



Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO

Radicación : 01087299 00000005

Folios: 152

Fecha (AÑO): 2004-04-28 14:13:08

Trámite : 002 PATENTES D 1 REGISTRO/ 400 OPOSICION

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE OPOSICIÓN
2000-12

①

OPOSICIÓN A:

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

②

Número del expediente: 01087299

Solicitante: Pharmacia Corporation

SOLICITUD
PUBLICADA

Apoderado: Emilio Ferrero

Título de la nueva creación o denominación del signo: Composiciones

inhibidoras de ciclooxigenasa-2 que tienen rápida acción de efecto terapéutico

Gaceta: N° 538 N° de publicación: 219

OPOSICIÓN PRESENTADA POR:

OPOSITOR

Nombre: Procaps S.A.

Dirección: Calle 80 N° 78B-201

Teléfono: 3530783 Fax: 3533949

E-mail:

Domicilio: Berranquilla/Cibola

IDENTIFICACIÓN

C.C. ☐ NT ☒

C.E. ☐ Otro ☐

Número 890106527-5

REPRESENTANTE
O APODERADO
(74)

Nombre: Luis Fernando

Dirección: Rincon Cuéller
Calle 119 A N° 53-99

Teléfono: 6133374 Fax: 6133418

E-mail: rincon@optimum-co.com

IDENTIFICACIÓN

C.C. ☒ NT ☐

C.E. ☐ Otro ☐

Número 79532186TP113438

④ FUNDAMENTOS DE LA OPOSICIÓN:

Causal: Arts. 1617, 18, 21, 38, 39, 42, 43, 45 de la Decisión 486 de la C.A.

Justificación: Falta de novedad y nivel inventivo /
Publicación anterior íntegramente expresada
como se detalla en los escritos adjuntos

SUPERINDUSTRIA Y COMERCIO

Radicacion : 01047299 00000005 Folios: 152
 Fecha (AMB): 2004-04-28 14:13:08
 Trámite : 002 PATENTES D 1 REGISTRO/ 400 OPOSICION
 Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 390176989-2

RECIBO OFICIAL DE CAJA : 04 - 33,743
 FECHA : ABRIL 29 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	13319174	26/04/2004	224,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	30003-01-04	PRESENTACION DE OBSERVACIONES	
12		MARCAS Y LEHAS COMERCIALES	224,000.00
		TOTAL	224,000.

SON: DOSCIENTOS VEINTICUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Comprobante de pago No.

04-33745

Fecha

Ab. 29/09

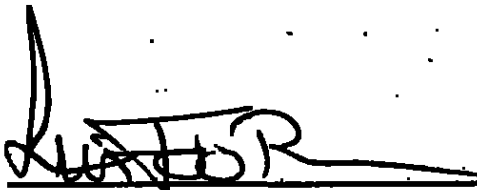
ANEXOS

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

NOMBRE:

Luis Fernando Rincón C.

FIRMA:



C.C. 79532186

TP. 113438

CÓMO DILIGENCIAR EL FORMULARIO UNICO DE OPOSICIÓN

- Si faltara espacio en algún recuadro de este impreso, utilice hojas complementarias.
- Los espacios sombreados corresponden a los requisitos mínimos que deben cumplirse para obtener fecha de presentación de la solicitud.
- Si alguna casilla del formulario no fuera cubierto, se cruzará una línea oblicua.

1. **Oposición a:** Corresponde al trámite al cual se le formula la oposición.
2. **Solicitud publicada:**
 - Número de expediente: Indicar el número asignado al trámite al cual se le formula oposición.
 - Solicitante: Indicar el nombre del solicitante del trámite al cual se le formula la oposición.
 - Apoderado: Indicar el nombre del apoderado en caso de que el solicitante del trámite al que se le formula la oposición actúe por intermedio de éste.
 - Título de la nueva creación o denominación del signo: En caso de ser un trámite de patente deberá indicar el título de la solicitud a la cual se le formula oposición. En caso de ser un trámite de registro de signo deberá indicar la denominación del mismo.
 - Gaceta: Número de la publicación correspondiente.
3. **Oposición presentada por:** Corresponde a los datos de la oposición que se presente.
 - Opositor: Es la persona jurídica o natural que presenta la oposición. Debe indicarse nombre, dirección, teléfono, fax, e-mail y domicilio (país, departamento y ciudad).
 - Representante o Apoderado: En este espacio debe indicarse el nombre del representante legal cuando el opositor sea una persona jurídica si no se está actuando a través de apoderado y deberá acreditarse tal calidad. Si se actúa a través de apoderado, debe indicarse el nombre del abogado que adelantará la actuación administrativa anexando el correspondiente poder. Si la solicitud la adelanta una persona natural sin apoderado, no debe diligenciarse esta casilla.
4. **Fundamentos de la oposición:**
 - Causal: corresponde a la indicación de la(s) causal(es) legales en que se basa la oposición, indicando expresamente la disposición normativa.
 - Justificación: motivos de hecho y argumentación en que se soporta la oposición.
5. **Comprobante de pago:** Referenciar el número y fecha del recibo de pago de la tasa establecida. Este comprobante deberá anexarse.
6. **Anexos:** Deben marcarse con una X las casillas correspondientes a los documentos que acompañarán la oposición. Al momento de presentar la oposición se deberán aportar las pruebas que el opositor tenga en su poder.
7. **Firma:** Si se actúa a través de abogado, la firma deberá ser la del apoderado; si actúa directamente una persona jurídica la firma deberá ser la de su representante legal, y si actúa directamente una persona natural ésta deberá firmar la solicitud.

IMPORTANTE:

Si no es especialista en la materia, le recomendamos:

Consultar la normatividad relacionada con este trámite en www.sic.gov.co o en la Biblioteca de la SIC, carrera 13 No. 27-00 piso 5 de lunes a viernes de 8:30 a.m. a 5:00 p.m. jornada continua.

Leer detenidamente los folletos y los instructivos para el diligenciamiento de los formularios.

Una vez radicada la solicitud, informarse permanentemente sobre el estado de su trámite y, si es del caso, contestar dentro del término los requerimientos notificados según las disposiciones legales vigentes.

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

Referencia :Expediente N° 01.087299
Asunto :Oposición a la solicitud de patente de Invención
titulada "**COMPOSICIONES INHIBIDORAS DE
CICLOOXIGENASA-2 QUE TIENEN RAPIDO
ACCESO DE EFECTO TERAPEUTICO**"
Solicitante: **PHARMACIA CORPORATION**
Observador: **PROCAPS S.A.**

Publicada en la gaceta 536 del 30 de enero de 2004

Yo, Luis Fernando Rincón Cuellar, abogado con tarjeta profesional N° 113438 del consejo superior de la judicatura, en mi condición de apoderado de la sociedad PROCAPS S.A. conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley, presento oposición a la concesión del registro de la patente de Invención titulada

"COMPOSICIONES INHIBIDORAS DE CICLOOXIGENASA-2 QUE TIENEN RAPIDO ACCESO DE EFECTO TERAPEUTICO", solicitada por PHARMACIA CORPORATION., y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

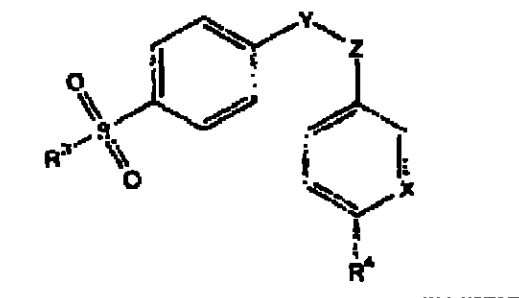
2. INTERES PARA ACTUAR

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, solicito a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

3. FUNDAMENTOS DE HECHO

3.1. La solicitud objeto de la presente oposición fue presentada el 10 de octubre de 2001, no se reivindicó prioridad sobre solicitud alguna y fue publicada en Colombia, en la Gaceta de la propiedad Industrial N° 536, del 30 de enero de 2004, bajo el N° de publicación NP. 640 (página 219).

3.2. La solicitud colombiana 01.087299 objeto de la presente oposición presenta una composición farmacéutica que comprende una o más unidades de dosis suministrables oralmente, cada una comprende una droga inhibitoria de ciclooxigenasa-2 selectiva de baja solubilidad en agua en una cantidad terapéuticamente efectiva, en donde la droga está presente en partículas sólidas que tienen un tamaño de partícula D90 de alrededor de 0,01 μm hasta alrededor de 200 μm , una porción suficiente en peso de la partícula siendo más pequeña que 1 μm para suministrar un Cmax sustancialmente mayor y/o un Tmax sustancialmente más corto en comparación con otras composiciones similares en donde sustancialmente todas las partículas son mayores de 1 μm . Adicionalmente el solicitante de esta patente indica que de 25 a 100% en peso de las partículas son menores a 1 μm . Indica que la composición farmacéutica está presente en sólidos que tienen la forma de tabletas o cápsulas. También indica que la composición farmacéutica puede estar en la forma de una suspensión líquida desde la cual se pueden obtener las dosis sencillas. Las partículas sólidas pueden tener un D25 de entre 450 a 1000 nm. El compuesto activo Inhibidor de la ciclooxigenasa 2 es el compuesto de la formula siguiente:



La composición farmacéutica presenta como inhibidor de la COX-2 a uno que puede ser seleccionado del grupo que consiste de celecoxib, deracoxib, valdecoxib, rofecoxib, 5-cloro-3-(4-metilsulfonil)fenil-2-(2-metil-5-piridinil)piridina, 2-(3,5-difluorofenil)-3-[4-metilsulfonil]fenil]-2-ciclopenteno-1-ona y (S)-6,8-dicloro-2-(trifluorometil)-2H-1benzopirano-3-acidocarboxílico.

También se deduce de las reivindicaciones que el compuesto activo preferido es el celecoxib y que éste se encuentra en la dosis suministrable en una cantidad que puede ir desde 10 hasta 1000 mg.

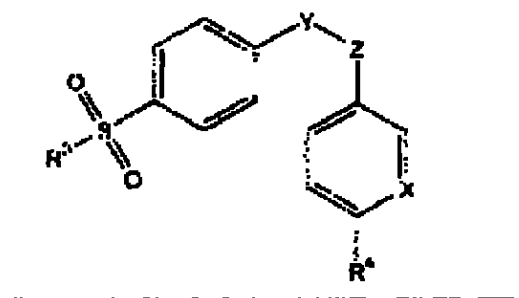
Las reivindicaciones 16 y 17 se refieren a un método de tratamiento para tratar un desorden relacionado donde el inhibidor de COX-2 puede ser indicado, el método comprende en administrar oralmente las unidades de dosificación en un

período de tiempo que puede ir de uno a seis días. La última reivindicación, la número 18, reclama el uso de partículas sólidas de un inhibidor de COX-2 en suspensión líquida para preparar un medicamento útil en el tratamiento de un desorden físico relacionado con la COX-2.

3.3. Con anterioridad a la fecha de prioridad de esta solicitud, el estado de la técnica ya revelaba los documentos WO0141760, de PHARMACIA CORPORATION, publicado el 14 de junio de 2001; y, el WO0032189, de G.D.SEARLE & CO, publicado el 8 de junio de 2000.

3.4. La solicitud WO0141760 se refiere a una composición farmacéutica que comprende una o más unidades de dosis suministrables oralmente, cada una comprende una droga inhibidora de ciclooxigenasa-2 selectiva de baja solubilidad en agua en una cantidad terapéuticamente efectiva, en donde la droga está presente en partículas sólidas que tienen un tamaño de partícula D90 de alrededor de 0,01 μm hasta alrededor de 200 μm , una porción suficiente en peso de la partícula siendo más pequeña que 1 μm para suministrar un Cmax sustancialmente mayor y/o un Tmax sustancialmente más corto en comparación con otras composiciones similares

en donde sustancialmente todas las partículas son mayores de 1 μm . El documento indica que de 25 a 100% en peso de las partículas son menores a 1 μm . La composición farmacéutica está presente en sólidos que tienen la forma de tabletas o cápsulas. Ésta puede estar en la forma de una suspensión líquida desde la cual se pueden obtener las dosis sencillas. Las partículas sólidas pueden tener un D25 de entre 450 a 1000 nm. El compuesto activo Inhibidor de la ciclooxigenasa 2 es el compuesto de la formula siguiente:



La composición farmacéutica presenta como inhibidor de la COX-2 a uno que puede ser seleccionado del grupo que consiste de celecoxib, deracoxib, valdecoxib, rofecoxib, 5-cloro-3-(4-metilsulfonil)fenil-2-(2-metil-5-piridinil)piridina, 2-(3,5-difluorofenil)-3-[4-metilsulfonil]fenil]-2-ciclopenteno-1-ona y (S)-6,8-dicloro-2-(trifluorometil)-2H-1benzopirano-3-acido carboxílico.

El compuesto activo preferido es el celecoxib y se encuentra presente en la dosis suministrable en una cantidad que puede ir desde 10 hasta 1000 mg.

3.5. Analizando la solicitud WO0141760, efectivamente esta revela con anterioridad una composición farmacéutica con **idénticas** características de dosis suministrables basadas en un Inhibidor de la COX-2, con la misma fórmula estructural y siendo el agente Inhibidor preferentemente el celecoxib. Así las cosas, lo expuesto en la solicitud colombiana 01.087299 a partir de sus reivindicaciones 1 a la 18, se encuentra totalmente descrito en dicha anterioridad, de tal forma que la solicitud colombiana no aporta un desarrollo tecnológico en dicha materia. Por lo tanto, dicha solicitud anterior afecta completamente el elemento de NOVEDAD consagrado en el artículo 16 de la Decisión 486.

3.6. De igual manera tampoco se cumple con el requisito de NIVEL INVENTIVO consagrado en el artículo 18, ya que para cualquier persona del oficio normalmente versada en la materia técnica la solicitud colombiana CO 01087299, se hubiera derivado de manera evidente al consultar el documento WO0141760.

3.7. Ahora bien, la solicitud anterior WO0032189 de G.D.SEARLE & CO publicada con anterioridad, el 8 de junio de 2000, también presenta composiciones de celecoxib con un D90 de menos de 200 micrones y tiene una porción suficiente en peso de la partícula con un D90 de menos de un (1) micrón. En esta solicitud se puede encontrar las consecuencias técnicas de disminuir el tamaño de partícula del celecoxib lo que ayuda claramente a incrementar la biodisponibilidad, reduciendo el Tmax (tiempo máximo) e incrementando la Cmax (concentración máxima). Estas composiciones en forma de tabletas y de suspensión son efectivos en el tratamiento de desordenes generados por la COX-2.

3.8. En consecuencia, y de acuerdo a lo descrito anteriormente, se deriva la IGUALDAD entre la solicitud colombiana 01087299 y la solicitud WO0032189; debemos subrayar el hecho de que la solicitud WO0032189 es anterior a la solicitud colombiana, y que por lo tanto, esta última carece en su totalidad del elemento NOVEDAD, que debe estar presente para que una solicitud de patente pueda ser concedida.

3.9. De igual manera tampoco se cumple con el requisito de NIVEL INVENTIVO consagrado en el artículo 18, ya que para cualquier persona del oficio normalmente versada en la materia técnica la solicitud colombiana CO 01087299, se hubiera derivado de manera evidente al consultar el documento WO0032189.

3.10. Las cláusulas 16 y 17 se refieren a métodos para el tratamiento humano o animal en enfermedades que son consecuencia de la COX-2, lo cual cae claramente dentro de las excepciones a la patentabilidad que consagra el artículo 20 de la decisión 486:

"Artículo 20, literal d: No serán patentables los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales."

3.11. La reivindicación número 18 es un uso; un uso no se encuentra dentro del espectro que se consagra en el artículo 14 de la Decisión 486:

"Artículo 14: Los países miembros otorgaran 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."

Un uso no es un producto, ni tampoco un uso es un procedimiento.

3.12. Así las cosas, la solicitud colombiana objeto de la presente oposición no es novedosa desde ningún punto de vista, pues a todas luces lo que allí se describe ya se revelaba con anterioridad en la solicitudes previas WO0141760 y WO0032189; a la vez que consultando dichos documentos claramente puede llegarse a la solución propuesta por la presente solicitud; por lo tanto consideramos que la concesión de esta solicitud colombiana atentaría abiertamente contra la normatividad colombiana, que explícitamente consagra la NOVEDAD y el NIVEL INVENTIVO como dos de los tres elementos esenciales para que de a lugar la concesión de una patente.

3.13. Con base en lo expuesto, atentamente me permito elevar la siguiente.

4. PETICION

4.1. Declarar fundada la presente oposición basada en lo que revelaban las anterioridades WO0141760 y WO0032189.

4.2. Negar la solicitud de patente Nº 01087299 titulada **"COMPOSICIONES INHIBIDORAS DE CICLOOXIGENASA-2 QUE TIENEN RAPIDO ACCESO DE EFECTO TERAPEUTICO"**.

5. PRUEBAS

5.1. Copias simples de las solicitudes PCT, WO0141760 y WO0032189.

6. ANEXOS

6.1 Los relacionados en el capítulo de PRUEBAS.

6.2 Poder Especial para la presente actuación

6.3 Certificado de Existencia y Representación de la sociedad denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA – PROCAPS LIMITADA"

Copia para traslado

7. FUNDAMENTOS DE DERECHO

La anterior se fundamenta en Artículo 14 y 42 de la Decisión 486 de la Comunidad Andina de Naciones y demás normas concordantes.

8. NOTIFICACIONES

Recibiré notificaciones en la Secretaría de su Despacho o en mi oficina de abogado ubicada en la calle 119ª N° 53-99 de esta ciudad.

Señora Jefe,



C.C. N° 75532186 de Bogotá

T.P. N° 113438 de Minjusticia.

**DILIGENCIA DE RECONOCIMIENTO
Y PRESENTACION PERSONAL**

Ante el Notario Once del Circulo de Santafé de Bogotá, compareció [Firma]

Quien exhibió la C.C. No. 11348
expedida en BK T.P. 11348

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

Santafé de Bogotá, D.C.

28 APR 2004

Firma del Declarante

HUELLA

Autorizó la anterior Diligencia

NOTARIO ONCE DEL CIRCULO DE SANTAFÉ DE BOGOTÁ

REPUBLICA DE COLOMBIA
NOTARIA 11 DEL CIRCULO DE
SANTAFÉ DE BOGOTÁ, D.C.

MONICA L. BASTISTA
NOTARIO ONCE(E)



192

Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Atención: Dra. Alix Céspedes de Vergel
Jefe División de Nuevas Creaciones
E. S. D.

PODER ESPECIAL

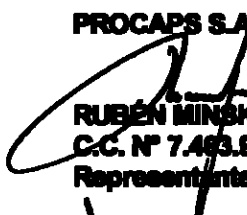
RUBÉN MINSKI GONTOVNIK, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de su firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorga a **LUIS FERNANDO RINCON CUELLAR**, abogado titulado, identificado como aparece al pie de su firma, con tarjeta profesional No. 113438 expedida por el Consejo Superior de la Judicatura, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 01 087.289, de título: "Composiciones Inhibidoras de ciclooxigenasa-2 que tienen rápido acceso de efecto terapéutico", publicada en la gaceta No. 538 del 30 enero de 2004, numero de publicación 640, y cuyo solicitante es la sociedad **Pharmacia Corporation**.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo queda autorizado 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.

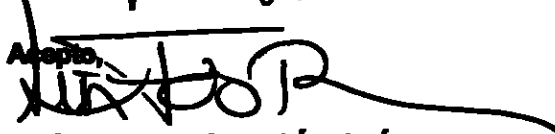
De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentra facultado para recibir, desistir, transigir, sustituir, y reasumir el presente poder, Incoar acciones, Interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los 14 días del mes de abril de 2004.

PROCAPS S.A.


RUBÉN MINSKI GONTOVNIK
C.C. N° 7.493.982 de Barranquilla
Representante Legal

Acepto,


LUIS FERNANDO RINCÓN CUÉLLAR
C.C. No. 78.632.188
T.P. 113438

CALLE 80 N° 788 - 201 • A.A. 50330 • P.B.X. (575) 3530783 - 3789000 - 3719900 • FAX: (575) 3533949 - 3558434
- 3533681 - 3532997 BARRANQUILLA - COLOMBIA • NIT: 890-108.527-5

15

DILIGENCIA DE PRESENTACION PERSONAL

DECRETO 860 DE 1970 - ART. 88

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

CERTIFICA

En Barranquilla a los 19 días del mes de Septiembre de 2004 Firmaron esta diligencia en su presencia: Ruben Minski Gaborwik

Ponamiento de las cédulas 7463.982.



Expediente:

3/16

y que los documentos que anteceden a la diligencia son los mismos que anteceden a la diligencia con sus firmas



Comparecientes

LA NOTARIA
REPUBLICA DE COLOMBIA
NOTARIA SEGUNDA DEL CIRCULO
DE BARRANQUILLA

2

Maria del S. Roman de Arteta
NOTARIA SEGUNDA DE BARRANQUILLA



***** Pag.01
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
08*****

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

PROCAPS S.A. -----

EN JUNIO DE ESTE A/O SE ELEGIRA JUNTA DIRECTIVA DE LA CAMARA DE COMER-
CIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA
QUINCENA DE MAYO. PARA INFORMACION DETALLADA DIRIGIRSE A LA SEDE
PRINCIPAL O COMUNICARSE AL SIGUIENTE TELEFONO 3303911

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

Que por Escritura Publica Nro. 1190 del 22 de Julio de 1,976,
otorgada en la Notaria Tercera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 28 de Julio de 1,976 bajo
el No. 6,070 del libro respectivo, fue constituida la sociedad
limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA"
"PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Publica Nro. 1307 del 28 de Junio de 1,979,
otorgada en la Notaria Tercera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 23 de Julio de 1,979 bajo
el No. 10,039 del libro respectivo, la sociedad antes mencionada
se transformo en sociedad anonima bajo la denominacion social de
"PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Publica Nro. 3810 del 31 de Dic/bre de 1,980,
otorgada en la Notaria Primera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 30 de Enero de 1,981 bajo
el No. 12,705 del libro respectivo, la sociedad antes mencionada
se transformo en sociedad de responsabilidad limitada bajo al razon
social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI -
MITADA".-----

C E R T I F I C A

Que por Escritura Publica Nro. 3755 del 10 de Nov/bre de 1,983,
otorgada en la Notaria Unica de Soledad, -----
inscrita en esta Camara de Comercio, el 22 de Nov/bre de 1,983 bajo
el No. 17,922 del libro respectivo, la sociedad antes mencionada
se transformo en sociedad anonima bajo la denominacion social de
"PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

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

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

PROCAPS S.A. -----

C E R T I F I C A

Que por Escritura Publica Nro. 3615 del 6 de Dic/bre de 1,996, otorgada en la Notaria 2a. de Barranquilla ----- inscrita en esta Camara de Comercio, el 20 de Dic/bre de 1,996 bajo el No. 67,218 del libro respectivo, la sociedad antes mencionada cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A -----

C E R T I F I C A

Que por Escritura Publica Nro. 3775 del 18 de Dic/bre de 1,996, otorgada en la Notaria 2a. de Barranquilla ----- inscrita en esta Camara de Comercio, el 23 de Enero de 1,997 bajo el No. 67,704 del libro respectivo, la sociedad antes mencionada cambio de razon social, por la denominacion PROCAPS S.A. -----

C E R T I F I C A

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

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

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. -----

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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

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

C E R T I F I C A

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

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-La fabri-
cacion de capsulas y otros productos similares a partir de materia-
les 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, alimen-
ticias y cosmeticas, asi como la comercializacion interna y externa
de los productos terminados, d) La compra, venta, importacion, ex-
portacion y distribucion de toda clase de elementos instru-
mentales y equipos medicos, quirurgicos, odontologicos, y hospitalarios
para la salud humana y animal. e) La compra, venta, exportacion y dis-
tribucion de dulces, confites, galletas y todo tipo de
golosinas o alimentos para el consumo humano. f) Actuar como re-
presentante o agente de personas naturales y juridicas, nacio-
nales y extranjeras en la realizacion de operaciones o tran-
sacciones relacionadas con la industria farmaceutica y en especial

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

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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, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o 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 gravámenes reales sobre sus bienes de cualquier naturaleza. -----

C E R T I F I C A

CAPITAL:	Nro. Acciones	Valor Accion
AUTORIZADO:		
\$*****2,000,000,000.00	2,000,000.00	1,000.00
SUSCRITO:		
\$*****1,212,449,000.00	1,212,449.00	1,000.00
PAGADO:		
\$*****1,212,449,000.00	1,212,449.00	1,000.00

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad corresponde a la Asamblea General de Accionistas; a la Junta Directiva,

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

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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 cuantía 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 día 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 cuantía sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambi representativa del mercado vigente el día 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 separadamente con el Presidente. El vicepresidente tendra las siguientes 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

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

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PROCAPS S.A. -----

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 cuantía 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 día en que se surta la aprobación o celebración 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 gravámenes 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 Junta 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 Gerente General designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente y el Vicepresidente. El Gerente General tendra las siguientes facultades entre otras: Ejecutar las decisiones de la Junta Directiva, del Presidente y del Vicepresidente. Ejercer la representación 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 cuantía 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 día en que se surta la aprobación o celebración 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 gravámenes sobre cualquiera de los

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



***** Pag.04
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A

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anteriores o facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que les correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva.-----

C E R T I F I C A

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

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

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

C E R T I F I C A

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

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

C E R T I F I C A

Que segun Acta No. 124 del 29 de Marzo de 1,999, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----

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

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PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 4 de Agosto de 1,999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos: -----

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

C E R T I F I C A

Que segun Acta No. 127 del 22 de Marzo de 2,000, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----

PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 29 de Mayo de 2,000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos: -----

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

C E R T I F I C A

Que segun Acta No. 11 del 1 de Febrero de 2,001, correspondiente a la Junta Directiva en Barranquilla de la sociedad: -----

PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 12 de Febrero de 2,001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos: -----

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

C E R T I F I C A

Que por escritura publica No. 2.608 del 5 de Octubre del 2.001, tor-
gada en la Notaria 2a. de Barranquilla, inscrita en esta Camara de
Comercio el 8 de Noviembre del 2.001, bajo los Nos. 95.771, 2.056,
2.057, 2.058, 2.059, 2.060, 2.061, 2.062 y 2.064 del libro respecti-
vo, se reforma totalmente el articulo 65, contenido en la escritura
publica No. 3:705 de Noviembre 6 de 1.998, de la Notaria Segunda del
Circuito de Barranquilla, y se constituyen los siguientes Apoderados
Generales, quienes tendran las funciones que a continuación
se indican en razon de su cargo en la sociedad: 1. Se con-
fiere Poder Especial, Amplio y Suficiente a los señores: WALTER
TANAKA TATEKAWA, C.C. No. 16.251.923; WILLIAM ALBERTO BARROS CERRA,
C.C. No. 8.715.941, para que cada uno en forma independiente en nom-

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



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bre y representacion de PROCAPS S.A., suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad, asi como para que responda todo tipo de requerimiento o solicitudes de informacion de las autoridades tributarias, aduaneras o cambiarias, en los ordenes Distrital, Departamental y Nacional. 2.-Se confiere Poder Especial, amplio y suficiente, a los siguientes señores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta por la suma de US\$800.000.00 (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transaccion. GUPO A: GUILLERMO LUIS URIBE OCHO C.C. No. 70.073.754, LINO LAZALA SILVA VARGAS C.C. No. 19.260.410, JAIRO MOLINA MEJIA C.C. No. 8.706.380, CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.-293. BRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, HENRY CARO DIAZ C.C. No. 19.395.298, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZGRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requiera por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C.C. No. 33.138.497, a la Doctora MARCELA CARVAJALINO PAGANO C.C. No. 22.579.748, y al Doctor DANIEL MORENO VILLALBA, C.C. No. 19.113.210; para que cada uno representen a PROCAPS S.A., ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como: Contestar e interponer demandas y requerimientos, comparecer en juicios, pedir la practica de pruebas, recibir notificaciones, interponer recursos y ejercer acciones contencioso administrativas y de tutela, transigir, conciliar, recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato. Para la celebracion de cualquier acuerdo conciliatorio o transaccional, judicial o extrajudicial, cualquiera que sea su cuantia, los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la sociedad. Los Apoderados podran presentar solicitudes de devolucion y/o compensacion de impuestos y recibir los pagos por devoluciones de impuestos, firmar, notificarse y realizar todo acto necesario para cumplir con el mandato encomendado.-----

C E R T I F I C A

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

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PROCAPS S.A. -----

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

C E R T I F I C A

Que segun Documento Privado del 13 de diciembre del 2.002, inscrito en esta Camara de Comercio el 15 de enero del 2.003 bajo el No.2.290 del libro respectivo, el senor RUBEN MINSKI GONTOVNIK, C.C.No.7.463.982, en calidad de REPRESENTANTE LEGAL, y en condicion de PRESIDENTE de PROCAPS S.A., mediante el presente documento otorgo PODER ESPECIAL al Sr. MARLON TATIS PAREDES, C.C.No.72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces. En consecuencia, el Sr. MARLON TATIS PAREDES, podra suscribir en representacion de PROCAPS S.A. declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces.-----

C E R T I F I C A

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

C E R T I F I C A

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

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

NO CAUSA IMPUESTO DE TIMBRE

**EL SECRETARIO
MARIBEL REYES OVIEDO**

Maribel Reyes

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 June 2001 (14.06.2001)

PCT

(10) International Publication Number
WO 01/41760 A2

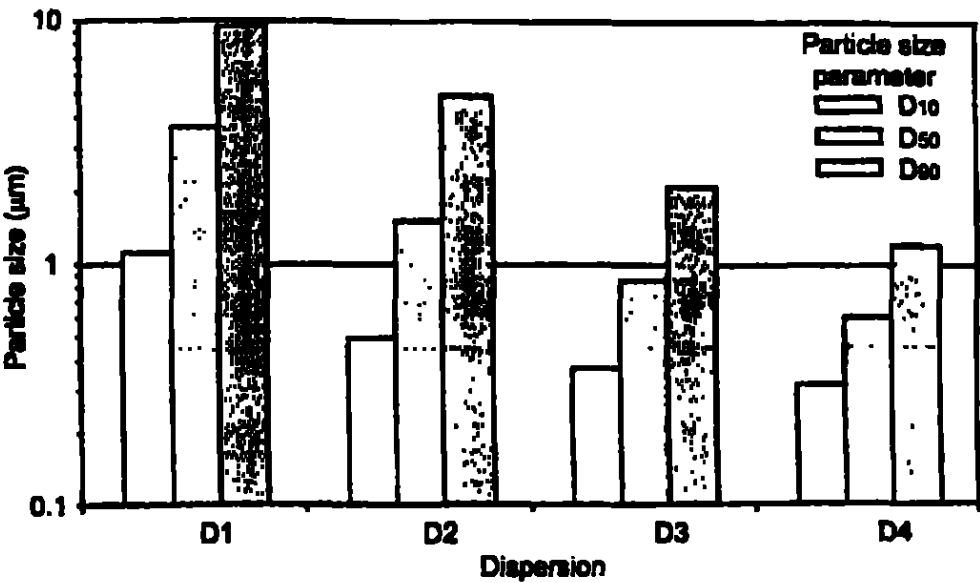
- (51) International Patent Classification⁷: A61K 31/415, 9/14, 9/51
- (21) International Application Number: PCT/US00/32434
- (22) International Filing Date: 6 December 2000 (06.12.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/169,836 8 December 1999 (08.12.1999) US
- (71) Applicant (for all designated States except US): PHARMACIA CORPORATION [US/US]; Corporate Patent Dept., P.O. Box 5110, Chicago, IL 60680 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): KARARLI, Tugrul, T. [US/US]; 8334 N. Kildare, Skokie, IL 60076 (US). KONTNY, Mark, J. [US/US]; 2343 Huntington Lakes Drive, Libertyville, IL 60048 (US). DESAI, Subhash [US/US]; 1011 Greenwood Avenue, Wilmette, IL (US).

- HAGEMAN, Michael, J. [US/US]; 5362 South 12th Street, Portage, MI 49024 (US). HASKELL, Royal, J. [US/US]; Kalamazoo, MI (US).
- (74) Agents: FORBES, James, C. et al.; Pharmacia Corporation, P.O. Box 5110, Chicago, IL 60680 (US).
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(54) Title: CYCLOOXYGENASE-2 INHIBITOR COMPOSITIONS HAVING RAPID ONSET OF THERAPEUTIC EFFECT



(57) Abstract: Pharmaceutical compositions are provided comprising one or more orally deliverable dose units, each comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in the form of solid particles, about 25 % to 100 % by weight of which are smaller than 1 µm. The compositions are useful in treatment or prophylaxis of cyclooxygenase-2 mediated conditions and disorders and have particular advantages where rapid onset of therapeutic effect is desired.

WO 01/41760 A2

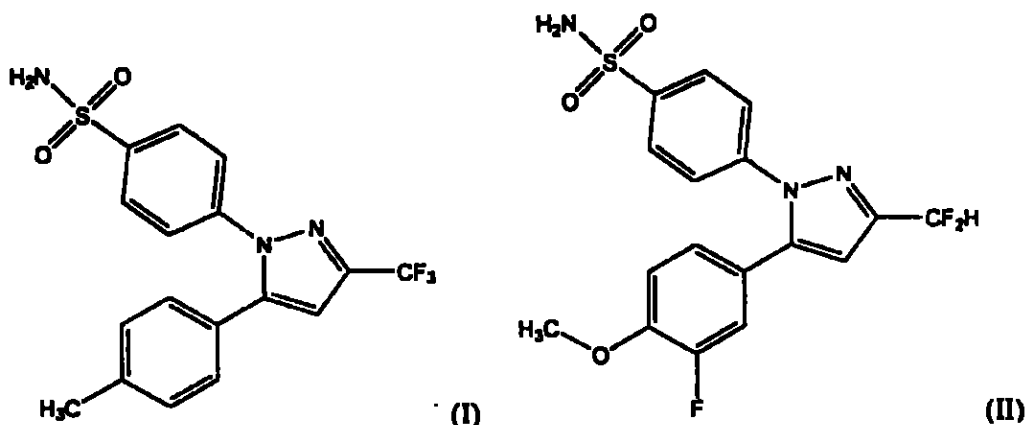
**CYCLOOXYGENASE-2 INHIBITOR COMPOSITIONS HAVING
RAPID ONSET OF THERAPEUTIC EFFECT**

FIELD OF THE INVENTION

The present invention relates to orally deliverable pharmaceutical compositions containing a selective cyclooxygenase-2 inhibitory drug as an active ingredient, to processes for preparing such compositions, to methods of treatment of cyclooxygenase-2 mediated disorders comprising orally administering such compositions to a subject, and to use of such compositions in manufacture of medicaments.

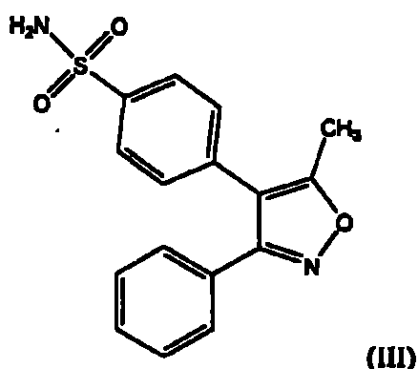
BACKGROUND OF THE INVENTION

Numerous compounds have been reported having therapeutically and/or prophylactically useful selective cyclooxygenase-2 (COX-2) inhibitory effect, and have been disclosed as having utility in treatment or prevention of specific COX-2 mediated disorders or of such disorders in general. Among such compounds are a large number of substituted pyrazolyl benzenesulfonamides as reported in U.S. Patent No. 5,760,068 to Talley *et al.*, including for example the compound 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, also referred to herein as celecoxib (I), and the compound 4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl-1H-pyrazol-1-yl]benzenesulfonamide, also referred to herein as deracoxib (II).

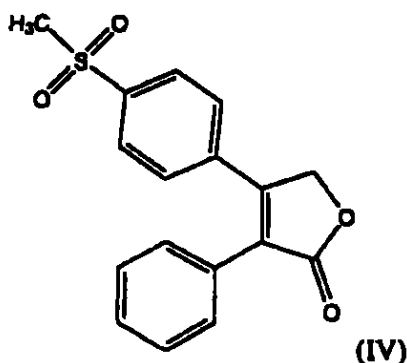


Other compounds reported to have therapeutically and/or prophylactically useful selective COX-2 inhibitory effect are substituted isoxazolyl benzenesulfonamides as reported in U.S. Patent No. 5,633,272 to Talley *et al.*,

including the compound 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide, also referred to herein as valdecoxib (III).

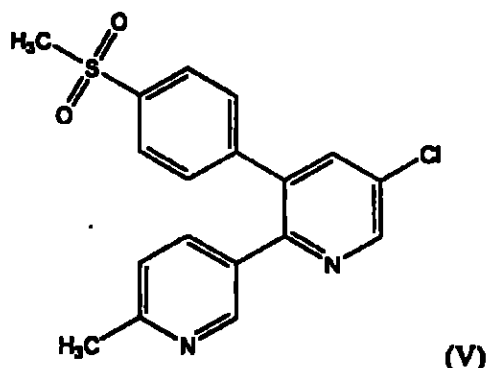


Still other compounds reported to have therapeutically and/or prophylactically useful selective COX-2 inhibitory effect are substituted (methylsulfonyl)phenyl furanones as reported in U.S. Patent No. 5,474,995 to Ducharme *et al.*, including the compound 3-phenyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one, also referred to herein as rofecoxib (IV).



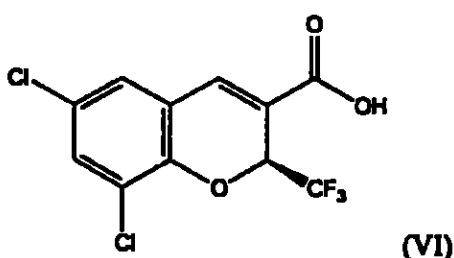
U.S. Patent No. 5,981,576 to Belley *et al.* discloses a further series of (methylsulfonyl)phenyl furanones said to be useful as selective COX-2 inhibitory drugs, including 3-(1-cyclopropylmethoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one and 3-(1-cyclopropylethoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one.

U.S. Patent No. 5,861,419 to Dube *et al.* discloses substituted pyridines said to be useful as selective COX-2 inhibitory drugs, including for example the compound 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine (V).



European Patent Application No. 0 863 134 discloses the compound 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one said to be useful as a selective COX-2 inhibitory drug.

U.S. Patent No. 6,034,256 discloses a series of benzopyrans said to be useful as selective COX-2 inhibitory drugs, including the compound (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid (VI).



Many selective COX-2 inhibitory drugs, including celecoxib, deracoxib, valdecoxib and rofecoxib, are hydrophobic and have low solubility in water. This has presented practical difficulties in formulating such drugs for oral administration, particularly where early onset of therapeutic effect is desired or required.

Illustratively, the formulation of celecoxib for effective oral administration to a subject has hitherto been complicated by the unique physical and chemical properties of celecoxib, particularly its low solubility and factors associated with its crystal structure, including cohesiveness, low bulk density and low compressibility. Celecoxib is unusually insoluble in aqueous media. Unformulated celecoxib is not readily dissolved and dispersed for rapid absorption in the gastrointestinal tract when administered orally, for example in capsule form. In addition, unformulated celecoxib, which has a crystal morphology that tends to form long cohesive needles, typically fuses into a monolithic mass upon compression in a tableting die. Even when blended with other substances, the celecoxib crystals tend to separate from the

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other substances and agglomerate together during mixing of the composition resulting in a non-uniformly blended composition containing undesirably large aggregates of celecoxib. Therefore, it is difficult to prepare a pharmaceutical composition containing celecoxib that has the desired blend uniformity. Further, handling problems arising for example from the low bulk density of celecoxib are encountered during preparation of celecoxib compositions. Accordingly, a need exists for solutions to numerous problems associated with preparation of compositions and dosage forms comprising celecoxib, particularly orally deliverable dose units.

Further, there exists an especial need for orally deliverable formulations of selective COX-2 inhibitory drugs of low water solubility including celecoxib, such formulations providing more rapid onset of therapeutic effect than the corresponding unformulated drugs or known formulations of these drugs. To the extent that rapid onset of therapeutic effect is related to pharmacokinetic parameters such as a high maximum blood serum concentration of the drug (C_{max}) and a short time from oral administration to reach such maximum blood serum concentration (T_{max}), there is an especial need for orally deliverable formulations of selective COX-2 inhibitory drugs of low water solubility including celecoxib, such formulations providing a greater C_{max} and/or an earlier T_{max} than the corresponding unformulated drugs or known formulations of these drugs.

As indicated hereinbelow, treatment with selective COX-2 inhibitory drugs including celecoxib is indicated or potentially indicated in a very wide array of COX-2 mediated conditions and disorders. It would be of benefit to provide formulations exhibiting pharmacokinetics consistent with rapid onset of therapeutic effect especially for treatment of acute disorders where early relief from pain or other symptoms is desired or required.

Such formulations would represent a significant advance in the treatment of COX-2 mediated conditions and disorders.

Selective COX-2 inhibitory drugs including celecoxib that are of low solubility in water are most conveniently formulated in solid particulate form. The individual or primary particles of the drug can be dispersed in a liquid medium, as in a suspension formulation, or can be aggregated to form secondary particles or granules that can be encapsulated to provide a capsule dosage form, or compressed or molded to provide a tablet dosage form.

Numerous processes are known for preparing drug formulations having primary particle sizes in a desired range, or having a desired mean particle size, or having a particle size distribution characterized by a parameter such as D_{90} , which is defined herein as a linear measure of diameter having a value such that 90% by weight of particles in the formulation, in the longest dimension of the particles, are smaller than that diameter. Other particle size parameters used herein are defined in similar fashion; for example D_{10} , D_{25} and D_{50} parameters relate to linear measures of diameter having values such that 10%, 25% and 50% respectively by weight are smaller than that diameter.

For consistency with prior publications, the terms "microparticle" and "nanoparticle" are defined herein as in U.S. Patent No. 5,384,124 to Courteille *et al.*, to refer to particles having respectively a diameter of about 1 μm to about 2000 μm , and a diameter of less than about 1 μm (1000 nm). The preparation of microparticles and nanoparticles, according to U.S. Patent No. 5,384,124, "is principally used to retard dissolution of active principles". However, U.S. Patent No. 5,145,684 to Liversidge *et al.* discloses nanoparticulate compositions said to provide "unexpectedly high bioavailability" of drugs, particularly drugs having low solubility in a liquid medium such as water. International Publication No. WO 93/25190 provides pharmacokinetic data from a rat study indicating a higher apparent rate of absorption from oral administration of a nanoparticulate (average particle size 240-300 nm) than from oral administration of a microparticulate (particle size range 20-30 μm) dispersion of naproxen.

Numerous processes for preparation of nanoparticulate compositions of therapeutic agents are known. Typically these processes use mechanical means, such as milling, to reduce particle size to a nano (less than 1 μm) range, or precipitate nano-sized particles from solution.

SUMMARY OF THE INVENTION

According to the present invention, a poorly water soluble selective COX-2 inhibitory drug provides more rapid onset of therapeutic effect if, upon oral administration of a composition comprising the drug, the drug exhibits pharmacokinetic properties 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 contemplated that a greater C_{max} and/or a shorter T_{max} are obtained by reduction of size of solid particles comprising the drug such that a substantial portion by weight of the particles are smaller than about 1 μm in diameter, in the longest dimension of the particles. Without being bound by theory, it is believed that the greater C_{max} and/or the shorter T_{max} result from faster dissolution of the drug when particle size is reduced to less than about 1 μm .

Accordingly, there is now provided a pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a selective COX-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in solid particles having a D_{50} particle size of about 0.01 to about 200 μm , a sufficient portion by weight of the particles being smaller than 1 μm to provide a substantially higher C_{max} and/or a substantially shorter T_{max} by comparison with an otherwise similar composition wherein substantially all of the particles are larger than 1 μm .

There is also provided a pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a selective COX-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in solid particles having a D_{50} particle size of about 0.01 to about 200 μm , and wherein about 25% to 100% by weight of the particles are smaller than 1 μm .

The dose units comprising the composition can be in the form of discrete solid articles such as tablets, 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, from which single dose units are measurably removable.

Also provided is a method of treating a medical condition or disorder in a subject where treatment with a COX-2 inhibitor is indicated, comprising orally administering one or more dose units of a composition of the invention one to about six times a day, preferably once or twice a day. 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 presents particle size data for celecoxib dispersions D1-D4 prepared as described in Example 1, as measured by Fraunhofer diffraction.

Fig. 2 shows optical micrographs of samples taken from dispersions D1-D4 under non-polarized (left) and polarized (right) light.

Fig. 3 shows time-course of *in vitro* dissolution of dispersions D1-D4.

Fig. 4 is a schematic representation of apparatus used to perform the *in vitro* dissolution assay of Example 3.

DETAILED DESCRIPTION OF THE INVENTION

Selective COX-2 inhibitory drugs for which the present invention is useful are drugs that inhibit COX-2 to a therapeutically useful degree while causing markedly less inhibition of cyclooxygenase-1 (COX-1) than conventional nonsteroidal anti-inflammatory drugs (NSAIDs).

The invention applies particularly to selective COX-2 inhibitory drugs of low water solubility, especially those having a solubility in distilled water at 25°C lower than about 10 g/l, preferably lower than about 1 g/l.

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 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.

The term "dose unit" herein means a portion of a pharmaceutical composition that contains an amount of a therapeutic agent, in the present case a selective COX-2 inhibitory drug, 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, administered as a single oral administration, provides a sufficient amount of the agent to result in the desired effect.

The term "present in solid particles" as applied to a selective COX-2 inhibitory drug herein encompasses compositions wherein the solid particles consist essentially

of the drug and compositions where the solid particles comprise the drug in intimate mixture with one or more other ingredients. These other ingredients can include one or more therapeutic agents other than the selective COX-2 inhibitory drug and/or one or more pharmaceutically acceptable excipients.

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, storage, disintegration, dispersion, dissolution, release or organoleptic 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 can include, by way of illustration and not limitation, diluents, disintegrants, binding agents, adhesives, wetting agents, lubricants, glidants, substances added to mask or counteract a disagreeable taste or odor, flavors, dyes, fragrances, and substances added to improve appearance of the composition.

The term "substantially homogeneous" with reference to a pharmaceutical composition that comprises several 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.

Compositions of the invention comprise one or more orally deliverable dose units. Each dose unit comprises a selective COX-2 inhibitory drug, illustratively celecoxib, in a therapeutically effective amount that is preferably about 10 mg to about 1000 mg.

It will be understood that a therapeutically effective amount of a selective COX-2 inhibitory drug for a subject is dependent *inter alia* on the body weight of the subject. Where the drug is celecoxib and 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. 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.

For other selective COX-2 inhibitory drugs, an amount of the drug per dose unit can be in a range known to be therapeutically effective for such drugs. Preferably, the amount per dose unit is in a range providing therapeutic equivalence to celecoxib in the dose ranges indicated immediately above.

Dose units of celecoxib compositions of the invention typically contain about 10 mg to about 400 mg of celecoxib, for example, a 10, 20, 37.5, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350 or 400 mg dose of celecoxib. Preferred dose units contain about 25 mg to about 400 mg of celecoxib. More preferred dose units contain about 50 mg to about 200 mg of celecoxib. A particular dose unit can be selected to accommodate the desired frequency of administration used to achieve a specified daily dosage. The amount of the unit dosage form of the composition that is administered and the dosage regimen for treating the condition or disorder will depend on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the condition or disorder, the route and frequency of administration, and the particular selective COX-2 inhibitory drug selected, and thus may vary widely. One or more dose units can be administered up to about 6 times a day. It is contemplated, however, that for most purposes a once-a-day or twice-a-day administration regimen provides the desired therapeutic efficacy.

A composition of the invention preferably contains 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 the selective COX-2 inhibitory drug, alone or in intimate mixture with one or more excipients. The drug is at least partly in nanoparticulate form, *i.e.*, in the form of solid particles of diameter less than 1 μm in the longest dimension of the particles.

The effects on pharmacokinetic properties of reducing particle size from the microparticle range (greater than 1 μm diameter) to the nanoparticle range are generally unpredictable for any particular drug or class of drugs. According to the present invention, for selective COX-2 inhibitory drugs of low water solubility, nanoparticulate compositions exhibit higher C_{max} and/or shorter T_{max} than microparticulate compositions. In one embodiment of the invention, therefore, the percentage by weight of the particles that are nanoparticles is sufficient to provide a substantially higher C_{max} and/or a substantially shorter T_{max} by comparison with an

comparative composition wherein substantially all of the particles are larger than 1 μm . Preferably a composition of this embodiment has a sufficient percentage by weight of nanoparticles to provide a substantially shorter T_{max} , and more preferably a sufficient percentage by weight of nanoparticles to provide both a substantially higher C_{max} and a substantially shorter T_{max} , than the comparative composition.

When administered orally to a fasting adult human, a celecoxib 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 celecoxib 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.

For selective COX-2 inhibitory drugs other than celecoxib, preferred compositions provide a minimum blood serum concentration of the drug that is therapeutically equivalent to the minimum celecoxib concentrations indicated immediately above.

In another embodiment of the invention, the selective COX-2 inhibitory drug, illustratively celecoxib, is present in solid particles having a D_{50} particle size of about 0.01 to about 200 μm , wherein about 25% to 100% by weight of the particles are nanoparticles. Where the percentage by weight of nanoparticles is relatively low, for example about 25% to about 50%, preferably the D_{50} particle size is about 0.01 to about 100 μm , more preferably about 0.01 to about 75 μm , still more preferably about 0.01 to about 40 μm , and even more preferably about 0.01 to about 25 μm . Particle size can vary continuously across the nanoparticulate and microparticulate range, or the composition can have a bimodal or multimodal particle size distribution, with one set of particles having a D_{50} particle size less than 1 μm and another set of particles having a D_{50} particle size substantially greater than 1 μm . It is generally preferred that at least about 50% by weight, and especially preferred that at least about 75% by weight, of the particles are nanoparticles. In one embodiment substantially all of the particles are smaller than 1 μm , i.e., the percentage by weight of nanoparticles is 100% or close to 100%.

Primary particles, generated for example by milling or grinding, or by precipitation from solution, can agglomerate to form secondary aggregate particles. The term "particle size" as used herein refers to size, in the longest dimension, of primary particles, unless the context demands otherwise.

In a preferred embodiment, a composition of the invention has a weight average particle size of about 100 nm to about 1000 nm, more preferably about 100 nm to about 900 nm, for example about 200 nm to about 400 nm, or about 500 nm to about 900 nm. The drug can be in crystalline or amorphous form in the nanoparticles. Processes for preparing nanoparticles that involve milling or grinding typically provide the drug in crystalline form, whereas processes that involve precipitation from solution frequently but not invariably provide the drug partly or wholly in amorphous form.

Compositions of the invention comprise a selective COX-2 inhibitory drug of low water solubility, for example celecoxib, partly or wholly in nanoparticulate form as described above, optionally together with one or more excipients selected from diluents, disintegrants, binding agents, wetting agents and lubricants. In one embodiment, nanoparticles comprising the drug have a surface modifying agent adsorbed on the surface thereof. In another embodiment, nanoparticles of the drug are contained in a matrix formed by a polymer. Preferably at least one of the excipients is a water soluble diluent or wetting agent. Such a water soluble diluent or wetting agent assists in the dispersion and dissolution of the drug when a composition of the invention is ingested. Preferably both a water soluble diluent and a wetting agent are present.

A composition of the invention can be a substantially homogeneous flowable mass such as a particulate or granular solid or a liquid, or it can be in the form of discrete articles such as capsules or tablets each comprising a single dose unit.

In a composition that is a substantially homogeneous flowable mass, single dose units are measurably removable using a suitable volumetric measuring device such as a spoon or cup. Suitable flowable masses include, but are not limited to, powders and granules. Alternatively, the flowable mass can be a suspension having the drug in a solid particulate phase dispersed in a liquid phase, preferably an aqueous phase. At least a portion of the particulate phase is nanoparticulate. In preparing such a suspension, use of a wetting agent such as polysorbate 80 or the like is likely to be

beneficial. A suspension can be prepared by dispersing nanoparticulate or partially nanoparticulate drug in the liquid phase; alternatively the drug can be precipitated from solution in a solvent such as an alcohol, preferably ethanol. The aqueous phase preferably comprises a palatable vehicle such as water, syrup or fruit juice, for example apple juice.

The selective COX-2 inhibitory drug can be any such drug known in the art, including without limitation compounds disclosed in the patents and publications listed below, each of which is individually incorporated herein by reference.

U.S. Patent No. 5,344,991 to Reitz & Li.

U.S. Patent No. 5,380,738 to Norman *et al.*

U.S. Patent No. 5,393,790 to Reitz *et al.*

U.S. Patent No. 5,401,765 to Lee.

U.S. Patent No. 5,418,254 to Huang & Reitz.

U.S. Patent No. 5,420,343 to Koszyk & Weier.

U.S. Patent No. 5,434,178 to Talley & Rogier.

U.S. Patent No. 5,436,265 to Black *et al.*

Above-cited U.S. Patent No. 5,466,823.

U.S. Patent No. 5,474,995 to Ducharme *et al.*

U.S. Patent No. 5,475,018 to Lee & Bertenshaw.

U.S. Patent No. 5,486,534 to Lee *et al.*

U.S. Patent No. 5,510,368 to Lau *et al.*

U.S. Patent No. 5,521,213 to Prasit *et al.*

U.S. Patent No. 5,536,752 to Ducharme *et al.*

U.S. Patent No. 5,543,297 to Cromlish *et al.*

U.S. Patent No. 5,547,975 to Talley *et al.*

U.S. Patent No. 5,550,142 to Ducharme *et al.*

U.S. Patent No. 5,552,422 to Gauthier *et al.*

U.S. Patent No. 5,585,504 to Desmond *et al.*

U.S. Patent No. 5,593,992 to Adams *et al.*

U.S. Patent No. 5,596,008 to Lee.

U.S. Patent No. 5,604,253 to Lau *et al.*

U.S. Patent No. 5,604,260 to Guay & Li.

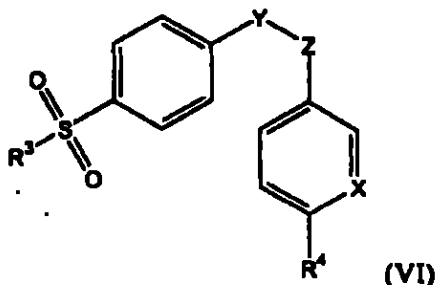
U.S. Patent No. 5,616,458 to Lipsky *et al.*
U.S. Patent No. 5,616,601 to Khanna *et al.*
U.S. Patent No. 5,620,999 to Weier *et al.*
Above-cited U.S. Patent No. 5,633,272.
U.S. Patent No. 5,639,780 to Lau *et al.*
U.S. Patent No. 5,643,933 to Talley *et al.*
U.S. Patent No. 5,658,903 to Adams *et al.*
U.S. Patent No. 5,668,161 to Talley *et al.*
U.S. Patent No. 5,670,510 to Huang & Reitz.
U.S. Patent No. 5,677,318 to Lau.
U.S. Patent No. 5,681,842 to Dellaria & Gane.
U.S. Patent No. 5,686,460 to Nicolai *et al.*
U.S. Patent No. 5,686,470 to Weier *et al.*
U.S. Patent No. 5,696,143 to Talley *et al.*
U.S. Patent No. 5,710,140 to Ducharme *et al.*
U.S. Patent No. 5,716,955 to Adams *et al.*
U.S. Patent No. 5,723,485 to Güngör & Teulon.
U.S. Patent No. 5,739,166 to Reitz *et al.*
U.S. Patent No. 5,741,798 to Lazcr *et al.*
U.S. Patent No. 5,756,499 to Adams *et al.*
U.S. Patent No. 5,756,529 to Isakson & Talley.
U.S. Patent No. 5,776,967 to Krefl *et al.*
U.S. Patent No. 5,783,597 to Beers & Wachter.
U.S. Patent No. 5,789,413 to Black *et al.*
U.S. Patent No. 5,807,873 to Nicolai & Teulon.
U.S. Patent No. 5,817,700 to Dube *et al.*
U.S. Patent No. 5,830,911 to Failli *et al.*
U.S. Patent No. 5,849,943 to Atkinson & Wang.
U.S. Patent No. 5,859,036 to Sartori *et al.*
U.S. Patent No. 5,861,419 to Dube *et al.*
U.S. Patent No. 5,866,596 to Sartori & Teulon.
U.S. Patent No. 5,869,524 to Failli.

U.S. Patent No. 5,869,660 to Adams *et al.*
U.S. Patent No. 5,883,267 to Rossen *et al.*
U.S. Patent No. 5,892,053 to Zhi *et al.*
U.S. Patent No. 5,922,742 to Black *et al.*
U.S. Patent No. 5,929,076 to Adams & Garigipati.
U.S. Patent No. 5,932,598 to Talley *et al.*
U.S. Patent No. 5,935,990 to Khanna *et al.*
U.S. Patent No. 5,945,539 to Haruta *et al.*
U.S. Patent No. 5,958,978 to Yamazaki *et al.*
U.S. Patent No. 5,968,958 to Guay *et al.*
U.S. Patent No. 5,972,950 to Nicolai & Toulon.
U.S. Patent No. 5,973,191 to Marnett & Kalgutkar.
U.S. Patent No. 5,981,576 to Belley *et al.*
U.S. Patent No. 5,994,381 to Haruta *et al.*
U.S. Patent No. 6,002,014 to Haruta *et al.*
U.S. Patent No. 6,004,960 to Li *et al.*
U.S. Patent No. 6,005,000 to Hopper *et al.*
U.S. Patent No. 6,020,343 to Belley *et al.*
U.S. Patent No. 6,020,347 to DeLaszlo & Hagmann.
U.S. Patent No. 6,034,256 to Carter *et al.*
U.S. Patent No. 6,040,319 to Corley *et al.*
U.S. Patent No. 6,040,450 to Davies *et al.*
U.S. Patent No. 6,046,208 to Adams *et al.*
U.S. Patent No. 6,046,217 to Friesen *et al.*
U.S. Patent No. 6,057,319 to Black *et al.*
U.S. Patent No. 6,063,804 to De Nanteuil *et al.*
U.S. Patent No. 6,063,807 to Chabrier de Lassauniere & Broquet.
U.S. Patent No. 6,071,954 to LeBlanc *et al.*
U.S. Patent No. 6,077,868 to Cook *et al.*
U.S. Patent No. 6,077,869 to Sui & Wachter.
U.S. Patent No. 6,083,969 to Ferro *et al.*
U.S. Patent No. 6,096,753 to Spohr *et al.*

U.S. Patent No. 6,133,292 to Wang *et al.*
International Patent Publication No. WO 94/15932.
International Patent Publication No. WO 96/19469.
International Patent Publication No. WO 96/26921.
International Patent Publication No. WO 96/31509.
International Patent Publication No. WO 96/36623.
International Patent Publication No. WO 96/38418.
International Patent Publication No. WO 97/03953.
International Patent Publication No. WO 97/10840.
International Patent Publication No. WO 97/13755.
International Patent Publication No. WO 97/13767.
International Patent Publication No. WO 97/25048.
International Patent Publication No. WO 97/30030.
International Patent Publication No. WO 97/34882.
International Patent Publication No. WO 97/46524.
International Patent Publication No. WO 98/04527.
International Patent Publication No. WO 98/06708.
International Patent Publication No. WO 98/07425.
International Patent Publication No. WO 98/17292.
International Patent Publication No. WO 98/21195.
International Patent Publication No. WO 98/22457.
International Patent Publication No. WO 98/32732.
International Patent Publication No. WO 98/41516.
International Patent Publication No. WO 98/43966.
International Patent Publication No. WO 98/45294.
International Patent Publication No. WO 98/47871.
International Patent Publication No. WO 99/01130.
International Patent Publication No. WO 99/01131.
International Patent Publication No. WO 99/01452.
International Patent Publication No. WO 99/01455.
International Patent Publication No. WO 99/10331.
International Patent Publication No. WO 99/10332.

International Patent Publication No. WO 99/11605.
International Patent Publication No. WO 99/12930.
International Patent Publication No. WO 99/14195.
International Patent Publication No. WO 99/14205.
International Patent Publication No. WO 99/15505.
International Patent Publication No. WO 99/23087.
International Patent Publication No. WO 99/24404.
International Patent Publication No. WO 99/25695.
International Patent Publication No. WO 99/35130.
International Patent Publication No. WO 99/61016.
International Patent Publication No. WO 99/61436.
International Patent Publication No. WO 99/62884.
International Patent Publication No. WO 99/64415.
International Patent Publication No. WO 00/01380.
International Patent Publication No. WO 00/08024.
International Patent Publication No. WO 00/10993.
International Patent Publication No. WO 00/13684.
International Patent Publication No. WO 00/18741.
International Patent Publication No. WO 00/18753.
International Patent Publication No. WO 00/23426.
International Patent Publication No. WO 00/24719.
International Patent Publication No. WO 00/26216.
International Patent Publication No. WO 00/31072.
International Patent Publication No. WO 00/40087.
International Patent Publication No. WO 00/56348.
European Patent Application No. 0 799 823.
European Patent Application No. 0 846 689.
European Patent Application No. 0 863 134.
European Patent Application No. 0 985 666.

Compositions of the invention are especially useful for compounds having the formula (VI):



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^3 where R^3 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups. Preferred such five- to six-membered rings are cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

Illustratively, compositions of the invention are suitable for celecoxib, deracoxib, valdecoxib, rofecoxib, 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, more particularly celecoxib and valdecoxib, and most particularly celecoxib.

The invention is illustrated herein with particular reference to celecoxib, and it will be understood that any other selective COX-2 inhibitory compound of low solubility in water can, if desired, be substituted in whole or in part for celecoxib in compositions herein described.

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, scleroderma, 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, 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 hemangiomas, 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.

For treatment of rheumatoid arthritis or osteoarthritis, compositions of the invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, still more preferably about 175 mg to about 400 mg, for example about 200 mg. A daily dose of celecoxib of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 8 mg/kg body weight, more preferably about 2 to about 6.7 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for example about 2.7 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to about four doses per day, preferably one or two doses per day.

For treatment of Alzheimer's disease or cancer, compositions of the invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 800 mg, more preferably about 150 mg to about 600 mg, and still more preferably about 175 mg to about 400 mg, for example about 400 mg. A daily dose of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 10.7 mg/kg body weight, more preferably about 2 to about 8 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for example about 5.3 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to about four doses per day, preferably one or two doses per day.

For pain management, compositions of the invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, and still more preferably about 175 mg to about 400 mg, for example about 200 mg. A daily dose of celecoxib of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 8 mg/kg body weight, more preferably about 2 to about 6.7 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for example about 2.7 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to about four doses per day. Administration at a rate of one 50 mg dose unit four times a day, one 100 mg dose unit or two 50 mg dose units twice a day or one 200 mg dose unit, two 100 mg dose units or four 50 mg dose units once a day is preferred.

For selective COX-2 inhibitory drugs other than celecoxib, appropriate doses can be selected by reference to the patent literature cited hereinabove.

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.

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

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invention with one or more compounds selected from aceclofenac, acemetacin, *e*-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid (aspirin), *S*-adenosylmethionine, alclofenac, alfenitanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylol, 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, dexoadrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenazole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodcinone 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

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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, parsalimide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenylamidol, piketoprofen, piminodine, pipebuzone, piperlyone, pirofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanyl, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide *o*-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanyl, 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.

Nanoparticles comprising or consisting essentially of a selective COX-2 inhibitory drug of low water solubility can be prepared according to any process

previously applied to preparation of other poorly water soluble drugs in nanoparticulate form. Suitable processes, without restriction, are illustratively disclosed for such other drugs in patents and publications listed below and incorporated herein by reference.

U.S. Patent No. 4,826,689 to Violante & Fischer.

Above-cited U.S. Patent No. 5,145,684.

U.S. Patent No. 5,298,262 to Na & Rajagopalan.

U.S. Patent No. 5,302,401 to Liversidge *et al.*

U.S. Patent No. 5,336,507 to Na & Rajagopalan.

U.S. Patent No. 5,340,564 to Illig & Sarpotdar.

U.S. Patent No. 5,346,702 to Na & Rajagopalan.

U.S. Patent No. 5,352,459 to Hollister *et al.*

U.S. Patent No. 5,354,560 to Lovreccich.

Above-cited U.S. Patent No. 5,384,124.

U.S. Patent No. 5,429,824 to Junc.

U.S. Patent No. 5,503,723 to Ruddy *et al.*

U.S. Patent No. 5,510,118 to Bosch *et al.*

U.S. Patent No. 5,518,187 to Bruno *et al.*

U.S. Patent No. 5,518,738 to Eickhoff *et al.*

U.S. Patent No. 5,534,270 to De Castro.

U.S. Patent No. 5,536,508 to Canal *et al.*

U.S. Patent No. 5,552,160 to Liversidge *et al.*

U.S. Patent No. 5,560,931 to Eickhoff *et al.*

U.S. Patent No. 5,560,932 to Bagchi *et al.*

U.S. Patent No. 5,565,188 to Wong *et al.*

U.S. Patent No. 5,569,448 to Wong *et al.*

U.S. Patent No. 5,571,536 to Eickhoff *et al.*

U.S. Patent No. 5,573,783 to Desieno & Stetsko.

U.S. Patent No. 5,580,579 to Ruddy *et al.*

U.S. Patent No. 5,585,108 to Ruddy *et al.*

U.S. Patent No. 5,587,143 to Wong.

U.S. Patent No. 5,591,456 to Franson *et al.*

U.S. Patent No. 5,622,938 to Wong.

U.S. Patent No. 5,662,883 to Bagchi *et al.*

U.S. Patent No. 5,665,331 to Bagchi *et al.*

U.S. Patent No. 5,718,919 to Ruddy *et al.*

U.S. Patent No. 5,747,001 to Wiedmann *et al.*

Above-cited International Patent Publication No. WO 93/25190.

International Patent Publication No. WO 96/24336.

International Patent Publication No. WO 97/14407.

International Patent Publication No. WO 98/35666.

International Patent Publication No. WO 99/65469.

International Patent Publication No. WO 00/18374.

International Patent Publication No. WO 00/27369.

International Patent Publication No. WO 00/30615.

One of ordinary skill in the art will readily adapt the processes therein described to preparation of a poorly water soluble selective COX-2 inhibitory drug in nanoparticulate form.

In one embodiment of the invention, nanoparticles of a selective COX-2 inhibitory drug are prepared by a milling process, preferably a wet milling process in presence of a surface modifying agent that inhibits aggregation and/or crystal growth of nanoparticles once created. In another embodiment of the invention, nanoparticles of a selective COX-2 inhibitory drug are prepared by a precipitation process, preferably a process of precipitation in an aqueous medium from a solution of the drug in a non-aqueous solvent. The non-aqueous solvent can be a liquefied, *e.g.*, supercritical, gas under pressure. Illustrative examples of these and other processes for preparing nanoparticles of a selective COX-2 inhibitory drug are presented with greater particularity below.

In one particular embodiment of the invention, nanoparticles are prepared by a process comprising the steps of (a) dispersing a selective COX-2 inhibitory drug and a surface modifying agent in a liquid dispersion medium; and (b) wet milling the resulting drug dispersion in presence of grinding media to result in crystalline nanoparticles of the drug having the surface modifying agent adsorbed on the surface thereof in an amount sufficient to maintain a weight average particle size of less than about 400 nm, substantially as disclosed in above-cited U.S. Patent No. 5,145,684.

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The surface modifying agent inhibits aggregation of the nanoparticles and can be any of various polymers, low molecular weight oligomers, natural products, surfactants, etc. The nanoparticles in this and related embodiments are referred to herein as being composed of a nanocrystalline drug/surface modifier complex.

In a related embodiment of the invention, a nanocrystalline drug/surface modifier complex prepared as described above comprises a purified surface modifying agent, for example a purified polymeric surfactant, to prevent particle aggregation during a subsequent sterilization step, substantially as disclosed in above-cited U.S. Patent No. 5,352,459.

In another related embodiment of the invention, a nanocrystalline drug/surface modifier complex prepared as described above comprises as a surface modifying agent the surfactant *p*-isononylphenoxypoly(glycidol), substantially as disclosed in above-cited U.S. Patent No. 5,340,564.

In another related embodiment of the invention, a nanocrystalline drug/surface modifier complex prepared as described above is associated with an anionic or cationic cloud point modifier to increase the cloud point of the surface modifying agent, substantially as described in above-cited U.S. Patents No. 5,298,262 (cationic or anionic surfactant as cloud point modifier), No. 5,336,507 (charged phospholipid as cloud point modifier), or No. 5,346,702 (non-ionic cloud point modifier).

In another related embodiment of the invention, a nanocrystalline drug/surface modifier complex prepared as described above further comprises a cryoprotectant, for example a carbohydrate or sugar alcohol, in an amount sufficient to permit the nanoparticles to be lyophilized, substantially as described in above-cited U.S. Patent No. 5,302,401. A preferred cryoprotectant of this embodiment is sucrose. The method of making nanoparticles having a surface modifier adsorbed on the surface thereof and a cryoprotectant associated therewith comprises contacting the nanoparticles with the cryoprotectant for a time and under conditions sufficient to permit lyophilization of the nanoparticles.

In another related embodiment of the invention, nanoparticulate drug particles having a surface modifying agent adsorbed on the surface thereof in an amount sufficient to maintain a weight average particle size of less than about 400 nm are prepared by a process comprising the steps of (a) dispersing the drug in a liquid dispersion medium wherein the drug is insoluble; and (b) grinding the medium (e.g.,

in a dispersion mill) in the presence of rigid grinding media, wherein pH of the medium is maintained within a range of about 2 to about 6, substantially as disclosed in above-cited U.S. Patent No. 5,552,160.

In another related embodiment of the invention, nanoparticles are prepared by a process comprising the steps of (a) providing a selective COX-2 inhibitory drug substance; (b) depyrogenating rigid grinding media, for example in an oven at about 200°C to about 300°C for about 6 to about 20 hours; mixing the drug substance and grinding media together and autoclaving at about 100°C to about 150°C for about 10 to about 60 minutes; and (c) adding a surface modifying agent (*e.g.*, selected from polymers, low molecular weight oligomers, natural products and surfactants) to the resulting autoclaved drug substance followed by wet grinding to provide and maintain a weight average particle size of less than about 400 nm, substantially as disclosed in above-cited U.S. Patent No. 5,534,270.

In another related embodiment of the invention, nanoparticles are prepared by a process comprising contacting a selective COX-2 inhibitory drug with a surface modifying agent (*e.g.*, by adding the drug to a liquid medium comprising the surface modifying agent and wet grinding in a dispersion mill) for a time and under conditions sufficient to provide and maintain a weight average particle size of less than about 400 nm, substantially as described in above-cited U.S. Patent No. 5,429,824. In this embodiment the surface modifying agent is a nonionic liquid polymer of the alkylaryl polyether alcohol type, for example tyloxapol. Optionally an additional surface modifying agent can be present.

In another related embodiment of the invention, nanoparticles are prepared by a process comprising the steps of (a) forming a premix of a selective COX-2 inhibitory drug and a surface modifier (*e.g.*, selected from polymers, low molecular weight oligomers, surfactants, *etc.*) in a liquid dispersion medium (*e.g.*, water, salt solution, ethanol, *etc.*); (b) transferring the premix to a microfluidizer having an interaction chamber capable of producing shear, impact, cavitation and attrition forces; (c) subjecting the premix to these forces at a temperature not exceeding about 40°C and a fluid pressure of about 20,000 to about 200,000 kPa by passing the premix through the interaction chamber to reduce the particle size of the drug and to obtain a homogeneous slurry thereof; (d) collecting the slurry from the interaction chamber into a receiving tank; (e) reintroducing the slurry into the interaction chamber to

further reduce particle size; and (f) repeating the collection and reintroduction steps until the weight average particle size of the drug is less than about 400 nm, substantially as disclosed in above-cited U.S. Patent No. 5,510,118.

In another related embodiment of the invention, nanoparticles are prepared by a process comprising the steps of (a) milling (e.g., in a dispersion mill), optionally in the presence of an oil, a selective COX-2 inhibitory drug in the presence of surface modifying agents (e.g., gelatin, casein, lecithin, polyvinylpyrrolidone, tyloxapol, poloxamers, other block polymers, etc.) substantially as disclosed in above-cited U.S. Patent No. 5,560,931. In this embodiment, the drug particles have a non-crosslinked modifier adsorbed on the surface thereof, and are suspended in an aqueous phase which is emulsified in a continuous oil phase. Weight average particle size is less than about 1000 nm. The oil phase can be oleic acid, as disclosed in above-cited U.S. Patent No. 5,571,536.

In another related embodiment of the invention, nanoparticles are prepared by a process comprising the steps of (a) introducing a selective COX-2 inhibitory drug, a liquid medium, grinding media and a surface modifying agent into a grinding vessel; and (b) wet grinding to reduce the weight average particle size of the drug to less than about 1000 nm, substantially as disclosed in above-cited U.S. Patents No. 5,565,188 (block copolymer as surface modifying agent containing one or more polyoxyethylene blocks and one or more polyoxy(higher alkylene) blocks wherein at least some of the blocks are linked together by an oxymethylene linking group) and No. 5,587,143 (block copolymer of ethylene oxide and butylene oxide as surface modifying agent).

In another related embodiment of the invention, a composition is provided comprising nanoparticulate selective COX-2 inhibitory drug particles having a block copolymer linked to at least one anionic group as a surface modifying agent adsorbed on the surface thereof. The composition is prepared by a process comprising the steps of (a) preparing the drug in particulate form, preferably at a particle size less than about 100 μm ; (b) adding the drug to a liquid medium in which it is essentially insoluble to form a premix; and (c) subjecting the premix to mechanical means to reduce the average particle size in the premix to less than about 1000 nm, substantially as disclosed in above-cited U.S. Patent No. 5,569,448. Preferably, the surface modifying agent is present in the premix.

In another related embodiment of the invention, nanoparticles are prepared by a process comprising the steps of (a) adding a selective COX-2 inhibitory drug and a surface modifying agent (*e.g.*, a steric stabilizer such as gelatin, casein, lecithin, gum acacia, cholesterol, tragacanth, sorbitan esters, polyethylene glycol, polyoxyethylene alkyl esters, polyoxyethylene stearates, *etc.*) to a liquid in which the drug is insoluble to form a premix, and (b) subjecting the premix to mechanical means (*e.g.*, in a dispersion mill) to reduce average particle size to less than about 400 nm, substantially as disclosed in above-cited U.S. Patent No. 5,573,783.

In another related embodiment of the invention, nanoparticles are prepared by a process comprising the steps of (a) dispersing a selective COX-2 inhibitory drug and a surface active agent (*e.g.*, poloxamers having a molecular weight of about 1,000 to about 15,000 daltons, polyvinyl alcohol, polyvinylpyrrolidone, hydroxypropylmethylcellulose, and polyoxyethylene sorbitan monoolcate) in a liquid dispersion medium in which the drug is poorly soluble, then applying mechanical means (*e.g.*, in a dispersion mill) to reduce drug particle size to less than about 400 nm, substantially as disclosed in above-cited U.S. Patent No. 5,585,108.

In another related embodiment of the invention, nanoparticles are prepared by a process comprising the steps of (a) adding a selective COX-2 inhibitory drug and hydroxypropylcellulose as a surface modifying agent to a liquid medium in which the drug is essentially insoluble to form a premix, and employing mechanical means (*e.g.*, in a dispersion mill) to reduce drug particle size to less than about 1000 nm, preferably less than about 400 nm, substantially as disclosed in above-cited U.S. Patent No. 5,591,456.

In another related embodiment of the invention, nanoparticles are prepared by a process as described herein that employs a surface modifying agent, the surface modifying agent being selected such that the resulting composition has a hydrophilic-lipophile balance (HLB) of about 4 to about 9, substantially as disclosed in above-cited International Patent Publication No. WO 00/30615.

In another particular embodiment of the invention, nanoparticles are prepared by a process comprising the steps of (a) mixing a selective COX-2 inhibitory drug with a support material, preferably a crosslinked, water-swellaable polymer; (b) grinding the resulting mixture in a grinding chamber which is saturated with a solvent vapor (*e.g.*, water, ethanol, isopropanol, chloroform, methanol, *etc.*); (c) drying the

ground mixture under vacuum; and (d) sieving the dried ground mixture to eliminate any aggregates formed, substantially as disclosed in above-cited U.S. Patent No. 5,354,560.

In another particular embodiment of the invention, nanoparticles are prepared by a process comprising the steps of (a) forming a paste comprising (i) nanoparticles of a selective COX-2 inhibitory drug, (ii) at least one thickening or binding agent (e.g., selected from polypeptides, high molecular weight polymers, colloids, *etc.*) and/or extender, (iii) one or more stabilizing agents to prevent settling and/or rising to the surface of the nanoparticles, and (iv) a suitable amount of water to adjust viscosity; and (b) lyophilizing the paste, substantially as disclosed in above-cited U.S. Patent No. 5,384,124.

In another particular embodiment of the invention, nanoparticles are prepared by a process comprising the steps of (a) preparing a selective COX-2 inhibitory drug in particulate form, preferably at a particle size smaller than about 100 μm ; (b) adding the prepared drug to a liquid medium (preferably comprising a surface modifying agent such as a hygroscopic sugar) in which the drug is essentially insoluble to form a premix; and (c) subjecting the premix to mechanical means to reduce the average particle size in the premix to less than about 1000 nm, substantially as disclosed in above-cited U.S. Patent No. 5,518,738. Preferably, polyvinylpyrrolidone and/or a wetting agent, e.g., sodium lauryl sulfate, are also present in the premix. Compositions prepared by this process preferably have a film adsorbed on the surface of the nanoparticles comprising a polyvinylpyrrolidone, a hygroscopic sugar and sodium lauryl sulfate.

In another particular embodiment of the invention, nanoparticles are prepared by a process comprising the steps of (a) co-solubilizing one or more polymeric constituents including, for example, a biodegradable polymer (e.g., polylactic acid, polyglycolic acid or co-polymers thereof, polyhydroxybutyric acid, polycaprolactone, polyorthoesters, *etc.*), a polysaccharide jellifying and/or bioadhesive polymer, and/or an amphiphilic polymer (e.g. polyethylene glycol, polyvinylpyrrolidone or polyvinyl alcohol) together with an agent modifying interface properties to form a polymer mixture, optionally in the presence of one or more solvents; (b) dissolving or suspending a selective COX-2 inhibitory drug in the polymer mixture; and (c) forming particles consisting of the polymers, the agent modifying the interface

properties and the drug by a technique of emulsion, extrusion, spray drying or spray congealing, substantially as disclosed in above-cited U.S. Patent No. 5,536,508. Nanoparticles prepared by this process preferably have a weight average particle size of about 0.1 μm to about 150 μm .

In another particular embodiment of the invention, nanoparticles are prepared by a process comprising the steps of (a) preparing a solution of a selective COX-2 inhibitory drug in a water-miscible organic solvent; (b) infusing an aqueous precipitating liquid (e.g., water, solution of mineral salt, or surfactant solution) into the solution to produce a suspension of precipitated, amorphous, solid drug in the form of non-aggregated particles; and (c) separating the particles from the precipitating liquid and washing in an aqueous washing liquid, substantially as disclosed in above-cited U.S. Patent No. 4,826,689.

In another particular embodiment of the invention, nanoparticles are prepared by a process comprising the steps of (a) dissolving a selective COX-2 inhibitory drug in an aqueous base (e.g., NaOH, KOH, CsOH, etc.) with stirring to form a solution; (b) adding a surface modifier (e.g., various polymers, surfactants, low molecular weight oligomers, etc.) to form a clear solution; and (c) neutralizing the clear solution with stirring and with an appropriate acid solution (e.g., HCl, HNO₃, HClO₄, H₂SO₄, formic acid, propionic acid, acetic acid, butyric acid, etc.), substantially as disclosed in above-cited U.S. Patents No. 5,560,932 and No. 5,580,579.

In another related embodiment of the invention, nanoparticles are prepared by a process comprising the steps of (a) dissolving a selective COX-2 inhibitory drug in a liquid medium base (e.g., NaOH, KOH, CsOH, trialkylamines, pyridine, etc.) comprising a non-toxic solvent in which the drug is poorly soluble to form a solution; (b) adding an aqueous solution of one or more surface modifying agents (e.g., anionic or nonionic surfactants, polymeric or oligomeric substances); and (c) neutralizing the resulting alkaline solution with an acid (e.g., HCl, HNO₃, HClO₄, H₂SO₄, formic acid, propionic acid, acetic acid, butyric acid, etc.), to form a dispersion, preferably having a Z-average particle diameter of less than about 100 nm as measured by photon correlation spectroscopy, substantially as disclosed in above-cited U.S. Patent No. 5,662,883.

In another related embodiment of the invention, nanoparticles are prepared by a process comprising the steps of (a) dissolving a selective COX-2 inhibitory drug and

a crystal growth modifier (*i.e.*, a compound that is substantially isostructural to the drug) in an aqueous base (*e.g.*, NaOH, KOH, CsOH, trialkylamines, pyridine, *etc.*) to form a solution; (b) adding an aqueous solution of one or more surface modifying agents (*e.g.*, a mixture of anionic surfactant, nonionic surfactant, polymeric substance and oligomeric substance); and neutralizing the resulting alkaline solution with an acid (*e.g.*, HCl, HNO₃, HClO₄, H₂SO₄, formic acid, propionic acid, acetic acid, butyric acid, *etc.*), to form a dispersion, preferably wherein the drug particles have a Z-average particle diameter of less than about 400 nm as measured by photon correlation spectroscopy, substantially as disclosed in above-cited U.S. Patent No. 5,665,331.

In another particular embodiment of the invention, nanoparticles having a weight average particle size of less than about 400 nm are prepared from a dispersion comprising a first particle distribution of a selective COX-2 inhibitory drug together with a surface modifying agent such as polysulfated tyloxapol by a process comprising the steps of (a) placing the dispersion between a first electrode and a second electrode; and (b) removing a portion of the dispersion at a position between the first electrode and the second electrode, this portion of the dispersion having a second particle size distribution that is smaller than the first particle distribution, substantially as disclosed in above-cited U.S. Patent No. 5,503,723.

In another particular embodiment of the invention, nanoparticles having a weight average particle size of up to about 300 nm are prepared by a process comprising the steps of (a) dissolving a selective COX-2 inhibitory drug in a solvent to form a solution; and (b) spraying the solution into a liquefied gas or supercritical fluid in presence of a surface modifying agent dispersed or dissolved in an aqueous phase, substantially as disclosed in above-cited International Patent Publication No. WO 97/14407.

In another related embodiment of the invention, nanoparticles having a weight average particle size of up to about 300 nm are prepared by a process comprising the steps of (a) dissolving a selective COX-2 inhibitory drug in a liquefied gas or supercritical fluid to form a solution; (b) preparing an aqueous phase containing a surface modifying agent; and (c) spraying the solution into the aqueous phase, substantially as disclosed in the same above-cited International Patent Publication No. WO 97/14407.

WO 01/41768

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In another related embodiment of the invention, nanoparticles are prepared by a process comprising the steps of (a) dissolving a selective COX-2 inhibitory drug and a surface modifying agent in a liquefied gas or supercritical fluid to form a solution; and (b) expanding the solution into an aqueous medium, substantially as disclosed in above-cited International Patent Publication No. WO 99/13755.

Excipients included in a composition of the invention can be solids or liquids or both. Compositions of the invention containing excipients can be prepared by any technique of pharmacy that comprises admixing the excipients with a selective COX-2 inhibitory drug that has been at least partially pre-prepared, optionally together with one or more excipients, in nanoparticulate form as indicated above.

Compositions suitable for buccal or sublingual administration include, for example, lozenges comprising the selective COX-2 inhibitory drug in a flavored base, such as sucrose and acacia or tragacanth, and pastilles comprising the drug in an inert base such as gelatin and glycerin or sucrose and acacia.

Liquid dosage forms for oral administration include pharmaceutically acceptable suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise, for example, wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Solid unit dosage forms for oral administration contain the selective COX-2 inhibitory drug in nanoparticulate form together with excipients and are most conveniently formulated 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., Celnab™ 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.,

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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., Vcogum™ 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

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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 selective COX-2 inhibitory drug 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 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 behenate (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.

In one embodiment of the invention, the composition is in the form of unit dose capsules or tablets and comprises a partially or wholly nanoparticulate selective COX-2 inhibitor, illustratively celecoxib, in a desired amount together with one or more excipients selected from the group consisting of pharmaceutically acceptable diluents, disintegrants, binding agents, wetting agents and lubricants. More preferably, the composition comprises one or more excipients selected from the group consisting of lactose (most preferably lactose monohydrate), sodium lauryl sulfate, polyvinylpyrrolidone, croscarmellose sodium, magnesium stearate and microcrystalline cellulose. Still more preferably, the composition comprises lactose monohydrate and croscarmellose sodium. Even more preferably, such a composition further comprises one or more of the carrier materials sodium lauryl sulfate, magnesium stearate and microcrystalline cellulose.

Excipients for capsule and 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.

Illustratively for tablet formulations, a complete blend of ingredients in an amount sufficient to make a uniform batch of tablets is subjected to tableting in a conventional production scale tableting machine at normal compression pressure (for example, applying a force of about 1 kN to about 50 kN in a typical tableting die). Any tablet hardness convenient with respect to handling, manufacture, storage and

ingestion can be obtained. For 100 mg tablets, hardness is preferably at least 4 kP, more preferably at least about 5 kP, and still more preferably at least about 6 kP. For 200 mg tablets, hardness is preferably at least 7 kP, more preferably at least about 9 kP, and still more preferably at least about 11 kP. The mixture, however, is not to be compressed to such a degree that there is subsequent difficulty in achieving hydration when exposed to gastric fluid.

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

Wet granulation, dry granulation or direct compression or encapsulation methods can be employed to prepare tablet or capsule compositions of the invention.

Although unit dose capsule and tablet compositions of the invention can be prepared, for example, by direct encapsulation or direct compression, they are preferably wet granulated prior to encapsulation or compression. Wet granulation, among other effects, densifies milled compositions resulting in improved flow properties, improved compression characteristics and easier metering or weight dispensing of the compositions for encapsulation or tableting. The secondary particle size resulting from granulation (i.e., granule size) is not narrowly critical, it being important only that the average granule size preferably is such as to allow for convenient handling and processing and, for tablets, to permit the formation of a directly compressible mixture that forms pharmaceutically acceptable tablets.

In an illustrative wet granulation process, any portion of the drug that is not to be included in nanoparticulate form (if desired, together with one or more carrier materials) is initially milled or micronized to a desired range of particle sizes greater than 1 μm . Although various conventional mills or grinders can be used, impact milling such as pin milling of the drug provides improved blend uniformity to the final composition relative to other types of milling. Cooling of the material being milled, for example, using liquid nitrogen, may be necessary during milling to avoid heating the drug to undesirable temperatures. The D_{90} particle size during this milling step is preferably reduced to less than about 25 μm .

The milled or micronized drug, if any, is then blended with the desired amount of nanoparticulate drug, prepared as indicated hereinabove to provide a partially or wholly nanoparticulate drug substance. Simultaneously or thereafter, the drug substance is blended, for example in a high shear mixer/granulator, planetary mixer,

twin-shell blender or sigma mixer, with one or more excipients, including excipients that have been milled together with the celecoxib or are present in the nanoparticles, to form a dry powder mixture. Typically, the drug substance is blended with one or more diluent(s), disintegrant(s) and/or binding agent(s) and, optionally, one or more wetting agent(s) in this step, but alternatively all or a portion of one or more of the excipients can be added in a later step. For example, in tablet formulations where croscarmellose sodium is employed as a disintegrant, it has been discovered that addition of a portion of the croscarmellose sodium during the blending step (providing intragranular croscarmellose sodium) and addition of the remaining portion after the drying step discussed below (providing extragranular croscarmellose sodium) can improve disintegration of the tablets produced. In this situation, preferably about 60% to about 75% of the croscarmellose sodium is added intragranularly and about 25% to about 40% of the croscarmellose sodium is added extragranularly. Similarly, for tablet formulations it has been discovered that addition of microcrystalline cellulose after the drying step below (extragranular microcrystalline cellulose) can improve compressibility of the granules and hardness of tablets prepared from the granules.

This blending step of the process preferably comprises blending of drug substance, lactose, polyvinylpyrrolidone and croscarmellose sodium. It has been discovered that a blending time as short as three minutes can provide a dry powder mixture having a sufficiently uniform distribution of the drug to provide a commercially acceptable tablet.

Water, preferably purified water, is then added to the dry powder mixture and the mixture is blended for an additional period of time, to form a wet granulated mixture. Preferably a wetting agent is used, and this is preferably first added to the water and mixed for at least 15 minutes, preferably at least 20 minutes, prior to adding the water to the dry powder mixture. The water can be added to the mixture at once, gradually over a period of time, or in several portions over a period of time. The water is preferably added gradually over a period of time. Alternatively, the wetting agent can be added to the dry powder mixture and water can then be added to the resulting mixture. An additional period of mixing after water addition is complete is preferred to ensure uniform distribution of water in the mixture.

The wet granulated mixture is preferably then wet milled, for example with a screening mill, to eliminate large agglomerates of material that form as a by-product

of the wet granulation operation. If not removed, these agglomerates would prolong the subsequent drying operation and increase variation with respect to moisture control.

The wet granulated or wet milled mixture is then dried, for example, in an oven or a fluid bed dryer, preferably a fluid bed dryer, to form dry granules. If desired, the wet granulated mixture can be extruded or spheronized prior to drying. For the drying process, conditions such as inlet air temperature and drying time are adjusted to achieve the desired moisture content for the dry granules. It may be desirable to combine two or more granulation sections for this drying step and subsequent processing steps.

To the extent necessary, the dry granules are then reduced in size in preparation for compression or encapsulation. Conventional particle size reduction equipment such as oscillators or impact mills (such as Fitz mills) can be employed.

A slight decrease in granule size has been observed as mixing time increases for mixtures containing lower water amounts. It is hypothesized that where water concentration is too low to fully activate the binding agent employed, cohesive forces between the primary particles within the granules are insufficient to survive the shearing forces generated by the mixing blades and granule size attrition rather than growth occurs. Conversely, increasing the amount of water to fully activate the binding agent allows cohesive forces between the primary particles to survive the shearing forces generated by the mixing blades and granule growth rather than attrition occurs with increased mixing time and/or water addition rate. Variation of the screen size of the wet mill tends to have a greater impact on the granule size than variation of the feed rate and/or mill speed.

The dry granules are then placed in a suitable blender, such as a twin-shell blender, and optionally a lubricant (such as magnesium stearate) and any additional carrier materials are added (such as extragranular microcrystalline cellulose and/or extragranular croscarmellose sodium in certain tablet formulations) to form a final blended mixture. Where the diluents include microcrystalline cellulose, the addition of a portion of the microcrystalline cellulose during this step has been found to materially increase granule compressibility and tablet hardness. However, increasing the amount of magnesium stearate above about 1% to about 2% tends to decrease tablet hardness and increase friability and dissolution time.

This final blended mixture is then encapsulated (or, if tablets are to be prepared, compressed into tablets of the desired weight and hardness using appropriately sized tooling). Conventional compression and encapsulation techniques known in the art can be employed. Suitable results are obtained for capsules by employing bed heights ranging from about 20 mm to about 60 mm, compaction settings ranging from about 0 to about 5 mm, and speeds from about 60,000 capsules per hour to about 130,000 capsules per hour. Slug formation can be minimized or eliminated by using the lowest compaction setting at which capsule weight control can be maintained. Where coated tablets are desired, conventional coating techniques known in the art can be employed.

This combination of operations produces granules that are uniform in drug content at the unit dose level, that readily disintegrate, that flow with sufficient ease so that weight variation can be reliably controlled during capsule filling or tableting, and that are dense enough in bulk so that the batch can be processed in the selected equipment and individual doses fit into the specified capsules or tablet dies.

The present invention is also directed to use of compositions of the invention in preparation of medicaments useful in treatment and/or prophylaxis of COX-2 mediated conditions and disorders, in particular such conditions and disorders where rapid onset of therapeutic effect is desired or required.

DESCRIPTION OF A PARTICULARLY PREFERRED EMBODIMENT

Patent and other literature relating to nanoparticulate drug compositions teaches that, in general, the smaller the drug particle size, the greater is the advantage in speed of onset of therapeutic effect, or other pharmacodynamic benefit, obtained upon oral administration. For example, at least the following patents propose reduction of particle size to about 400 nm or smaller.

Above-cited U.S. Patent No. 5,145,684.

Above-cited U.S. Patent No. 5,298,262.

Above-cited U.S. Patent No. 5,302,401.

Above-cited U.S. Patent No. 5,336,507.

Above-cited U.S. Patent No. 5,340,564.

Above-cited U.S. Patent No. 5,346,702.

Above-cited U.S. Patent No. 5,352,459.

Above-cited U.S. Patent No. 5,429,824.

Above-cited U.S. Patent No. 5,503,723.

Above-cited U.S. Patent No. 5,510,118.

Above-cited U.S. Patent No. 5,534,270.

Above-cited U.S. Patent No. 5,552,160.

Above-cited U.S. Patent No. 5,573,783.

Above-cited U.S. Patent No. 5,585,108.

Above-cited U.S. Patent No. 5,591,456.

Above-cited U.S. Patent No. 5,662,883.

Above-cited U.S. Patent No. 5,665,331.

In general, however, the smaller the drug particle size, the more grinding or milling time, energy and labor is required to produce the particles and consequently, the more costly and less efficient is the process. Thus, smaller nano-sized drug particles are generally significantly more expensive and labor-intensive to produce in quantity than larger nano-sized drug particles.

Surprisingly, we have now discovered that a selective COX-2 inhibitory drug composition having a weight average particle size of about 450 nm to about 1000 nm (referred to herein as a "sub-micron" formulation and particle size) exhibits onset time and bioavailability substantially equal to that of a comparative composition having a weight average particle size of about 200 to about 400 nm, as measured *in vitro* and *in vivo*. The sub-micron formulation requires less milling time and energy than the formulation comprising smaller nanoparticles with a weight average particle size in the 200-400 nm range.

It is further contemplated that certain advantages in addition to cost saving are obtainable with sub-micron as opposed to smaller particle sizes. For example, in situations where ultra-fine particles tend to agglomerate or fail to disperse in the gastrointestinal fluid, the slightly larger sub-micron particles can exhibit enhanced dispersion.

Accordingly, in a particularly preferred embodiment of the present invention, there is provided a pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a selective COX-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in solid particles having a D_{50} particle size of about 450 nm to about 1000 nm, and more

preferably about 500 nm to about 900 nm, the composition providing at least a substantially similar C_{max} and/or at most a substantially similar T_{max} by comparison with an otherwise similar composition having a D_{50} particle size of less than 400 nm, and/or providing a substantially greater C_{max} and/or a substantially shorter T_{max} by comparison with an otherwise similar composition having a D_{50} particle size larger than 1000 nm.

There is also provided a pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a selective COX-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in solid particles, about 25% to 100% by weight of which have a particle size of about 450 nm to about 1000 nm, more preferably about 500 nm to about 900 nm.

There is also provided a pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a selective COX-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in solid particles having a weight average particle size of about 450 nm to about 1000 nm, and more preferably about 500 nm to about 900 nm, the composition providing at least a substantially similar C_{max} and/or at most a substantially similar T_{max} by comparison with an otherwise similar composition having a weight average particle size of less than 400 nm, and/or providing a substantially greater C_{max} and/or a substantially shorter T_{max} by comparison with an otherwise similar composition having a weight average particle size larger than 1000 nm. For purposes of this description, "weight average particle size" can be considered synonymous with D_{50} particle size.

Sub-micron particles of a selective COX-2 inhibitory drug can be prepared by modification of processes described hereinabove for preparation of nanoparticles, or by a process as illustratively set forth in Example 1 below.

EXAMPLES

Example 1

Dispersions D1-D4 containing 5% by weight celecoxib were prepared by the process described below. The dispersions differed only in the particle size range of the celecoxib.

1. Celecoxib was micronized in an air jet mill to form a drug powder.

2. The drug powder was added to an aqueous solution containing 2.5% low viscosity hydroxypropylcellulose (HPC-SL) and 0.12% sodium dodecyl sulfate, to form a suspension.
3. The suspension was wet milled to form an intermediate dispersion according to the following protocol. A sample amount of 6.0 ml of the suspension (containing 20% celecoxib), a magnetic stir bar, 8 ml of lead-free glass beads, and 50 μ l of antifoaming agent (Sigma Antifoam A Concentrate) were added to a 20 ml scintillation vial. To provide an intermediate dispersion having a target particle size range of 6-7 μ m (i.e., the size range achieved in the micronizing step, used to provide a comparative composition), the vial was shaken for two minutes. To provide intermediate dispersions having smaller target particle size ranges, the vial was suspended over a high-strength rotating magnet so that milling occurred by agitation of the glass beads by rotation of the magnetic stir bar. Target particle size ranges were varied by controlling magnet rotation rate, milling time and/or bead size, as shown in Table 1. Small aliquots were removed at intervals in order to monitor progress of particle size reduction.
4. The resulting intermediate dispersion in each case was transferred to a larger vial and diluted with fresh vehicle to form a final dispersion. Nominal celecoxib concentration in the final dispersions was 5% by weight.

Table 1. Milling conditions used to produce celecoxib dispersions D1-D4.

Dispersion	Target size range (μ m)	Bead size (mm)	Milling time (min)	Milling speed (rpm)
D1	6-7	3.3 - 3.6	--	--
D2	1-3	3.3 - 3.6	26	900
D3	0.5-0.9	1.25 - 1.55	25	900
D4	0.2-0.4	0.5	52	1250

Example 2

Celecoxib particle size in dispersions D1-D4 as prepared in Example 1 was determined by laser (Fraunhofer) diffraction and by optical microscopy.

Fraunhofer scattering was measured on static dispersion samples using a Sympatec spectrometer. Samples were diluted with water into a static cell at a

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concentration that maintained a reduction in laser intensity of approximately 20%. The choice of collection lens was determined by the population of large material present in suspension, and thus was different for each sample. However, the smallest focal length optic appropriate was used in each case. No Mie scattering corrections were applied. The results, presented in Fig. 1, show a D_{50} particle size consistent with the target size range. D_{50} and other particle size parameters shown in Fig. 1 are believed to be overestimated for the 0.2-0.4 μm celecoxib dispersion, since this size range is at the very limit of detection by this technique.

In order to visually confirm particle sizes, optical microscopy was used. Observations were carried out using an Olympus BH-2 microscope with attached video camera. Images were then digitized (Snappy 4.0; Play Inc., Rancho Cordova, CA) and manipulated (Paint Shop Pro 6.02; JASC, Eden Prairie, MN) as appropriate. Fig. 2 shows micrographs of samples taken from celecoxib dispersions D1-D4 with non-polarized (left) and polarized (right) light. The bar represents 10 μm . Significant Brownian motion was observed in dispersions D3 and D4, an observation consistent with presence of very small nanoparticles. In contrast, only slight Brownian motion was noted in dispersion D2 and none at all in dispersion D1.

Example 3

Dissolution characteristics of celecoxib crystals in dispersions D1-D4 of Example 1 were evaluated in an *in vitro* dissolution assay performed as described below. Fig. 4 is a schematic representation of the apparatus used in this experiment. The dissolution vessel is a 600 ml jacketed beaker. The jacket is connected to a temperature-controlled water circulator, which serves to maintain the temperature of the dissolution fluid at 37° C. A standard USP II dissolution paddle is utilized to stir the dissolution fluid. The paddle is driven by a computer-controlled constant-velocity motor, which is set to operate at 75 rpm throughout the course of the assay.

Dispersion samples are injected into the dissolution vessel just below the surface of the dissolution fluid. A sample is introduced in this way to minimize likelihood that particles become trapped on the surface of the fluid. Simultaneously, a data acquisition program is initiated. A sample point is taken at 30 seconds and then every 30 seconds thereafter for the duration of the assay. Dissolution progress is then followed for 60 minutes for each sample studied. The concentration of dissolved drug

6x

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in the vessel is monitored via an *in situ* fiber-optic probe, which measures the optical absorbance of dissolved drug in the dissolution fluid. The probe remains submerged in the fluid throughout the course of the assay. The concentration of dissolved drug in the fluid is determined from the measured absorbance values according to the Beer-Lambert equation

$$c = \frac{A}{l \cdot \epsilon}$$

where A is the measured absorbance at 254 nm, l is the path length of the probe in cm, ϵ is the absorption coefficient at 254 nm in ml/(μ g.cm), and c is drug concentration in μ g/ml. The path length of the fiber-optic probe is fixed at 1 cm. A typical calibration procedure using a standard solution of celecoxib is used to determine the absorption coefficient at 254 nm.

An attached personal computer is configured to record an absorbance value every 30 seconds. Thus an experimental data set consists of *in situ* absorbance values at 30-second intervals for the entire course of the experiment. The absorbance values are then converted to drug concentration via the Beer-Lambert equation above.

Prior to analyzing dispersions of the invention, a dissolution vessel was filled with 500 ml of dissolution fluid (deionized water), and allowed to equilibrate to 37°C. A dissolution paddle and fiber-optic probe were placed into the vessel and also allowed to equilibrate to 37° C. Celecoxib dispersions D1-D4 prepared as in Example 1 were sonicated for approximately 5 minutes before assay. Each dispersion was hand shaken and immediately thereafter a 40 μ l sample of the dispersion was extracted with a micropipette for placement in the dissolution fluid as described above.

Fig. 3 shows dissolution rates of dispersions D1-D4. To facilitate comparison, all of the dissolution traces are normalized to the same value at 60 min. This normalization step is necessary, when comparing very similar dissolution profiles, to compensate for small variations in sample volume. The plot shows the normalized percentage of celecoxib dissolved as a function of time.

Overall, comparative dispersion D1 dissolved much more slowly than did dispersions D2, D3 and D4 of the present invention, all of which dissolved at substantially similar rates. This result suggests that there is no significant functional advantage in dissolution rate to be obtained by milling celecoxib particles to a weight average particle size less than 400 nm as compared to a weight average particle size in

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the 450 nm to 1000 nm range. All nanoparticulate dispersions show a significant advantage in dissolution rate by comparison with the micronized celecoxib dispersion.

Example 4

Pharmacokinetic properties of celecoxib dispersions D1-D4 prepared as in Example 1 were evaluated in an *in vivo* dog study.

Eight male beagle dogs were given a 10 mg/kg dose of each of the four celecoxib dispersions D1-D4. Venous blood was collected pre-dose, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 5, 8, and 24 hours post dose. Plasma was separated from blood by centrifugation and plasma drug concentration was determined by high performance liquid chromatography. The resulting pharmacokinetic data are shown in Table 2.

Table 2. Pharmacokinetic parameters of celecoxib dispersions D1-D4

	Dispersion			
	D1	D2	D3	D4
T _{max} (h)	1.2	0.84	0.72	0.72
C _{max} (ng/ml)	1400	4850	6120	6310
AUC (h*ng/ml)	14600	32700	37500	43500

T_{max}, C_{max} and AUC (total bioavailability) values of dispersions D3 (target particle size range 0.5-0.9 μ m) and D4 (target particle size range 0.2-0.4 μ m) were very similar. Dispersion D2 (target particle size range 1-3 μ m) exhibited slightly longer T_{max} and moderately lower C_{max} and AUC values than dispersions D4 and D3. T_{max} of dispersion D1 was much longer and C_{max} and AUC were much lower than those of dispersions D2, D3 and D4.

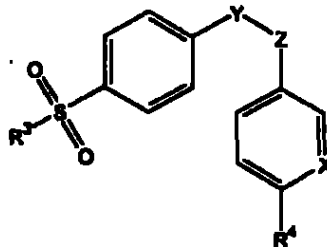
These results suggest that where fast onset therapeutic effect is desired, good bioavailability will be obtained with celecoxib milled to a target particle size range of 0.5-0.9 μ m and a D₅₀ particle size as determined by Fraunhofer scattering (Fig. 1) of about 0.9 μ m. No significant benefit is gained by expending additional time and energy to mill celecoxib particles to a target particle size range of 0.2-0.4 μ m.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm , a sufficient portion by weight of the particles being smaller than 1 μm to provide a substantially higher C_{max} and/or a substantially shorter T_{max} by comparison with an otherwise similar composition wherein substantially all of the particles are larger than 1 μm .
2. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a selective cyclooxygenase-2 inhibitory drug of low water solubility in a therapeutically effective amount, wherein the drug is present in solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm , and wherein about 25% to 100% by weight of the particles are smaller than 1 μm .
3. The composition of Claim 1 or Claim 2 wherein substantially all of the particles are smaller than 1 μm .
4. The composition of any of Claims 1 to 3 wherein the dose units are in the form of discrete solid articles.
5. The composition of Claim 4 wherein the solid articles are tablets or capsules.
6. The composition of any of Claims 1 to 3 that is in the form of a substantially homogeneous flowable mass from which single dose units are measurably removable.
7. The composition of Claim 6 wherein the substantially homogeneous flowable mass is a liquid suspension.
8. The composition of any of Claims 1 to 7 wherein the solid particles have a D_{50} particle size of about 450 nm to about 1000 nm.
9. The composition of any of Claims 1 to 7 wherein about 25% to 100% by weight of the solid particles have a particle size of about 450 nm to about 1000 nm.
10. The composition of any of Claims 1 to 7 wherein the solid particles have a

weight average particle size of about 450 nm to about 1000 nm.

11. The composition of any of Claims 1 to 10 wherein the selective cyclooxygenase-2 inhibitory drug is a compound of formula



where R³ is a methyl or amino group, R⁴ is hydrogen or a C₁₋₄ alkyl or alkoxy group, X is N or CR⁵ where R⁵ is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups.

12. The composition of Claim 11 wherein the five- to six-membered ring is selected from the group consisting of cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.
13. The composition of any of Claims 1 to 10 wherein the selective cyclooxygenase-2 inhibitory drug is selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.
14. The composition of Claim 13 wherein the selective cyclooxygenase-2 inhibitory drug is celecoxib.
15. The composition of Claim 14 comprising about 10 mg to about 1000 mg celecoxib in each dose unit.
16. 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 any of Claims 1 to 15 one to about six times a day.

17. The method of Claim 16 wherein the medical condition or disorder is accompanied by acute pain.
18. A method of use of solid particles of a selective cyclooxygenase-2 inhibitory drug of low water solubility in manufacture of a medicament useful in treatment or prophylaxis of a COX-2 mediated condition or disorder, said solid particles having a D_{90} particle size of about 0.01 μm to about 200 μm , and wherein about 25% to 100% by weight of the solid particles are smaller than 1 μm .

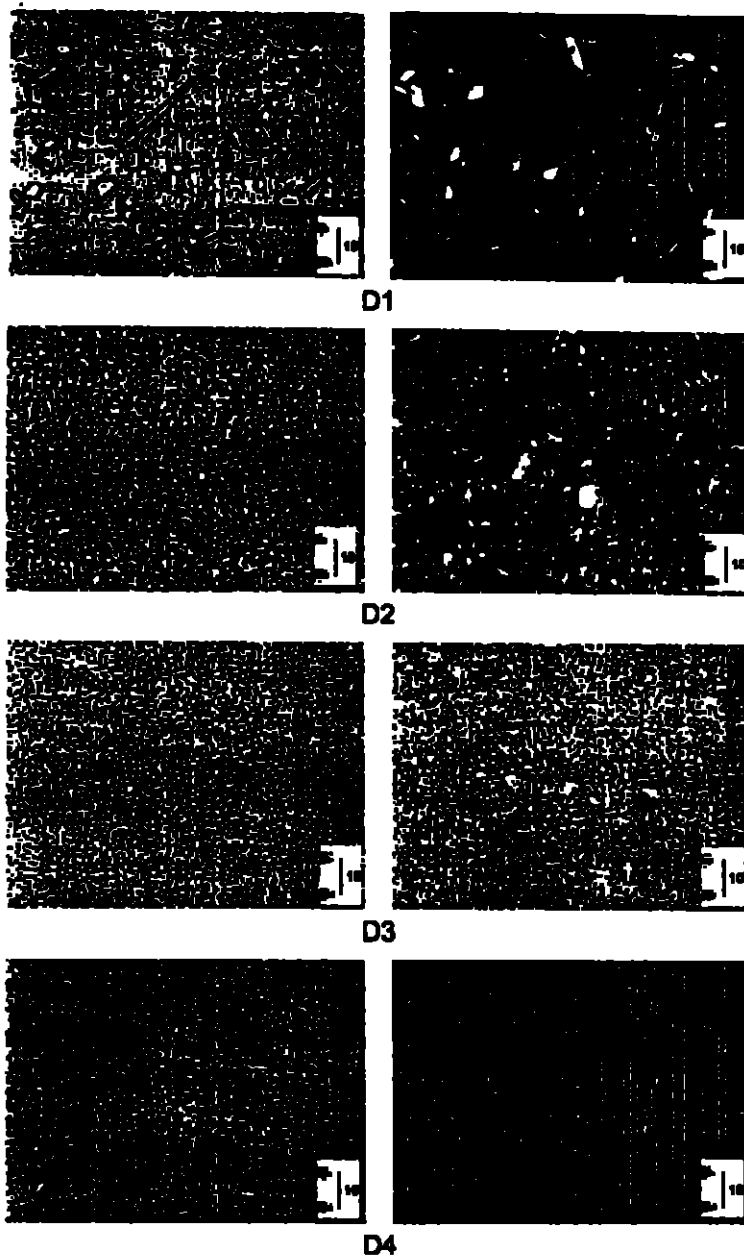


Fig. 2

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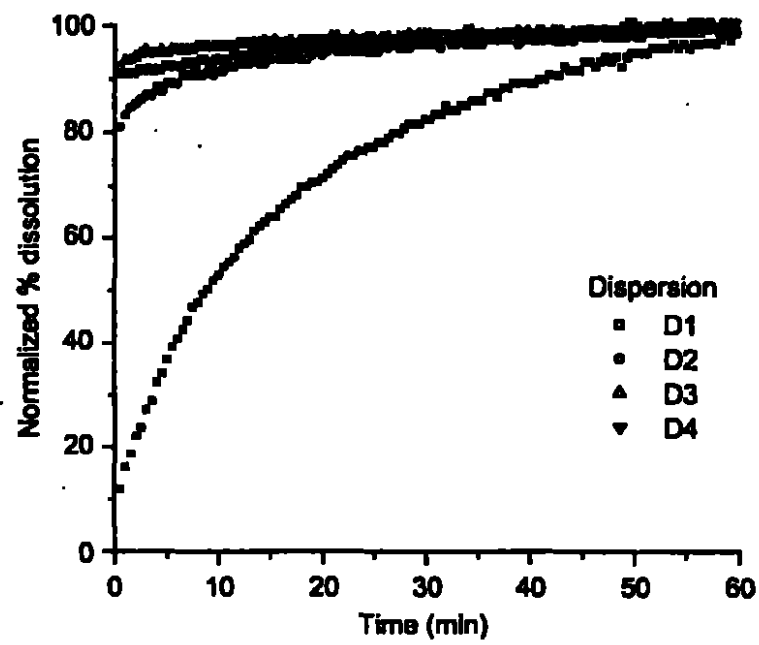


Fig. 3

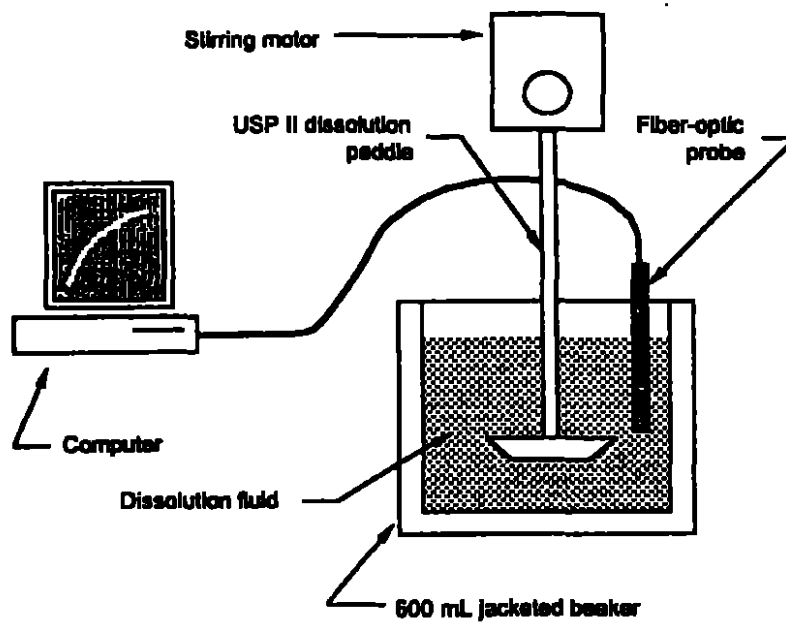


Fig. 4

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(21) International Application Number: PCT/US99/28411 (22) International Filing Date: 30 November 1999 (30.11.99) (30) Priority Data: 60/110,333 30 November 1998 (30.11.98) US (71) Applicant (for all designated States except US): G. D. SEARLE & CO. (US/US); 5200 Old Orchard Road, Skokie, IL 60077 (US). (72) Inventors; and (73) Inventors/Applicants (for US only): GAO, Danchen (CN/US); 1446 S. Prairie Avenue, Chicago, IL 60605 (US). HLINAK, Anthony, J. (US/US); 1803 Longmeadow Drive, Lindenhurst, IL 60046 (US). MAZLIARY, Ahmad, M. (US/US); 1461 Lancaster Lane, Algonquin, IL 60102 (US). TRU-ELOVE, James, E. (US/US); 1006 Regency Lane, Libertyville, IL 60048 (US). VAUGHN, Margaret, B., Woodhull (US/US); 764 Rosewood, Winnetka, IL 60093 (US). (74) Agent: STREIT, Richard, J.; Ladas & Parry, 224 S. Michigan Avenue, Chicago, IL 60604 (US).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KR, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, 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.	
(54) Title: CILCOXIB COMPOSITIONS (57) Abstract Pharmaceutical compositions are provided comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients. The compositions are useful in treatment or prophylaxis of cyclooxygenase-2 mediated conditions and disorders.		

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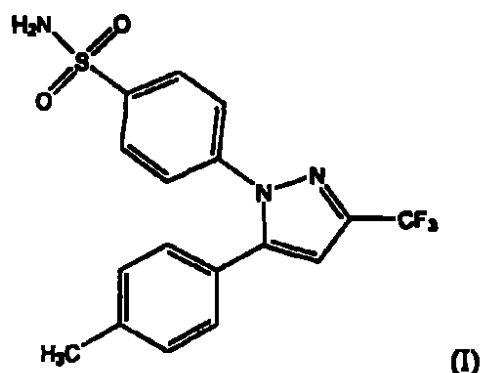
CELECOXIB COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to orally deliverable pharmaceutical compositions containing celecoxib as an active ingredient, to processes for preparing such compositions, to methods of treatment of cyclooxygenase-2 mediated disorders comprising orally administering such compositions to a subject, and to the use of such compositions in the manufacture of medicaments.

BACKGROUND OF THE INVENTION

The compound 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (also referred to herein as celecoxib) was previously reported in Talley *et al.*, U.S. Patent No. 5,466,823 which describes and claims a class of 1,5-diaryl pyrazoles and their salts together with processes for the preparation of such compounds. Celecoxib has the structure:



The 1,5-diaryl pyrazole compounds reported in U.S. Patent No. 5,466,823 are described therein as useful in treating inflammation and inflammation-related disorders. U.S. Patent No. 5,466,823 contains general references to formulations for the administration of these 1,5-diaryl pyrazoles, including orally deliverable dosage forms such as tablets and capsules. Talley *et al.*, U.S. Patent No. 5,760,068 reports a class of 1,5-diaryl pyrazole compounds including celecoxib that are described as selective inhibitors of cyclooxygenase-2 and that can be administered to treat, among other conditions and disorders, pathological conditions associated with rheumatoid arthritis and osteoarthritis.

Penning *et al.*, "Synthesis and Biological Evaluation of the 1,5-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (SC-58635, Celecoxib)",

J. Med. Chem. 40 (1997):1347-1365, discloses the preparation of a series of sulfonamide-containing 1,5-diarylpyrazole derivatives, including celecoxib, and the evaluation of those derivatives as cyclooxygenase-2 inhibitors.

Simon *et al.*, "Preliminary Study of the Safety and Efficacy of SC-58635, a Novel Cyclooxygenase 2 Inhibitor", Arthritis & Rheumatism, Vol. 41, No. 9, September 1998, pp. 1591-1602, discloses a study of the efficacy and safety of celecoxib in the treatment of osteoarthritis and rheumatoid arthritis.

Lipsky *et al.*, "Outcome of Specific COX-2 Inhibition in Rheumatoid Arthritis", J. Rheumatology, Vol. 24, Suppl. 49, pp. 9-14 (1997), discloses that in patients with rheumatoid arthritis the specific inhibition of cyclooxygenase-2 by celecoxib is sufficient to suppress signs and symptoms of inflammatory disease activity.

European Patent Application No. 0 863 134 A1, published September 9, 1998, discloses compositions comprising a cyclooxygenase-2 inhibitor, specifically 2-(3,5-difluorophenyl)-3-(4-methyl-sulfonyl)phenyl)-2-cyclopenten-1-one, in combination with excipient ingredients including microcrystalline cellulose, lactose monohydrate, hydroxypropyl cellulose, croscarmellose sodium and magnesium stearate.

The formulation of celecoxib for effective oral administration to a subject has hitherto been complicated by the unique physical and chemical properties of the compound, particularly its low solubility and factors associated with its crystal structure, including cohesiveness, low bulk density and low compressibility. Celecoxib is unusually insoluble in aqueous media. Unformulated celecoxib is not readily dissolved and dispersed for rapid absorption in the gastrointestinal tract when administered orally, for example in capsule form. In addition, unformulated celecoxib, which has a crystal morphology that tends to form long cohesive needles, typically fuses into a monolithic mass upon compression in a tableting die. Even when blended with other substances, the celecoxib crystals tend to separate from the other substances and agglomerate together during mixing of the composition resulting in a non-uniformly blended composition containing undesirably large aggregates of celecoxib. Therefore, it is difficult to prepare a pharmaceutical composition containing celecoxib that has the desired blend uniformity. Further, handling problems are encountered during the preparation of pharmaceutical compositions comprising celecoxib. For example, the low bulk density of celecoxib makes it

SUMMARY OF THE INVENTION

There is now provided a pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients.

In one embodiment, a single dose unit, upon oral administration to a fasting subject, provides a time course of blood serum concentration of celecoxib having at least one of the following:

- (a) a time to reach 100 ng/ml not greater than about 0.5 h after administration;
- (b) a time to reach maximum concentration (T_{max}) not greater than about 3 h after administration;
- (c) a duration of time wherein concentration remains above 100 ng/ml not less than about 12 h;
- (d) a terminal half-life ($T_{1/2}$) not less than about 10 h; and
- (e) a maximum concentration (C_{max}) not less than about 200 ng/ml.

In another embodiment, the composition has a relative bioavailability not less than about 50% by comparison with an orally delivered solution containing an equivalent amount of celecoxib.

In still another embodiment, the composition has a distribution of celecoxib primary particle sizes such that D_{90} is less than about 200 μm (90% of a sample of particles is smaller than the D_{90} value) in the longest dimension of the particles.

The dose units comprising the composition can be in the form of discrete solid articles such as tablets, 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, from which single dose units are measurably removable.

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 orally administering a composition of the invention once or twice a day.

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

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a flow diagram illustrating a representative method for the preparation of pharmaceutical compositions of the present invention in the form of capsules.

Figure 2 is a flow diagram illustrating an alternative method for the preparation of pharmaceutical compositions of the present invention in the form of capsules.

DETAILED DESCRIPTION OF THE INVENTION

Novel pharmaceutical compositions according to the present invention comprise one or more orally deliverable dose units, wherein each dose unit comprises particulate celecoxib in an amount from about 10 mg to about 1000 mg and are superior immediate release compositions capable of providing rapid relief from a cyclooxygenase-2 mediated disorder when orally administered to a subject suffering from such a disorder.

It is believed, without being bound by theory, that the strong clinical benefits afforded by these compositions result from improved bioavailability of celecoxib, in particular from surprisingly effective absorption of celecoxib in the gastrointestinal tract. Such effective absorption can be verified by one of skill in the art by monitoring blood serum concentration of celecoxib in a treated subject for a period of time following administration. It is desired to reach, in as short a time as possible, a threshold of celecoxib concentration in the blood serum consistent with effective cyclooxygenase-2 inhibition, without having that concentration subsequently decrease too rapidly so that the beneficial effects of the celecoxib can be maintained for as long a time as possible.

In one embodiment of the invention, therefore, each orally deliverable dose unit, upon oral administration, provides a time course of blood serum concentration of celecoxib characterized by at least one of the following:

- (a) a time to reach a blood serum concentration of about 100 ng/ml that is not greater than about 0.5 hour after administration;
- (b) a time to reach a maximum blood serum concentration (T_{max}) of celecoxib that is not greater than about 3 hours after administration, preferably not greater than about 2 hours after administration;
- (c) a duration of time wherein the blood serum concentration remains above

about 100 ng/ml that is not less than about 12 hours;

(d) a terminal half life ($T_{1/2}$) that is not less than about 10 hours; and

(e) a maximum blood serum concentration (C_{max}) that is not less than about 200 ng/ml, preferably not less than about 300 ng/ml, and more preferably not less than about 400 ng/ml.

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It will be understood that the amount of celecoxib in a dose unit effective to provide blood serum concentrations meeting any of criteria (a) to (e) immediately above is dependent on the body weight of the treated subject. Where the subject is a child or a small animal (e.g., a dog), for example, an amount of celecoxib relatively low in the indicated range of about 10 mg to about 1000 mg is likely to provide blood serum concentrations consistent with at least one of criteria (a) to (e). Where the subject is an adult human or a large animal (e.g., a horse), the indicated blood serum concentrations of celecoxib are likely to require dose units containing a relatively greater amount of celecoxib. For an adult human, a suitable amount of celecoxib per dose unit in a composition of the present invention to provide the indicated blood serum concentrations is typically about 75 mg to about 400 mg.

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Bioavailability of orally delivered celecoxib in an absolute sense is difficult to measure, because intravenous delivery (normally the standard against which such bioavailability is determined) is highly problematical with a drug having very low solubility in water, as is the case with celecoxib. Relative bioavailability is, however, determinable by comparison with an orally administered solution of celecoxib in a suitable solvent. It has been found that surprisingly high relative bioavailability is obtainable with orally delivered compositions of the present invention. Thus in one embodiment of the invention, each orally deliverable dose unit, upon oral administration, has a relative bioavailability of not less than about 50%, preferably not less than about 70%, by comparison with an orally delivered solution of celecoxib containing an equivalent amount of celecoxib. As indicated hereinbelow, bioavailability is derived from an integrated measure of blood serum concentration of celecoxib over a period of time following oral administration.

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Compositions of the present invention contain celecoxib in particulate form. Primary celecoxib particles, generated for example by milling or grinding, or by precipitation from solution, can agglomerate to form secondary aggregate particles. The term "particle size" as used herein refers to size, in the longest dimension, of

In yet another embodiment, the novel pharmaceutical compositions of the invention comprise celecoxib together with one or more carrier materials or excipients selected from diluents, disintegrants, binding agents, wetting agents and lubricants. Preferably at least one of the carrier materials is a water soluble diluent or wetting agent. Such a water soluble diluent or wetting agent assists in the dispersion and dissolution of the celecoxib when the pharmaceutical composition is ingested. Preferably both a water soluble diluent and a wetting agent are present. A composition of the invention can be a substantially homogeneous flowable mass such as a particulate or granular solid or a liquid, or it can be in the form of discrete articles such as capsules or tablets each comprising a single dose unit.

In a composition that is a substantially homogeneous flowable mass, single dose units are measurably removable using a suitable volumetric measuring device such as a spoon or cup. Suitable flowable masses include, but are not limited to, powders and granules. Alternatively, the flowable mass can be a suspension having the celecoxib in a solid particulate phase dispersed in a liquid phase, preferably an aqueous phase. In preparing such a suspension, use of a wetting agent such as polysorbate 80 or the like is likely to be beneficial. A suspension can be prepared by dispersing milled celecoxib in the liquid phase; alternatively the celecoxib can be precipitated from solution in a solvent such as an alcohol, preferably ethanol. The aqueous phase preferably comprises a palatable vehicle such as water, syrup or fruit juice, for example apple juice.

Utility of compositions of the invention

Compositions of the present invention are useful in treatment and prevention of a very wide range of disorders mediated by cyclooxygenase-2. Presently contemplated compositions are useful for, but not limited to, the treatment of inflammation in a subject, as an analgesic for example in the treatment of pain and headaches, and as an antipyretic in the treatment of fever. For example, such compositions are useful to treat arthritic disorders, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis. Such compositions are also useful in the treatment of asthma, bronchitis, menstrual cramps, preterm labor, tendinitis, bursitis, allergic neuritis, cytomegalovirus infectivity, apoptosis including HIV-induced

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apoptosis, lumbago, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, acne, UV damage, burns and dermatitis, and post-operative inflammation including that following ophthalmic surgery such as cataract surgery or refractive surgery. Contemplated compositions are useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. Contemplated compositions are useful in treating inflammation in such diseases as migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, scleroderma, 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. Contemplated compositions are useful in the treatment of ophthalmic diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue. Contemplated compositions are useful in the treatment of pulmonary inflammation, such as that associated with viral infections and cystic fibrosis, and in bone resorption such as that associated with osteoporosis. Contemplated compositions are useful for the treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, 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.

Compositions of the invention are especially useful as anti-inflammatory agents, such as for the treatment of arthritis, with the additional benefit of having significantly less harmful side effects than compositions of conventional nonsteroidal anti-inflammatory drugs (NSAIDs).

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

Contemplated compositions are useful in the treatment of pain, including but not limited to postoperative pain, dental pain, muscular pain, and pain resulting from cancer.

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Contemplated compositions are useful for, but not limited to, treating and preventing inflammation-related cardiovascular disorders in a subject. Such compositions are useful for treatment and prevention of 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 for, but not limited to, the treatment of angiogenesis-related disorders in a subject. Compositions of the invention can be administered to a subject in need of angiogenesis inhibition. Such compositions are useful for the 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 hemangiomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis.

Contemplated compositions are useful for the prevention or treatment of benign and malignant tumors/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 and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer and 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, pancreas cancer, ovary cancer,

prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamous cell and basal cell cancers. Compositions of the invention can also be used to treat the fibrosis which occurs with radiation therapy. Such compositions can be used to treat subjects having adenomatous polyps, including those with familial
5 adenomatous polyposis (FAP). Additionally, such compositions can be used to prevent polyps from forming in patients at risk of FAP.

Compositions of the present invention possess anti-inflammatory, antipyretic and analgesic properties similar or superior to those of compositions of conventional nonsteroidal anti-inflammatory drugs. Contemplated compositions also inhibit
10 hormone-induced uterine contractions and have potential anti-cancer effects, but with a diminished ability to induce some of the mechanism-based side effects of conventional NSAIDs. 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
15 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.

Contemplated compositions are useful for the relief of pain, fever and
20 inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, 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 injuries
25 following surgical and dental procedures. In addition, contemplated compositions inhibit cellular neoplastic transformations and metastatic tumor growth and hence can be used in the treatment of cancer, such as cancer of the colon. Contemplated compositions are also of use in the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in diabetic retinopathy and tumor
30 angiogenesis.

Contemplated compositions inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence can be of use in the treatment of dysmenorrhea, premature labour, asthma and eosinophil-

related disorders. They also can be of use in the treatment of Alzheimer's disease, for decreasing bone loss particularly in postmenopausal women (*i.e.*, treatment of osteoporosis), and for treatment of glaucoma.

By virtue of their high cyclooxygenase-2 (COX-2) inhibitory activity and/or
5 their specificity for inhibition of cyclooxygenase-2 over cyclooxygenase-1 (COX-1),
compositions of the invention are useful as an alternative to conventional NSAIDs,
particularly 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
10 disorders including anemia such as hypoprothrombinemia, hemophilia or other
bleeding problems; kidney disease; or in patients prior to surgery or patients taking
anticoagulants. A brief description of the potential utility of cyclooxygenase-2
inhibitors is given in an article by John Vane, Nature, Vol. 367, pp. 215-216, 1994,
and in an article in Drug News and Perspectives, Vol. 7, pp. 501-512, 1994.

15 Preferred uses for the pharmaceutical compositions of the present invention
are for the 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), the treatment of
Alzheimer's disease, and colon cancer chemoprevention.

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

25 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, monamine uptake
inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P
antagonists, neurokinin-1 receptor antagonists and sodium channel blockers, among
30 others. Preferred combination therapies comprise use of a composition of the
invention with compounds selected from morphine, meperidine, codeine, pentazocine,
buprenorphine, butorphanol, dezocine, meptazinol, hydrocodone, oxycodone,
methadone, DuP-747, Dynorphine A, Enadoline, RP-60180, HN-11608, E-2078,

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ICI-204448, acetaminophen (paracetamol), propoxyphene, nalbuphine, E-4018, filenadol, mirfentanil, amitriptyline, DuP-631, GP-531, acadesine, AKI-1, AKI-2, GP-1683, GP-3269, 4030W92, tramadol racemate and isolated (+) and (-) enantiomers, AXC-3742, SNX-111, ADL2-1294, CT-3, and CP-99994.

5 Definitions

The term "active ingredient" herein means celecoxib unless the context demands otherwise.

The term "excipient" herein includes any substance used as a vehicle for delivery of the active ingredient to a subject, and any substance added to the active ingredient, for example to improve its handling properties or to permit the resulting composition to be formed into an orally deliverable unit dose having the desired shape and consistency. Excipients can include, by way of illustration and not by limitation, diluents, disintegrants, binding agents, adhesives, wetting agents, lubricants, glidants, substances added to mask or counteract a bad taste or odor, flavors, dyes, substances added to improve appearance of a dosage form, and any other substance other than the active ingredient conventionally used in the preparation of oral dosage forms.

The term "adjuvant" herein means a substance that, when present in or added to a pharmaceutical composition comprising an active ingredient, increases or otherwise improves the action of the active ingredient.

The term "unit dose" herein refers to an amount of active ingredient intended for a single oral administration to a subject for treatment or prevention of a cyclooxygenase-2 mediated condition or disorder. Treatment of a cyclooxygenase-2 mediated disorder may require periodic administration of unit doses of celecoxib, for example one unit dose two or more times a day, one unit dose with each meal, one unit dose every four hours or other interval, or only one unit dose per day.

The term "dose unit" herein means a portion of a pharmaceutical composition that contains a single unit dose of the active ingredient. For purposes of the present invention, a dose unit can be in the form of a discrete article such as a tablet or capsule, or can be a measurable volume of a solution, suspension or the like containing a unit dose of the active ingredient.

The term "orally deliverable" herein means intended to be administered to the gastrointestinal tract of a subject via the mouth of said subject.

The term "substantially homogeneous", when used herein to describe a pharmaceutical composition that contains a combination of components, means that the components are fully mixed so that the individual components are neither separated into discrete layers nor form concentration gradients within the composition.

The term "bioavailability" herein relates to a measure of the amount of active ingredient that is absorbed via the gastrointestinal tract into the bloodstream. More specifically, "bioavailability" is used herein to denote $AUC_{(0-\infty)}$ for a specific orally administered composition expressed as a percentage of $AUC_{(0-\infty)}$ for the active ingredient delivered intravenously at the same dosage rate.

The term "relative bioavailability" herein denotes $AUC_{(0-\infty)}$ for a specific orally administered composition expressed as a percentage of $AUC_{(0-\infty)}$ for an orally administered solution of the active ingredient at the same dosage rate.

The terms " $AUC_{(0-24)}$ ", " $AUC_{(0-48)}$ " and " $AUC_{(0-72)}$ " herein mean the area under the curve relating blood serum concentration to time after administration from 0 to 24 hours, 48 hours or 72 hours respectively, as determined using the linear trapezoidal rule, and are expressed in units of (ng/ml)h.

The term " $AUC_{(0-LQC)}$ " herein means the area under the curve relating blood serum concentration to time after administration from 0 hours to the time of last quantifiable concentration ("LQC"), as determined using the linear trapezoidal rule, and is expressed in units of (ng/ml)h.

The term " $AUC_{(0-\infty)}$ " herein is calculated as $AUC_{(0-LQC)} + LQC/(-b)$, where LQC is the last quantifiable blood serum concentration and b is the slope from the calculation of $T_{1/2}$, and is expressed in units of (ng/ml)h.

The term " C_{max} " herein means the maximum observed blood serum concentration or the maximum blood serum concentration calculated or estimated from a concentration/time curve, and is expressed in units of ng/ml.

The term " T_{max} " herein means the time after administration at which C_{max} occurs, and is expressed in units of hours (h).

The term " $T_{1/2}$ " herein means the terminal half-life of blood serum concentration, determined via simple linear regression of natural log (ln) concentration vs. time for data points in the terminal phase of the concentration-time

curve. $T_{1/2}$ is computed as $-\ln(2)/(-b)$ and is expressed in units of hours (h).

The term "rate of absorption" herein means $C_{max}/AUC_{(0-LQC)}$.

Celecoxib dosage provided by compositions of the invention

The pharmaceutical compositions of the present invention are suitable for
5 administration of celecoxib in a daily dosage amount from about 10 mg to about 1000
mg. Each dose unit of a composition of the invention typically comprises an amount
of celecoxib from about one-tenth of the daily dosage amount to the whole of a daily
dosage amount. Compositions of the invention comprise celecoxib in an amount of
about 10 mg to about 1000 mg, preferably about 50 mg to about 800 mg, more
10 preferably about 75 mg to about 400 mg, and most preferably about 100 mg to about
200 mg, per dose unit. Where the dose units are in the form of discrete articles
suitable for oral administration, for example capsules or tablets, each such article
comprises about 10 mg to about 1000 mg, preferably about 50 mg to about 800 mg,
more preferably about 75 mg to about 400 mg, and most preferably about 100 mg to
15 about 200 mg, of celecoxib.

Dose units of compositions of the invention typically contain, for example, a
10, 20, 25, 37.5, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350 or 400 mg dose of
celecoxib. Preferred compositions have dose units containing about 100 mg or about
200 mg of celecoxib. The particular dose unit can be selected to accommodate the
20 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.

25 It has been discovered, however, that a once-a-day or twice-a-day
administration regimen to provide the required daily dosage of celecoxib exhibits
improved efficacy relative to other administration regimens, for compositions
illustrated herein. Accordingly, once-a-day or twice-a-day oral administration of a
composition of the invention is preferred for providing therapeutically or
30 prophylatically effective inhibition of cyclooxygenase-2 mediated disorders.

Treatment of specific conditions and disorders

The pharmaceutical compositions of the present invention are useful where

administration of a cyclooxygenase-2 inhibitor is indicated. It has been found that these compositions are particularly effective in the treatment of, for example, rheumatoid arthritis and osteoarthritis, and for pain management generally (particularly post-oral surgery pain, post-general surgery pain, post-orthopedic surgery pain, and acute flares of osteoarthritis), the treatment of Alzheimer's disease, and colon cancer chemoprevention.

For the treatment of rheumatoid arthritis, compositions of the invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, and still more preferably about 175 to about 400, for example about 200 mg. A daily dose of celecoxib of about 0.67 to about 13.3 mg/kg body weight, preferably about 1.33 to about 8.00 mg/kg body weight, more preferably about 2.00 to about 6.67 mg/kg body weight, and still more preferably about 2.33 to about 5.33 mg/kg body weight, for example about 2.67 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to four doses per day, preferably one or two doses per day. Administration of a composition of the invention at the rate of one 100 mg dose unit twice a day is preferred for most patients, but some patients may benefit from administration of one 200 mg dose unit or two 100 mg dose units twice a day.

For the treatment of osteoarthritis, compositions of the invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, and still more preferably about 175 to about 400, for example about 200 mg. A daily dose of celecoxib of about 0.67 to about 13.3 mg/kg body weight, preferably about 1.33 to about 8.00 mg/kg body weight, more preferably about 2.00 to about 6.67 mg/kg body weight, and still more preferably about 2.33 to about 5.33 mg/kg body weight, for example about 2.67 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to four doses per day, preferably one or two doses per day. Administration of a composition of the invention at the rate of one 100 mg dose unit twice a day or of one 200 mg dose unit or two 100 mg dose units once a day is preferred.

For the treatment of Alzheimer's disease, compositions of the invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg,

preferably about 100 mg to about 800 mg, more preferably about 150 mg to about 600 mg, and still more preferably about 175 to about 400, for example about 400 mg. A daily dose of about 0.67 to about 13.3 mg/kg body weight, preferably about 1.33 to about 10.67 mg/kg body weight, more preferably about 2.00 to about 8.00 mg/kg body weight, and still more preferably about 2.33 to about 5.33 mg/kg body weight, for example about 5.33 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to four doses per day, preferably one or two doses per day. Administration of a composition of the invention at the rate of one 200 mg dose unit or two 100 mg dose units twice a day is preferred for most patients.

For the treatment of cancer, compositions of the invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 800 mg, more preferably about 150 mg to about 600 mg, and still more preferably about 175 to about 400, for example about 400 mg. A daily dose of about 0.67 to about 13.3 mg/kg body weight, preferably about 1.33 to about 10.67 mg/kg body weight, more preferably about 2.00 to about 8.00 mg/kg body weight, and still more preferably about 2.33 to about 5.33 mg/kg body weight, for example about 5.33 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to four doses per day, preferably two doses per day. Administration of a composition of the invention at the rate of one 200 mg dose unit or two 100 mg dose units twice a day is preferred for most patients.

In general, a composition of the invention is preferably administered at a dose suitable to provide an average blood serum concentration of celecoxib of at least about 100 ng/ml in a subject over a period of about 24 hours after administration.

It has been found that the pharmaceutical compositions of the present invention provide a therapeutic effect as cyclooxygenase-2 inhibitors over an interval of about 12 to about 24 hours after oral administration. Preferred compositions provide such therapeutic effect over about 24 hours, enabling once-a-day oral administration.

While the amount of celecoxib in the novel compositions of the invention preferably is in a range disclosed herein, the compositions also may be useful for the administration of an amount of celecoxib falling outside the disclosed dosage ranges.

Preparation of celecoxib

The celecoxib used in the novel pharmaceutical compositions of the present invention can be prepared in the manner set forth in Talley *et al.*, U.S. Patent 5,466,823, or in Zhi *et al.*, WO 96/37476.

5 Form of compositions of the invention

The pharmaceutical compositions of the present invention comprise celecoxib in association with one or more preferably non-toxic, pharmaceutically acceptable carriers, excipients and adjuvants (collectively referred to herein as "carrier materials" or "excipients") suitable for oral administration. The carrier materials must be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. Compositions of the present invention can be adapted for administration by any suitable oral route by selection of appropriate carrier materials and a dosage of celecoxib effective for the treatment intended. Accordingly, any carrier materials employed can be solids or liquids, or both, and the composition preferably contains 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. Such pharmaceutical compositions of the invention can be prepared by any of the well known techniques of pharmacy, comprising admixing the components.

20 A composition of the invention contains a desired amount of celecoxib per dose unit and can be in the form of, for example, a tablet, 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 oral administration. Such a composition is preferably made in the form of discrete dose units each containing a predetermined amount of celecoxib, such as tablets or capsules. These oral dosage forms may further comprise, for example, buffering agents. Tablets, pills and the like additionally can be prepared with or without coatings.

25 Compositions of the invention suitable for buccal or sublingual administration include, for example, lozenges comprising celecoxib in a flavored base, such as sucrose, and acacia or tragacanth, and pastilles comprising celecoxib in an inert base such as gelatin and glycerin or sucrose and acacia.

Liquid dosage forms for oral administration include pharmaceutically

acceptable suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise, for example, wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

5 As indicated above, compositions of the invention can be prepared by any suitable method of pharmacy which includes the step of bringing into association the celecoxib and the carrier material or carrier materials. In general, the compositions are prepared by uniformly and intimately admixing celecoxib with a liquid or finely divided solid carrier, or both, and then, if necessary, encapsulating or shaping the
10 product. For example, a tablet can be prepared by compressing or molding a powder or granules of the compound, together with one or more excipients. Compressed tablets can be prepared by compressing, in a suitable machine, a free-flowing composition, such as a powder or granules, comprising celecoxib optionally mixed with one or more binding agent(s), lubricant(s), inert diluent(s), wetting agent(s)
15 and/or dispersing agent(s). Molded tablets can be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Carrier materials or excipients

As noted above, the pharmaceutical compositions of the present invention comprise celecoxib in a therapeutically or prophylactically effective amount per dose
20 unit in combination with one or more pharmaceutically acceptable carrier materials appropriate for oral administration. Compositions of the present invention preferably comprise celecoxib in a desired amount admixed with one or more carrier materials selected from the group consisting of pharmaceutically acceptable diluents, disintegrants, binding agents, adhesives, wetting agents, lubricants, and anti-adherent
25 agents. More preferably, such compositions are tableted or encapsulated for convenient administration in the form of immediate release capsules or tablets.

Through the selection and combination of carrier materials used in the pharmaceutical compositions of the present invention, compositions can be provided exhibiting improved performance with respect to, among other properties, efficacy,
30 bioavailability, clearance time, stability, compatibility of celecoxib and carrier materials, safety, dissolution profile, disintegration profile and/or other pharmacokinetic, chemical and/or physical properties. The carrier materials

RS

preferably are water soluble or water dispersible and have wetting properties to offset the low aqueous solubility and hydrophobicity of celecoxib. Where the composition is formulated as a tablet, the combination of carrier materials selected provides tablets that can exhibit improvement, among other properties, in dissolution and

5 disintegration profiles, hardness, crushing strength, and/or friability.

Diluents

The pharmaceutical compositions of the present invention optionally comprise one or more pharmaceutically acceptable diluents as a carrier material. Suitable diluents include, either individually or in combination, lactose USP; lactose USP,

10 anyhydrous; lactose USP, spray dried; starch USP; directly compressible starch; mannitol USP; sorbitol; dextrose monohydrate; microcrystalline cellulose NF; dibasic calcium phosphate dihydrate NF; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate NF; calcium lactate trihydrate granular NF; dextrates, NF (e.g., Emdex); Celutab; dextrose (e.g.,

15 Cerelease); inositol; hydrolyzed cereal solids such as the Maltrons and Mor-Rex; amylose; Rexcel; powdered cellulose (e.g., Elecma); 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

20 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

25 added to a wet granulated composition after the drying step) can be used to improve hardness (for tablets) and/or disintegration time. Lactose, especially lactose monohydrate, is particularly preferred. Lactose typically provides pharmaceutical compositions having suitable celecoxib release rates, stability, pre-compression flowability, and/or drying properties at a relatively low diluent cost. It provides a

30 high density substrate that aids densification during granulation (where wet granulation is employed) and therefore improves blend flow properties.

Disintegrants

The pharmaceutical compositions of the present invention optionally comprise one or more pharmaceutically acceptable disintegrants as a carrier material, particularly for tablet formulations. Suitable disintegrants include, either individually or in combination, starches; sodium starch glycolate; clays (such as Veegum HV);
5 celluloses (such as purified cellulose, methylcellulose, sodium carboxymethylcellulose, and carboxymethylcellulose); alginates; pregelatinized corn starches (such as National 1551 and National 1550); crospovidone USP NF; and gums (such as agar, guar, locust bean, Karaya, pectin, and tragacanth). Disintegrants may
10 be added at any suitable step during the preparation of the pharmaceutical composition, particularly prior to granulation or during the 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.

15 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 6%, 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 compositions of the present invention.

20 Binding agents and adhesives

The pharmaceutical compositions of the present invention optionally comprise one or more pharmaceutically-acceptable binding agents or adhesives as a carrier material, particularly for tablet formulations. Such binding agents and adhesives preferably impart sufficient cohesion to the powder being tableted to allow for normal
25 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; starch; cellulose materials such as, but not limited to, methylcellulose and sodium carboxymethylcellulose (e.g., Tylose);
30 alginic acid and salts of alginic acid; magnesium aluminum silicate; polyethylene glycol; guar gum; polysaccharide acids; bentonites; polyvinylpyrrolidone; polymethacrylates; hydroxypropylmethylcellulose (HPMC); hydroxypropylcellulose

(Klucel); ethylcellulose (Ethocel); pregelatinized starch (such as National 1511 and Starch 1500). 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.

- 5 Polyvinylpyrrolidone is a preferred binding agent used to impart cohesive properties to a powder blend of celecoxib and other excipients for granulation of a celecoxib formulation. Polyvinylpyrrolidone, if present, preferably constitutes about 0.5% to about 10%, more preferably about 0.5% to about 7%, and still more preferably about 0.5% to about 5% of the total weight of the composition.
- 10 Polyvinylpyrrolidone viscosities up to about 20 cPs may be used although viscosities of about 6 cPs or lower are preferred, particularly about 3 cPs or lower. Polyvinylpyrrolidone provides cohesiveness to the powder blend and facilitates the necessary binding to form granules during wet granulation. In addition, compositions of the present invention comprising polyvinylpyrrolidone, particularly compositions
- 15 prepared by wet granulation, have been found to exhibit improved bioavailability relative to other compositions.

Wetting Agents

- Celecoxib is largely insoluble in aqueous solution. Accordingly, the pharmaceutical compositions of the present invention optionally but preferably
- 20 comprise one or more pharmaceutically acceptable wetting agents as a carrier material. Such wetting agents are preferably selected to maintain celecoxib in close association with water, a condition that is believed to improve the relative bioavailability of the pharmaceutical composition. Suitable wetting agents include, either individually or in combination, oleic acid; glyceryl monostearate; sorbitan
- 25 monooleate; sorbitan monolaurate; triethanolamine oleate; polyoxyethylene sorbitan monooleate; polyoxyethylene sorbitan monolaurate; sodium oleate; and sodium lauryl sulfate. Wetting agents that are anionic surfactants are preferred. 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
- 30 composition.

Sodium lauryl sulfate is a preferred wetting agent. Sodium lauryl sulfate, if present, constitutes about 0.25% to about 7%, more preferably about 0.4% to about

6%, and still more preferably about 0.5 to about 5% of the total weight of the composition.

Lubricants

The pharmaceutical compositions of the present invention optionally comprise one or more pharmaceutically acceptable lubricants and/or glidants as a carrier material. Suitable lubricants and/or glidants include, either individually or in combination, glyceryl behenate (Compritol 888); stearates (magnesium, calcium, and sodium); stearic acid; hydrogenated vegetable oils (e.g., Sterotex); talc; waxes; Stearowet; boric acid; sodium benzoate; sodium acetate; sodium fumarate; sodium chloride; DL-leucine; polyethylene glycols (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.

Other carrier materials (such as anti-adherent agents, colorants, flavors, sweeteners and preservatives) are known in the pharmaceutical art and can be included in compositions of the present invention. For example, iron oxide can be added to the composition to provide a yellow color.

Capsules and tablets

In one embodiment of the present invention, the pharmaceutical composition is in the form of unit dose capsules or tablets and comprises celecoxib in a desired amount and a binding agent. The composition preferably further comprises one or more carrier materials selected from the group consisting of pharmaceutically acceptable diluents, disintegrants, binding agents, wetting agents, and lubricants. More preferably, the composition comprises one or more carrier materials selected from the group consisting of lactose, sodium lauryl sulfate, polyvinylpyrrolidone, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. Still more preferably, the composition comprises lactose monohydrate and croscarmellose sodium. Still more preferably, the composition further comprises one or more of the

- In another embodiment, the pharmaceutical composition comprises:
- (a) about 1 to about 95 weight percent of celecoxib;
 - 5 (b) about 5 to about 99 weight percent of a pharmaceutically acceptable diluent;
 - (c) about 0.5 to about 30 weight percent of a pharmaceutically acceptable disintegrant; and
 - (d) about 0.5 to about 25 weight percent of a pharmaceutically acceptable
10 binding agent.
- In addition, this pharmaceutical composition optionally comprises:
- (e) about 0.25 to about 15 weight percent of a pharmaceutically acceptable wetting agent; and/or
 - (f) about 0.1 to about 10 weight percent of a pharmaceutically acceptable
15 lubricant.

The term "weight percent" as used herein means the weight percent of a specified ingredient based upon the total weight of all ingredients of the composition.

- In another embodiment, the pharmaceutical composition comprises:
- (a) about 1 to about 95 weight percent of celecoxib;
 - 20 (b) about 5 to about 99 weight percent of lactose;
 - (c) about 2 to about 6 weight percent of croscarmellose sodium; and
 - (d) about 0.5 to about 10 weight percent of polyvinylpyrrolidone.
- In addition, this pharmaceutical composition optionally comprises:
- (e) about 0.25 to about 7 weight percent of sodium lauryl sulfate;
 - 25 (f) about 0.1 to about 10 weight percent of magnesium stearate; and/or
 - (g) about 1 to about 99 weight percent of microcrystalline cellulose.

- In another embodiment, the pharmaceutical composition comprises:
- (a) about 80 to about 220 mg of celecoxib;
 - (b) about 30 to about 225 mg of lactose;
 - 30 (c) about 0.5 to about 25 mg of croscarmellose sodium; and
 - (d) about 0.5 to about 25 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

- (e) about 0.5 to about 25 mg of sodium lauryl sulfate;
- (f) about 0.2 to about 10 mg of magnesium stearate; and/or
- (g) about 1 mg to about 70 mg of microcrystalline cellulose.

In another embodiment, the pharmaceutical composition comprises:

- 5 (a) about 25 to about 85 weight percent of celecoxib;
- (b) about 5 to about 70 weight percent of lactose;
- (c) about 0.2 to about 5 weight percent of croscarmellose sodium; and
- (d) about 0.5 to about 7 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

- 10 (e) about 0.4 to about 6 weight percent of sodium lauryl sulfate;
- (f) about 0.2 to about 8 weight percent of magnesium stearate; and/or
- (g) about 0.1 to about 15 weight percent of microcrystalline cellulose.

The composition of this embodiment preferably is in the form of a unit dosage capsule.

15 In another embodiment, the pharmaceutical composition comprises:

- (a) about 27 to about 47 weight percent of celecoxib;
- (b) about 45 to about 65 weight percent of lactose;
- (c) about 0.5 to about 5 weight percent of croscarmellose sodium; and
- (d) about 0.5 to about 5 weight percent of polyvinylpyrrolidone.

20 In addition, this pharmaceutical composition optionally comprises:

- (e) about 0.25 to about 7 weight percent of sodium lauryl sulfate; and/or
- (f) about 0.25 to about 5 weight percent of magnesium stearate.

The composition of this embodiment preferably is in the form of a unit dosage capsule. In this embodiment, the pharmaceutical composition preferably comprises:

- 25 (a) about 32 to about 42 weight percent of celecoxib;
- (b) about 50 to about 60 weight percent of lactose;
- (c) about 0.5 to about 3 weight percent of croscarmellose sodium; and
- (d) about 1 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

- 30 (e) about 0.4 to about 6 weight percent of sodium lauryl sulfate; and/or
- (f) about 0.5 to about 3 weight percent of magnesium stearate.

In this embodiment, the pharmaceutical composition more preferably

comprises:

- (a) about 35 to about 39 weight percent of celecoxib;
- (b) about 54 to about 57 weight percent of lactose;
- (c) about 0.5 to about 2 weight percent of croscarmellose sodium; and
- 5 (d) about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

- (e) about 2 to about 4 weight percent of sodium lauryl sulfate; and/or
- (f) about 0.5 to about 2 weight percent of magnesium stearate.

In another embodiment, the pharmaceutical composition comprises:

- 10 (a) about 65 to about 85 weight percent of celecoxib;
- (b) about 8 to about 28 weight percent of lactose;
- (c) about 0.5 to about 5 weight percent of croscarmellose sodium; and
- (d) about 0.5 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

- 15 (e) about 0.25 to about 7 weight percent of sodium lauryl sulfate; and/or
- (f) about 0.25 to about 5 weight percent of magnesium stearate.

The composition of this embodiment preferably is in the form of a unit dosage capsule. In this embodiment, the pharmaceutical composition preferably comprises:

- 20 (a) about 69 to about 79 weight percent of celecoxib;
- (b) about 13.5 to about 23.5 weight percent of lactose;
- (c) about 0.5 to about 3 weight percent of croscarmellose sodium; and
- (d) about 1 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

- (e) about 0.4 to about 6 weight percent of sodium lauryl sulfate; and/or
- 25 (f) about 0.5 to about 3 weight percent of magnesium stearate.

In this embodiment, the pharmaceutical composition more preferably comprises:

- (a) about 72 to about 76 weight percent of celecoxib;
- (b) about 16.5 to about 20.5 weight percent of lactose;
- 30 (c) about 0.5 to about 2 weight percent of croscarmellose sodium; and
- (d) about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

- (e) about 2 to about 4 weight percent of sodium lauryl sulfate; and/or
- (f) about 0.5 to about 2 weight percent of magnesium stearate.

In another embodiment, the pharmaceutical composition comprises:

- (a) about 30 to about 50 weight percent of celecoxib;
- 5 (b) about 30 to about 50 weight percent of lactose;
- (c) about 0.5 to about 6 weight percent of croscarmellose sodium; and
- (d) about 0.5 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

- (e) about 1 to about 20 weight percent of microcrystalline cellulose;
- 10 (f) about 0.25 to about 7 weight percent of sodium lauryl sulfate; and/or
- (g) about 0.25 to about 5 weight percent of magnesium stearate.

The composition of this embodiment preferably is in the form of a unit dosage tablet. In this embodiment, the pharmaceutical composition preferably comprises:

- (a) about 35 to about 45 weight percent of celecoxib;
- 15 (b) about 35 to about 45 weight percent of lactose;
- (c) about 1 to about 5 weight percent of croscarmellose sodium; and
- (d) about 1 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

- (e) about 5 to about 15 weight percent of microcrystalline cellulose;
- 20 (f) about 0.4 to about 6 weight percent of sodium lauryl sulfate; and/or
- (g) about 0.5 to about 3 weight percent of magnesium stearate.

In this embodiment, the pharmaceutical composition more preferably comprises:

- (a) about 38 to about 42 weight percent of celecoxib;
- 25 (b) about 38 to about 42 weight percent of lactose;
- (c) about 1.5 to about 4.5 weight percent of croscarmellose sodium; and
- (d) about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

- (e) about 8 to about 12 weight percent of microcrystalline cellulose;
- 30 (f) about 2 to about 4 weight percent of sodium lauryl sulfate; and/or
- (g) about 0.5 to about 2 weight percent of magnesium stearate.

In another embodiment, the pharmaceutical composition comprises:

- (a) about 95 to about 105 mg of celecoxib;
- (b) about 145 to about 155 mg of lactose monohydrate;
- (c) about 0.5 to about 8 mg of croscarmellose sodium; and
- (d) about 2 to about 12 mg of polyvinylpyrrolidone.

5 In addition, this pharmaceutical composition optionally comprises:

- (e) about 3 to about 13 mg of sodium lauryl sulfate; and/or
- (f) about 0.5 to about 8 mg of magnesium stearate.

The composition of this embodiment preferably is in the form of a unit dosage capsule. In this embodiment, the pharmaceutical composition preferably comprises:

- 10 (a) about 98 to about 102 mg of celecoxib;
- (b) about 148 to about 152 mg of lactose monohydrate;
- (c) about 1.5 to about 4.5 mg of croscarmellose sodium; and
- (d) about 4.5 to about 8.5 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

- 15 (e) about 6 to about 10 mg of sodium lauryl sulfate; and/or
- (f) about 1 to about 5 mg of magnesium stearate.

In another embodiment, the pharmaceutical composition comprises:

- (a) about 195 to about 205 mg of celecoxib;
- (b) about 45 to about 55 mg of lactose monohydrate;
- 20 (c) about 0.5 to about 8 mg of croscarmellose sodium; and
- (d) about 2 to about 12 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

- (e) about 3 to about 13 mg of sodium lauryl sulfate; and/or
- (f) about 0.5 to about 8 mg of magnesium stearate.

25 The composition of this embodiment preferably is in the form of a unit dosage capsule. In this embodiment, the pharmaceutical composition preferably comprises:

- (a) about 198 to about 202 mg of celecoxib;
- (b) about 48 to about 52 mg of lactose monohydrate;
- (c) about 1.5 to about 4.5 mg of croscarmellose sodium; and
- 30 (d) about 4.5 to about 8.5 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

- (e) about 6 to about 10 mg of sodium lauryl sulfate; and/or

(f) about 1 to about 5 mg of magnesium stearate.

In another embodiment, the pharmaceutical composition comprises:

(a) about 95 to about 105 mg of celecoxib;

(b) about 92 to about 112 mg of lactose monohydrate;

5 (c) about 2 to about 13 mg of croscarmellose sodium; and

(d) about 1 to about 11 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

(e) about 20 to about 30 mg of microcrystalline cellulose;

(f) about 3 to about 13 mg of sodium lauryl sulfate; and/or

10 (g) about 0.5 to about 7 mg of magnesium stearate.

The composition of this embodiment preferably is in the form of a unit dosage tablet. In this embodiment, the pharmaceutical composition preferably comprises:

(a) about 98 to about 102 mg of celecoxib;

(b) about 100 to about 104 mg of lactose monohydrate;

15 (c) about 5 to about 10 mg of croscarmellose sodium; and

(d) about 4 to about 8.5 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

(e) about 23 to about 27 mg of microcrystalline cellulose;

(f) about 5 to about 10 mg of sodium lauryl sulfate; and/or

20 (g) about 0.5 to about 4 mg of magnesium stearate.

In another embodiment, the pharmaceutical composition comprises:

(a) about 195 to about 205 mg of celecoxib;

(b) about 199 to about 209 mg of lactose monohydrate;

(c) about 10 to about 20 mg of croscarmellose sodium; and

25 (d) about 7.5 to about 17.5 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

(e) about 45 to about 55 mg of microcrystalline cellulose;

(f) about 10 to about 20 mg of sodium lauryl sulfate; and/or

(g) about 0.5 to about 9 mg of magnesium stearate.

30 The composition of this embodiment preferably is in the form of a unit dosage tablet. In this embodiment, the pharmaceutical composition preferably comprises:

(a) about 98 to about 102 mg of celecoxib;

- (b) about 202 to about 206 mg of lactose monohydrate;
- (c) about 13 to about 17 mg of croscarmellose sodium; and
- (d) about 10.5 to about 14.5 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

- 5 (e) about 48 to about 52 mg of microcrystalline cellulose;
- (f) about 13 to about 17 mg of sodium lauryl sulfate; and/or
- (g) about 2 to about 6 mg of magnesium stearate.

Celecoxib particle size in capsules and tablets

- It has been discovered that reduction of celecoxib particle size can improve celecoxib bioavailability when administered orally in the form of capsules or tablets. Accordingly, the D_{90} particle size of the celecoxib preferably is less than about 200 μm , more preferably less than about 100 μm , still more preferably less than about 75 μm , still more preferably less than about 40 μm , and most preferably less than about 25 μm . For example, as illustrated in Example 11, reducing the D_{90} particle size of the starting material celecoxib from about 60 μm to about 30 μm can materially improve the bioavailability of the composition. In addition or alternatively, the celecoxib preferably has a mean particle size in the range of about 1 μm to about 10 μm , more preferably about 5 μm to about 7 μm .

Granulation secondary particle size and flow properties

- Although the pharmaceutical compositions of the present invention can be prepared, for example, by direct encapsulation or direct compression, they preferably are wet granulated prior to encapsulation or compression. Wet granulation, among other effects, densifies milled compositions resulting in improved flow properties, improved compression characteristics and easier metering or weight dispensing of the compositions for encapsulation or tableting. The secondary particle size resulting from granulation (*i.e.*, granule size) is not narrowly critical, it being important only that the average granule size preferably is such as to allow for convenient handling and processing and, for tablets, to permit the formation of a directly compressible mixture that forms pharmaceutically acceptable tablets.
- The desired tap and bulk densities of the granules are normally about 0.3 g/ml to about 1.0 g/ml.

Release profile of capsules and tablets

Capsule and tablet compositions of the present invention preferably are immediate release compositions that release at least about 50% of the celecoxib, as measured *in vitro*, within about 45 minutes of ingestion. More preferably, they
5 release at least about 60% of the celecoxib within about 45 minutes of ingestion. Still more preferably, they release at least about 75% of the celecoxib within about 45 minutes of ingestion.

Especially preferred capsule and tablet compositions of the invention release at least about 50% of the celecoxib within about 15 minutes of ingestion, and/or at least
10 about 60% of the celecoxib within about 30 minutes after ingestion.

Disintegration profile of capsules and tablets

Carrier materials for immediate release capsule and tablet compositions of the invention preferably are selected to provide a disintegration time of less than about 30 minutes, preferably about 25 minutes or less, more preferably about 20 minutes or
15 less, and still more preferably about 15 minutes or less.

Hardness

For tablet formulations, the complete mixture in an amount sufficient to make a uniform batch of tablets is subjected to tableting in a conventional production scale tableting machine at normal compression pressure (for example, applying a force of
20 about 1 kN to about 50 kN in a typical tableting die). Any tablet hardness convenient with respect to handling, manufacture, storage and ingestion may be employed. For 100 mg tablets, hardness is preferably at least 4 kP, more preferably at least about 5 kP, and still more preferably at least about 6 kP. For 200 mg tablets, hardness is
— preferably at least 7 kP, more preferably at least about 9 kP, and still more preferably at least about 11 kP. The mixture, however, is not to be compressed to such a degree
25 that there is subsequent difficulty in achieving hydration when exposed to gastric fluid.

Friability

For tablet formulations, tablet friability preferably is less than about 1.0%,
30 more preferably less than 0.8%, and still more preferably less than about 0.5% in a standard test.

Method of treatment

The present invention also is directed to a therapeutic method of treating a condition or disorder where treatment with a cyclooxygenase-2 inhibitor is indicated, the method comprising oral administration of a pharmaceutical composition of the present invention to a patient in need thereof. The dosage regimen to prevent, give relief from, or ameliorate the condition or disorder preferably corresponds to the once-a-day or twice-a-day treatments discussed above, but can be modified in accordance with a variety of factors. These include the type, age, weight, sex, diet, and medical condition of the patient 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 of a patient suffering from a condition or disorder where treatment with a cyclooxygenase-2 inhibitor is indicated can begin with the dosages 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. Patients undergoing treatment with a composition of the invention can be routinely monitored by any of the methods well known in the art to determine the effectiveness of therapy. Continuous analysis of such data permits modification of the treatment regimen during therapy so that optimally effective amounts of celecoxib are administered at any point in time, and so that the duration of treatment can be determined as well. In this way, the treatment regimen/dosing schedule can be rationally modified over the course of therapy so that the lowest amount of celecoxib exhibiting satisfactory effectiveness is administered, and so that administration is continued only so long as is necessary to successfully treat the condition or disorder.

Methods for preparation of celecoxib compositions

The present invention also is directed to methods for the preparation of pharmaceutical compositions comprising celecoxib. In particular, the invention is directed to methods for preparing pharmaceutical compositions comprising celecoxib in particulate form. More particularly, the invention is directed to methods for preparing celecoxib compositions in the form of discrete unit dose tablets or capsules, such that each tablet or capsule contains an amount of celecoxib sufficient to provide

a therapeutic effect for about 12 to 24 hours. Each dose unit preferably contains, for example, about 100 mg to about 200 mg of celecoxib. According to the present invention, wet granulation, dry granulation or direct compression or encapsulation methods can be employed to prepare tablet or capsule compositions of the invention.

5 Wet granulation is a preferred method of preparing pharmaceutical compositions of the present invention. In the wet granulation process, celecoxib (if desired, together with one or more carrier materials) is initially milled or micronized to the desired particle size. Although various conventional mills or grinders can be used, impact milling such as pin milling of the celecoxib provides improved blend
10 uniformity to the final composition relative to other types of milling. Cooling of the celecoxib, for example, using liquid nitrogen, may be necessary during milling to avoid heating the celecoxib to undesirable temperatures. As previously discussed, reduction of the D_{90} particle size during this milling step to less than about 200 μm , preferably less than about 100 μm , more preferably less than about 75 μm , still more
15 preferably less than about 40 μm , and most preferably less than about 25 μm , can materially increase the bioavailability of the celecoxib.

 The milled or micronized celecoxib is then blended, for example in a high shear mixer/granulator, planetary mixer, twin-shell blender or sigma mixer, with one or more carrier materials, including carrier materials milled together with the
20 celecoxib, to form a dry powder mixture. Typically, the drug is blended with one or more diluent(s), disintegrant(s) and/or binding agent(s) and, optionally, one or more wetting agent(s) in this step, but alternatively all or a portion of one or more of the carrier materials can be added in a later step. For example, in tablet formulations where croscarmellose sodium is employed as a disintegrant, it has been discovered
25 that addition of a portion of the croscarmellose sodium during the blending step (providing intragranular croscarmellose sodium) and addition of the remaining portion after the drying step discussed below (providing extragranular croscarmellose sodium) can improve disintegration of the tablets produced. In this situation, preferably about 60% to about 75% of the croscarmellose sodium is added intragranularly and about
30 25% to about 40% of the croscarmellose sodium is added extragranularly. Similarly, for tablet formulations it has been discovered that addition of microcrystalline cellulose after the drying step below (extragranular microcrystalline cellulose) can improve compressibility of the granules and hardness of the tablets prepared from the

granules.

This blending step of the process preferably comprises blending of celecoxib, lactose, polyvinylpyrrolidone and croscarmellose sodium. It has been discovered that blending times as short as three minutes can provide a dry powder mixture having a sufficiently uniform distribution of celecoxib. For example, the dry powder mixtures used in the preparation of 100 mg dose capsules (1080 kg total batch size) and 200 mg dose capsules (918 kg total batch size), respectively, had celecoxib concentrations exhibiting measured relative standard deviation values of 3.6% or less and 1.1% or less, respectively.

Water, preferably purified water, is then added to the dry powder mixture and the mixture is blended for an additional period of time, to form a wet granulated mixture. Preferably a wetting agent is used, and this is preferably first added to the water and mixed for at least 15 minutes, preferably at least 20 minutes, prior to adding the water to the dry powder mixture. The water can be added to the mixture at once, gradually over a period of time, or in several portions over a period of time. The water preferably is added gradually over a period of time. Alternatively, the wetting agent can be added to the dry powder mixture and water then can be added to the resulting mixture.

For the illustrative 100 mg dose capsules (1080 kg batch), for example, water addition rates of about 5 to about 25 kg/minute, preferably about 7 to about 20 kg/minute, and still more preferably about 8 to about 18 kg/minute, provide suitable results. An additional period of mixing after the water addition is complete is preferred to ensure the uniform distribution of the water in the mixture. For this illustrative batch additional mixing times of about 2 to about 10 minutes, preferably about 3 to about 9 minutes, and more preferably about 3 to about 7 minutes, provide suitable results. The wet granulated mixture of this batch preferably comprises about 2% to about 15%, more preferably about 4% to about 12%, and still more preferably about 6% to about 10%, water by weight.

For the illustrative 200 mg dose capsules (918 kg batch), for example, water addition rates of about 5 to about 25 kg/minute, preferably about 7 to about 23 kg/minute, and still more preferably about 8 to about 21 kg/minute, provide suitable results. An additional period of mixing after the water addition is complete is preferred to ensure the uniform distribution of the water in the mixture. For this

illustrative batch additional mixing times of about 2 to about 15 minutes, preferably about 3 to about 12 minutes, and more preferably about 3 to about 10 minutes, provide suitable results. The wet granulated mixture of this batch preferably comprises about 2% to about 15%, more preferably about 6% to about 14%, and still
5 more preferably about 8% to about 13%, water by weight.

The wet granulated mixture preferably is then wet milled, for example with a screening mill, to eliminate large agglomerations of material that form as a by-product of the wet granulation operation. If not removed, these agglomerations would prolong the subsequent fluidized bed drying operation and increase the variation with respect
10 to moisture control. For the illustrative 100 mg dose capsules (1080 kg batch) and 200 mg dose capsules (918 kg batch), for example, suitable granulations can be obtained using feed rates up to about 50%, preferably about 2% to about 30%, and still more preferably about 5% to about 20%, of maximum feed rate.

The wet granulated or wet milled mixture is then dried, for example, in an
15 oven or a fluidized bed dryer, preferably a fluidized bed drier, to form dry granules. If desired, the wet granulated mixture can be extruded or spheronized prior to drying. For the drying process, conditions such as inlet air temperature and drying time are adjusted to achieve the desired moisture content for the dry granules. It may be desirable to combine two or more granulation sections for this drying step and
20 subsequent processing steps.

For the illustrative 100 mg dose capsules (1080 kg batch) or 200 mg dose capsules (918 kg batch) discussed above, dryer inlet temperature can be fixed at 60°C although other inlet temperatures can be used, preferably in the range of about 50°C to about 70°C. Air flow rate can be varied in the range of about 1000 to about 8000
25 cubic feet per minute, preferably about 2000 to about 7000 cubic feet per minute, and more preferably about 4000 to about 7000 cubic feet per minute, with a damper opening of about 10% to about 90%, preferably about 20% to about 80%, and still more preferably about 30% to about 70%. Dryer loads of about 35% to about 100%, preferably about 50% to about 100%, and still more preferably about 90% to about
30 100%, can be used. Average loss on drying of dry granules prepared under these conditions is generally about 0.1% to about 2.0% by weight.

To the extent necessary, the dry granules are then reduced in size in preparation for compression or encapsulation. Conventional particle size reduction

equipment such as oscillators or impact mills (such as Fitz mills) can be employed. For the illustrative 100 mg dose capsules (1080 kg batch), for example, suitable granule size reduction can be obtained using feed rates of about 20% to about 70%, preferably about 30% to about 60%; mill speeds of about 20% to about 70%,
5 preferably about 40% to about 60%; and screen sizes of about 0.020 inch (0.5 mm) to about 0.070 inch (1.7 mm), preferably about 0.028 inch (0.7 mm) to about 0.040 inch (1.0 mm). For the illustrative 200 mg dose capsules (918 kg batch), for example, suitable granulations can be obtained using feed rates of about 10% to about 70%, preferably about 20% to about 60%; mill speeds of about 20% to about 60%,
10 preferably about 30% to about 50%; and screen sizes of about 0.020 inch (0.5 mm) to about 0.080 inch (1.9 mm), preferably about 0.028 inch (0.7 mm) to about 0.063 inch (1.6 mm). Smaller screen sizes such as 0.028 inch (0.7 mm), however, were observed to result in lower throughput of product. Larger screen sizes such as 0.063 inch (1.6 mm) resulted in an increased population of granules larger in size than 850 μ m.
15 Screen sizes around about 0.040 inch (1.0 mm) appear to eliminate an excessive population of granules larger in size than 850 μ m without significantly decreasing throughput.

Variation of the wet granulation and wet milling parameters discussed above can be employed to adjust granule size distributions. For example, a slight decrease in
20 granule size has been observed as mixing time increases for mixtures containing lower water amounts. It is hypothesized that where the water concentration is too low to fully activate the binding agent employed, the cohesive forces between the primary particles within the granules are insufficient to survive the shearing forces generated by the mixing blades and granule size attrition rather than growth occurs. Conversely,
25 increasing the amount of water to fully activate the binding agent allows cohesive forces between the primary particles to survive the shearing forces generated by the mixing blades and granule growth rather than attrition occurs with increased mixing time and/or water addition rate. Variation of the screen size of the wet mill tends to have a greater impact on the granule size than variation of the feed rate and/or mill
30 speed.

The dry granules are then placed in a suitable blender, such as a twin-shell blender, and optionally a lubricant (such as magnesium stearate) and any additional carrier materials are added (such as extragranular microcrystalline cellulose and/or

extragranular croscarmellose sodium in certain tablet formulations) to form a final blended mixture. Blending times depend in part upon the process equipment employed. For the 100 mg dose capsules and 200 mg dose capsules (1080 kg and 918 kg batches) discussed above, blending times of at least about 5 minutes at blender loads ranging from about 15% to about 60% and blender rotational speeds of at least about 10 revolutions per minute consistently provided a blended material that was extremely uniform with respect to celecoxib concentration. The relative standard deviations measured for unit dose blend samples were 3.9% or less and 2.2% or less for the 100 mg and 200 mg dose capsules, respectively. Where the diluents include microcrystalline cellulose, the addition of a portion of the microcrystalline cellulose during this step has been found to materially increase granule compressibility and tablet hardness. In addition, increasing the amount of magnesium stearate above about 1% to about 2% was observed to decrease tablet hardness and increase friability and dissolution time.

This final blended mixture is then encapsulated (or, if tablets are to be prepared, compressed into tablets of the desired weight and hardness using appropriately sized tooling). Conventional compression and encapsulation techniques known to those of ordinary skill in the art can be employed. Suitable results have been obtained for capsules by employing bed heights ranging from about 20 mm to about 60 mm, compaction settings ranging from about 0 to about 5 mm, and speeds from about 60,000 capsules per hour to about 130,000 capsules per hour. Weight control of the dose was observed to decrease with either (i) low speed and high compaction, or (ii) high speed and high bed heights. Accordingly, these combinations of parameters preferably are carefully controlled. It has also been discovered that slug formation can be minimized or eliminated by using the lowest compaction setting at which capsule weight control can be maintained. Where coated tablets are desired, conventional coating techniques known to those of ordinary skill in the art can be employed.

This combination of unit operations produces granules that are uniform in celecoxib content at the unit dose level, that readily disintegrate, that flow with sufficient ease so that weight variation can be reliably controlled during capsule filling or tableting, and that are dense enough in bulk so that the batch can be processed in the selected equipment and individual doses fit into the specified capsules or tablet

dies.

Use in the Preparation of Medicaments

The present invention also is directed to use of compositions of the present invention in preparation of medicaments useful in the treatment and/or prophylaxis of cyclooxygenase-2 mediated conditions and disorders.

EXAMPLES

The following examples illustrate aspects of the present invention but should not be construed as limitations. The experimental procedures used to generate the data shown are discussed in more detail below. The symbols and conventions used in these examples are consistent with those used in the contemporary pharmaceutical literature. Unless otherwise stated, (i) all percentages recited in these examples are by weight based on total composition weight, (ii) total composition weight for capsules is the total capsule fill weight and does not include the weight of the actual capsule employed, and (iii) coated tablets are coated with a conventional coating material such as Opadry White YS-1-18027A and the weight fraction of the coating is about 3% of the total weight of the coated tablet.

Example 1: 100 mg dose capsule

A capsule was prepared having the following composition:

Table 1

Ingredient	Weight fraction (%)	Amount (mg)
Celecoxib	37.04	100
Lactose monohydrate (NF, Ph Eur)	55.46	149.75
Sodium lauryl sulfate (NF, Ph Eur)	3	8.1
Povidone (K29-32 USP)	2.5	6.75
Croscarmellose sodium (NF, Ph Eur)	1	2.7
Magnesium stearate (NF, Ph Eur)	1	2.7
Total capsule fill weight	100	270

The above unit dose composition was placed in a hard gelatin capsule (white opaque, size #2) comprising titanium dioxide (USP), gelatin (NF), and blue ink (SB-6018).

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The lactose monohydrate used in each of the examples herein is commercially available from Formost Farms, Baraboo, Wisconsin. The Ac-Di-Sol brand of croscarmellose sodium used in each of the examples herein is commercially available from FMC Corporation, Chicago, Illinois. The sodium lauryl sulfate used in each of the examples herein is commercially available from Henkel Corporation, Cincinnati, Ohio. The povidone (polyvinylpyrrolidone) used in each of the examples herein is commercially available from International Specialty Products. The magnesium stearate used in each of the examples herein is commercially available from Mallinckrodt Inc., St. Louis, Missouri. The Opadry White YS-1-18027A used to prepare the coated tablets disclosed in the examples of this application is a ready-to-coat coating formulation commercially available from Colorcon, West Point, Pennsylvania.

Capsule doses of any desired strength from 25 mg to 225 mg can be accommodated by adjusting the weight of celecoxib and correspondingly increasing or decreasing the amount of lactose as necessary to provide a total fill weight of 270 mg.

Example 2: 200 mg dose capsule

A capsule was prepared having the following composition:

Table 2

Ingredient	Weight fraction (%)	Amount (mg)
Celecoxib	74.07	200
Lactose monohydrate (NF, Ph Eur)	18.43	49.75
Sodium lauryl sulfate(NF, Ph Eur)	3	8.10
Povidone (K29-32 USP)	2.5	6.75
Croscarmellose sodium	1	2.7
Magnesium stearate (NF, Ph Eur)	1	2.7
Total capsule fill weight	100	270

The above unit dose composition was placed in a hard gelatin capsule (white opaque, size #2) comprising titanium dioxide (USP), gelatin (NF), and blue ink (SB-6018).

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Example 3: 100 mg dose tablet

Tablets were prepared having the following composition:

Table 3

Ingredient	Amount/tablet (mg)	Weight fraction (%)	Amount/batch (kg)
Celecoxib	100	40	6.40
Lactose monohydrate (NF)	101.88	40.75	6.52
Sodium lauryl sulfate (NF)	7.5	3	0.48
Povidone (K29/32, USP)	6.25	2.5	0.40
Croscarmellose sodium (Type A, NF)	7.5	3	0.48
Microcrystalline cellulose (Avicel PH-102, NF)	25	10	1.60
Magnesium stearate (NF)	1.88	0.75	0.12
Total	250.01	100	16
Opadry White YS-1-18027A	7.50		

The tablets prepared were 0.210 inch x 0.465 inch (5.0 mm x 11.2 mm) modified oval shaped tablets.

The Avicel brand of microcrystalline cellulose was used in the preparation of the tablets of Examples 3 and 4 and is commercially available from FMC Corporation, Philadelphia, Pennsylvania.

Tablet dose strengths between 25 mg to 225 mg can be accomodated by increasing or decreasing the amounts of celecoxib and each of the carrier materials described above so as to maintain the same weight fractions exemplified above.

Example 4: 200 mg dose tablet

Tablets were prepared having the following composition:

Table 4

Ingredient	Amount/tablet (mg)	Weight fraction (%)	Amount/batch (kg)
Celecoxib	200	40	6.40

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Ingredient	Amount/tablet (mg)	Weight fraction (%)	Amount/batch (kg)
Lactose monohydrate (NF)	203.75	40.75	6.52
Sodium lauryl sulfate (NF)	15	3	0.48
Povidone (K29/32, USP)	12.5	2.5	0.40
Croscarmellose sodium (Avicel PH-102, NF)	15	3	0.48
Microcrystalline cellulose (Type A, NF)	50	10	1.60
Magnesium stearate (NF)	3.75	0.75	0.12
Total	500	100	16
Opadry White YS-1-18027A	15.0		

The tablets prepared were 0.275 inch x 0.496 inch (6.6 mm x 11.9 mm) modified capsule shaped tablets.

Example 5: Disintegration tests

Tablets were prepared as in Examples 3 and 4 except that they were left
5 uncoated. Six identical tablets were separately placed into one of six tubes having a wire mesh screen bottom in a disintegration basket. A water bath was preheated to 37°C ± 2°C and maintained at that temperature for the duration of the disintegration test. A 1000 ml beaker was placed in the water bath. The beaker was filled with a sufficient amount of water to ensure that the wire mesh screen of the tubes would
10 remain at least 2.5 cm below the water surface during the test. The disintegration basket was inserted in the water and repeatedly raised and lowered until the test was complete while maintaining the wire mesh screen of the tubes at least 2.5 cm below the water surface. Disintegration time for each tablet was the time, measured from time of insertion of the basket, at which the very last portion of the tablet passed
15 through the screen at the bottom of the tube. The mean results for the uncoated tablets of Examples 3 and 4 are reported in Table 5.

Table 5

Tablet	Disintegration time
Example 3: 100 mg dose tablet (uncoated)	4 minutes 35 seconds
Example 4: 200 mg dose tablet (uncoated)	7 minutes 40 seconds

Example 6: Dissolution tests

The apparatus of USP method 2 (with paddles) was used to determine the dissolution rate of the capsules of Examples 1 and 2 and the tablets of Examples 3 and 4, which for the purpose of these tests were left uncoated. A 1% sodium lauryl sulfate/0.04M Na₂PO₄ (pH = 12) solution, 1000 ml, was used as the dissolution fluid. The solution was maintained at a temperature of 37°C ± 5°C and stirred at 50 rpm during the test. Twelve identical tablets or capsules were tested. The 12 tablets or capsules were each separately placed in one of 12 standard dissolution vessels, and at each of 15, 30, 45 and 60 minutes later, a 5 ml aliquot of solution was removed from each vessel. The sample from each vessel was filtered and the absorbance of the sample measured (UV spectrophotometer; 2 mm pathlength quartz cell; 243 nm or wavelength of UV maxima; blank: dissolution medium). Percent dissolution was calculated based on the measured absorbances. The mean results of the dissolution tests are reported in Table 6. Note that solubility at the elevated pH of these test conditions is not indicative of solubility in the gastrointestinal tract.

Table 6

Composition	% Dissolved			
	15 minutes	30 minutes	45 minutes	60 minutes
Example 1: 100 mg capsule	89	99	100	100
Example 2: 200 mg capsule	55	82	89	92
Example 3: 100 mg tablet	81	93	94	95
Example 4: 200 mg tablet	60	96	98	98

Example 7: Particle size analysis

Table 7A shows the results of a particle size sieve analysis of the wet granulated pharmaceutical compositions of Examples 1 and 2, respectively, prior to encapsulation. "Percent retained on screen" means the percentage by weight of the

total batch having a particle size larger than the indicated sieve size.

Table 7A

Sieve size (µm)	Percent retained on screen			
	Example 1: 100 mg capsule		Example 2: 200 mg capsule	
	Lower limit	Upper limit	Lower limit	Upper limit
850	0	1.3	1.1	10.7
425	2.8	14.9	4.3	25.4
250	10.0	25.5	10.8	35.4
180	15.3	39.0	17.3	39.2
106	32.5	64.5	35.2	58.2
75	37.1	77.5	39.5	71.8
0	100	100	100	100

5 Table 7B shows the results of a particle size sieve analysis of the wet granulated pharmaceutical compositions of Examples 3 and 4, respectively, prior to compression into the tablets. "Percent of batch" means the percentage by weight of the total batch having a particle size between the indicated sieve size and the next smaller sieve size indicated. "Cumulative percent of batch" reports the percentage by weight of the total batch having a particle size larger than the indicated sieve size.

Table 7B

Sieve size (µm)	Example 3: 100 mg tablet		Example 4: 200 mg tablet	
	Percent of batch	Cumulative percent of batch	Percent of batch	Cumulative percent of batch
840 (20 mesh screen)	1	1	0.79	0.79
420 (40 mesh screen)	24.6	25.6	24.85	25.64
250 (60 mesh screen)	18.4	44	19.13	44.77
177 (80 mesh screen)	9.6	53.6	11.05	55.82

Sieve size (µm)	Example 3: 100 mg tablet		Example 4: 200 mg tablet	
	Percent of batch	Cumulative percent of batch	Percent of batch	Cumulative percent of batch
149 (100 mesh screen)	6.6	60.2	6.9	62.72
105 (140 mesh screen)	11.6	71.8	11.44	74.16
74 (200 mesh screen)	8.8	80.6	8.28	82.45
Fines	19.4	100	17.55	100

Example 8: Bulk density analysis

Table 8 shows the results of a bulk density analysis of the wet granulated pharmaceutical compositions of Examples 1, 2, 3 and 4 prior to encapsulation or compression into tablets.

5

Table 8

Composition	Bulk density (g/ml)	Tapped density (g/ml)	Loss on drying (%)
Example 1: 100 mg capsule	0.77	1.02	0.6
Example 2: 200 mg capsule	0.61	0.96	0.5
Example 3: 100 mg tablet	0.73	0.87	1.37
Example 4: 200 mg tablet	0.72	0.86	1.4

Example 9: Tablet Analysis Program

Table 9 shows the results of a tablet analysis program ("TAP analysis") for a sampling of 10 tablets having the composition of the tablets of each of Examples 3 and 4.

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Table 9

Tablet	Average weight (mg)	Average thickness (mm)	Hardness (kP)
Example 3: 100 mg tablet	248	3.85	8.2
Example 4: 200 mg tablet	500	5.22	14.6

Example 10: Friability test

Tablets collectively weighing 12 g were placed in a rotating drum. Extraneous dust was first removed from the drum and the tablets. The drum was started and rotation continued for ten minutes at a minimum of 25 rpm. The rotation of the drum was stopped and the tablets removed. Loose dust on the tablets as well as any broken tablets were removed and the intact tablets were weighed. The percent loss of the test samples from the tablets of Examples 3 and 4 was calculated and is reported below in Table 10.

Table 10

Tablet	Percent loss
Example 3: 100 mg tablet	0.33
Example 4: 200 mg tablet	0.16

Example 11-1: Bioavailability in a dog model

Healthy female beagle dogs weighing 9 to 13 pounds (4.1 to 5.9 kg) received the following single doses of celecoxib: (1) an intravenous infusion of 0.5 mg/kg body weight of celecoxib followed by a second intravenous infusion of 5.0 mg/kg body weight of celecoxib; (2) 5 mg/kg body weight celecoxib in the form of an oral solution; and (3) 5.0 mg/kg body weight of neat unformulated celecoxib in the form of an oral capsule. The vehicle for the intravenous and oral solution doses was a mixture of polyethylene glycol having an average molecular weight of 400 (PEG-400) and water in a ratio of 2:1 by volume. Each intravenous infusion was given over a period of 15 minutes with 15 to 30 minutes separating the two infusions.

Multiple blood samples were collected from each animal by venipuncture or indwelling catheter into heparinized tubes. Celecoxib concentration in blood serum was measured by HPLC and the resulting data were used to calculate the pharmacokinetic parameters presented in Table 11-1 below.

Table 11-1

Pharmacokinetic parameter	Intravenous infusion	Oral solution	Capsule, unformulated
C _{max} (ng/ml)	6950	2190	517

Pharmacokinetic parameter	Intravenous infusion	Oral solution	Capsule, unformulated
T _{max} (h)	Not applicable	0.5	3.0
AUC _{0-∞} (ng/ml)h	31200	16200	4800
Clearance (ml/min.kg)	3.08	5.14	17.4
T _{1/2} (h)	8.84	9.15	11.8
Bioavailability (%)	Not applicable	57.1	16.9

Example 11-2: Relative bioavailability of formulations in a dog model

The effect of such formulation parameters as celecoxib particle size, increased concentration of wetting agent, pH, and dispersion of celecoxib as a suspension were evaluated relative to an oral solution on bioavailability in a dog model. The effect of
5 micronizing the celecoxib (mean particle size 10-20 μm) prior to formulating was tested in composition A. The combined effect of micronization, added wetting agent (sodium lauryl sulfate), and increased micro-environmental pH (Na₂PO₄·12H₂O) was tested in composition B. The effect of bringing wetting agent (Tween 80) into intimate contact with celecoxib (co-precipitating vs. simple dry mixing) was tested in
10 composition C. The effect of further reducing particle size (approximating 1 μm) and dispersing the particles in a suspension was tested in composition D. A solution of celecoxib similar to that used in Example 11-1 (composition E) was included as a reference. In addition, data from Example 11-1 for unmilled, unformulated celecoxib in a capsule (composition F) is also included as a reference. The specific
15 compositions of formulations A, B, C, D, E and F are summarized in Table 11-2A.

Table 11-2A

Ingredient	Weight fraction (% dry basis)					
	A	B	C	D	E	F
celecoxib (micronized)	25	25				
celecoxib/tween 80 ⁽¹⁾			25			
celecoxib (dispersed) ⁽²⁾				100		
celecoxib (solution) ⁽³⁾					100	

Ingredient	Weight fraction (% dry basis)					
	A	B	C	D	E	F
celecoxib (unmilled)						100
sodium lauryl sulfate	2	25				
Avicel 101	73	25	75			
Na ₂ PO ₄ H ₂ O		25				
Total	100	100	100	100	100	100

- (1) Precipitated from ethanol solution using an aqueous solution of 5% polysorbate 80 as an antisolvent.
- (2) Prepared as a suspension by ball-milling the drug in a slurry of polysorbate 80 and polyvinylpyrrolidone until particles were approximately 1 μ m in diameter as estimated by microscopy.
- (3) Solution in PEG-400/water (2:1 v/v).

The compositions were administered to groups of three male and three female dogs. Group 1 dogs were administered 5 mg per kg body weight celecoxib in solution E and in capsule formulations A and B in a nonrandomized crossover design. Group 2 dogs were administered 5 mg per kg body weight celecoxib in capsule formulation C and in suspension D in a nonrandomized crossover design. Plasma samples were collected over a 24-hour period and analyzed for celecoxib by HPLC.

The results of the study (Tables 11-2B, 11-2C and 11-2D) indicated that decreasing the particle size (composition A) or co-precipitating the celecoxib with a wetting agent (composition C) increased the bioavailability (as measured by AUC₍₀₋₂₄₎) of celecoxib compared to the earlier study of unformulated celecoxib shown in Example 11-1. The bioavailability of celecoxib was greater from the PEG-400/water solution (composition E) and the suspension (composition D). The bioavailability from the suspension having approximately 1 μ m particle size was similar to that from the solution and provided strong indication that celecoxib availability from wet granulated solid compositions can be improved by reduced celecoxib particle size (for example by pin milling of celecoxib prior to formulation), increased wetting of the celecoxib (for example by including sodium lauryl sulfate in the granulating fluid) and improved dispersibility (for example by including croscarmellose sodium in the

granulation). The bioavailability data contained in Tables 11-2C and 11-2D for each formulation represent the bioavailability of that formulation as a percent of the bioavailability experimentally measured for intravenous administration of celecoxib, using the solution (composition E) data as a bridge between the studies of Examples 11-1 and 11-2.

Table 11-2B

Time (h)	Blood serum celecoxib concentration ($\mu\text{g/ml}$)					
	A	B	C	D	E	F
0	0	0	0	0	0	0
0.5	0.0143	0.247	0.0635	0.453	0.824	0.205
1.0	0.244	0.228	0.443	0.826	0.820	0.333
2.0	0.318	0.138	0.717	0.865	0.604	0.262
3.0	0.189	0.0860	0.492	0.741	0.517	0.517
4.0	0.145	0.0707	0.384	0.576	0.413	0.234
6.0	0.107	0.0664	0.233	0.354	0.286	--
7.0	--	--	--	--	--	0.197
8.0	0.0828	0.0624	0.160	0.234	0.187	--
12.0	0.0939	0.0431	0.0865	0.142	0.0802	--
24.0	--	0.0404	0.0408	0.0394	0.0159	--

Table 11-2C

Pharmacokinetic parameter	Value for female dogs					
	A	B	C	D	E	F
C_{max} (ng/ml)	360 ± 60	250 ± 70	790 ± 190	1010 ± 270	840 ± 240	500
T_{max} (h)	1.3 ± 0.2	0.7 ± 0.2	1.5 ± 0.3	1.7 ± 0.44	0.67 ± 0.18	3.0
Bioavailability (%)	31.2 ± 2.9	24.9 ± 1.4	46.3 ± 9.5	69.5 ± 9.6	62.4 ± 9.4	16.9

Table 11-2D

Pharmacokinetic parameter	Value for male dogs					
	A	B	C	D	E	F
C _{max} (ng/ml)	520 ± 110	450 ± 180	640 ± 260	830 ± 330	1520±200	500
T _{max} (h)	5.3 ± 3.3	3.3 ± 1.3	1.5 ± 0.5	5.7 ±3.42	1.5	3.0
Bioavailability (%)	49.4±12.0	54.2±13.1	42.9±13.1	87.5±20.6	89.4 ± 4.5	16.9

Example 11-3

Various formulations containing sodium lauryl sulfate (0-5% by weight) and croscarmellose sodium (0-5% by weight) were screened for relative wettability and disintegration tendency. Relative wettability was estimated by measuring the time required for water to penetrate a column of granulated material prepared from each formulation. Disintegration tendency was determined by measuring the weight of granulated material retained on a 20 mesh (850 mm) screen after soaking the material in 37°C water for 5 minutes. The specific compositions of compositions A through H evaluated are summarized in Table 11-3A.

Table 11-3A

Composition	Weight fraction (%)							
	A ⁽¹⁾	B	C	D	E	F	G	H
Celccoxib	74.7	74.7	74.7	74.7	74.7	74.7	74.7	74.7
Lactose	15.8	15.8	21.8	19.8	17.8	15.8	17.8	11.8
Polyvinylpyrrolidone	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sodium lauryl sulfate	3.0	3.0	0.0	1.0	1.0	1.0	3.0	5.0
Ac-di-sol	3.0	3.0	0.0	1.0	3.0	5.0	1.0	5.0
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

⁽¹⁾ Sodium lauryl sulfate was added as a dry powder

Results are summarized in Table 11-3B. Penetration tests were done in

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triplicate. Disintegration tests were done in duplicate. Results of the penetration study indicated that wet application of sodium lauryl sulfate (Composition B) was superior to dry application (Composition A) and that formulations containing 3% to 5% sodium lauryl sulfate (Compositions B, G and H) were superior to those with lesser amounts of sodium lauryl sulfate (Compositions C through F). Formulations containing 3% sodium lauryl sulfate (Compositions B and G) were similar to those containing 5% sodium lauryl sulfate (Composition H). Results of the disintegration study indicated that complete disintegration could be achieved with sodium crosscarmellose concentrations as low as 1% (Composition G) at a wetting agent concentration of 3%. Complete disintegration could also be achieved with higher amounts of disintegrant (Compositions B, F and H) regardless of wetting agent concentration. Composition G exhibited both superior penetration and complete disintegration with the minimum amount of excipient required.

Table 11-3B

Composition	% Sodium lauryl sulfate/ % Ac-di-sol	Penetration time	Disintegration
A ^(m)	3/3	>18 hours	0.1-0.5%
B	3/3	5-60 minutes	none detected
C	0/0	>4 to >18 hours	20-26%
D	1/1	>4 to >18 hours	10-13%
E	1/3	2 to 4 hours	4-6%
F	1/5	1 to 4 hours	none detected
G	3/1	10 to 40 minutes	none detected
H	5/5	10 to 55 minutes	none detected

15 **Example 12**

The following formulations were evaluated for wetting effects and mixture uniformity:

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Table 12

Ingredient	Weight fraction (%)							
	Lactose dry blend		Microcrystalline cellulose dry blend		Polyvinylpyrrolidone granulation ¹		Polysorbate 80 granulation ¹	
Celecoxib	5	60	5	60	5	60	5	60
Lactose	94.5	39.5	--	--	92	37	93.5	38.5
Microcrystalline cellulose	--	--	94.5	39.5	--	--	--	--
Polysorbate 80	--	--	--	--	--	--	1.0	1.0
Povidone (K29-32)	--	--	--	--	2.5	2.5	--	--
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

¹ In this formulation polyvinylpyrrolidone was added to the blend as a dry powder prior to granulation with water.

² In this formulation celecoxib and lactose were granulated with an aqueous solution of polysorbate 80.

The 5% celecoxib blends exhibited better blend homogeneity than the 60% celecoxib blends. The measured relative standard deviations for the 5% celecoxib blends ranged from 0.4% to 3.5% while the measured relative standard deviations for the 60% celecoxib blends ranged from 4.7% to 6.3%. In addition to being less homogeneous, the 60% celecoxib blends contained relatively large granules (greater than 420 µm) that were superpotent (containing 124% to 132% higher concentrations of celecoxib relative to other granules).

Four similar formulations were prepared containing 25% celecoxib loading instead of 5% or 60% celecoxib loading as above. The bioavailability of these formulations was evaluated in a dog model, by a procedure similar to that outlined for Examples 11-1 and 11-2. The polyvinylpyrrolidone wet granulation formulation exhibited the highest bioavailability (about 74%).

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Example 13

Capsules having the following formulations were prepared and evaluated:

Table 13A

Ingredient	Amount (mg)		
	5 mg capsule	20 mg capsule	100 mg capsule
Celecoxib	5	20	100
Lactose	92	77	61.9
Povidone (K29-32)	2.5	2.5	4
Magnesium stearate	0.5	0.5	0.8
Total	100	100	166.7
Capsule shell	1	1	1
Capsule size	#3	#3	#3

5 The celecoxib was milled by multiple passes through an oscillating mill fitted with successively smaller screen sizes (#14, #20, #40). The D_{90} particle size of the celecoxib particles added to this mixture was less than about 37 μm . Celecoxib, lactose and polyvinylpyrrolidone were mixed in a planetary mixer bowl and wet-granulated with water. The granulation was then tray dried at 60°C, milled through a 40 mesh screen, lubricated with magnesium stearate in a V-blender and encapsulated
10 on a dosator-type encapsulator. The *in vitro* dissolution profile of the capsules was determined using USP method 2 and a 15 mM phosphate buffer at pH 10 as dissolution medium. About 50% *in vitro* dissolution was achieved after about 15 minutes with greater than 95% *in vitro* dissolution after about 30 minutes.

The absorption, distribution, metabolism and elimination profile of this
15 100 mg unit dose capsule was compared to the profile of a suspension of ^{14}C -celecoxib. The study was an open-label, randomized crossover study carried out in ten healthy male subjects. The suspension was prepared by dissolving celecoxib in ethanol containing 5% polysorbate 80 and adding that mixture to apple juice prior to administration. Subjects receiving the suspension ingested a 300 mg dose of
20 celecoxib. Subjects receiving capsule-form celecoxib received three 100 mg unit dose capsules for a total dose of 300 mg of celecoxib. The rate of absorption from the

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capsule was slower than from the suspension, but was equivalent to the suspension when measured by AUC_{0-48} . Mean results are reported in Table 13B below.

Celecoxib was largely metabolized with only about 2.56% of the radioactive dose in either urine or feces.

5

Table 13B

Pharmacokinetic parameter	Suspension	Capsules
$AUC_{(0-48)}$ ((ng/ml)h)	8706.7	8763.1
C_{max} (ng/ml)	1526.5	1076.5
T_{max} (h)	1.42	1.94
$T_{1/2}$ (h)	11.53	15.57

Example 14

Capsules having the following compositions were prepared and evaluated:

Table 14

Ingredient	Amount (mg)	
	100 mg capsule	200 mg capsule
Celecoxib	100	200
Lactose	223.4	120.1
Povidone (K29-32)	8.3	8.3
Magnesium stearate	1.7	5
Total	333.4	333.4
Capsule size	#1	#1

- 10 These formulations were prepared in a manner similar to the formulations of Example 13 except that an impact-type pin mill was used instead of an oscillating mill. Particle size was further reduced by use of the pin mill. For the 100 mg capsule about 30% *in vitro* dissolution was achieved after about 15 minutes with greater than 85% *in vitro* dissolution after about 30 minutes. For the 200 mg capsule about 50% *in vitro* dissolution was achieved after about 15 minutes with greater than 85% *in vitro*

dissolution after about 30 minutes.

Example 15: Preparation of 100 mg dose capsules

Capsules providing a 100 mg or 200 mg dose of celecoxib, and having the composition shown in Examples 1 or 2 respectively, can be prepared in accordance with acceptable pharmaceutical manufacturing practices in the manner illustrated by Figure 1 or Figure 2. Tablets providing a 100 mg or 200 mg dose of celecoxib, and having the composition shown in Examples 3 or 4 respectively, can be prepared by appropriately modifying the process of Figure 1 or Figure 2 to account for the extragranular addition of croscarmellose sodium and microcrystalline cellulose, and tableting instead of encapsulating the composition.

In an illustrative process for the bulk formulation of 100 mg dose capsules using the starting materials described below, a typical batch consists of four identical granulation sections, although the number of granulation sections is not narrowly critical and depends largely upon equipment handling capacity and batch size needed.

Milling. The celecoxib was milled in an impact-type pin mill with counter rotating disks. At mill speeds ranging from about 8960 rpm/5600 rpm to about 11200 rpm/5600 rpm (rotating rpm/counter-rotating rpm), particle size varied within relatively narrow ranges (D_{90} of 30 μ m or less) suggesting that mill speed is not narrowly critical to the bulk drug micronization process. Figure 2 is a flow diagram showing a preferred embodiment wherein the celecoxib starting material is impact milled, preferably with a pin mill, prior to blending with the carrier materials.

Dry mixing. The celecoxib, lactose, polyvinylpyrrolidone and croscarmellose sodium were transferred to a 1200 L Niro Fielder PMA-1200 high speed granulator and mixed for about 3 minutes at fast chopper and impeller speeds. This dry mixing time provided adequate mixing of celecoxib with the carrier materials prior to the start of the wet granulation step.

Wet granulation. Sodium lauryl sulfate (8.1 kg) was dissolved in purified USP water (23.7 kg). The resulting solution was progressively added to the granulator at a rate of about 14 kg/minute. Total granulation time was about 6.5 minutes. During this granulation, the main blade and chopper blade of the granulator were placed on the fast speed setting. The wet granulated mixture contained about 8.1% water by weight. Alternatively, the sodium lauryl sulfate can be mixed with the celecoxib, lactose,

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polyvinylpyrrolidone and croscarmellose sodium in the dry mixing step and purified USP water can be added to this dry mixture comprising sodium lauryl sulfate.

Drying. The product of the wet granulation operation was delumped using a Quadro Comil Model 198 S screening mill equipped with rotating impeller and a coarse screen. Wet milling was used to eliminate large material lumps that formed as a by-product of the wet granulation operation. If not removed, these lumps would have prolonged the subsequent fluidized bed drying operation and increased the variation with respect to moisture control. The delumped granules were transferred to an Aeromatic Fluid Bed Dryer T-8. The inlet air temperature and flow rate were adjusted to about 60°C and about 5000 to 6000 ft³/minute (about 140 to 170 m³/minute). The granules were dried in the fluidized bed dryer to reduce the moisture content to 0.5% to 2.5%. Moisture content was monitored using a Computrac Moisture Analyzer. Drying continued until the loss on drying of the granulation was not more than 1.0%. It may be desirable to combine two or more granulation sections for this drying step and subsequent processing steps.

Dry milling. The dry granules were passed through a Fluid Air Mill Model 007 impact (conventional hammer) mill equipped with a 0.028 inch to 0.063 inch (0.7 mm to 1.5 mm) screen, knives forward, and operated at 2400 rpm speed. Dry milling was used in combination with the wet granulation step to control the final size distribution of the granules.

Blending and lubrication. The milled granules were then placed in a PK Cross-Flow Blender 75 Cubic Foot diffusion mixer/V-blender. The magnesium stearate was added and the mixture blended for about 5 minutes. The blending time provided blended material that was uniform with respect to the concentration of celecoxib. Blender rotational speed was 10.6 revolutions per minute. The final blend was used to combine materials from multiple granulation sections into a single uniform mixture and to evenly distribute lubricant into the material prior to encapsulation.

Encapsulation. The granulated powder blend was encapsulated using an MG2 G100 or G120 encapsulator. The capsules were polished.

The above sequence of unit operations produced granules that were highly uniform in celecoxib content at the unit dose level, that readily dissolved *in vitro*, that

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flowed with sufficient ease so that weight variation could be reliably controlled during capsule filling, and that were dense enough in bulk so that the batch could be processed in the selected equipment and individual doses fit into the specified capsules.

5 Example 16: Bioequivalency study

The bioequivalency and safety of 200 mg doses of celecoxib were evaluated in an open-label, randomized, single dose, three-way crossover study of a group of 46 healthy adult humans. The subjects received three single 200 mg doses of celecoxib administered as (A) one 200 mg dose capsule, (B) two 100 mg dose capsules, or (C) two 100 mg dose capsules (from a different batch run). Treatments were separated by seven days. The specific pharmaceutical compositions of the 100 mg dose capsule and the 200 mg dose capsules are disclosed in Examples 1 and 2, respectively. The subjects, who had fasted overnight, received single oral doses of the study medication together with about 180 ml of water at 0800 hours. The subjects continued to fast and remained in an upright position for four hours after dose administration. Blood samples were collected at -0.25 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours post dose. Analyses of the separated plasma were performed at PPD Pharmaco, Richmond, VA. Celecoxib plasma concentrations were determined using a validated high performance liquid chromatography ("HPLC") procedure with a lower limit of detection of 10.0 ng/ml. Each subject was separately tested. A minimum seven day wash-out period was allowed between administration of each single 200 mg dose. The mean results obtained from the 46 subjects tested are reported in Tables 16A and 16B below.

Table 16A

Time (h)	Plasma celecoxib concentration (ng/ml)		
	One 200 mg capsule	Two 100 mg capsules (Batch 1)	Two 100 mg capsules (Batch 2)
-0.25	0.22	0.00	0.00
0.5	103.74	117.89	212.61
1.0	418.24	446.39	647.00
1.5	575.68	606.97	826.90
2.0	646.83	656.98	862.23

Time (h)	Plasma celecoxib concentration (ng/ml)		
	One 200 mg capsule	Two 100 mg capsules (Batch 1)	Two 100 mg capsules (Batch 2)
3.0	686.19	666.55	781.13
4.0	621.02	595.21	660.15
6.0	389.00	387.41	383.81
8.0	322.24	332.51	323.59
12.0	214.63	208.06	209.96
16.0	149.11	146.40	144.23
24.0	116.09	111.77	113.21
36.0	52.76	48.27	46.98
48.0	27.24	26.47	22.44

Table 16B

Pharmacokinetic parameter	Value of pharmacokinetic parameter		
	One 200 mg capsule	Two 100 mg capsules (Batch 1)	Two 100 mg capsules (Batch 2)
AUC ₍₀₋₄₈₎ ((ng/ml)h)	8107.07	7976.56	8535.49
AUC _(0-LQC) ((ng/ml)h)	8063.17	7953.71	8501.94
AUC _(0-∞) ((ng/ml)h)	8828.64	8640.46	9229.52
C _{max} (ng/ml)	801.19	815.21	959.50
T _{max} (h)	2.46	2.84	2.23
T _{1/2} (h)	12.22	13.52	10.67
C _{min} /AUC _(0-LQC)	0.10	0.10	0.20

Example 17: Effect of food study

- An open-label randomized, single dose, four-way crossover study was employed to evaluate the dose proportionality and the effect of food on the pharmacokinetic profile of celecoxib in healthy adult subjects. Safety was assessed based on adverse events, vital signs and clinical laboratory tests. Twenty four healthy adult subjects were randomized to receive the following single doses of celecoxib: (A) a 50 mg dose capsule under fasting conditions, (B) a 50 mg dose capsule immediately following a high fat breakfast, (C) a 100 mg dose capsule under fasting conditions,

and (D) a 100 mg dose capsule immediately following a high fat breakfast. The subjects received the study medication on days 1, 8, 15 and 22 in one of four treatment sequences (ADBC; BACD; CBDA; and DCAB). The specific composition of the 100 mg dose capsule is disclosed in Example 1. The specific composition of the 50 mg dose capsule is disclosed in Table 17A below:

Table 17A

Ingredient	Amount (mg)
Celecoxib	50.00
Lactose monohydrate	199.8
Sodium lauryl sulfate	8.1
Povidone (K29-32)	6.8
Croscarmellose sodium	2.7
Magnesium stearate	2.7
Total capsule fill weight	270.0

The above unit dose composition was placed in a hard gelatin capsule (white opaque, size #2).

Blood samples were collected at -0.25 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours post dose. Analyses of the separated plasma were performed at PPD Pharmaco, Richmond, VA. Celecoxib plasma concentrations were determined using a validated high performance liquid chromatography ("HPLC") procedure with a lower limit of detection of 10.0 ng/ml. There were no clinically significant changes in vital signs or physical examinations. All adverse events were mild in severity. The mean results obtained from the 24 subjects tested are reported in Tables 17B and 17C below.

Table 17B

Time (h)	Plasma celecoxib concentration (ng/ml)			
	100 mg capsule (fasting)	100 mg capsule (high fat breakfast)	50 mg capsule (fasting)	50 mg capsule (high fat breakfast)
-0.25	0.00	0.00	0.00	0.00

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Time (h)	Plasma celecoxib concentration (ng/ml)			
	100 mg capsule (fasting)	100 mg capsule (high fat breakfast)	50 mg capsule (fasting)	50 mg capsule (high fat breakfast)
0.5	63.96	1.35	52.90	2.38
1.0	225.65	14.00	155.07	11.98
1.5	344.77	49.37	202.22	29.85
2.0	354.45	139.43	220.15	63.00
3.0	348.03	438.99	253.85	186.94
4.0	333.86	600.00	244.80	298.23
6.0	196.53	355.65	118.58	188.90
8.0	152.35	314.54	91.79	165.85
12.0	121.08	179.04	61.13	88.76
16.0	86.13	102.12	39.51	51.86
24.0	61.77	49.31	28.22	22.81
36.0	38.00	17.88	10.69	8.75
48.0	17.77	7.91	5.77	3.80

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Table 17C

Pharmacokinetic parameter	Value of pharmacokinetic parameter			
	100 mg capsule (fasting)	100 mg capsule (high fat breakfast)	50 mg capsule (fasting)	50 mg capsule (high fat breakfast)
AUC _(0-4h) ((ng/ml)h)	4463.28	5214.86	2426.23	2601.10
AUC _(0-12h) ((ng/ml)h)	4415.59	5105.50	2352.68	2501.56
AUC _(0-∞) ((ng/ml)h)	5126.74	5419.21	2693.80	2759.42
C _{max} (mg/ml)	455.00	746.96	321.46	354.17
T _{max} (h)	2.60	5.00	2.92	4.46
T _{1/2} (h)	16.02	6.86	11.01	6.49
C _{max} /AUC _(0-12h)	0.11	0.15	0.16	0.16

Example 18: Pharmacokinetics of suspension versus capsule formulation

The pharmacokinetics and bioavailability of an oral fine suspension and two oral capsules containing celecoxib were evaluated in an open-label, randomized, single dose, crossover study. Thirty six healthy adult subjects were randomized to receive the following single doses of celecoxib: (A) one 200 mg dose capsule, (B) two 100 mg dose capsules, and (C) a 200 mg oral fine suspension. The entire treatment duration was 18 days. On days 1, 8 and 15 the subjects received one of the three treatments according to a randomization schedule. Treatments were separated by seven days. The specific pharmaceutical composition of the 200 mg dose capsule is disclosed in Example 2. The specific pharmaceutical composition of the 100 mg dose capsules is disclosed in Table 18A below.

Table 18A

Ingredient	Amount (mg)	Weight %
Celecoxib	100.0	60.0
Lactose Monohydrate	61.7	37.0
Povidone, K29-32	4.20	2.51

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Ingredient	Amount (mg)	Weight %
Magnesium Stearate	0.80	0.48

The pharmaceutical composition used in the 100 mg dose capsules was prepared by passing the celecoxib starting material through a 40 mesh oscillating screen (no other milling was performed), wet granulating the celecoxib, lactose and povidone in a low shear planetary mixer, tray drying and milling the granulated mixture, adding magnesium stearate to the granulated mixture and blending to form the final pharmaceutical composition.

The oral fine suspension was prepared by dissolving celecoxib in ethanol containing 5% polysorbate 80 and adding that mixture to apple juice prior to administration.

Blood samples were collected at -0.25 (predose) and through 72 hours post dose. Each subject was separately tested after receiving the 200 dose mg capsule, 100 mg dose capsules and oral fine suspension. A minimum of a seven day wash-out period was allowed between administration of each 200 mg dose. The mean results obtained from the 36 subjects tested are reported in Table 18B below.

Table 18B

Pharmacokinetic parameter	Value of pharmacokinetic parameter		
	Two 100 mg capsules	One 200 mg capsule	200 mg oral fine suspension
AUC ₍₀₋₇₂₎ ((ng/ml)h)	7247.5 ± 2427.5	7648.1 ± 2412.1	7736.2 ± 2488.2
AUC _(0-∞) ((ng/ml)h)	7562.4 ± 2494.0	7830.3 ± 2448.4	8001.2 ± 2535.6
C _{max} (ng/ml)	619.7 ± 249.4	704.6 ± 265.7	1228.8 ± 452.0
T _{max} (h)	3.00 ± 0.99	2.83 ± 1.06	0.79 ± 0.32
T _{1/2} (h)	13.96 ± 5.27	11.92 ± 3.60	13.33 ± 6.69
Clearance ₍₀₋₇₂₎ (l/h)	30.4 ± 9.8	28.4 ± 7.8	28.1 ± 7.8

In general, the rate of celecoxib absorption (higher C_{max} and shorter T_{max}) was greater for the oral fine suspension than for the capsules. The overall extent of celecoxib absorption for the oral fine suspension, however, as measured by AUC₍₀₋₇₂₎ or AUC_(0-∞), was similar to the overall extent of celecoxib absorption for the capsules.

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As various changes could be made in the above formulations and methods without departing from the scope of the invention, it is intended that all matter contained in the above description be interpreted as illustrative and not in a limiting sense.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, wherein a single dose unit, upon oral administration to a fasting subject, provides a time course of blood serum concentration of celecoxib characterized by at least one of
 - (a) a time to reach 100 ng/ml not greater than about 0.5 h after administration;
 - 10 (b) a time to reach maximum concentration (T_{max}) not greater than about 3 h after administration;
 - (c) a duration of time wherein concentration remains above 100 ng/ml not less than about 12 h;
 - (d) a terminal half-life ($T_{1/2}$) not less than about 10 h; and
 - 15 (e) a maximum concentration (C_{max}) not less than about 200 ng/ml.
2. A composition of Claim 1 wherein the time course of blood serum concentration of celecoxib is characterized by a T_{max} not greater than about 3 h, preferably not greater than about 2 h, and more preferably not greater than about 1.7 h, after administration.
- 20 3. A composition of Claim 1 wherein the C_{max} is not less than about 200 ng/ml, preferably not less than about 400 ng/ml.
4. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, and having relative bioavailability not less than about 50%, preferably not less than about 70%, by comparison with an orally delivered solution containing an equivalent amount of celecoxib.
- 25 5. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, and having a distribution of celecoxib particle sizes
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such that D_{90} of the particles is less than 200 μm , preferably less than 100 μm , more preferably less than 40 μm , and most preferably less than 25 μm , in the longest dimension of said particles.

- 5 6. A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, and having a mean celecoxib particle size of about 1 μm to about 10 μm .
- 10 7. A composition of any of Claims 1 to 6 wherein the amount of celecoxib in each dose unit is about 50 mg to about 800 mg, preferably about 75 mg to about 400 mg, and more preferably about 100 mg to about 200 mg.
8. A composition of any of Claims 1 to 7 that is suitable, by oral administration to a subject of a dose unit once or twice a day, for providing therapeutically or prophylactically effective inhibition of cyclooxygenase-2.
- 15 9. A composition of any of Claims 1 to 7 that is suitable, by oral administration to a subject of a dose unit once or twice a day, for treatment or prophylaxis of a cyclooxygenase-2 mediated condition or disorder.
10. A composition of any of Claims 1 to 9 wherein said dose units are in a form of discrete solid articles.
- 20 11. A composition of Claim 10 wherein said articles are tablets, pills, hard or soft capsules, lozenges, sachets or pastilles.
12. A composition of Claim 10 in the form of unit dosage capsules or tablets.
13. A composition of Claim 12 wherein said excipients are selected from the group consisting of pharmaceutically acceptable diluents, disintegrants, binding agents, wetting agents and lubricants.
- 25 14. A composition of Claim 12 wherein said excipients include one or more pharmaceutically acceptable diluents in a total amount of about 5% to about 99% by weight, preferably about 10% to about 85% by weight, of the composition.

15. A composition of Claim 14 wherein said diluents are selected from the group consisting of lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose, dibasic calcium phosphate, sucrose-based diluents, confectioner's sugar, monobasic calcium sulfate monohydrate, calcium sulfate dihydrate, calcium lactate trihydrate, dextrates, Celutab, inositol, hydrolyzed cereal solida, amylose, Rexcel, powdered cellulose, calcium carbonate, glycine and bentonite.
16. A composition of Claim 14 wherein said diluents are selected from the group consisting of lactose and microcrystalline cellulose.
17. A composition of Claim 14 wherein said diluents comprise lactose.
18. A composition of Claim 12 wherein said excipients include one or more pharmaceutically acceptable disintegrants in a total amount of about 0.2% to about 30% by weight, preferably about 0.2% to about 10% by weight, of the composition.
19. A composition of Claim 18 wherein said disintegrants are selected from the group consisting of starches, sodium starch glycolate, clays, celluloses, alginates, pregelatinized corn starches, crospovidone and gums.
20. A composition of Claim 18 wherein said disintegrants comprise croscarmellose sodium.
21. A composition of Claim 12 wherein said excipients include one or more pharmaceutically acceptable binding agents in a total amount of about 0.5% to about 25% by weight, preferably about 0.75% to about 15% by weight, of the composition.
22. A composition of Claim 21 wherein said binding agents are selected from the group consisting of acacia, tragacanth, sucrose, gelatin, glucose, starch, celluloses, methylcellulose, sodium carboxymethylcellulose, alginic acid and salts thereof, magnesium aluminum silicate, polyethylene glycols, guar gum, polysaccharide acids, bentonites, polyvinylpyrrolidone, polymethacrylates, hydroxypropylmethylcellulose, hydroxypropylcellulose, ethylcellulose and pregelatinized starch.

23. A composition of Claim 21 wherein said binding agents comprise polyvinylpyrrolidone.
24. A composition of Claim 12 wherein said excipients include one or more pharmaceutically acceptable wetting agents in a total amount of about 0.25% to about 15% by weight, preferably about 0.4% to about 10% by weight, of the composition.
25. A composition of Claim 24 wherein said wetting agents comprise an anionic surfactant, preferably sodium lauryl sulfate.
26. A composition of Claim 12 wherein said excipients include one or more pharmaceutically acceptable lubricants in a total amount of about 0.1% to about 10% by weight, preferably about 0.2% to about 8% by weight, of the composition.
27. A composition of Claim 26 wherein said lubricants are selected from the group consisting of glyceryl behenate, stearates, stearic acid, hydrogenated vegetable oils, talc, waxes, Stearowet, boric acid, sodium benzoate, sodium acetate, sodium chloride, DL-leucine, polyethylene glycols, sodium oleate, sodium lauryl sulfate and magnesium lauryl sulfate.
28. A composition of Claim 26 wherein said lubricants comprise magnesium stearate.
29. A composition of Claim 12 comprising
- (a) one or more pharmaceutically acceptable diluents in a total amount of about 10% to about 85% by weight of the composition;
 - (b) one or more pharmaceutically acceptable disintegrants in a total amount of about 0.2% to about 10% by weight of the composition; and
 - (c) one or more pharmaceutically acceptable binding agents in an amount of about 0.5% to about 10% by weight of the composition.
30. A composition of Claim 29 further comprising (d) one or more pharmaceutically acceptable wetting agents in a total amount of about 0.4% to about 10% by weight of the composition.
31. A composition of Claim 29 or Claim 30 further comprising (e) one or more

pharmaceutically acceptable lubricants in a total amount of about 0.2% to about 8% by weight of the composition.

32. A composition of any of Claims 29 to 31 wherein said diluents comprise lactose.
- 5 33. A composition of any of Claims 29 to 32 wherein said disintegrants comprise croscarmellose sodium.
34. A composition of any of Claims 29 to 33 wherein said binding agents comprise polyvinylpyrrolidone.
35. A composition of any of Claims 30 to 34 wherein said wetting agents
10 comprise sodium lauryl sulfate.
36. A composition of any of Claims 31 to 35 wherein said lubricants comprise magnesium stearate.
37. A composition of any of Claims 12 to 36 wherein celecoxib is present in an
15 amount of about 1% to about 95% by weight, preferably about 25% to about 85% by weight, of the composition.
38. A composition of Claim 12 comprising
 - (a) about 1 to about 95 weight percent of celecoxib;
 - (b) about 5 to about 99 weight percent of lactose;
 - (c) about 2 to about 10 weight percent of croscarmellose sodium;
 - 20 (d) about 0.5 to about 10 weight percent of polyvinylpyrrolidone;
 - (e) 0 to about 7 weight percent of sodium lauryl sulfate; and
 - (f) 0 to about 5 weight percent of magnesium stearate.
39. A composition of Claim 12 comprising
 - (a) about 25 to about 85 weight percent of celecoxib;
 - 25 (b) about 5 to about 70 weight percent of lactose;
 - (c) about 0.2 to about 6 weight percent of croscarmellose sodium;
 - (d) about 0.5 to about 10 weight percent of polyvinylpyrrolidone;
 - (e) about 0.4 to about 6 weight percent of sodium lauryl sulfate; and
 - (f) about 0.2 to about 8 weight percent of magnesium stearate.
- 30 40. A composition of Claim 12 comprising

- (a) about 27 to about 47 weight percent of celecoxib;
 - (b) about 45 to about 65 weight percent of lactose;
 - (c) about 0.5 to about 5 weight percent of croscarmellose sodium; and
 - (d) about 0.5 to about 5 weight percent of polyvinylpyrrolidone.
- 5 41. A composition of Claim 12 comprising
- (a) about 32 to about 42 weight percent of celecoxib;
 - (b) about 50 to about 60 weight percent of lactose;
 - (c) about 0.5 to about 3 weight percent of croscarmellose sodium;
 - (d) about 1 to about 5 weight percent of polyvinylpyrrolidone; and
- 10 (e) about 0.4 to about 6 weight percent of sodium lauryl sulfate.
42. A composition of Claim 12 comprising
- (a) about 35 to about 39 weight percent of celecoxib;
 - (b) about 54 to about 57 weight percent of lactose;
 - (c) about 0.5 to about 2 weight percent of croscarmellose sodium;
 - 15 (d) about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone;
 - (e) about 2 to about 4 weight percent of sodium lauryl sulfate; and
 - (f) about 0.5 to about 2 weight percent of magnesium stearate.
43. A composition of Claim 12 comprising
- (a) about 65 to about 85 weight percent of celecoxib;
 - 20 (b) about 8 to about 28 weight percent of lactose;
 - (c) about 0.5 to about 5 weight percent of croscarmellose sodium; and
 - (d) about 0.5 to about 5 weight percent of polyvinylpyrrolidone.
44. A composition of Claim 12 comprising
- (a) about 69 to about 79 weight percent of celecoxib;
 - 25 (b) about 13.5 to about 23.5 weight percent of lactose;
 - (c) about 0.5 to about 3 weight percent of croscarmellose sodium;
 - (d) about 1 to about 5 weight percent of polyvinylpyrrolidone; and
 - (e) about 0.4 to about 6 weight percent of sodium lauryl sulfate.
45. A composition of Claim 12 comprising
- 30 (a) about 72 to about 76 weight percent of celecoxib;
 - (h) about 16.5 to about 20.5 weight percent of lactose;

- (c) about 0.5 to about 2 weight percent of croscarmellose sodium;
 - (d) about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone;
 - (e) about 2 to about 4 weight percent of sodium lauryl sulfate; and
 - (f) about 0.5 to about 2 weight percent of magnesium stearate.
- 5 46. A composition of Claim 12 comprising
- (a) about 30 to about 50 weight percent of celecoxib;
 - (b) about 30 to about 50 weight percent of lactose;
 - (c) about 0.5 to about 10 weight percent of croscarmellose sodium; and
 - (d) about 0.5 to about 5 weight percent of polyvinylpyrrolidone.
- 10 47. A composition of Claim 12 comprising
- (a) about 35 to about 45 weight percent of celecoxib;
 - (b) about 35 to about 45 weight percent of lactose;
 - (c) about 1 to about 5 weight percent of croscarmellose sodium;
 - (d) about 1 to about 5 weight percent of polyvinylpyrrolidone; and
 - 15 (e) about 5 to about 15 weight percent of microcrystalline cellulose.
48. A composition of Claim 12 comprising
- (a) about 38 to about 42 weight percent of celecoxib;
 - (b) about 38 to about 42 weight percent of lactose;
 - (c) about 1.5 to about 4.5 weight percent of croscarmellose sodium;
 - 20 (d) about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone;
 - (e) about 8 to about 12 weight percent of microcrystalline cellulose;
 - (f) about 2 to about 4 weight percent of sodium lauryl sulfate; and
 - (g) about 0.5 to about 2 weight percent of magnesium stearate.
49. A composition of Claim 12 comprising, in each dose unit,
- 25 (a) about 80 to about 220 mg of celecoxib;
 - (b) about 30 to about 225 mg of lactose;
 - (c) about 0.5 to about 25 mg of croscarmellose sodium;
 - (d) about 0.5 to about 25 mg of polyvinylpyrrolidone;
 - (e) 0 to about 70 mg of microcrystalline cellulose;
 - 30 (f) 0 to about 25 mg of sodium lauryl sulfate; and
 - (g) 0 to about 10 mg of magnesium stearate.

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50. A composition of Claim 12 comprising unit dosage capsules each containing
- (a) about 100 mg of celecoxib;
 - (b) about 149.75 mg of lactose monohydrate;
 - (c) about 2.7 mg of croscarmellose sodium;
 - 5 (d) about 6.75 mg of polyvinylpyrrolidone;
 - (e) about 8.1 mg of sodium lauryl sulfate; and
 - (f) about 2.7 mg of magnesium stearate.
51. A composition of Claim 12 comprising unit dosage capsules each containing
- (a) about 200 mg of celecoxib;
 - 10 (b) about 49.75 mg of lactose monohydrate;
 - (c) about 2.7 mg of croscarmellose sodium;
 - (d) about 6.75 mg of polyvinylpyrrolidone;
 - (e) about 8.1 mg of sodium lauryl sulfate; and
 - (f) about 2.7 mg of magnesium stearate.
- 15 51. A composition of Claim 12 comprising unit dosage tablets each containing
- (a) about 100 mg of celecoxib;
 - (b) about 101.88 mg of lactose monohydrate;
 - (c) about 7.5 mg of croscarmellose sodium;
 - (d) about 6.25 mg of polyvinylpyrrolidone;
 - 20 (e) about 25 mg of microcrystalline cellulose;
 - (f) about 7.5 mg of sodium lauryl sulfate; and
 - (g) about 1.88 mg of magnesium stearate.
52. A composition of Claim 12 comprising unit dosage tablets each containing
- (a) about 200 mg of celecoxib;
 - 25 (b) about 203.8 mg of lactose monohydrate;
 - (c) about 15 mg of croscarmellose sodium;
 - (d) about 12.5 mg of polyvinylpyrrolidone;
 - (e) about 50 mg of microcrystalline cellulose;
 - (f) about 15 mg of sodium lauryl sulfate; and
 - 30 (g) about 3.75 mg of magnesium stearate.
53. A composition of Claim 12 comprising unit dosage capsules or tablets each providing a 100 mg or 200 mg dose of celecoxib.

54. A composition of Claim 12 wherein the celecoxib, together with one or more excipients, is directly encapsulated or directly compressed into tablets.
55. A composition of Claim 12 wherein the celecoxib, together with one or more excipients, is wet granulated prior to encapsulation or compression into tablets.
56. A composition of Claim 12 wherein the celecoxib, together with one or more excipients, is dry granulated prior to encapsulation or compression into tablets.
57. A composition of any of Claims 1 to 9 that is a substantially homogeneous flowable mass from which single dose units are measurably removable.
- 10 58. A composition of Claim 57 wherein said flowable mass is a particulate or granular solid.
59. A composition of Claim 57 wherein said flowable mass is a suspension having the celecoxib in a solid particulate phase dispersed in an aqueous phase.
- 15 60. A composition of Claim 59 wherein said excipients include a pharmaceutically acceptable wetting agent.
61. A composition of Claim 60 wherein said wetting agent is polysorbate 80.
62. A composition of Claim 60 or 61 further comprising a solvent from which the celecoxib is precipitated to prepare the suspension.
63. A composition of Claim 62 wherein said solvent is an alcohol, preferably ethanol.
- 20 64. A composition of Claim 59 wherein the aqueous phase comprises a palatable vehicle selected from the group consisting of water, syrup and fruit juice.
65. A composition of Claim 64 wherein the vehicle is fruit juice, preferably apple juice.
- 25 66. A composition of any of Claims 1 to 65 providing, upon oral ingestion, a therapeutic effect as a cyclooxygenase-2 inhibitor over an interval of about 12 to about 24 h after ingestion.
67. A composition of Claim 66 wherein the therapeutic effect is provided over an interval of about 24 h after ingestion.

68. A composition of any of Claims 1 to 65 wherein, upon oral ingestion, at least about 50% of the celecoxib is released, as determined in vitro, within about 15 minutes after ingestion.
- 5 69. A composition of any of Claims 1 to 68 further comprising one or more opioid or analgesic drugs.
70. A composition of Claim 69 wherein said opioid or analgesic drugs are selected from the group consisting of narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic analgesics, monamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P
10 antagonists, neurokinin-1 receptor antagonists and sodium channel blockers.
71. A composition of Claim 69 wherein said opioid or analgesic drugs are selected from the group consisting of morphine, meperidine, codeine, pentacozine, buprenorphine, butorphanol, dexocine, meptazinol, hydrocodone, oxycodone, methadone, DuP 747, Dynorphine A, Enadoline, RP-60180, HN-11608,
15 E-2078, ICI-204448, acetaminophen, propoxyphene, nalbuphene, E-4018, filenadol, mirfentanil, amitriptyline, DuP 631, GP-531, acadesine, AKI-1, AKI-2, GP-1683, GP-3269, 4030W92, tramadol racemate and isolated (+) and (-) enantiomers, AXC-3742, SNX-111, ADL2-1294, CT-3 and CP-99994.
- 20 72. A method of treating a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering to the subject a composition of any of Claims 1 to 71 once or twice a day.
73. A method of Claim 72 wherein the condition or disorder is rheumatoid arthritis.
- 25 74. A method of Claim 72 wherein the condition or disorder is osteoarthritis.
75. A method of Claim 72 wherein the condition or disorder, or a symptom of the condition or disorder, is pain.
76. A method of use of a composition of any of Claims 1 to 9 in the manufacture of a medicament for the treatment or prophylaxis of a cyclooxygenase-2
30 mediated condition or disorder.

77. A method of Claim 76 wherein the condition or disorder is rheumatoid arthritis.
78. A method of Claim 76 wherein the condition or disorder is osteoarthritis.
79. A method of Claim 76 wherein the condition or disorder, or a symptom of the condition or disorder, is pain.
- 5
80. A method of preparing a composition of Claim 12 comprising
- (a) wet granulating celecoxib together with one or more excipients to form a wet granulated mixture;
 - (b) drying the wet granulated mixture; and
 - 10 (c) encapsulating the dried granulated mixture or compressing the dried granular mixture into tablets.
81. A method of Claim 80 wherein, prior to the wet granulating step, the celecoxib is milled such that D_{90} of the resulting particles is less than 200 μm , preferably less than 100 μm , more preferably less than 40 μm , and most preferably less than 25 μm , in the longest dimension of said particles.
- 15
82. A method of Claim 81 wherein said milling is performed with a pin mill to provide celecoxib particles of D_{90} less than 25 μm , in the longest dimension of said particles.
83. A method of Claim 82 wherein said milling results in a mean celecoxib particle size of about 1 μm to about 10 μm , preferably about 5 μm to about 7 μm .
- 20

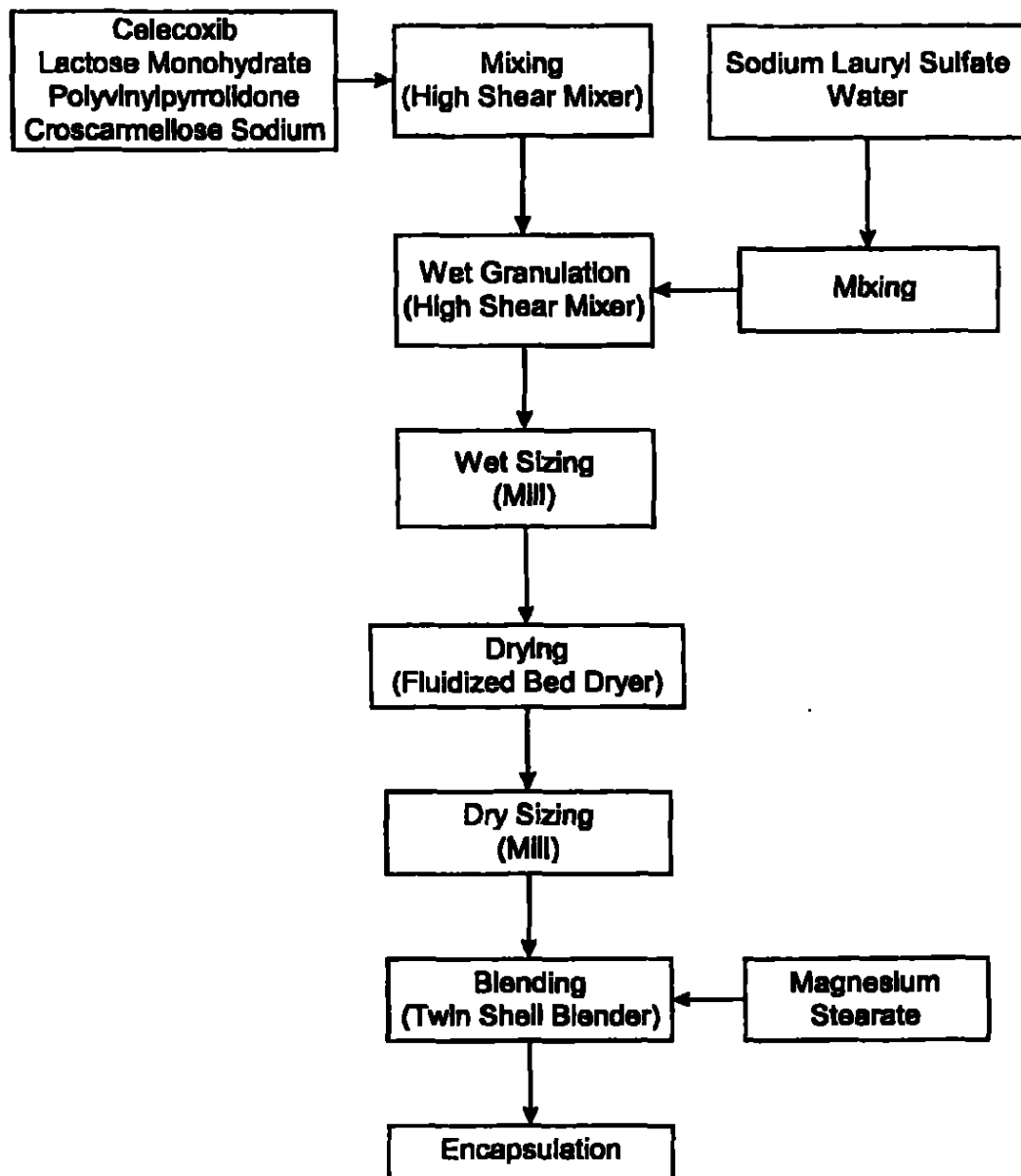


Figure 1

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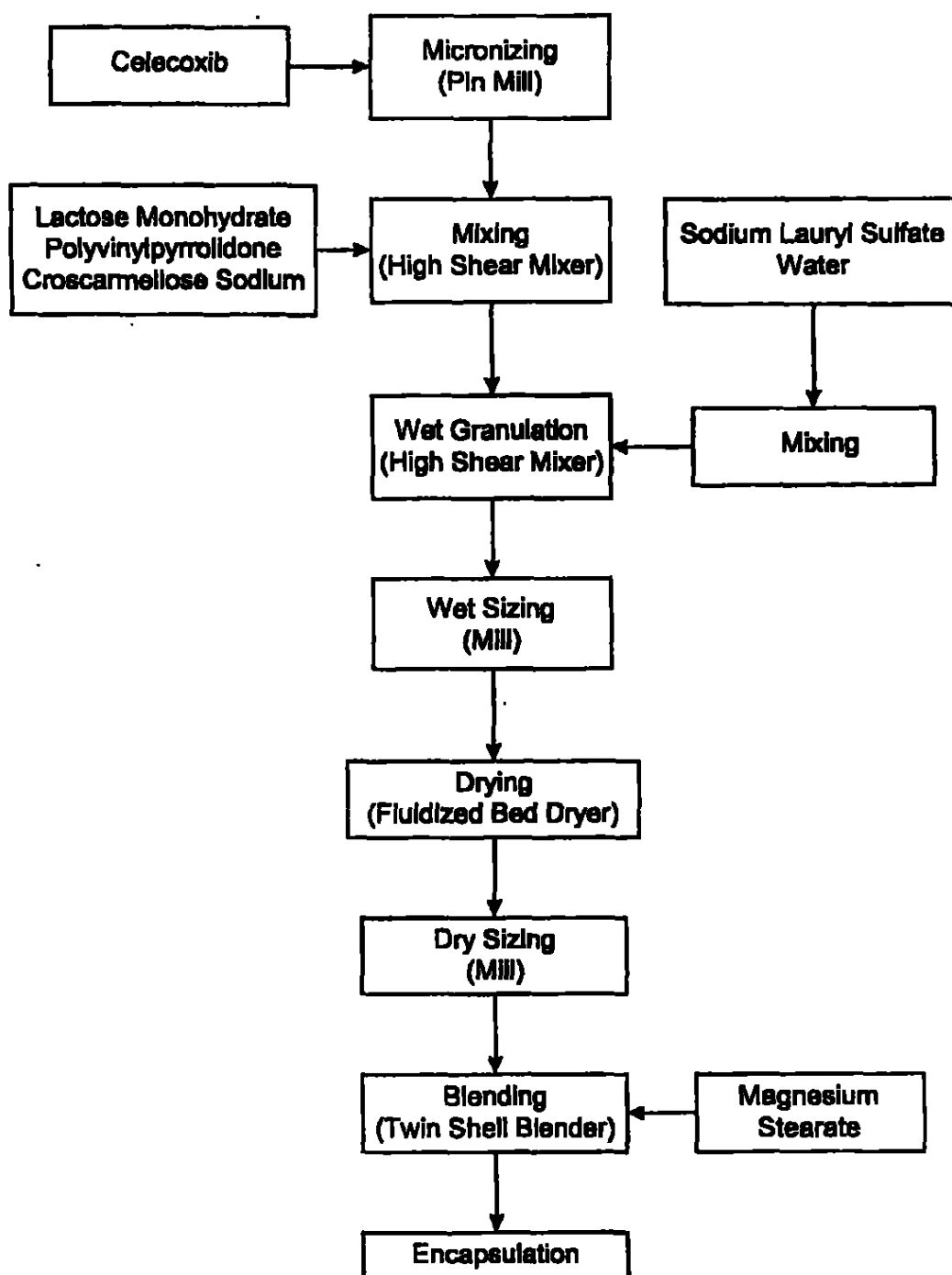


Figure 2

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