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NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión
486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

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Bogotá D.C, AGOSTO DE 2007

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(71) Applicant *(for all designated States except AT)*: NOVARTIS AG [CH/CH]; Schwarzwaldallee 215, CH–4058 Basel (CH).

(72) Inventors: NOVARTIS–ERFINDUNGEN VERWALTUNGS-GESELLSCHAFT MBH; Brunner Strasse 59, A–1235 Vienna (AT). FUJIMOTO, Roger, Aki; 21 Molly Stark Drive, Morristown, NJ 07960 (US). MCQUIRE, Leslie, Wighton; 17 Crown Drive, Warren, NJ 07059 (US). MUGRAGE, Benjamin, Biro; 10 Courter Street, Basking Ridge, NJ 07920 (US). VAN DUZER, John, Henry; 304 County Road 579, Asbury, NJ 08802 (US). XU, Daqiang; 12 Kathryn Drive, Whippany, NJ 07981 (US).

(74) Agent: BECKER, Konrad; Novartis AG, Patent– und Markenabteilung, Lichtstrasse 35, CH–4002 Basel (CH).

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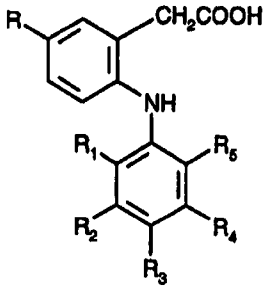
(54) Title: CERTAIN 5–ALKYL–2–ARYLAMINOPHENYLACETIC ACIDS AND DERIVATIVES



(I)

(57) Abstract

Disclosed are the compounds of formula (I), wherein R is methyl or ethyl; R_1 is chloro or fluoro; R_2 is hydrogen or fluoro; R_3 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy; R_4 is hydrogen or fluoro; and R_5 is chloro, fluoro, trifluoromethyl or methyl; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof; as selective COX–2 cyclooxygenase inhibitors.

CERTAIN 5-ALKYL-2-ARYLAMINOPHENYLACETIC ACIDS AND DERIVATIVES

The invention relates to 5-alkyl-2-arylaminophenylacetic acids and derivatives thereof as defined herein which are particularly potent and selective cyclooxygenase-2 (COX-2) inhibitors, methods for preparation thereof, pharmaceutical compositions comprising said compounds, methods of selectively inhibiting COX-2 activity and of treating conditions in mammals which are responsive to COX-2 inhibition using said compounds or pharmaceutical compositions comprising said compounds of the invention.

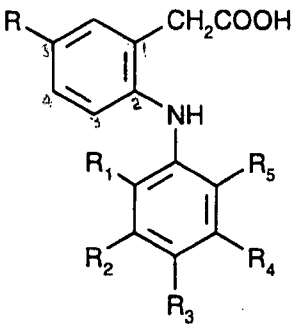
Various substituted 2-arylaminophenylacetic acids and derivatives thereof have been disclosed e.g. in J. Med. Chem. 33, 2358 (1990), U.S. patents 3,558,690, 3,652,762, 4,173,577 and 4,548,952, DE 3445011, and in PCT applications WO 97/09977 and WO 96/00716 as non-steroidal antiinflammatory agents and cyclooxygenase inhibitors. As to 5-alkyl-2-arylaminophenylacetic acids, the only example known to be described in the literature is 5-methyl-2-(2,6-dimethylanilino)-phenylacetic acid and its sodium salt (U.S. patent 3,558,690) for which no biological data has been reported.

Non-steroidal antiinflammatory agents block prostaglandin synthesis by inhibition of the enzyme cyclooxygenase. Cyclooxygenase is now known to comprise a constitutive isoform (cyclooxygenase-1, COX-1) and an inducible isoform (cyclooxygenase-2, COX-2). COX-1 appears responsible for protective beneficial features of prostaglandins, e.g. for the gastrointestinal tract, kidney, etc., while the inducible isoform COX-2 appears responsible for pathological conditions associated with prostaglandins, such as inflammatory conditions. A limitation to the use of classical nonsteroidal antiinflammatory drugs (NSAIDs including diclofenac sodium which is the sodium salt of 2,6-dichloroanilinophenylacetic acid) is gastrointestinal toxicity now attributed to the inhibition of the COX-1 isoform of cyclooxygenase. Selective inhibition of inducible COX-2 in vivo has been reported to be antiinflammatory and non-ulcerogenic (Proc. Natl. Acad. Sci. (USA) 1994; 91:3228-3232).

The present invention provides novel 5-alkyl substituted 2-arylaminophenylacetic acids and derivatives which surprisingly inhibit COX-2 without significantly inhibiting COX-1. The invention thus provides novel nonsteroidal antiinflammatory agents which are surprisingly free

of undesirable side effects usually associated with the classical nonsteroidal antiinflammatory agents, such as gastrointestinal and renal side effects.

The invention relates to compounds of formula I



(I)

wherein R is methyl or ethyl;
R_1 is chloro or fluoro;
R_2 is hydrogen or fluoro;
R_3 is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxy;
R_4 is hydrogen or fluoro; and
R_5 is chloro, fluoro, trifluoromethyl or methyl;
pharmaceutically acceptable salts thereof; and
pharmaceutically acceptable prodrug esters thereof.

A particular embodiment of the invention relates to the compounds of formula I wherein R is methyl or ethyl; R_1 is chloro or fluoro; R_2 is hydrogen; R_3 is hydrogen, fluoro, chloro, methyl or hydroxy; R_4 is hydrogen; and R_5 is chloro, fluoro or methyl; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable esters thereof.

A preferred embodiment relates to the compounds of formula I wherein R is methyl or ethyl; R_1 is fluoro; R_2 is hydrogen; R_3 is hydrogen, fluoro or hydroxy; R_4 is hydrogen; and R_5 is chloro; pharmaceutically acceptable salts thereof; and pharmaceutically acceptable prodrug esters thereof.

disorders in mammals, including inflammation, pyresis, pain, osteoarthritis, rheumatoid arthritis, migraine headache, neurodegenerative diseases (such as multiple sclerosis), Alzheimer's disease, osteoporosis, asthma, lupus and psoriasis.

The compounds of the present invention are further useful for the treatment of neoplasia particularly neoplasia that produce prostaglandins or express cyclooxygenase, including both benign and cancerous tumors, growths and polyps. Compounds of the present invention may be employed for the treatment of any neoplasia as for example recited in International Patent Application Publication No. WO 98/16227, published 23 April 1998, in particular epithelium cell-derived neoplasia. Compounds of the present invention are in particular useful for the treatment of liver, bladder, pancreas, ovarian, prostate, cervical, lung and breast cancer and, especially gastrointestinal cancer, for example cancer of the colon, and skin cancer, for example squamus cell or basal cell cancers and melanoma.

The term "treatment" as used herein is to be understood as including both therapeutic and prophylactic modes of therapy, e.g. in relation to the treatment of neoplasia, therapy to prevent the onset of clinically or preclinically evident neoplasia, or for the prevention of initiation of malignant cells or to arrest or reverse the progression of premalignant to malignant cells, as well as the prevention or inhibition of neoplasia growth or metastasis. In this context, the present invention is, in particular, to be understood as embracing the use of compounds of the present invention to inhibit or prevent development of skin cancer, e.g. squamus or basal cell carcinoma consequential to UV light exposure, e.g. resultant from chronic exposure to the sun.

The compounds of the invention have activity in the above indications while substantially avoiding undesirable gastrointestinal ulceration associated with conventional cyclooxygenase inhibitors.

The compounds of the invention are also UV absorbers and are useful for blocking or absorbing UV radiation; for instance, for the treatment and prevention of sunburn, e.g. in suntan products

The compounds of the invention may also be used in ocular applications which include the treatment of ocular disorders, in particular of ocular inflammatory disorders, of ocular pain

including pain associated with ocular surgery such as PRK or cataract surgery, of ocular allergy, of photophobia of various etiology, of elevated intraocular pressure (in glaucoma) by inhibiting the production of trabecular meshwork inducible glucocorticoid response (TIGR) protein, and of dry eye disease.

The above-cited properties are demonstrable in vitro and in vivo tests using advantageously mammals, e.g. rats, mice, dogs, monkeys and isolated cells or enzyme preparations thereof. Said compounds can be applied in vitro in the form of solutions, e.g. aqueous solutions, and in vivo advantageously orally, topically or parenterally, e.g. intravenously. The dosage in vitro may range from about 10^{-5} to 10^{-9} molar concentrations. The dosage in vivo may range, depending on the route of administration, between about 1 and 100 mg/kg.

Cyclooxygenase inhibition is determined in vitro using cellular assays for inhibition of both cyclooxygenase-1 and cyclooxygenase-2.

The cellular assays for testing cyclooxygenase inhibitors are based on the fact that the cyclooxygenase enzyme (prostaglandin H synthase) catalyzes the rate limiting step in prostaglandin synthesis from arachidonic acid. Two enzymes mediate the reaction: COX-1 is a constitutive form of the enzyme whereas COX-2 is induced in response to various growth factors and cytokines. Cell lines have been established which express one form of the enzyme: a human skin fibroblast line which can be induced with IL-1 to synthesize COX-2, and the kidney epithelial cell line 293 which has been stably transfected to constitutively express COX-1. Both isoforms metabolize arachidonic into the stable metabolite prostaglandin E_2. Arachidonic acid can be added exogenously to increase output to easily measurable levels. The levels of prostaglandin E_2 in the extracellular medium are assayed by radioimmunoassay as a measure of enzyme activity. The relative activities of each isoform are compared to assess compound selectivity.

In vitro cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibition is determined in the cell-based assays in order to assess the in vitro activity and selectivity for COX-2 inhibition, using a prostaglandin E_2 radioimmunoassay. The cells utilized are primary human fibroblasts induced with interleukin-1 to produce COX-2, and the human kidney epithelial cell line 293 stably transfected to produce COX-1 constitutively. Cells are plated out into well plates in which the assay is performed. Fibroblasts are stimulated to synthesize COX-2 by treatment

including man, to inhibit COX-2-activity, and for the treatment of COX-2 dependent disorders, and comprise an effective amount of a pharmacologically active compound of the invention, alone or in combination, with one or more pharmaceutically acceptable carriers.

More particularly, the pharmaceutical compositions comprise an effective cyclooxygenase-2 inhibiting amount of a compound of the invention which is substantially free of cyclooxygenase-1 inhibiting activity and of side effects attributed thereto.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders e.g. magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1 to 75%, preferably about 1 to 50%, of the active ingredient.

Tablets may be either film coated or enteric coated according to methods known in the art.

Suitable formulations for transdermal application include an effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound

of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable formulations for topical application, e.g. to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, for example, for delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for dermal application, e.g. for the treatment of skin cancer, for example, for prophylactic use in sun creams, lotions sprays and the like. In this regard it is noted that compounds of the present invention, for example the compounds of examples 2 and 9 hereinafter, are capable of absorbing UV rays in the range of 290-320 nm while allowing passage of tanning rays at higher wavelenghts. They are thus particularly suited for use in topical, including cosmetic formulations as aforesaid well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives. Formulations suitable for topical application can be prepared e.g. as described in U.S. patent 4,784,808. Formulations for ocular administration can be prepared e.g. as described in U.S. patent 4,829,088 and 4,960,799.

The pharmaceutical formulations contain an effective COX-2 inhibiting amount of a compound of the invention as defined above, either alone or in combination with another therapeutic agent.

Suitable additional active agents for use in relation to the treatment of neoplasia include e.g. any of the anti-neoplastic agents or radioprotective agents recited in the aforementioned International Patent Publication WO 98/16227 commencing at page 24, line 19.

In conjunction with another active ingredient, a compound of the invention may be administered either simultaneously, before or after the other active ingredient, either separately by the same or different route of administration or together in the same pharmaceutical formulation.

The dosage of active compound administered is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of administration. A unit dosage for oral administration to a mammal of about 50 to 70 kg may contain between about 5 and 500 mg, of the active ingredient.

The present invention also relates to methods of using the compounds of the invention and their pharmaceutically acceptable salts, or pharmaceutical compositions thereof, in mammals for inhibiting COX-2 and for the treatment of COX-2 dependent conditions as described herein, e.g. inflammation, pain, rheumatoid arthritis, osteoarthritis, ocular disorders, in particular ocular inflammatory disorders, glaucoma and dry eye disease.

Further the invention relates to use of the compounds of the invention for the preparation of medicaments for treatment of COX-2 diseases and conditions.

Particularly the present invention relates to a method of selectively inhibiting cyclooxygenase-2 activity in a mammal without substantially inhibiting cycloxygenase-1 activity which comprises administering to a mammal in need thereof an effective cyclooxygenase-2 inhibiting amount of a compound of the invention.

Thus the present invention also relates to a method of treating cyclooxygenase-2 dependent disorders in mammals, which comprises administering to a mammal in need thereof an effective cyclooxygenase-2 inhibiting amount of a compound of the invention.

More particularly the present invention relates to a method of treating cyclooxygenase-2 dependent disorders in mammals while substantially eliminating undesirable side effects associated with cyclooxygenase-1 inhibiting activity which comprises administering to a mammal in need thereof an effective cyclooxygenase-2 inhibiting amount of a compound of the invention which is substantially free of cyclooxygenase-1 inhibiting activity.

More specifically such relates to a method of treating rheumatoid arthritis, osteoarthritis, pain or inflammation in mammals without causing undesirable gastrointestinal ulceration, which method comprises administering to a mammal in need thereof a correspondingly effective amount of a compound of the invention.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees Centrigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g. microanalysis and

and R_5 is chloro, fluoro or methyl; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof.

4. A compound according to claim 1 as disclosed in any of Examples 1 to 37; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable prodrug ester thereof

5. A pharmaceutical composition comprising an effective cyclooxygenase-2 inhibiting amount of a compound of claim 1 or 2 in combination with one or more pharmaceutically acceptable carriers.

6. A method of treating cyclooxygenase-2 dependent disorders in mammals which comprises administering to a mammal in need thereof an effective cyclooxygenase-2 inhibiting amount of a compound according to claim 1 or 2.

7. A method of selectively inhibiting cyclooxygenase-2 activity in a mammal without substantially inhibiting cycloxygenase-1 activity which comprises administering to a mammal in need thereof an effective cyclooxygenase-2 inhibiting amount of a compound of claim 1 or 2.

8. A method of treating rheumatoid arthritis, osteoarthritis, pain, inflammation, ocular inflammatory disorders, glaucoma or dry eye disease in mammals which comprises administering to a mammal in need thereof a correspondingly effective amount of a compound of claim 1 or 2.

9. A method for the preparation of a compound of formula I which comprise:

(a) coupling a compound of formula II or IIa

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(71) Applicant *(for all designated States except US)*: G. D. SEARLE & CO. [US/US]; 5200 Old Orchard Road, Skokie, IL 60077 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: GAO, Danchen [CN/US]; 1446 S. Prairie Avenue, Chicago, IL 60605 (US). HLINAK, Anthony, J. [US/US]; 1803 Longmeadow Drive, Lindenhurst, IL 60046 (US). MAZHARY, Ahmad, M. [US/US]; 1461 Lancaster Lane, Algonquin, IL 60102 (US). TRUELOVE, James, E. [US/US]; 1006 Regency Lane, Libertyville, IL 60048 (US). VAUGHN, Margaret, B., Woodhull [US/US]; 764 Rosewood, Winnetka, IL 60093 (US).

(74) Agent: STREIT, Richard, J.; Ladas & Parry, 224 S. Michigan Avenue, Chicago, IL 60604 (US).

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(54) Title: CELECOXIB COMPOSITIONS

(57) Abstract

Pharmaceutical compositions are provided comprising one or more orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients. The compositions are useful in treatment or prophylaxis of cyclooxygenase–2 mediated conditions and disorders.

PPI no
21, 24

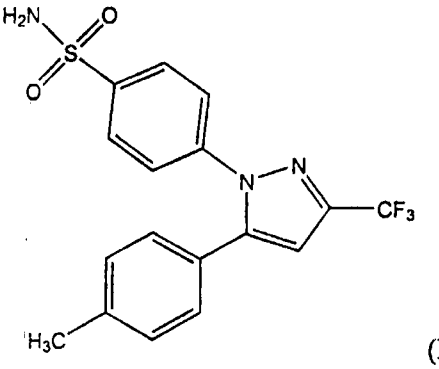
CELECOXIB COMPOSITIONS

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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



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

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

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

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

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

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

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

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 particular, a need exists for orally deliverable celecoxib 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;
(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;
(16) reduced wet granulation time; and
(17) reduced drying time for wet granulated mixtures.

As is indicated hereinbelow, celecoxib treatment is indicated or potentially indicated in a very wide array of cyclooxygenase-2 mediated conditions and disorders. It would therefore be of great benefit to provide a range of formulations having bioavailability characteristics tailored to different indications. It would be of especial benefit to provide formulations exhibiting pharmacokinetics consistent with a more rapid onset effect than is possible with unformulated celecoxib.

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

SUMMARY OF THE INVENTION

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

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

(a) a time to reach 100 ng/ml not greater than about 0.5 h after administration;

(b) a time to reach maximum concentration (T_{max}) not greater than about 3 h after administration;

(c) a duration of time wherein concentration remains above 100 ng/ml not less than about 12 h;

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

(e) a maximum concentration (C_{max}) not less than about 200 ng/ml.

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

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

The dose units comprising the composition can be in the form of discrete solid articles such as tablets, pills, hard or soft capsules, lozenges, sachets or pastilles; alternatively the composition can be in the form of a substantially homogeneous flowable mass, such as a particulate or granular solid or a liquid suspension, from which single dose units are measurably removable.

Also provided is a method of treating a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitor is indicated, comprising orally administering a composition of the invention once or twice a day.

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

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

DETAILED DESCRIPTION OF THE INVENTION

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

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

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

(a) a time to reach a blood serum concentration of about 100 ng/ml that is not greater than about 0.5 hour after administration;

(b) a time to reach a maximum blood serum concentration (T_{max}) of celecoxib that is not greater than about 3 hours after administration, preferably not greater than about 2 hours after administration;

(c) a duration of time wherein the blood serum concentration remains above

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

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

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

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

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

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

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

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

Utility of compositions of the invention

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

apoptosis, lumbago, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, acne, UV damage, burns and dermatitis, and post-operative inflammation including that following ophthalmic surgery such as cataract surgery or refractive surgery. Contemplated compositions are useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. Contemplated compositions are useful in treating inflammation in such diseases as migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's disease, sclerodoma, rheumatic fever, type I diabetes, neuromuscular junction disease including myasthenia gravis, white matter disease including multiple sclerosis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, gingivitis, nephritis, hypersensitivity, swelling occurring after injury including brain edema, myocardial ischemia, and the like. 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.

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 hypoprothrombinemia, hemophilia or other bleeding problems; kidney disease; or in patients prior to surgery or patients taking anticoagulants. A brief description of the potential utility of cyclooxygenase-2 inhibitors is given in an article by John Vane, Nature, Vol. 367, pp. 215-216, 1994, and in an article in Drug News and Perspectives, Vol. 7, pp. 501-512, 1994.

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.

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

The present compositions can be used in combination therapies with opioids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e. non-addictive) analgesics, monamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers, among others. Preferred combination therapies comprise use of a composition of the invention with compounds selected from morphine, meperidine, codeine, pentazocine, buprenorphine, butorphanol, dezocine, meptazinol, hydrocodone, oxycodone, methadone, DuP-747, Dynorphine A, Enadoline, RP-60180, HN-11608, E-2078,

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

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

Celecoxib dosage provided by compositions of the invention

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

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

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

Treatment of specific conditions and disorders

The pharmaceutical compositions of the present invention are useful where

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

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

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

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

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

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

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

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

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

Preparation of celecoxib

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

Form of compositions of the invention

The pharmaceutical compositions of the present invention comprise celecoxib in association with one or more preferably non-toxic, pharmaceutically acceptable carriers, excipients and adjuvants (collectively referred to herein as "carrier materials" or "excipients") suitable for oral administration. The carrier materials must be acceptable in the sense of being compatible with the other ingredients of the composition and must not be deleterious to the recipient. Compositions of the present invention can be adapted for administration by any suitable oral route by selection of appropriate carrier materials and a dosage of celecoxib effective for the treatment intended. Accordingly, any carrier materials employed can be solids or liquids, or both, and the composition preferably contains about 1% to about 95%, preferably about 10% to about 90%, more preferably about 25% to about 85%, and still more preferably about 30% to about 80%, by weight of celecoxib. Such pharmaceutical compositions of the invention can be prepared by any of the well known techniques of pharmacy, comprising admixing the components.

A composition of the invention contains a desired amount of celecoxib per dose unit and can be in the form of, for example, a tablet, a pill, a hard or soft capsule, a lozenge, a cachet, a dispensable powder, granules, a suspension, an elixir, a liquid, or any other form reasonably adapted for oral administration. Such a composition is preferably made in the form of discrete dose units each containing a predetermined amount of celecoxib, such as tablets or capsules. These oral dosage forms may further comprise, for example, buffering agents. Tablets, pills and the like additionally can be prepared with or without coatings.

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

Liquid dosage forms for oral administration include pharmaceutically

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

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

Carrier materials or excipients

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

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

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

Diluents

The pharmaceutical compositions of the present invention optionally comprise one or more pharmaceutically acceptable diluents as a carrier material. Suitable diluents include, either individually or in combination, lactose USP; lactose USP, anyhydrous; lactose USP, spray dried; starch USP; directly compressible starch; mannitol USP; sorbitol; dextrose monohydrate; microcrystalline cellulose NF; dibasic calcium phosphate dihydrate NF; sucrose-based diluents; confectioner's sugar; monobasic calcium sulfate monohydrate; calcium sulfate dihydrate NF; calcium lactate trihydrate granular NF; dextrates, NF (*e.g.*, Emdex); Celutab; dextrose (*e.g.*, Cerelose); inositol; hydrolyzed cereal solids such as the Maltrons 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 pharmaceutical compositions having suitable celecoxib release rates, 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.

Disintegrants:

The pharmaceutical compositions of the present invention optionally comprise one or more pharmaceutically acceptable disintegrants as a carrier material, particularly for tablet formulations. Suitable disintegrants include, either individually or in combination, starches; sodium starch glycolate; clays (such as Veegum HV); celluloses (such as purified cellulose, methylcellulose, sodium carboxymethylcellulose, and carboxymethylcellulose); alginates; pregelatinized corn starches (such as National 1551 and National 1550); crospovidone USP NF; and gums (such as agar, guar, locust bean, Karaya, pectin, and tragacanth). Disintegrants may be added at any suitable step during the preparation of the pharmaceutical composition, particularly prior to granulation or during the lubrication step prior to compression. Such disintegrants, if present, constitute in total about 0.2% to about 30%, preferably about 0.2% to about 10%, and more preferably about 0.2% to about 5%, of the total weight of the composition.

Croscarmellose sodium is a preferred disintegrant for tablet or capsule disintegration, and, if present, preferably constitutes about 0.2% to about 10%, more preferably about 0.2% to about 6%, and still more preferably about 0.2% to about 5%, of the total weight of the composition. Croscarmellose sodium confers superior intragranular disintegration capabilities to compositions of the present invention.

Binding agents and adhesives

The pharmaceutical compositions of the present invention optionally comprise one or more pharmaceutically-acceptable binding agents or adhesives as a carrier material, particularly for tablet formulations. Such binding agents and adhesives preferably impart sufficient cohesion to the powder being tableted to allow for normal 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); alginic acid and salts of alginic acid; magnesium aluminum silicate; polyethylene glycol; guar gum; polysaccharide acids; bentonites; polyvinylpyrrolidone; polymethacrylates; hydroxypropylmethylcellulose (HPMC); hydroxypropylcellulose

(Klucel); ethylcellulose (Ethocel); pregelatinized starch (such as National 1511 and Starch 1500). Such binding agents and/or adhesives, if present, constitute in total about 0.5% to about 25%, preferably about 0.75% to about 15%, and more preferably about 1% to about 10%, of the total weight of the composition.

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

Wetting Agents

Celecoxib is largely insoluble in aqueous solution. Accordingly, the pharmaceutical compositions of the present invention optionally but preferably comprise one or more pharmaceutically acceptable wetting agents as a carrier material. Such wetting agents are preferably selected to maintain celecoxib in close association with water, a condition that is believed to improve the relative bioavailability of the pharmaceutical composition. Suitable wetting agents include, either individually or in combination, oleic acid; glyceryl monostearate; sorbitan 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.

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

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

Lubricants

The pharmaceutical compositions of the present invention optionally comprise one or more pharmaceutically acceptable lubricants and/or glidants as a carrier material. Suitable lubricants and/or glidants include, either individually or in combination, glyceryl behapate (Compritol 888); stearates (magnesium, calcium, and sodium); stearic acid; hydrogenated vegetable oils (*e.g.*, Sterotex); talc; waxes; Stearowet; boric acid; sodium benzoate; sodium acetate; sodium fumarate; sodium chloride; DL-leucine; polyethylene glycols (*e.g.*, Carbowax 4000 and Carbowax 6000); sodium oleate; sodium lauryl sulfate; and magnesium lauryl sulfate. Such lubricants, if present, constitute in total about 0.1% to about 10%, preferably about 0.2% to about 8%, and more preferably about 0.25% to about 5%, of the total weight of the composition.

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

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

Capsules and tablets

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

carrier materials sodium lauryl sulfate, magnesium stearate, and microcrystalline cellulose.

In another embodiment, the pharmaceutical composition comprises:

(a) about 1 to about 95 weight percent of celecoxib;

(b) about 5 to about 99 weight percent of a pharmaceutically acceptable diluent;

(c) about 0.5 to about 30 weight percent of a pharmaceutically acceptable disintegrant; and

(d) about 0.5 to about 25 weight percent of a pharmaceutically acceptable binding agent.

In addition, this pharmaceutical composition optionally comprises:

(e) about 0.25 to about 15 weight percent of a pharmaceutically acceptable wetting agent; and/or

(f) about 0.1 to about 10 weight percent of a pharmaceutically acceptable lubricant.

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

In another embodiment, the pharmaceutical composition comprises:

(a) about 1 to about 95 weight percent of celecoxib;

(b) about 5 to about 99 weight percent of lactose;

(c) about 2 to about 6 weight percent of croscarmellose sodium; and

(d) about 0.5 to about 10 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

(e) about 0.25 to about 7 weight percent of sodium lauryl sulfate;

(f) about 0.1 to about 10 weight percent of magnesium stearate; and/or

(g) about 1 to about 99 weight percent of microcrystalline cellulose.

In another embodiment, the pharmaceutical composition comprises:

(a) about 80 to about 220 mg of celecoxib;

(b) about 30 to about 225 mg of lactose;

(c) about 0.5 to about 25 mg of croscarmellose sodium; and

(d) about 0.5 to about 25 mg of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

(e) about 0.5 to about 25 mg of sodium lauryl sulfate;

(f) about 0.2 to about 10 mg of magnesium stearate; and/or

(g) about 1 mg to about 70 mg of microcrystalline cellulose.

In another embodiment, the pharmaceutical composition comprises:

(a) about 25 to about 85 weight percent of celecoxib;

(b) about 5 to about 70 weight percent of lactose;

(c) about 0.2 to about 5 weight percent of croscarmellose sodium; and

(d) about 0.5 to about 7 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

(e) about 0.4 to about 6 weight percent of sodium lauryl sulfate;

(f) about 0.2 to about 8 weight percent of magnesium stearate; and/or

(g) about 0.1 to about 15 weight percent of microcrystalline cellulose.

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

In another embodiment, the pharmaceutical composition comprises:

(a) about 27 to about 47 weight percent of celecoxib;

(b) about 45 to about 65 weight percent of lactose;

(c) about 0.5 to about 5 weight percent of croscarmellose sodium; and

(d) about 0.5 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

(e) about 0.25 to about 7 weight percent of sodium lauryl sulfate; and/or

(f) about 0.25 to about 5 weight percent of magnesium stearate.

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

(a) about 32 to about 42 weight percent of celecoxib;

(b) about 50 to about 60 weight percent of lactose;

(c) about 0.5 to about 3 weight percent of croscarmellose sodium; and

(d) about 1 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

(e) about 0.4 to about 6 weight percent of sodium lauryl sulfate; and/or

(f) about 0.5 to about 3 weight percent of magnesium stearate.

In this embodiment, the pharmaceutical composition more preferably

comprises:

(a) about 35 to about 39 weight percent of celecoxib;

(b) about 54 to about 57 weight percent of lactose;

(c) about 0.5 to about 2 weight percent of croscarmellose sodium; and

(d) about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

(e) about 2 to about 4 weight percent of sodium lauryl sulfate; and/or

(f) about 0.5 to about 2 weight percent of magnesium stearate.

In another embodiment, the pharmaceutical composition comprises:

(a) about 65 to about 85 weight percent of celecoxib;

(b) about 8 to about 28 weight percent of lactose;

(c) about 0.5 to about 5 weight percent of croscarmellose sodium; and

(d) about 0.5 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

(e) about 0.25 to about 7 weight percent of sodium lauryl sulfate; and/or

(f) about 0.25 to about 5 weight percent of magnesium stearate.

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

(a) about 69 to about 79 weight percent of celecoxib;

(b) about 13.5 to about 23.5 weight percent of lactose;

(c) about 0.5 to about 3 weight percent of croscarmellose sodium; and

(d) about 1 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

(e) about 0.4 to about 6 weight percent of sodium lauryl sulfate; and/or

(f) about 0.5 to about 3 weight percent of magnesium stearate.

In this embodiment, the pharmaceutical composition more preferably comprises:

(a) about 72 to about 76 weight percent of celecoxib;

(b) about 16.5 to about 20.5 weight percent of lactose;

(c) about 0.5 to about 2 weight percent of croscarmellose sodium; and

(d) about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

(e) about 2 to about 4 weight percent of sodium lauryl sulfate; and/or

(f) about 0.5 to about 2 weight percent of magnesium stearate.

In another embodiment, the pharmaceutical composition comprises:

(a) about 30 to about 50 weight percent of celecoxib;

(b) about 30 to about 50 weight percent of lactose;

(c) about 0.5 to about 6 weight percent of croscarmellose sodium; and

(d) about 0.5 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

(e) about 1 to about 20 weight percent of microcrystalline cellulose;

(f) about 0.25 to about 7 weight percent of sodium lauryl sulfate; and/or

(g) about 0.25 to about 5 weight percent of magnesium stearate.

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

(a) about 35 to about 45 weight percent of celecoxib;

(b) about 35 to about 45 weight percent of lactose;

(c) about 1 to about 5 weight percent of croscarmellose sodium; and

(d) about 1 to about 5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

(e) about 5 to about 15 weight percent of microcrystalline cellulose;

(f) about 0.4 to about 6 weight percent of sodium lauryl sulfate; and/or

(g) about 0.5 to about 3 weight percent of magnesium stearate.

In this embodiment, the pharmaceutical composition more preferably comprises:

(a) about 38 to about 42 weight percent of celecoxib;

(b) about 38 to about 42 weight percent of lactose;

(c) about 1.5 to about 4.5 weight percent of croscarmellose sodium; and

(d) about 1.5 to about 4.5 weight percent of polyvinylpyrrolidone.

In addition, this pharmaceutical composition optionally comprises:

(e) about 8 to about 12 weight percent of microcrystalline cellulose;

(f) about 2 to about 4 weight percent of sodium lauryl sulfate; and/or

(g) about 0.5 to about 2 weight percent of magnesium stearate.

In another embodiment, the pharmaceutical composition comprises:

Method of treatment

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

Initial treatment of a patient suffering from a condition or disorder where treatment with a cyclooxygenase-2 inhibitor is indicated can begin with the dosages indicated above. Treatment is generally continued as necessary over a period of several weeks to several months or years until the condition or disorder has been controlled or eliminated. Patients undergoing treatment with a composition of the invention can be routinely monitored by any of the methods well known in the art to determine the effectiveness of therapy. Continuous analysis of such data permits modification of the treatment regimen during therapy so that optimally effective amounts of celecoxib are administered at any point in time, and so that the duration of treatment can be determined as well. In this way, the treatment regimen/dosing schedule can be rationally modified over the course of therapy so that the lowest amount of celecoxib exhibiting satisfactory effectiveness is administered, and so that administration is continued only so long as is necessary to successfully treat the condition or disorder.

Methods for preparation of celecoxib compositions

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

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

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

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