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(71) Applicant *(for all designated States except US)*: **PHARMACIA CORPORATION** [US/US]; Corporate Patent Department, 800 North Lindbergh Blvd., Mail Zone O4E0680-9889, St. Louis, MI63167 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **REO, Joseph, P.** [US/US]; 5668 Bob White Avenue, Kalamazoo, MI 49009 (US). **SHAH, Uday, J.** [US/US]; 3683 Leatherleaf Court, Hoffman Estates, IL 60195 (US). **YAMAMOTO, Ken** [JP/US]; 7596 Carnoustie Street, Portage, MI 49024 (US).

(74) Agents: **FOURNIER, David, B.** et al.; Pharmacia Corporation, Corporate Patent Department, 800 North Lindbergh Blvd., Mail Zone O4E, St.Louis, MO 63167 (US).

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(54) Title: INTRAORALLY DISINTEGRATING VALDECOXIB COMPOSITIONS PREPARED BY SPRAY DRYING PROCESS

(57) Abstract: Orally disintegrating valdecoxib fast-melt tablets and processes for preparing such dosage forms are provided. The compositions are useful in treatment or prophylaxis of cycloosygenase-2 mediated conditions and disorders.

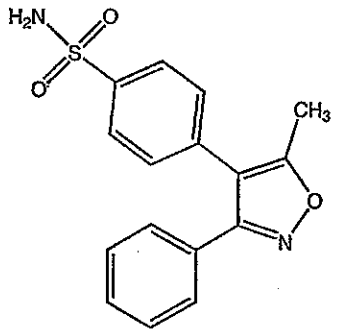
INTRAORALLY DISINTEGRATING VALDECOXIB COMPOSITIONS PREPARED BY SPRAY DRYING PROCESS

FIELD OF THE INVENTION

The present invention relates to intraorally disintegrating pharmaceutical compositions containing valdecoxib as an active ingredient, to processes for preparing such compositions, and to methods of treatment of cyclooxygenase-2 mediated disorders comprising orally administering such compositions to a subject.

BACKGROUND OF THE INVENTION

The compound 4-(5-methyl-3-phenyl-4-isoxazolyl)benzenesulfonamide, also referred to herein as valdecoxib, was disclosed in U.S. Patent No. 5,633,272 to Talley, *et al.*, herein incorporated by reference, together with processes for preparing this and related compounds. Valdecoxib has the structure:



(I)

The compounds reported in above-cited U.S. Patent No. 5,633,272, including valdecoxib, are disclosed therein as useful anti-inflammatory, analgesic and antipyretic drugs having a high degree of selectivity for inhibition of cyclooxygenase-2 (COX-2) over cyclooxygenase-1 (COX-1). Above-cited U.S. Patent No. 5,633,272 also contains general references to formulations for the administration of such compounds, including orally deliverable dosage forms such as tablets and capsules.

Valdecoxib has extremely low solubility in water. See for example Dionne (1999), "COX-2 inhibitors - IBC Conference, 12-13 April 1999, Coronado, CA, U.S.A.", IDrugs, 2(7), 664-666.

U.S. Patent No. 5,576,014, incorporated herein by reference, discloses an intrabuccally dissolving compressed molding prepared by a wet granulation process wherein a low moldability saccharide is granulated with a high moldability saccharide to form a granulate, which is then compressed into a molding. The resulting molding

can incorporate a drug and is said to show quick disintegration and dissolution in the buccal cavity but to maintain sufficient hardness so as not break during production and distribution. The compressed molding of U.S. Patent No. 5,576,014 is a type of dosage form known as a "fast-melt tablet", exhibiting rapid disintegration, usually associated with the carrier materials, typically sugars, and concomitant rapid dissolution or dispersion of the drug in the mouth, usually without need for water other than that contained in saliva. A drug formulated in such a tablet is readily swallowed.

Co-assigned International Patent Publication No. WO 01/41761 discloses orally deliverable valdecoxib compositions having fast-onset properties. None of the compositions disclosed therein is an intraorally disintegrating composition.

A well-known problem with many intraorally disintegrating compositions, even those containing sugars and/or sweetening and/or flavoring agents, is an unpleasant taste resulting from the presence of an active drug therein. Generally, as the amount of active drug present in a particular intraorally disintegrating dosage form decreases, and/or as the aqueous solubility of a drug decreases, the less bitter and/or sour will be the taste of the dosage form. See for example Lieberman et al. (1989), Pharmaceutical Dosage Forms: Tablets Vol. 1, pp. 381. Marcel Dekker, New York. Valdecoxib, a drug with very low water solubility and with relatively low dose requirements, would therefore be expected when formulated as an intraorally disintegrating composition to have acceptable or, at worst, only moderately unpleasant organoleptic properties. Surprisingly, however, we have now discovered that valdecoxib has an extremely unpleasant taste. Thus, there remains a need for intraorally disintegrating valdecoxib compositions having acceptable organoleptic properties.

Taste-masking technologies which act by inhibiting oral dissolution of moderately or highly water soluble drugs have been applied to pharmaceutical dosage forms. See for example Lieberman et al. (1989), *op. cit.* In such cases, improved taste is believed to result from a decrease in the amount of drug which dissolves in the mouth prior to entry into the gastrointestinal tract. Given the already extremely low aqueous solubility of valdecoxib, however, it was not expected that any further reduction in oral dissolution of valdecoxib would lead to improved organoleptic

properties. Further, it was expected that additional reduction in aqueous solubility of valdecoxib would result in unacceptable delay of therapeutic onset. Surprisingly, however, we have now discovered processes for preparing organoleptically acceptable intraorally disintegrating valdecoxib compositions, which compositions exhibit improved organoleptic properties, yet which still exhibit rapid onset of therapeutic effect.

SUMMARY OF THE INVENTION

Accordingly, there is now provided a process for preparing an intraorally disintegrating valdecoxib composition (*e.g.* a fast-melt tablet), the process comprising a step of providing valdecoxib in particulate form; a step of dissolving at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution in water in a vessel; a step of dispersing the valdecoxib in the water, and an optional step of heating the water. The dissolving, dispersing and optional heating steps are performed in any order or simultaneously to result in a sprayable liquid. The process further comprises a step of spray drying the sprayable liquid to form a tableting blend and a step of compressing the tableting blend to form a tablet. In the process, the at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution can be dissolved in the water in a total amount such that upon completion of the process, the at least one excipient which exhibits rapid oral dissolution comprises about 50% to about 99%, preferably about 50% to about 95% and more preferably about 50% to about 90%, by weight, of the tablet.

The process optionally further comprises a step of adding to the vessel a wetting agent or an aqueous solution of such wetting agent, prior to the spray drying step.

Compositions prepared by such a process represent an embodiment of the present invention.

There is also now provided an intraorally disintegrating composition comprising (a) particulate valdecoxib in a therapeutically effective amount, and (b) at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution which is in intimate association with the valdecoxib particles. The composition is organoleptically acceptable and the at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution is present in a total amount of about 50% to

about 99%, preferably about 50% to about 95%, and more preferably about 50% to about 90%, by weight of the composition.

The present invention also provides the use of the composition defined above for the manufacture of a medicament for treating or preventing a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitory drug is indicated.

An "intimate association" in the present context includes, for example, valdecoxib admixed with the excipient which exhibits rapid oral dissolution, valdecoxib embedded or incorporated in the excipient which exhibits rapid oral dissolution, valdecoxib forming a coating on particles of the excipient which exhibits rapid oral dissolution or *vice versa,* and a substantially homogeneous dispersion of valdecoxib throughout the excipient which exhibits rapid oral dissolution. Such an intimate association is illustratively formed by processes disclosed hereinabove; alternatively or additionally, other means for forming such an intimate association may be employed in preparing compositions of the invention.

Valdecoxib in intimate association with an excipient which exhibits rapid oral dissolution is also referred to herein as a "valdecoxib composite". The term "substantially homogeneous" herein with reference to a composite or pharmaceutical composition that comprises multiple components means that the components are sufficiently mixed such that individual components are not present as discrete layers and do not form concentration gradients within the composition. Without being bound by theory, it is believed that the relatively high ratio of excipient which exhibits rapid oral dissolution to valdecoxib in processes and compositions of the invention and/or the intimate association of the valdecoxib with the excipient which exhibits rapid oral dissolution results in formation of a valdecoxib composite which has improved organoleptic properties.

A particularly useful intraorally disintegrating composition of the present invention is a rapidly disintegrating oral dosage form that dissolves in the mouth without need for drinking water or other fluid *(e.g.* a fast-melt). The term "fast-melt" as used herein refers to a composition such as a tablet wherein an active agent or drug is distributed or dispersed in a matrix formed by a carrier that, upon oral administration of the composition to a subject, disintegrates in the oral cavity, thereby releasing the drug, typically in particulate form, for entry to the gastrointestinal tract by swallowing, and subsequent absorption. The term "oral cavity" includes the entire interior of the mouth, including not only the buccal cavity (that part of the oral cavity anterior to the teeth and gums) but also the sublingual and supralingual spaces.

An "organoleptically acceptable" dosage form or a dosage form having "acceptable organoleptic properties" herein is one that, upon intraoral interaction in an amount providing a single dose of the therapeutic agent, does not have an excessively unpleasant taste, smell or mouth feel, for example a pronouncedly bitter taste, as perceived by a majority of human subjects, or as determined by analysis of a blind taste evaluation study as is described hereinbelow.

Processes and compositions of the invention have been found to overcome the unacceptable organoleptic properties of valdecoxib without unacceptably sacrificing rapid onset characteristics or therapeutic effectiveness. Thus, in a significant advance in the art, valdecoxib is now presented in an organoleptically acceptable fast-melt formulation. Particular advantages of compositions of the invention is that they have improved organoleptic properties, acceptable therapeutic onset characteristics, and such compositions can be efficiently prepared by processes described herein.

DETAILED DESCRIPTION OF THE INVENTION

A particular embodiment of the invention is an oral fast-melt composition comprising (a) particulate valdecoxib in a therapeutically effective amount and (b) at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution; wherein the composition is organoleptically acceptable. The at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution is in intimate association with the valdecoxib particles in the composition, and is present in a total amount of about 50% to about 99%, preferably about 50% to about 95%, and more preferably about 50% to about 90%, by weight.

A related embodiment of the invention provides an intraorally disintegrating composition comprising (a) particulate valdecoxib in a therapeutically effective amount, and (b) at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution and which is in intimate association with said valdecoxib particles; wherein the composition is organoleptically acceptable; wherein the at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution is present in a total amount of about 50% to about 99%, by weight of the composition; and wherein the composition disintegrates within about 60 seconds, preferably within about 30 seconds, and more preferably within about 15 seconds, after placement in the oral cavity of a human subject.

Another related embodiment of the invention provides an intraorally disintegrating composition comprising (a) particulate valdecoxib in a therapeutically effective amount, and (b) at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution and which is in intimate association with said valdecoxib particles; wherein the composition is organoleptically acceptable; wherein the at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution is present in a total amount of about 50% to about 99%, by weight of the composition; and wherein the composition, when placed in United States Pharmacopeia 24 *in vitro* disintegration Test Number 701, exhibits a disintegration time of less than about 300 seconds, preferably less than about 200 seconds, and more preferably less than about 100 seconds.

Another embodiment of the invention provides an intraorally disintegrating composition comprising (a) particulate valdecoxib in a therapeutically effective amount, and (b) at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution and which is in intimate association with said valdecoxib particles; wherein the composition is organoleptically acceptable; wherein the at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution is present in a total amount of about 50% to about 99%, by weight of the composition; and wherein administration of the composition to a human subject results in a valdecoxib threshold concentration for therapeutic effect within about 0.5 h, preferably within about 0.3 h, of oral administration.

By "a threshold concentration for therapeutic effect" is meant a minimum concentration of valdecoxib in blood serum consistent with therapeutic benefit for the particular indication for which the valdecoxib is administered. Typically this threshold concentration is at least about 20 ng/ml, for example about 25 ng/ml to about 75 ng/ml.

It will be understood that the amount of valdecoxib effective to provide a threshold concentration for therapeutic effect is dependent, *inter alia*, 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 valdecoxib relatively low in the therapeutically effective range of about 1 mg to about 100 mg is likely to provide blood serum concentrations consistent with threshold concentration and C_{max} criteria. Where the

subject is an adult human or a large animal (*e.g.*, a horse), the indicated blood serum concentrations of valdecoxib are likely to require a relatively greater dosage amount of valdecoxib. For an adult human, a suitable amount of valdecoxib per dose in a composition of the present invention to provide the indicated blood serum concentrations is typically about 5 mg to about 40 mg.

A related embodiment of the invention provides an intraorally disintegrating composition comprising (a) particulate valdecoxib in a therapeutically effective amount, and (b) at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution and which is intimate association with the valdecoxib particles; wherein the composition is organoleptically acceptable; wherein the at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution is present in a total amount of about 50% to about 99%, by weight of the composition; and wherein administration of the composition to a human subject results in a maximum blood serum concentration (C_{max}) not less than about 100 ng/ml.

Another related embodiment of the invention provides an intraorally disintegrating composition comprising (a) particulate valdecoxib in a therapeutically effective amount, and (b) at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution and which is intimate association with the valdecoxib particles; wherein the composition is organoleptically acceptable; wherein the at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution is present in a total amount of about 50% to about 99%, by weight of the composition; and wherein administration of the composition to a human subject results in a time to reach maximum blood serum concentration (T_{max}) not greater than about 5 h, preferably not greater than about 4 h, and more preferably not greater than about 3 h.

Ingredients of compositions of the invention

A composition of the invention comprises valdecoxib as active ingredient and at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution. Optionally, a composition of the invention can contain one or more additional pharmaceutically acceptable excipients including, but not limited to, water-soluble lubricants, water-insoluble lubricants, disintegrants, glidants, sweeteners, flavoring agents, colorants, *etc.* Such optional additional components should be physically and chemically compatible with the other ingredients of the composition

and must not be deleterious to the recipient.

Valdecoxib

Processes and compositions of the invention are particularly suitable for valdecoxib as the active drug. Processes for preparing particulate valdecoxib are known *per se*, for example as is described in above-cited U.S. Patent No. 5,474,995, incorporated herein by reference. Importantly, any solid state form of valdecoxib, illustratively that described in International Patent Publication No. 98/06708, incorporated herein by reference, can be used in processes and compositions of the invention.

A valdecoxib dosage unit of the invention comprises valdecoxib in a therapeutically effective amount of about 1 mg to about 100 mg, preferably about 5 mg to about 50 mg. Compositions of the invention contain valdecoxib in particulate form. Primary valdecoxib 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. Particle size is believed to be an important parameter affecting clinical effectiveness of valdecoxib. Thus, in one embodiment, a valdecoxib dosage form has a distribution of valdecoxib particle sizes such that the D_{90} particle size is less than about 75 μm. The "D_{90} particle size" is defined herein as a particle size such that 90% by weight of the particles are smaller, in their longest dimension, than that particle size.

In addition or alternatively, valdecoxib particles in a dosage form of the invention preferably have a weight average particle size of about 1 μm to about 10 μm, most preferably about 5 μm to about 7 μm.

Excipients which exhibit rapid oral dissolution

Suitable excipients which exhibit rapid oral dissolution are those pharmaceutically acceptable excipients which are soluble, freely soluble, or very soluble in water, for example as described in Ansel et al. (1995) Pharmaceutical Dosage Forms and Drug Delivery Systems 6th Ed, pp. 228. Williams & Wilkins, Baltimore. Preferably, such excipients have a sweet taste. A presently preferred class of excipients which exhibit rapid oral dissolution for use in compositions and processes of the invention are carbohydrates. Particularly preferred excipients which

exhibit rapid oral dissolution are saccharides including both low moldability and high moldability saccharides.

Presently preferred low moldability saccharides include lactose and mannitol, particularly mannitol in its non-direct compression or powder form as described in Kibbe (2000) Handbook of Pharmaceutical Excipients, 3rd Ed., Pharmaceutical Press, pp. 324-328. Presently preferred high moldability saccharides include maltose, maltitol and sorbitol. Alternatively, certain oligosaccharides can be useful. The oligosaccharide used is not particularly limited so long as it shows rapid dissolution in the oral cavity and consists of two or more monosaccharide residues. Where an oligosaccharide is used, one consisting of 2 to 6 monosaccharide residues is preferable, and the type and combination of monosaccharide residues constituting the oligosaccharide are not limited. Particularly preferred high moldability saccharides are maltose and maltitol, more particularly maltose.

Where both a high moldability saccharide and low moldability saccharide are present in a composition of the invention, the weight ratio of high moldability saccharide to low moldability saccharide is important in maintaining a combination of acceptable tablet hardness and rapid intraoral disintegration. A suitable ratio is about 2 to about 20 parts by weight, preferably about 5 to about 10 parts by weight, and more preferably about 5 to about 7.5 parts by weight, of the high moldability saccharide per 100 parts by weight of the low moldability saccharide.

If the ratio of high to low moldability saccharide is less than about 2:100 by weight, tablets typically do not achieve their desired hardness, resulting in increased breakage during storage, transportation or handling. Alternatively, if the ratio of high to low moldability saccharide exceeds about 20:100 by weight, the tablets become too hard and desired rapid disintegration in the oral cavity is not achieved.

One or more excipients which exhibit rapid oral dissolution are typically present in compositions of the invention in a total amount of about 45% to about 95%, preferably about 50% to about 87%, and more preferably about 55% to about 80%.

Wetting agents

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable wetting agents. Surfactants, hydrophilic polymers and certain clays can be useful as wetting agents to aid in wetting of a hydrophobic drug,

such as valdecoxib, during the spray dry granulation process.

Non-limiting examples of surfactants that can be used as wetting agents in compositions of the present invention include quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10, and octoxynol 9, poloxamers (polyoxyethylene and polyoxypropylene block copolymers), polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides (*e.g.*, Labrasol™ of Gattefossé), polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example polyoxyethylene (20) cetostearyl ether, polyoxyethylene fatty acid esters, for example polyoxyethylene (40) stearate, polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80 (*e.g.*, Tween™ 80 of ICI), propylene glycol fatty acid esters, for example propylene glycol laurate (*e.g.*, Lauroglycol™ of Gattefossé), sodium lauryl sulfate, fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate, glyceryl fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, tyloxapol, and mixtures thereof. Sodium lauryl sulfate is a preferred wetting agent in compositions of the present invention.

One or more wetting agents, if desired, are typically present in compositions of the present invention in a total amount of about 0.05% to about 5%, preferably about 0.075% to about 2.5%, and more preferably about 0.25% to about 1%, for example about 0.5%, by weight of the composition.

Water-insoluble lubricants

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable water-insoluble lubricants as a carrier material. Suitable water-insoluble lubricants include, either individually or in combination, glyceryl behapate (*e.g.* Compritol™ 888), stearates (magnesium, calcium, and sodium), stearic acid, hydrogenated vegetable oils (*e.g.*, Sterotex™), colloidal silica, talc, waxes and mixtures thereof. Optionally a water-insoluble lubricant can be used in mixture with a wetting agent, as for example in calcium stearate/sodium lauryl sulfate mixtures (*e.g.*, Sterowet™).

Magnesium stearate, stearic acid and mixtures thereof are preferred water-insoluble lubricants.

One or more water-insoluble lubricants optionally are present in compositions of the present invention in a typical total amount of about 0.05% to about 5%, preferably about 0.75% to about 2.5%, and more preferably about 1% to about 2%, for example, about 1.5%, by weight of the composition.

Water-soluble lubricants

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable water-soluble lubricants. Water-soluble lubricants can help to improve tablet dissolution characteristics. Water-soluble lubricants that can be used in compositions of the present invention either individually or in combination include, for example, boric acid, sodium benzoate, sodium acetate, sodium fumarate, sodium chloride, DL-leucine, polyethylene glycols (*e.g.*, Carbowax™ 4000 and Carbowax™ 6000), and sodium oleate.

Disintegrants

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable disintegrants. However, the oral fast-melt tablets provided herein typically disintegrate rapidly in the oral cavity and have no requirement for added disintegrant. Suitable disintegrants, if desired, 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), croscarmellose sodium, alginates, pregelatinized corn starches (such as National™ 1551 and National™ 1550), crospovidone, 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 a blending step prior to tablet compression. Croscarmellose sodium and sodium starch glycolate are preferred disintegrants.

One or more disintegrants optionally are present in a total amount of about 0.05% to about 15%, preferably about 0.5% to about 10%, and more preferably about 1% to about 3.5%, by weight of the composition.

Glidants

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable glidants, for example to enhance flow of tableting material into tablet dies, to prevent sticking of tableting material to punches and dies, or to produce tablets having a sheen. Glidants may be added at any suitable step during preparation of the composition, particularly prior to granulation or during a blending step prior to tablet compression.

Without being bound by theory, it is believed that, in some situations, glidants, for example talc or silicon dioxide, act to reduce interfacial tension between drug particles, having the effect of inhibiting and/or reducing drug agglomeration, act to decrease electrostatic charges on the surface of drug powders, and act to reduce interparticular friction and surface rugosity of drug particles. See, for example, York (1975) J. Pharm. Sci., 64(7), 1216-1221.

Silicon dioxide is a preferred glidant. Suitable silicon dioxide products for use in preparing compositions of the invention include fumed silica or colloidal silica (*e.g.*, Cab-O-Sil™ of Cabot Corp. and Aerosil™ of Degussa). Silicon dioxide, when present in compositions of the invention, is present in a total amount of about 0.05% to about 5%, preferably about 0.1% to about 2%, and more preferably about 0.25% to about 1%, for example, about 0.5%, by weight of the composition.

Sweetening agents

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable sweeteners. Non-limiting examples of sweeteners that can be used in compositions of the present invention include mannitol, propylene glycol, sodium saccharin, acesulfame K, neotame, aspartame, *etc.*

Flavoring agents

Compositions of the present invention optionally comprise one or more pharmaceutically acceptable flavoring agents. Non-limiting examples of flavoring agents that can be used in compositions of the present invention include peppermint, spearmint, grape, cherry, strawberry, lemon, *etc.*

Tablet characteristics

Size and shape

In a preferred embodiment, compositions of the invention are in the form of discrete solid dosage units, most preferably tablets. Tablets of the invention can be made to any desired size, for example 8 mm, 10 mm, 12 mm, *etc.*; shape, for example round, oval, oblong, *etc.*; weight; and thickness. Optionally, solid dosage units of the invention may have etchings or monograms on one or both sides.

Disintegration

Preferred tablet compositions of the invention disintegrate in less than 300 seconds, preferably less than about 200 seconds, and more preferably less than about 100 seconds, for example about 30 seconds after placement in a standard *in vitro* disintegration assay (*e.g.*, conducted according to U.S. Pharmacopeia 24 (2000), Test No. 701).

Alternatively or additionally, preferred fast-melt compositions of the invention disintegrate within about 60 seconds, preferably within about 30 seconds, and more preferably within about 15 seconds after placement in the oral cavity of a subject.

Hardness

Solid dosage forms of the invention have a hardness that can depend on size and shape as well as on composition, among other characteristics. Tablet hardness can be measured by any method known in the art, for example by a tablet hardness meter (*e.g.*, Schleuniger). Preferably, compositions of the invention have a hardness of about 1 to about 10 kp, and more preferably of about 1 to about 6 kp.

In a presently preferred embodiment, solid dosage forms of the invention have sufficient hardness for handling and, therefore, can be put into practical use in the same manner as the case of ordinary tablets. The term "sufficient hardness for handling" as used herein means a hardness which can withstand removal from at least a standard type of blister packaging, or such a hardness as will withstand other handling such as packaging, delivery, carrying and the like.

Tablets of the invention preferably have a minimum hardness so as to resist breakage of the tablet during removal from standard blister packaging by pushing the tablet through a cover sheet. A suitable hardness is about 1 kp or more for a tablet having a diameter of about 8 mm, about 1.5 kp or more for a tablet having a diameter of about 10 mm, and about 2 kp or more when the tablet has a diameter of about

12 mm.

In another presently preferred embodiment, tablets of the invention have sufficient hardness such that a plurality of such tablets can be packaged together, for example in a glass or plastic bottle, without individual packaging, yet do not exhibit substantial breakage or sticking and/or melding together during normal shipping and handling. Tablets intended for such packaging preferably have a hardness of about 3 kp or more.

Packaging

Compositions of the invention can be packaged in any suitable manner known in the art. For example, a multiplicity of fast-melt tablets can be packaged together, for example in a glass or plastic bottle or container. Alternatively, fast-melt tablets of the invention can be individually wrapped, for example in plastic or foil, or packaged in known forms of blister packaging. Blister packaging with improved force distribution properties such as is disclosed in U.S. Patent No. 5,954,204 to Grabowski, incorporated herein by reference, can be especially useful to package fast-melt tablets of the invention.

Administration of fast-melt tablets

Compositions of the present invention can be taken by a subject by any oral administration means in accordance with the subject's choice or condition. For example, fast-melt tablets of the invention can be taken without water. Upon placement in the oral cavity and especially in the cheek or above the tongue, such a tablet is exposed to saliva and rapidly disintegrates and dissolves therein. The rate of disintegration and/or dissolution increases further when an intraoral pressure, for example a pressure between the palate and tongue or a licking or sucking pressure, is applied to the tablet.

Alternatively, a tablet of the present invention can be taken with the aid of water in an amount sufficient to wet the oral cavity and to assist in disintegration of the tablet. Also, a tablet of the invention can be swallowed together with a small amount of water after complete or partial disintegration in the oral cavity. Compositions of the invention can also be swallowed directly with water.

Method to make fast-melt tablets

The process described below is a non-limiting, illustrative method to make valdecoxib fast-melt tablets of the invention. Importantly, specific settings and parameters of the production process can be readily optimized by one of skill in the art in order to produce tablets with particularly desired characteristics.

In this illustrative process, maltose and mannitol are dissolved in a vessel of water which is heated to approximately 50 °C to about 80 °C, for example about 70 °C. Valdecoxib is then dispersed in the vessel using a homogenizer. A wetting agent, for example sodium lauryl sulfate, is dissolved in a second vessel of water. The contents of the first and second vessels are then combined to form a mixture. The mixture is spray dried using a Niro Laboratory Mobile Minor Spray Dryer to form a dry granulation. The dry granulation is then optionally blended with any desired excipients, for example flavorants, sweeteners and lubricants, to form a tableting blend. The resulting tableting blend is then compressed on a rotary tablet press to a target tablet weight and hardness. The resulting tablets are then subjected to treatment, for example air flow treatment, in a humidity-controlled chamber with the effect of increasing tablet hardness.

Tablet compression

Compression is the process by which an appropriate volume of a tableting blend of granules produced as described above is compressed between an upper and lower punch to consolidate material into a single solid dosage form such as a tablet. In processes for manufacture of fast-melt tablets of the present invention, any suitable means for compression can be used including, for example, a single punch tablet machine or a high speed rotary tablet press. The tableting pressure is not limited, and an appropriate pressure can be selected depending on the desired hardness and dissolution properties of the resulting tablets. Where tablets are to undergo temperature and humidity treatment as described immediately below, the tablets are preferably compressed to an initial hardness (prior to temperature and humidity treatment) of about 0.75 to about 1.5 kp.

Temperature and humidity treatment

Optionally, tablets of the invention can undergo heat and humidity treatment after the tablet compression step. Such treatment can be performed in a humidity

chamber, for example, to increase hardness of the tablets. Illustratively, during this treatment, tablets are first subjected to low temperature, high humidity air flow conditions, for example, about 25°C to about 32°C and about 80% relative humidity, for a period of about 45 to about 120 minutes. Tablets are then subjected to high temperature, low humidity conditions, for example about 35°C to about 50°C and 30% relative humidity for a period of about 45 to about 120 minutes. Without being bound by theory, it is believed that treatment of fast-melt tablets in a low temperature/high humidity chamber followed by treatment in a high temperature/low humidity chamber increases tablet hardness and reduces tablet friability without sacrificing desired fast-melt characteristics such as rapid disintegration and rapid dissolution.

Utility of compositions of the invention

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

or patients taking anticoagulants.

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, bursitis, allergic neuritis, cytomegalovirus infectivity, apoptosis including HIV-induced apoptosis, lumbago, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, acne, burns, dermatitis and ultraviolet radiation damage including sunburn, and post-operative inflammation including that following ophthalmic surgery such as cataract surgery or refractive surgery.

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

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

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

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

Such compositions are useful for treatment of certain central nervous system disorders, such as cortical dementias including Alzheimer's disease, neurodegeneration, and central nervous system damage resulting from stroke, ischemia and trauma. The term "treatment" in the present context includes partial or total inhibition of dementias, including Alzheimer's disease, vascular dementia,

multi-infarct dementia, pre-senile dementia, alcoholic dementia and senile dementia.

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

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

Such compositions are useful for, 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, treatment of angiogenesis-related disorders in a subject, for example to inhibit tumor angiogenesis. Such compositions are useful for 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 glaucoma, including neovascular glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemangiomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis.

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

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

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

Besides being useful for human treatment, compositions of the invention are also useful for veterinary treatment of companion animals, exotic animals, 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 invention also is directed to a therapeutic method of treating a condition or disorder where treatment with a cyclooxygenase-2 inhibitory drug is indicated, the method comprising oral administration of one or more compositions 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 once-a-day or twice-a-day treatment, but can be modified in accordance with a variety of factors. These include the type, age, weight, sex, diet and medical condition of the 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 inhibitory drug is indicated can begin with a dose regimen as indicated above. Treatment is generally continued as necessary over a period of several weeks to several months or years until the condition or disorder has been controlled or eliminated. 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 data from such monitoring permits modification of the treatment regimen during therapy so that optimally effective amounts of the drug are administered at any point in time, and so that the duration of treatment can be determined. In this way, the treatment regimen and dosing schedule can be rationally modified over the course of therapy so that the lowest amount of the drug exhibiting satisfactory effectiveness is administered, and so that administration is continued only for so long as is necessary to successfully treat the condition or disorder.

The present compositions can be used in combination therapies with opioids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e. non-addictive) analgesics, 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 one or more compounds selected from aceclofenac, acemetacin, *e*-acetamidocaproic acid, acetaminophen, acetaminosalol, acetanilide, acetylsalicylic

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

salicylate, naproxen, narceine, nefopam, nicomorphine, nifenazone, niflumic acid, nimesulide, 5'-nitro-2'-propoxyacetanilide, norlevorphanol, normethadone, normorphine, norpipanone, olsalazine, opium, oxaceprol, oxametacine, oxaprozin, oxycodone, oxymorphone, oxyphenbutazone, papaveretum, paranyline, parsalmide, pentazocine, perisoxal, phenacetin, phenadoxone, phenazocine, phenazopyridine hydrochloride, phenocoll, phenoperidine, phenopyrazone, phenyl acetylsalicylate, phenylbutazone, phenyl salicylate, phenyramidol, piketoprofen, piminodine, pipebuzone, piperylone, piprofen, pirazolac, piritramide, piroxicam, pranoprofen, proglumetacin, proheptazine, promedol, propacetamol, propiram, propoxyphene, propyphenazone, proquazone, protizinic acid, ramifenazone, remifentanil, rimazolium metilsulfate, salacetamide, salicin, salicylamide, salicylamide *o*-acetic acid, salicylsulfuric acid, salsalte, salverine, simetride, sodium salicylate, sufentanil, sulfasalazine, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, tetrandrine, thiazolinobutazone, tiaprofenic acid, tiaramide, tilidine, tinoridine, tolfenamic acid, tolmetin, tramadol, tropesin, viminol, xenbucin, ximoprofen, zaltoprofen and zomepirac (see The Merck Index, 12th Edition (1996), Therapeutic Category and Biological Activity Index, lists therein headed "Analgesic", "Anti-inflammatory" and "Antipyretic").

Particularly preferred combination therapies comprise use of a composition of the invention, for example valdecoxib 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 valdecoxib can be formulated separately from the valdecoxib or co-formulated with the valdecoxib in a composition of the invention. Where valdecoxib 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.

In an embodiment of the invention, particularly where the cyclooxygenase-2 mediated condition is headache or migraine, the valdecoxib composition is administered in combination therapy with a vasomodulator, preferably a xanthine derivative having vasomodulatory effect, more preferably an alkylxanthine compound.

Combination therapies wherein an alkylxanthine compound is co-administered

with a valdecoxib composition as provided herein are embraced by the present embodiment of the invention whether or not the alkylxanthine is a vasomodulator and whether or not the therapeutic effectiveness of the combination is to any degree attributable to a vasomodulatory effect. The term "alkylxanthine" herein embraces xanthine derivatives having one or more C_{1-4} alkyl, preferably methyl, substituents, and pharmaceutically acceptable salts of such xanthine derivatives. Dimethylxanthines and trimethylxanthines, including caffeine, theobromine and theophylline, are especially preferred. Most preferably, the alkylxanthine compound is caffeine.

The total and relative dosage amounts of valdecoxib and of the vasomodulator or alkylxanthine are selected to be therapeutically and/or prophylactically effective for relief of pain associated with the headache or migraine. Suitable dosage amounts will depend on the severity of pain and the particular vasomodulator or alkylxanthine selected. For example, in a combination therapy with valdecoxib and caffeine, typically the valdecoxib will be administered in a daily dosage amount of about 1 mg to about 100 mg, preferably about 5 mg to about 50 mg, and the caffeine in a daily dosage amount of about 1 mg to about 500 mg, preferably about 10 mg to about 400 mg, more preferably about 20 mg to about 300 mg.

The vasomodulator or alkylxanthine component of the combination therapy can be administered in any suitable dosage form by any suitable route, preferably orally. The vasomodulator or alkylxanthine can optionally be coformulated with the valdecoxib in the molded article of the invention. Thus a molded article of the invention optionally comprises both valdecoxib and a vasomodulator or alkylxanthine such as caffeine, in total and relative amounts consistent with the dosage amounts set out hereinabove.

The phrase "in total and relative amounts effective to relieve pain", with respect to amounts of valdecoxib and a vasomodulator or alkylxanthine in a composition of the present embodiment, means that these amounts are such that (a) together these components are effective to relieve pain, and (b) each component is or would be capable of contribution to a pain-relieving effect if the other component is or were not present in so great an amount as to obviate such contribution.

EXAMPLES

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

Example 1

Valdecoxib Fast-Melt Tablets (Batch A, hereinafter also referred to as Fast-Melt A) were prepared according to the following procedure. Maltose (28.03 g) and mannitol (367.6 g) were dissolved in water in a first vessel with heat (70 °C) and stirring. Valdecoxib (46.25 g) was dispersed in the maltose/mannitol solution and homogenized for ten minutes using a Silverson homogenizer. Sodium lauryl sulfate (SLS) was dissolved in water in a second vessel with gentle agitation to form a wetting agent solution. The wetting agent solution was added to the first vessel to form a sprayable solution. The sprayable solution was spray dried to form a dry granulation using a Niro Laboratory Mobile Minor Spray Dryer under the following conditions: spray rate: 32 g/min; inlet process gas flow: 2.8 mbar; system pressure: 1.6 mbar; inlet process gas pressure 20 mbar; atomization pressure 1.6 bar; percent atomization flow: 57; inlet temperature: 160 °C; outlet temperature: about 55 °C; atomization air heater temperature: 287 °C.

Magnesium stearate (1 g), stearic acid (3 g), acesulfame K (1 g) and peppermint flavor (1 g) were added to a polyethylene bag and vigorously shaken to form a mixture. The mixture was then geometrically diluted with the dry granulation prepared above until 200 g of dry granulation had been added. Tablets were then prepared by individually compressing 400 mg of the tableting blend to form tablets having an intermediate hardness of 1.5 kp. Resulting tablets were placed in a chamber maintained at 25 °C and 80% relative humidity for 1 hour, and at 40 °C and 30% relative humidity for a second hour. Composition (% weight) of Fast-Melt A is shown in Table 1.

Table 1. Composition of Fast-Melt A

Component	Amount
Valdecoxib	10
Maltose	6.06
Mannitol	79.48
SLS	1.45
Magnesium stearate	0.5
Stearic acid	1.5
Acesulfame K	0.5
Peppermint	0.5

Example 2

A study was performed in order to determine pharmacokinetic properties of the Valdecoxib Fast-Melt A in beagle dogs. Valdecoxib Fast-Melt A was individually administered to each of 4 dogs. Venous blood was collected pre-dose, and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hours after oral dose administration. Plasma was separated from blood by centrifugation at 3000 G and samples were stored at -20°C until analysis. Concentrations of valdecoxib in plasma were determined using an HPLC assay. Results are shown in Table 2.

Table 2 Pharmacokinetic properties of Valdecoxib Fast-Melt A in Dogs

Parameter	Fast-Melt A
C_{max} (ng/ml)	8800
AUC (h*ng/ml)	2710
T_{max} (h)	1.4

Example 3

Valdecoxib Fast-Melt Tablets (Batch B, hereinafter also referred to as Fast-Melt B) were prepared according to the following procedure. Maltose (0.158 kg) and mannitol (2.047 kg) were dissolved in water (14.167 kg) with mixing to form a solution. Sodium lauryl sulfate (0.037 kg) was added to the solution with mixing until dissolved. Valdecoxib (0.258 kg) was dispersed in the solution and homogenized at approximately 5000 RPM for 15 minutes using a Silverson homogenizer to form a slurry. The slurry was then mixed with a conventional marine-type impeller at approximately 300 RPM for approximately 2 hours. The slurry was spray dried to form a dry granulation using a Niro Laboratory Mobile Minor Spray Dryer under the

following conditions: spray rate: 30 g/min; inlet process gas flow: 40 mm H_2O; chamber pressure: -100 mm H_2O; fluid spray atomization pressure 1.0 bar; percent atomization flow: 70; inlet air temperature: 175 °C; outlet air temperature: about 90 °C. The total theoretical yield was 2.500 Kg. The above procedure was performed in duplicate to result in spray dried granulation Lot A (1414.3 g) and Lot B (1971.9 g).

Spray dried granulation Lot A and Lot B were and sieved and the sieved granulations were dry blended with peppermint flavor (17.5 g) and acesulfame K (17.5 g) in a V-blender for 15 minutes to form a mixture. Magnesium stearate (17.5 g), micronized stearic acid (52.5 g) and colloidal silicon dioxide (8.8 g) were added to the mixture with additional mixing to form a tableting blend. Tablets were compressed from the tableting blend to a target hardness of 1.5 Kp and a target tablet weight of 391.58 mg. After compression, tablets were transferred to an IBC humidity treatment chamber (17 liter) maintained at 25 °C, 80% relative humidity and 75 CFM air flow for 1 hour, and at 40 °C, 30% relative humidity and 75 CFM air flow for a second hour. Composition of Fast-Melt B (mg/tablet) is shown in Table 3.

Table 3. Composition of Fast-Melt B.

Component	Amount (mg)
Granulation Lot A	158.22
Granulation Lot B	220.61
Magnesium stearate NF	1.96
Stearic acid NF (micronized)	5.87
Colloidal silicon dioxide	1.00
Acesulfame K	1.96
Peppermint	1.96
Total	391.58

Example 4

In vitro dissolution profiles of Fast-Melt B of Example 3 and a commercial 40 mg Bextra® tablet were determined using 1000 ml of 1% sodium lauryl sulfate solution and USP Type II Apparatus. Data are shown in Table 4. Fast-melt B exhibited very rapid dissolution with all of the valdecoxib being dissolved by 15 minutes in the assay.

Table 4. Amount (% weight) of valdecoxib dissolved

Time (min)	Fast-Melt B	Bextra® Tablet

15	101	62
30	101	79
45	100	88
60	101	93

Example 5

Fast-Melt B of Example 3 was individually administered to 25 human subjects. Oral bioavailability parameters were determined and compared with those of a 40 mg commercial Bextra® tablet. Data are shown in Table 5.

Table 5. Oral bioavailability of Fast-Melt B and a 40 mg Bextra® tablet in human subjects

Parameter	Fast-Melt B	Bextra® tablet
T_{max} (hr)	3.22	3.3
C_{max} (ng/ml)	580	468
AUC (ng/ml)/hr	6833	6126

These data indicate that Fast-Melt B exhibits very good bioavailability properties upon administration to human subjects.

Example 6

Fast-Melt B of Example 3 was evaluated in a taste study according to the following procedure. Four to five professional sensory panelists were selected and each panelist was given a Fast-Melt tablet to place on his/her tongue. The panelist gently rolled the tablet against the roof of his/her mouth without chewing, and simultaneously recorded sensory information and time to complete disintegration. Sensory information included organoleptic attributes associated with each tablet such as flavor quality, bitterness, fullness, texture, mouth feel and aftertaste. Each of these attributes were defined along a categorical unit scale of 1 - 5 to express perceptual differences from other commercially marketed melt products, by comparison with comparator valdecoxib fast-melt tablets which comprised one of cherry, strawberry, orange, peppermint, or spearmint flavor, and by comparison with fast-melt tablets comprising different active ingredients.

After total disintegration of a tablet, the panelist recorded sensory aftertaste over a period of 30 minutes. Each tablet was evaluated in triplicate and all samples were coded for presentation to panelists. Fast-Melt B exhibited an average

disintegration time of 23.6 seconds. Overall, valdecoxib Fast-Melt B exhibited acceptable flavor quality (data not shown) and disintegration time.

WHAT IS CLAIMED IS:

1. An oral fast-melt composition comprising:
   (a) particulate valdecoxib in a therapeutically effective amount, and
   (b) at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution and which is in intimate association with the valdecoxib particles;

   wherein the at least one excipient which exhibits rapid oral dissolution is present in a total amount of about 50% to about 99%, by weight.

2. The composition of Claim 1 wherein the at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution is a carbohydrate.

3. The composition of Claim 1 wherein the at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution is a saccharide.

4. The composition of Claim 1 wherein the at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution is selected from the group consisting of maltose, maltitol, sorbitol, lactose and mannitol.

5. The composition of Claim 1 wherein the at least one excipient which exhibits rapid oral dissolution is present in a total amount of about 50% to about 90%, by weight.

6. The composition of Claim 1 wherein the at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution comprises a saccharide of high moldability and a saccharide of low moldability.

7. The composition of Claim 6 wherein the weight ratio of saccharide of high moldability to saccharide of low moldability is about 2 to about 20 parts of saccharide of high moldability per 100 parts of saccharide of low moldability.

8. The composition of Claim 6 wherein the weight ratio of saccharide of high moldability to saccharide of low moldability is about 5 to about 7.5 parts of saccharide of high moldability per 100 parts of saccharide of low moldability.

9. The composition of Claim 1 having a hardness of about 1 to about 10 kp.

10. The composition of Claim 1 wherein the valdecoxib is present in an amount of about 5 to about 50 mg.

11. The composition of Claim 1 which, when placed in United States Pharmacopeia 24 *in vitro* disintegration Test Number 701, exhibits a disintegration time of less

than about 300 seconds.

12. The composition of Claim 1 which, when placed in United States Pharmacopeia 24 *in vitro* disintegration Test Number 701, exhibits a disintegration time of less than about 100 seconds.

13. The composition of Claim 1 which disintegrates within about 60 seconds after placement in the oral cavity of a human subject.

14. The composition of Claim 1 which disintegrates within about 30 seconds after placement in the oral cavity of a human subject.

15. The composition of Claim 1 which is organoleptically acceptable.

16. A process for preparing an intraorally disintegrating valdecoxib tablet composition, the process comprising:

a step of providing valdecoxib in particulate form;

a step of dissolving at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution in water in a vessel, said at least one excipient being dissolved in a total amount such that upon completion of the process the excipient comprises about 50% to about 99% of the total tablet weight;

a step of dispersing the valdecoxib in the water;

wherein said dissolving and dispersing steps are performed in any order or simultaneously to result in a sprayable liquid;

a step of spray drying the sprayable liquid to form a tableting blend; and

a step of compressing the tableting blend to form a tablet.

17. The process of Claim 16 further comprising a step of heating the vessel of water prior to, simultaneously with or after said dissolving and/or dispersing steps, but prior to said spray drying step.

18. The process of Claim 16 further comprising a step of dissolving a wetting agent in the water prior to, simultaneously with, or after said dispersing and/or dissolving steps, but prior to said spray drying step.

19. The process of Claim 16 further comprising a step of dissolving an aqueous solution of a wetting agent in the water prior to, simultaneously with, or after said dispersing and/or dissolving steps, but prior to said spray drying step.

20. The process of Claim 16 wherein the at least one pharmaceutically acceptable

excipient which exhibits rapid oral dissolution is a carbohydrate.

21. The process of Claim 16 wherein the at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution is a saccharide.
22. The process of Claim 16 wherein the at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution is selected from the group consisting of maltose, maltitol, sorbitol, lactose and mannitol.
23. The process of Claim 16 wherein the at least one excipient which exhibits rapid oral dissolution is dissolved in a total amount such that upon completion of the process the excipient comprises about 50% to about 95% of the total tablet weight.
24. The process of Claim 16 wherein the at least one excipient which exhibits rapid oral dissolution is dissolved hi a total amount such that upon completion of the process the excipient comprises about 50% to about 90% of the total tablet weight.
25. The process of Claim 16 wherein the at least one pharmaceutically acceptable excipient which exhibits rapid oral dissolution comprises a saccharide of high moldability and a saccharide of low moldability.
26. The process of Claim 25 wherein the weight ratio of saccharide of high moldability to saccharide of low moldability is about 2 to about 20 parts of saccharide of high moldability per 100 parts of saccharide of low moldabiliry.
27. The process of Claim 25 wherein the weight ratio of saccharide of high moldability to saccharide of low moldability is about 5 to about 7.5 parts of saccharide of high moldability per 100 parts of saccharide of low moldability.
28. An intraorally disintegrating valdecoxib tablet composition prepared by the process Claim 16.
29. Use of the composition of claim 1 for the manufacture of a medicament for treating or preventing a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitory drug is indicated.
30. Use of the composition of claim 28 for the manufacture of a medicament for treating or preventing a medical condition or disorder in a subject where treatment with a cyclooxygenase-2 inhibitory drug is indicated.