260 260

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-007599- -00010-0000
Fecha: 2009-03-30 14:11:07 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 400 OPOSIOBSERVTER Folios: 97

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: 07-07599
Solicitante: NYCOMED DANMARK APS.
Apoderado: LUIS PATIÑO LEYVA
Título de la nueva creación o denominación del signo: ELABORACIÓN DE COMPLICACIONES FARMACEUTICAS DE LIBERACIÓN RÁPIDA DE DROGAS INSOLUBLES EN AGUA Y COMPOSICIONES FARMACEUTICAS OBTENIDAS POR EL PROCESO DE LA INVENCION.
Gaceta: 599

③ OPOSICIÓN PRESENTADA POR:

SOLICITANTE

Nombre: PROCAPS S.A
Dirección: CALLE 80 No. 78B -201
Nacionalidad o Domicilio:
Lugar de Constitución: COLOMBIA BARRANQUILLA
Teléfono: (571)3719900 Fax: (571)3730818
E-mail: negocios@optimum-co.com

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. 119-95 104
Teléfono: (571) 2131213 Fax: (571) 6121979
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 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".

2000 504

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 interes, 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 T.P. 83823

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

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente Nº 07 007.599

Asunto : Oposición a la solicitud de patente de Invención titulada **"ELABORACIÓN DE COMPLICACIONES FARMACÉUTICAS DE LIBERACIÓN RÁPIDA DE DROGAS INSOLUBLES EN AGUA Y COMPOSICIONES FARMACÉUTICAS OBTENIDAS POR EL PROCESO DE LA INVENCIÓN"**

Solicitante : NYCOMED DANMARK APS

Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial

Nº 599 del 31 de Diciembre de 2008

Yo, ***ELIANA ISAURA MORENO BOHORQUEZ,*** abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad ***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 **"ELABORACIÓN DE COMPLICACIONES FARMACÉUTICAS DE LIBERACIÓN RÁPIDA DE DROGAS INSOLUBLES EN AGUA Y COMPOSICIONES**

FARMACÉUTICAS OBTENIDAS POR EL PROCESO DE LA INVENCIÓN", cuyo titular es **NYCOMED DANMARK APS,** y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular LISINA, ARGININA, HISTIDINA, AINES o BROMAZEPAM. 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 26 de enero de 2007 reivindicando prioridad bajo la solicitud DK20040001021 del 2004-06-29; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial **N° 599 del 31 de Diciembre de 2008,** cuya publicación internacional corresponde a la WO2006000228 del 2006-10-05.

2.2. La solicitud colombiana **07 007.599** objeto de la presente oposición, se refiere a un proceso de elaboración de una forma de dosificación oral que tiene rápida disolución de la droga activa en el fluido gástrico, caracterizado porque comprende las etapas de: a) proveer una droga activa, con una solubilidad a temperatura ambiente menor que 0,1% p/v en ácido clorhídrico 0,1 N o con un valor de pKa menor que 5,5; y b) proporcionar una o más sustancias alcalinas; c) mezclar dicha droga activa y dicha sustancia alcalina y opcionalmente uno o más excipientes por molienda conjunta sin agregar líquido, y opcionalmente d) mezclar uno o más excipientes farmacéuticamente aceptables y opcionalmente e) comprimir dicha mezcla c) o d) en forma de una tableta; donde en el paso c) de molienda conjunta se aplica únicamente a la droga activa y la(s) sustancia(s) alcalina(s). Adicionalmente se refiere un proceso de elaboración de una forma de dosificación oral que tiene rápida disolución de la droga activa en el fluido gástrico, caracterizado porque comprende las etapas de: a) proveer una droga activa, con una solubilidad a temperatura ambiente menor que 0,1% p/v en ácido clorhídrico 0,1 N o con un valor de pKa menor que 5,5; y proporcionar una o más sustancia(s) alcalina(s); moler dicha(s) sustancia(s) alcalina(s) sin adicionar líquidos, mezclar dicha(s) sustancia(s) alcalina(s) en c) con dicha droga activa, y opcionalmente e) mezclar uno o mas excipientes farmacéuticamente aceptables, y f) comprimir dicha mezcla d) o e) en forma de una tableta.

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: WO9909988 publicada el 4 de marzo de 1999.
- D2: WO0141536 publicada el 14 de junio de 2001.

2.4. Ahora bien, el documento D1, particularmente en la descripción revela composiciones farmacéuticas que contienen carboxamidas enólicas del tipo de agente antiinflamatorio de meloxicam que exhiben una mejorada biodisponibilidad, solubilidad acuosa, mejorado comportamiento de disolución sobre una amplia gama de pH, que está preparado por la modificación de la estructura de cristal del activo por la homogeneización en seco o humedad mecánica que incluye dos componentes, donde uno de ellos es seleccionado de un grupo oligo y un mejorador de disolución o agente alcalizante. Particularmente, en el ejemplo IV/11 y IV/12 así como en las cláusulas 1, 6, 9, 17 y 21 se define un proceso que comprende los pasos de co-mezclar ciclodextrina beta, meloxicam (NSAID) y carbonato de sodio bajo condiciones en seco. Como tal la disolución es caracterizada en la tabla 13.

2.5. En combinación, el documento D2 por su parte revela una composición farmacéutica que comprende un inhibidor de celocoxib y uno o varios excipientes. Particularmente, en el ejemplo 6 revela un proceso que comprende los pasos de co-mezclar un compuesto polimérica de celecoxib y carbonato de sodio en condiciones en seco.

2.6. Por lo tanto además, como lo revela dicha anterioridad D2 en el ejemplo 6, un proceso que comprende los pasos de co-mezclar un compuesto polimérica de celecoxib y carbonato de sodio en condiciones en seco, donde dicho conocimiento en combinación con aquel revelado en la solicitud D1, en el ejemplo IV/11 y IV/12 así como en las cláusulas 1, 6, 9, 17 y 21 donde se define un proceso que

comprende los pasos de co-mezclar ciclodextrina beta, meloxicam (NSAID) y carbonato de sodio bajo condiciones en seco, es posible derivar de manera evidente a un proceso de elaboración de una forma de dosificación oral que tiene rápida disolución de la droga activa en el fluido gástrico y a una composición tal y como aquella revelada en la presente solicitud. Por lo tanto, visto dicho documento D2 en combinación con el documento D1, la presente solicitud carece evidentemente de altura inventiva.

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

2.8. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana **07 007599** 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.

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

2.9.1. **CARENCIA DE ALTURA INVENTIVA**. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- "*Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.*". A la fecha de prioridad, 29 de junio de 2004, a partir del documento D2 en combinación con D1, puede llegar de manera evidente a un proceso de elaboración de una forma de dosificación oral que tiene rápida disolución de la droga activa en el fluido gástrico y a una composición tal y como aquella revelada en la presente solicitud, sobre el cual busca protección en el capitulo reivindicatorio.

2.10. 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.

2.11. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"ELABORACIÓN DE COMPLICACIONES FARMACÉUTICAS DE LIBERACIÓN RÁPIDA DE DROGAS INSOLUBLES EN AGUA Y COMPOSICIONES FARMACÉUTICAS OBTENIDAS POR EL PROCESO DE LA INVENCIÓN"**, cuyo titular es **NYCOMED DANMARK APS**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial **N° 599 del 31 de diciembre de 2008.**

3. PRUEBAS

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

- D1: WO9909988 publicada el 4 de marzo de 1999.
- D2: WO0141536 publicada el 14 de junio de 2001.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

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

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

4.3. En las demás normas concordantes.

5. ANEXOS

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

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

- D1. WO9909988 publicada el 4 de marzo de 1999.
- D2. WO0141536 publicada el 14 de junio de 2001.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-007599- -00010-0000
Fecha: 2009-03-30 14:11:07 Dep: 2020 NUECREACIONE
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 400 OPOSIOBSERVTER Folios: 97

RECIBO OFICIAL DE CAJA : 09 - 24,459
FECHA : MARZO 30 DE 2009

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

TANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	19814664	13/03/2009	170,000.00
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	108513543	17/02/2009	170,000.00
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	108516343	03/03/2009	2,583,000.00
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	108516354	03/03/2009	170,000.00
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754387	108530763	09/02/2009	452,000.00

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

CANT.	REMISIICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	287,000.00
		TOTAL : $	287,000.00

SON: DOSCIENTOS OCHENTA Y SIETE 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. 07 007.599, titulada **"ELABORACIÓN DE COMPLICACIONES FARMACÉUTICAS DE LIBERACIÓN RÁPIDA DE DROGAS INSOLUBLES EN AGUA Y COMPOSICIONES FARMACÉUTICAS OBTENIDAS POR EL PROCESO DE LA INVENCIÓN",** cuyo titular es **NYCOMED DANMARK APS.,** publicada en la gaceta No. 599 del 31 de diciembre de 2008.

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

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

Dado y Firmado en Barranquilla (Colombia) a los 12 días del mes de Marzo de 2009.

PROCAPS S.A.

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

Acepto:

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

LA PRESENTE DILIGENCIA SE PRACTICA A PETICION DE PARTE INTERESADA

NOTARIA PRIMERA DEL CIRCULO DE BARRANQUILLA
DILIGENCIA DE RECONOCIMIENTO

Ante el Notario Primero de Barranquilla Compareció: Walter Tanaka Tatekawa

Identificado con: 16.251.923 de Palmira Valle y declaro que es cierto el contenido del documento anterior y suya la firma.

Barranquilla. 16 MAR. 2009

El suscrito Notario Primero del Circulo de Barranquilla, hace constar que la Huella Dactilar que aquí aparece, fué impresa por. Walter Tanaka Tatekawa

REPUBLICA DE COLOMBIA
Carlos J. Puche Mogollón
NOTARIO
NOTARIA 1ra. DE BARRANQUILLA

NOTARIA PRIMERA DE CHIA
PRESENTACION PERSONAL

Este memorial dirigido a Superintendencia de Industria y Comercio

fué presentado personalmente ante el suscrito notario por Eliana Isaura Moreno Bohorquez

Identificado C.C. 51.975664 Bta

T.P. de Abogado No. 93823. C.S.J.

Chia. 26 MAR 2009

REPUBLICA DE COLOMBIA
M. DEL PILAR HERRERA VERGARA
NOTARIA PRIMERA DE CHIA

CAMARA DE COMERCIO DE BARRANQUILLA

CAMARA DE COMERCIO
DE BARRANQUILLA
09**********

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

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 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
09**********

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

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 fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas,alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados, d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos,quirurgicos,odontologicos,y hospitalarios para la salud humana y animal. e)La compra,venta,exportacion y disdistribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c). d) y e) antes descritos; g) Prestar los servicios de asesoria 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, cosmeticos y farmaceuticos para uso humano, animal o industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista,

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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 o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravamenes reales sobre sus bienes de cualquier naturaleza.----------

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
$**********2,000,000,000	**********2,000,000	**********1,000
Suscrito		
$**********1,229,071,000	**********1,229,071	**********1,000
Pagado		
$**********1,229,071,000	**********1,229,071	**********1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponderá 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 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

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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

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

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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

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.	

********** 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
09**********

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

C E R T I F I C A

Que según Acta No. 127 del 22 de Marzo de 2000 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS

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

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

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

Cargo/Nombre	Identificación
Suplente del Revisor Fiscal.	
Lozada Villareal Milena	CC.******32,748,111

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 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 ------

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

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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: 19 de Marzo de 2008.

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

Cámara de Comercio Bucaramanga

D2

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant (*for all designated States except US*): HEXAL AG [DE/DE]; Industriestrasse 25, D–83607 Holzkirchen (DE).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): STRUENGMANN, Andreas [DE/DE]; Industriestrasse 25, D–83607 Holzkirchen (DE). FREUDENSPRUNG, Brigitte [DE/DE]; Industriestrasse 25, D–83706 Holzkirchen (DE). KLOKKERS, Karin [DE/DE]; Industriestrasse 25, D–83607 Holzkirchen (DE).

(74) Agents: BOETERS, Hans, D. et al.; Bereiteranger 15, D–81541 Muenchen (DE).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
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(54) Title: NEW PHARMACEUTICAL COMPOSITIONS OF MELOXICAM WITH IMPROVED SOLUBILITY AND BIOAVAILABILITY

(57) Abstract

Pharmaceutical compositions containing enoiic carboxamide type antiinflammatory agent meloxicam that exhibit improved wettability, aqueous solubility, dissolution behaviour over a broad range of pH, and that are prepared by crystal structure modification of the drug through dry or wet mechanical homogenization with two further components – one of them is selected from a group of oligo – and dissolution improving, or alkalizing agent. The application of the formulations according to the present invention results in an improved biovailability and effectiveness of meloxicam.

sides the effective antiinflammatory, antipyretic and analgesic activity (cyclo-oxygenase inhibitor, with relative COX-2 selectivity) of meloxicam it has been shown, that it prevents the development of colorectal cancer.

It is known, that meloxicam is crystallized in four different prototropic forms, the anion, the acidic enol, the zwitterion, and the cationic form, depending upon the pH value of the solution. Meloxicam has a low solubility in acidic or neutral medium. Therefore the preparation of pharmaceutical formulations results in complicated and difficulty production processes. Furthermore the low solubility of meloxicam leads to unsteady resorption and consequently to non-uniform plasma levels in vivo.

JP 04321624 discloses the improvement of bioavailability of numerous non-steroidal antiinflammatory agents (e.g. indomethacin, fentanyl, flurbiprofen, piroxicam, lornoxicam and meloxicam) by formulating the drugs with styrene-isoprene-styrene block polymer and with crotamiton. An improved drug transdermal delivery is achieved in this way.

WO 93/01814 discloses ophthalmic meloxicam containing compositions for treating ocular inflammation and microbial infections. It describes instillable ophthalmic compositions of medium viscosity contain an anti-inflammatory oxicam as active ingredient, together with a gelling acrylic acid polymer and a base, such that the resultant aqua solution has the desired fluidity and an pH between 6,5 and 8.

IT 01251650 discloses an inclusion complex of meloxicam with cyclodextrin. The molar ratio of meloxicam to cyclodextrin is 1:2,5 claiming a real inclusion complex. The methods described

in the patent application are energy- and time consuming traditional techniques for complexing meloxicam.

Summary of the invention:

Main object of the present invention is to provide new compositions of meloxicam with improved solubility and bioavailability.

It has now surprisingly been found, that the solubility and bioavailability of meloxicam can be improved by mixing meloxicam with special additives using different production processes (co-milling, co-grinding, co-kneading etc.). It has further been found, that it is possible to produce special dosage forms containing meloxicam, resulting from the improved solubility.

Thus, the problem underlying the invention is solved by mixing meloxicam with additives like surfactants and/ or co-solvents and/ or hydrotropic agents and/ or alkalizing agents and/ or cyclodextrins and/ or hydrocolloids and/ or pharmaceutically acceptable polymers.

In one embodiment of the invention meloxicam is mixed with surfactants, especially polyoxyethylensorbitan-mono-fatty acids, diethylenglycolmonoethylether and nonylphenoltetraethylenglycolether.

In a further embodiment of the invention the solubility and bioavailability of meloxicam can be improved by micronisation of the substance in the presence of suitable co-solvents like propylenglycol, glycerol, polyethylenglycol and ethanol.

The addition of hydrotropic agents to meloxicam during micronisation can also improve solubility and bioavailability. Preferred hydrotropic agents are for example sodium-glycinate, nicotinamide, methylglucamin or a combination thereof.

The use of cyclodextrin in combination with meloxicam can improve the solubility and bioavailability without forming a real inclusion complex of cyclodextrin and meloxicam.

Suitable cyclodextrins are for example ß-cyclodextin hydrate (BCDx), 6-mono-amino-beta-cyclodextrin (AMBCDx), γ-cyclodextrin hydrate (GCDx), branchend-ß-cyclodextrin (glycosyl-maltosyl-substituted type, enzyme-modified ß-cyclodextrin hydrate derivative) and hydroxypropyl-ß-cyclodextrin (with a degree of hydroxyalkylation between 4.0- 5.0).

Cyclodextrins are used preferably in an amount of meloxicam : cyclodextrin = 1 : 99 and especially 30 : 70 (w/w).

Combinations of the cyclodextrin meloxicam product with above mentioned additives result in further improvement of solubility and bioavailability.

Suitable additives are surfactants, co-solvents, hydrotropic components, alkalizing additives, hydrocolloids and pharmaceutically acceptable polymers, especially methyl-cellulose-propylene-glycol ether, tris-hydroxymethyl-aminomethane, 2,6-diamino-hexanoic acid (D,L-lysine), mannitol, polyethylenglycol, propylenglycol, diethanolamine, ethylenamine, monoethanolamine, triethanolamine, diisopropylamine, dibutylamine, pentylamine, sodium-carbonate, sodium dodecyl sulfate, ammonium-carbonate,

Example I/1.

10 g meloxicam and 90 g microcrystalline cellulose (AVICEL) were intensively co-ground for 6 hours at room temperature in a ceramic ball mill in presence of 0.25 % (w/w) of the following surfactants:

TWEEN-80 and Solutol HS 15. The co-ground system was then dried to constant weight and passed through a 0.075 mm sieve.

The in vitro dissolution test shows that the composition according to example I/1 have significantly enhanced dissolution (table 1). The control composition consists of cellulose and meloxicam and was prepared under identical conditions as the surfactant-meloxicam-cellulose compositions.

Table 1. *In vitro dissolution of meloxicam (at pH 7.6, 37°C) from solid cellulose-based compositions after a 6-hour mechanical treatment.*

sample	dissolved meloxicam (in µg/ml)			
	5. min.	15. min	30. min.	45. min.
control	115	225	280	478
Tween-80	130	255	324	550
Solutol	145	280	400	590

Similar effects of the mentioned additives to the dissolution rates of meloxicam were observed at pH 6.6 in distilled water and at pH 1.2 in hydrochloric acid.

Table 2. Effect of co-solvents on the meloxicam dissolution in pH 7.6 buffer at 37 °C .

cosolvent	dissolved meloxicam in µg/ml			
	5.min.	15. min.	30.min.	45. min.
control	120*	231	379	490
PEG 400	305	355	480	580
prop.glycol	290	360	460	550

Example III/1.

25 g meloxicam and 75 g lactose were intensively co-ground in a ball mill for 4 hours without (control) and in presence of 20% (by weight) of nicotinamide and 20% of sodium-glycinate, respectively. The solid compositions were sieved through a 0.071 mm sieve and tested for meloxicam dissolution at pH=1.2 at 37 °C. Results are listed in table 3.

Table 3. Effect of hydrotropic additives to the meloxicam dissolution rate in pH 1.2 buffer at 37°C.

hydrotropes	dissolved meloxicam in µg/ml			
	5.min.	15. min.	30.min.	45. min.
control	0.20*	0.70	0.76	0.75
Na-glycinate	0.60	0.75	0.80	0.80
nicotinamide	0.80	0.85	0.98	0.90

Example IV/1.

The co-grinding of the solid components meloxicam and beta-cyclodextrin hydrate (BCDx) in a ceramic ball-mill for sufficient time results at ambient temperature in novel type solid state-structure of these solids, as proved by X-ray diffractometry and also by microscopy. The composition after grinding process also exhibited an improved dissolution profile compared to meloxicam, ground alone under the same conditions.

Thus 11.35 g crystalline beta-cyclodextrin hydrate (BCDx) with 13.8 % water content and 1.76 g crystalline meloxicam were intensively ball-milled for 6 hours at 25 °C to reach metastable amorphous state. The resulting solid composition was passed through a sieve of 250 μm.

Characteristics of the meloxicam composition according to example IV./1.: The product appears as a slightly yellow, free-flowing, non-hygroscopic powder.

As high resolution Differential Scanning Calorimetry investigations indicate this composition shows two distinct endothermic peaks -related to meloxicam -on the heat-flow curve at 255 °C, 280 °C. This phenomenon is attributed most probably to the co-existence of different solid state prototropic forms of the drug which are generated by the mechanical manipulation in presence of the hydrated beta-cyclodextrin. The DSC of pure meloxicam shows a melting endothermic heat flow at 267-270 °C which is in good agreement with literature data of the melting point of meloxicam (268°C).(See figure 1.)

The meloxicam content of the composition according to example IV/1. is 13.1% and the product has a loss of weight between 5.9-6.6 % after the drying. The X-ray powder diffraction analysis of the ball milled co-ground system according to example IV/1. indicates that the micronisation treatment results in the decrease of crystallinity, but without complete amorphisation of the system.

The dissolution characteristics of the meloxicam composition according to example IV/1. is shown in table 4.

The following standard method was used for the determination of the dissolution rate of the drug compositions: In vitro dissolution properties of the cyclodextrin based meloxicam compositions were studied under non-sink conditions in two different buffer systems, pH 1.3 and 7.6, respectively and in deionised water (pH=6.6) at 37 °C.

The stirring rate was 160 r.p.m.. To ensure comparable particle size distribution the samples were passed through a sieve of 80 mesh prior to dissolution testing. Sampling time intervals were 5, 10, 15, 30, 45 and 60 minutes.

Table 4.: *In vitro rates of dissolution of free meloxicam and of the composition according to example IV./1. at pH 1.3 and 7.6 at 37°C*

Dissolved meloxicam in solution in µg/ml				
minutes	free meloxicam		composition according to example IV/1.	
	pH: 1.3	pH: 7.6	pH:1.3	pH:7.6
5	0.30	38	2.5	975
10	0.38	218	2.6	981
15	0.44	320	2.7	1026
30	0.56	390	2.8	1046
45	0.59	485	2.7	1091
60	0.65	550	3.9	1117

The solubility enhancement at gastric pH was about 5-fold.

Example:IV/2.

1.0 g meloxicam, 9.0 g beta-CD hydrate (BCDx), 0.01g Methocel® and 5 ml of deionised water were added to a ceramic mortar and were intensively co-kneaded for 45 minutes at room temperature. The wet homogenisate was passed through a 2 mm sieve and dried at 40 °C yielding a hard, yellowish solid. The dry product was sieved through a 0.25 mm sieve. (9.53 g, meloxicam content: 8.7 % by weight.)

The solid state investigation of the product according to example IV/2. by DSC revealed the existence of a novel type of structure of the active ingredient, which is characterized by DSC heat-flow curves at the temperature range of 160-320 °C. This indicates the co-existence of two different allotropic forms of meloxicam, evidenced by negative enthalpy changes (melting) at around 250 and 293 °C respectively. None of these enthalpy changes are identical with the sharp melting heat flow of meloxicam itself that appears at 264-266°C. The simple mechanical mixture of meloxicam with beta-CD hydrate resulted in a composition that had a DSC pattern with a melting range (255-265°C)near the melting point of meloxicam. (See Figure 2.)

Dissolution characteristics of the product according to example IV/2. are shown in table 5.

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Table 5.: In vitro rates of dissolution of free meloxicam (130 mg) and of the composition according to example IV./2. (1500 mg) at pH 1.3 and 7.6, 37°C.

Dissolved meloxicam in solution in µg/ml				
min-utes	free meloxicam		composition according to example IV/2.	
	pH: 1.3	pH: 7.6	pH:1.3	pH:7.6
5	0.45	38	7.4	917
10	0.62	218	7.8	990
15	0.67	320	7.7	1067
30	0.74	390	7.7	1077
45	0.73	485	7.9	1149
60	0.67	550	6.4	1199

Example:IV/3.

1.0 g meloxicam, 9.0 g of beta-CD hydrate (BCDx), 0.01g of tris-hydroxymethyl-aminomethane and 5 ml of deionised water were added to a twin-screw kneader and were intensively co-kneaded for 45 minutes at room temperature. The wet homogenisate was passed through a 2 mm sieve and dried at 40 °C yielding a hard, yellowish extrudate. The dry, solid product was sieved through a 0.25 mm sieve. (Yield: 10.03 g yellow powder, meloxicam content: 8.9 % by weight.)

The DSC pattern of the product according to example IV./3. showed the co-existence of two different allotropic forms of meloxicam with the characteristic negative enthalpy changes of 256 and 294 °C. (See figure 3.)

Dissolution characteristics of the product according to Example IV/3. in comparison with free meloxicam are shown in table 6.

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Table 6.: In vitro rates of dissolution of free meloxicam (130 mg) and of the composition according to example IV./3. (1500 mg) at pH 1.3 and 7.6 at 37°C

Dissolved meloxicam in solution in µg/ml				
min-utes	free meloxicam		composition according to example IV/3.	
	pH: 1.3	pH: 7.6	pH:1.3	pH:7.6
5	0.45	38	6.8	1237
10	0.62	218	6.1	1252
15	0.67	320	5.9	1278
30	0.74	390	6.7	1280
45	0.73	485	6.1	1287
60	0.67	550	5.2	1310

Example:IV/4.

1.0 g meloxicam, 9.0 g o beta-CD hydrate (BCDx), 0.01g 2,6-diamino-hexanoic acid (DL-lysine) and 5 ml deionised water were added to a twin-screw kneader and were intensively co-kneaded for 45 minutes at room temperature. The wet mixture was dried at 40 °C yielding a hard, yellowish solid. The dry, solid product was sieved through a 0.25 mm sieve. (Yield: 9.9 g yellow powder, with a meloxicam content of 9.8 % by weight.)

Thermoanalytical study proved the existence of two different types of solid forms of meloxicam with melting heat flow curves at around 256 and 292°C respectively.(See figure 4.)

The improvement of dissolution characteristics of the product according to example IV/4. in comparison with free meloxicam are shown in table 7.

Table 7.: In vitro rates of dissolution of free meloxicam (130 mg) and of the composition according to example IV./4. (1300 mg) at pH 1.3 and 7.6 at 37°C

Dissolved meloxicam in solution in µg/ml				
min-utes	free meloxicam		composition according to example IV/4.	
	pH: 1.3	pH: 7.6	pH:1.3	pH:7.6
5	0.45	38	6.9	1134
10	0.62	218	4.8	1150
15	0.67	320	4.9	1160
30	0.74	390	4.9	1175
45	0.73	485	4.3	1187
60	0.67	550	4.6	1217

Example IV/5.

15.2 g 6-mono-amino-beta-cyclodextrin (AMBCDx), 3 ml water and 1.8 g crystalline meloxicam were intensively kneaded for 60 minutes at 25 °C. The resulting wet mixture was passed through a 2 mm sieve and dried at 40 °C to constant weight. The resulting yellowish solid was milled into a fine powder and sieved through a 0.25mm sieve. Yield: 16.6 g powder with a meloxicam content of 10.4 % by weight.

The solid meloxicam composition according to example IV/5. showed significantly improved dissolution.

The improved dissolution of meloxicam composition according to example IV/5. is shown in table 9.

Table 9.: The in vitro rate of dissolution of meloxicam composition according to example IV/5. (pH:1.2, at 37 °C)

minutes	meloxicam (µg/ml)
5	7.7
10	9.0
30	9.2
45	9.5
60	9.5*

* control: meloxicam showed a dissolution rate of 0.8 µg/ml at 60 min.

Example IV/6.

113.5 g solid, dry beta cyclodextrin hydrate (BCDx) are mixed thoroughly with 35.14 g crystalline meloxicam at 25°C in a high-speed twin-screw kneader for 10 minutes. 7.43 g polyethyleneglycol (PEG-400) are added to the kneading machine. The reaction mixture is thoroughly kneaded for 0.5 hours at 60°C, then for 2 hours at 25 °C. The resulting composition is directly transferred into a granulating machine and the granulation process is performed in the presence of 10 ml of a 0.1% aqueous sodium-carboxymethyl-cellulose solution. The granules are dried at 40 °C to constant weight.

The resulting free-flowing, slightly yellow granules can be used directly for tabletting.

Yield: 155 g granule, with a meloxicam content of 22.0%.

Example IV/7.

129.7 g crystalline gamma-cyclodextrin (GCDX) hydrate are intensively co-milled at room temperature in a ceramic ball mill with 17.57 g solid meloxicam for 3 hours at 25 °C. Yield: 146.2 g of slightly yellow, powder is obtained. The solid composition appears as a nearly amorphous powder with a meloxicam content of 11.8 % by weight and exhibits an enhanced dissolution in water.

Example IV/8.

16 g branched-beta-cyclodextrin (a glucosyl-maltosyl-substituted type, enzyme-modified beta-CDx derivative) are intensively kneaded in a twin-screw kneader with 1.8 g meloxicam in presence of 2.0 ml propyleneglycol for 30 minutes at 40 °C until a dense creamy paste is obtained. The paste is kneaded further for additional 3 hours at 25 °C, and dried at room temperature to constant weight. The dry product appears as a slightly yellow-coloured, hard solid which is further ground to give a fine powder and passed through a 250 µm sieve. Yield: 17.5 g yellow, slightly hygroscopic, amorphous powder, with a meloxicam content of 10.0 %. The loss of weight by drying of the sample according to example 8. is 6,0 %.

Example IV/9.

16 g hydroxypropyl-beta-cyclodextrin (with a degree of hydroxyalkylation between 4.0-5.0) are intensively mixed in powder form in a ceramic ball mill with 1.8 g of meloxicam. The mixture is then further co-milled for 3 hours at 25 °C to reach desired metastable physical state. Yield: 17.2 g yellowish,

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Table 11.: In vitro rates of dissolution of free meloxicam and of the composition according to example IV/10. at pH 1.3 and 7.6 at 37°C

Dissolved meloxicam in solution in µg/ml				
minutes	free meloxicam		composition according to example IV/10.	
	pH: 1.3	pH: 7.6	pH:1,3	pH:7.6
5	0.4	38	7.2	880
10	0.6	188	10	900
15	0.7	320	12	1100
30	0.7	390	12	1246
45	0.7	485	14.7	1391
60	0.6	550	13.9	1388

Example IV/11.

10.5 g beta-cyclodextrin-hydrate were mechanically treated by intense co-grinding with 1.6 g solid meloxicam and 1.5 g diethanolamine for 30 minutes at 40 °C, and for 2 hours at 25 °C. The resulting slightly yellow mixture was dried at 45 °C to constant weight and passed through a 0.071mm sieve. The obtained solid composition had a meloxicam content of 11.9 % by weight.

The dissolution rate of the composition according to example IV/12. is shown in table 13.

Table 13.: In vitro dissolution of free meloxicam and of the composition according to example IV/12. at pH 1.3 and in deionised water (pH=6.6) at 37°C

Dissolved meloxicam in solution in µg/ml				
minutes	free meloxicam		Composition according to example IV/12.	
	pH: 1.3	pH: 6.6	pH:1.3	pH:6.6
5	0.4	23	8.0	700
10	0.6	148	8.3	626
15	0.7	232	9.6	659
30	0.7	390	10.1	780
45	0.7	415	10.0	896
60	0.6	475	12.1	940

The use of other pharmaceutically acceptable amines with a high boiling point (like ethylenediamine, monoethanolamine, triethanolamine, di-isopropylamine, dibutylamine, pentylamine etc.) and of other pharmaceutically acceptable solid alkalizing agents (like sodium-carbonate, ammonium-carbonate, powdered sodium-hydroxide, sodium-phosphate, etc.) resulted in improved solubility and bioavailability.

Example IV/12.

113.5 g solid, beta cyclodextrin hydrate (BCDx) are intensively co-milled in a ceramic ball mill with high energy with 35.14 g crystalline meloxicam and 0.5g sodium carbonate at 25 °C for 30 minutes.

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2. Composition according to claim 1, **characterized** by cyclodextrins, microcrystalline cellulose, lactose and/or starch as oligo- or polysaccharide.

3. Composition according to claim 1 or 2, **characterized** by polyoxyethylene-sorbitan-mono-fatty acid, diethyleneglycol monoethylether and /or nonylphenol tetraethyleneglycol ether as surfactant.

4. Composition according to any of the preceding claims, **characterized** by an amount of 1 to 99 and preferably about 20% by weight of a hydrotropic agent (based on the total weight of the composition).

5. Composition according to any of the preceding claims, **characterized** by sodium glycinate, nicotinamide and/or methylglucamine as hydrotropic agent.

6. Composition according to any of the preceding claims, **characterized** by sodium carbonate, ammonium carbonate, sodium hydroxide, especially powdered sodium hydroxide, and/or sodium phosphate as alkalizing agent.

7. Composition according to any of the preceding claims, **characterized** by ß-cyclodextrin hydrate (BCDx), 6-monoamino-beta-cyclodextrin (AMBCDx), gamma-cyclodextrin hydrate (GCDx), branched ß-cyclodextrin, especially a branched ß-cyclodextrin of the glycosyl/maltosyl substituted type or a ß-cyclodextrin hydrate derivative, and/or hydroxypropyl-

ß-cyclodextrin as oligo- or polysaccharide, especially of a hydroxyalkylation degree in the range of 4.0 to 5.0.

8. Composition according to any of the preceding claims, **characterized** by methylcellulose-propylene-glycol ether, tris-hydroxymethylaminomethane, 2,6-diamino-hexanoic acid (D,L-lysine), mannitol, polyethyleneglycol, propyleneglycol, diethanolamine, ethyleneamine, monoethanolamine, triethanolamine, diisopropylamine, dibutylamine, pentylamine, sodium dodecylsulfate, methylglucamine, polyvinylpyrrolidone, cellulose ether, polyoxyethylene-polyoxypropylene-block-copolymers and/or nicotinamide as pharmaceutically acceptable additive.

9. Composition according to any of the preceding claims, obtainable by co-milling, co-grinding or co-kneading meloxicam in the presence of a pharmaceutically acceptable additive.

10. Composition according to any of the preceding claims, obtainable by micronizing meloxicam in the presence of a pharmaceutically acceptable additive.

11. Composition according to any of the preceding claims, obtainable by wet mechanical homogenization of its components in the presence of water, preferably in an amount of 5 to 50 % by weight (based on the total weight of the composition).

12. Pharmaceutical composition comprising meloxicam as active ingredient, as oligosaccharide and/or a polysaccharide, water as aqueous vehicle, a co-solvent and facultative auxiliary agents.

13. Composition according to claim 12, **characterized** by

cyclodextrins microcrystalline cellulose, lactose and/or starch as oligo- or polysaccharide.

14. Composition according to claim 12 or 13, **characterized** by an amount of 0.1 to 25 and preferably about 5.0 % by weight co-solvent (based on the amount of water or on the total weight of the composition).

15. Composition according to any of claims 12 to 14, **characterized** by i-propanol, propyleneglycol, glycerol, polyethyleneglycol and/or ethanol as co-solvent.

16. Composition according to any of claims 12 to 15, **characterized** by an amount of 1 to 99 and preferably about 20% by weight of a hydrotropic agent (based on the total weight of the composition).

17. Composition according to any of claims 12 to 16, **characterized** by one ore more additional pharmaceutical acceptable additives selected from the group consisting of surfactants, hydrotropic agents, alkalizing agents, cyclodextrins, hydrocolloids and polymers, preferably selected from the group consisting of methylcellulose-propylene-glycol ether, tris-hydroxymethylaminomethane, 2,6-diamino-hexanoic acid (D,L-lysine), mannitol, polyethyleneglycol, propyleneglycol, diethanolamine, ethyleneamine, monoethanolamine, triethanolamine, diisopropylamine, dibutylamine, pentylamine, sodium carbonate, sodium dodecylsulfate, ammonium carbonate, sodium hydroxide, especially powdered sodium hydroxide, sodium phosphate, methylglucamine, polyvinylpyrrolidone, cellulose ether, polyoxyethylene-polyoxypropylene-block-copolymers and/or nicotinamide as pharmaceutically acceptable additive.

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18. Composition according to any of claims 12 or 17, obtainable by micronizing meloxicam in the presence of an oligosaccharide and/or polysaccharide, water and a co-solvent as pharmaceutically acceptable additive.

19. Composition according to any of the preceding claims, obtainable by wet mechanical homogenization of its components in the presence of water, preferably in an amount of 5 to 50 % by weight (based on the total weight of the composition).

20. Composition according to any of the preceding claims for oral, rectal, transdermal, ophthalmic or parenteral administration.

21. Composition according to any of the preceding claims, **characterized** in that it is provided as tablet, effervescent tablet, sachet, aromatized effervescent sachet, tab, hydrogel, ophthalmic ointment, ophthalmic hydrogel or retal suppository.

22. Compositon according to any of the preceding claims, **characterized** in that it is provided as controlled release tablet for oral application.

23. Composition according to claim 21 or 22, **characterized** in that it is provided as multi-layer tablet, especially a two-layer tablet, wherin
- one of the layers comprises meloxicam together with at least one pharmaceutically acceptable additive for rapid release and

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Information on patent family members

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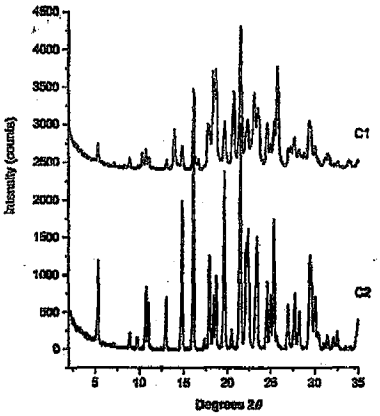
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(54) Title: SOLID-STATE FORM OF CELECOXIB HAVING ENHANCED BIOAVAILABILITY



(57) Abstract: The selective cyclooxygenase-2 inhibitory drug celecoxib is provided in amorphous form. Also provided is a celecoxib drug substance wherein the celecoxib is present, in at least a detectable amount, as amorphous celecoxib. Also provided is a celecoxib-crystallization inhibitor composite comprising particles of amorphous celecoxib or a celecoxib drug substance of the invention in intimate association with one or more crystallization inhibitors, for example polymers. Also provided is a pharmaceutical composition comprising such a celecoxib-crystallization inhibitor composite and one or more excipients. Also provided are processes for preparing amorphous celecoxib, a celecoxib drug substance of the invention, a celecoxib-crystallization inhibitor composite of the invention, and a pharmaceutical composition of the invention. Also provided is a method of treating a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising administering, for example orally, a composition of the invention in a therapeutically effective amount.

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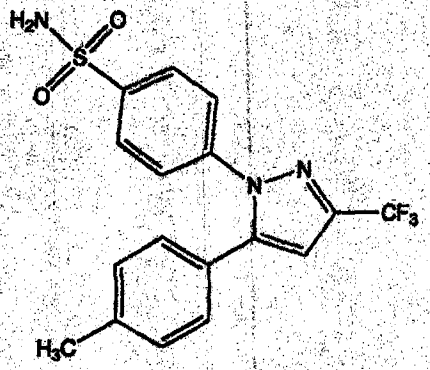
SOLID-STATE FORM OF CELECOXIB HAVING ENHANCED BIOAVAILABILITY

FIELD OF THE INVENTION

The present invention relates to the selective cyclooxygenase-2 inhibitory drug celecoxib and in particular to solid-state forms of that drug, to pharmaceutical compositions comprising such solid-state forms, and to processes for preparing them. The invention further relates to methods of treatment of cyclooxygenase-2 mediated disorders comprising administering such solid-state forms or compositions thereof to a subject, and to use of such solid-state forms in the manufacture of medicaments.

BACKGROUND OF THE INVENTION

Celecoxib, also known as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (I), the active ingredient of Celebrex® marketed by Pharmacia Corp., has a therapeutically and prophylactically useful selective cyclooxygenase-2 inhibitory effect, and has utility in treatment and prevention of specific cyclooxygenase-2 mediated disorders and of such disorders in general. Celecoxib has the structure:



(I)

Processes for preparing celecoxib are set forth in U.S. Patent No. 5,466,823 to Talley *et al.* and in U.S. Patent No. 5,892,053 to Zhi & Newaz, both incorporated herein by reference. Co-assigned International Patent Publication No. WO 00/32189, incorporated herein by reference, discloses that celecoxib has a crystal morphology which tends to form long, cohesive needles. Co-assigned International Patent Publication No. WO 00/42021, incorporated herein by reference, discloses a solvated crystalline form of celecoxib and a method for desolvation of that crystalline form.

A need for new forms of celecoxib, in particular forms suitable for preparing rapid-onset compositions, exists. Rapid-onset drug-delivery systems can provide significant benefits over conventional dosage forms. Generally, rapid-onset preparations provide a short period to therapeutic or prophylactic response compared to conventional immediate-release or sustained-release dosage forms. For example, in treatment of acute pain, a rapid-onset dosage form of celecoxib would be useful to provide fast pain relief.

However, celecoxib presents certain challenges for formulation as a rapid-onset dosage form, particularly as a rapid-onset oral dosage form. For example, celecoxib has very low solubility in aqueous media and therefore is not readily dissolved and dispersed for rapid absorption in the gastrointestinal tract when administered orally, for example in tablet or capsule form. In addition, celecoxib has a relatively high dose requirement further increasing difficulties of providing a sufficient therapeutically effective dose for rapid absorption.

Celecoxib crystals also present formulation difficulties as a result of unique physical and chemical characteristics such as electrostatic and cohesive properties, low bulk density, low compressibility and poor flow properties. Due at least in part to these properties, celecoxib crystals tend to segregate and agglomerate together during mixing, resulting in a non-uniformly blended composition containing undesirably large, insoluble aggregates of celecoxib. For these and other reasons, therefore, it is difficult to prepare an orally deliverable, rapid-onset composition containing celecoxib that has the desired blend uniformity.

The bioavailability of an orally administered drug, as measured by its entry into systemic circulation in the bloodstream, depends on at least two fundamental processes: drug dissolution in gastrointestinal fluids (*in vivo* drug release) and subsequent absorption of the dissolved drug. Several factors influence dissolution of a drug from its carrier, including surface area of the drug presented to the dissolution solvent medium, solubility of the drug substance in the specific solvent medium, and driving forces of the saturation concentration of dissolved materials in the solvent medium. Notwithstanding these factors, a strong correlation has been established between the *in vitro* dissolution time determined by standard assay procedures for an oral dosage form and the rate of *in vivo* drug release. This correlation is so firmly

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established in the art that dissolution time has become generally descriptive of drug release potential for the active component of the particular unit dosage composition.

When the process of *in vivo* drug release is slower than the process of absorption, absorption is said to be dissolution rate-limited. Since dissolution precedes absorption in the overall process, any change in the drug release or dissolution process will subsequently influence drug absorption. See for example Lieberman *et al.* (1989), Pharmaceutical Dosage Forms: Tablets, Vol. 1, pp. 34-36. Marcel Dekker, New York. It is clear, therefore, that dissolution time determined for a composition is one of the important fundamental characteristics for consideration when evaluating compositions intended for fast-onset delivery, particularly where drug absorption is dissolution rate-limited.

Crystalline solids, due to their highly organized, lattice-like structures, typically require a significant amount of energy for dissolution. The energy required for a drug molecule to escape from a crystal, for example, is greater than is required for the same drug molecule to escape from a non-crystalline, amorphous form. Importantly, however, crystalline drug forms which have been transformed into amorphous forms tend to revert to a steady state of low energy, namely the crystalline form, over time and thus may not have an adequate shelf life. An amorphous form of celecoxib has not hitherto been known in the art.

As indicated hereinbelow, treatment with celecoxib is indicated in a very wide array of cyclooxygenase-2 mediated conditions and disorders. Therefore, if an amorphous form of celecoxib could be prepared, and in particular if a storage-stable composition comprising such an amorphous form of celecoxib could be developed exhibiting enhanced bioavailability, for example through rapid dissolution of the drug, a significant advance would be realized in treatment of cyclooxygenase-2 mediated conditions and disorders, particularly in treatment of acute disorders where early relief from pain or other symptoms is desired.

SUMMARY OF THE INVENTION

Celecoxib provides a more rapid onset of therapeutic effect if, upon oral administration of a composition comprising celecoxib, pharmacokinetic properties are exhibited leading to a greater maximum blood serum concentration (C_{max}) and/or a shorter time following the administration to reach that maximum (T_{max}). It is

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contemplated that a greater C_{max} and/or a shorter T_{max} can result from faster dissolution of celecoxib when provided in amorphous form than in crystalline form.

Accordingly, the present invention provides amorphous celecoxib. There is also provided a celecoxib drug substance wherein the celecoxib is present, in at least a detectable amount, as amorphous celecoxib. The term "celecoxib drug substance" as used herein means celecoxib *per se* as qualified by the context in which the term is used, and can refer to unformulated celecoxib or to celecoxib present as an ingredient of a pharmaceutical composition.

As a further embodiment of the invention, there is provided a celecoxib-crystallization inhibitor composite comprising particles of amorphous celecoxib or a celecoxib drug substance of the invention in intimate association with one or more crystallization inhibitors. The crystallization inhibitors are selected and present in an amount sufficient to substantially reduce conversion of amorphous celecoxib to crystalline celecoxib. Preferred crystallization inhibitors are polymers that form with the celecoxib a celecoxib-polymer composite.

There is also provided a composition comprising a celecoxib-crystallization inhibitor composite, for example a celecoxib-polymer composite, as defined herein. The composition comprises dose units that can be in the form of discrete solid articles such as tablets, caplets, pills, hard or soft capsules, lozenges, sachets or pastilles; alternatively the composition can be in the form of a substantially homogeneous flowable mass, such as a particulate or granular solid or a liquid suspension, for example an imbibable dispersion, from which single dose units are measurably removable.

Also provided are processes for preparing amorphous celecoxib, for preparing a celecoxib drug substance of the invention and for preparing a celecoxib-crystallization inhibitor composite, for example a celecoxib-polymer composite, of the invention.

A preferred process for preparing a celecoxib drug substance of the invention comprises (a) a step of melting celecoxib, for example crystalline celecoxib; and (b) a step of rapidly cooling the resulting melted celecoxib to form a celecoxib drug substance wherein the celecoxib is present, in at least a detectable amount, in amorphous form. Optionally, this process can further comprise (c) a step of grinding

the celecoxib drug substance to form a celecoxib powder.

A celecoxib-crystallization inhibitor composite of the invention can be prepared by a process comprising (a) a step of dissolving celecoxib and one or more crystallization inhibitors in a solvent liquid to form a solution; and (b) a step of drying the solution to form a celecoxib-crystallization inhibitor composite wherein the celecoxib and the crystallization inhibitor are in intimate association and wherein a substantial portion of the celecoxib is present in amorphous form. Optionally, this process can further comprise (c) a step of grinding the celecoxib-crystallization inhibitor composite to provide a celecoxib-crystallization inhibitor composite powder.

A celecoxib drug substance or powder thereof, or a celecoxib-crystallization inhibitor composite or powder thereof, prepared according to such processes can be further formulated to provide a pharmaceutical dosage form.

Also provided is a method of treating a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising administering, for example orally, a composition of the invention in a therapeutically effective amount. Such a method is particularly useful where the medical condition or disorder is accompanied by acute pain.

Other features of this invention will be in part apparent and in part pointed out hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows a powder X-ray diffraction profile of a celecoxib drug substance C1 prepared in Example 1, by comparison with crystalline celecoxib C2.

Fig. 2 shows powder X-ray diffraction profiles of a celecoxib-polymer composite C3 of the invention immediately after preparation (T1) and following storage for 2 weeks at 40°C and 75% relative humidity (T2).

Fig. 3 shows powder X-ray diffraction profiles of a celecoxib-polymer composite C4 of the invention immediately after preparation (T1) and following storage for 2 weeks at 40°C and 75% relative humidity (T2).

Fig. 4 shows a differential scanning calorimetry (DSC) thermogram of a celecoxib drug substance C1 comprising no polymer.

Fig. 5 shows a DSC thermogram of a celecoxib-polymer composite C3 of the invention wherein the polymer is hydroxypropylmethylcellulose.

Fig. 6 shows a DSC thermogram of a celecoxib-polymer composite C4 of the invention wherein the polymer is polyvinylpyrrolidone.

DETAILED DESCRIPTION OF THE INVENTION

Amorphous celecoxib

The invention provides a novel amorphous form of celecoxib. The term "amorphous", as used herein, refers to solid-state particles lacking a regular crystalline structure. Without being bound by theory, it is believed that amorphous celecoxib particles require less energy for dissolution than crystalline celecoxib particles of similar dimensions, and that this reduced dissolution energy requirement contributes, at least in part, to increased dissolution rate and/or decreased therapeutic onset time exhibited by amorphous celecoxib and compositions thereof.

Celecoxib drug substance of the invention

In addition to amorphous celecoxib *per se*, the invention provides a celecoxib drug substance that comprises amorphous celecoxib. At least a detectable amount of amorphous celecoxib is present. Preferably, about 10% to about 100%, more preferably about 25% to about 100%, still more preferably about 60% to about 100%, and even more preferably about 80% to about 100%, by weight of the celecoxib in a celecoxib drug substance of the invention is amorphous. In a particular embodiment, substantially all of the celecoxib is amorphous, *i.e.*, the celecoxib drug substance is substantially phase pure amorphous celecoxib.

A preferred celecoxib drug substance is an entirely solid-state substance wherein the fraction, if any, of the celecoxib that is not amorphous, is crystalline. For example, a microparticulate or nanoparticulate celecoxib drug substance of this embodiment can, in addition to an amorphous celecoxib fraction, comprise a fraction of microcrystalline or nanocrystalline celecoxib, though this crystalline fraction is preferably small, for example, less than about 50%, more preferably less than about 25%, and still more preferably less than about 10%, by weight of the total celecoxib present.

In one embodiment, the amount of amorphous celecoxib in a celecoxib drug substance is sufficient to provide increased dissolution rate as measured in a standard *in vitro* dissolution assay and/or improved bioavailability (*e.g.*, shorter time to reach a

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threshold therapeutic concentration in blood plasma, greater C_{max} and/or shorter T_{max}) as measured in a standard *in vivo* pharmacokinetic study, compared with an otherwise similar celecoxib drug substance wherein all, or a substantial portion of, the celecoxib is crystalline.

Amorphous celecoxib or a celecoxib drug substance of the invention can be prepared by any suitable process, not limited to processes described herein.

One illustrative process comprises (a) a step of melting solid-state celecoxib, *e.g.*, crystalline celecoxib; and (b) a step of rapidly cooling the resulting melted celecoxib to form a celecoxib drug substance wherein the celecoxib is present, in at least a detectable amount, in amorphous form. This process optionally further comprises (c) a step of grinding the celecoxib drug substance resulting from step (b) to form a drug powder.

Melting step (a) can be performed by any technique known in the art, for example, by heating the celecoxib in an oven at about 150°C to about 180°C. Cooling step (b) can be performed by any suitable method, for example by floating a container holding the melted celecoxib in liquid nitrogen. The optional grinding step (c) can be performed by any suitable method, for example by grinding in a mortar and pestle or by grinding in a mill, for example a media mill.

A celecoxib drug substance or drug powder prepared according to the above process or any other process can be administered orally, rectally or parenterally without further formulation, or in simple suspension in water or another pharmaceutically acceptable liquid. Alternatively, the celecoxib drug substance or drug powder can be directly filled into capsules for oral administration. Preferably, however, the celecoxib drug substance or drug powder is subjected to further processing, typically with one or more excipients, to prepare a pharmaceutical composition, for example an oral dosage form, as described hereinbelow.

Celecoxib-crystallization inhibitor composites

In a presently preferred embodiment of the invention there is provided a celecoxib-crystallization inhibitor composite comprising particles of amorphous celecoxib or a celecoxib drug substance having at least a detectable amount of amorphous celecoxib, in intimate association with one or more crystallization inhibitors. An "intimate association" in the present context includes, for example,

celecoxib admixed with the crystallization inhibitor, celecoxib embedded or incorporated in the crystallization inhibitor, celecoxib forming a coating on particles of the crystallization inhibitor or *vice versa*, and a substantially homogeneous dispersion of celecoxib throughout the crystallization inhibitor. The term "substantially homogeneous" herein with reference to a composite or pharmaceutical composition that comprises multiple components means that the components are sufficiently mixed such that individual components are not present as discrete layers and do not form concentration gradients within the composition.

A celecoxib-crystallization inhibitor composite of this embodiment preferably comprises about 1% to about 95%, preferably about 10% to about 90%, more preferably about 25% to about 85%, and still more preferably about 30% to about 80%, by weight, of celecoxib. As indicated above, celecoxib in such a composite exists, at least in a detectable amount, in amorphous form. Preferably, about 10% to about 100%, more preferably about 50% to about 100%, and still more preferably about 75% to about 100%, by weight of the total celecoxib in the composite is amorphous celecoxib.

In composites of this embodiment, a fraction of the celecoxib can be present as microcrystalline or nanocrystalline celecoxib, though this fraction is preferably small, for example less than about 50%, more preferably less than about 25%, and still more preferably less than about 10%, by weight of the total celecoxib in the composite.

Crystallization inhibitors include any material which substantially reduces conversion of amorphous celecoxib to crystalline celecoxib, for example, polymers, carbohydrates, lipids, *etc*. The term "substantially" with respect to reducing such conversion includes completely inhibiting, preventing, slowing, delaying, decreasing or restricting crystallization of celecoxib to a measurable degree. It will be understood that both selection of crystallization inhibitor(s) and the amount of crystallization inhibitor(s) used in a composite of the invention influences stability of amorphous celecoxib therein.

Crystallization inhibitors are preferably polymers, more preferably polymers of low solubility in water. Still more preferably, such polymers are substantially non-crosslinked.

Non-limiting examples of suitable polymers that can be used as crystallization

inhibitors include, either alone or in combination, polyvinylpyrrolidone (PVP or povidone, *e.g.*, Kollidon™ CLM of BASF), hydroxypropylmethylcellulose (HPMC, *e.g.*, Methocel™ E5 Premium), HPMC phthalate, ethylcellulose, hydroxyethylcellulose, sodium carboxymethylcellulose (carmellose sodium), calcium carboxymethylcellulose, dextran, acacia, starches such as sodium starch glycolate (SSG, *e.g.*, Explotab™ R of Mendell), β-cyclodextrin (*e.g.*, Kleptose™ 4PC of Roquette), block copolymers of ethylene oxide and propylene oxide (*e.g.*, Pluronic™ F-68 and F-108), polyvinyl alcohol and polyethylene glycol (PEG). Povidone and HPMC are preferred polymers for use as crystallization inhibitors and form celecoxib-polymer composites of the invention.

HPMCs vary in the chain length of their cellulosic backbone and consequently in their viscosity as measured for example at a 2% by weight concentration in water. HPMC used in celecoxib-polymer composites of the invention should have a viscosity, 2% in water, of about 100 to about 100,000 cP, preferably about 1000 to about 15,000 cP, for example about 4000 cP. Molecular weight of HPMC used in celecoxib-polymer composites of the invention is preferably greater than about 10,000 but preferably not greater than about 1,500,000, more preferably not greater than about 1,000,000, still more preferably not greater than about 500,000, and even more preferably not greater than about 150,000.

HPMCs also vary in the relative degree of substitution of available hydroxyl groups on the cellulosic backbone by methoxy and hydroxypropoxy groups. With increasing hydroxypropoxy substitution, the resulting HPMC becomes more hydrophilic in nature. It is preferred in celecoxib-HPMC composites of the present invention to use HPMC having about 15% to about 35%, preferably about 19% to about 32%, and more preferably about 22% to about 30%, methoxy substitution, and having about 3% to about 15%, preferably about 4% to about 12%, and more preferably about 7% to about 12%, hydroxypropoxy substitution.

HPMCs which can be used in the present invention are illustratively available under the brand names Methocel™ of Dow Chemical Co. and Metolose™ of Shin-Etsu Chemical Co. Examples of particularly suitable HPMCs having medium viscosity include Methocel™ E4M and Methocel™ K4M, both of which have a viscosity, 2% in water, of about 4000 cP. Examples of HPMCs having higher

viscosity include Methocel™ E10M, Methocel™ K15M and Methocel™ K100M, which have viscosities, 2% in water, of 10,000 cP, 15,000 cP and 100,000 cP respectively.

Preferred povidones used in celecoxib-polymer composites of the invention have a molecular weight of about 2,500 to about 3,000,000, preferably about 8,000 to about 1,000,000, and more preferably about 10,000 to about 400,000, for example, about 50,000. Preferably, povidone used in celecoxib-polymer composites have a dynamic viscosity, 10% in water at 20°C, of about 1.3 to about 700, preferably about 1.5 to about 300, and more preferably about 3.5 to about 8.5 mPa s.

In celecoxib-crystallization inhibitor composites, for example celecoxib-polymer composites, of the invention, the amount of crystallization inhibitor is preferably sufficient such when maintained in an open dish at ambient temperature for a period of 7 days, transformation of amorphous celecoxib to crystalline celecoxib is no greater than about 50%, preferably no greater than about 25%, and more preferably no greater than about 10%, by weight of all celecoxib in the composite.

Typically, depending on the particular polymer(s) used, one or more polymers are present in a contemplated celecoxib-polymer composite in a total amount of about 10% to about 80%, preferably about 15% to about 75%, and more preferably about 25% to about 65%, by weight. Preferably, the weight ratio of celecoxib to polymer is about 1:1000 to about 10:1, more preferably about 1:10 to about 5:1, and still more preferably about 1:2 to about 2.5:1.

A celecoxib-crystallization inhibitor composite of the invention can be prepared by any suitable process, not limited to processes described herein.

One illustrative process comprises (a) a step of dissolving celecoxib and one or more crystallization inhibitors in a solvent liquid to form a solution; and (b) a step of drying the solution to form a celecoxib-crystallization inhibitor composite wherein the celecoxib and the crystallization inhibitor are in intimate association and wherein at least a detectable fraction of the celecoxib is in amorphous form. Optionally, this process can further comprise a step (c) of grinding the celecoxib-crystallization inhibitor composite to form a celecoxib-crystallization inhibitor composite powder.

Suitable solvent liquids which can be used to prepare a celecoxib-crystallization inhibitor composite, for example a celecoxib-polymer composite, can

comprise any pharmaceutically acceptable solvent in which celecoxib can be dissolved. Heat and stirring can be used to facilitate drug dissolution in the solvent liquid. The solvent liquid can also comprise a non-solvent fraction, for example, water. Non-limiting examples of suitable solvents that may be used in solvent liquids of the invention include, for example, water-alcohol mixtures, methanol, ethanol, isopropanol, higher alcohols, propylene glycol, ethyl caprylate, propylene glycol laurate, PEG, diethyl glycol monoethyl ether (DGME), tetraethylene glycol dimethyl ether, triethylene glycol monoethyl ether, polysorbate 80, *etc.* Ethanol and isopropanol are preferred solvents.

It has surprisingly been found that use of isopropanol as a solvent permits a relatively high loading of celecoxib and polymer in the solution to be dried; accordingly isopropanol is presently an especially preferred solvent.

The drying step (b) can be performed by any suitable means, for example, by evaporation, lyophilization, conventional heating (*e.g.*, in an oven), spray drying, *etc.* Spray drying is a preferred method of drying. Any suitable spray drying method known in the art can be employed. Generally, spray drying is a process by which a solution comprising dissolved drug and crystallization inhibitor is rapidly sprayed over a current of warm air, resulting in formation of dry powder.

The optional grinding step (c) can be performed by any suitable method, for example by grinding in a mortar and pestle or by grinding in a mill, for example a media mill.

A celecoxib-crystallization inhibitor composite, for example a celecoxib-polymer composite or a powder thereof, prepared according to the above process or any other process, can be administered orally, rectally or parenterally without further formulation, or in simple suspension in water or another pharmaceutically acceptable liquid. Alternatively, the composite or powder thereof can be directly filled into capsules for oral administration. Preferably, however, the composite or powder thereof is subjected to further processing, typically with one or more additional excipients, to prepare a pharmaceutical composition, for example an oral dosage form, as described hereinbelow.

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Pharmaceutical compositions

Amorphous celecoxib, a celecoxib drug substance or a celecoxib-crystallization inhibitor composite as provided herein can be further formulated together with one or more pharmaceutically acceptable excipients to produce a pharmaceutical composition. The term "excipient" herein means any substance, not itself a therapeutic agent, used as a carrier or vehicle for delivery of a therapeutic agent to a subject or added to a pharmaceutical composition to improve its handling or storage properties or to permit or facilitate formation of a dose unit of the composition into a discrete article such as a capsule or tablet suitable for oral administration. Excipients include, by way of illustration and not limitation, diluents, disintegrants, binding agents, adhesives, wetting agents, lubricants, glidants, crystallization inhibitors, surface modifying agents, substances added to mask or counteract a disagreeable taste or odor, flavors, dyes, fragrances, and substances added to improve appearance of the composition.

Excipients employed in compositions of the invention can be solids or liquids or both. Compositions of the invention containing excipients can be prepared by any known technique of pharmacy that comprises admixing an excipient with a drug or therapeutic agent. A composition of the invention contains a desired amount of celecoxib per dose unit and, if intended for oral administration, can be in the form, for example, of a tablet, a caplet, a pill, a hard or soft capsule, a lozenge, a cachet, a dispensable powder, granules, a suspension, an elixir, a liquid, or any other form reasonably adapted for such administration. If intended for parenteral administration, it can be in the form, for example, of a suspension. If intended for rectal administration, it can be in the form, for example, of a suppository. Presently preferred are oral dosage forms that are discrete dose units each containing a predetermined amount of the drug, such as tablets or capsules.

Non-limiting examples follow of excipients that can be used to prepare pharmaceutical compositions of the invention.

Compositions of the invention optionally comprise one or more pharmaceutically acceptable diluents as excipients. Suitable diluents illustratively include, either individually or in combination, lactose, including anhydrous lactose and lactose monohydrate; starches, including directly compressible starch and

hydrolyzed starches (*e.g.*, Celutab™ and Emdex™); mannitol; sorbitol; xylitol; dextrose (*e.g.*, Cerelose™ 2000) and dextrose monohydrate; dibasic calcium phosphate dihydrate; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate; granular calcium lactate trihydrate; dextrates; inositol; hydrolyzed cereal solids; amylose; celluloses including microcrystalline cellulose, food grade sources of α- and amorphous cellulose (*e.g.*, Rexcel™) and powdered cellulose; calcium carbonate; glycine; bentonite; polyvinylpyrrolidone; and the like. Such diluents, if present, constitute in total about 5% to about 99%, preferably about 10% to about 85%, and more preferably about 20% to about 80%, of the total weight of the composition. The diluent or diluents selected preferably exhibit suitable flow properties and, where tablets are desired, compressibility.

Lactose and microcrystalline cellulose, either individually or in combination, are preferred diluents. Both diluents are chemically compatible with celecoxib. The use of extragranular microcrystalline cellulose (that is, microcrystalline cellulose added to a wet granulated composition after a drying step) can be used to improve hardness (for tablets) and/or disintegration time. Lactose, especially lactose monohydrate, is particularly preferred. Lactose typically provides compositions having suitable release rates of celecoxib, stability, pre-compression flowability, and/or drying properties at a relatively low diluent cost. It provides a high density substrate that aids densification during granulation (where wet granulation is employed) and therefore improves blend flow properties.

Compositions of the invention optionally comprise one or more pharmaceutically acceptable disintegrants as excipients, particularly for tablet formulations. Suitable disintegrants include, either individually or in combination, starches, including sodium starch glycolate (*e.g.*, Explotab™ of PenWest) and pregelatinized corn starches (*e.g.*, National™ 1551, National™ 1550, and Colocorn™ 1500), clays (*e.g.*, Veegum™ HV), celluloses such as purified cellulose, microcrystalline cellulose, methylcellulose, carboxymethylcellulose and sodium carboxymethylcellulose, croscarmellose sodium (*e.g.*, Ac-Di-Sol™ of FMC), alginates, crospovidone, and gums such as agar, guar, locust bean, karaya, pectin and tragacanth gums.

Disintegrants may be added at any suitable step during the preparation of the composition, particularly prior to granulation or during a lubrication step prior to compression. Such disintegrants, if present, constitute in total about 0.2% to about 30%, preferably about 0.2% to about 10%, and more preferably about 0.2% to about 5%, of the total weight of the composition.

Croscarmellose sodium is a preferred disintegrant for tablet or capsule disintegration, and, if present, preferably constitutes about 0.2% to about 10%, more preferably about 0.2% to about 7%, and still more preferably about 0.2% to about 5%, of the total weight of the composition. Croscarmellose sodium confers superior intragranular disintegration capabilities to granulated compositions of the present invention.

Compositions of the invention optionally comprise one or more pharmaceutically acceptable binding agents or adhesives as excipients, particularly for tablet formulations. Such binding agents and adhesives preferably impart sufficient cohesion to the powder being tableted to allow for normal processing operations such as sizing, lubrication, compression and packaging, but still allow the tablet to disintegrate and the composition to be absorbed upon ingestion. Suitable binding agents and adhesives include, either individually or in combination, acacia; tragacanth; sucrose; gelatin; glucose; starches such as, but not limited to, pregelatinized starches (*e.g.*, National™ 1511 and National™ 1500); celluloses such as, but not limited to, methylcellulose and carmellose sodium (*e.g.*, Tylose™); alginic acid and salts of alginic acid; magnesium aluminum silicate; PEG; guar gum; polysaccharide acids; bentonites; povidone, for example povidone K-15, K-30 and K-29/32; polymethacrylates; HPMC; hydroxypropylcellulose (*e.g.*, Klucel™); and ethylcellulose (*e.g.*, Ethocel™). Such binding agents and/or adhesives, if present, constitute in total about 0.5% to about 25%, preferably about 0.75% to about 15%, and more preferably about 1% to about 10%, of the total weight of the composition.

Compositions of the invention optionally comprise one or more pharmaceutically acceptable wetting agents as excipients. Such wetting agents are preferably selected to maintain the celecoxib in close association with water, a condition that is believed to improve bioavailability of the composition.

Non-limiting examples of surfactants that can be used as wetting agents in

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compositions of the invention include quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10, and octoxynol 9, poloxamers (polyoxyethylene and polyoxypropylene block copolymers), polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides (*e.g.*, Labrasol™ of Gattefossé), polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example polyoxyethylene (20) cetostearyl ether, polyoxyethylene fatty acid esters, for example polyoxyethylene (40) stearate, polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80 (*e.g.*, Tween™ 80 of ICI), propylene glycol fatty acid esters, for example propylene glycol laurate (*e.g.*, Lauroglycol™ of Gattefossé), sodium lauryl sulfate, fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate, glyceryl fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, tyloxapol, and mixtures thereof. Such wetting agents, if present, constitute in total about 0.25% to about 15%, preferably about 0.4% to about 10%, and more preferably about 0.5% to about 5%, of the total weight of the composition.

Wetting agents that are anionic surfactants are preferred. Sodium lauryl sulfate is a particularly preferred wetting agent. Sodium lauryl sulfate, if present, constitutes about 0.25% to about 7%, more preferably about 0.4% to about 4%, and still more preferably about 0.5% to about 2%, of the total weight of the composition.

Compositions of the invention optionally comprise one or more pharmaceutically acceptable lubricants (including anti-adherents and/or glidants) as excipients. Suitable lubricants include, either individually or in combination, glyceryl behapate (*e.g.*, Compritol™ 888); stearic acid and salts thereof, including magnesium, calcium and sodium stearates; hydrogenated vegetable oils (*e.g.*, Sterotex™); colloidal silica; talc; waxes; boric acid; sodium benzoate; sodium acetate; sodium fumarate; sodium chloride; DL-leucine; PEG (*e.g.*, Carbowax™ 4000 and Carbowax™ 6000); sodium oleate; sodium lauryl sulfate; and magnesium lauryl sulfate. Such lubricants, if present, constitute in total about 0.1% to about 10%, preferably about 0.2% to about 8%, and more preferably about 0.25% to about 5%, of the total weight of the

composition.

Magnesium stearate is a preferred lubricant used, for example, to reduce friction between the equipment and granulated mixture during compression of tablet formulations.

Suitable anti-adherents include talc, cornstarch, DL-leucine, sodium lauryl sulfate and metallic stearates. Talc is a preferred anti-adherent or glidant used, for example, to reduce formulation sticking to equipment surfaces and also to reduce static in the blend. Talc, if present, constitutes about 0.1% to about 10%, more preferably about 0.25% to about 5%, and still more preferably about 0.5% to about 2%, of the total weight of the composition.

Other excipients such as colorants, flavors and sweeteners are known in the pharmaceutical art and can be used in compositions of the present invention. Tablets can be coated, for example with an enteric coating, or uncoated. Compositions of the invention can further comprise, for example, buffering agents.

Optionally, one or more effervescent agents can be used as disintegrants and/or to enhance organoleptic properties of compositions of the invention. When present in compositions of the invention to promote dosage form disintegration, one or more effervescent agents are preferably present in a total amount of about 30% to about 75%, and preferably about 45% to about 70%, for example about 60%, by weight of the composition.

According to a particularly preferred embodiment of the invention, an effervescent agent, present in a solid dosage form in an amount less than that effective to promote disintegration of the dosage form, provides improved dispersion of the celecoxib in an aqueous medium. Without being bound by theory, it is believed that the effervescent agent is effective to accelerate dispersion of celecoxib from the dosage form in the gastrointestinal tract, thereby further enhancing absorption and rapid onset of therapeutic effect. When present in a pharmaceutical composition of the invention to promote intragastrointestinal dispersion but not to enhance disintegration, one or more effervescent agents are preferably present in an amount of about 2.5% to about 15%, more preferably about 5% to about 10%, by weight of the composition.

Suitable effervescent agents include, for example, either alone or in

combination, sodium bicarbonate, anhydrous citric acid, tartaric acid and dibasic sodium phosphate. Sodium bicarbonate and anhydrous citric acid are preferred effervescent agents.

Solid dosage forms of the invention can be prepared by any suitable process, not limited to processes described herein.

An illustrative process comprises (a) a step of blending amorphous celecoxib, a celecoxib drug substance, or a celecoxib-crystallization inhibitor composite of the invention with one or more excipients to form a blend, and (b) a step of tableting or encapsulating the blend to form tablets or capsules respectively.

In a preferred process, solid dosage forms are prepared by a process comprising (a) a step of blending amorphous celecoxib, a celecoxib drug substance, or a celecoxib-crystallization inhibitor composite of the invention with one or more excipients to form a blend, (b) a step of granulating the blend to form a granulate, and (c) a step of tableting or encapsulating the blend to form tablets or capsules respectively. Step (b) can be accomplished by any dry or wet granulation technique known in the art, but is preferably a wet granulation step followed by a step of drying the resulting granulate prior to tableting or encapsulating. One or more diluents, one or more disintegrants and one or more binding agents are preferably added, for example in the blending step, a wetting agent can optionally be added, for example in the granulating step, and one or more disintegrants are preferably added after granulating but before tableting or encapsulating. A lubricant is preferably added before tableting. Blending and granulating can be performed independently under low or high shear. A process is preferably selected that forms a granulate that is uniform in drug content, that readily disintegrates, that flows with sufficient ease so that weight variation can be reliably controlled during capsule filling or tableting, and that is dense enough in bulk so that a batch can be processed in the selected equipment and individual doses fit into the specified capsules or tablet dies.

In an alternative embodiment, solid dosage forms are prepared by a process that includes a spray drying step, wherein the amorphous celecoxib, celecoxib drug substance or celecoxib-crystallization inhibitor composite is suspended with one or more excipients in one or more sprayable liquids, preferably a non-aqueous sprayable liquid, and then is rapidly spray dried over a current of warm air. This spray drying

process for preparing a pharmaceutical composition can be performed in addition to any spray drying step used in preparation of a celecoxib-crystallization inhibitor composite as described hereinabove, but formation of the celecoxib-crystallization inhibitor composite is preferably combined with a spray drying step for preparation of the pharmaceutical composition.

A granulate or spray dried powder resulting from any of the above illustrative processes can be compressed or molded to prepare tablets or encapsulated to prepare capsules. Conventional tableting and encapsulation techniques known in the art can be employed. Where coated tablets are desired, conventional coating techniques are suitable.

Excipients for tablet compositions of the invention are preferably selected to provide a disintegration time of less than about 30 minutes, preferably about 25 minutes or less, more preferably about 20 minutes or less, and still more preferably about 15 minutes or less, in a standard disintegration assay.

Any tablet hardness convenient with respect to handling, manufacture, storage and ingestion can be employed. For example, for 100 mg celecoxib tablets, hardness is preferably at least about 4 kP, more preferably at least about 5 kP, and still more preferably at least about 6 kP. For 200 mg celecoxib tablets, hardness is preferably at least about 7 kP, more preferably at least about 9 kP, and still more preferably at least about 11 kP. The material to be tableted, however, should not be compressed to such a degree that there is subsequent difficulty in achieving hydration when exposed to gastric fluid.

Tablet friability preferably is less than about 1.0%, more preferably less than 0.8%, and still more preferably less than about 0.5% in a standard test.

Celecoxib dosage

Celecoxib dosage forms of the invention preferably comprise celecoxib in a daily dosage amount of about 10 mg to about 1000 mg, more preferably about 25 mg to about 400 mg, and most preferably about 50 mg to about 200 mg.

Compositions of the invention comprise one or more orally deliverable dose units. Each dose unit comprises celecoxib in a therapeutically effective amount that is preferably about 10 mg to about 1000 mg. The term "dose unit" herein means a portion of a pharmaceutical composition that contains an amount of a therapeutic or

prophylactic agent, in the present case celecoxib, suitable for a single oral administration to provide a therapeutic effect. Typically one dose unit, or a small plurality (up to about 4) of dose units, in a single administration provides a dose comprising a sufficient amount of the agent to result in the desired effect. Administration of such doses can be repeated as required, typically at a dosage frequency of 1 to about 4 times per day.

It will be understood that a therapeutically effective amount of celecoxib for a subject is dependent *inter alia* on the body weight of the subject. A "subject" herein to which a therapeutic agent or composition thereof can be administered includes a human patient of either sex and of any age, and also includes any nonhuman animal, particularly a warm-blooded animal, more particularly a domestic or companion animal, illustratively a cat, dog or horse. When the subject is a child or a small animal (*e.g.*, a dog), for example, an amount of celecoxib relatively low in the preferred range of about 10 mg to about 1000 mg is likely to provide blood serum concentrations consistent with therapeutic effectiveness. Where the subject is an adult human or a large animal (*e.g.*, a horse), achievement of such blood serum concentrations of celecoxib are likely to require dose units containing a relatively greater amount of celecoxib.

Typical dose units in a composition of the invention contain about 10, 20, 25, 37.5, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350 or 400 mg of celecoxib. For an adult human, a therapeutically effective amount of celecoxib per dose unit in a composition of the present invention is typically about 50 mg to about 400 mg. Especially preferred amounts of celecoxib per dose unit are about 100 mg to about 200 mg, for example about 100 mg or about 200 mg.

A dose unit containing a particular amount of celecoxib can be selected to accommodate any desired frequency of administration used to achieve a desired daily dosage. The daily dosage and frequency of administration, and therefore the selection of appropriate dose unit, depends on a variety of factors, including the age, weight, sex and medical condition of the subject, and the nature and severity of the condition or disorder, and thus may vary widely.

When administered orally to a fasting adult human, a 100 mg dose unit preferably exhibits a T_{max} of less than about 90 minutes, more preferably less than

about 60 minutes and most preferably less than about 45 minutes, and a C_{max} of at least about 100 ng/ml, more preferably at least about 200 ng/ml. Typically a composition of the invention provides a blood serum concentration of celecoxib of at least about 50 ng/ml within 30 minutes of oral administration; preferred compositions achieve such a concentration in as little as 15 minutes. This early rise in blood serum concentration is believed to be associated with the rapid onset of therapeutic effect achieved by compositions of the present invention.

The term "oral administration" herein includes any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is immediately swallowed. Thus "oral administration" includes buccal and sublingual as well as esophageal administration. Absorption of the agent can occur in any part or parts of the gastrointestinal tract including the mouth, esophagus, stomach, duodenum, ileum and colon. The term "orally deliverable" herein means suitable for oral administration.

Utility of compositions of the invention

Compositions of the invention are useful in treatment and prevention of a very wide range of disorders mediated by COX-2, including but not restricted to disorders characterized by inflammation, pain and/or fever. Such compositions are especially useful as anti-inflammatory agents, such as in treatment of arthritis, with the additional benefit of having significantly less harmful side effects than compositions of conventional nonsteroidal anti-inflammatory drugs (NSAIDs) that lack selectivity for COX-2 over COX-1. In particular, compositions of the invention have reduced potential for gastrointestinal toxicity and gastrointestinal irritation including upper gastrointestinal ulceration and bleeding, reduced potential for renal side effects such as reduction in renal function leading to fluid retention and exacerbation of hypertension, reduced effect on bleeding times including inhibition of platelet function, and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects, by comparison with compositions of conventional NSAIDs. Thus compositions of the invention are particularly useful as an alternative to conventional NSAIDs where such NSAIDs are contraindicated, for example in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent

history of gastrointestinal lesions; gastrointestinal bleeding, coagulation disorders including anemia such as hypoprothrombinemia, hemophilia or other bleeding problems; kidney disease; or in patients prior to surgery or patients taking anticoagulants.

Contemplated compositions are useful to treat a variety of arthritic disorders, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis.

Such compositions are useful in treatment of asthma, bronchitis, menstrual cramps, preterm labor, tendinitis, bursitis, allergic neuritis, cytomegalovirus infectivity, apoptosis including HIV-induced apoptosis, lumbago, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, acne, burns, dermatitis and ultraviolet radiation damage including sunburn, and post-operative inflammation including that following ophthalmic surgery such as cataract surgery or refractive surgery.

Such compositions are useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis.

Such compositions are useful in treating inflammation in such diseases as migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury including brain edema, myocardial ischemia, and the like.

Such compositions are useful in treatment of ophthalmic diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue.

Such compositions are useful in treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis, and in bone resorption such as that associated with osteoporosis.

Such compositions are useful for treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease,

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neurodegeneration, and central nervous system damage resulting from stroke, ischemia and trauma. The term "treatment" in the present context includes partial or total inhibition of dementias, including Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia and senile dementia.

Such compositions are useful in treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome and liver disease.

Such compositions are useful in treatment of pain, including but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer. For example, such compositions are useful for relief of pain, fever and inflammation in a variety of conditions including rheumatic fever, influenza and other viral infections including common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, and trauma following surgical and dental procedures.

Such compositions are useful for treating and preventing inflammation-related cardiovascular disorders, including vascular diseases, coronary artery disease, aneurysm, vascular rejection, arteriosclerosis, atherosclerosis including cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including Chlamydia-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries.

Such compositions are useful in treatment of angiogenesis-related disorders in a subject, for example to inhibit tumor angiogenesis. Such compositions are useful in treatment of neoplasia, including metastasis; ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, macular degeneration, retrolental fibroplasia and neovascular glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemaginomas, angiofibroma of the nasopharynx and

avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis.

Such compositions are useful in prevention and treatment of benign and malignant tumors and neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer, skin cancer such as squamous cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Neoplasias for which compositions of the invention are contemplated to be particularly useful are gastrointestinal cancer, Barrett's esophagus, liver cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer. Such compositions can also be used to treat fibrosis that occurs with radiation therapy. Such compositions can be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, such compositions can be used to prevent polyps from forming in patients at risk of FAP.

Such compositions inhibit prostanoid-induced smooth muscle contraction by inhibiting synthesis of contractile prostanoids and hence can be of use in treatment of dysmenorrhea, premature labor, asthma and eosinophil-related disorders. They also can be of use for decreasing bone loss particularly in postmenopausal women (*i.e.*, treatment of osteoporosis), and for treatment of glaucoma.

Preferred uses for compositions of the invention are for treatment of rheumatoid arthritis and osteoarthritis, for pain management generally (particularly post-oral surgery pain, post-general surgery pain, post-orthopedic surgery pain, and acute flares of osteoarthritis), for treatment of Alzheimer's disease, and for colon cancer chemoprevention.

Besides being useful for human treatment, compositions of the invention are useful for veterinary treatment of companion animals, exotic animals, farm animals, and the like, particularly mammals. More particularly, compositions of the invention are useful for treatment of COX-2 mediated disorders in horses, dogs and cats.

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Method of treatment

The present invention is further directed to a therapeutic method of treating a condition or disorder where treatment with a COX-2 inhibitory drug is indicated, the method comprising oral administration of a composition of the invention to a subject in need thereof. The dosage regimen to prevent, give relief from, or ameliorate the condition or disorder preferably corresponds to once-a-day or twice-a-day treatment, but can be modified in accordance with a variety of factors. These include the type, age, weight, sex, diet and medical condition of the subject and the nature and severity of the disorder. Thus, the dosage regimen actually employed can vary widely and can therefore deviate from the preferred dosage regimens set forth above.

Initial treatment can begin with a dose regimen as indicated above. Treatment is generally continued as necessary over a period of several weeks to several months or years until the condition or disorder has been controlled or eliminated. Subjects undergoing treatment with a composition of the invention can be routinely monitored by any of the methods well known in the art to determine effectiveness of therapy. Continuous analysis of data from such monitoring permits modification of the treatment regimen during therapy so that optimally effective doses are administered at any point in time, and so that the duration of treatment can be determined. In this way, the treatment regimen and dosing schedule can be rationally modified over the course of therapy so that the lowest amount of the composition exhibiting satisfactory effectiveness is administered, and so that administration is continued only for so long as is necessary to successfully treat the condition or disorder.

The present compositions can be used in combination therapies with opioids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e. non-addictive) analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers, among others. Preferred combination therapies comprise use of a composition of the invention with one or more compounds selected from aceclofenac, acemetacin, *e*-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid (aspirin), *S*-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac,

aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylon, aminopyrine, amixetrine, ammonium salicylate, ampiroxicam, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylmorphine, bermoprofen, bezitramide, α-bisabolol, bromfenac, *p*-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphene, carprofen, carsalam, chlorobutanol, chlorthenoxazin, choline salicylate, cinchophen, cinmetacin, ciramadol, clidanac, clometacin, clonitazene, clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide, crotethamide, desomorphine, dexoxadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamizole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamic acid, epirizole, eptazocine, etersalate, ethenzamide, ethoheptazine, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flunoxaprofen, fluoresone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone, hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isoladol, isomethadone, isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac, *p*-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lornoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone hydrochloride, methotrimeprazine, metiazinic acid, metofoline, metopon, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone,

normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsalmide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, piprofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide *o*-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen and zomepirac (see The Merck Index, 12th Edition, Therapeutic Category and Biological Activity Index, ed. S. Budavari (1996), pp. Ther-2 to Ther-3 and Ther-12 (Analgesic (Dental), Analgesic (Narcotic), Analgesic (Non-narcotic), Anti-inflammatory (Nonsteroidal)).

Particularly preferred combination therapies comprise use of a composition of the invention with an opioid compound, more particularly where the opioid compound is codeine, meperidine, morphine or a derivative thereof.

A celecoxib composition of the invention can also be administered in combination with a second selective COX-2 inhibitory drug, for example valdecoxib, rofecoxib, *etc.*

The compound to be administered in combination with celecoxib can be formulated separately from the celecoxib or co-formulated with the celecoxib in a composition of the invention. Where celecoxib is co-formulated with a second drug, for example an opioid drug, the second drug can be formulated in immediate-release, rapid-onset, sustained-release or dual-release form.

EXAMPLES

The following examples illustrate aspects of the present invention but are not to be construed as limitations.

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Example 1

A celecoxib drug substance C1 and celecoxib-polymer composites C3 and C4 were prepared by the following spray drying process. Celecoxib in crystalline form (a celecoxib drug substance C2 of prior art) was added to a solvent, with stirring at a temperature of 70-75°C, to prepare solutions S1, S3 and S4 having the composition shown in Table 1,. Solutions S1 and S4 were prepared in 95% ethanol. Solution S3 was prepared in 70% isopropanol.

Table 1. Composition (mg/ml) of solutions S1, S3 and S4.

Component	S1	S3	S4
Celecoxib	30	100	30
HPMC	-	50	-
Povidone	-	-	15

Each of solutions S1, S3 and S4 was spray dried individually at room temperature using a Yamato GB-21 spray dryer to form powders C1, C3 and C4, respectively, under the following conditions: (a) liquid flow rate of 10 ml/min; (b) inlet air temperature of 115°C; (c) outlet air temperature of 75°C, and (d) drying airflow of 3.75 TMF. Powders C3 and C4 are celecoxib-polymer composites of the invention, each comprising 67% celecoxib and 33% polymer.

Example 2

A celecoxib drug substance C10 was prepared by the following melt/quench cool process.

Approximately 5 g of crystalline celecoxib (the prior art celecoxib drug substance C2) was weighed into a metal foil tray and placed in an oven at 180°C for 5 minutes to melt the celecoxib. This was then quench cooled by floating the foil tray containing the melted celecoxib on liquid nitrogen, resulting in the formation of celecoxib drug substance C10 of the present invention. This drug substance could be gently ground by mortar and pestle to produce a celecoxib drug substance powder.

Example 3

Powder X-ray diffraction (PXRD) analysis was used to determine the relative crystalline and amorphous celecoxib content of celecoxib drug substance C1 and celecoxib-polymer composites C3 and C4 as prepared in Example 1, by comparison with crystalline celecoxib drug substance C2. Data were collected using a Scintag

Advanced Diffraction System operating under Scintag DMS/NT software. This system uses a peltier cooled solid state detector and a copper X-ray source maintained at 45 kV and 40 mA to provide $CuK\alpha_1$ emission at 1.5406 Å. The beam aperture was controlled using tube divergence and anti-scatter slits of 2 and 4 mm respectively, while the detector anti-scatter and receiving slits were set at 0.5 and 0.3 mm respectively. Data were collected from 2° to 35° two-theta (2θ) using a scan step of 0.03°/point and a one second/point integration time. The samples were prepared using Scintag round top-loading stainless steel sample cups, and were fitted with 12 mm diameter aluminum inserts to accommodate small sample volumes.

The results of the PXRD analyses are shown as bands in Figs. 1-3. The appearance of larger, spiked peaks on a band indicates crystallinity whereas compressed peaks are indicative of amorphous material.

Fig. 1 shows that celecoxib alone (with no polymer) spray dried from an ethanol solution (C1) produced a strong crystalline signal similar to that of a crystalline celecoxib control (C2). If there is an amorphous component in celecoxib drug substance C1 it is a minor component.

Fig. 2 shows that when celecoxib was spray dried with HPMC (2:1 ratio by weight), the resulting celecoxib-polymer composite C3 was initially (at time T1) non-crystalline, *i.e.*, the celecoxib in this composite was substantially phase pure amorphous celecoxib. When analysis was conducted on a sample that had been stored for two weeks at 40°C and 75% relative humidity (at time T2), some recrystallization had occurred, as indicated by presence of crystalline peaks.

Fig. 3 shows that when celecoxib was spray dried with povidone (2:1 ratio by weight) the resulting celecoxib-polymer composite C4 was initially (at time T1) non-crystalline, *i.e.*, the celecoxib in this composite was substantially phase pure amorphous celecoxib. When analysis was conducted on a sample that had been stored for two weeks at 40°C and 75% relative humidity (at time T2), essentially no recrystallization had occurred, as indicated by absence of crystalline peaks.

Example 4

Differential scanning calorimetry (DSC) was used to determine relative crystalline and amorphous celecoxib content of celecoxib drug substance C1 and celecoxib-polymer composites C3 and C4 as prepared in Example 1. DSC was

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performed using a TA Instruments DSC 2920 differential scanning calorimeter with parameters set as follows: (a) temperature range of 50-200°C; (b) heating rate of 2°C/min, modulating ± 0.5°C every 30 sec; (c) sample size of 3 mg; (d) hermetically sealed aluminum pans.

Figs. 4-6 show DSC thermograms for the spray dried powders of Example 1.

Fig. 4 displays a thermogram for celecoxib drug product C1, exhibiting a large melting endotherm at 159.4°C (onset) with an area of 96.42 J/g. No other transitions are evident. The magnitude of the endotherm suggests that a substantial portion of C1 was crystalline. Any amorphous celecoxib present in the sample was not detectable by this technique.

Fig. 5 displays a thermogram for celecoxib-polymer composite C3 (2:1 celecoxib:HPMC ratio). This material exhibits an apparent glass transition at 122.9°C (onset), followed by a small melting endotherm at 150.1°C with an area of 4.379 J/g. The endotherm indicates that most of the celecoxib in C3 is amorphous, but that a small amount of crystalline celecoxib is present.

Fig. 6 displays a thermogram for celecoxib-polymer composite C4 (2:1 celecoxib:povidone ratio). This material exhibits an apparent glass transition at 111.4°C (onset). No other transitions are evident, indicating that the material is substantially phase pure amorphous celecoxib.

Example 5

DSC was also used to determine relative crystalline and amorphous content of celecoxib drug substance C10 prepared as in Example 2. DSC was performed using a TA Instruments MDSC differential scanning calorimeter at a scan rate of 5°C/min.

A first significant thermal event was observed at about 54°C, representing a glass transition temperature indicative of amorphous celecoxib. An exothermic peak observed at 100-105°C was consistent with a crystallization event and represents conversion of amorphous celecoxib to a crystalline state. As was shown by the presence of a endothermic peak, the resulting crystalline celecoxib melted at about 165°C.

Example 6

Tablets having the composition shown in Table 2 were prepared from

celecoxib-polymer composite C4 by the following procedure. Composite C4, sodium lauryl sulfate and effervescent agents (citric acid and sodium bicarbonate) were admixed and milled for 10 min in a McCrone mill to form a powder mixture. The powder mixture was ground together with lactose, microcrystalline cellulose and sodium starch glycolate using a mortar and pestle to form a ground powder mixture. The ground powder mixture was then compressed using a Carver press to form tablets, which are illustrative of a pharmaceutical composition of the invention.

Table 2. Composition of tablets prepared from celecoxib-polymer composite C4

Component	Amount/tablet (mg)
Composite C4	300
Sodium lauryl sulfate	3
Citric acid	15.9
Sodium bicarbonate	25.2
Lactose	50
Microcrystalline cellulose	57
Sodium starch glycolate	48
Total	499

Example 7

Tablets prepared as described in Example 6 were compared with a crystalline celecoxib capsule in an *in vivo* bioavailability assay in dogs. In a crossover design, each of six beagle dogs received a 200 mg dose of celecoxib in the form of the tablet composition of Example 6, and then after a washout period, the dogs each received a 200 mg dose of celecoxib in the form of a commercial Celebrex® 200 mg capsule, which contains celecoxib entirely in crystalline form. Blood plasma was collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 5, 8 and 24 hours post-dose. Celecoxib concentrations in plasma were measured using liquid chromatography/mass spectrometry. C_{max}, T_{max} and AUC (area under the curve, a measure of total bioavailability) were calculated from the data in accordance with standard procedure in the art. Mean results for all dogs are shown in Table 3.

The tablet of Example 6 prepared from amorphous celecoxib exhibited a significantly greater C_{max} (maximum blood plasma concentration), a comparable T_{max}, and a significantly greater AUC than the capsule formulated from crystalline celecoxib. As a measure of relative onset time, the time taken for the tablet of the invention to reach a plasma concentration equal to the C_{max} of the crystalline

WHAT IS CLAIMED IS:

1. Amorphous celecoxib.

2. A celecoxib drug substance wherein the celecoxib is present, in at least a detectable amount, as amorphous celecoxib.

3. The drug substance of Claim 2 wherein the amorphous celecoxib is present in an amount of about 10% to about 100% by weight of the celecoxib.

4. The drug substance of Claim 2 that comprises substantially phase pure amorphous celecoxib.

5. A celecoxib-crystallization inhibitor composite comprising particles of amorphous celecoxib or a celecoxib drug substance of any of Claims 2 to 4 in intimate association with one or more crystallization inhibitor(s) in an amount effective to reduce transformation of amorphous celecoxib to crystalline celecoxib.

6. The composite of Claim 5 wherein the crystallization inhibitor is a polymer.

7. The composite of Claim 6 wherein the polymer is selected from polyvinylpyrrolidone and hydroxypropylmethylcellulose.

8. The composite of Claim 6 wherein the polymer is polyvinylpyrrolidone.

9. The composite of any of Claims 5 to 8 wherein the crystallization inhibitor(s) are present in a total amount of about 10% to about 80% by weight of the composite.

10. A pharmaceutical composition comprising (a) amorphous celecoxib, a celecoxib drug substance of any of Claims 2 to 4, or a celecoxib-crystallization inhibitor composite of any of Claims 5 to 9, in a total celecoxib dosage amount of about 10 mg to about 1000 mg, and (b) one or more pharmaceutically acceptable excipients.

11. A process for preparing a celecoxib drug substance, the process comprising

(a) melting celecoxib;

(b) rapidly cooling the resulting melted celecoxib to form a celecoxib drug substance wherein the celecoxib is present, in at least a detectable amount,

in amorphous form; and optionally

(c) grinding the celecoxib drug substance to form a celecoxib drug substance powder.

12. A process for preparing a celecoxib-crystallization inhibitor composite, the process comprising

(a) dissolving celecoxib and one or more crystallization inhibitors in a solvent liquid to form a solution;

(b) drying the solution to form a celecoxib-crystallization inhibitor composite wherein the celecoxib is present, at least in a detectable amount, in amorphous form; and optionally

(c) grinding the celecoxib drug substance to form a celecoxib-crystallization inhibitor composite powder.

13. The process of Claim 12 wherein drying step (b) is performed by spray drying.

14. The process of Claim 12 or Claim 13 wherein the solvent liquid comprises isopropanol.

15. A process for preparing a pharmaceutical composition, the process comprising

(a) blending amorphous celecoxib, a celecoxib drug substance of any of Claims 2 to 4, or a celecoxib-crystallization inhibitor composite of any of Claims 5 to 9, with one or more excipients to form a blend; and

(b) tableting or encapsulating the blend to form celecoxib tablets or capsules respectively.

16. The process of Claim 15, further comprising granulating the blend to form a granulate prior to tableting or encapsulating.

17. The process of Claim 16 wherein granulating is performed by wet granulation to form a wet granulate, and wherein the wet granulate is dried prior to tableting or encapsulating.

18. A method of treating a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering one or more dose units of a composition of Claim 10 once or twice a day.

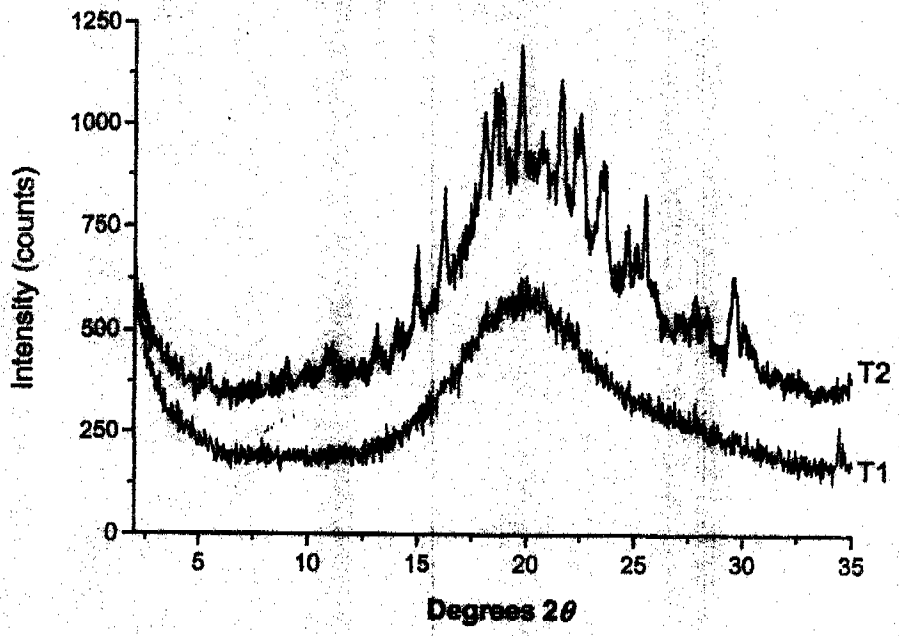

1250
1000
750
500
250
0
Intensity (counts)
5
10
15
20
25
30
35
Degrees 2θ
T2
T1

Fig. 2

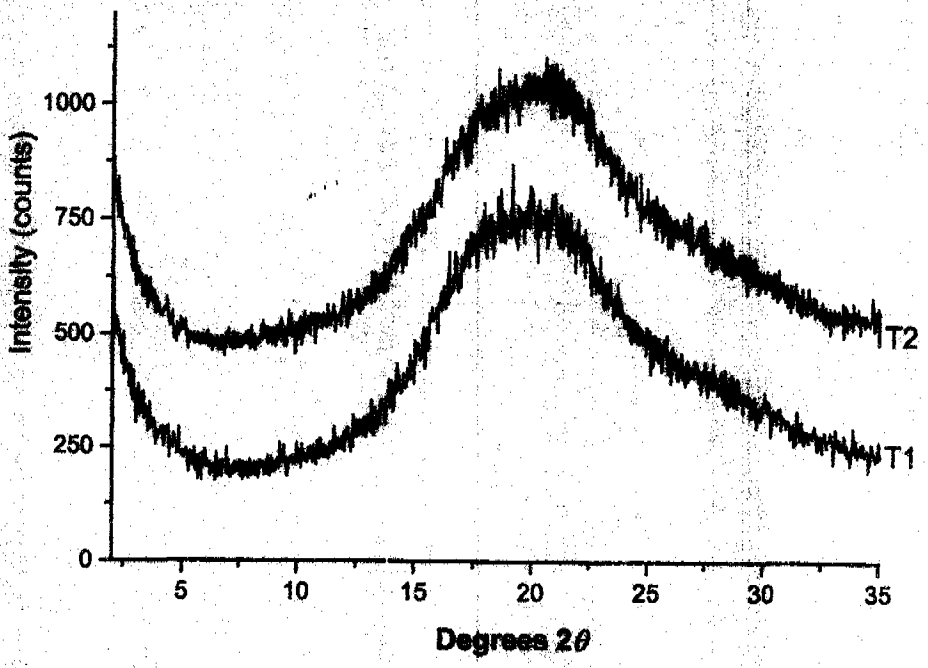

1000
750
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Intensity (counts)
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Degrees 2θ
T2
T1

Fig. 3

Copia

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : **Expediente Nº 07 007.599**

Asunto : **Oposición a la solicitud de patente de Invención titulada "ELABORACIÓN DE COMPLICACIONES FARMACÉUTICAS DE LIBERACIÓN RÁPIDA DE DROGAS INSOLUBLES EN AGUA Y COMPOSICIONES FARMACÉUTICAS OBTENIDAS POR EL PROCESO DE LA INVENCIÓN"**

Solicitante : **NYCOMED DANMARK APS**

Opositora : **PROCAPS S.A.**

Publicada en la Gaceta de la Propiedad Industrial

Nº 599 del 31 de Diciembre de 2008

Yo, ***ELIANA ISAURA MORENO BOHORQUEZ,*** abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad ***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 **"ELABORACIÓN DE COMPLICACIONES FARMACÉUTICAS DE LIBERACIÓN RÁPIDA DE DROGAS INSOLUBLES EN AGUA Y COMPOSICIONES**

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FARMACÉUTICAS OBTENIDAS POR EL PROCESO DE LA INVENCIÓN", cuyo titular es **NYCOMED DANMARK APS,** y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular LISINA, ARGININA, HISTIDINA, AINES o BROMAZEPAM. 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 26 de enero de 2007 reivindicando prioridad bajo la solicitud DK20040001021 del 2004-06-29; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial **Nº 599 del 31 de Diciembre de 2008,** cuya publicación internacional corresponde a la WO2006000228 del 2006-10-05.

2.2. La solicitud colombiana **07 007.599** objeto de la presente oposición, se refiere a un proceso de elaboración de una forma de dosificación oral que tiene rápida disolución de la droga activa en el fluido gástrico, caracterizado porque comprende las etapas de: a) proveer una droga activa, con una solubilidad a temperatura ambiente menor que 0,1% p/v en ácido clorhídrico 0,1 N o con un valor de pKa menor que 5,5; y b) proporcionar una o más sustancias alcalinas; c) mezclar dicha droga activa y dicha sustancia alcalina y opcionalmente uno o más excipientes por molienda conjunta sin agregar líquido, y opcionalmente d) mezclar uno o más excipientes farmacéuticamente aceptables y opcionalmente e) comprimir dicha mezcla c) o d) en forma de una tableta; donde en el paso c) de molienda conjunta se aplica únicamente a la droga activa y la(s) sustancia(s) alcalina(s). Adicionalmente se refiere un proceso de elaboración de una forma de dosificación oral que tiene rápida disolución de la droga activa en el fluido gástrico, caracterizado porque comprende las etapas de: a) proveer una droga activa, con una solubilidad a temperatura ambiente menor que 0,1% p/v en ácido clorhídrico 0,1 N o con un valor de pKa menor que 5,5; y proporcionar una o más sustancia(s) alcalina(s); moler dicha(s) sustancia(s) alcalina(s) sin adicionar líquidos, mezclar dicha(s) sustancia(s) alcalina(s) en c) con dicha droga activa, y opcionalmente e) mezclar uno o mas excipientes farmacéuticamente aceptables, y f) comprimir dicha mezcla d) o e) en forma de una tableta.

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:

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- D1: WO9909988 publicada el 4 de marzo de 1999.
- D2: WO0141536 publicada el 14 de junio de 2001.

2.4. Ahora bien, el documento D1, particularmente en la descripción revela composiciones farmacéuticas que contienen carboxamidas enólicas del tipo de agente antiinflamatorio de meloxicam que exhiben una mejorada biodisponibilidad, solubilidad acuosa, mejorado comportamiento de disolución sobre una amplia gama de pH, que está preparado por la modificación de la estructura de cristal del activo por la homogeneización en seco o humedad mecánica que incluye dos componentes, donde uno de ellos es seleccionado de un grupo oligo y un mejorador de disolución o agente alcalizante. Particularmente, en el ejemplo IV/11 y IV/12 así como en las cláusulas 1, 6, 9, 17 y 21 se define un proceso que comprende los pasos de co-mezclar ciclodextrina beta, meloxicam (NSAID) y carbonato de sodio bajo condiciones en seco. Como tal la disolución es caracterizada en la tabla 13.

2.5. En combinación, el documento D2 por su parte revela una composición farmacéutica que comprende un inhibidor de celocoxib y uno o varios excipientes. Particularmente, en el ejemplo 6 revela un proceso que comprende los pasos de co-mezclar un compuesto polimérica de celecoxib y carbonato de sodio en condiciones en seco.

2.6. Por lo tanto además, como lo revela dicha anterioridad D2 en el ejemplo 6, un proceso que comprende los pasos de co-mezclar un compuesto polimérica de celecoxib y carbonato de sodio en condiciones en seco, donde dicho conocimiento en combinación con aquel revelado en la solicitud D1, en el ejemplo IV/11 y IV/12 así como en las cláusulas 1, 6, 9, 17 y 21 donde se define un proceso que

comprende los pasos de co-mezclar ciclodextrina beta, meloxicam (NSAID) y carbonato de sodio bajo condiciones en seco, es posible derivar de manera evidente a un proceso de elaboración de una forma de dosificación oral que tiene rápida disolución de la droga activa en el fluido gástrico y a una composición tal y como aquella revelada en la presente solicitud. Por lo tanto, visto dicho documento D2 en combinación con el documento D1, la presente solicitud carece evidentemente de altura inventiva.

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

2.8. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana **07 007599** 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.

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

2.9.1. **CARENCIA DE ALTURA INVENTIVA**. Según la Decisión 486 de la Comunidad Andina de Naciones, Articulo 18.- "*Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.*". A la fecha de prioridad, 29 de junio de 2004, a partir del documento D2 en combinación con D1, puede llegar de manera evidente a un proceso de elaboración de una forma de dosificación oral que tiene rápida disolución de la droga activa en el fluido gástrico y a una composición tal y como aquella revelada en la presente solicitud, sobre el cual busca protección en el capítulo reivindicatorio.

2.10. 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.

2.11. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"ELABORACIÓN DE COMPLICACIONES FARMACÉUTICAS DE LIBERACIÓN RÁPIDA DE DROGAS INSOLUBLES EN AGUA Y COMPOSICIONES FARMACÉUTICAS OBTENIDAS POR EL PROCESO DE LA INVENCIÓN"**, cuyo titular es **NYCOMED DANMARK APS**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial **N° 599 del 31 de diciembre de 2008.**

3. PRUEBAS

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

- D1: WO9909988 publicada el 4 de marzo de 1999.
- D2: WO0141536 publicada el 14 de junio de 2001.