

Brigard & Castro
Abogados

Apartado 3692

Cra. 7 16-56
Bogotá - Colombia S.A.

Tel. Conm. 3802200
Tel./Fax: (57.1) 2827976
(57.1) 3802700

E.Mail:bricas@brigardycastro.com.co

AS: 84.048

Señores

**SUPERINTENDENCIA DE INDUSTRIA
DIVISION DE NUEVAS CREACIONES**

E. S. D.

REGISTRO Y COMERCIO
Radicación : 00097644 00000003 Folio 114
Fecha (RPA): 2001-07-27 16:34:25
Trámite : 002 PATENTES D I REGISTRO/ 444 MEDICINA
Procedencia: 2000 DIVISION DE NUEVAS CREACIONES

REF: Expediente No.00 097.644 - Solicitud de Patente
a favor de PHARMACIA CORPORATION
titulada: COMPOSICIONES DE LIBERACIÓN DUAL DE UN INHIBIDOR
DE CICLOOXIGENASA-2

RAMIRO CASTRO DUQUE, vecino de Bogotá, portador de la tarjeta profesional No. 1003, obrando como apoderado de la sociedad *PHARMACIA CORPORATION*, según lo acredita el documento de poder presentado en esa División, para dar cumplimiento al requerimiento notificado por fijación en lista el 29 de Marzo de 2001, cuyo término fue prorrogado mediante escrito radicado el 25 de Mayo de 2001 y de acuerdo con los artículos 38 y 39 de la Decisión 486 de la comisión de la Comunidad Andina, me permito anexar al presente escrito los siguientes documentos:

1. Documentos donde consta la cesión del derecho a la Patente otorgado por los inventores al solicitante, debidamente apostillados.
2. Copias certificadas por la Oficina de Patentes de Estados Unidos de las dos primeras solicitudes presentadas para la misma invención, de las cuales REIVINDICAMOS PRIORIDAD.

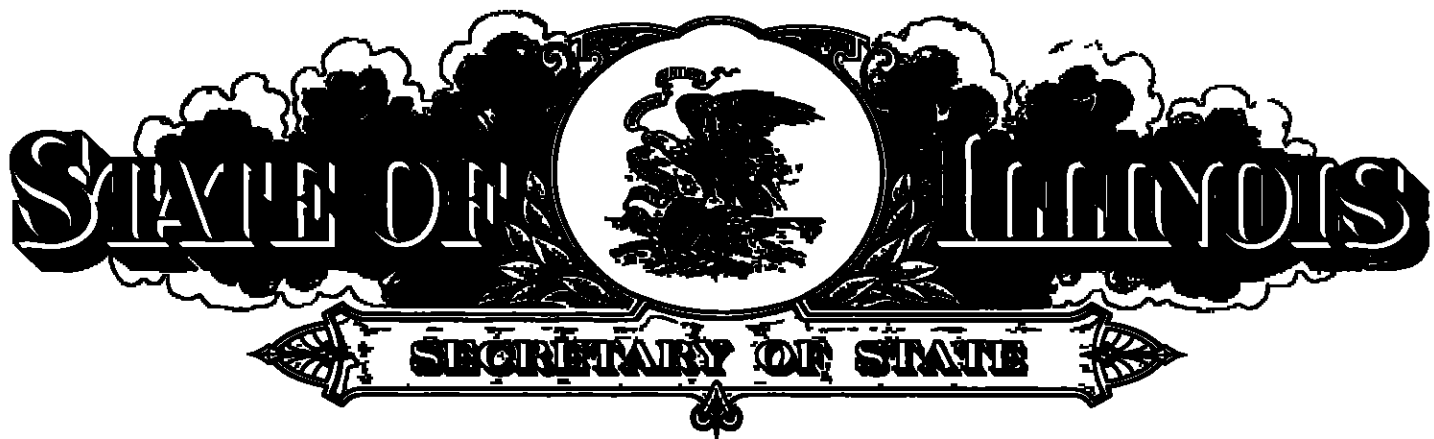
Del señor Jefe,



RAMIRO CASTRO DUQUE
C.C. No. 170.322 de Bogotá
Código 340
Cra 7 No. 16-56 Piso 9

Bogotá, Julio 27, 2001
CPB/hsr.

84248
93



SPRINGFIELD, ILLINOIS

APOSTILLE

(Convention de La Haye du 5 Octobre 1961)

1 Country United States of America

This public document

2 has been signed by DAVID D ORR

3 acting in the capacity of COUNTY CLERK, COOK COUNTY

4 bears the seal/stamp of STATE OF ILLINOIS

Certified

5 Springfield, Illinois

6 JULY 23, 2001

7 by the Secretary of State, State of Illinois

8 No 5266

9 Seal/Stamp

10 Signature

Jesse White

JESSE WHITE
SECRETARY OF STATE
STATE OF ILLINOIS

3X1K1E
94



STATE OF ILLINOIS)
) SS
COOK COUNTY)

CERTIFICATE OF AUTHORITY

I, DAVID ORR County Clerk of Cook County in the State of Illinois, certify that

Mia S. Gordon

the person named in the seal and signature on the attached document,
is a Notary Public for the State of Illinois and was authorized to
act as such at the time of the document's notarization

To verify this Certificate of Authority for a Notarial Act, I have
affixed my signature and seal of office this 20th day
of July, 2001

David Orr

Cook County Clerk, State of Illinois

Harriet Luster

Deputy

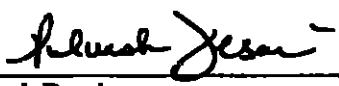
FORM N 5

COLOMBIA PATENTS

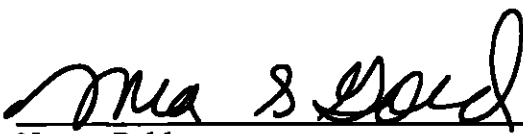
ASSIGNMENT OF PRIORITY RIGHTS

By this instrument, Subhash Desai, Sreekant Nadkarni, Randy J Wald, and Gary A. DeBrincat, being the inventor(s) of of an invention entitled DUAL-RELEASE COMPOSITIONS OF A CYCLOOXYGENASE-2 INHIBITOR for which an application for patent was filed in the Patent Office of United States of America under serial No 60/171,738 on 22 December 1999, 60/181,604 on 10 February 2000, and 60/202,270 on 05 May 2000 hereby assign(s) and Transfer(s) to PHARMACIA CORPORATION all his/her/their rights in connection with the said invention in the Republic of Colombia and declare(s) that full consent has been given in order that a corresponding application be filed in the National Department of Industrial Property of claiming priority of the said application under the International Convention

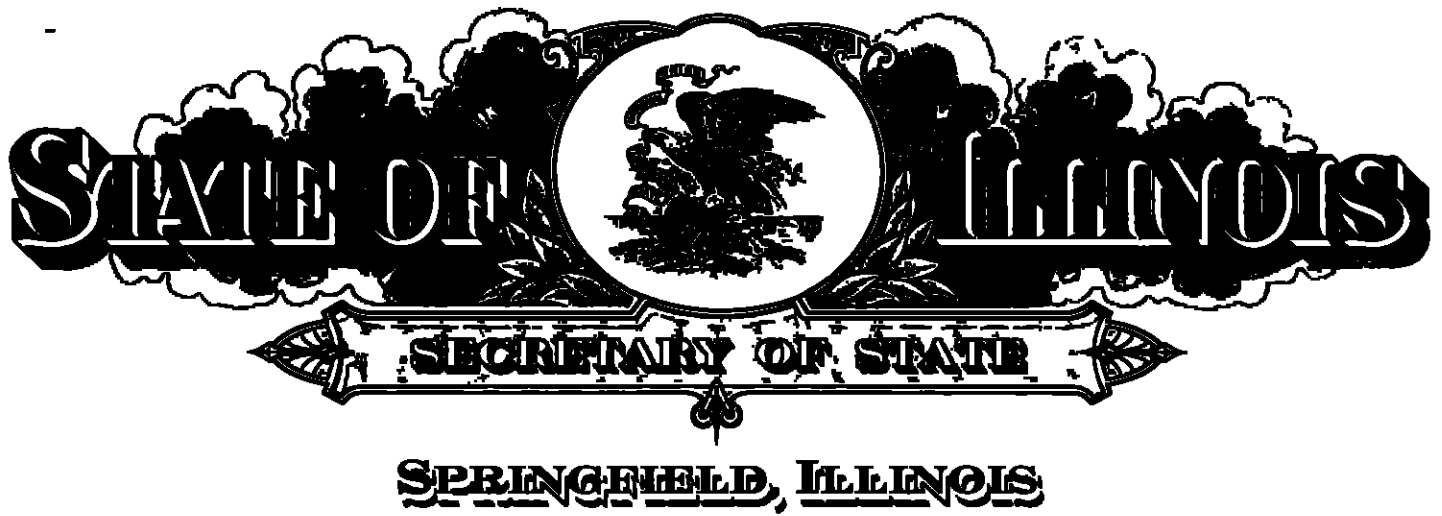
In testimony thereof the present is signed in the city of Skokie, Illinois USA on the 31st day of the month of January 2001


Subhash Desai

On this 31st day of January 2001, before me, a notary Public appeared Subhash Desai who signed this Assignment as their free and voluntary act


Notary Public





APOSTILLE

(Convention de La Haye du 5 Octobre 1961)

- 1 Country United States of America
This public document
2 has been signed by DAVID D ORR
3 acting in the capacity of COUNTY CLERK, COOK COUNTY
4 bears the seal/stamp of STATE OF ILLINOIS

Certified

- 5 Springfield, Illinois
6 JULY 23, 2001
7 by the Secretary of State, State of Illinois
8 No 5265
9 Seal/Stamp

10 Signature

Jesse White

JESSE WHITE
SECRETARY OF STATE
STATE OF ILLINOIS

STATE OF ILLINOIS)
) SS
COOK COUNTY)



SKAKIE

CERTIFICATE OF AUTHORITY

I, DAVID ORR, County Clerk of Cook County in the State of Illinois, certify that

Connie Robin

the person named in the seal and signature on the attached document, is a Notary Public for the State of Illinois and was authorized to act as such at the time of the document's notarization

To verify this Certificate of Authority for a Notarial Act, I have affixed my signature and seal of office this 20th day of July, 2001

David Orr
Cook County Clerk, State of Illinois

Harriet Tusty
Deputy

FORM N 5

COLOMBIA PATENTS

ASSIGNMENT OF PRIORITY RIGHTS

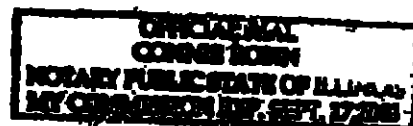
By this instrument, Subhash Desai, Sreekant Nadkarni, Randy J Wald, and Gary A. DeBrincat, being the inventor(s) of an invention entitled DUAL-RELEASE COMPOSITIONS OF A CYCLOOXYGENASE-2 INHIBITOR for which an application for patent was filed in the Patent Office of United States of America under serial No 60/171,738 on 22 December 1999, 60/181,604 on 10 February 2000, and 60/202,270 on 05 May 2000 hereby assign(s) and Transfer(s) to PHARMACIA CORPORATION all his/her/their rights in connection with the said invention in the Republic of Colombia and declare(s) that full consent has been given in order that a corresponding application be filed in the National Department of Industrial Property of claiming priority of the said application under the International Convention

In testimony thereof the present is signed in the city of Skokie, Illinois USA on the twentieth day of the month of July 2001

Sreekant Nadkarni
Sreekant Nadkarni

On this 20 day of July 2001, before me, a notary Public appeared Sreekant Nadkarni who signed this Assignment as their free and voluntary act

Cornie Koli
Notary Public



q1

COLOMBIA PATENTS

ASSIGNMENT OF PRIORITY RIGHTS

By this instrument, Gary A. DeBrincat, being one of the inventor(s) of of an invention entitled DUAL RELEASE COMPOSITIONS OF A CYCLOOXYGENASE-2 INHIBITOR for which an application for patent was filed in the Patent Office of United States of America under serial No 60/171,738 on 22 December 1999, 60/181,604 on 10 February 2000, and 60/202,270 on 05 May 2000 hereby assign(s) and Transfer(s) to PHARMACIA CORPORATION all his/her/their rights in connection with the said invention in the Republic of Colombia and declare(s) that full consent has been given in order that a corresponding application be filed in the National Department of Industrial Property of claiming priority of the said application under the International Convention

In testimony thereof the present is signed in the city of Kalamazoo, Michigan, USA on the 20th day of the month of July 2001

Gary A. DeBrincat
Gary A. DeBrincat

On this 20th day of July 2001, before me, a Notary Public in Kalamazoo County, Michigan, appeared Gary A. DeBrincat who signed this Assignment as his free and voluntary act

Debra J. Marquette

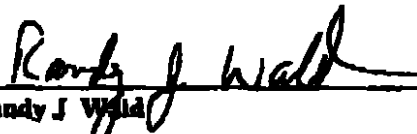
DEBRA J. MARQUETTE
Notary Public Kalamazoo County, MI
My Commission Expires 6/28/2004

COLOMBIA PATENTS

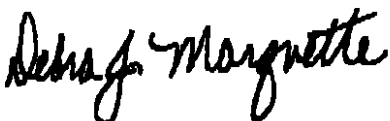
ASSIGNMENT OF PRIORITY RIGHTS

By this instrument, Randy J Wald, being one of the inventor(s) of an invention entitled, DUAL-RELEASE COMPOSITIONS OF A CYCLOOXYGENASE-2 INHIBITOR for which an application for patent was filed in the Patent Office of United States of America under serial No 60/171,738 on 22 December 1999, 60/181 604 on 10 February 2000, and 60/202,270 on 05 May 2000 hereby assign(s) and Transfer(s) to PHARMACIA CORPORATION all his/her/their rights in connection with the said invention in the Republic of Colombia and declare(s) that full consent has been given in order that a corresponding application be filed in the National Department of Industrial Property of claiming priority of the said application under the International Convention

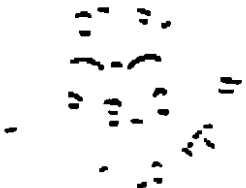
In testimony thereof the present is signed in the city of Kalamazoo, Michigan, USA on the 25th day of the month of July 2001


Randy J Wald

On this 25th day of July 2001, before me, a Notary Public in Kalamazoo County, Michigan, appeared Randy J Wald who signed this Assignment as his free and voluntary act.



DEBBA J MARQUETTE
Notary Public, Kalamazoo County, MI
My Commission Expires 03/31/2006



84048 Cides,
101 103

PA 347745



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

January 04, 2001

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

APPLICATION NUMBER 60/181,604

FILING DATE February 10, 2000

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



**H L JACKSON
Certifying Officer**

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Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(b)(2).

Docket Number	C-3280/1	Type a plus sign (+) inside this box	+
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INVENTOR(S)/APPLICANT(S)					
LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE CITY AND EITHER STATE OR FOREIGN COUNTRY		
Doss Nadkarni	Subhash Sreekant		Wilmette, Illinois Gurnee, Illinois		
TITLE OF THE INVENTION (see description and)					
DUAL-RELEASE CELECOXIB COMPOSITIONS					
CORRESPONDENCE ADDRESS					
Jennifer Amundson, Paralegal Monsanto/G. D. Searle, Mail Zone 1810 Patent Department Central P.O. Box 5110 Chicago					
STATE	ILLINOIS	ZIP CODE	60680-5110	COUNTRY	USA
ENCLOSED APPLICATION PARTS (check all that apply)					
☒ Specifications	Number of Pages	45	☐ Small Entity Statement		
☐ Drawings	Number of Sheets		Other (specify)		
METHOD OF PAYMENT (check one)					
☐ A check or money order is enclosed to cover the Provisional Filing Fee			PROVISIONAL FILING FEE AMOUNT(S)	\$150.00	
☒ The Commissioner is hereby authorized to charge Filing Fee and credit Deposit Account Number	19-1025				

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- ☒ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE

James C. Forbes

Date

February 10, 2000

TYPED or PRINTED NAME
James C. Forbes

REGISTRATION NO.
(if appropriate)

39,457

- ☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

Declaration Statement: This form is intended to take 2 hours to complete. Time will vary depending upon the needs of the individual case. Any statements on the nature of how you are required to complete this form should be sent to the Office of American Quality and Information Systems, Patent and Trademark Office, Washington, DC 20231, and to the Office of Information and Regulatory Affairs, Office of Management and Budget (Project 0471-0072), Washington, DC 20503. DO NOT SEND FORM OR COMPLETED FORMS TO THIS ADDRESS. SEND TO Assistant Commissioner for Patents, Washington, DC 20231.

PATENT
C-3280/1

PROVISIONAL UNITED STATES PATENT APPLICATION

for

DUAL-RELEASE CELECOXIB COMPOSITIONS

by

Subhash Desai and Sreekanth Nadkarni

EXPRESS MAIL MAILING LABEL	
NUMBER	TB015691258US
DATE OF DEPOSIT	February 10, 2000
I hereby certify that this Patent Application is being deposited with the United States Postal Service "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service under 37 C.F.R. §1 10 on the date indicated above and is addressed to:	
Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231	
Signature	Michelle A. Spudis

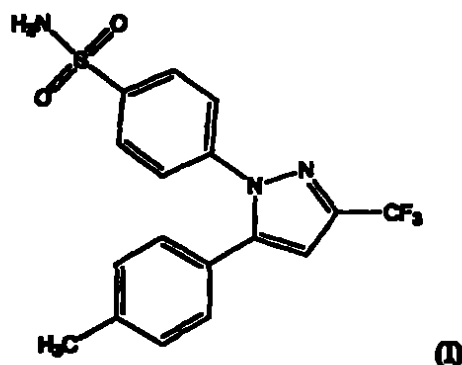
DUAL-RELEASE CELECOXIB COMPOSITIONS

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

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



Celecoxib is a hydrophobic compound and has very low solubility in water. This property has presented practical difficulties in formulating celecoxib for oral administration, particularly where early onset of therapeutic effect is desired or required. Furthermore, celecoxib has a relatively short half-life in the bloodstream following administration to a subject. This property has favored celecoxib administration regimens involving twice-a-day or more frequent administration.

A dosage form of celecoxib that simultaneously overcomes problems associated with both of these properties, thereby providing rapid onset of therapeutic

effect coupled with once-a-day administration, would represent a major advance in the art.

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 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 difficult to process the small quantities required during formulation of the pharmaceutical compositions. Accordingly, a need exists for solutions to numerous problems associated with preparation of suitable pharmaceutical compositions and dosage forms comprising celecoxib, particularly orally deliverable dose units.

In general, a need exists for orally deliverable formulations of celecoxib, such formulations possessing one or more of the following characteristics relative to unformulated celecoxib or other celecoxib compositions:

- (1) improved solubility;
- (2) shorter disintegration time;
- (3) shorter dissolution time;
- (4) decreased tablet friability;
- (5) increased tablet hardness,
- (6) improved wettability;
- (7) improved compressibility;

- (8) improved flow properties of liquid and particulate solid compositions,
(9) improved physical stability of the finished composition,
(10) reduced tablet or capsule size;
(11) improved blend uniformity;
5 (12) improved dose uniformity;
(13) improved control of weight variation during encapsulation and/or
tableting;
(14) increased granule density for wet granulated compositions,
(15) reduced water requirement for wet granulation,
10 (16) reduced wet granulation time; and
(17) reduced drying time for wet granulated mixtures.

More specifically, there exists an especial need for orally deliverable
formulations of celecoxib, such formulations providing both rapid onset of therapeutic
effect and longer duration of therapeutic effect than unformulated celecoxib or known
15 formulations of celecoxib. 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 celecoxib, such formulations providing a greater C_{max}
20 and/or an earlier T_{max} than unformulated celecoxib or known formulations of
celecoxib. At the same time, to the extent that long duration of therapeutic effect is
related to pharmacokinetic parameters such as long half-life of blood serum
concentration of the drug after C_{max} is reached, also known as terminal half-life ($T_{1/2}$),
there is an especial need for orally deliverable formulations of celecoxib, such
25 formulations providing a longer $T_{1/2}$ than unformulated celecoxib or known
formulations of celecoxib. A single composition that satisfies both the need for a
greater C_{max} and/or an earlier T_{max} and the need for a greater $T_{1/2}$ would dramatically
enhance the therapeutic utility of celecoxib in a wide variety of situations.

As is indicated hereinbelow, treatment with celecoxib is indicated or
30 potentially indicated in a very wide array of cyclooxygenase-2 mediated conditions
and disorders. It would be of benefit to provide formulations exhibiting
pharmacokinetics consistent with rapid onset and long duration of therapeutic effect

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especially for treatment of disorders where early relief from pain or other symptoms is desired or required and where once-a-day administration is required or preferred.

Cyclooxygenase-2 inhibitory drugs including celecoxib that are of low solubility in water are conveniently formulated in solid particulate form. The individual or primary particles of the drug can 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 and used in the art 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 volume of particles in the formulation, in the longest dimension of the particles, are smaller than that diameter. For practical purposes a determination of D_{90} based on 90% by weight rather than by volume is generally suitable.

For consistency with prior publications, the terms "microparticle" and "nanoparticle" are defined herein as in U.S. Patent No. 5,384,124 to Courtaille *et al.*, to refer to particles having respectively a diameter of between 1 μm and 2000 μm , and a diameter of less than 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 Liveridge *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. Illustrative processes are disclosed in the references

individually cited immediately below

- U S Patent No. 4,826,689 to Violante & Fischer
 Above-cited U.S. Patent No. 5,145,684 to Liversidge *et al.*
 U S Patent No. 5,298,262 to Na & Rajagopalan.
 5 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 Ilhg & Sarpotdar
 U S Patent No. 5,346,702 to Na & Rajagopalan.
 U S Patent No. 5,352,459 to Holhster *et al.*
 10 U.S. Patent No. 5,354,560 to Lovrecich.
 Above-cited U.S. Patent No. 5,384,124 to Courteille *et al.*
 U S Patent No. 5,429,824 to June.
 U.S. Patent No. 5,510,118 to Bosch *et al.*
 U S Patent No. 5,518,738 to Eickhoff *et al.*
 15 U.S. Patent No. 5,503,723 to Ruddy & Eickhoff.
 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.*
 20 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 Deneno & Stetsko.
 25 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 & Snyder
 U S Patent No. 5,662,883 to Bagchi *et al.*
 30 U.S. Patent No. 5,665,331 to Bagchi *et al.*
 U S Patent No. 5,718,919 to Ruddy & Roberts.
 U.S. Patent No. 5,747,001 to Wiedmann *et al.*

International Publication No. WO 93/25190

International Publication No. WO 96/24336.

International Publication No. WO 98/35666.

Alternatively, celecoxib can be formulated in solution in a pharmaceutically acceptable solvent such as polyethylene glycol having an average molecular weight of about 400 ("PEG-400"). Solution formulations typically permit rapid absorption of the dissolved drug, in some cases giving even more rapid onset of therapeutic effect than is possible with nanoparticulate formulations.

Solutions and suspensions of nanoparticles and/or microparticles can be formulated as liquid dosage forms, the required dose being measured, for example using a cup, at the time of administration. Alternatively, solutions and suspensions can be formulated as flowable liquids or as gels in unit dose articles such as sachets or soft capsules. Sachets are opened and only the contents administered orally to the subject, soft capsules are a more convenient dosage form as the entire capsule is orally administered. Typically the contents of a soft capsule are in gel form and the terms "softgel" or "gelcap" are sometimes used to describe these formulations.

Anti-inflammatory, antipyretic and analgesic drugs, for example nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids have not frequently been formulated as rapid-release solutions, gels or soft capsules for oral administration. However, illustrative processes for preparing such formulations are disclosed in the references individually cited immediately below

U S Patent No 5,859,060 to Platt.

European Patent Application No 0 945 131

Japanese Land-Open Patent Application No 03/106815

Extending the half-life of an orally administered drug is achievable by a variety of controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release technologies known in the art. Typically such technologies involve formulating the drug in a polymer matrix from which the drug is gradually released, or protecting the drug from immediate release by means of a barrier layer which degrades over time in the gastrointestinal tract. Examples of barrier layers include liposomes, nanocapsules, microcapsules and coatings on granules, beads or tablets. Dosage forms can be liquids (e.g.,

suspensions) or unit dose articles (e.g., tablets, capsules, soft capsules).

Illustrative processes that can be used are disclosed for controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release formulations of opioids, NSAIDs and other analgesic, antipyretic and anti-inflammatory drugs in the references individually cited immediately below

U S Patent No. 3,362,880 to Jeffries.

U S Patent No. 4,308,251 to Dunn & Lampard.

U S Patent No. 4,571,333 to Haas & Kent.

U S Patent No. 4,601,894 to Haas & Vadino.

U.S. Patent No. 4,708,861 to Popescu *et al.*

U.S. Patent No. 4,749,575 to Rotman.

U S Patent No. 4,795,641 to Kashdan.

U.S. Patent No. 4,803,079 to Haas & Kent.

U.S. Patent No. 4,867,985 to Henfield *et al.*

U.S. Patent No. 4,980,175 to Chevin & Mackie.

U S Patent No. 5,160,742 to Mazur *et al.*

U S Patent No. 5,273,760 to Oshlack *et al.*

U S Patent No. 5,275,820 to Chang.

U S Patent No. 5,292,534 to Valentine & Valentine.

U.S. Patent No. 5,415,871 to Pankhania *et al.*

U S Patent No. 5,427,799 to Valentine & Valentine.

U.S. Patent No. 5,451,409 to Rencher *et al.*

U.S. Patent No. 5,460,825 to Rocha.

U.S. Patent No. 5,472,712 to Oshlack *et al.*

U S Patent No. 5,518,730 to Fusz.

U S Patent No. 5,523,095 to Modi.

U S Patent No. 5,536,505 to Wilson *et al.*

U S Patent No. 5,858,344 to Müller & Cramer

Belgian Patent Application No. 900 824.

European Patent Application No. 0 147 780

European Patent Application No. 0 438 249

European Patent Application No. 0 516 141

111

European Patent Application No. 0 875 245

European Patent Application No. 0 945 137

French Patent Application No 2 584 604

Japanese Laid-Open Patent Application No. 56/030402.

5 Japanese Laid-Open Patent Application No. 60/072813

Japanese Laid-Open Patent Application No. 63/174925

Japanese Laid-Open Patent Application No 10/298064.

International Publication No. WO 87/00044

International Publication No WO 89/08119

10 International Publication No WO 91/16920

International Publication No WO 93/10760.

International Publication No WO 93/10769

International Publication No. WO 93/12765

International Publication No. WO 93/17673

15 International Publication No WO 95/14460

International Publication No. WO 96/16638

International Publication No WO 98/01117

International Publication No. WO 99/51209

20 Attempts have been made to formulate certain NSAIDs, opioids or other analgesic, antipyretic or anti-inflammatory drugs in single dual-release compositions having both an immediate-release fraction and a controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release fraction of the drug. Such compositions have been disclosed, for example, for NSAIDs generally in the references individually cited immediately below

25 U.S. Patent No. 4,980,170 to Schneider *et al*

International Publication No WO 99/12524

Such dual-release compositions have illustratively been disclosed for ibuprofen in the references individually cited immediately below

U.S. Patent No. 5,681,583 to Conte *et al*

30 International Publication No WO 96/41617

Such dual-release compositions have illustratively been disclosed for naproxen in the references individually cited immediately below

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U S Patent No. 4,888,178 to Rotim & March

U S Patent No. 5,609,884 to Desai.

Selective cyclooxygenase-2 inhibitory drugs have not previously been formulated in dual-release dosage forms. Certain drugs of this class have a sufficiently long half-life, even when conventionally formulated for oral delivery, to be suitable for once-a-day administration. For example, Canadian Patent Application No. 2,254,061 discloses that the selective cyclooxygenase-2 inhibitor 3-phenyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one, also known as rofecoxib, has a half-life sufficient to provide therapeutic benefit over a 24-hour period.

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SUMMARY OF THE INVENTION

According to the present invention, the selective cyclooxygenase-2 inhibitory compound celecoxib is formulated in an orally deliverable dosage form having dual-release properties such that onset of therapeutic effect is more rapid, yet at the same time the duration of therapeutic effect is longer, than is achieved with known formulations of celecoxib.

An embodiment of the invention is a composition comprising celecoxib that, upon oral administration thereof to a subject, exhibits pharmacokinetic properties leading to (a) a greater maximum blood serum celecoxib concentration (C_{max}) and/or a shorter time following the administration to reach that maximum (T_{max}), and (b) a longer terminal half-life of blood serum celecoxib concentration ($T_{1/2}$), than previous compositions. It is contemplated that a greater C_{max} and/or a shorter T_{max} (i.e., immediate release properties) are obtained by providing a first fraction of the celecoxib in the composition (i) in the form of solid particles comprising celecoxib having a D_{50} particle size less than about 1 μm , or (ii) in the form of a solution of celecoxib in a pharmaceutically acceptable solvent. It is contemplated that a longer $T_{1/2}$ is obtained by providing a second fraction of the celecoxib in the composition (i) in the form of solid particles comprising celecoxib having a D_{50} particle size greater than about 25 μm , or (ii) in the form of particles of any convenient D_{50} particle size providing controlled release, slow release, programmed release, timed release, pulse release, sustained release or extended release of celecoxib. Preferably the $T_{1/2}$ thereby obtained results in maintenance of a therapeutic blood serum concentration of celecoxib for at least about 24 hours following oral administration.

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Accordingly, there is now provided a pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a first fraction of celecoxib in an amount of about 10 mg to about 400 mg, this first fraction being in solution in a pharmaceutically acceptable solvent and/or present in immediate-release solid particles having a D_{50} particle size less than about 1 μm , and a second fraction of celecoxib in an amount of about 10 mg to about 400 mg, this second fraction being present in solid particles having a D_{50} particle size greater than about 25 μm and/or in controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release particles, wherein the first fraction and the second fraction of celecoxib are present in a ratio of about 10:1 to about 1:10 in the composition.

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.

In a particularly preferred embodiment the dose units are tablets each comprising a first fraction of celecoxib in an amount of about 10 mg to about 400 mg, this first fraction being present in immediate-release solid particles having a D_{50} particle size less than about 1 μm , and a second fraction of celecoxib in an amount of about 10 mg to about 400 mg, this second fraction being distributed in a sustained-release matrix comprising hydroxypropylmethylcellulose (HPMC) having a viscosity, 2% in water, of about 100 to about 8000 cPs, wherein the first fraction and the second fraction of celecoxib are present in a ratio of about 10:1 to about 1:10 in the composition. The two fractions of celecoxib can be more or less homogeneously distributed throughout each tablet, but preferably the two fractions are individually contained in discrete layers or zones of each tablet.

In another particularly preferred embodiment the dose units are tablets or, more preferably, capsules each comprising a first fraction of celecoxib in an amount of about 10 mg to about 400 mg, this first fraction being present in immediate-release solid particles having a D_{50} particle size less than about 1 μm , and a second fraction of celecoxib in an amount of about 10 mg to about 400 mg, this second fraction being

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present in a multiplicity of solid beads each having a sustained-release coating that comprises one or more pharmaceutically acceptable swellable or erodible polymers, wherein the first fraction and the second fraction of celecoxib are present in a ratio of about 10:1 to about 1:10 in the composition. Preferred swellable or erodible polymers are ethylcellulose and polymers and copolymers of acrylic acid, methacrylic acid and esters thereof. Preferably the first fraction of celecoxib is present in a multiplicity of solid beads similar in size to the beads containing the second fraction but having no coating or having a coating that is not a sustained-release coating.

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 one or more dose units, typically 1 to about 4 dose units, of a composition of the invention once a day

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

DETAILED DESCRIPTION OF THE INVENTION

The term "oral administration" herein includes any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is 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.

A "subject" herein to which a therapeutic agent or composition thereof can be administered includes a human patient of either sex and of any age, and also includes any nonhuman animal, particularly a domestic or companion animal, illustratively a cat, dog or horse.

The term "dose unit" herein means a portion of a pharmaceutical composition that contains an amount of a therapeutic agent, in the present case celecoxib, suitable for a single oral administration to provide a therapeutic effect. Typically one dose unit, or a small plurality (up to about 4) of dose units, provides a sufficient amount of the agent to result in the desired effect.

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The term "present in solid particles" as applied to celecoxib herein encompasses compositions wherein the solid particles consist essentially of celecoxib and compositions wherein the solid particles comprise celecoxib in intimate mixture with one or more other ingredients. These other ingredients can include one or more therapeutic agents other than celecoxib and/or one or more pharmaceutically acceptable excipients.

The terms "controlled-release", "slow-release", "programmed-release", "timed-release", "pulse-release", "sustained-release" and "extended-release" in relation to particles or formulations herein have meanings as accorded in the above-cited references, the pertinent disclosure of all of which is hereby incorporated by reference. Suitable processes for preparing such "controlled-release", "slow-release", "programmed-release", "timed-release", "pulse-release", "sustained-release" or "extended-release" particles comprising celecoxib useful in compositions of the present invention include those disclosed for other drugs in the above-cited references.

The term "excipient" herein means any substance, not itself a therapeutic agent, used as a carrier or vehicle for delivery of a therapeutic agent to a subject or added to a pharmaceutical composition to improve its handling or storage properties or to permit or facilitate formation of a dose unit of the composition into a discrete article such as a capsule or tablet suitable for oral administration. Excipients can include, by way of illustration and not limitation, diluents, disintegrants, binding agents, adhesives, wetting agents, polymers, 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.

Novel pharmaceutical compositions according to the present invention comprise one or more orally deliverable dose units. Each dose unit comprises celecoxib in a therapeutically effective total amount of about 20 mg to about 800 mg, partitioned between two fractions each of about 10 mg to about 400 mg as described herein.

It will be understood that a therapeutically effective amount of celecoxib for a subject is dependent *inter alia* on the body weight of the subject. Where the subject is a child or a small animal (e.g., a dog), for example, an amount of celecoxib relatively low in the disclosed range of about 20 mg to about 800 mg is likely to provide blood serum concentrations consistent with therapeutic effectiveness. Where the subject is an adult human or a large animal (e.g., a horse), achievement of such blood serum concentrations of celecoxib are likely to require dose units containing a relatively greater amount of celecoxib.

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

In one embodiment, the first fraction of celecoxib in a composition of the invention, which is the fraction providing immediate release, is in the form of particles having a D_{50} particle size less than about 1 μm . Typically in this embodiment substantially all the particles are nanoparticles, i.e., solid particles of diameter less than 1 μm in the longest dimension of the particles. In such particles, celecoxib can be present alone or in intimate mixture with one or more excipients.

The effects on pharmacokinetic properties of reducing particle size from the microparticle range (greater than 1 μm diameter) to the nanoparticle range is generally unpredictable for any particular drug or class of drugs. According to the present invention, celecoxib in nanoparticulate form exhibits higher C_{max} and/or shorter T_{max} than celecoxib in microparticulate form.

Considering only the nanoparticulate component of a composition of this embodiment of the invention, average particle size is preferably about 0.1 to about 0.8 μm (about 100 to about 800 nm), more preferably about 0.15 to about 0.6 μm (about 150 to about 600 nm), and most preferably about 0.2 to about 0.4 μm (about 200 to about 400 nm). Celecoxib 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 typically provide the drug in amorphous form.

In one embodiment, celecoxib nanoparticles have a surface modifying agent adsorbed on the surface thereof. In another embodiment, celecoxib nanoparticles are contained in a matrix formed by a polymer. Preferably excipients are present and most preferably include 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 a nanoparticulate composition is ingested. Preferably both a water soluble diluent and a wetting agent are present.

Nanoparticles comprising or consisting essentially of a celecoxib can be prepared according to any process previously applied to the preparation of other poorly water soluble drugs in nanoparticulate form. Suitable processes, without restriction, are illustratively disclosed for such other drugs in the above-cited references, the pertinent disclosure of all of which is hereby incorporated by reference.

In another embodiment, the first fraction of celecoxib in a composition of the invention, which is the fraction providing immediate release, is in solution in a pharmaceutically acceptable solvent. Polyethylene glycol, for example PEG-400, has been found to be a suitable solvent, either alone or in mixture with water.

Illustratively, a mixture of 2 parts PEG-400 to 1 part water has been found to be a useful solvent base for an orally deliverable celecoxib solution. According to the present invention, orally administered celecoxib in dissolved form exhibits higher C_{max} and/or shorter T_{max} than celecoxib in any other orally administered form so far evaluated.

Although a celecoxib solution can be presented to the subject in bulk liquid form, it can alternatively be presented in pre-measured unit dose form, for example as a soft capsule. Optionally a pharmaceutically acceptable gelling agent can be added to the solution to form a gel. Softgels or gelcaps, which are soft capsules containing a gel, are therefore suitable dosage forms for compositions of the invention.

When administered orally to a fasting adult human, a 100 mg dose unit of a composition of the invention preferably exhibits a T_{max} of less than about 1.5 h, more preferably less than about 1 h and most preferably less than about 0.75 h, and a C_{max} of at least about 100 ng/ml, more preferably at least about 200 ng/ml. Typically a composition of the invention provides a blood serum concentration of celecoxib of at

least about 50 ng/ml within 30 minutes of oral administration, preferred compositions achieve such a concentration in as little as 15 minutes. This early rise in blood serum concentration is believed to be associated with the rapid onset of therapeutic effect achieved by compositions of the present invention.

5 In addition to the first fraction of celecoxib, which as explained above is the immediate-release fraction, a composition of the invention further comprises a second fraction of celecoxib that is the controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release fraction. In one embodiment, this fraction comprises celecoxib microparticles having a D₉₀ particle
10 size greater than about 25 μ m. Preferably the D₉₀ particle size of this fraction is about 25 μ m to about 200 μ m, more preferably about 25 μ m to about 100 μ m, for example about 40 μ m to about 75 μ m.

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

Preferably excipients are associated with or present in the primary microparticles and these excipients more preferably include a water soluble diluent or wetting agent or both.

20 In another embodiment, the second fraction of celecoxib is in the form of particles of any convenient size that are controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release particles prepared by any process disclosed for drugs other than celecoxib in the above-cited references, such process being adapted as necessary for the specific properties of
25 celecoxib.

The particles comprising the second fraction of celecoxib can optionally be dispersed as a suspension in a liquid diluent. In one embodiment of the invention, the particles comprising the second fraction are in stable suspension in a matrix solution comprising the first fraction of celecoxib. This suspension can be presented as a bulk
30 liquid or can be in a pre-measured dosage form such as soft capsules, optionally as softgels or gelscaps as described above.

When administered orally to a fasting adult human, a 100 mg dose unit of a

composition of the invention preferably exhibits a $T_{1/2}$ of at least about 9 h, more preferably at least about 12 h and most preferably at least about 15 h. The $T_{1/2}$ is preferably such as to maintain a blood serum concentration of celecoxib of at least about 50 ng/ml, preferably at least about 100 ng/ml, for about 18 h, more preferably for about 24 h, following administration. This maintenance of blood serum concentration is believed to be associated with the long duration of therapeutic effect achieved by oral administration of a single dose of a composition of the present invention. In particular, it is believed that this maintenance of blood serum concentration is what enables a once-a-day administration regimen for preferred compositions of the invention.

One embodiment of the invention is a pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a first fraction of celecoxib in immediate-release form in an amount of about 10 mg to about 400 mg, and a second fraction of celecoxib in controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release form in an amount of about 10 mg to about 400 mg, this composition providing, upon a single administration of 1 to about 4 dose units to a subject, (a) a C_{max} greater than about 100 ng/ml, (b) a T_{max} shorter than about 1.5 h and (c) a $T_{1/2}$ longer than about 9 h.

A preferred composition provides, upon a single administration of 1 to about 4 dose units to a subject, (a) a C_{max} greater than about 200 ng/ml, (b) a T_{max} shorter than about 0.75 h, (c) a blood serum concentration of at least 50 ng/ml, preferably at least 100 ng/ml, within about 15 minutes after such administration, and (d) a $T_{1/2}$ such that blood serum concentration remains above about 50 ng/ml, preferably above about 100 ng/ml, for at least 18 h, preferably for about 24 h, after such administration. It is preferred that blood serum concentration declines to a low level around or shortly after 24 h following administration, in other words that the composition provide a clearance time for celecoxib consistent with once-a-day administration.

A preferred composition has pharmacokinetic properties sufficient to provide rapid onset of therapeutic effect within about 1 h, and a duration of therapeutic effect of about 24 h, after oral administration thereof to a subject having a cyclooxygenase-2 mediated disorder.

A particularly preferred composition has the first fraction of celecoxib in an

immediate-release form and the second fraction of celecoxib in a pulse-release form that releases a pulse of celecoxib about 8 h to about 12 h after administration. Such a composition is of especial utility for treatment of conditions such as osteoarthritis. For example, administration of such a composition at bedtime provides rapid onset of
 5 pain relief and enables pain-free sleep, and the pulse-release characteristic is timed to provide reduction in morning stiffness

The weight ratio of the first to the second fraction of celecoxib in a composition of the invention is about 1:10 to about 10:1, preferably about 1:5 to about 5:1, for example about 1:1 or about 1:2

10 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
 15 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 fluid suspension as described above. In preparing such a suspension, use of a wetting agent such as polysorbate 80 is likely to be beneficial. A suspension can be prepared by dispersing nanoparticulate and/or microparticulate celecoxib in the liquid phase; alternatively the
 20 particulate celecoxib can be precipitated from solution in a solvent such as an alcohol, preferably ethanol. The liquid phase preferably comprises a palatable vehicle such as water, syrup or fruit juice, for example apple juice.

Compositions of the present invention are useful in treatment and prevention of a very wide range of disorders mediated by cyclooxygenase-2. Presently
 25 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
 30 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

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, periarthritis 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.

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,

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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 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 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 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 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 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 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 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 disorders including anemia such as hypoprothrombemia, 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.

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.

By virtue of the rapid onset of therapeutic effect exhibited by compositions of the invention, these compositions have particular advantages over prior formulations of celecoxib for treatment of acute cyclooxygenase-2 mediated disorders, especially for the relief of pain. At the same time, by virtue of the long duration of therapeutic effect exhibited by compositions of the invention, these compositions have particular advantages over prior formulations of celecoxib for treatment of chronic cyclooxygenase-2 mediated disorders, where once-a-day treatment is especially desirable. Compositions of the invention are uniquely advantageous where a combination of rapid onset and long duration of therapeutic effect is required.

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 celecoxib composition of
- 5 the invention with compounds selected from aceclofenac, aceemetacin, *e*-acetamidocaproic acid, acetaminophen, acetaminosalol, acetamide, acetylsalicylsalicylic acid, *S*-adenosymethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorthenoxazin, 3-amino-4-hydroxybutric acid, 2-amino-4-picolone,
- 10 aminopropylion, aminopyrine, amoxetina, ammonium salicylate, amproxicam, antolmetin guacal, amleridina, antipyrine, antipyrine salicylate, antrafenne, apazone, aspirin, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzylnorphine, bernoprofen, bestramide, α -bisabolol, bromfenac, *p*-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligemin, buccetin, buclorixio
- 15 acid, bucolome, bufexamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbuphene, carprofen, carsalam, chlorobutanol, chlorthenoxazin (e), choline salicylate, cinchophen, cummetacin, caramadol, chdanac, clometacin, clomizene, clonixin, clonirac, clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate, cropropamide,
- 20 crotethamide, desomorphine, dexoradrol, dextromoramide, dezocine, diampromide, diclofenac sodium, difenamazole, difenpiramide, diflunisal, dihydrocodeine, dihydrocodemone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, dimopheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrene, ditazol, droxicam, emorfazone, enfenamic
- 25 acid, epirizole, eptazocine, etarsalate, etbenzamide, etioheptazine, etiohexazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etomidazene, eugenol, felbinac, fenbufen, fenclorizic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradol, feprazone, floctafenne, flufenamic acid, flunoxaprofen, fluorezone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentisic acid, glafenine,
- 30 glucametacin, glycol salicylate, gunazulene, 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, meptazmol, mesalamine, metazocine, methadone hydrochloride, methotrimetrazine, 5 metazinic acid, metofoline, metopon, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morphine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifedazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, 10 olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsalinide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenylamidol, pikeprofen, piminodine, pipebutazone, piperylone, pirofen, 15 pirazolac, pirtramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinc acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide *o*-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide 20 diamutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofemic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesin, viminol, xenbutin, 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 25 Ther-12 (Analgesic (Dental), Analgesic (Narcotic), Analgesic (Non-narcotic), Anti-inflammatory (Nonsteroidal)). Particularly preferred combination therapies comprise use of a celecoxib composition of the invention with an opioid compound, more particularly where the opioid compound is codeine, meperidine, morphine or a derivative thereof. The compound to be administered in combination with celecoxib 30 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-

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release, sustained-release or dual-release form.

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

For the 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, 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 or two doses per day, but with preferred compositions of the invention one dose per day is effective. Administration of a composition of the invention at the rate of one 200 mg dose unit or two 100 mg dose units once a day is preferred for most patients, but some patients may benefit from administration of up to double that dose.

For the 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 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 or two doses per day, but with preferred compositions of the invention one dose per day is effective. Administration of a composition of the

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invention at the rate of one 400 mg dose unit or two 200 mg dose units once a day is preferred for most patients.

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 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 or two doses per day, but with preferred compositions of the invention one dose per day is effective. Administration of a composition of the invention at the rate of one 200 mg dose unit or two 100 mg dose units once a day is preferred.

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.

While the amount of celecoxib in 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.

Excipients employed in a composition of the invention can be solids or liquids or both. 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.

A composition of the invention is preferably made in the form of discrete dose units each containing a predetermined amount of the cyclooxygenase-2 inhibitor, such as tablets, pills, hard or soft capsules, lozenges, cachets, dispensable powders, granules, suspensions, elixirs or other liquids, or any other form reasonably adapted for oral administration. Such oral dosage forms can further comprise, for example, buffering agents. Tablets, pills and the like additionally can be prepared with or without coatings.

Compositions of the invention suitable for buccal or sublingual administration

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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.

Excipient-containing compositions of the invention can be prepared by any suitable method of pharmacy which includes the step of bringing into association the excipient(s) with the celecoxib, in a combination of dissolved, suspended, nanoparticulate, microparticulate or controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release forms thereof. In general, such compositions are prepared by uniformly and intimately admixing the celecoxib with a liquid or finely divided diluent, or both, and then, if necessary or desired, encapsulating or shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of celecoxib, 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) and/or dispersing agent(s). Molded tablets can be made by molding, in a suitable machine, celecoxib moistened with an inert liquid diluent.

Compositions of the present invention preferably comprise celecoxib in a desired amount admixed with one or more excipients selected from the group consisting of pharmaceutically acceptable diluents, disintegrants, binding agents, adhesives, wetting agents, lubricants, and anti-adherent agents. In addition, celecoxib nanoparticles, microparticles and/or controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release particles, if present, can optionally contain one or more matrix polymers and/or surface modifying agents. Celecoxib particles can be aggregated into beads which are enveloped in a coating conferring controlled-release, slow-release, programmed-release, timed-

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release, pulse-release, sustained-release or extended-release properties to the celecoxib in such beads.

Through appropriate selection and combination of excipients, compositions can be provided exhibiting improved performance with respect to, among other properties, efficacy, 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 excipients 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 excipients selected provides tablets that can exhibit improvement, among other properties, in dissolution and disintegration profiles, hardness, crushing strength, and/or friability.

Compositions of the invention optionally comprise one or more pharmaceutically acceptable diluents as excipients. Suitable diluents include, either individually or in combination, lactose USP; lactose USP, anhydrous, 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., Cerelease); inositol, hydrolyzed cereal solids such as the Maltroins and Mor-Rex; amylose; Rexcel, powdered cellulose (e.g., Elcema); 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 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 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.

5 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, sodium starch glycolate; clays (such as Veegum HV), celluloses (such as purified cellulose, methylcellulose, sodium carboxymethylcellulose and
10 carboxymethylcellulose), alginates, pregelatinized corn starches (such as National 1551 and National 1550); croscarmellose sodium, crospovidone USP NF; and gums (such as agar, guar, locust bean, Karaya, pectin, and tragacanth). Disintegrants may be added at any suitable step during the preparation of the composition, particularly prior to granulation or during the lubrication step prior to compression. Such disintegrants,
15 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.

Compositions of the invention optionally comprise one or more pharmaceutically acceptable binding agents or adhesives as excipients, particularly for
20 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,
25 tragacanth, sucrose; gelatin; glucose; starch; cellulose materials such as, but not limited to, methylcellulose and sodium carboxymethylcellulose (e.g., Tylose); alginic acid and salts of alginic acid, magnesium aluminum silicate; polyethylene glycol, guar gum, polysaccharide acids, bentonite; polyvinylpyrrolidone; polymethacrylates, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (Klucel);
30 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.

Compositions of the invention optionally comprise one or more pharmaceutically acceptable wetting agents as excipients. Such wetting agents are preferably selected to maintain the celecoxib in close association with water, a condition that is believed to improve the relative bioavailability of the composition. Suitable wetting agents include, either individually or in combination, oleic acid, glyceryl monostearate, sorbitan 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 composition.

Compositions of the invention optionally comprise one or more pharmaceutically acceptable lubricants and/or glidants as excipients. 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., Starotex), 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.

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

Although unit dose hard capsule and tablet compositions of the 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

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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.

5 The desired tap and bulk densities of the granules are normally about 0.3 g/ml to about 1.0 g/ml.

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
10 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
15 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.

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

The first and second fractions of celecoxib can be intimately coformulated, for example within individual granules that are subsequently encapsulated or compressed into tablets. Alternatively, the first and second fractions of celecoxib can be spatially separated in a composition of the invention. Illustratively, within a single hard
25 capsule there can be separate granules or beads, for example coated beads, containing celecoxib in immediate-release form or in controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release form. Within a single unit dose tablet there can be separate layers containing celecoxib in immediate-release form or in controlled-release, slow-release,
30 programmed-release, timed-release, pulse-release, sustained-release or extended-release form. For example, a two-layer celecoxib tablet similar to that described for naproxen in above-cited U.S. Patent No. 5,609,884 can be prepared

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In a particularly preferred embodiment of the present invention, the second fraction of celecoxib is distributed in a sustained-release matrix comprising HPMC having a viscosity, 2% in water, of about 100 to about 8000 cPs. Compositions of this embodiment of the invention are referred to for convenience herein as "dual-release matrix compositions". When formulated as tablets, which are a preferred dosage form for this embodiment, such compositions are referred to herein as "dual-release matrix tablets".

A matrix composition of the invention comprises HPMC in an amount sufficient to extend the release profile of the celecoxib. Typically such an amount is about 0.1% to about 40%, preferably about 5% to about 30%, for example about 10%, of the composition by weight. Preferably the weight ratio of HPMC to the second fraction of celecoxib is about 1:1 to about 1:12, more preferably about 1:1 to about 1:6.

HPMCs vary in the chain length of their cellulosic backbone. This directly affects the viscosity of an aqueous dispersion of the HPMC. Viscosity is normally measured at a 2% by weight concentration of the HPMC in water. HPMCs having viscosity, 2% in water, of less than about 100 cPs can be useful, for example as binding agents, but tend not to have useful release-extending properties for medicaments. Such HPMCs are said to have good binding properties and less desirable sustaining properties. The term "binding properties" herein refers to suitability as a binding agent for tablet production by wet granulation, wherein, for example, HPMC is dissolved in water for spraying onto dry powders to be granulated. The term "sustaining properties" herein refers to suitability as a release-extending matrix. HPMCs with good sustaining properties are typically too viscous for use as a binding agent in wet granulation techniques. According to the present invention, the HPMC(s) used to form the release-extending matrix of a dual-release celecoxib composition should have a viscosity, 2% in water, of about 100 to about 8000 cPs, preferably about 1000 to about 8000 cPs, for example about 4000 cPs.

HPMCs also vary in the degree of substitution of available hydroxyl groups on the cellulosic backbone by methoxyl groups and by hydroxypropoxyl groups. With increasing hydroxypropoxyl substitution, the resulting HPMC becomes more hydrophilic in nature. It is preferred in dual-release matrix compositions of the

present invention to use HPMCs having about 15% to about 35%, more preferably about 19% to about 30%, and most preferably about 19% to about 24%, methoxyl substitution, and having about 3% to about 15%, more preferably about 4% to about 12%, and most preferably about 7% to about 12%, hydroxypropoxyl substitution.

- 5 HPMCs which are relatively hydrophilic in nature and which may be used in the present invention are illustratively available under the brand names Methocel™ of Dow Chemical Co. and Metolose™ of Shin-Etsu Chemical Co. Examples of HPMCs of a low viscosity grade, generally unsuitable in compositions of the present invention except as binding agents, include Methocel™ E5, Methocel™ E15 LV, Methocel™ E50 LV, Methocel™ K100 LV and Methocel™ F50 LV, whose 2% by weight aqueous solutions have viscosities of 5 cPs, 15 cPs, 50 cPs, 100 cPs and 50 cPs, respectively. Examples of HPMCs having medium viscosity include Methocel™ E4M and Methocel™ K4M both of whose 2% by weight aqueous solutions have a viscosity of 4000 cPs. Examples of HPMCs having high viscosity, generally unsuitable for use in compositions of the present invention, include Methocel™ E10M, Methocel™ K15M and Methocel™ K100M whose 2% by weight aqueous solutions have viscosities of 10,000 cPs, 15,000 cPs and 100,000 cPs, respectively.

- Various HPMC products are described in Formulating for Controlled Release with Methocel Premium Cellulose Ethers, Dow Chemical Co., 1997. The methoxyl and hydroxypropoxyl substitution type and content for selected HPMC products is provided in Table 1, below.

Table 1 Properties of selected HPMC products

Methocel™ E4MP (USP 2910)	Nominal Viscosity, 2% in Water	4,000 cPs
	Methoxyl, %	28-30
	Hydroxypropoxyl, %	7-12
Methocel™ K4MP (USP 2208)	Nominal Viscosity, 2% in Water	4,000 cPs
	Methoxyl, %	19-24
	Hydroxypropoxyl, %	7-12
Methocel™ E10MP (USP 2910)	Nominal Viscosity, 2% in Water	10,000 cPs
	Methoxyl, %	28-30
	Hydroxypropoxyl, %	7-12
Methocel™ K15MP (USP 2208)	Nominal Viscosity, 2% in Water	15,000 cPs
	Methoxyl, %	19-24
	Hydroxypropoxyl, %	7-12

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An illustrative presently preferred HPMC with sustained-release properties is one with substitution type 2208, denoting about 19% to about 24% methoxyl substitution and about 7% to about 12% hydroxypropoxyl substitution, and with a nominal viscosity, 2% in water, of about 4000 cPs. A "controlled release" grade is especially preferred, having a particle size such that at least 90% passes through a #100 USS mesh screen. An example of a commercially-available HPMC meeting these specifications is Methocel™ K4M, of Dow Chemical Co

Without being bound by any particular hypothesis as to how the HPMC matrix according to the invention provides superior sustained-release characteristics, it is believed that upon oral ingestion and contact with gastrointestinal fluids, HPMC on or close to the tablet surface partially hydrates and thereby swells to form a gel layer having the celecoxib distributed in a three-dimensional matrix therein. It is further believed that this outer three-dimensional gel matrix layer slows dissolution of the tablet. As the outer gel layer slowly dissolves, disperses or erodes, celecoxib is released from this layer into the gastrointestinal fluid where it is available for absorption. Meanwhile, hydration of the HPMC matrix gradually advances towards the center of the tablet, permitting further release of celecoxib over time by the same process hypothetically described above. Since the celecoxib is distributed throughout the tablet at a more or less uniform concentration throughout the HPMC matrix, a fairly constant amount of celecoxib can, according to the present non-limiting theory, be released per unit time *in vivo* by dissolution, dispersion or erosion of the outer portions of the tablet.

Overall release rate and consequently drug availability are dependent on the rate of diffusion of the drug through the outer gel layer and the rate of erosion of this layer of the tablet. Preferably T-90% (the time required for 90% celecoxib release) *in vivo* is less than 24 hours, so that a clearance time exists whereby the tablet is suitable for once-a-day administration.

In another particularly preferred embodiment of the present invention, the second fraction of celecoxib is present in a multiplicity of solid beads, pellets or granules each having a coating comprising a swellable or erodible polymer. Such beads, pellets or granules are referred to herein as "beads" or "coated beads" and are typically dense, hard, substantially spherical and of low friability. Compositions of

this embodiment of the invention are referred to for convenience herein as "dual-release coated bead compositions" When formulated as capsules, which are a preferred dosage form for this embodiment, such compositions are referred to herein as "dual-release coated bead capsules"

5 In a dual-release coated bead composition of the present invention, whether encapsulated or tableted, the first fraction of celecoxib can be present in any suitable immediate-release form but is preferably in the form of nanoparticulate celecoxib and is preferably formulated into beads of similar size to the coated beads containing the second, sustained-release, fraction of celecoxib Such beads containing the first, 10 immediate-release, fraction are either uncoated or coated with a material that does not slow or extend release of the celecoxib. The demands of a dual-release celecoxib composition are met surprisingly well by a dual-release coated bead preparation wherein the beads containing the sustained-release fraction of celecoxib are coated with an erodible barrier layer comprising at least one swellable polymer that is 15 substantially insoluble in gastrointestinal fluid. The beads optionally contain pharmaceutically acceptable excipients such as lactose and microcrystalline cellulose and are preferably about 0.1 mm to about 1.0 mm, more preferably about 0.15 mm to about 0.5 mm, in diameter For example, the beads can be of such a range of sizes that they pass through a 0.425 mm sieve but are retained on a 0.18 mm sieve. The 20 beads can be prepared by mixing and granulation of celecoxib with one or more excipients, followed by extrusion, spheronization, drying and sieving the particles to the desired size range, followed by application of the swellable or erodible polymer coating to the beads containing that fraction of the celecoxib that is desired to exhibit sustained release.

25 In a sustained-release coating preferred according to the present invention, the beads containing the second fraction of celecoxib together with one or more excipients are coated with one or more swellable or erodible polymers selected from hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose, hydroxyethylcellulose, ethylcellulose (e.g. Surelease™), hydroxyethylmethylcellulose, 30 methylcellulose, and polymers and copolymers of acrylic acid and methacrylic acid and esters thereof (e.g. Eudragit™ RL, Eudragit™ RS, Eudragit™ L100, Eudragit™ S100, Eudragit™ NE) The swellable or erodible polymers can be combined with one

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or more water-soluble substances such as sugar, lactose and salts to form a partly erodible film with a pH-independent or pH-dependent release rate.

Eudragit™ of Rohm Pharma is a trade name applied to a range of products useful for film coating of sustained-release particles. These products are of varying solubility in gastrointestinal fluids. Eudragit™ RL and Eudragit™ RS are copolymers synthesized from acrylic and methacrylic esters with a low content of quaternary ammonium groups. Eudragit™ RL and RS differ in the molar ratios of such ammonium groups to the remaining neutral (meth)acrylic acid esters (1:20 and 1:40 respectively). Eudragit™ NE is an aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate. Characteristics of Eudragit™ polymers are described in Eudragit: Sustained-release formulations for oral dosage forms, Rohm Basic Info 2.

Ethylcellulose, available for example under the trade name Surelease™, is another suitable material which is available in different grades and in special quantities for aqueous based barrier coatings. According to the present invention it is preferred to use ethylcellulose having a viscosity of about 5 to about 15 cPa, but other types of cellulose-based swellable or erodible polymers can also be used.

In the coating procedure the swellable or erodible polymers are dissolved or dispersed in a solvent or mixture of solvents such as ethanol, acetone, methyl isobutyl ketone (MIBK) and water. Plasticizers and/or pigments can optionally be used to modify the technical properties or change the permeability of the coating. The coating preferably has virtually pH-independent permeability properties throughout a pH range of about 1.0 to about 7.0. At higher pH a reduction in the release rate of celecoxib can be observed, however, this is not due to properties of the polymeric layer but results from reduced solubility of celecoxib at high pH values.

An illustrative suitable coating composition according to the present invention comprises ethylcellulose and HPMC together with triethyl citrate as a plasticizer. An example of such a coating composition contains 90% polymer consisting of ethylcellulose and HPMC in a weight ratio of 55:35 to 80:20, with 10% triethyl citrate.

Each coated bead containing celecoxib represents an individual sustained-release unit, releasing the drug at a rate that is preferably independent of its position in

the gastrointestinal tract. Overall dissolution profile and celecoxib availability are dependent on the rate of drug diffusion through the sustained-release coating and on the rate of erosion of the coating in the gastrointestinal tract.

In a process for preparing a coated bead composition, celecoxib and diluents, preferably lactose and/or microcrystalline cellulose, are mixed and granulated by the following illustrative method. Celecoxib is added to a mixture of lactose and microcrystalline cellulose (e.g., Avicel™ PH-101, Avicel™ RC-581, Avicel™ RC-591 or a mixture thereof) in a total amount of 1000-4000 g and dry-mixed in a high shear mixer (e.g., Niro-Fielder mixer) at a high mixing speed for 2-5 minutes. Water (300-700 grams) is added and the resulting mass is granulated for 2-5 minutes at high speed.

Extrusion of the resulting material can be performed for example in a NICA E-140 extruder (Lexus Medical AB, Sweden) through a perforated screen with drilled orifices of 0.25-1.0 mm diameter. The speed of the agitator and the feeder are preferably set on the lowest values.

Spheronization of the resulting extrudate can be conducted for example in a NICA Marumerizer (Ferro Mecano AB, Sweden). The speed of the Marumerizer plate is preferably adjusted to 500-10,000 rpm. Spheronization continues for 2-10 minutes, with about 1000 g wet extrudate on the plate at each run.

Drying of the resulting spheronized beads can be performed in a fluidized bed dryer (e.g., Aeromatic AG, West Germany) at an inlet temperature of 50-90°C. A net device can be placed in the top of the fluidized bed to avoid loss of beads to the cyclone output. The batch is preferably divided into sub-batches of 200-800 g. Each sub-batch is dried for 10-60 minutes at an air volume of 100-400 m³/h in order to obtain individual beads rather than aggregates. If necessary, the sub-batches are then mixed and the whole batch dried for 5-30 minutes to an end product temperature of 40-60°C. A yield of dry beads of 1600-2000 g can be expected.

Sizing of the resulting dry beads can be performed using analytical sieves. Two sieves are selected from a set of sieve sizes, for example of 850 µm, 600 µm, 425 µm, 300 µm, 250 µm and 180 µm.

Celecoxib beads manufactured as above can be coated with swellable or erodible polymers to prepare sustained-release coated beads. Immediate-release beads

are not so coated. Both sustained-release and immediate-release beads are present in a dual-release composition of the invention. For example, Surelease™ or Eudragit™ RS can be applied as a 10-20% by weight solids dispersion, using spray coating equipment (e.g., Wurster). The spray gun is mounted at a height of 0.25 cm to 5 cm over the bottom of the bed. An ethanol/MIBK mixture is pumped through the system prior to the start of the coating operation. Celecoxib beads are pre-heated at 50-80°C with an air velocity of 100-400 m³/h for 30-90 minutes. The coating is applied using the following typical process parameters: atomizing pressure 1.0-3.0 bar, air temperature 50-80°C, air velocity 100-400 m³/h and solution flow about 10-80 ml/minute.

The coated beads manufactured as above, together with immediate-release beads, are encapsulated by a conventional encapsulation process.

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 one or more dose units 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 the once-a-day treatment 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 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 of a subject 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. 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 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

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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

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

WHAT IS CLAIMED IS

- 1 A pharmaceutical composition comprising one or more orally deliverable dose
units, each comprising a first fraction of celecoxib in an amount of about 10
mg to about 400 mg, said first fraction being in solution in a pharmaceutically
5 acceptable solvent and/or present in immediate-release solid particles having a
D₉₀ particle size less than about 1 μ m, and a second fraction of celecoxib in an
amount of about 10 mg to about 400 mg, said second fraction being present in
solid particles having a D₉₀ particle size greater than about 25 μ m and/or in
controlled-release, slow-release, programmed-release, timed-release, pulse-
10 release, sustained-release or extended-release particles, wherein said first
fraction and said second fraction of celecoxib are present in a ratio of about
10:1 to about 1:10 in the composition.
- 2 The composition of Claim 1 wherein said first fraction of celecoxib is in
solution in a pharmaceutically acceptable solvent.
- 15 3 The composition of Claim 2 wherein said solvent comprises polyethylene
glycol.
- 4 The composition of Claim 2 wherein particles comprising said second fraction
of celecoxib are in stable suspension in a matrix solution comprising said first
fraction.
- 20 5 The composition of Claim 4 that is in the form of unit dose soft capsules.
- 6 The composition of Claim 1 wherein said first fraction of celecoxib is present
in immediate-release solid particles having a D₉₀ particle size less than about
1 μ m.
- 7 The composition of Claim 6 that is in the form of unit dose hard capsules.
- 25 8 The composition of Claim 7 wherein said first fraction and said second
fraction of celecoxib are present in separate granules or beads within said
capsules.
- 9 The composition of Claim 8 wherein said second fraction of celecoxib is
present in coated granules or beads having controlled-release, slow-release,

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programmed-release, timed-release, pulse-release, sustained-release or extended-release properties.

10. The composition of Claim 6 that is in the form of unit dose tablets
11. The composition of Claim 10 wherein said first fraction and said second
5 fraction of celecoxib are present in separate layers within said tablets.
12. The composition of Claim 11 wherein said second fraction of celecoxib is present in particles having controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release properties
- 10 13. The composition of Claim 1 wherein each of said dose units contains celecoxib in an amount of about 50 mg to about 400 mg.
14. The composition of Claim 1 further comprising one or more opioid or analgesic drugs.
15. The composition of Claim 14 wherein said opioid or analgesic drugs are
15 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 antagonists, neurokinin-1 receptor antagonists and sodium channel blockers.
- 20 16. The composition of Claim 14 wherein said opioid or analgesic drugs are selected from the group consisting of aceclofenac, acemetacin, *s*-acetamidocaproic acid, acetaminophen, acetaminosalol, acetaminide, acetylsalicylsalicylic acid, *S*-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum
25 bis(acetylsalicylate), amfenac, aminochlorphenoxazin, 3-amino-4-hydroxybutric acid, 2-amino-4-picoline, aminopropylol, aminopyrine, amixetrine, ammonium salicylate, amproxican, antolmetm guacil, anilendine, antipyrine, antipyrine salicylate, antrafemine, apazone, aspirin, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine,
30 benzyllmorphine, bermoprofen, bezitramide, α -bisabolol, bromfenac,

- 5 *p*-bromoacetanilide, 5-bromosalicylic acid acetate, bromosalganin, bucetin,
 bucloxic acid, buclome, bufexamac, bumadizon, buprenorphine, butacetin,
 butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbiphen,
 carprofen, carsalam, chlorobutanol, chlorthenoxazin (e), choline salicylate,
 cinchophen, cinmetacin, curamadol, clidanac, clometacin, clonitazene,
 clonixin, clopirac, clove, codeine, codeine methyl bromide, codeine phosphate,
 codeine sulfate, cropropamide, crotethamide, desomorphine, dexoxadrol,
 dextromoramide, dezocine, diampromide, diclofenac sodium, difenamisole,
 difenpiramide, diflunisal, dihydrocodeine, dihydrocodeinone enol acetate,
 10 dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol,
 dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone,
 diprocetyl, dipyrone, dritazol, droxicam, emorfazone, enfensamic acid, eparizole,
 eptazocine, eteralate, ethenzamide, ethoheptazine, ethoxazone,
 ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene,
 15 eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl,
 fentiazac, fepradinol, feprazone, floctafenine, flufenamic acid, flumoxaprofen,
 fluorenone, flupirtine, fluproquazone, flurbiprofen, foafosal, gentisic acid,
 glafenine, glucametacin, glycol salicylate, guaiazulene, hydrocodone,
 hydromorphone, hydroxypethidine, ibufenac, ibuprofen, ibuproxam, imidazole
 20 salicylate, indomethacin, indoprofen, isofezolac, isoladol, isomethadone,
 isonixin, isoxepac, isoxicam, ketobemidone, ketoprofen, ketorolac,
p-lactophenetide, lafetamine, levorphanol, lofentanyl, lonazolac, lomoxicam,
 loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic
 acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine,
 25 methadone hydrochloride, methotrimetrazine, metiazine acid, metofoline,
 metopon, mofebutazone, mofezolac, morazone, morphine, morphine
 hydrochloride, morphine sulfate, morpholine salicylate, myrophine,
 nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceane, nefopam,
 nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-
 30 propoxyacetamide, norlevorphanol, normethadone, normorphine,
 norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin,
 oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, — — — —

- paralimide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine,
 phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone,
 phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenylramidol,
 piketoprofen, piminodine, pipebuzone, piperylone, pirofen, pirazolac,
 5 pirtramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol,
 propacetamol, propiram, propoxyphene, propyphenazone, proquazone,
 protizmic acid, ramifenazone, remifentanyl, rimazolium metilsulfate,
 salacetamide, salicin, salicylamide, salicylamide *o*-acetic acid, salicylsulfonic
 acid, salealte, salverme, simetride, sodium salicylate, sufentanyl, sulfasalazine,
 10 sulindac, superoxide dismutase, suprofen, suribuzone, talniflumate, temdap,
 tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofemic acid,
 tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropeam,
 viminol, xenbucin, ximoprofen, zaltoprofen and zomepirac.
- 17 The composition of Claim 14 wherein said opioid or analgesic drugs are
 15 selected from codeine, meperidine, morphine and derivatives thereof.
- 18 A pharmaceutical composition comprising one or more orally deliverable dose
 units, each comprising a first fraction of celecoxib in immediate-release form
 in an amount of about 10 mg to about 400 mg, and a second fraction of
 celecoxib in controlled-release, slow-release, programmed-release, timed-
 20 release, pulse-release, sustained-release or extended-release form in an amount
 of about 10 mg to about 400 mg, said composition providing, upon a single
 oral administration of 1 to about 4 dose units to a subject, (a) a C_{max} greater
 than about 100 ng/ml, (b) a T_{max} shorter than about 1.5 h and (c) a $T_{1/2}$ longer
 than about 9 h.
- 25 19 The composition of Claim 18 providing, upon a single oral administration of 1
 to about 4 dose units to a subject, (a) a C_{max} greater than about 200 ng/ml, (b) a
 T_{max} shorter than about 0.75 h, (c) a blood serum concentration of at least 50
 ng/ml within about 15 minutes after said administration, and (d) a $T_{1/2}$ such
 30 that blood serum concentration remains above about 50 ng/ml for at least 18 h
 after said administration.
- 20 The composition of Claim 18 that has pharmacokinetic properties sufficient to

provide onset of therapeutic effect within about 1 h, and a duration of therapeutic effect for at least about 24 h, of oral administration thereof to a subject having a cyclooxygenase-2 mediated disorder

- 21 A pharmaceutical composition comprising one or more orally deliverable dose
5 units, each comprising a first fraction of celecoxib in immediate-release form
in an amount of about 10 mg to about 400 mg, said first fraction being present
in immediate-release solid particles having a D_{90} particle size less than about
1 μm , and a second fraction of celecoxib in an amount of about 10 mg to about
400 mg, said second fraction being distributed in a sustained-release matrix
10 comprising hydroxypropylmethylcellulose having a viscosity, 2% in water, of
about 100 to about 8000 cP; wherein said first fraction and said second
fraction of celecoxib are present in a ratio of about 10:1 to about 1:10 in the
composition.
- 22 The composition of Claim 21 wherein said dose units are tablets.
- 15 23 The composition of Claim 22 wherein said first fraction and said second
fraction of celecoxib are individually contained in discrete layers or zones of
each tablet.
- 24 A pharmaceutical composition comprising one or more orally deliverable dose
20 units, each comprising a first fraction of celecoxib in an amount of about 10
mg to about 400 mg, said first fraction being present in immediate-release
solid particles having a D_{90} particle size less than about 1 μm , and a second
fraction of celecoxib in an amount of about 10 mg to about 400 mg, said
second fraction being present in a multiplicity of solid beads each having a
sustained-release coating that comprises one or more pharmaceutically
25 acceptable swellable or erodible polymers, wherein said first fraction and said
second fraction of celecoxib are present in a ratio of about 10:1 to about 1:10
in the composition.
- 25 The composition of Claim 24 wherein said dose units are capsules
- 26 The composition of Claim 24 wherein said first fraction of celecoxib is present
30 in a multiplicity of solid beads similar in size to the beads containing said

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second fraction of celecoxib, but having no coating or having a coating that is not a sustained-release coating.

- 27 The composition of Claim 24 wherein said swellable or erodible polymers are selected from ethylcellulose and polymers and copolymers of acrylic acid, methacrylic acid and esters thereof.
- 5
- 28 A method of treating a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering 1 to about 4 dose units of a composition of any of Claims 1, 18, 21 or 24 once a day
- 10 29 The method of Claim 28 wherein said condition or disorder is selected from rheumatoid arthritis, osteoarthritis, cancer, Alzheimer's disease and post-surgical pain.

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ABSTRACT

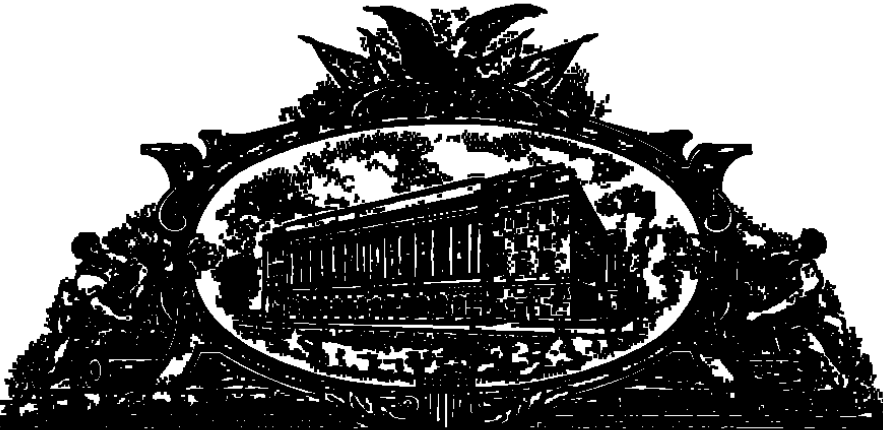
Pharmaceutical compositions are provided comprising one or more orally deliverable dose units, each comprising celecoxib in an immediate-release fraction and a controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release fraction. The compositions are useful in treatment or prophylaxis of cyclooxygenase-2 mediated conditions and disorders.

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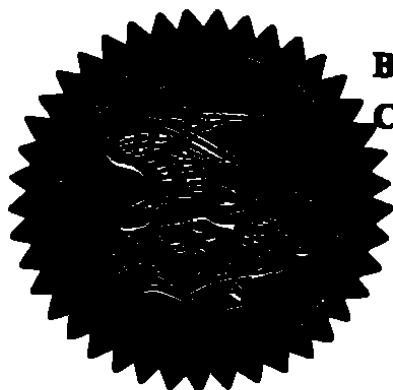
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OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT
APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A
FILING DATE UNDER 35 USC 111**

APPLICATION NUMBER. 60/202,270

FILING DATE May 05, 2000



**By Authority of the
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**P. R. GRANT
Certifying Officer**

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PTOEN/14(4-85)
Approved for use through 04/1/94. OMB 0551-0037
Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(b)(2).

Doclet Number	C-3280/2/US	Type a plus sign (+) inside this box	+
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INVENTOR(s)/APPLICANT(s)					
LAST NAME	FIRST NAME	MI	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)		
Desai Nadkarni	Subhash Sreekant		Wilmette, Illinois Gurnee, Illinois		
TITLE OF THE INVENTION (200 character limit)					
DUAL-RELEASE CELECOXIB COMPOSITIONS					
CORRESPONDENCE ADDRESS					
Jennifer Annandson, Paralegal Pharmacia Corporation, Mail Zone 1810 Patent Department Central P.O. Box 5110 Chicago					
STATE	Illinois	ZIP CODE	60680-5110	COUNTRY	USA
ENCLOSED APPLICATION PARTS (check all that apply)					
☒ Specification	Number of Pages	46	☐ Small Entity Statement		
☐ Drawing(s)	Number of Sheets		Other (specify)		
METHOD OF PAYMENT (check one)					
☐ A check or money order is enclosed to cover the Provisional Filing Fee			PROVISIONAL FILING FEE AMOUNT(\$)		\$150.00
☒ The Commissioner is hereby authorized to charge Filing Fee and credit Deposit Account Number:	19-1025				

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.
☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE

James C Forbes

Date

May 5, 2000

TYPED or PRINTED NAME
James C. Forbes

REGISTRATION NO.
(if appropriate)

39,457

☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

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PATENT
C-3280/2/US

PROVISIONAL UNITED STATES PATENT APPLICATION

for

DUAL-RELEASE CELECOXIB COMPOSITIONS

by

Subhash Desai and Sreckant Nadkarni

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EXPRESS MAIL MAILING LABEL	
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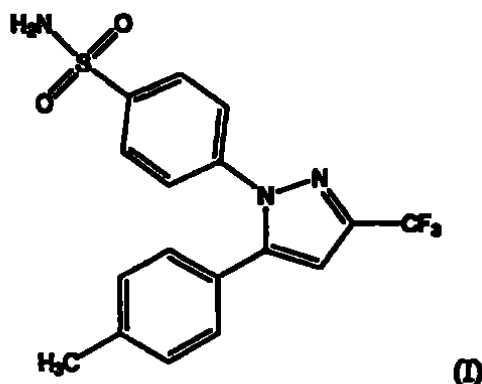
DUAL-RELEASE CELECOXIB COMPOSITIONS

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

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



Celecoxib is a hydrophobic compound and has very low solubility in water. This property has presented practical difficulties in formulating celecoxib for oral administration, particularly where early onset of therapeutic effect is desired or required. Furthermore, celecoxib has a relatively short half-life in the bloodstream following administration to a subject. This property has favored celecoxib administration regimens involving twice-a-day or more frequent administration.

A dosage form of celecoxib that simultaneously overcomes problems associated with both of these properties, thereby providing rapid onset of therapeutic

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effect coupled with once-a-day administration, would represent a major advance in the art.

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 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 difficult to process the small quantities required during formulation of the pharmaceutical compositions. Accordingly, a need exists for solutions to numerous problems associated with preparation of suitable pharmaceutical compositions and dosage forms comprising celecoxib, particularly orally deliverable dose units.

In general, a need exists for orally deliverable formulations of celecoxib, such formulations possessing one or more of the following characteristics relative to unformulated celecoxib or other celecoxib compositions

- (1) improved solubility;
- (2) shorter disintegration time;
- (3) shorter dissolution time;
- (4) decreased tablet friability;
- (5) increased tablet hardness,
- (6) improved wettability;
- (7) improved compressibility;

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- 5 (8) improved flow properties of liquid and particulate solid compositions,
(9) improved physical stability of the finished composition,
(10) reduced tablet or capsule size;
(11) improved blend uniformity;
(12) improved dose uniformity;
(13) improved control of weight variation during encapsulation and/or
tableting;
(14) increased granule density for wet granulated compositions;
(15) reduced water requirement for wet granulation,
10 (16) reduced wet granulation time; and
(17) reduced drying time for wet granulated mixtures.

More specifically, there exists an especial need for orally deliverable
formulations of celecoxib, such formulations providing both rapid onset of therapeutic
effect and longer duration of therapeutic effect than unformulated celecoxib or known
15 formulations of celecoxib. 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 celecoxib, such formulations providing a greater C_{max}
20 and/or an earlier T_{max} than unformulated celecoxib or known formulations of
celecoxib. At the same time, to the extent that long duration of therapeutic effect is
related to pharmacokinetic parameters such as long half-life of blood serum
concentration of the drug after C_{max} is reached, also known as terminal half-life ($T_{1/2}$),
there is an especial need for orally deliverable formulations of celecoxib, such
25 formulations providing a longer $T_{1/2}$ than unformulated celecoxib or known
formulations of celecoxib. A single composition that satisfies both the need for a
greater C_{max} and/or an earlier T_{max} and the need for a greater $T_{1/2}$ would dramatically
enhance the therapeutic utility of celecoxib in a wide variety of situations.

As is indicated hereinbelow, treatment with celecoxib is indicated or
30 potentially indicated in a very wide array of cyclooxygenase-2 mediated conditions
and disorders. It would be of benefit to provide formulations exhibiting
pharmacokinetics consistent with rapid onset and long duration of therapeutic effect

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especially for treatment of disorders where early relief from pain or other symptoms is desired or required and where once-a-day administration is required or preferred.

Cyclooxygenase-2 inhibitory drugs including celecoxib that are of low solubility in water are 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 and used in the art 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 volume of particles in the formulation, in the longest dimension of the particles, are smaller than that diameter. For practical purposes a determination of D_{90} based on 90% by weight rather than by volume is generally suitable.

For consistency with prior publications, the terms "microparticle" and "nanoparticle" are defined herein as in U.S. Patent No. 5,384,124 to Courtaile *et al.*, to refer to particles having respectively a diameter of between 1 μm and 2000 μm , and a diameter of less than 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 Liveridge *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. Illustrative processes are disclosed in the references

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individually cited immediately below

- U.S. Patent No. 4,826,689 to Violante & Fischer
Above-cited U.S. Patent No. 5,145,684 to Liversidge *et al.*
U.S. Patent No. 5,298,262 to Na & Rajagopalan.
5 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 Ilhg & Sarpotdar
U.S. Patent No. 5,346,702 to Na & Rajagopalan.
U.S. Patent No. 5,352,459 to Holhster *et al.*
10 U.S. Patent No. 5,354,560 to Lovrencich.
Above-cited U.S. Patent No. 5,384,124 to Courteille *et al.*
U.S. Patent No. 5,429,824 to Juna.
U.S. Patent No. 5,510,118 to Bosch *et al.*
U.S. Patent No. 5,518,738 to Hickhoff *et al.*
15 U.S. Patent No. 5,503,723 to Ruddy & Hickhoff.
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 Hickhoff *et al.*
20 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 Hickhoff *et al.*
U.S. Patent No. 5,573,783 to Demeno & Stetako.
25 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 & Snyder
U.S. Patent No. 5,662,883 to Bagchi *et al.*
30 U.S. Patent No. 5,665,331 to Bagchi *et al.*
U.S. Patent No. 5,718,919 to Ruddy & Roberts.
U.S. Patent No. 5,747,001 to Wiedmann *et al.*

005050-02226766

International Publication No WO 93/25190.

International Publication No. WO 96/24336.

International Publication No. WO 98/35666.

Alternatively, celecoxib can be formulated in solution in a pharmaceutically acceptable solvent such as polyethylene glycol having an average molecular weight of about 400 ("PEG-400"). Solution formulations typically permit rapid absorption of the dissolved drug, in some cases giving even more rapid onset of therapeutic effect than is possible with nanoparticulate formulations.

Solutions and suspensions of nanoparticles and/or microparticles can be formulated as liquid dosage forms, the required dose being measured, for example using a cup, at the time of administration. Alternatively, solutions and suspensions can be formulated as flowable liquids or as gels in unit dose articles such as sachets or soft capsules. Sachets are opened and only the contents administered orally to the subject; soft capsules are a more convenient dosage form as the entire capsule is orally administered. Typically soft capsule walls are composed predominantly of gelatin and the terms "softgel" or "gelcap" are sometimes used to describe these formulations.

Anti-inflammatory, antipyretic and analgesic drugs, for example nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids have not frequently been formulated as rapid-release solutions, gels or soft capsules for oral administration. However, illustrative processes for preparing such formulations are disclosed in the references individually cited immediately below

U.S. Patent No. 5,859,060 to Platt.

European Patent Application No. 0 945 131

Japanese Laid-Open Patent Application No 03/106815

Extending the half-life of an orally administered drug is achievable by a variety of controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release technologies known in the art. Typically such technologies involve formulating the drug in a polymer matrix from which the drug is gradually released, or protecting the drug from immediate release by means of a barrier layer which degrades over time in the gastrointestinal tract. Examples of barrier layers include liposomes, nanocapsules, microcapsules and coatings on granules, beads or tablets. Dosage forms can be liquids (e.g.,

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suspensions) or unit dose articles (e.g., tablets, capsules, soft capsules).

Illustrative processes that can be used are disclosed for controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release formulations of opioids, NSAIDs and other analgesic, antipyretic and anti-inflammatory drugs in the references individually cited immediately below

U.S. Patent No. 3,362,880 to Jeffries.

U.S. Patent No. 4,308,251 to Dunn & Lampard.

U S Patent No. 4,571,333 to Hmas & Kent.

U S. Patent No. 4,601,894 to Hanna & Vadmo.

U.S. Patent No. 4,708,861 to Popescu *et al.*

U S Patent No 4,749,575 to Rotman.

U S. Patent No. 4,795,641 to Kaahdan.

U S Patent No. 4,803,079 to Hmas & Kent.

U S. Patent No. 4,867,985 to Heafield *et al.*

U S Patent No 4,980,175 to Chavkin & Mackles

U.S. Patent No. 5,160,742 to Mazer *et al.*

U.S. Patent No. 5,273,760 to Oshlack *et al.*

U.S. Patent No. 5,275,820 to Chang.

U.S. Patent No. 5,292,534 to Valentine & Valentine.

U.S. Patent No. 5,415,871 to Pankhama *et al.*

U.S. Patent No. 5,427,799 to Valentine & Valentine.

U.S. Patent No. 5,451,409 to Rencher *et al.*

U.S. Patent No. 5,460,825 to Rocha.

U.S. Patent No. 5,472,712 to Oshlack *et al.*

U.S. Patent No. 5,518,730 to Fmaz.

U S Patent No. 5,523,095 to Modi.

U S Patent No. 5,536,505 to Wilson *et al.*

U.S. Patent No. 5,858,344 to Miller & Cremer

Belgian Patent Application No 900 824.

European Patent Application No. 0 147 780

European Patent Application No. 0 438 249

European Patent Application No. 0 516 141

European Patent Application No. 0 875 245

European Patent Application No. 0 945 137

French Patent Application No. 2 584 604.

Japanese Laid-Open Patent Application No. 56/030402.

5 Japanese Laid-Open Patent Application No. 60/072813

Japanese Laid-Open Patent Application No. 63/174925.

Japanese Laid-Open Patent Application No. 10/298064.

International Publication No. WO 87/00044.

International Publication No. WO 89/08119

10 International Publication No. WO 91/16920

International Publication No. WO 93/10760

International Publication No. WO 93/10769

International Publication No. WO 93/12765

International Publication No. WO 93/17673

15 International Publication No. WO 95/14460

International Publication No. WO 96/16638

International Publication No. WO 98/01117

International Publication No. WO 99/51209

20 Attempts have been made to formulate certain NSAIDs, opioids or other analgesic, antipyretic or anti-inflammatory drugs in single dual-release compositions having both an immediate-release fraction and a controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release fraction of the drug. Such compositions have been disclosed, for example, for NSAIDs generally in the references individually cited immediately below

25 U S Patent No. 4,980,170 to Schneider *et al.*

International Publication No. WO 99/12524.

Such dual-release compositions have illustratively been disclosed for ibuprofen in the references individually cited immediately below

U S Patent No. 5,681,583 to Conte *et al.*

30 International Publication No. WO 96/41617

Such dual-release compositions have illustratively been disclosed for naproxen in the references individually cited immediately below

U.S. Patent No. 4,888,178 to Rotim & Marchi

U.S. Patent No. 5,609,884 to Desai

Selective cyclooxygenase-2 inhibitory drugs have not previously been formulated in dual-release dosage forms. Certain drugs of this class have a sufficiently long half-life, even when conventionally formulated for oral delivery, to be suitable for once-a-day administration. For example, Canadian Patent Application No. 2,254,061 discloses that the selective cyclooxygenase-2 inhibitor 3-phenyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one, also known as rofecoxib, has a half-life sufficient to provide therapeutic benefit over a 24-hour period.

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SUMMARY OF THE INVENTION

According to the present invention, the selective cyclooxygenase-2 inhibitory compound celecoxib is formulated in an orally deliverable dosage form having dual-release properties such that onset of therapeutic effect is more rapid, yet at the same time the duration of therapeutic effect is longer, than is achieved with known formulations of celecoxib.

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An embodiment of the invention is a composition comprising celecoxib that, upon oral administration thereof to a subject, exhibits pharmacokinetic properties leading to (a) a greater maximum blood serum celecoxib concentration (C_{max}) and/or a shorter time following the administration to reach that maximum (T_{max}), and (b) a longer terminal half-life of blood serum celecoxib concentration ($T_{1/2}$), than previous compositions. It is contemplated that a greater C_{max} and/or a shorter T_{max} (i.e., immediate release properties) are obtained by providing a first fraction of the celecoxib in the composition (i) in the form of solid particles comprising celecoxib having a D_{90} particle size less than about 1 μm , or (ii) in the form of a solution of celecoxib in a pharmaceutically acceptable solvent. It is contemplated that a longer $T_{1/2}$ is obtained by providing a second fraction of the celecoxib in the composition (i) in the form of solid particles comprising celecoxib having a D_{90} particle size greater than about 25 μm , or (ii) in the form of particles of any convenient D_{90} particle size providing controlled release, slow release, programmed release, timed release, pulse release, sustained release or extended release of celecoxib. Preferably the $T_{1/2}$ thereby obtained results in maintenance of a therapeutic blood serum concentration of celecoxib for at least about 24 hours following oral administration.

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Accordingly, there is now provided a pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a first fraction of celecoxib in an amount of about 10 mg to about 400 mg, this first fraction being in solution in a pharmaceutically acceptable solvent and/or present in immediate-release solid particles having a D_{50} particle size less than about 1 μm , and a second fraction of celecoxib in an amount of about 10 mg to about 400 mg, this second fraction being present in solid particles having a D_{50} particle size greater than about 25 μm and/or in controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release particles, wherein the first fraction and the second fraction of celecoxib are present in a ratio of about 10:1 to about 1:10 in the composition.

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.

In a particularly preferred embodiment the dose units are tablets each comprising a first fraction of celecoxib in an amount of about 10 mg to about 400 mg, this first fraction being present in immediate-release solid particles having a D_{50} particle size less than about 1 μm , and a second fraction of celecoxib in an amount of about 10 mg to about 400 mg, this second fraction being distributed in a sustained-release matrix comprising hydroxypropylmethylcellulose (HPMC) having a viscosity, 2% in water, of about 100 to about 8000 cPs, wherein the first fraction and the second fraction of celecoxib are present in a ratio of about 10:1 to about 1:10 in the composition. The two fractions of celecoxib can be more or less homogeneously distributed throughout each tablet, but preferably the two fractions are individually contained in discrete layers or zones of each tablet.

In another particularly preferred embodiment the dose units are tablets or, more preferably, capsules each comprising a first fraction of celecoxib in an amount of about 10 mg to about 400 mg, this first fraction being present in immediate-release solid particles having a D_{50} particle size less than about 1 μm , and a second fraction of celecoxib in an amount of about 10 mg to about 400 mg, this second fraction being

present in a multiplicity of solid beads each having a sustained-release coating that comprises one or more pharmaceutically acceptable swellable or erodible polymers, wherein the first fraction and the second fraction of celecoxib are present in a ratio of about 10:1 to about 1:10 in the composition. Preferred swellable or erodible polymers are ethylcellulose and polymers and copolymers of acrylic acid, methacrylic acid and esters thereof. Preferably the first fraction of celecoxib is present in a multiplicity of solid beads similar in size to the beads containing the second fraction but having no coating or having a coating that is not a sustained-release coating.

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 one or more dose units, typically 1 to about 4 dose units, of a composition of the invention once a day.

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

DETAILED DESCRIPTION OF THE INVENTION

The term "oral administration" herein includes any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is 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.

A "subject" herein to which a therapeutic agent or composition thereof can be administered includes a human patient of either sex and of any age, and also includes any nonhuman animal, particularly a domestic or companion animal, illustratively a cat, dog or horse.

The term "dose unit" herein means a portion of a pharmaceutical composition that contains an amount of a therapeutic agent, in the present case celecoxib, suitable for a single oral administration to provide a therapeutic effect. Typically one dose unit, or a small plurality (up to about 4) of dose units, provides a sufficient amount of the agent to result in the desired effect.

The term "present in solid particles" as applied to celecoxib herein encompasses compositions wherein the solid particles consist essentially of celecoxib and compositions wherein the solid particles comprise celecoxib in intimate mixture with one or more other ingredients. These other ingredients can include one or more therapeutic agents other than celecoxib and/or one or more pharmaceutically acceptable excipients.

The terms "controlled-release", "slow-release", "programmed-release", "timed-release", "pulse-release", "sustained-release" and "extended-release" in relation to particles or formulations herein have meanings as accorded in the above-cited references, the pertinent disclosure of all of which is hereby incorporated by reference. Suitable processes for preparing such "controlled-release", "slow-release", "programmed-release", "timed-release", "pulse-release", "sustained-release" or "extended-release" particles comprising celecoxib useful in compositions of the present invention include those disclosed for other drugs in the above-cited references.

The term "excipient" herein means any substance, not itself a therapeutic agent, used as a carrier or vehicle for delivery of a therapeutic agent to a subject or added to a pharmaceutical composition to improve its handling or storage properties or to permit or facilitate formation of a dose unit of the composition into a discrete article such as a capsule or tablet suitable for oral administration. Excipients can include, by way of illustration and not limitation, diluents, disintegrants, binding agents, adhesives, wetting agents, polymers, 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.

Novel pharmaceutical compositions according to the present invention comprise one or more orally deliverable dose units. Each dose unit comprises celecoxib in a therapeutically effective total amount of about 20 mg to about 800 mg, partitioned between two fractions each of about 10 mg to about 400 mg as described herein.

It will be understood that a therapeutically effective amount of celecoxib for a subject is dependent *inter alia* on the body weight of the subject. Where the subject is a child or a small animal (e.g., a dog), for example, an amount of celecoxib relatively low in the disclosed range of about 20 mg to about 800 mg is likely to provide blood serum concentrations consistent with therapeutic effectiveness. Where the subject is an adult human or a large animal (e.g., a horse), achievement of such blood serum concentrations of celecoxib are likely to require dose units containing a relatively greater amount of celecoxib

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

In one embodiment, the first fraction of celecoxib in a composition of the invention, which is the fraction providing immediate release, is in the form of particles having a D_{50} particle size less than about 1 μm . Typically in this embodiment substantially all the particles are nanoparticles, i.e., solid particles of diameter less than 1 μm in the longest dimension of the particles. In such particles, celecoxib can be present alone or in intimate mixture with one or more excipients.

The effects on pharmacokinetic properties of reducing particle size from the microparticle range (greater than 1 μm diameter) to the nanoparticle range is generally unpredictable for any particular drug or class of drugs. According to the present invention, celecoxib in nanoparticulate form exhibits higher C_{max} and/or shorter T_{max} than celecoxib in microparticulate form.

Considering only the nanoparticulate component of a composition of this embodiment of the invention, average particle size is preferably about 0.1 to about 0.8 μm (about 100 to about 800 nm), more preferably about 0.15 to about 0.6 μm (about 150 to about 600 nm), and most preferably about 0.2 to about 0.4 μm (about 200 to about 400 nm). Celecoxib 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 typically provide the drug in amorphous form.

In one embodiment, celecoxib nanoparticles have a surface modifying agent adsorbed on the surface thereof. In another embodiment, celecoxib nanoparticles are contained in a matrix formed by a polymer. Preferably excipients are present and most preferably include 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 a nanoparticulate composition is ingested. Preferably both a water soluble diluent and a wetting agent are present.

Nanoparticles comprising or consisting essentially of celecoxib can be prepared according to any process previously applied to the preparation of other poorly water soluble drugs in nanoparticulate form. Suitable processes, without restriction, are illustratively disclosed for such other drugs in the above-cited references, the pertinent disclosure of all of which is hereby incorporated by reference.

In another embodiment, the first fraction of celecoxib in a composition of the invention, which is the fraction providing immediate release, is in solution in a pharmaceutically acceptable solvent. Polyethylene glycol, for example PEG-400, has been found to be a suitable solvent, either alone or in mixture with water. Illustratively, a mixture of 2 parts PEG-400 to 1 part water has been found to be a useful solvent base for an orally deliverable celecoxib solution. According to the present invention, orally administered celecoxib in dissolved form exhibits higher C_{max} and/or shorter T_{max} than celecoxib in any other orally administered form so far evaluated.

Although a celecoxib solution can be presented to the subject in bulk liquid form, it can alternatively be presented in pre-measured unit dose form, for example as a soft capsule. Optionally a pharmaceutically acceptable gelling agent can be added to the solution to form a gel. Softgels or gelcaps, which are soft capsules containing a gel, are therefore suitable dosage forms for compositions of the invention.

When administered orally to a fasting adult human, a 100 mg dose unit of a composition of the invention preferably exhibits a T_{max} of less than about 1.5 h, more preferably less than about 1 h and most preferably less than about 0.75 h, and a C_{max} of at least about 100 ng/ml, more preferably at least about 200 ng/ml. Typically a composition of the invention provides a blood serum concentration of celecoxib of at

least about 50 ng/ml within 30 minutes of oral administration, preferred compositions achieve such a concentration in as little as 15 minutes. This early rise in blood serum concentration is believed to be associated with the rapid onset of therapeutic effect achieved by compositions of the present invention.

- 5 In addition to the first fraction of celecoxib, which as explained above is the immediate-release fraction, a composition of the invention further comprises a second fraction of celecoxib that is the controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release fraction. In one embodiment, this fraction comprises celecoxib microparticles having a D_{50} particle size greater than about 25 μm . Preferably the D_{50} particle size of this fraction is about 25 μm to about 200 μm , more preferably about 25 μm to about 100 μm , for example about 40 μm to about 75 μm .

- 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.

- Preferably excipients are associated with or present in the primary microparticles and these excipients more preferably include a water soluble diluent or wetting agent or both.

- 20 In another embodiment, the second fraction of celecoxib is in the form of particles of any convenient size that are controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release particles prepared by any process disclosed for drugs other than celecoxib in the above-cited references, such process being adapted as necessary for the specific properties of celecoxib.

- The particles comprising the second fraction of celecoxib can optionally be dispersed as a suspension in a liquid diluent. In one embodiment of the invention, the particles comprising the second fraction are in stable suspension in a matrix solution comprising the first fraction of celecoxib. This suspension can be presented as a bulk liquid or can be in a pre-measured dosage form such as soft capsules, optionally as softgels or galecaps as described above.

When administered orally to a fasting adult human, a 100 mg dose unit of a

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A particularly preferred composition has the first fraction of celecoxib in an

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immediate-release form and the second fraction of celecoxib in a pulse-release form that releases a pulse of celecoxib about 8 h to about 12 h after administration. Such a composition is of especial utility for treatment of conditions such as osteoarthritis. For example, administration of such a composition at bedtime provides rapid onset of pain relief and enables pain-free sleep, and the pulse-release characteristic is timed to provide reduction in morning stiffness.

The weight ratio of the first to the second fraction of celecoxib in a composition of the invention is about 1:10 to about 10:1, preferably about 1.5 to about 5:1, for example about 1:1 or about 1:2.

10 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 fluid suspension as described above. In preparing such a suspension, use of a wetting agent such as polysorbate 80 is likely to be beneficial. A suspension can be prepared by dispersing nanoparticulate and/or microparticulate celecoxib in the liquid phase; alternatively the particulate celecoxib can be precipitated from solution in a solvent such as an alcohol, preferably ethanol. The liquid phase preferably comprises a palatable vehicle such as water, syrup or fruit juice, for example apple juice.

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, treatment of inflammation in a subject, as an analgesic for example in treatment of pain and headaches, and as an antipyretic in 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 treatment of asthma, bronchitis, menstrual cramps, preterm labor, tendinitis, burns, allergic neuritis, cytomegalovirus infectivity, apoptosis including HIV-induced

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

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Contemplated compositions are useful for, but not limited to, treating and

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in treatment of dysmenorrhea, premature labor, asthma and eosinophil-related disorders. They also can be of use in treatment of Alzheimer's disease, for decreasing bone loss particularly in postmenopausal women (i.e., treatment of osteoporosis), and for treatment of glaucoma.

5 By virtue of their high cyclooxygenase-2 (COX-2) inhibitory activity and/or their selectivity 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
10 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.

Preferred uses for the pharmaceutical compositions of the present invention
15 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.

By virtue of the rapid onset of therapeutic effect exhibited by compositions of
20 the invention, these compositions have particular advantages over prior formulations of celecoxib for treatment of acute cyclooxygenase-2 mediated disorders, especially for the relief of pain. At the same time, by virtue of the long duration of therapeutic effect exhibited by compositions of the invention, these compositions have particular advantages over prior formulations of celecoxib for treatment of chronic
25 cyclooxygenase-2 mediated disorders, where once-a-day treatment is especially desirable. Compositions of the invention are uniquely advantageous where a combination of rapid onset and long duration of therapeutic effect is required.

The present compositions can be used in combination therapies with opioids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa
30 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

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- others. Preferred combination therapies comprise use of a composition of the invention with one or more compounds selected from aceclofenac, acemetacin, *e*-acetamidocaproic acid, acetaminophen, acetammosalol, acetanilide, acetylsalicylic acid (aspirin), *S*-adenosylmethionine, alclofenac, alfentanil, allylprodine, 5
- alminoprofen, aloxiprin, alphaprodine, aluminum bis(acetylsalicylate), amfenac, aminochlorothanoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picolina, aminopropylion, aminopyrine, amixetrina, ammonium salicylate, ampiroxicam, antolmetin guacil, amleridine, antipyrine, antipyrine salicylate, antrafemine, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzyimorphine, 10
- bermoprofen, beztramide, α -bisabolol, bromfenac, *p*-bromoacetanilide, 5-bromosalicylic acid acetate, bromosaligenin, bucetin, bucloxic acid, bucolome, bupixamac, bumadizon, buprenorphine, butacetin, butibufen, butophanol, calcium acetylsalicylate, carbamazepine, carbrifene, carprofen, carsalam, chlorobutanol, chlorothanoxazin, choline salicylate, cinchophen, cimetacin, cismadol, chidanac, 15
- clometacin, clonitazene, clonixin, cloparac, clove, codema, codeme methyl bromide, codeme phosphate, codeme sulfate, cropropamide, crotethamide, desomorphine, dexoxadrol, dextromoramide, dezoeme, diampromide, diclofenac sodium, difenamisole, difenpiramide, difinusal, dihydrocodema, dihydrocodemone enol acetate, dihydromorphine, dihydroxyaluminum acetylsalicylate, dimenoxadol, 20
- dimenpheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone, ditazol, droxicam, emorfazone, enfenamie acid, epirizole, eptazocine, etersalate, etbenzamide, ethoheptazina, ethoxazene, ethylmethylthiambutene, ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac, fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentiazac, fepradinol, feprazone, 25
- floctafenine, flufenamic acid, flunoxaprofen, fluorenone, flupirtine, fluproquazone, flurbiprofen, fosfosal, gentinic 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, 30
- p*-lactophenetide, lefetamine, levorphanol, lofentanil, lonazolac, lornoxicam, loxoprofen, lysine acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic acid, meperidine, meptazinol, mesalamine, metazocine, methadone

- hydrochloride, methotrimeprazine, metazinc acid, metofoline, metopon, mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride, morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine, 1-naphthyl salicylate, naproxen, narceine, nefopam, nicomorphine, nifazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpiperone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, paralimide, pentazocine, peroxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenylramdol, piketoprofen, piminodine, pipebuzone, piperylone, pirofen, pirazolac, pirtramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinc acid, ramifenazone, ramifenamil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide *o*-acetic acid, salicylsulfuric acid, salicic, salverine, smetride, sodium salicylate, sufentanil, sulfasalazine, subinac, superoxide dismutase, suprofen, suribuzone, tabufumate, tamdap, tenoxicam, terofenamate, tetrandrine, thiazobutazone, tiaprofemic acid, tiaramide, tiidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesun, 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 celecoxib composition of the invention with an opioid compound, more particularly where the opioid compound is codeine, meperidine, morphine or a derivative thereof.

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.

A dose unit containing a particular amount of celecoxib can be selected to accommodate any desired frequency of administration used to achieve a desired daily

dosage. The daily dosage and frequency of administration, and therefore the selection of appropriate dose unit, depends on a variety of factors, including the age, weight, sex and medical condition of the subject, and the nature and severity of the condition or disorder, and thus may vary widely

5 For the 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, 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 or two doses per day, but with preferred compositions of the invention one dose per day is effective. Administration of a composition of the invention at the rate of one 200 mg dose unit or two 100 mg dose units once a day is preferred for most patients, but some patients may benefit from administration of up to double that dose.

20 For the 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 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 or two doses per day, but with preferred compositions of the invention one dose per day is effective. Administration of a composition of the invention at the rate of one 400 mg dose unit or two 200 mg dose units once a day is preferred for most patients

30 For pain management, compositions of the invention can be used to provide a

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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 or two doses per day, but with preferred compositions of the invention one dose per day is effective. Administration of a composition of the invention at the rate of one 200 mg dose unit or two 100 mg dose units once a day is preferred.

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.

While the amount of celecoxib in 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.

Excipients employed in a composition of the invention can be solids or liquids or both. 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.

A composition of the invention is preferably made in the form of discrete dose units each containing a predetermined amount of the cyclooxygenase-2 inhibitor, such as tablets, pills, hard or soft capsules, lozenges, cachets, dispensable powders, granules, suspensions, elixirs or other liquids, or any other form reasonably adapted for oral administration. Such oral dosage forms can further comprise, for example, buffering agents. Tablets, pills and the like additionally can be prepared with or without coatings.

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.

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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.

Excipient-containing compositions of the invention can be prepared by any suitable method of pharmacy which includes the step of bringing into association the excipient(s) with the celecoxib, in a combination of dissolved, suspended, nanoparticulate, microparticulate or controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release forms thereof. In general, such compositions are prepared by uniformly and intimately admixing the celecoxib with a liquid or finely divided diluent, or both, and then, if necessary or desired, encapsulating or shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of celecoxib, 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) and/or dispersing agent(s). Molded tablets can be made by molding, in a suitable machine, celecoxib moistened with an inert liquid diluent.

Compositions of the present invention preferably comprise celecoxib in a desired amount admixed with one or more excipients selected from the group consisting of pharmaceutically acceptable diluents, disintegrants, binding agents, adhesives, wetting agents, lubricants, and anti-adherent agents. In addition, celecoxib nanoparticles, microparticles and/or controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release particles, if present, can optionally contain one or more matrix polymers and/or surface modifying agents. Celecoxib particles can be aggregated into beads which are enveloped in a coating conferring controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release properties to the celecoxib in such beads.

Through appropriate selection and combination of excipients, compositions

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can be provided exhibiting improved performance with respect to, among other properties, efficacy, 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 excipients 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 excipients selected provides tablets that can exhibit improvement, among other properties, in dissolution and disintegration profiles, hardness, crushing strength, and/or friability.

Compositions of the invention optionally comprise one or more pharmaceutically acceptable diluents as excipients. Suitable diluents include, either individually or in combination, lactose, including lactose USP, anhydrous lactose USP and spray-dried lactose USP, starch, including starch USP and directly compressible starch, mannitol, sorbitol, dextrose monohydrate; microcrystalline cellulose; dibasic calcium phosphate dihydrate; sucrose-based diluents including confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate; calcium lactate trihydrate; dextrates (e.g., Emdex™); Celutab™; dextrose (e.g., Cerolose™); mositol, hydrolyzed cereal solids such as Maltron™ products and Mor-Rex™; amylose; Rexcel™; powdered cellulose (e.g., Elcema™); 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 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 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; sodium starch glycolate; clays (such as Veegum™ HV); celluloses (such as purified cellulose, methylcellulose, sodium carboxymethylcellulose and carboxymethylcellulose); alginates, pregelatinized corn starches (such as National 1551 and National 1550), croscarmellose sodium, croscopovidone; and gums (such as agar, guar, locust bean, karaya, pectin, and tragacanth gums). Disintegrants can be added at any suitable step during the preparation of the 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.

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; starch, cellulose materials such as, but not limited to, methylcellulose and sodium carboxymethylcellulose (e.g., Tylose™); alginate acid and salts of alginate acid, magnesium aluminum silicate; polyethylene glycol, guar gum, polysaccharide acids, bentonites; polyvinylpyrrolidone; polymethacrylates, hydroxypropylmethylcellulose (HPMC); hydroxypropylcellulose (Klucel™); ethylcellulose (Ethocel™), and 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.

Compositions of the invention optionally comprise one or more

pharmaceutically acceptable wetting agents as excipients. Such wetting agents are preferably selected to maintain the celecoxib in close association with water, a condition that is believed to improve the relative bioavailability of the composition. Suitable wetting agents include, either individually or in combination, oleic acid, glyceryl monooleate, sorbitan 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 composition.

Compositions of the invention optionally comprise one or more pharmaceutically acceptable lubricants and/or glidants as excipients. 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.

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

Although unit dose hard capsule and tablet compositions of the 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.

5 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 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 10 100 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 15 fluid.

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

20 The first and second fractions of celecoxib can be intimately coformulated, for example within individual granules that are subsequently encapsulated or compressed into tablets. Alternatively, the first and second fractions of celecoxib can be spatially separated in a composition of the invention. Illustratively, within a single hard capsule there can be separate granules or beads, for example coated beads, containing celecoxib in immediate-release form or in controlled-release, slow-release, 25 programmed-release, timed-release, pulse-release, sustained-release or extended-release form. Within a single unit dose tablet there can be separate layers containing celecoxib in immediate-release form or in controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release form. For example, a two-layer celecoxib tablet similar to that described for 30 naproxen in above-cited U.S. Patent No. 5,609,884 can be prepared.

In a particularly preferred embodiment of the present invention, the second fraction of celecoxib is distributed in a sustained-release matrix comprising HPMC

having a viscosity, 2% in water, of about 100 to about 8000 cPa. Compositions of this embodiment of the invention are referred to for convenience herein as "dual-release matrix compositions" When formulated as tablets, which are a preferred dosage form for this embodiment, such compositions are referred to herein as "dual-release matrix tablets"

A matrix composition of the invention comprises HPMC in an amount sufficient to extend the release profile of the celecoxib. Typically such an amount is about 0.1% to about 40%, preferably about 5% to about 30%, for example about 10%, of the composition by weight. Preferably the weight ratio of HPMC to the second fraction of celecoxib is about 1:1 to about 1:12, more preferably about 1:1 to about 1:6.

HPMCs vary in the chain length of their cellulosic backbone. This directly affects the viscosity of an aqueous dispersion of the HPMC. Viscosity is normally measured at a 2% by weight concentration of the HPMC in water. HPMCs having viscosity, 2% in water, of less than about 100 cPa can be useful, for example as binding agents, but tend not to have useful release-extending properties for medicaments. Such HPMCs are said to have good binding properties and less desirable sustaining properties. The term "binding properties" herein refers to suitability as a binding agent for tablet production by wet granulation, wherein, for example, HPMC is dissolved in water for spraying onto dry powders to be granulated. The term "sustaining properties" herein refers to suitability as a release-extending matrix. HPMCs with good sustaining properties are typically too viscous for use as a binding agent in wet granulation techniques. According to the present invention, the HPMC(s) used to form the release-extending matrix of a dual-release celecoxib composition should have a viscosity, 2% in water, of about 100 to about 8000 cPa, preferably about 1000 to about 8000 cPa, for example about 4000 cPa.

HPMCs also vary in the degree of substitution of available hydroxyl groups on the cellulosic backbone by methoxyl groups and by hydroxypropoxyl groups. With increasing hydroxypropoxyl substitution, the resulting HPMC becomes more hydrophilic in nature. It is preferred in dual-release matrix compositions of the present invention to use HPMCs having about 15% to about 35%, more preferably about 19% to about 30%, and most preferably about 19% to about 24%, methoxyl

substitution, and having about 3% to about 15%, more preferably about 4% to about 12%, and most preferably about 7% to about 12%, hydroxypropoxyl substitution.

HPMCs which are relatively hydrophilic in nature and which may be used in the present invention are illustratively available under the brand names Methocel™ of Dow Chemical Co. and Metolose™ of Shin-Etsu Chemical Co. Examples of HPMC's of a low viscosity grade, generally unsuitable in compositions of the present invention except as binding agents, include Methocel™ E5, Methocel™ E15 LV, Methocel™ E50 LV, Methocel™ K100 LV and Methocel™ F50 LV, whose 2% by weight aqueous solutions have viscosities of 5 cPs, 15 cPs, 50 cPs, 100 cPs and 50 cPs, respectively. Examples of HPMC's having medium viscosity include Methocel™ E4M and Methocel™ K4M both of whose 2% by weight aqueous solutions have a viscosity of 4000 cPs. Examples of HPMC's having high viscosity, generally unsuitable for use in compositions of the present invention, include Methocel™ E10M, Methocel™ K15M and Methocel™ K100M whose 2% by weight aqueous solutions have viscosities of 10,000 cPs, 15,000 cPs and 100,000 cPs, respectively.

Various HPMC products are described in Formulating for Controlled Release with Methocel Premium Cellulose Ethers, Dow Chemical Co., 1997. The methoxyl and hydroxypropoxyl substitution type and content for selected HPMC products is provided in Table 1, below.

Table 1 Properties of selected HPMC products

Methocel™ E4MP (USP 2910)	Nominal Viscosity, 2% in Water	4,000 cPs
	Methoxyl, %	28-30
	Hydroxypropoxyl, %	7-12
Methocel™ K4MP (USP 2208)	Nominal Viscosity, 2% in Water	4,000 cPs
	Methoxyl, %	19-24
	Hydroxypropoxyl, %	7-12
Methocel™ E10MP (USP 2910)	Nominal Viscosity, 2% in Water	10,000 cPs
	Methoxyl, %	28-30
	Hydroxypropoxyl, %	7-12
Methocel™ K15MP (USP 2208)	Nominal Viscosity, 2% in Water	15,000 cPs
	Methoxyl, %	19-24
	Hydroxypropoxyl, %	7-12

An illustrative presently preferred HPMC with sustained-release properties is one with substitution type 2208, denoting about 19% to about 24% methoxyl substitution and about 7% to about 12% hydroxypropoxyl substitution, and with a

nominal viscosity, 2% in water, of about 4000 cPa. A "controlled release" grade is especially preferred, having a particle size such that at least 90% passes through a #100 USS mesh screen. An example of a commercially-available HPMC meeting these specifications is Methocel™ K4M, of Dow Chemical Co.

5 Without being bound by any particular hypothesis as to how the HPMC matrix according to the invention provides superior sustained-release characteristics, it is believed that upon oral ingestion and contact with gastrointestinal fluids, HPMC on or close to the tablet surface partially hydrates and thereby swells to form a gel layer having the celecoxib distributed in a three-dimensional matrix therein. It is further
10 believed that this outer three-dimensional gel matrix layer slows dissolution of the tablet. As the outer gel layer slowly dissolves, disperses or erodes, celecoxib is released from this layer into the gastrointestinal fluid where it is available for absorption. Meanwhile, hydration of the HPMC matrix gradually advances towards the center of the tablet, permitting further release of celecoxib over time by the same
15 process hypothetically described above. Since the celecoxib is distributed throughout the tablet at a more or less uniform concentration throughout the HPMC matrix, a fairly constant amount of celecoxib can, according to the present non-limiting theory, be released per unit time *in vivo* by dissolution, dispersion or erosion of the outer portions of the tablet.

20 Overall release rate and consequently drug availability are dependent on the rate of diffusion of the drug through the outer gel layer and the rate of erosion of this layer of the tablet. Preferably T-90% (the time required for 90% celecoxib release) *in vivo* is less than 24 hours, so that a clearance time exists whereby the tablet is suitable for once-a-day administration.

25 Dual-release matrix tablets of the invention can be prepared for example by co-compressing a first granulated mixture containing celecoxib in nanoparticulate form with a second granulated mixture containing celecoxib in an HPMC matrix. The first granulated mixture can be prepared according to information provided hereinabove. The second granulated mixture can be prepared illustratively as follows.

30 A mixer (e.g., a 60 L Baker Perkins blender) is loaded with lactose, micronized celecoxib, microcrystalline cellulose (e.g., an Avicel™ product), HPMC (e.g., Methocel™ K4M), and a binder (e.g., Pharmacoat™ 603), preferably in this

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order These materials are mixed, for example for three minutes with a slow main blade setting and a slow chopper blade setting, to form a dry powder mixture.

5 The dry powder mixture is wet granulated, conveniently in the same blender with the main blade and chopper blade on a fast speed setting. Water is added in an amount and at a rate appropriate to the amount of dry powder mixture, illustratively at about 1-1.5 kg/minute for about 3 minutes. The resulting wet granulated mixture is blended for an additional period of time to ensure uniform distribution of water in the granulation. The wet granulated mixture contains about 30% water by weight.

10 The wet granulated mixture is dried, for example in an Aeromatic fluid bed dryer with inlet air temperature set at about 60°C, to reduce the moisture content to about 1% to about 3% by weight. Moisture content of the granules can be monitored, for example using a Computrac Moisture Analyzer

15 The resulting dry granules are milled and screened, for example by passing through a Fitzpatrick mill (D6A) with 20-mesh screen, knives forward and medium speed setting (1500-2500 rpm).

20 The resulting screened granules are placed in a mixer, for example a Paterson-Kelley 2 cubic foot V-blender. Talc is added to the granules and the granules are blended for about 5 minutes. Magnesium stearate is then added to the granules and the granules are blended for about 3 minutes. The resulting lubricated granules are ready for co-compression together with the first granulated mixture to form dual-release matrix tablets.

25 In another particularly preferred embodiment of the present invention, the second fraction of celecoxib is present in a multiplicity of solid beads, pellets or granules each having a coating comprising a swellable or erodible polymer. Such beads, pellets or granules are referred to herein as "beads" or "coated beads" and are typically dense, hard, substantially spherical and of low friability. Compositions of this embodiment of the invention are referred to for convenience herein as "dual-release coated bead compositions". When formulated as capsules, which are a preferred dosage form for this embodiment, such compositions are referred to herein as "dual-release coated bead capsules".

30 In a dual-release coated bead composition of the present invention, whether encapsulated or tableted, the first fraction of celecoxib can be present in any suitable

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immediate-release form but is preferably in the form of nanoparticulate celecoxib and is preferably formulated into beads of similar size to the coated beads containing the second, sustained-release, fraction of celecoxib. Such beads containing the first, immediate-release, fraction are either uncoated or coated with a material that does not
5 slow or extend release of the celecoxib. The demands of a dual-release celecoxib composition are met surprisingly well by a dual-release coated bead preparation wherein the beads containing the sustained-release fraction of celecoxib are coated with an erodible barrier layer comprising at least one swellable polymer that is substantially insoluble in gastrointestinal fluid. The beads optionally contain
10 pharmaceutically acceptable excipients such as lactose and microcrystalline cellulose and are preferably about 0.1 mm to about 1.0 mm, more preferably about 0.15 mm to about 0.5 mm, in diameter. For example, the beads can be of such a range of sizes that they pass through a 0.425 mm sieve but are retained on a 0.18 mm sieve. The beads can be prepared by mixing and granulation of celecoxib with one or more
15 excipients, followed by extrusion, spheronization, drying and sieving the particles to the desired size range, followed by application of the swellable or erodible polymer coating to the beads containing that fraction of the celecoxib that is desired to exhibit sustained release.

In a sustained-release coating preferred according to the present invention, the
20 beads containing the second fraction of celecoxib together with one or more excipients are coated with one or more swellable or erodible polymers selected from hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose, hydroxyethylcellulose, ethylcellulose (e.g. Surelease™), hydroxyethylmethylcellulose, methylcellulose, and polymers and copolymers of acrylic acid and methacrylic acid
25 and esters thereof (e.g. Eudragit™ RL, Eudragit™ RS, Eudragit™ L100, Eudragit™ S100, Eudragit™ NE). The swellable or erodible polymers can be combined with one or more water-soluble substances such as sugar, lactose and salts to form a partly erodible film with a pH-independent or pH-dependent release rate.

Eudragit™ of Rohm Pharma is a trade name applied to a range of products
30 useful for film coating of sustained-release particles. These products are of varying solubility in gastrointestinal fluids. Eudragit™ RL and Eudragit™ RS are copolymers synthesized from acrylic and methacrylic esters with a low content of quaternary

ammonium groups. Eudragit™ RL and RS differ in the molar ratios of such ammonium groups to the remaining neutral (meth)acrylic acid esters (1:20 and 1:40 respectively). Eudragit™ NE is an aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate. Characteristics of Eudragit™ polymers are described in Eudragit: Sustained-release formulations for oral dosage forms, Rohm Basic Info 2

Ethylcellulose, available for example under the trade name Surelease™, is another suitable material which is available in different grades and in special qualities for aqueous based barrier coatings. According to the present invention it is preferred to use ethylcellulose having a viscosity of about 5 to about 15 cP, but other types of cellulose-based swellable or erodible polymers can also be used.

In the coating procedure the swellable or erodible polymers are dissolved or dispersed in a solvent or mixture of solvents such as ethanol, acetone, methyl isobutyl ketone (MIBK) and water. Plasticizers and/or pigments can optionally be used to modify the technical properties or change the permeability of the coating. The coating preferably has virtually pH-independent permeability properties throughout a pH range of about 1.0 to about 7.0. At higher pH a reduction in the release rate of celecoxib can be observed, however, this is not due to properties of the polymeric layer but results from reduced solubility of celecoxib at high pH values.

An illustrative suitable coating composition according to the present invention comprises ethylcellulose and HPMC together with triethyl citrate as a plasticizer. An example of such a coating composition contains 90% polymer consisting of ethylcellulose and HPMC in a weight ratio of 55:35 to 80:10, with 10% triethyl citrate.

Each coated bead containing celecoxib represents an individual sustained-release unit, releasing the drug at a rate that is preferably independent of its position in the gastrointestinal tract. Overall dissolution profile and celecoxib availability are dependent on the rate of drug diffusion through the sustained-release coating and on the rate of erosion of the coating in the gastrointestinal tract.

In a process for preparing a coated bead composition, celecoxib and diluents, preferably lactose and/or microcrystalline cellulose, are mixed and granulated by the following illustrative method. Celecoxib is added to a mixture of lactose and

microcrystalline cellulose (e.g., Avicel™ PH-101, Avicel™ RC-581, Avicel™ RC-591 or a mixture thereof) in a total amount of 1000-4000 g and dry-mixed in a high shear mixer (e.g., Niro-Felder mixer) at a high mixing speed for 2-5 minutes. Water (300-700 grams) is added and the resulting mass is granulated for 2-5 minutes at high speed.

Extrusion of the resulting material can be performed for example in a NICA B-140 extruder (Lexus Medical AB, Sweden) through a perforated screen with drilled orifices of 0.25-1.0 mm diameter. The speed of the agitator and the feeder are preferably set on the lowest values.

Spheronization of the resulting extrudate can be conducted for example in a NICA Marumerizer (Ferro Mecano AB, Sweden). The speed of the Marumerizer plate is preferably adjusted to 500-10,000 rpm. Spheronization continues for 2-10 minutes, with about 1000 g wet extrudate on the plate at each run.

Drying of the resulting spheronized beads can be performed in a fluidized bed dryer (e.g., Aeromatic AG, West Germany) at an inlet temperature of 50-90°C. A net device can be placed in the top of the fluidized bed to avoid loss of beads to the cyclone output. The batch is preferably divided into sub-batches of 200-800 g. Each sub-batch is dried for 10-60 minutes at an air volume of 100-400 m³/h in order to obtain individual beads rather than aggregates. If necessary, the sub-batches are then mixed and the whole batch dried for 5-30 minutes to an end product temperature of 40-60°C. A yield of dry beads of 1600-2000 g can be expected.

Sizing of the resulting dry beads can be performed using analytical sieves. Two sieves are selected from a set of sieve sizes, for example of 850 µm, 600 µm, 425 µm, 300 µm, 250 µm and 180 µm.

Celecoxib beads manufactured as above can be coated with swellable or erodible polymers to prepare sustained-release coated beads. Immediate-release beads are not so coated. Both sustained-release and immediate-release beads are present in a dual-release composition of the invention. For example, Surelease™ or Eudragit™ RS can be applied as a 10-20% by weight solids dispersion, using spray coating equipment (e.g., Wurster). The spray gun is mounted at a height of 0.25 cm to 5 cm over the bottom of the bed. An ethanol/MIBK mixture is pumped through the system prior to the start of the coating operation. Celecoxib beads are pre-heated at 50-80°C

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with an air velocity of 100-400 m³/h for 30-90 minutes. The coating is applied using the following typical process parameters: atomizing pressure 1.0-3.0 bar, air temperature 50-80°C, air velocity 100-400 m³/h and solution flow about 10-80 ml/minute.

- 5 The coated beads manufactured as above, together with immediate-release beads, are encapsulated by a conventional encapsulation process.

- 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 one or more dose units of a composition
10 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 the once-a-day treatment 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 subject and the nature and severity of the disorder. Thus, the dosage regimen actually
15 employed can vary widely and can therefore deviate from the preferred dosage regimens set forth above.

- Initial treatment of a subject 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
20 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 the effectiveness of therapy. Continuous analysis of such data permits modification of the treatment regimen during therapy so that optimally effective
25 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
30 condition or disorder.

 The present invention also is directed to use of compositions of the invention in preparation of medicaments useful in the treatment and/or prophylaxis of

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cyclooxygenase-2 mediated conditions and disorders, in particular such conditions and disorders where a combination of rapid onset and long duration of therapeutic effect is desired or required.

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WHAT IS CLAIMED IS

- 1 A pharmaceutical composition comprising one or more orally deliverable dose
units, each comprising a first fraction of celecoxib in an amount of about 10
mg to about 400 mg, said first fraction being in solution in a pharmaceutically
5 acceptable solvent and/or present in immediate-release solid particles having a
D₅₀ particle size less than about 1 μ m, and a second fraction of celecoxib in an
amount of about 10 mg to about 400 mg, said second fraction being present in
solid particles having a D₅₀ particle size greater than about 25 μ m and/or in
controlled-release, slow-release, programmed-release, timed-release, pulse-
10 release, sustained-release or extended-release particles, wherein said first
fraction and said second fraction of celecoxib are present in a ratio of about
10:1 to about 1:10 in the composition.
- 2 The composition of Claim 1 wherein said first fraction of celecoxib is in
solution in a pharmaceutically acceptable solvent.
- 15 3 The composition of Claim 2 wherein said solvent comprises polyethylene
glycol.
4. The composition of Claim 2 wherein particles comprising said second fraction
of celecoxib are in stable suspension in a matrix solution comprising said first
fraction.
- 20 5 The composition of Claim 4 that is in the form of unit dose soft capsules.
- 6 The composition of Claim 1 wherein said first fraction of celecoxib is present
in immediate-release solid particles having a D₅₀ particle size less than about
1 μ m.
- 7 The composition of Claim 6 that is in the form of unit dose hard capsules.
- 25 8 The composition of Claim 7 wherein said first fraction and said second
fraction of celecoxib are present in separate granules or beads within said
capsules.
- 9 The composition of Claim 8 wherein said second fraction of celecoxib is
present in coated granules or beads having controlled-release, slow-release,

programmed-release, timed-release, pulse-release, sustained-release or extended-release properties

10. The composition of Claim 6 that is in the form of unit dose tablets.
11. The composition of Claim 10 wherein said first fraction and said second
5 fraction of celecoxib are present in separate layers within said tablets.
12. The composition of Claim 11 wherein said second fraction of celecoxib is present in particles having controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release properties.
- 10 13. The composition of Claim 1 wherein each of said dose units contains celecoxib in an amount of about 50 mg to about 400 mg.
14. The composition of Claim 1 further comprising one or more opioid or analgesic drugs.
15. The composition of Claim 14 wherein said opioid or analgesic drugs are
15 selected from the group consisting of narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers.
- 20 16. The composition of Claim 14 wherein said opioid or analgesic drugs are selected from the group consisting of aceclofenac, aceemetacin, *e*-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic acid (aspirin), *S*-adenosylmethionine, alclofenac, alfentanil, allylprodine, alminoprofen, aloxiprin, alphaprodine, aluminum
25 bis(acetylsalicylate), amfenac, aminochlorphenoxazin, 3-amino-4-hydroxybutyric acid, 2-amino-4-picoline, aminopropylion, aminopyrine, amixetrine, ammonium salicylate, amproxican, amtolmetin guacil, anileridine, antipyrine, antipyrine salicylate, antrafenne, apazone, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, benzydimorphine,
30 bermoprofen, beztramide, α -bisabolol, bromfenac, *p*-bromoacetanilide,

5-bromosalicylic acid acetate, bromosaligenin, buccetin, bucloxic acid,
 bucoloma, bufexamac, bumadizon, buprenorphine, butacetyl, butibufen,
 butophanol, calcium acetylsalicylate, carbamazepine, carbiphen, carprofen,
 carsalam, chlorobutanol, chlorphenoxazone, choline salicylate, cinchophen,
 5 cimetacin, cirmadol, clidanac, clometacin, clonitazene, clonixin, clopirac,
 clove, codeine, codeine methyl bromide, codeine phosphate, codeine sulfate,
 cropropamide, crotethamide, desomorphine, dexoxadrol, dextromoramide,
 dezocine, diampromide, diclofenac sodium, difenamilazole, difenpiramide,
 diflunisal, dihydrocodeine, dihydrocodeinone enol acetate, dihydromorphine,
 10 dihydroxyaluminum acetylsalicylate, dimenoxadol, dimepheptanol,
 dimethylthiambutene, dioxaphetyl butyrate, dipipanone, diprocetyl, dipyrone,
 ditazol, droxicam, emorfazone, enfenamic acid, epirizole, eptazocine,
 etersalate, ethenzamide, ethoheptazine, ethoxazone, ethylmethylthiambutene,
 ethylmorphine, etodolac, etofenamate, etonitazene, eugenol, felbinac,
 15 fenbufen, fenclozic acid, fendosal, fenoprofen, fentanyl, fentazac, fepradinol,
 feprazone, floctafenone, flufenamic acid, flunoxaprofen, fluorenone, flupirtine,
 fluproquazone, flurbiprofen, fosfosal, gentaic acid, glafemine, glucametacin,
 glycol salicylate, guaiazulene, hydrocodone, hydromorphone,
 hydroxyphenidine, ibufenac, ibuprofen, ibuproxam, imidazole salicylate,
 20 indomethacin, indoprofen, isofluzolac, isoladol, isomethadone, isonixin,
 isoxepac, isoxicam, ketobermidone, ketoprofen, ketorolac, *p*-lactophenolide,
 lefetamine, levorphanol, lofenamil, lonazolac, lomoxicam, loxoprofen, lyaine
 acetylsalicylate, magnesium acetylsalicylate, meclofenamic acid, mefenamic
 acid, meperidine, meptazolol, mesalamine, metazocine, methadone
 25 hydrochloride, methotrimeprazine, metiazinic acid, metofoline, metopon,
 mofebutazone, mofezolac, morazone, morphine, morphine hydrochloride,
 morphine sulfate, morpholine salicylate, myrophine, nabumetone, nalbuphine,
 1-naphthyl salicylate, naproxen, narceme, nefopam, ncomorphine, nifenazone,
 niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol,
 30 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, phenylramidol, piktoprofen, pimmodine, pipebuzone, piperyone, pirofen, pirazolac, pirtramide, piroxicam, pranoprofen,
- 5 proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizimic acid, ramifenazone, remifentanyl, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide *o*-acetic acid, salicylsulfonic acid, salsalta, salverme, sumetride, sodium salicylate, sufentanyl, sulfasalazine, sulindac, superoxide dismutase,
- 10 suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, timoridine, tolfenamic acid, tolmetin, tramadol, tropeam, vimmol, xenbucm, ximoprofen, zaltoprofen and zomepirac.
- 17 The composition of Claim 14 wherein said opioid or analgesic drugs are
15 selected from codeine, meperidine, morphine and derivatives thereof.
- 18 A pharmaceutical composition comprising one or more orally deliverable dose units, each comprising a first fraction of celecoxib in immediate-release form in an amount of about 10 mg to about 400 mg, and a second fraction of celecoxib in controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release form in an amount
20 of about 10 mg to about 400 mg, said composition providing, upon a single oral administration of 1 to about 4 dose units to a subject, (a) a C_{max} greater than about 100 ng/ml, (b) a T_{max} shorter than about 1.5 h and (c) a $T_{1/2}$ longer than about 9 h.
- 25 19 The composition of Claim 18 providing, upon a single oral administration of 1 to about 4 dose units to a subject, (a) a C_{max} greater than about 200 ng/ml, (b) a T_{max} shorter than about 0.75 h, (c) a blood serum concentration of at least 50 ng/ml within about 15 minutes after said administration, and (d) a $T_{1/2}$ such that blood serum concentration remains above about 50 ng/ml for at least 18 h
30 after said administration.
- 20 The composition of Claim 18 that has pharmacokinetic properties sufficient to

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provide onset of therapeutic effect within about 1 h, and a duration of therapeutic effect for at least about 24 h, of oral administration thereof to a subject having a cyclooxygenase-2 mediated disorder

- 21 A pharmaceutical composition comprising one or more orally deliverable dose
5 units, each comprising a first fraction of celecoxib in immediate-release form
in an amount of about 10 mg to about 400 mg, said first fraction being present
in immediate-release solid particles having a D_{50} particle size less than about
1 μm , and a second fraction of celecoxib in an amount of about 10 mg to about
400 mg, said second fraction being distributed in a sustained-release matrix
comprising hydroxypropylmethylcellulose having a viscosity, 2% in water, of
about 100 to about 8000 cPa, wherein said first fraction and said second
fraction of celecoxib are present in a ratio of about 10:1 to about 1:10 in the
composition.
22. The composition of Claim 21 wherein said dose units are tablets.
- 15 23 The composition of Claim 22 wherein said first fraction and said second
fraction of celecoxib are individually contained in discrete layers or zones of
each tablet.
24. A pharmaceutical composition comprising one or more orally deliverable dose
20 units, each comprising a first fraction of celecoxib in an amount of about 10
mg to about 400 mg, said first fraction being present in immediate-release
solid particles having a D_{50} particle size less than about 1 μm , and a second
fraction of celecoxib in an amount of about 10 mg to about 400 mg, said
second fraction being present in a multiplicity of solid beads each having a
sustained-release coating that comprises one or more pharmaceutically
25 acceptable swellable or erodible polymers; wherein said first fraction and said
second fraction of celecoxib are present in a ratio of about 10:1 to about 1:10
in the composition.
- 25 The composition of Claim 24 wherein said dose units are capsules.
26. The composition of Claim 24 wherein said first fraction of celecoxib is present
30 in a multiplicity of solid beads similar in size to the beads containing said

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second fraction of celecoxib, but having no coating or having a coating that is not a sustained-release coating.

- 27 The composition of Claim 24 wherein said swellable or erodible polymers are selected from ethylcellulose and polymers and copolymers of acrylic acid, methacrylic acid and esters thereof.
- 5
- 28 A method of treating a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering 1 to about 4 dose units of a composition of any of Claims 1, 18, 21 or 24 once a day
- 10 29 The method of Claim 28 wherein said condition or disorder is selected from rheumatoid arthritis, osteoarthritis, cancer, Alzheimer's disease and post-surgical pain.

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ABSTRACT

Pharmaceutical compositions are provided comprising one or more orally deliverable dose units, each comprising celecoxib in an immediate-release fraction and a controlled-release, slow-release, programmed-release, timed-release, pulse-release, sustained-release or extended-release fraction. The compositions are useful in treatment or prophylaxis of cyclooxygenase-2 mediated conditions and disorders.

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