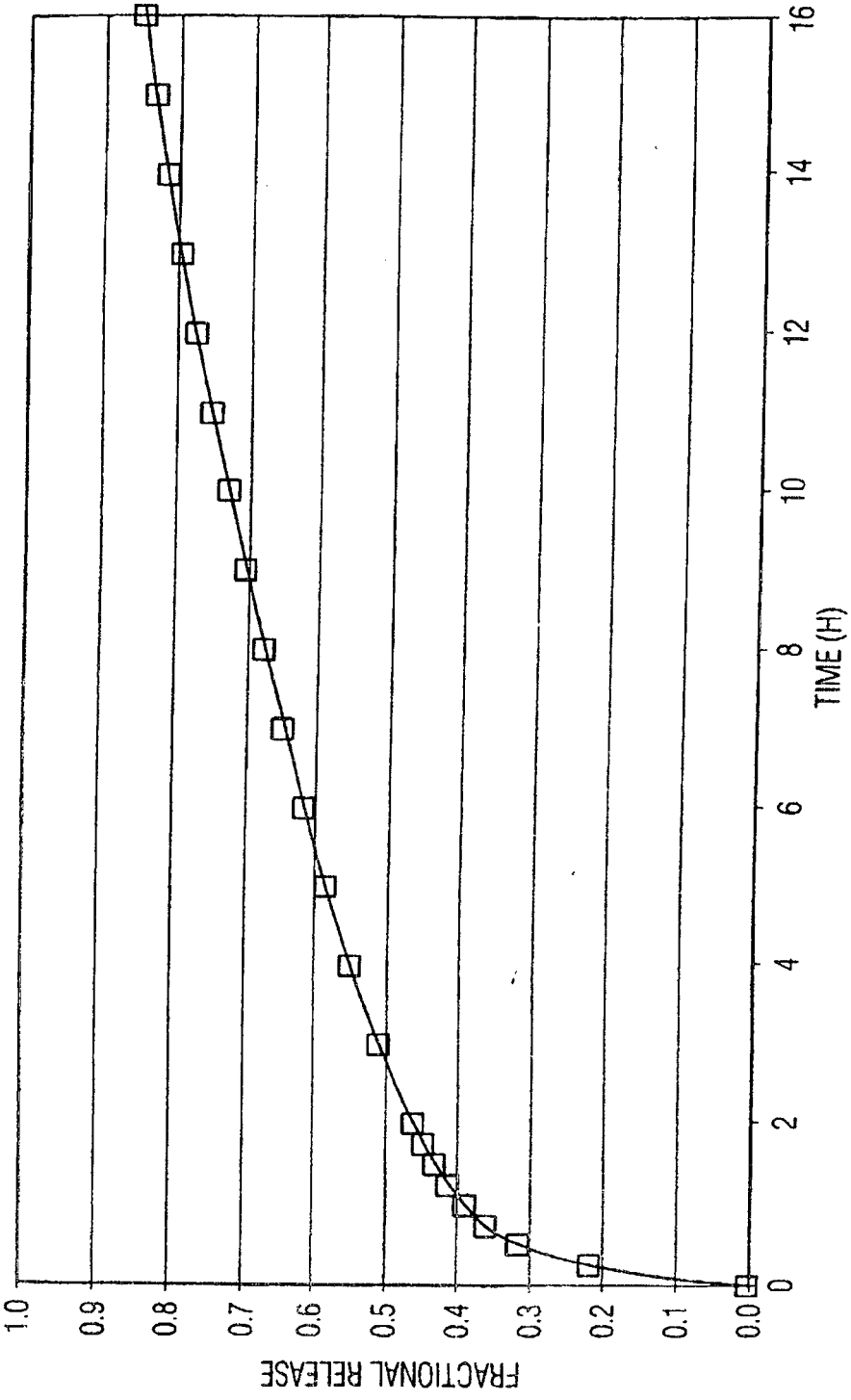

FRACTIONAL RELEASE
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
TIME (H)
0
2
4
6
8
10
12
14
16

FIG. 13

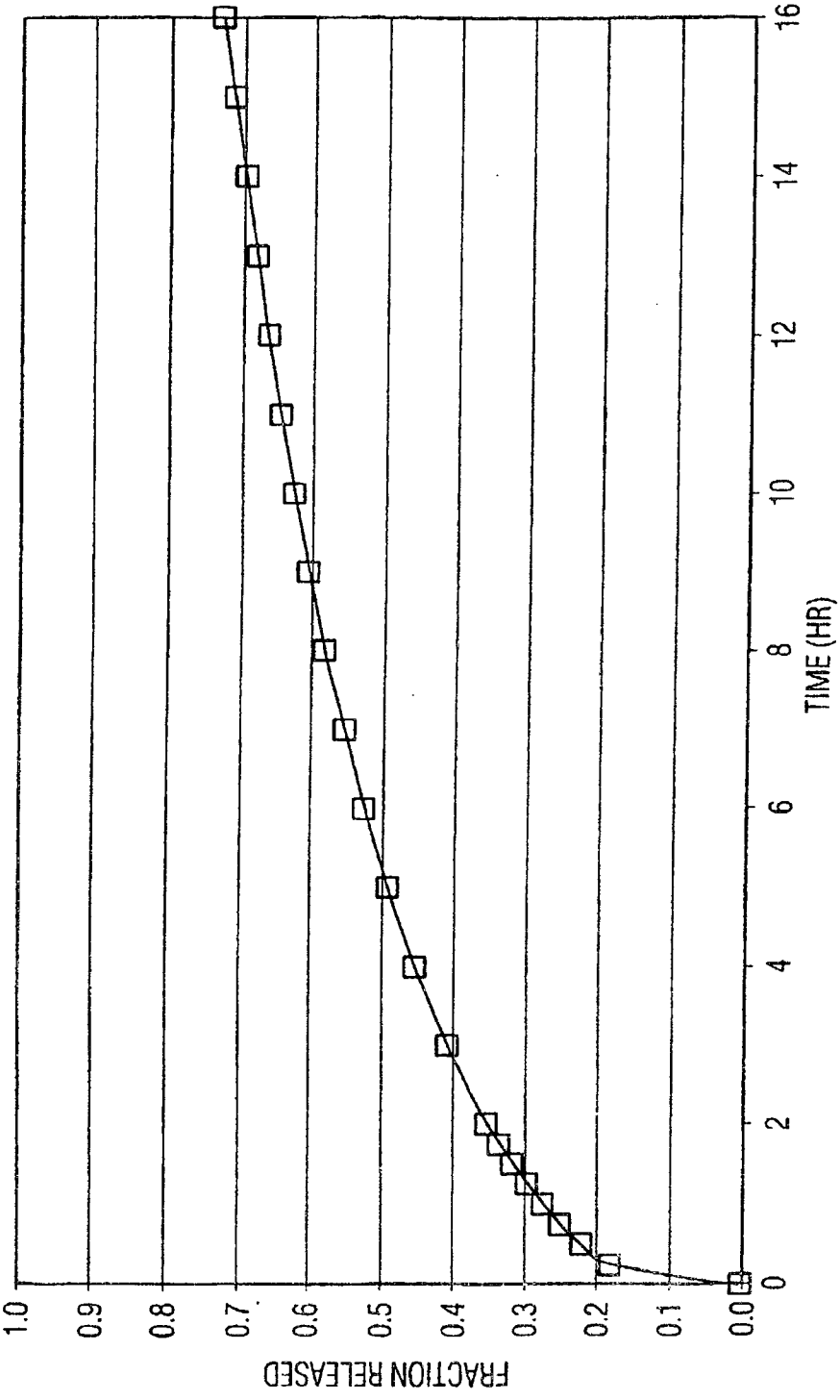

FRACTION RELEASED
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
TIME (HR)
0
2
4
6
8
10
12
14
16

FIG. 14

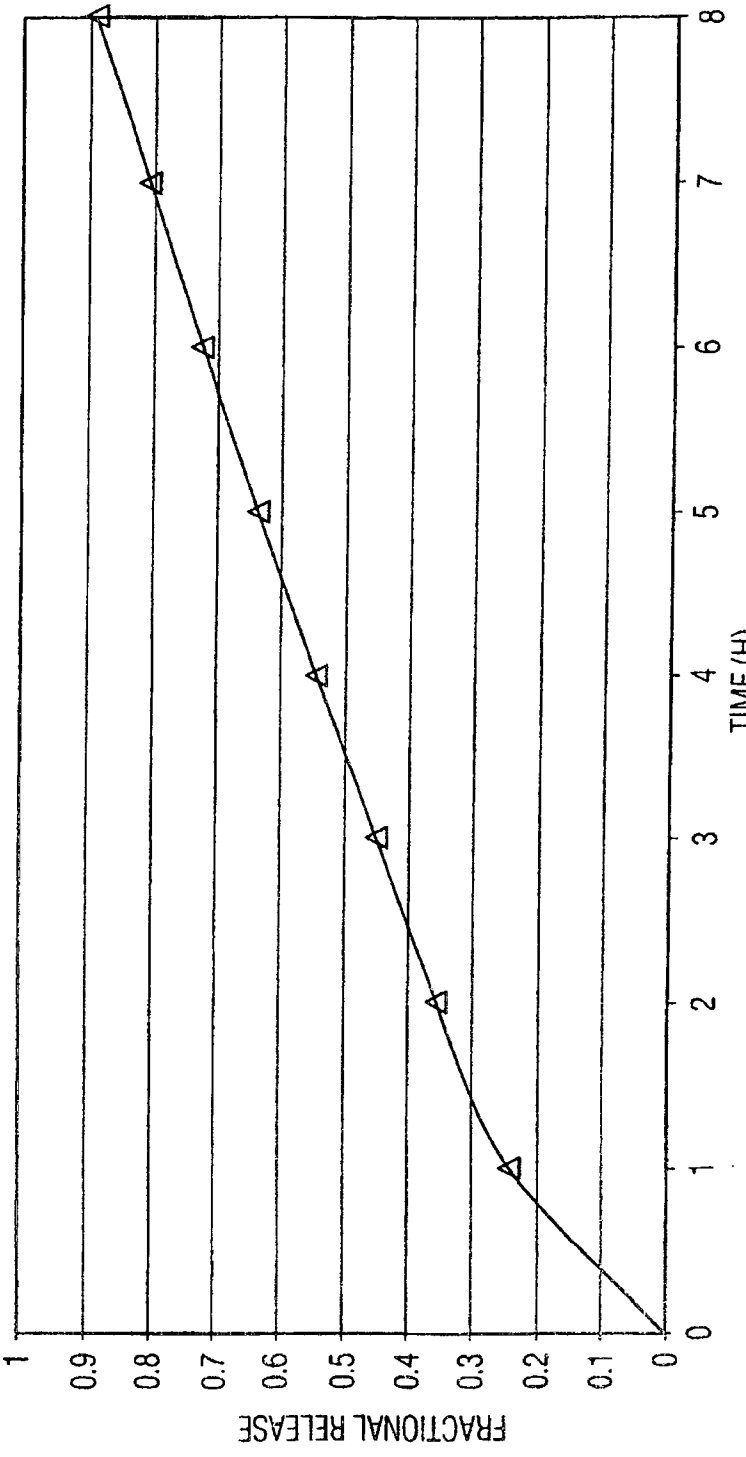

FRACTIONAL RELEASE
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
TIME (H)
0
1
2
3
4
5
6
7
8

FIG. 15

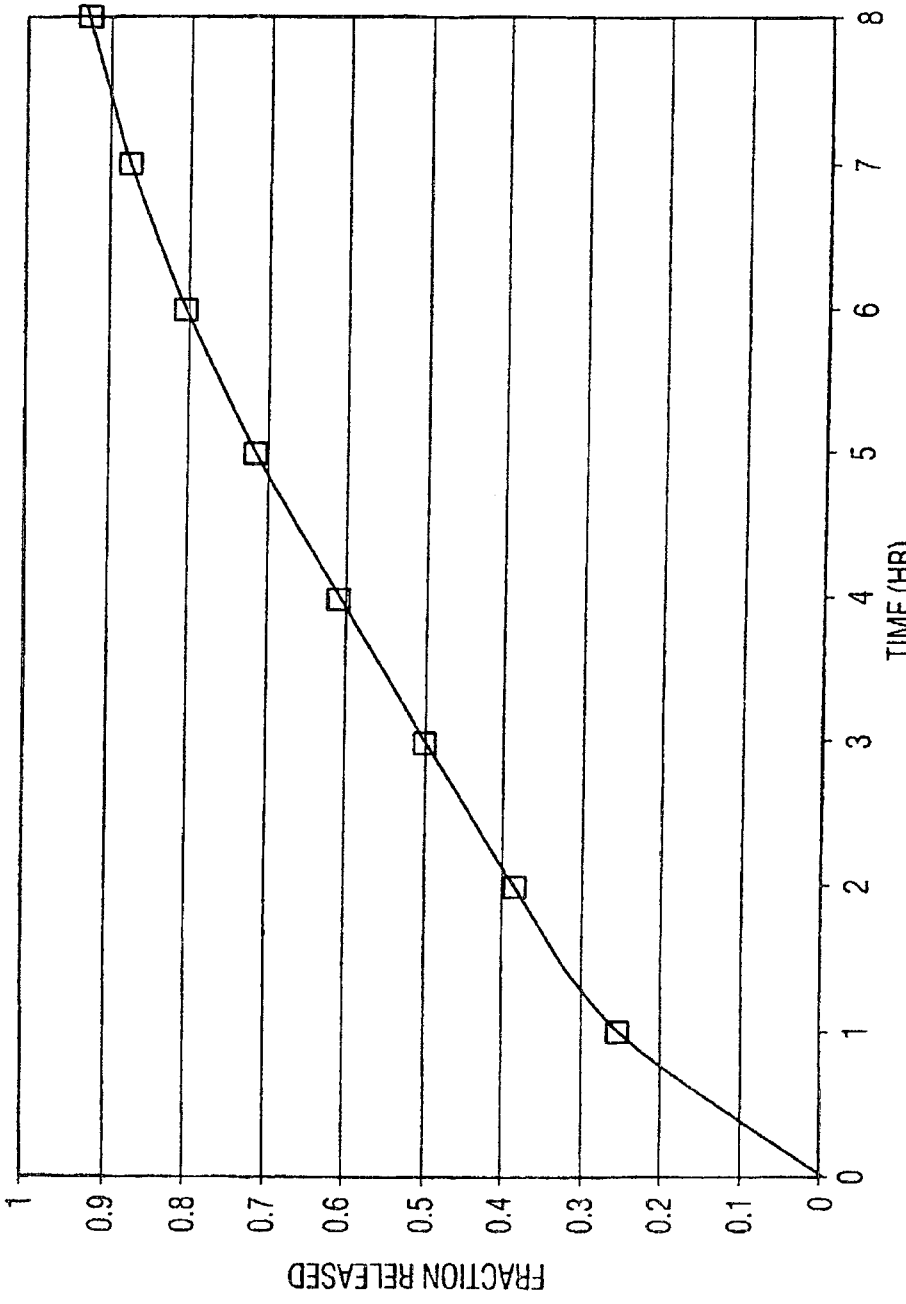

FRACTION RELEASED
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
TIME (HR)
0
1
2
3
4
5
6
7
8

FIG. 16

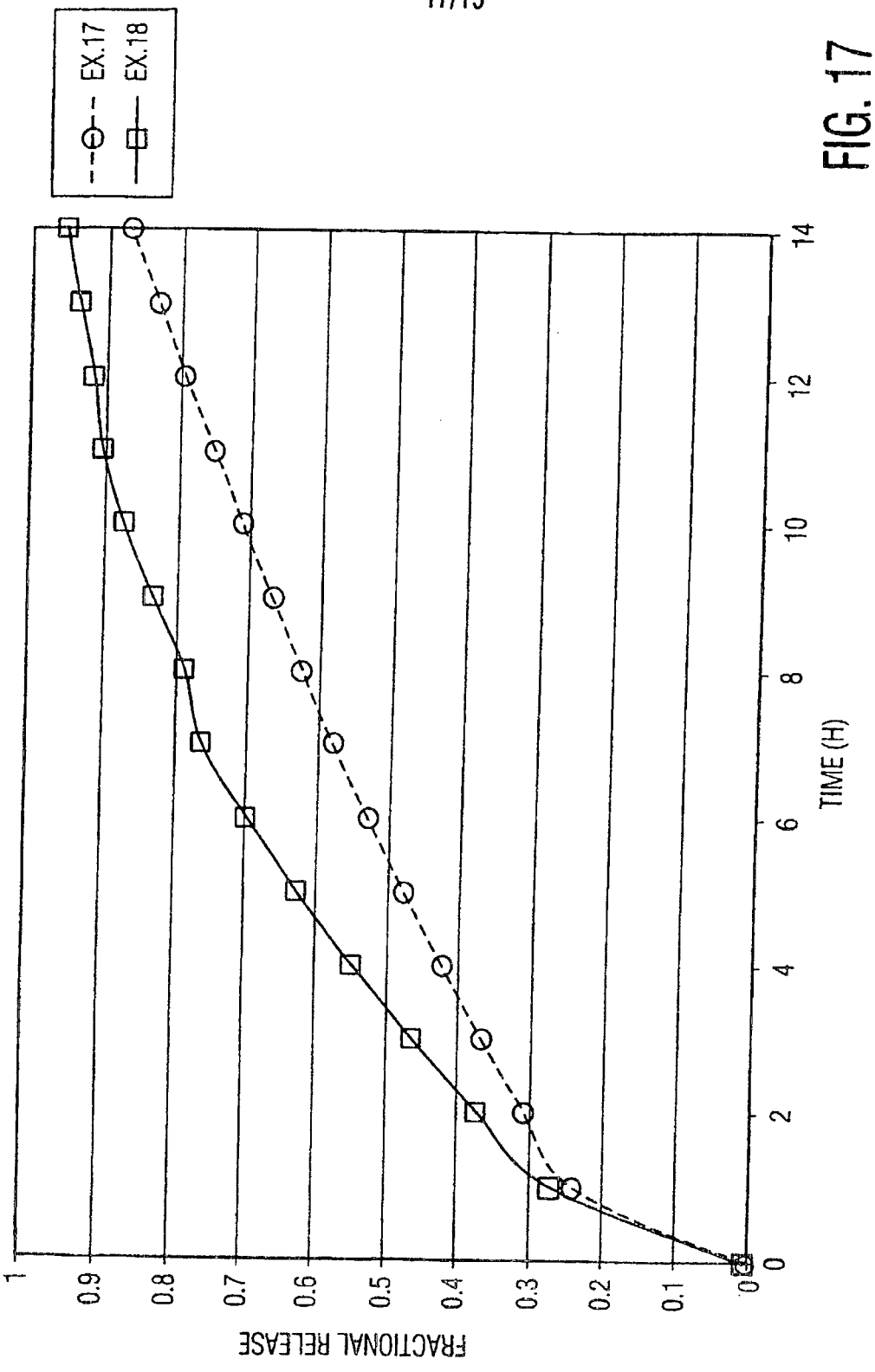

EX.17
EX.18
FRACTIONAL RELEASE
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
TIME (H)
0
2
4
6
8
10
12
14

FIG. 17

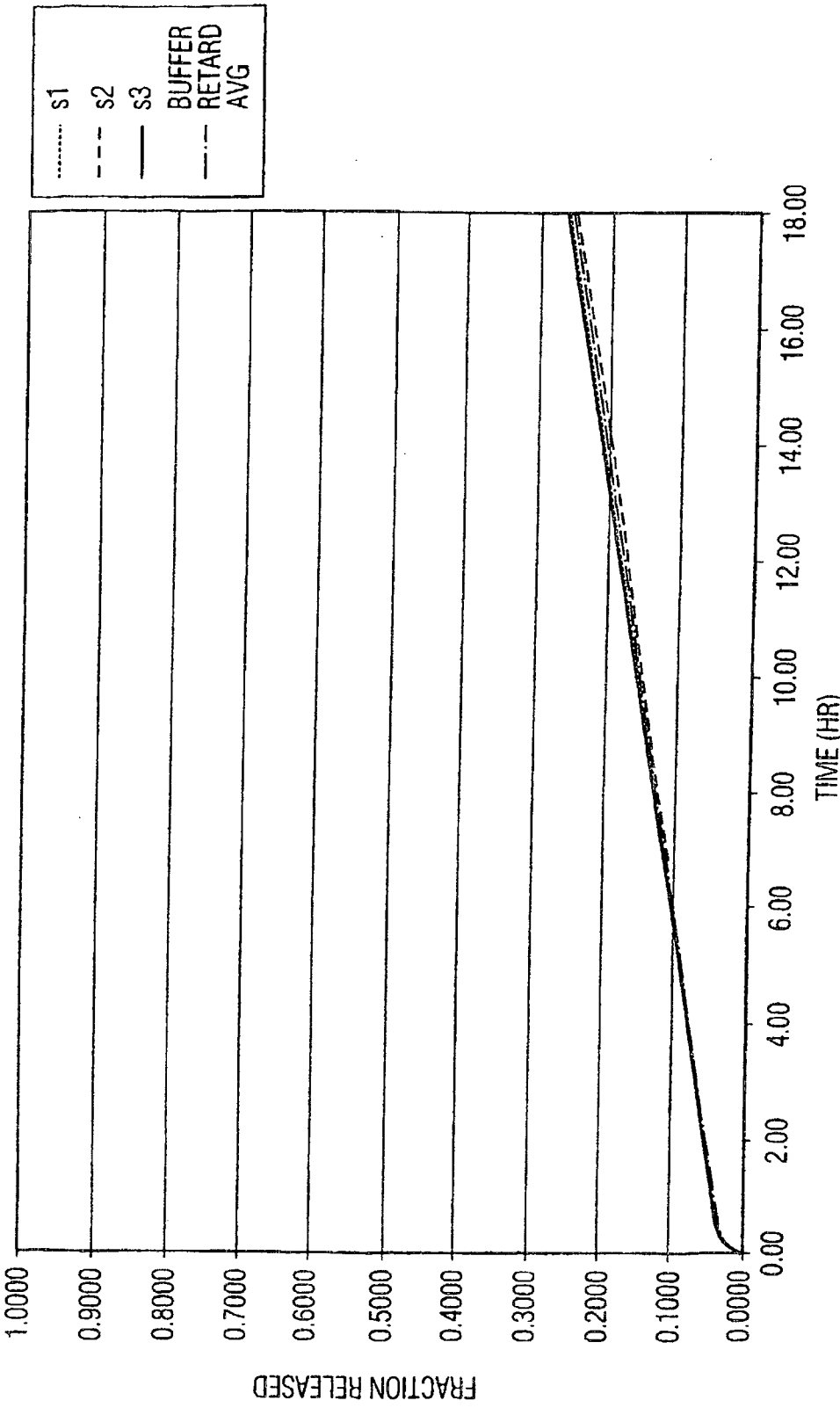

s1
s2
s3
BUFFER RETARD AVG
1.0000
0.9000
0.8000
0.7000
0.6000
0.5000
0.4000
0.3000
0.2000
0.1000
0.0000
FRACTION RELEASED
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
16.00
18.00
TIME (HR)

FIG. 18

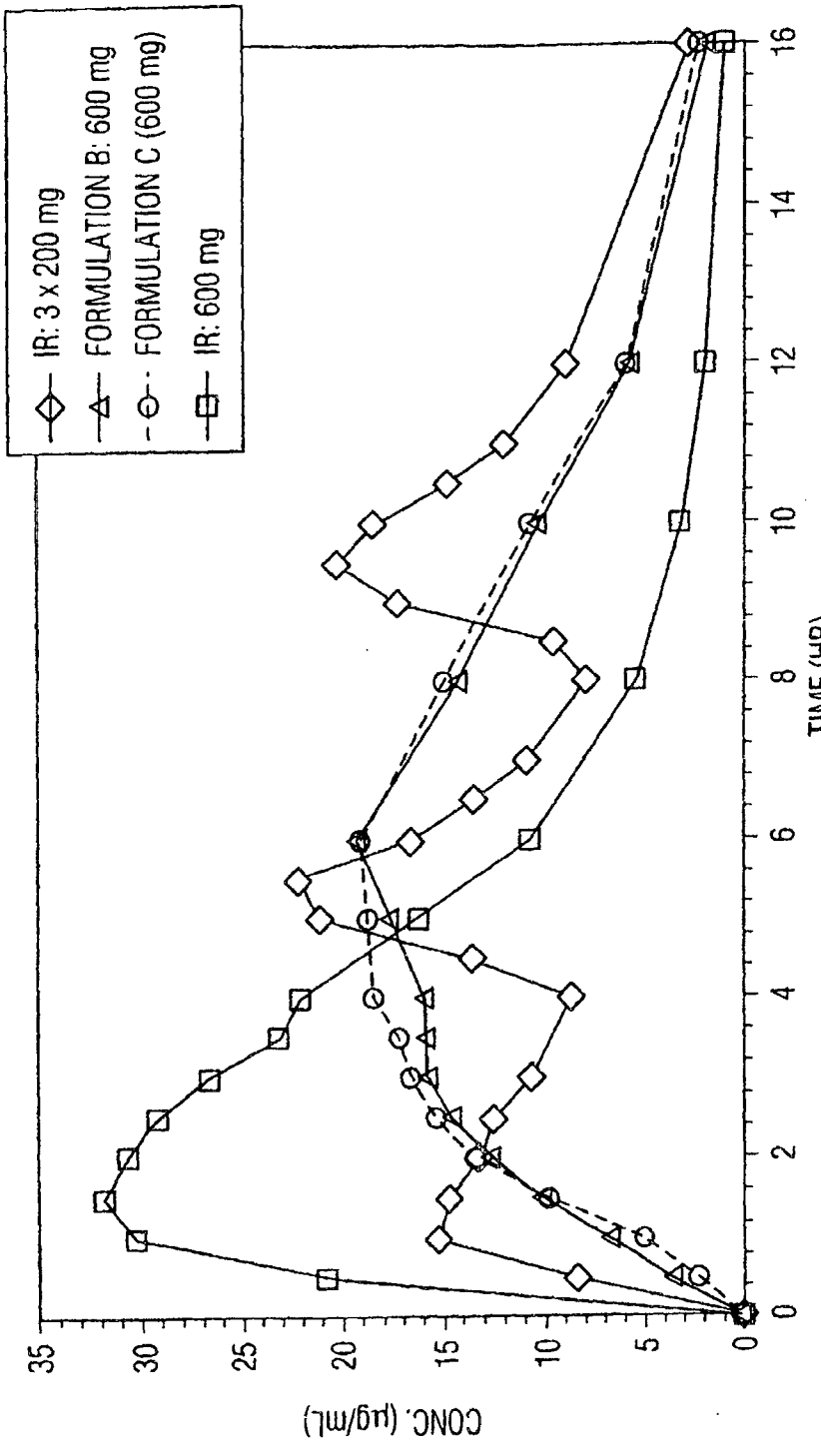

IR: 3 x 200 mg
FORMULATION B: 600 mg
FORMULATION C (600 mg)
IR: 600 mg
CONC. (µg/mL)
0
5
10
15
20
25
30
35
0
2
4
6
8
10
12
14
16
TIME (HR)

FIG. 19