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Dependencia: 2020 DIVISION DE NUEVAS SOLICITUDES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)	Nombre: **PHARMACIA CORPORATION** Dirección: 700 Chesterfield Parkway West, Chesterfield, MO 63017-1732, Estados Unidos Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual____ Número 170.322 TP 1003
4 INVENTOR (ES) (72)	Nombre: Guang Wei Lu Dirección: 3172 Birchwood Court, Ann Arbor, MI 48015, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos de América	

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6 Título (54): FORMULACIÓN DE SUSPENSIÓN ORAL ESTABILIZADA

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2020-F08 (01-11-15)

1 2

10 ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $422.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso.
- [ ] Documento de cesión del Inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [x] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] Otros Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

C.C. 170.322 de Bogotá T.P. 1003 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

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SUPERINTENDENCIA Y [illegible]

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

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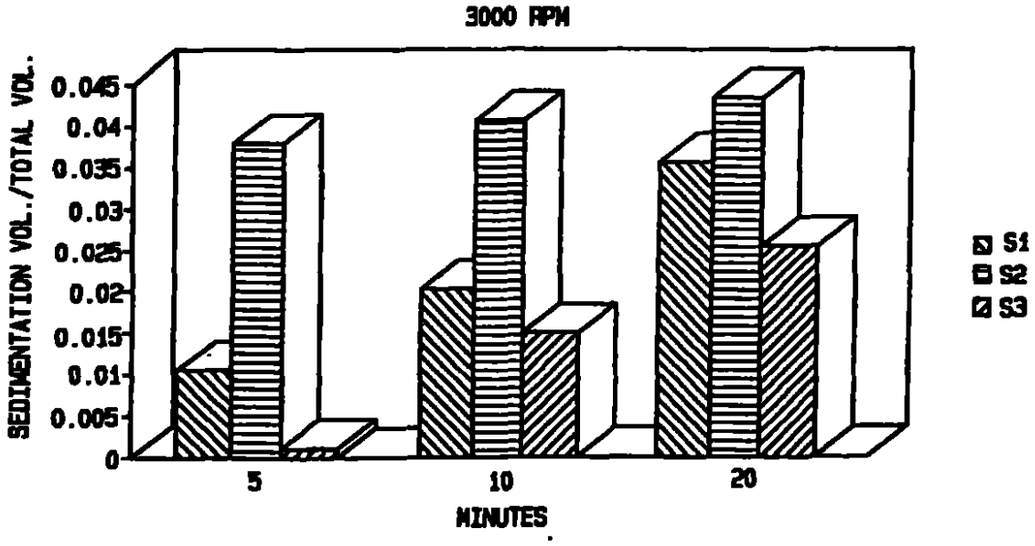
Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: STABILIZED ORAL SUSPENSION FORMULATION



(57) Abstract: Orally deliverable pharmaceutical compositions are provided comprising a drug of low water solubility suspended in an aqueous liquid vehicle comprising a wetting agent, a thixotropic thickening agent, and an inorganic suspending agent. The compositions are thixotropic, substantially deflocculated, and substantially physically stable.

WO 03/013473 A1

STABILIZED ORAL SUSPENSION FORMULATION

FIELD OF THE INVENTION

[0001] The present invention relates to orally deliverable pharmaceutical compositions comprising a drug of low water solubility, to methods of treatment comprising orally administering such compositions to a subject in need thereof, and to the use of such compositions in the manufacture of medicaments.

BACKGROUND OF THE INVENTION

[0002] Liquid dosage forms, for example solutions, suspensions, elixirs and syrups, have become an important method by which drugs are delivered to subjects. Such dosage forms are known to provide ease of administration for some patients who have difficulty swallowing solid dosage forms and to increase compliance among certain patient populations by enhancing taste and/or texture of the drug being administered. A yet further advantage of liquid dosage forms is that metering of dosages is continuously variable, providing infinite dose flexibility. The benefits of ease of swallowing and dose flexibility are particularly advantageous for infants, children and the elderly.

[0003] In some instances, suspensions can be an advantageous liquid dosage form. For example, some drugs are chemically unstable in solution but are stable when suspended. Additionally, some drugs have a disagreeable taste when in solution but are palatable when administered as undissolved particles.

[0004] Unfortunately, many useful drugs are hydrophobic having low solubility in aqueous media and therefore are difficult to formulate as suspensions in aqueous vehicle. Specifically, because of these properties, wetting agents are often required in order to facilitate suspension of hydrophobic drug particles in aqueous media. Surface active wetting agents (*i.e.* surfactants), for example sodium lauryl sulfate, are known to increase suspendability of hydrophobic drugs in aqueous media at least in part by reducing interfacial tension between drug particles and the suspension vehicle, thereby allowing penetration of suspension vehicle into drug aggregates and/or drug particle pores. In addition to advantageous drug-suspending effects, however, use of surfactants in suspensions also often leads to the undesirable

result of solubilized and/or dissolved free drug. Since solubilized and/or dissolved drug is susceptible to chemical degradation and/or interaction with other ingredients, suspensions comprising free drug can be chemically unstable.

[0005] Another undesirable consequence of using relatively high amounts of surfactant to facilitate suspension of low solubility drugs is that, since surfactants stabilize air bubbles, air entrained during homogenization or shaking of such a suspension tends to remain entrapped therein. As this entrapped air varies depending on agitation force, duration of agitation, and time since agitation, suspension volume necessarily changes making volumetric extraction of uniform doses over time difficult or impossible.

[0006] If a drug of low water solubility is to be administered as a suspension, it is desirable that the suspension exhibit slow sedimentation in order to provide suitable dose uniformity. Conversely, where rapid sedimentation occurs, as in the case of an unstructured vehicle, the suspension must be shaken prior to each administration in order to achieve dose uniformity. Other factors being equal (*e.g.* drug particle size, uniformity and density), as viscosity of a particular suspension vehicle increases, velocity of drug particle sedimentation decreases. Therefore, it is desirable that a suspension be suitably viscous so as to inhibit or slow sedimentation of drug particles. However, while such increased viscosity facilitates physical stability, it can also make difficult pouring or administering the suspension. Many suspensions known in the art have failed to adequately address this apparent tradeoff between suitable physical stability and suitable pourability.

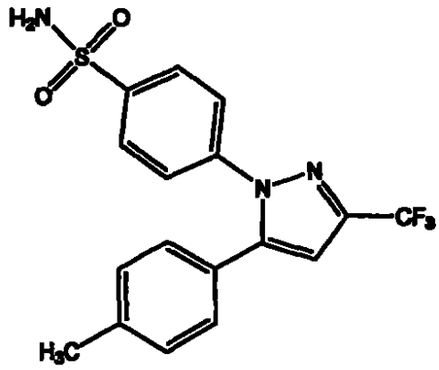
[0007] U.S. Patent No. 5,112,604 to Beaurline discloses an oral suspension formulation capable of providing dose uniformity for a period of about 90 days. However, no information related to rheology or pourability is disclosed therein.

[0008] Deflocculated suspensions are also desirable in many instances. In a structured vehicle, larger particles generally sediment faster than do smaller particles. Therefore, a deflocculated suspension wherein drug particles exist as separate entities (as opposed to loose aggregates or flocs) is desirable with respect to slow sedimentation velocity. A further advantage of deflocculated suspensions is that they do not require addition of flocculating agents. Common flocculating agents such as electrolytes (*e.g.* magnesium aluminum silicate or aluminum chloride) can result in

catalyzation of chemical reactions and subsequent degradation of drug or other ingredients. Therefore, with respect to both reduced sedimentation velocity and chemical stability, a deflocculated suspension is more desirable than a flocculated suspension.

[0009] Accordingly, there remains a need in the art for suspension formulations of drugs of low water solubility which suspensions are chemically and physically stable and have suitable rheologic properties for pouring and administration.

[0010] An illustrative class of drugs for which this need is apparent is the class of selective cyclooxygenase-2 (COX-2) inhibitory drugs of low water solubility. Numerous compounds have been reported having therapeutically and/or prophylactically useful selective cyclooxygenase-2 (COX-2) inhibitory effect, and have been disclosed as having utility in treatment or prevention of specific COX-2 mediated disorders or of such disorders in general. Among such compounds are a large number of substituted pyrazolyl benzenesulfonamides as reported in U.S. Patent No. 5,760,068 to Talley *et al.*, including for example the compound 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, also referred to herein as celecoxib (I), and the compound 4-[5-(3-fluoro-4-methoxyphenyl)-3-difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide, also referred to herein as deracoxib (II).



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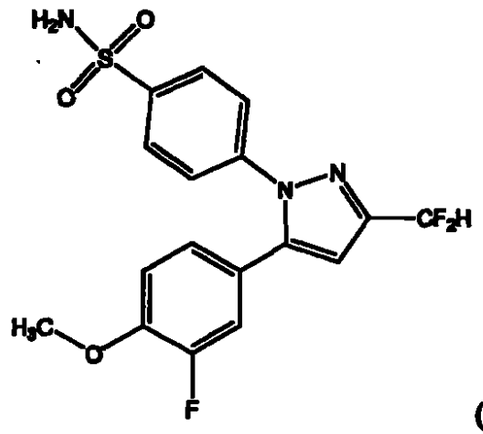
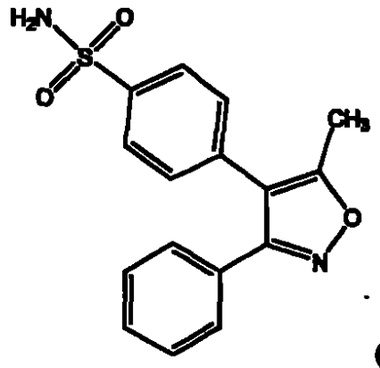


(II)

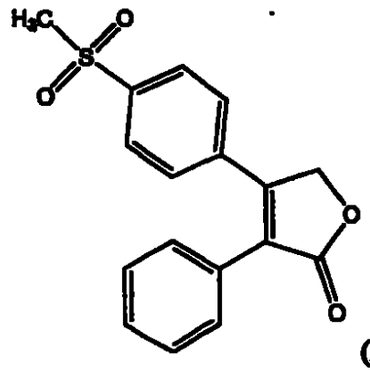
[0011] Other compounds reported to have therapeutically and/or prophylactically useful selective COX-2 inhibitory effect are substituted isoxazolyl benzenesulfonamides as reported in U.S. Patent No. 5,633,272 to Talley *et al.*,

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



(III)

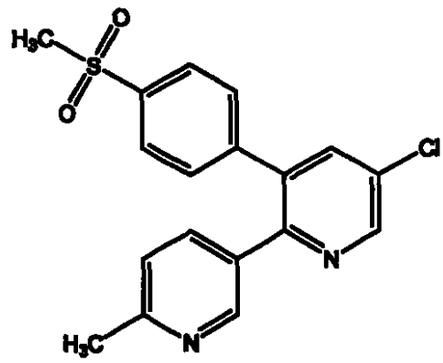
[0012] Still other compounds reported to have therapeutically and/or prophylactically useful selective COX-2 inhibitory effect are substituted (methylsulfonyl)phenyl furanones as reported in U.S. Patent No. 5,474,995 to Ducharme *et al.*, including the compound 3-phenyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one, also referred to herein as rofecoxib (IV).



(IV)

[0013] U.S. Patent No. 5,981,576 to Belley *et al.* discloses a further series of (methylsulfonyl)phenyl furanones said to be useful as selective COX-2 inhibitory drugs, including 3-(1-cyclopropylmethoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one and 3-(1-cyclopropylethoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]-5H-furan-2-one.

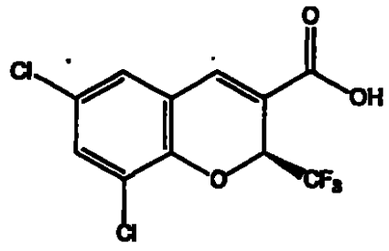
[0014] U.S. Patent No. 5,861,419 to Dube *et al.* discloses substituted pyridines said to be useful as selective COX-2 inhibitory drugs, including for example the compound 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine (V), also referred to herein as etoricoxib.



(V)

[0015] European Patent Application No. 0 863 134 discloses the compound 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one said to be useful as a selective COX-2 inhibitory drug.

[0016] U.S. Patent No. 6,034,256 discloses a series of benzopyrans said to be useful as selective COX-2 inhibitory drugs, including the compound (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid (VI).



(VI)

[0017] Liquid dosage forms comprising selective COX-2 inhibitory drugs of low water solubility have been disclosed. For example, above-cited U.S. Patent No. 5,760,068 discloses that its subject pyrazolyl benzenesulfonamides, of which celecoxib and deracoxib are examples, can be administered parenterally as isotonic solutions in a range of solvents including polyethylene glycol and propylene glycol.

[0018] Above-cited U.S. Patent No. 5,633,272 discloses that its subject isoxazolyl benzenesulfonamides, of which valdecoxib is an example, can be administered parenterally as isotonic solutions in a range of solvents including polyethylene glycol and propylene glycol.

[0019] Above-cited U.S. Patent No. 5,474,995 discloses that its subject (methylsulfonyl)phenyl furanones, of which rofecoxib is an example, can be administered parenterally in an isotonic solution in 1,3-butanediol. Also disclosed in U.S. Patent No. 5,474,995 are syrups and elixirs for oral administration, formulated with propylene glycol as a sweetening agent.

[0020] Moreover, a suspension of particulate celecoxib in an unstructured vehicle of apple juice was disclosed in co-assigned PCT patent No. WO 00/32189. No information is provided therein on chemical or physical stability of such a composition.

[0021] As indicated hereinbelow, treatment with COX-2 inhibitory drugs of low water solubility is indicated in a very wide array of cyclooxygenase-2 mediated disorders and conditions. Therefore, if an orally deliverable, physically and chemically stable, yet still readily pourable, aqueous suspension of a drug of low solubility, for example a selective COX-2 inhibitory drug, could be prepared, a significant advance would be realized in treatment of many conditions and disorders, particularly where easy to swallow dosage forms of various drugs are desired.

SUMMARY OF THE INVENTION

[0022] There is now provided an orally deliverable pharmaceutical composition comprising a drug of low water solubility and an aqueous liquid vehicle that comprises (a) a pharmaceutically acceptable wetting agent, (b) a pharmaceutically acceptable thixotropic thickening agent, and (c) a pharmaceutically acceptable inorganic suspending agent, wherein at least a substantial portion of the drug is suspended in particulate form in the vehicle to form a suspension and wherein the wetting agent, thickening agent, and suspending agent are present in total and relative amounts such that the suspension is thixotropic, substantially deflocculated, and substantially physically stable.

[0023] In a preferred embodiment, the drug is a selective COX-2 inhibitory drug of low water solubility.

[0024] The term "substantially physically stable" as used to describe a suspension herein means that (a) drug particles remain suspended in the suspension vehicle such that dose uniformity is obtainable, as determined for example from two or more aliquots drawn volumetrically, during a stationary room temperature storage

period of at least 48 hours after the suspension is prepared, and/or (b) the suspension exhibits substantially uniform drug particle dispersion and substantially no phase separation during a stationary room temperature storage period of at least 48 hours after preparation.

[0025] The term "dose uniformity" herein means that, with respect to two or more aliquots drawn volumetrically from the same suspension, either drawn simultaneously or at different time points and drawn from the same or different locations within the suspension, all aliquots contain substantially similar amounts (*i.e.* ± about 15%) of suspended drug and substantially similar amounts of free drug. An amount of drug in a given volume of suspension can be measured by any suitable method, for example by high performance liquid chromatography.

[0026] A "thixotropic" suspension herein is a suspension for which, when an applied stress is continued and/or increased, viscosity substantially decreases. This definition includes suspensions defined elsewhere as being pseudoplastic or shear-thinning.

[0027] The term "flocculated" herein refers to drug particles in suspension which coagulate and/or agglomerate together to form loosely packed aggregates or flocs. A "flocculated suspension" herein is a suspension wherein at least a visible portion of all drug particles are flocculated drug particles. The term "substantially deflocculated" herein refers to drug particles in suspension which do not coagulate and/or agglomerate together to form flocs. A "deflocculated suspension" herein is a suspension wherein substantially no visible portion of drug particles are flocculated.

[0028] Typically, given a flocculated suspension and a deflocculated suspension having the same drug particle size distribution, drug particle shape, drug particle density, and vehicle viscosity, drug particles in the deflocculated suspension will sediment more slowly than will drug particles in the flocculated suspension. Additionally, when placed in a suspension vehicle of low viscosity, for example an unstructured vehicle, deflocculated drug particles will generally settle to form a tightly packed layer of sediment which is not readily dispersed upon moderate shaking, while flocculated particles will generally settle to form a fluffy, loose layer of sediment which can be redispersed with moderate shaking.

[0029] A "structured vehicle" herein is a vehicle comprising one or more viscosity imparting suspending agents which substantially reduce the rate of sedimentation of dispersed particles.

[0030] Also provided by the present invention are methods for therapeutic and/or prophylactic use of compositions of the present invention, and a method of use of a composition of the invention in manufacture of a medicament useful for treating and/or preventing a COX-2 mediated disease or disorder.

[0031] Compositions of the invention have been found to resolve at least some of the difficulties alluded to above in a surprisingly effective manner. First, compositions of the invention are substantially physically stable. Second, compositions of the invention are thixotropic and therefore are readily poured and administered upon mild agitation. Third, due at least in part to reduced free drug concentration, compositions of the invention have enhanced chemical stability.

[0032] Other features of this invention will be in part apparent and in part pointed out hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] Fig. 1 shows sediment volume resulting from centrifugation of Celecoxib Suspensions S1-S3 of Example 1 at 1500 rpm for 5, 10 and 30 minutes, as described in Example 3.

[0034] Fig. 2 shows sediment volume resulting from centrifugation of Celecoxib Suspensions S1 and S3 of Example 1 at 2500 rpm for 30, 60 and 90 minutes, as described in Example 3.

[0035] Fig. 3 shows sediment volume resulting from centrifugation of Celecoxib Suspensions S1-S3 of Example 1 at 3000 rpm for 5, 10 and 20 minutes, as described in Example 3.

DETAILED DESCRIPTION OF THE INVENTION

[0036] Novel pharmaceutical compositions according to the present invention comprise one or more orally deliverable dose units. The term "orally deliverable" herein means suitable for oral administration. The term "oral administration" herein includes any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the

mouth of the subject, whether or not the agent or composition is swallowed. Thus "oral administration" includes buccal and sublingual as well as esophageal administration. Absorption of the agent can occur in any part or parts of the gastrointestinal tract including the mouth, esophagus, stomach, duodenum, jejunum, ileum and colon. The term "dose unit" herein means a portion of a pharmaceutical composition that contains an amount of a therapeutic agent suitable for a single oral administration to provide a therapeutic effect. Typically one dose unit, or a small plurality (up to about 4) of dose units, provides a sufficient amount of the agent to result in the desired effect.

Drug of low water solubility

[0037] Each dose unit or small plurality of dose units comprises, in a therapeutically and/or prophylactically effective total amount, a drug of low water solubility. A "drug of low water solubility" or "poorly water solubility drug" herein refers to any drug or compound having a solubility in water, measured at 37°C, not greater than about 10 mg/ml, and preferably not greater than about 1 mg/ml. It is contemplated that compositions of the invention are especially advantageous for drugs having a solubility in water, measured at 37°C, not greater than about 0.1 mg/ml.

[0038] Solubility in water for many drugs can be readily determined from standard pharmaceutical reference books, for example The Merck Index, 11th ed., 1989 (published by Merck & Co., Inc., Rahway, NJ); the United States Pharmacopoeia, 24th ed. (USP 24), 2000; The Extra Pharmacopoeia, 29th ed., 1989 (published by Pharmaceutical Press, London); and the Physicians Desk Reference (PDR), 2001 ed. (published by Medical Economics Co., Montvale, NJ), each of which is individually incorporated herein by reference.

[0039] For example, individual drugs of low solubility as defined herein include those drugs categorized as "slightly soluble", "very slightly soluble", "practically insoluble" and "insoluble" in USP 24, pp. 2254-2298; and those drugs categorized as requiring 100 ml or more of water to dissolve 1 g of the drug, as listed in USP 24, pp. 2299-2304.

[0040] Illustratively, suitable drugs of low water solubility include, without limitation, drugs from the following classes: abortifacients, ACE inhibitors, α- and β-adrenergic agonists, α- and β-adrenergic blockers, adrenocortical

suppressants, adrenocorticotropic hormones, alcohol deterrents, aldose reductase inhibitors, aldosterone antagonists, anabolics, analgesics (including narcotic and non-narcotic analgesics), androgens, angiotensin II receptor antagonists, anorexics, antacids, anthelminthics, antiacne agents, antiallergics, antialopecia agents, antiamebics, antiandrogens, antianginal agents, antiarrhythmics, antiarteriosclerotics, antiarthritic/antirheumatic agents (including selective COX-2 inhibitors), antiasthmatics, antibacterials, antibacterial adjuncts, anticholinergics, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antidiarrheal agents, antidiuretics, antidotes to poison, antidyskinetics, antieczematics, antiemetics, antiestrogens, antifibrotics, antiflatulents, antifungals, antiglaucoma agents, antigonadotropins, antigout agents, antihistaminics, antihyperactives, antihyperlipoproteinemics, antihyperphosphatemics, antihypertensives, antihyperthyroid agents, antihypotensives, antihypothyroid agents, anti-inflammatories, antimalarials, antimanics, antimethemoglobinemics, antimigraine agents, antimuscarinics, antimycobacterials, antineoplastic agents and adjuncts, antineutropenics, antiosteoporotics, antipagetics, antiparkinsonian agents, antipheochromocytoma agents, antipneumocystis agents, antiprostatic hypertrophy agents, antiprotozoals, antipruritics, antipsoriatics, antipsychotics, antipyretics, antirickettsials, antiseborrheics, antiseptics/disinfectants, antispasmodics, antisyphylitics, antithrombocythemics, antithrombotics, antitussives, antiulcératives, antiurolithics, antivenins, antiviral agents, anxiolytics, aromatase inhibitors, astringents, benzodiazepine antagonists, bone resorption inhibitors, bradycardic agents, bradykinin antagonists, bronchodilators, calcium channel blockers, calcium regulators, carbonic anhydrase inhibitors, cardiotonics, CCK antagonists, chelating agents, cholelitholytic agents, choleretics, cholinergics, cholinesterase inhibitors, cholinesterase reactivators, CNS stimulants, contraceptives, debriding agents, decongestants, depigmentors, dermatitis herpetiformis suppressants, digestive aids, diuretics, dopamine receptor agonists, dopamine receptor antagonists, ectoparasiticides, emetics, enkephalinase inhibitors, enzymes, enzyme cofactors, estrogens, expectorants, fibrinogen receptor antagonists, fluoride supplements, gastric and pancreatic secretion stimulants, gastric cytoprotectants, gastric proton pump inhibitors, gastric secretion inhibitors, gastroprokinetics, glucocorticoids, α-glucosidase inhibitors, gonad-stimulating principles, growth hormone inhibitors,

growth hormone releasing factors, growth stimulants, hemstinics, hematopoietics, hemolytics, hemostatics, heparin antagonists, hepatic enzyme inducers, hepatoprotectants, histamine H_2 receptor antagonists, HIV protease inhibitors, HMG CoA reductase inhibitors, immunomodulators, immunosuppressants, insulin sensitizers, ion exchange resins, keratolytics, lactation stimulating hormones, laxatives/cathartics, leukotriene antagonists, LH-RH agonists, lipotropics, 5-lipoxygenase inhibitors, lupus erythematosus suppressants, matrix metalloproteinase inhibitors, mineralocorticoids, miotics, monoamine oxidase inhibitors, mucolytics, muscle relaxants, mydriatics, narcotic antagonists, neuroprotectives, nootropics, ovarian hormones, oxytocics, pepsin inhibitors, pigmentation agents, plasma volume expanders, potassium channel activators/openers, progestogens, prolactin inhibitors, prostaglandins, protease inhibitors, radio-pharmaceuticals, 5α-reductase inhibitors, respiratory stimulants, reverse transcriptase inhibitors, sedatives/hypnotics, serenics, serotonin noradrenaline reuptake inhibitors, serotonin receptor agonists, serotonin receptor antagonists, serotonin uptake inhibitors, somatostatin analogs, thrombolytics, thromboxane A_2 receptor antagonists, thyroid hormones, thyrotropic hormones, tocolytics, topoisomerase I and II inhibitors, uricosurics, vasomodulators including vasodilators and vasoconstrictors, vasoprotectants, xanthine oxidase inhibitors, and combinations thereof.

[0041] Non-limiting illustrative examples of suitable drugs of low water solubility include acetohexamide, acetylsalicylic acid, alclofenac, allopurinol, atropine, benzthiazide, carprofen, celecoxib, chlordiazepoxide, chlorpromazine, clonidine, codeine, codeine phosphate, codeine sulfate, deracoxib, diacerein, diclofenac, diltiazem, estradiol, etodolac, etoposide, etoricoxib, fenbufen, fenclofenac, fenprofen, fentiazac, flurbiprofen, griseofulvin, haloperidol, ibuprofen, indomethacin, indoprofen, ketoprofen, lorazepam, medroxyprogesterone acetate, megestrol, methoxsalen, methylprednisone, morphine, morphine sulfate, naproxen, nicergoline, nifedipine, niflumic, oxaprozin, oxazepam, oxyphenbutazone, paclitaxel, phenindione, phenobarbital, piroxicam, pirprofen, prednisolone, prednisone, procaine, progesterone, pyrimethamine, rofecoxib, sulfadiazine, sulfamerazine, sulfisoxazole, sulindac, suprofen, temazepam, tiaprofenic acid, tilomisole, tolmetic, valdecoxib, *etc.*

[0042] The amount of drug incorporated in a dosage form of the

invention can be selected according to known principles of pharmacy. A therapeutically effective amount of drug is specifically contemplated. The term "therapeutically and/or prophylactically effective amount" as used herein refers to an amount of drug that is sufficient to elicit the required or desired therapeutic and/or prophylactic response. Preferably, the therapeutic agent is present in the suspension at a concentration of at least about 0.01%, at least about 0.1%, at least about 1% or at least about 10% up to a concentration of, preferably, no more than about 90%, no more than about 75%, no more than about 50% or no more than about 35% on a weight/weight basis. Unless otherwise indicated, all percentage values given herein are intended to be calculated on a weight/weight basis.

[0043] In a particularly preferred embodiment, the drug is a selective COX-2 inhibitory drug of low water solubility. Any such selective COX-2 inhibitory drug known in the art can be used, including without limitation compounds disclosed in the patents and publications listed below.

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

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

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

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

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

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

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

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

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

Above-cited U.S. Patent No. 5,474,995.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

U.S. Patent No. 5,616,458 to Lipsky *et al.*

U.S. Patent No. 5,616,601 to Khanna *et al.*

U.S. Patent No. 5,620,999 to Weier *et al.*

Above-cited U.S. Patent No. 5,633,272.

U.S. Patent No. 5,639,780 to Lau *et al.*

U.S. Patent No. 5,643,933 to Talley *et al.*

U.S. Patent No. 5,658,903 to Adams *et al.*

U.S. Patent No. 5,668,161 to Talley *et al.*

U.S. Patent No. 5,670,510 to Huang & Reitz.

U.S. Patent No. 5,677,318 to Lau.

U.S. Patent No. 5,681,842 to Dellaria & Gane.

U.S. Patent No. 5,686,460 to Nicolaï *et al.*

U.S. Patent No. 5,686,470 to Weier *et al.*

U.S. Patent No. 5,696,143 to Talley *et al.*

U.S. Patent No. 5,710,140 to Ducharme *et al.*

U.S. Patent No. 5,716,955 to Adams *et al.*

U.S. Patent No. 5,723,485 to Gingör & Teulon.

U.S. Patent No. 5,739,166 to Reitz *et al.*

U.S. Patent No. 5,741,798 to Lazer *et al.*

U.S. Patent No. 5,756,499 to Adams *et al.*

U.S. Patent No. 5,756,529 to Isakson & Talley.

U.S. Patent No. 5,776,967 to Kreft *et al.*

U.S. Patent No. 5,783,597 to Beers & Wachter.

U.S. Patent No. 5,789,413 to Black *et al.*

U.S. Patent No. 5,807,873 to Nicolaï & Teulon.

U.S. Patent No. 5,817,700 to Dube *et al.*

U.S. Patent No. 5,830,911 to Failli *et al.*

U.S. Patent No. 5,849,943 to Atkinson & Wang.

U.S. Patent No. 5,859,036 to Sartori *et al.*

Above-cited U.S. Patent No. 5,861,419.

U.S. Patent No. 5,866,596 to Sartori & Teulon.

U.S. Patent No. 5,869,524 to Failli.

U.S. Patent No. 5,869,660 to Adams *et al.*

U.S. Patent No. 5,883,267 to Rossen *et al.*

U.S. Patent No. 5,892,053 to Zhi *et al.*

U.S. Patent No. 5,922,742 to Black *et al.*

U.S. Patent No. 5,929,076 to Adams & Garigipati.

U.S. Patent No. 5,932,598 to Talley *et al.*

U.S. Patent No. 5,935,990 to Khanna *et al.*

U.S. Patent No. 5,945,539 to Haruta *et al.*

U.S. Patent No. 5,958,978 to Yamazaki *et al.*

U.S. Patent No. 5,968,958 to Guay *et al.*

U.S. Patent No. 5,972,950 to Nicolaï & Teulon.

U.S. Patent No. 5,973,191 to Marnett & Kalgutkar.

Above-cited U.S. Patent No. 5,981,576.

U.S. Patent No. 5,994,381 to Haruta *et al.*

U.S. Patent No. 6,002,014 to Haruta *et al.*

U.S. Patent No. 6,004,960 to Li *et al.*

U.S. Patent No. 6,005,000 to Hopper *et al.*

U.S. Patent No. 6,020,343 to Belley *et al.*

U.S. Patent No. 6,020,347 to DeLaszlo & Hagmann.

Above-cited U.S. Patent No. 6,034,256.

U.S. Patent No. 6,040,319 to Corley *et al.*

U.S. Patent No. 6,040,450 to Davies *et al.*

U.S. Patent No. 6,046,208 to Adams *et al.*

U.S. Patent No. 6,046,217 to Friesen *et al.*

U.S. Patent No. 6,057,319 to Black *et al.*

U.S. Patent No. 6,063,804 to De Nanteuil *et al.*

U.S. Patent No. 6,063,807 to Chabrier de Lassauniere & Broquet.

U.S. Patent No. 6,071,954 to LeBlanc *et al.*

U.S. Patent No. 6,077,868 to Cook *et al.*

U.S. Patent No. 6,077,869 to Sui & Wachter.

U.S. Patent No. 6,083,969 to Ferro *et al.*

U.S. Patent No. 6,096,753 to Spohr *et al.*

U.S. Patent No. 6,133,292 to Wang *et al.*

International Patent Publication No. WO 94/15932.

International Patent Publication No. WO 96/19469.

International Patent Publication No. WO 96/26921.

International Patent Publication No. WO 96/31509.

International Patent Publication No. WO 96/36623.

International Patent Publication No. WO 96/38418.

International Patent Publication No. WO 97/03953.

International Patent Publication No. WO 97/10840.

International Patent Publication No. WO 97/13755.

International Patent Publication No. WO 97/13767.

International Patent Publication No. WO 97/25048.

International Patent Publication No. WO 97/30030.

International Patent Publication No. WO 97/34882.

International Patent Publication No. WO 97/46524.

International Patent Publication No. WO 98/04527.

International Patent Publication No. WO 98/06708.

International Patent Publication No. WO 98/07425.

International Patent Publication No. WO 98/17292.

International Patent Publication No. WO 98/21195.

International Patent Publication No. WO 98/22457.

International Patent Publication No. WO 98/32732.

International Patent Publication No. WO 98/41516.

International Patent Publication No. WO 98/43966.

International Patent Publication No. WO 98/45294.

International Patent Publication No. WO 98/47871.

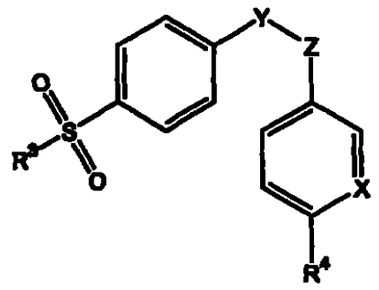
International Patent Publication No. WO 99/01130.
International Patent Publication No. WO 99/01131.
International Patent Publication No. WO 99/01452.
International Patent Publication No. WO 99/01455.
International Patent Publication No. WO 99/10331.
International Patent Publication No. WO 99/10332.
International Patent Publication No. WO 99/11605.
International Patent Publication No. WO 99/12930.
International Patent Publication No. WO 99/14195.
International Patent Publication No. WO 99/14205.
International Patent Publication No. WO 99/15505.
International Patent Publication No. WO 99/23087.
International Patent Publication No. WO 99/24404.
International Patent Publication No. WO 99/25695.
International Patent Publication No. WO 99/35130.
International Patent Publication No. WO 99/61016.
International Patent Publication No. WO 99/61436.
International Patent Publication No. WO 99/62884.
International Patent Publication No. WO 99/64415.
International Patent Publication No. WO 00/01380.
International Patent Publication No. WO 00/08024.
International Patent Publication No. WO 00/10993.
International Patent Publication No. WO 00/13684.
International Patent Publication No. WO 00/18741.
International Patent Publication No. WO 00/18753.
International Patent Publication No. WO 00/23426.
Above-cited International Patent Publication No. WO 00/24719.
International Patent Publication No. WO 00/26216.
International Patent Publication No. WO 00/31072.
International Patent Publication No. WO 00/40087.
International Patent Publication No. WO 00/56348.
European Patent Application No. 0 799 823.

European Patent Application No. 0 846 689.

Above-cited European Patent Application No. 0 863 134.

European Patent Application No. 0 985 666.

[0044] Compositions of the invention are especially useful for compounds having the formula (VII):



(VII)

[0045]

where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups. Preferred such five- to six-membered rings are cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

[0046] Illustratively, celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methyl-1-butoxy)-5-[4-(methylsulfonyl)phenyl]-3-(2H)-pyridazinone, more particularly celecoxib, valdecoxib, rofecoxib and etoricoxib, and still more particularly celecoxib and valdecoxib, are useful in compositions of the invention.

[0047] The invention is illustrated herein with particular reference to celecoxib, and it will be understood that any other drug of low solubility in water can, if desired, be substituted in whole or in part for celecoxib in compositions herein described.

[0048] Where the drug is celecoxib, the composition typically comprises celecoxib in a therapeutically and/or prophylactically effective total amount

of about 2 mg to about 1000 mg per dose unit. Where the drug is a selective COX-2 inhibitory drug other than celecoxib, the amount of the drug per dose unit is therapeutically equivalent to about 2 mg to about 1000 mg of celecoxib.

[0049] It will be understood that a therapeutically and/or prophylactically effective amount of a drug for a subject is dependent *inter alia* on the body weight of the subject. A "subject" herein to which a therapeutic agent or composition thereof can be administered includes a human subject or patient of either sex and of any age, and also includes any nonhuman animal, particularly a domestic or companion animal, illustratively a cat, dog or horse.

[0050] Where the subject is an infant, child or a small animal (*e.g.*, a dog), for example, an amount of celecoxib relatively low in the preferred range of about 2 mg to about 1000 mg is likely to be consistent with therapeutic effectiveness. Where the subject is an adult human or a large animal (*e.g.*, a horse), therapeutic effectiveness is likely to require dose units containing a relatively greater amount of celecoxib. For an adult human, a therapeutically effective amount of celecoxib per dose unit in a composition of the present invention is typically about 50 mg to about 400 mg. Especially preferred amounts of celecoxib per dose unit are about 100 mg to about 200 mg.

[0051] For other selective COX-2 inhibitory drugs, an amount of the drug per dose unit can be in a range known to be therapeutically effective for such drugs. Preferably, the amount per dose unit is in a range providing therapeutic equivalence to celecoxib in the dose ranges indicated immediately above.

[0052] A celecoxib suspension composition of the present invention preferably comprises about 0.01 to about 15%, more preferably about 0.01 to about 10%, and yet more preferably about 0.01 to about 5% by total weight, of celecoxib. Generally, these concentrations will correspond to celecoxib in an amount of about 1% to about 90%, more preferably about 1% to about 75%, more preferably about 1% to about 50%, and still more preferably about 1% to about 35%, by weight of all dry, non-liquid components.

[0053] Where the selective COX-2 inhibitory drug is other than celecoxib and is therapeutically effective at lower dosages than celecoxib, the minimum amount of COX-2 inhibitory drug in suspension can be lower than that

indicated immediately above for celecoxib; for example, in the case of valdecoxib, the drug can be present in an amount of about 0.1% by total weight.

[0054] Preferably about 50% to 100%, more preferably about 75% to 100%, still more preferably about 85% to 100%, and yet more preferably substantially all of the celecoxib present in compositions of the invention is suspended in particulate form. It is also preferred in compositions of the invention that less than about 25%, more preferably less than about 10%, yet more preferably less than about 5%, and still more preferably substantially no portion, of the celecoxib is in dissolved and/or solubilized form.

[0055] Particulate celecoxib present in suspension compositions of the invention preferably has a D_{90} particle size of about 0.5 μm to about 50 μm, more preferably about 0.5 μm to about 40 μm, and still more preferably 0.5 μm to about 30 μm. D_{90} is defined herein as a linear measure of diameter having a value such that 90% by weight of particles in the formulation, in the longest dimension of the particles, are smaller than that diameter.

Wetting agent

[0056] One or more wetting agents are present in suspension compositions of the invention. The one or more wetting agent is believed to facilitate suspension of drug particles of low water solubility, but may have other functions.

[0057] Surfactants, hydrophilic polymers and certain clays can be useful as wetting agents to aid in suspension of a hydrophobic drug such as celecoxib. Surfactants, including nonionic, anionic, cationic and zwitterionic surfactants, are preferred wetting agents in suspension compositions of the invention. Non-limiting examples of surfactants that can be used as wetting agents in compositions of the invention include quaternary ammonium compounds, for example benzalkonium chloride, benzethonium chloride and cetylpyridinium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, for example nonoxynol 9, nonoxynol 10, and octoxynol 9, poloxamers (polyoxyethylene and polyoxypropylene block copolymers), polyoxyethylene fatty acid glycerides and oils, for example polyoxyethylene (8) caprylic/capric mono- and diglycerides (*e.g.*, Labrasol™ of Gattefossé), polyoxyethylene (35) castor oil and polyoxyethylene (40) hydrogenated castor oil; polyoxyethylene alkyl ethers, for example polyoxyethylene (20) cetostearyl

ether, polyoxyethylene fatty acid esters, for example polyoxyethylene (40) stearate, polyoxyethylene sorbitan esters, for example polysorbate 20 and polysorbate 80 (*e.g.*, Tween™ 80 of ICI), propylene glycol fatty acid esters, for example propylene glycol laurate (*e.g.*, Lauroglycol™ of Gattefossé), sodium lauryl sulfate, fatty acids and salts thereof, for example oleic acid, sodium oleate and triethanolamine oleate, glyceryl fatty acid esters, for example glyceryl monostearate, sorbitan esters, for example sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate and sorbitan monostearate, tyloxapol, and mixtures thereof. A preferred class of wetting agents is polyoxyethylene sorbitan esters.

[0058] Benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, dioctyl sodium sulfosuccinate, nonoxynol 9, nonoxynol 10, octoxynol 9, polyoxyethylene (8) caprylic/capric mono- and diglycerides, polyoxyethylene (35) castor oil, polyoxyethylene (20) cetostearyl ether, polyoxyethylene (40) hydrogenated castor oil, polyoxyethylene (10) oleyl ether, polyoxyethylene (40) stearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, propylene glycol laurate, sodium lauryl sulfate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate and tyloxapol are preferred wetting agents. Polysorbate 80 is a particularly preferred wetting agent.

[0059] Too much or inappropriate selection of wetting agent, for example surfactants, can be undesirable for several reasons. High free surfactant concentration can result in flocculated drug particles which sediment more rapidly than do deflocculated drug particles. High free surfactant concentration can also lead to dissolved and/or solubilized drug which, by comparison with the same drug in particulate form, can be more susceptible to chemical degradation and can produce an unpleasant taste. Therefore, in a particularly preferred embodiment, one or more wetting agents are present in a total amount sufficient to facilitate drug particle suspension, but in a substantially non-drug-solubilizing and non-drug-dissolving amount.

[0060] In another preferred embodiment, one or more wetting agents are present in total and relative amounts sufficient to suspend in particulate form at least about 75%, more preferably at least about 85%, and still more preferably substantially all of the drug, but in total and relative amounts less than will result in

about 25% or more, preferably in about 10% or more, and more preferably in substantially any portion, of solubilized and/or dissolved drug being present in the composition.

[0061] Too much surfactant can also lead to retention of entrapped air within a suspension composition of the invention. Generally, when a suspension is homogenized during preparation, air is entrained therein. Without being bound by theory, surfactants and other wetting agents are believed to stabilize air bubbles at least in part by decreasing surface tension at the bubble surface. Thus, by comparison with a suspension comprising relatively high amounts of free surfactant, a suspension having decreased free surfactant concentration is believed to exhibit less stable entrained air bubbles and, subsequently, to exhibit improved dose/volume uniformity.

[0062] Generally, one or more wetting agent(s) constitute, in total, about 0.01% to about 2%, preferably about 0.1% to about 1.5%, and more preferably about 0.25% to about 0.75%, of the total weight of the composition.

Thixotropic thickening agent

[0063] Compositions of the invention comprise one or more thixotropic thickening agents. Suitable thixotropic thickening agents are natural or synthetic polymers which, when added to aqueous medium, impart thixotropic characteristics thereto. Preferred thixotropic thickening agents are cellulosic polymers such as methylcellulose, microcrystalline cellulose (*e.g.* *Avicel* of FMC Corp.), polyvinylpyrrolidone, hydroxypropyl methycellulose, *etc.* More preferably, thixotropic thickening agents in compositions of the invention are polysaccharide gums. Suitable polysaccharide gums include, by way of non-limiting illustration, xanthan, guar, acacia, and tragacanth gums.

[0064] Thixotropic thickening agents are preferably present in compositions of the invention in a total amount of about 0.25% to about 2%, preferably about 0.3% to about 2%, and more preferably about 0.4% to about 2%, on a weight/weight basis. While the term polysaccharide gum is sometimes used herein to refer to a thixotropic thickening agent, such agents are not limited to polysaccharide gums.

Inorganic suspending agent

[0065] Any pharmaceutically acceptable inorganic suspending agent can be used in compositions of the invention. Non-limiting illustrative examples of suitable inorganic suspending agents include silicon dioxide, bentonite, hydrated aluminum silicate (*e.g.* kaolin) and mixtures thereof. Silicon dioxide is a particularly preferred inorganic suspending agent. Although the term colloidal silicon dioxide is sometimes used herein to refer to an inorganic suspending agent, inorganic suspending agents are not limited to colloidal silicon dioxide.

[0066] While colloidal silicon dioxide at relatively high concentrations (*e.g* about 5 to about 15%) is known to impart thixotropic characteristics in certain gel and semi-solid preparations, we have unexpectedly discovered that a small amount of colloidal silicon dioxide (*e.g.* about 2% or less) has a synergistic effect with polysaccharide gum, enhancing thixotropic characteristics of compositions of the invention. Specifically, the presence of both colloidal silicon dioxide and a polysaccharide gum in compositions of the invention enhances thixotropic characteristics more than was expected from addition of the individual thixotropy-enhancing effects of the two respective components.

[0067] Surprisingly, we have also discovered that addition of a small amount of colloidal silicon dioxide to suspension compositions of the invention leads to improved chemical stability of drug present therein. Without being held to a particular theory, it is presently believed that colloidal silicon dioxide in compositions of the invention adsorbs wetting agent resulting in lower free wetting agent concentration compared to an otherwise similar composition having no colloidal silicon dioxide; in turn, the lower free wetting agent concentration is believed to result in reduced free drug concentration and subsequently, an increased proportion of drug present in particulate form which is less susceptible to chemical degradation than is free drug.

[0068] Colloidal silicon dioxide in compositions of the invention also provides the surprising advantage of reduced retention of entrapped air and subsequently, improved dose uniformity. As is described above, free wetting agent can stabilize air bubbles entrapped within a suspension. Without being bound by theory, adsorption of free wetting agent by colloidal silicon dioxide present in

compositions of the invention is believed to result in reduced free wetting agent concentration and, subsequently, more unstable entrapped air bubbles.

[0069] Any pharmaceutically acceptable source of colloidal silicon dioxide can be used in compositions of the invention. Non-limiting synonyms for, and examples of, suitable colloidal silicon dioxides include *Aerosil*™ of Degussa, *Cab-O-Sil*™ of Cabot Corp., fumed silica, light anhydrous silicic acid, silicic anhydride, silicon dioxide fumed, colloidal silica, *etc.*

[0070] In a presently preferred embodiment, the colloidal silicon dioxide has a specific surface area of about 50 to about 400, more preferably about 100 to about 400, and still more preferably about 150 to about 400 m^2/g. Preferred colloidal silicon dioxides also have a weight average particle diameter of about 7 to about 40 nm, and more preferably about 10 to about 25 nm. *Cab-O-Sil*™ is a particularly preferred colloidal silicon dioxide for use in compositions of the invention.

[0071] One or more inorganic suspending agents are generally present in compositions of the invention in a total amount of about 0.01% to about 3.0%, preferably about 0.1% to about 2.0%, and more preferably about 0.25% to about 1.0%, by weight.

Thixotropic features

[0072] A beneficial feature of compositions of the invention is that at steady state they are substantially physically stable yet upon mild agitation they are readily pourable. The term "readily pourable" herein means that the composition will be easily poured from a suitable container such as a jar or bottle. The relatively high yield value of compositions of the invention promotes physical stability. "Yield value" herein (also referred to herein as maximum viscosity) is a measure of a suspension's initial resistance to flow under stress.

[0073] Total and relative amounts of wetting agent, inorganic suspending agent, and thixotropic thickening agent can be readily optimized within the ranges herein provided by one skilled in the art in order to provide suitable rheologic characteristics, deflocculation of drug particles, and minimal free drug concentration. Such optimization will take into account other relevant factors such as

the particular drug, drug particle size, uniformity and density, drug concentration, additional excipients present, desired shelf life, *etc.*

[0074] For practical purposes, whether a particular composition is thixotropic herein can be determined according to Test I.

Test I:

[0075] After standing at rest for at least 60 minutes, a 1 ml sample is drawn from a test suspension and is placed into a P45 Cup of a HAAKE CV100 viscometer (equipped with a PK30-4 spindle) which is maintained at 25 °C throughout the test.

[0076] A sheer stress is applied to the sample and is incrementally increased from 0 to 3 sec^{-1} over a period of 3 minutes and then incrementally decreased from 3 to 0 sec^{-1} over another period of 3 minutes. Dynamic viscosity is measured at a sheer rate of 2 sec^{-1} where a steady state is obtained. Yield value is calculated using linear regression of the data from 2 sec^{-1} to 3 sec^{-1}.

[0077] If, during the test, the sample has a maximum viscosity of about 5 to about 50 Pa•s and a dynamic viscosity, measured at 2 sec^{-1}, of about 0.3 to about 20 Pa•s, the composition is deemed thixotropic.

[0078] Preferably, the thixotropic thickening agent and inorganic suspending agent are present in total and relative amounts such that, when a composition of the invention is analyzed according to Test I, the composition has a maximum viscosity of about 5 to about 40, more preferably about 5 to about 30, and still more preferably about 5 to about 25 Pa•s and, at a shear rate of 2 sec^{-1}, the composition has a dynamic viscosity of about 0.3 to about 20, preferably about 0.4 to about 15, and yet more preferably about 0.5 to about 7 Pa•s.

[0079] Generally, the thixotropic thickening agent and inorganic suspending agent will be present in a weight ratio of about 10:1 to about 1:10, preferably about 5:1 to about 1:5, and more preferably about 2:1 to about 1:2.

[0080] Importantly, because compositions of the invention are substantially deflocculated and substantially physically stable, shaking or agitation is not required in order to re-disperse drug particles or to mix the suspension prior to administration. Moderate shaking will facilitate pourability of suspension compositions of the invention.

Pharmaceutical excipients

[0081] Compositions of the invention can comprise any additional pharmaceutically acceptable excipients. The term "excipient" herein means any substance, not itself a therapeutic agent, used as a carrier or vehicle for delivery of a therapeutic agent to a subject or added to a pharmaceutical composition to improve its handling, storage, disintegration, dispersion, dissolution, release or organoleptic properties or to permit or facilitate formation of a dose unit of the composition into a discrete article such as a capsule suitable for oral administration. Excipients can include, by way of illustration and not limitation, diluents, polymers, substances added to mask or counteract a disagreeable taste or odor, flavors, dyes, preservatives, fragrances, and substances added to improve appearance of the composition.

[0082] Compositions of the invention can be prepared by any suitable process, not limited to processes described herein. One illustrative process comprises admixing celecoxib, one or more wetting agents, a polysaccharide gum, and silicon dioxide together with any other desired excipients to form a powder blend, and homogenizing the powder blend together with water for form a suspension.

Utility of compositions of the invention

[0083] Where compositions of the invention comprise a COX-2 inhibitory drug of low water solubility, they are useful in treatment and prevention of a very wide range of disorders mediated by COX-2, including but not restricted to disorders characterized by inflammation, pain and/or fever. Such compositions are especially useful as anti-inflammatory agents, such as in treatment of arthritis, with the additional benefit of having significantly less harmful side effects than compositions of conventional nonsteroidal anti-inflammatory drugs (NSAIDs) that lack selectivity for COX-2 over COX-1. In particular, compositions of the invention have reduced potential for gastrointestinal toxicity and gastrointestinal irritation including upper gastrointestinal ulceration and bleeding, reduced potential for renal side effects such as reduction in renal function leading to fluid retention and exacerbation of hypertension, reduced effect on bleeding times including inhibition of platelet function, and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects, by comparison with compositions of conventional NSAIDs. Thus compositions of the invention are particularly useful as an alternative

to conventional NSAIDs where such NSAIDs are contraindicated, for example in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; gastrointestinal bleeding, coagulation disorders including anemia such as hypoprothrombinemia, hemophilia or other bleeding problems; kidney disease; or in patients prior to surgery or patients taking anticoagulants.

[0084] Contemplated compositions are useful to treat a variety of arthritic disorders, including but not limited to rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis.

[0085] Such compositions are useful in treatment of asthma, bronchitis, menstrual cramps, preterm labor, tendinitis, bursitis, allergic neuritis, cytomegalovirus infectivity, apoptosis including HIV-induced apoptosis, lumbago, liver disease including hepatitis, skin-related conditions such as psoriasis, eczema, acne, burns, dermatitis and ultraviolet radiation damage including sunburn, and post-operative inflammation including that following ophthalmic surgery such as cataract surgery or refractive surgery.

[0086] Such compositions are useful to treat gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis.

[0087] 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.

[0088] Such compositions are useful in treatment of ophthalmic diseases, such as retinitis, conjunctivitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue.

[0089] 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.

[0090] 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.

[0091] Such compositions are useful in treatment of allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome and liver disease.

[0092] 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.

[0093] Such compositions are useful for treating and preventing inflammation-related cardiovascular disorders, including vascular diseases, coronary artery disease, aneurysm, vascular rejection, arteriosclerosis, atherosclerosis including cardiac transplant atherosclerosis, myocardial infarction, embolism, stroke, thrombosis including venous thrombosis, angina including unstable angina, coronary plaque inflammation, bacterial-induced inflammation including Chlamydia-induced inflammation, viral induced inflammation, and inflammation associated with surgical procedures such as vascular grafting including coronary artery bypass surgery, revascularization procedures including angioplasty, stent placement, endarterectomy, or other invasive procedures involving arteries, veins and capillaries.

[0094] Such compositions are useful in treatment of angiogenesis-related disorders in a subject, for example to inhibit tumor angiogenesis.

Such compositions are useful in treatment of neoplasia, including metastasis; ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, macular degeneration, retrolental fibroplasia and neovascular glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemaginomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis.

[0095] Such compositions are useful in prevention and treatment of benign and malignant tumors and neoplasia including cancer, such as colorectal cancer, brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer, skin cancer such as squamous cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that effect epithelial cells throughout the body. Neoplasias for which compositions of the invention are contemplated to be particularly useful are gastrointestinal cancer, Barrett's esophagus, liver cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, cervical cancer, lung cancer, breast cancer and skin cancer. Such compositions can also be used to treat fibrosis that occurs with radiation therapy. Such compositions can be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, such compositions can be used to prevent polyps from forming in patients at risk of FAP.

[0096] Such compositions inhibit prostanoid-induced smooth muscle contraction by inhibiting synthesis of contractile prostanoids and hence can be of use in treatment of dysmenorrhea, premature labor, asthma and eosinophil-related disorders. They also can be of use for decreasing bone loss particularly in postmenopausal women (*i.e.*, treatment of osteoporosis), and for treatment of glaucoma.

[0097] Preferred uses for compositions of the invention are for treatment of rheumatoid arthritis and osteoarthritis, for pain management generally

(particularly post-oral surgery pain, post-general surgery pain, post-orthopedic surgery pain, and acute flares of osteoarthritis), for treatment of Alzheimer's disease, and for colon cancer chemoprevention.

[0098] For treatment of rheumatoid arthritis or osteoarthritis, compositions of the invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, still more preferably about 175 mg to about 400 mg, for example about 200 mg. A daily dose of celecoxib of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 8 mg/kg body weight, more preferably about 2 to about 6.7 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for example about 2.7 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to about four doses per day, preferably one or two doses per day.

[0099] For treatment of Alzheimer's disease or cancer, compositions of the invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 800 mg, more preferably about 150 mg to about 600 mg, and still more preferably about 175 mg to about 400 mg, for example about 400 mg. A daily dose of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 10.7 mg/kg body weight, more preferably about 2 to about 8 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for example about 5.3 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to about four doses per day, preferably one or two doses per day.

[00100] For pain management, compositions of the invention can be used to provide a daily dosage of celecoxib of about 50 mg to about 1000 mg, preferably about 100 mg to about 600 mg, more preferably about 150 mg to about 500 mg, and still more preferably about 175 mg to about 400 mg, for example about 200 mg. A daily dose of celecoxib of about 0.7 to about 13 mg/kg body weight, preferably about 1.3 to about 8 mg/kg body weight, more preferably about 2 to about 6.7 mg/kg body weight, and still more preferably about 2.3 to about 5.3 mg/kg body weight, for example about 2.7 mg/kg body weight, is generally appropriate when administered in a composition of the invention. The daily dose can be administered in one to about

four doses per day. Administration at a rate of one 50 mg dose unit four times a day, one 100 mg dose unit or two 50 mg dose units twice a day or one 200 mg dose unit, two 100 mg dose units or four 50 mg dose units once a day is preferred.

[00101] For selective COX-2 inhibitory drugs other than celecoxib, appropriate doses can be selected by reference to the patent literature cited hereinabove.

[00102] Besides being useful for human treatment, compositions of the invention are useful for veterinary treatment of companion animals, exotic animals, farm animals, and the like, particularly mammals. More particularly, compositions of the invention are useful for treatment of COX-2 mediated disorders in horses, dogs and cats.

[00103] The present invention is further directed to a therapeutic method of treating a condition or disorder where treatment with a COX-2 inhibitory drug is indicated, the method comprising oral administration of a composition of the invention to a subject in need thereof. The dosage regimen to prevent, give relief from, or ameliorate the condition or disorder preferably corresponds to once-a-day or twice-a-day treatment, but can be modified in accordance with a variety of factors. These include the type, age, weight, sex, diet and medical condition of the subject and the nature and severity of the disorder. Thus, the dosage regimen actually employed can vary widely and can therefore deviate from the preferred dosage regimens set forth above.

[00104] Initial treatment can begin with a dose regimen as indicated above. Treatment is generally continued as necessary over a period of several weeks to several months or years until the condition or disorder has been controlled or eliminated. Subjects undergoing treatment with a composition of the invention can be routinely monitored by any of the methods well known in the art to determine effectiveness of therapy. Continuous analysis of data from such monitoring permits modification of the treatment regimen during therapy so that optimally effective doses are administered at any point in time, and so that the duration of treatment can be determined. In this way, the treatment regimen and dosing schedule can be rationally modified over the course of therapy so that the lowest amount of the composition exhibiting satisfactory effectiveness is administered, and so that administration is

continued only for so long as is necessary to successfully treat the condition or disorder.

[00105] The present compositions can be used in combination therapies with opioids and other analgesics, including narcotic analgesics, Mu receptor antagonists, Kappa receptor antagonists, non-narcotic (i.e. non-addictive) analgesics, monoamine uptake inhibitors, adenosine regulating agents, cannabinoid derivatives, Substance P antagonists, neurokinin-1 receptor antagonists and sodium channel blockers, among others. Preferred combination therapies comprise use of a composition of the invention with one or more compounds selected from the group consisting of 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, 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").

[00106] Particularly preferred combination therapies comprise use of a composition of the invention with an opioid compound, more particularly where the opioid compound is codeine, meperidine, morphine or a derivative thereof.

[00107] The compound to be administered in combination with a selective COX-2 inhibitory drug can be formulated separately from the drug or co-formulated with the drug in a composition of the invention. Where a selective COX-2 inhibitory drug is co-formulated with a second drug, for example an opioid drug, the second drug can be formulated in immediate-release, rapid-onset, sustained-release or dual-release form.

EXAMPLES

[00108] The following Examples are provided for illustrative purposes only and are not to be interpreted as limiting the scope of the present invention. The Examples will permit better understanding of the invention and better perception of its advantages.

Example 1

[00109] Six celecoxib suspensions were prepared comprising components shown in Table 1. All components were admixed, and suspensions were homogenized for 5 minutes using a Silverson Laboratory Mixer Emulsifier.

Table 1. Composition (%) of Celecoxib Suspensions S1-S6.

Component	S1	S2	S3	S4	S5	S6
Celecoxib	2	2	2	2	2	2
Xanthan gum	0.5	-	0.5	0.5	0.5	-
Colloidal silica	-	0.5	0.5	1.0	2.0	1.0
Polysorbate 80	0.5	0.5	0.5	0.5	0.5	0.5
Sucrose	30	30	30	30	30	30
Citric acid	1.31	1.31	1.31	1.31	1.31	1.31
Sodium citrate	1.11	1.11	1.11	1.11	1.11	1.11
Tutti fruti	0.1	0.1	0.1	0.1	0.1	0.1
Sodium benzoate	0.2	0.2	0.2	0.2	0.2	0.2
FD&C red #40	0.1	0.1	0.1	0.1	0.1	0.1
Water	to 100	to 100	to 100	to 100	to 100	to 100

Example 2

[00110] Celecoxib Suspensions S1-S6 of Example 1 were maintained at room temperature for 24 hours before sampling. A 1.5 ml sample of each suspension was then drawn and individually centrifuged at 15,800 g for 60 minutes or at 43,000 g for 10 minutes. After centrifugation, 0.1 to 0.5 ml aliquots of supernatant were removed from each suspension with a pipette; each aliquot was individually diluted with methanol (from 1:2 to 2:10) to precipitate xanthan gum. The diluted samples were then centrifuged at 15,800 g for 15 minutes. Free drug concentration, shown in Table 2, was determined for Suspensions S1 and S3-S5 via high performance liquid chromatography (HPLC) analysis of the diluted supernatant.

Table 2. Free drug concentration (mg/ml) in Celecoxib Suspensions S1 and S3-S5.

Celecoxib Suspension	Free drug concentration
S1	0.311
S3	0.187
S4	0.009
S5	0.010

[00111] As shown in Table 2, Celecoxib Suspensions comprising colloidal silicon dioxide (S3-S5) had reduced free drug concentration compared to Celecoxib Suspension S1 which comprised no colloidal silicon dioxide. These data suggest that drug in Celecoxib Suspensions comprising colloidal silicon dioxide are less susceptible to chemical degradation than in those suspensions without colloidal silicon dioxide.

Example 3

[00112] To assess the effects of colloidal silicon dioxide on sedimentation and physical stability, 10 ml aliquots of Celecoxib Suspensions S1-S3 were individually centrifuged at three different rates. At several time points during centrifugation, the resulting sediment volumes were quantified (Figs. 1-3). As shown in Fig. 1, after 5, 15 and 30 minutes of centrifugation at 1500 rpm, Celecoxib Suspension S2 (comprising colloidal silicon dioxide but no xanthan gum) resulted in a sediment volume of 0.0375 ml, whereas no sediment was observed in vessels containing Celecoxib Suspensions S1 (xanthan gum but no colloidal silicon dioxide) and S3 (both xanthan gum and colloidal silicon dioxide).

[00113] As shown in Fig. 2, after centrifugation at 2500 rpm for 30, 60 and 90 minutes, Celecoxib Suspension S1 exhibited greater sediment volume than did Celecoxib Suspension S3. Moreover, as shown in Fig. 3, centrifugation of Celecoxib Suspensions S1 and S2 at 3,000 rpm for 5, 10 and 20 minutes resulted in greater sediment volume than did centrifugation of Celecoxib Suspension S3 under the same conditions.

[00114] These data indicate that presence of both xanthan gum and

colloidal silicon dioxide greatly increase anti-sedimentation properties of Celecoxib Suspensions compared to suspensions comprising either xanthan gum or colloidal silicon dioxide alone. This anti-sedimentation effect indicates an increase in physical stability of the Celecoxib suspension.

Example 4

[00115] Rheology of Celecoxib Suspensions S1-S4 and S6 was determined according to above-described Test I. Resulting dynamic viscosities, measured at 2 sec^{-1}, and yield values are shown in Table 3.

Table 3. Rheology of Celecoxib Suspensions S1-S4 and S6.

Celecoxib Suspension	Dynamic Viscosity (Pa•s) (at shear rate of 2 sec^{-1})	Yield Value (Pa)
S1	3.21	5.3
S2	0.08	0.14
S3	3.58	6.2
S4	5.49	8.5
S6	0.13	0.16

[00116] As shown in Table 3, presence of both xanthan gum and colloidal silicon dioxide (Celecoxib Suspensions S3 and S4) had a synergistic effect on yield value as compared to the Celecoxib Suspension comprising colloidal silicon dioxide but no xanthan gum (S2 and S6) and the Celecoxib Suspension comprising xanthan gum but no colloidal silicon dioxide (S1). This increase in yield value indicates the presence of relatively high flow resistance at low stresses, for example gravitational stresses involved in particle sedimentation. Despite high yield values exhibited by Celecoxib Suspensions S3 and S4, dynamic viscosities, measured at a shear rate of 2 sec^{-1}, were still relatively low indicating good fluidity of the suspensions after yield value was reached. These data indicate that Celecoxib Suspensions S3 and S4 are thick at rest but fluid after moderate agitation. This increased thickness at rest will result in increased physical stability.

Example 5

[00117] Five celecoxib suspensions, S7-S11, were prepared containing components shown in Table 4. All components were admixed, and suspensions were

homogenized for 5 minutes using a Silverson Laboratory Mixer Emulsifier.

Table 4. Composition (%) of Celecoxib Suspensions S7-S11.

Component	S7	S8	S9	S10	S11
Celecoxib	2	2	2	2	2
Xanthan gum	0.5	0.1	0.1	0.2	0.5
Colloidal silica	0.5	0.5	-	0.5	0.5
Polysorbate 80	0.25	0.25	0.25	0.25	0.25
Sucrose	38.25	30	30	30	30
Citric acid	1.31	1.31	1.31	1.31	1.31
Sodium citrate	1.11	1.11	1.11	1.11	1.11
Tutti fruti	0.05	0.1	0.1	0.1	0.1
Sodium benzoate	0.2	0.2	0.2	0.2	0.2
FD&C red #40	0.015	0.015	0.015	0.015	0.015
70% sorbitol solution	45	-	-	-	-
Water	to 100	to 100	to 100	to 100	to 100

Example 6

[00118] Rheology of Celecoxib Suspensions S7-S11 was determined according to above-described Test I. Dynamic viscosities, measured at 2 sec^{-1}, and yield values are shown in Table 5.

Table 5. Rheology of Celecoxib Suspensions S7-S11.

Celecoxib Suspension	Dynamic Viscosity (Pa•s) (at shear rate of 2 sec^{-1})	Yield Value (Pa)
S7	22.04	19
S8	0.612	0.75
S9	0.184	0.19
S10	0.855	1.2
S11	3.566	5.9

[00119] As shown in Table 5, the presence of a very low amount of xanthan gum (0.2% or less) in Celecoxib Suspensions S8, S9 and S10 was insufficient, even with silicon dioxide present (S8 and S10), to impart suitable physical stability and thixotropic characteristics on the suspensions. In contrast,

xanthan gum at 0.5% provided suitable rheologic characteristics for Celecoxib Suspension S11. Results for celecoxib Suspension S7 show suggest that high concentrations of sugar in compositions of the invention greatly increase both yield value and dynamic viscosity such that the suspension is not readily pourable even after mild agitation.

[00120] All references cited in this specification are hereby incorporated by reference. The discussion of the references herein is intended merely to summarize the assertions made by their authors and no admission is made that any reference constitutes prior art relevant to patentability. Applicants reserve the right to challenge the accuracy and pertinency of the cited references.

WHAT IS CLAIMED IS:

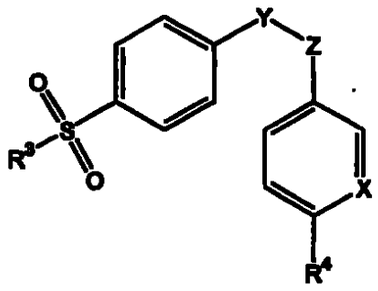
1. An orally deliverable pharmaceutical composition comprising a drug of low water solubility and an aqueous liquid vehicle that comprises (a) a pharmaceutically acceptable wetting agent, (b) a pharmaceutically acceptable thixotropic thickening agent, and (c) a pharmaceutically acceptable inorganic suspending agent.

2. The composition of Claim 1 wherein at least a substantial portion of the drug is suspended in particulate form in the vehicle to form a suspension and wherein the wetting agent, thickening agent and suspending agent are present in total and relative amounts such that the suspension is thixotropic, substantially deflocculated, and substantially physically stable.

3. The composition of Claim 1 wherein the drug is present in a therapeutically and/or prophylactically effective total amount.

4. The composition of Claim 1 wherein the drug is a selective cyclooxygenase-2 inhibitory drug of low water solubility.

5. The composition of Claim 4 wherein the selective cyclooxygenase-2 inhibitory drug is a compound of formula



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups.

6. The composition of Claim 5 wherein the five- to six-membered ring is selected from the group consisting of cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

7. The composition of Claim 4 wherein the selective cyclooxygenase-2 inhibitory drug is selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

8. The composition of Claim 4 wherein the selective cyclooxygenase-2 inhibitory drug is celecoxib.

9. The composition of Claim 1 wherein the drug is present in an amount of about 0.01% to about 15%, by total weight of the composition.

10. The composition of Claim 1 wherein the drug is present in an amount of about 0.01% to about 5%, by total weight of the composition.

11. The composition of Claim 1 wherein the wetting agent is selected from the group consisting of quaternary ammonium compounds, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, poloxamers, polyoxyethylene fatty acid glycerides and oils, polyoxyethylene alkyl ethers, polyoxyethylene fatty acid esters, polyoxyethylene sorbitan esters, propylene glycol fatty acid esters, sodium lauryl sulfate, fatty acids and salts thereof, glyceryl fatty acid esters, sorbitan esters, tyloxapol and mixtures thereof.

12. The composition of Claim 1 wherein the wetting agent is selected from the group consisting of benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, dioctyl sodium sulfosuccinate, nonoxynol 9, nonoxynol 10, octoxynol 9, polyoxyethylene 8 caprylic/capric mono- and diglycerides, polyoxyethylene 35 castor oil, polyoxyethylene 20 cetostearyl ether, polyoxyethylene 40 hydrogenated castor oil, polyoxyethylene 10 oleyl ether, polyoxyethylene 40 stearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, propylene glycol laurate, sodium lauryl sulfate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, tyloxapol and combinations thereof.

13. The composition of Claim 1 wherein the wetting agent is polysorbate 80.

14. The composition of Claim 1 wherein the wetting agent is present in an amount

of about 0.01% to about 2%, by weight.

15. The composition of Claim 1 wherein the wetting agent is present in an amount of about 0.25% to about 0.75%, by weight.

16. The composition of Claim 1 wherein the thixotropic thickening agent is a cellulosic polymer.

17. The composition of Claim 16 wherein the thixotropic thickening agent is selected the group consisting of from methylcellulose, microcrystalline cellulose, polyvinylpyrrolidone, and hydroxypropyl methycellulose.

18. The composition of Claim 1 wherein the thixotropic thickening agent is a polysaccharide gum.

19. The composition of Claim 18 wherein the polysaccharide gum is selected from the group consisting of xanthan, guar, acacia, and tragacanth gums.

20. The composition of Claim 18 wherein the polysaccharide gum is xanthan gum.

21. The composition of Claim 1 wherein the thixotropic thickening agent is present in an amount of about 0.25% to about 2%, by weight.

22. The composition of Claim 1 wherein the thixotropic thickening agent is present in an amount of about 0.4% to about 2%, by weight.

23. The composition of Claim 1 wherein the inorganic suspending agent is selected from the group consisting of colloidal silicon dioxide, bentonite and kaolin.

24. The composition of Claim 1 wherein the inorganic suspending agent is colloidal silicon dioxide.

25. The composition of Claim 24 wherein the colloidal silicon dioxide has a specific surface area of about 50 to about 400 m^2/g.

26. The composition of Claim 24 wherein the colloidal silicon dioxide has a specific surface area of about 150 to about 400 m^2/g.

27. The composition of Claim 24 wherein the colloidal silicon dioxide has a weight average particle diameter of about 7 to about 40 nm.

28. The composition of Claim 24 wherein the colloidal silicon dioxide has a weight average particle diameter of about 10 to about 25 nm. .

29. The composition of Claim 1 wherein the inorganic suspending agent is present in an amount of about 0.01% to about 3%, by weight.

30. The composition of Claim 24 wherein the inorganic suspending agent is present in an amount of about 0.25% to about 1%, by weight.

31. The composition of Claim 1 wherein the thixotropic thickening agent and the inorganic suspending agent are present in a weight ratio of about 10:1 to about 1:10.

32. The composition of Claim 1 wherein the thixotropic thickening agent and the inorganic suspending agent are present in a weight ratio of about 2:1 to about 1:2.

33. The composition of Claim 1 wherein about 75% to 100% of the drug is suspended in particulate form.

34. The composition of Claim 1 wherein substantially all of the drug is suspended in particulate form.

35. The composition of Claim 1 wherein less than about 25% of the drug is dissolved and/or solubilized.

36. The composition of Claim 1 wherein substantially no portion of the drug is dissolved and/or solubilized.

37. The composition of Claim 1 which, when analyzed according to Test I, has a maximum viscosity of about 5 to about 50 Pa•s and a dynamic viscosity measured at 2 sec^{-1} of about 0.3 to about 20 Pa•s.

38. The composition of Claim 1 which, when analyzed according to Test I, has a maximum viscosity of about 5 to about 25 Pa•s and a dynamic viscosity measured at 2 sec^{-1} of about 0.5 to about 7 Pa•s.

39. A method for increasing the physical stability of a pharmaceutical composition of a drug of low water solubility, the method comprising adding to the composition a pharmaceutically acceptable thixotropic agent and a

pharmaceutically acceptable inorganic suspending agent in amounts which act synergistically to increase physical stability of the composition.

40. The method of Claim 39 wherein the composition further comprises a wetting agent.

41. The method of Claim 40 wherein a substantial portion of the drug is suspended in particulate form in the vehicle to form a suspension.

42. The method of Claim 41 wherein the composition is substantially deflocculated.

43. The method of Claim 39 wherein the thixotropic thickening agent is a cellulosic polymer.

44. The method of Claim 43 wherein the thixotropic thickening agent is selected from the group consisting of methylcellulose, microcrystalline cellulose, polyvinylpyrrolidone, and hydroxypropyl methycellulose.

45. The method of Claim 39 wherein the thixotropic thickening agent is a polysaccharide gum.

46. The method of Claim 45 wherein the polysaccharide gum is selected from the group consisting of xanthan, guar, acacia, and tragacanth gums.

47. The method of Claim 45 wherein the polysaccharide gum is xanthan gum.

48. The method of Claim 39 wherein the thixotropic thickening agent is present in an amount of about 0.25% to about 2%, by weight.

49. The method of Claim 39 wherein the thixotropic thickening agent is present in an amount of about 0.4% to about 2%, by weight.

50. The method of Claim 39 wherein the inorganic suspending agent is selected from the group consisting of colloidal silicon dioxide, bentonite and kaolin.

51. The method of Claim 39 wherein the inorganic suspending agent is colloidal silicon dioxide.

52. The method of Claim 51 wherein the colloidal silicon dioxide has a specific surface area of about 50 to about 400 m^2/g.

53. The method of Claim 51 wherein the colloidal silicon dioxide has a specific surface area of about 150 to about 400 m^2/g.

54. The method of Claim 51 wherein the colloidal silicon dioxide has a weight average particle diameter of about 7 to about 40 nm.

55. The method of Claim 51 wherein the colloidal silicon dioxide has a weight average particle diameter of about 10 to about 25 nm.

56. The method of Claim 39 wherein the inorganic suspending agent is present in an amount of about 0.01% to about 3%, by weight.

57. The method of Claim 56 wherein the inorganic suspending agent is present in an amount of about 0.25% to about 1%, by weight.

58. The method of Claim 39 wherein the thixotropic thickening agent and the inorganic suspending agent are present in a weight ratio of about 10:1 to about 1:10.

59. The method of Claim 39 wherein the thixotropic thickening agent and the inorganic suspending agent are present in a weight ratio of about 2:1 to about 1:2.

60. The method of Claim 40 wherein the wetting agent is selected from the group consisting of quaternary ammonium compounds, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, poloxamers, polyoxyethylene fatty acid glycerides and oils, polyoxyethylene alkyl ethers, polyoxyethylene fatty acid esters, polyoxyethylene sorbitan esters, propylene glycol fatty acid esters, sodium lauryl sulfate, fatty acids and salts thereof, glyceryl fatty acid esters, sorbitan esters, tyloxapol and mixtures thereof.

61. The method of Claim 40 wherein the wetting agent is selected from the group consisting of benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, dioctyl sodium sulfosuccinate, nonoxynol 9, nonoxynol 10, octoxynol 9, polyoxyethylene 8 caprylic/capric mono- and diglycerides, polyoxyethylene 35 castor oil, polyoxyethylene 20 cetostearyl ether, polyoxyethylene 40 hydrogenated castor oil, polyoxyethylene 10 oleyl ether, polyoxyethylene 40 stearate, polysorbate 20, polysorbate 40, polysorbate 60,

polysorbate 80, propylene glycol laurate, sodium lauryl sulfate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, tyloxapol and combinations thereof.

62. The method of Claim 40 wherein the wetting agent is polysorbate 80.

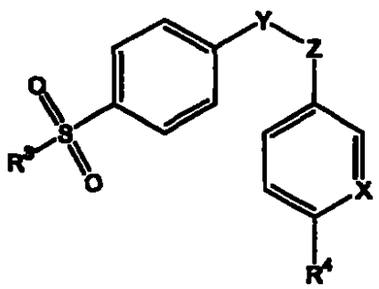
63. The method of Claim 40 wherein the wetting agent is present in an amount of about 0.01% to about 2%, by weight.

64. The method of Claim 40 wherein the wetting agent is present in an amount of about 0.25% to about 0.75%, by weight.

65. The method of Claim 39 wherein the drug is present in a therapeutically and/or prophylactically effective total amount.

66. The method of Claim 39 wherein the drug is a selective cyclooxygenase-2 inhibitory drug of low water solubility.

67. The method of Claim 66 wherein the selective cyclooxygenase-2 inhibitory drug is a compound of formula



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups.

68. The method of Claim 67 wherein the five- to six-membered ring is selected from the group consisting of cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

69. The method of Claim 68 wherein the selective cyclooxygenase-2 inhibitory

drug is selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

70. The method of Claim 69 wherein the selective cyclooxygenase-2 inhibitory drug is celecoxib.

71. The method of Claim 39 wherein the drug is present in an amount of about 0.01% to about 15%, by total weight of the composition.

72. The method of Claim 39 wherein the drug is present in an amount of about 0.01% to about 5%, by total weight of the composition.

73. The method of Claim 41 wherein about 75% to 100% of the drug is suspended in particulate form.

74. The method of Claim 73 wherein substantially all of the drug is suspended in particulate form.

75. The method of Claim 39 wherein less than about 25% of the drug is dissolved and/or solubilized.

76. The method of Claim 39 wherein substantially no portion of the drug is dissolved and/or solubilized.

77. The method of Claim 39 wherein the composition has a maximum viscosity of about 5 to about 50 Pa•s and a dynamic viscosity measured at 2 sec^{-1} of about 0.3 to about 20 Pa•s when analyzed according to Test I.

78. The method of Claim 39 wherein the composition has a maximum viscosity of about 5 to about 25 Pa•s and a dynamic viscosity measured at 2 sec^{-1} of about 0.5 to about 7 Pa•s when analyzed according to Test I.

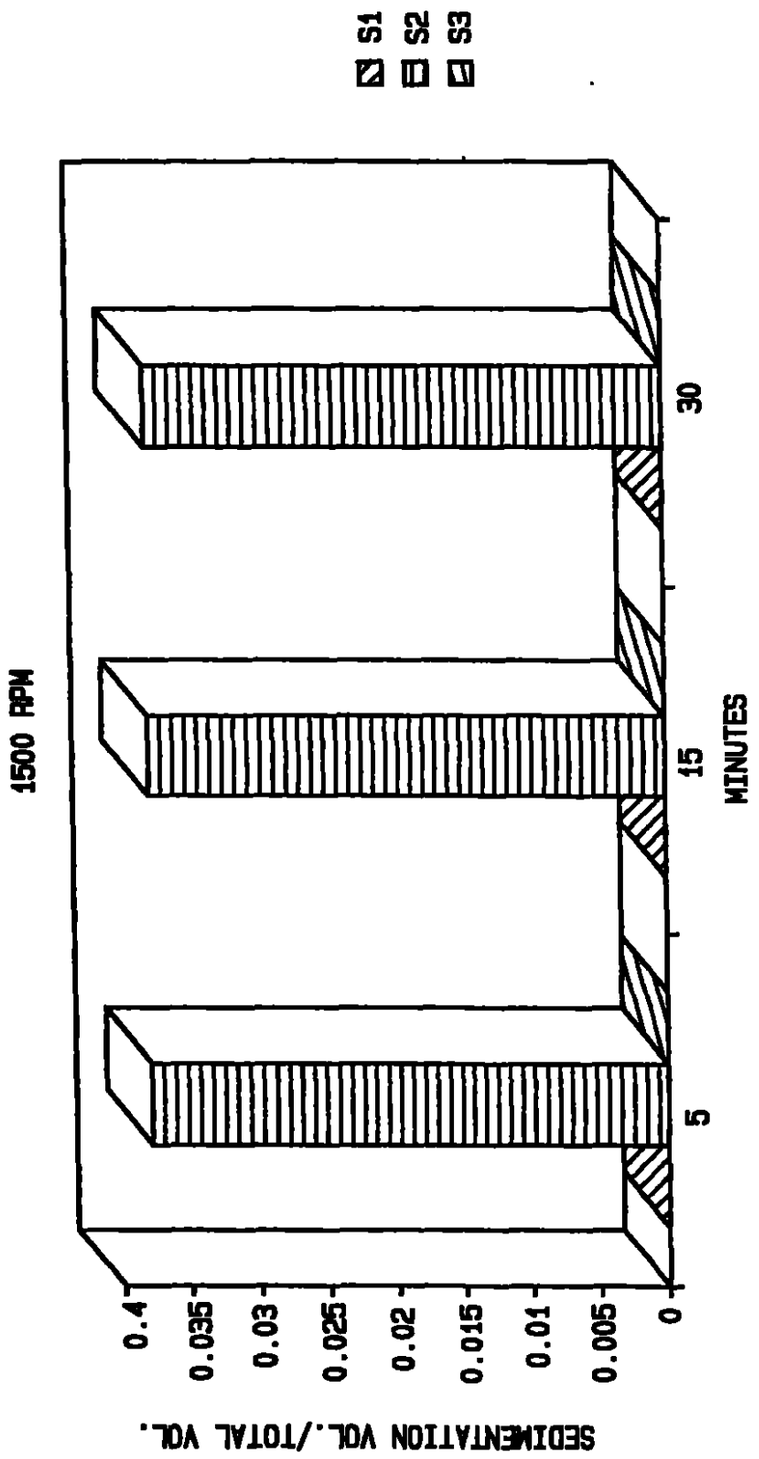
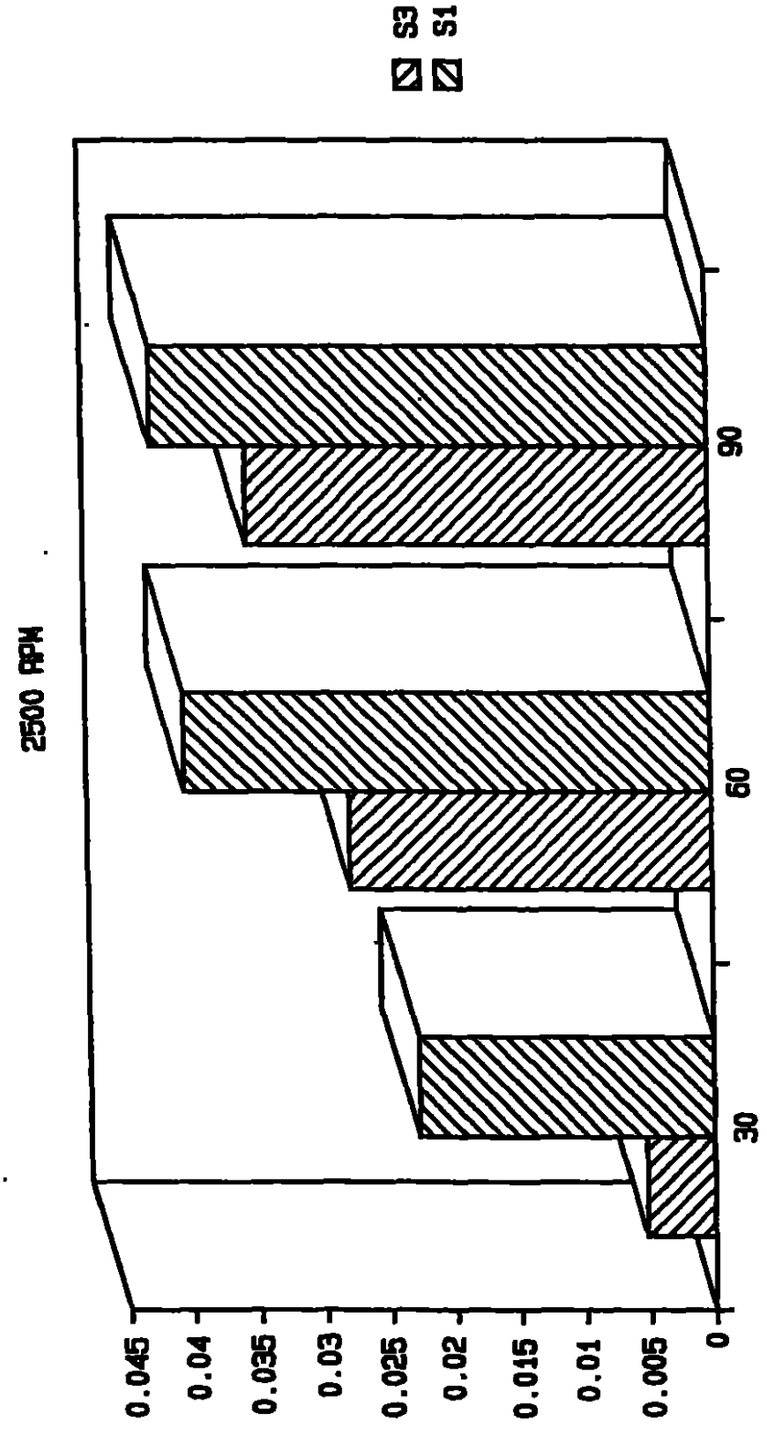

S1
S2
S3
1500 RPM
30
15
5
MINUTES
0.4
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
SEDIMENTATION VOL./TOTAL VOL.

FIG. 1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S1
2500 RPM
90
60
30
MINUTES
0.045
0.04
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
SEDIMENTATION VOL./TOTAL VOL.

FIG. 2

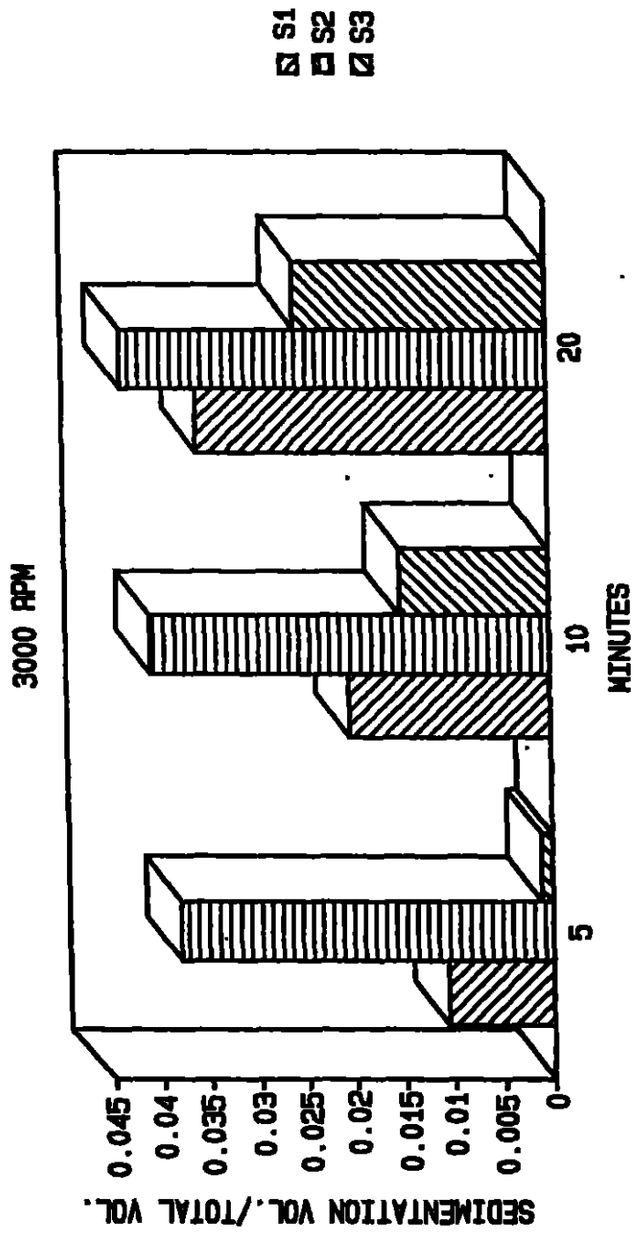
S1
S2
S3
3000 RPM
20
10
5
MINUTES
0.045
0.04
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
SEDIMENTATION VOL./TOTAL VOL.

FIG. 3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/24746

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/10 A61K31/415 A61K31/635

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 20798 A (RIKER LABORATORIES INC) 28 October 1993 (1993-10-28) page 1, line 5 - line 8 page 2, line 21 - line 29 page 2, line 35 -page 3, line 33 page 10; table 1 page 12; table 3 claim 1	1-3, 9-12,14, 15,18, 19,23, 24,31, 39-42, 45-47, 50,51, 56-58, 60,61, 71,72
Y	-/--	4-8,13, 16,17,

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 October 2002	28/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	VON EGGELKRAUT, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
		21,22, 25-28, 33-36, 43,44, 52-55, 62-64, 66,73-76
	& US 5 112 604 A 12 May 1992 (1992-05-12) cited in the application	
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	page 1, paragraph 2 page 3, line 11,12 page 3, last paragraph -page 4, line 10 page 9; example 10	
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	page 1, line 4 - line 8 page 3, line 28 - line 44 page 5; example 3	
Y	WO 00 32189 A (GAO DANCHEN ;SEARLE & CO (US); MAZHARY AHMAD M (US); HLINAK ANTHON) 8 June 2000 (2000-06-08) cited in the application	4-8,13, 16,17, 21,22, 25-28, 33-36, 43,44, 52-55, 62-64, 66,73-76
	page 47, line 3-5 page 61, line 7 - line 9	
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P,A	WO 02 05799 A (HASSAN FRED ;FORBES JAMES C (US); PHARMACIA CORP (US)) 24 January 2002 (2002-01-24) page 101, line 8 -page 102, line 6 page 113, line 10 -page 114, line 17	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/24746

56

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Continuation of Box I.2

Present claims 1 and 39 relate to an extremely large number of possible compounds, characterised by having a low water solubility. In fact, the claims contain so many options that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear, namely the compounds specified in claims 4-8 and 66-70.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/24746

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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			US	2002077328 A1	20-06-2002

TRADUCCIÓN

(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES (PCT)

(19) Organización Mundial de la Propiedad Intelectual
Dirección Internacional

(43) Fecha de Publicación Internacional 20 de febrero de 2003 (20.02.2003)

PCT

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(21) Solicitud Internacional Nro: PCT/US02/24746

(22) Fecha de presentación internacional: . 5 agosto 2002 (05.08.2002)

(25) Idioma de presentación: inglés

(26) Idioma de publicación: inglés

(30) Datos de Prioridad:
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(72) Inventores; y
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(74) Mandatarios: HOLLAND, Donald, R. et al.; Harness, Dickey & Pierce; P.L.C, Suite 400, 7700 Bonhomme, St. Louis, MO 63105 (EE.UU.)

(81)Países designados (nacional): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

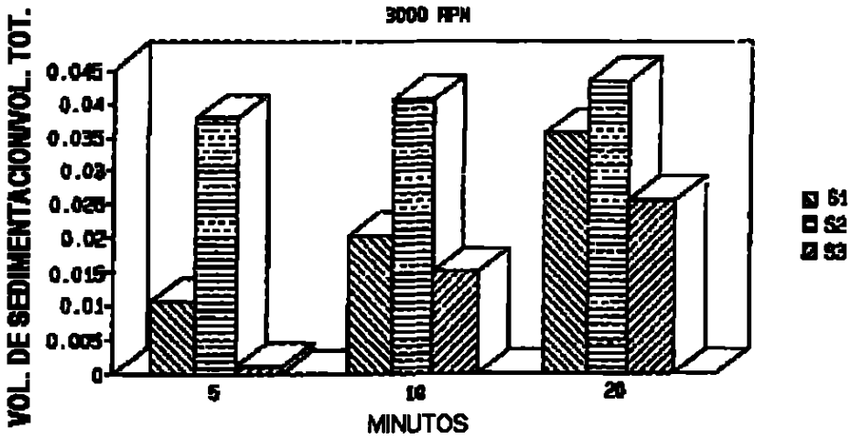
(84)Países designados (regional): patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), patente Euroasiatica (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), patente Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publicada:
- con el informe de la búsqueda internacional

Respecto de los códigos de dos letras y otras abreviaturas ver "Guidance Notes on Codes and Abbreviations" al comienzo de cada edición del Boletín de PCT.

WO 03/013473 A1

(54) TÍTULO: FORMULACIÓN DE SUSPENSIÓN ORAL ESTABILIZADA



(57) RESUMEN

Se proveen composiciones farmacéuticas para administrar en forma oral que comprenden una droga de baja solubilidad en agua suspendida en un vehículo líquido acuoso que comprende un agente humectante, un agente espesante tixotrópico, y un agente de suspensión inorgánico. Las composiciones son tixotrópicas, sustancialmente desfloculadas y físicamente son estables de manera sustancial.

FORMULACIÓN DE SUSPENSIÓN ORAL ESTABILIZADA

CAMPO DE LA INVENCIÓN

[0001] La presente invención se refiere a composiciones farmacéuticas para administrar en forma oral que comprenden una droga de baja solubilidad en agua, a métodos de tratamiento que comprenden administrar en forma oral dichas composiciones a un sujeto que las necesita, y al uso de dichas composiciones en la fabricación de medicamentos.

ANTECEDENTES DE LA INVENCIÓN

[0002] Las formas líquidas de dosificación, por ejemplo soluciones, suspensiones, elixires y jarabes, se han transformado en un importante método para administrar drogas a los sujetos. Se sabe que dichas formas de dosificación proveen una fácil administración para algunos pacientes con dificultades para tragar formas de dosificación sólidas y un aumento del cumplimiento en ciertas poblaciones de pacientes mejorando el sabor y/o la textura de la droga que se está administrando. Una ventaja aún adicional de las formas líquidas de dosificación es que se puede variar de manera continua la medida de las dosificaciones, proveyendo una infinita flexibilidad de dosis. Los beneficios de la facilidad de tragar y de la flexibilidad de dosis son ventajosos en particular para lactantes, niños, y personas mayores.

[0003] En algunos casos, las suspensiones pueden ser una forma de dosificación líquida ventajosa. Por ejemplo, algunas drogas son químicamente inestables en solución pero son estables cuando están en suspensión. Además, algunas drogas tienen un sabor desagradable cuando están en solución pero tienen un sabor aceptable cuando se administran como partículas sin disolver.

[0004] Desafortunadamente, muchas drogas útiles son hidrofóbicas, con una baja solubilidad en medios acuosos y por lo tanto son difíciles de formular como suspensiones en vehículos acuosos. De manera específica, debido a dichas propiedades, frecuentemente se requiere el uso de agentes humectantes para facilitar la suspensión de las partículas de droga hidrofóbica en medios acuosos. Se sabe que los agentes humectantes que actúan sobre la tensión superficial (es decir tensioactivos), por ejemplo laurilsulfato de sodio, aumentan la capacidad de suspender drogas hidrofóbicas en medios acuosos por lo menos en parte, al reducir la tensión interfacial entre las partículas de droga y el vehículo de la suspensión, permitiendo de esa manera la penetración del vehículo de la suspensión dentro de los agregados de droga y/o de los poros de las partículas de droga. Sin embargo, además de los efectos ventajosos de suspender la droga, frecuentemente el uso de tensioactivos en suspensiones causa también el resultado no deseable de tener droga libre solubilizada y/o disuelta. Como la droga solubilizada y/o disuelta es susceptible a la degradación y/o a la interacción química con otros ingredientes, las suspensiones que comprenden droga libre pueden ser químicamente inestables.

[0005] Otra consecuencia no deseable del uso de cantidades relativamente altas de tensioactivo para facilitar la suspensión de drogas de baja solubilidad es que, como los tensioactivos estabilizan las burbujas de aire, el aire atrapado durante la homogeneización o al agitar una suspensión con dichas características tiende a permanecer atrapado en la misma. Como dicho aire atrapado varía dependiendo de la fuerza de agitación, de la duración de la agitación, y del tiempo transcurrido desde la agitación, el

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volumen de la suspensión cambia necesariamente, haciendo que sea difícil o imposible la extracción de dosis volumétricamente uniformes durante el transcurso del tiempo.

[0006] Si se debe administrar una droga de baja solubilidad en agua en forma de suspensión, se desea que dicha suspensión muestre una lenta sedimentación para proveer una uniformidad apropiada de la dosis. A la inversa, si ocurre una rápida sedimentación, como en el caso de un vehículo sin estructura, para conseguir la uniformidad de dosis se debe agitar la suspensión antes de cada administración. Manteniendo iguales otros factores (por ejemplo tamaño de partícula, uniformidad y densidad de la droga), a medida que aumenta la viscosidad de un vehículo en particular de la suspensión, disminuye la velocidad de sedimentación de las partículas de droga. Por lo tanto, se desea que una suspensión sea apropiadamente viscosa, de tal manera que se inhiba o se haga más lenta la sedimentación de las partículas de droga. Sin embargo, aunque dicha mayor viscosidad favorece la estabilidad física, la misma también puede hacer difícil verter o administrar la suspensión. Muchas suspensiones que se conocen en el arte no han podido solucionar de manera adecuada dicho aparente conflicto entre una estabilidad física apropiada y la posibilidad de verterla de manera apropiada.

[0007] La Patente de los EE.UU. No. 5.112.604 de Beaurline expone una formulación de suspensión oral capaz de proveer uniformidad de dosis durante un período de aproximadamente 90 días. Sin embargo, en la misma no se expone información relacionada con la reología o la facilidad de verterla.

[0008] En muchos casos también se desean suspensiones desfloculadas. En general, en un vehículo estructurado las partículas más

grandes sedimentan más rápidamente que las partículas más pequeñas. Por lo tanto, en lo que respecta a una lenta velocidad de sedimentación, es deseable una suspensión desfloculada donde las partículas de droga existan como entidades por separado (como opuesto a agregados sueltos o flóculos). Una ventaja adicional de las suspensiones desfloculadas es que no requieren el agregado de agentes floculantes. Los agentes floculantes comunes, como por ejemplo electrolitos (por ejemplo silicoaluminato de magnesio o cloruro de aluminio) pueden causar la catálisis de reacciones químicas y la subsiguiente degradación de la droga o de otros ingredientes. Por lo tanto, con respecto tanto a la menor velocidad de sedimentación como a la estabilidad química, es más deseable una suspensión desfloculada que una suspensión floculada.

[0009] Por lo tanto, en el arte sigue existiendo una necesidad de formulaciones en suspensión de drogas de baja solubilidad en agua donde dichas suspensiones son química y físicamente estables y tienen propiedades reológicas que son apropiadas para verterlas y para su administración.

[0010] Una clase de drogas que sirve como ilustración, para la cual es evidente dicha necesidad es la clase de drogas inhibidoras selectivas de ciclooxigenasa-2 (COX-2) de baja solubilidad en agua. Se ha informado sobre muchos compuestos con efecto inhibidor selectivo de ciclooxigenasa-2 (COX-2) útil para uso terapéutico y/o para la profilaxis, y se ha informado que son útiles para el tratamiento o la prevención de trastornos específicos mediados por COX-2 o de trastornos con dichas características en general. Entre los compuestos con dichas características figura una gran cantidad de bencensulfonamidas sustituidas con pirazolilo, según se informa en la Patente de los EE.UU. No. 5.760.068 de Talley *et* al., que incluyen por ejemplo el

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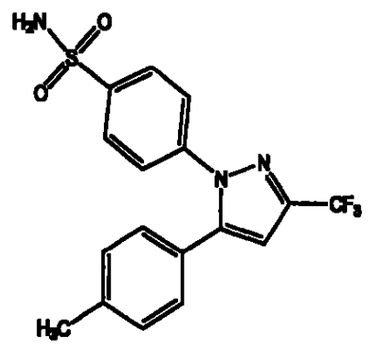
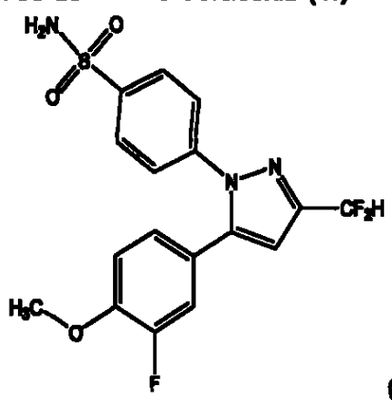
compuesto 4-[5-(4-metilfenil)-3-(trifluorometil)-1H-pirazol-1-il]bencensulfonamida, que aquí también se denomina celecoxib (1), y el compuesto 4-[5-(3-fluoro-4-metoxifenil)-3-difluorometil)-1H-pirazol-1-il]bencensulfonamida, que aquí también se denomina deracoxib (1I).

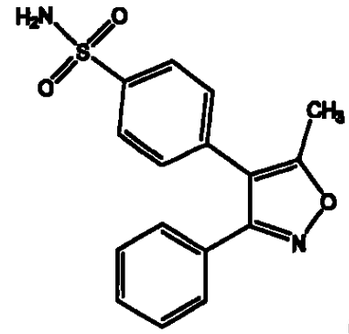


(I)



(II)

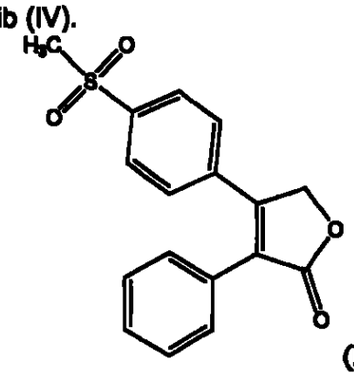
[0011] Otros compuestos que se ha informado que tienen un efecto inhibidor selectivo de COX-2 útil para uso terapéutico y/o para la profilaxis son las bencensulfonamidas sustituidas con isoxazolilo según se informa en la Patente de los EE.UU. No. 5.633.272 de Talley *et* al., que incluyen el compuesto 4-[5-metil-3-fenilisoxazol-4-il]bencensulfonamida, que aquí también se denomina valdecoxib (III).



(III)

[0012] Aún otros compuestos que se ha informado que tienen un efecto

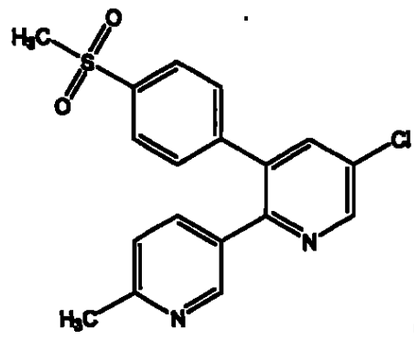
inhibidor selectivo de COX-2 útil para uso terapéutico y/o para la profilaxis son las furanonas sustituidas con (metilsulfonil)fenilo según se informa en la Patente de los EE.UU. No. 5.474.995 de Ducharme *et* al., que incluyen el compuesto 3-fenil-4-[4-(metilsulfonil)fenil]-5-H-furan-2-ona, que aquí también se denomina rofecoxib (IV).



(IV)

[0013] La Patente de los EE.UU. No. 5.981.576 de Belley *et* al. expone una serie adicional de (metilsulfonil)fenilfuranonas que se dice que son útiles como drogas inhibidoras selectivas de COX-2, que incluyen la 3-(1-ciclopropylmetoxi)-5,5-dimetil-4-[4(metilsulfonil)fenil]-5H-furan-2-ona y la 3-(1-ciclopropiletoxi)-5,5-dimetil-4[4-(metilsulfonil)fenil]-5H-furan-2-ona.

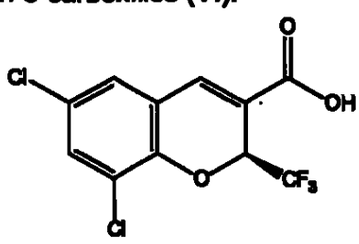
[0014] La Patente de los EE.UU. No. 5.861.419 de Dube *et* al. expone piridinas sustituidas que se dice que son útiles como drogas inhibidoras selectivas de COX-2, que incluyen por ejemplo el compuesto 5-cloro-3-(4-metilsulfonil)fenil-2-(2-metil-5-piridinil)piridina (V), que aquí también se denomina etoricoxib.



(V)

[0015] La Solicitud de patente Europea No. 0 863 134 expone el compuesto 2-(3,5-difluorofenil)-3-[4-(metilsulfonil)fenil]-2-ciclopenten-1-ona que se dice que es útil como droga inhibidora selectiva de COX-2.

[0016] La Patente de los EE.UU. No. 6.034.256 expone una serie de benzopiranos que se dice que son útiles como drogas inhibidoras selectivas de COX-2, que incluyen el compuesto ácido (S)-6,8-dicloro-2-(trifluorometil)-2H-1-benzopiran-3-carboxílico (VI).



(VI)

[0017] Se ha informado sobre formas líquidas de dosificación que comprenden drogas inhibidoras selectivas de COX-2 de baja solubilidad en agua. Por ejemplo, la Patente de los EE.UU. No. 5.760.068 citada anteriormente expone que sus sujetos pirazolilbencensulfonamidas, de las cuales celecoxib y deracoxib son ejemplos, se pueden administrar por vía

parenteral como soluciones isotónicas en una variedad de solventes que incluyen polietilenglicol y propilenglicol.

[0018] La Patente de los EE.UU. No. 5.633.272 citada anteriormente expone que sus sujetos isoxazolilbencensulfonamidas, de las cuales el valdecoxib es un ejemplo, se pueden administrar por vía parenteral como soluciones isotónicas en una variedad de solventes que incluyen polietilenglicol y propilenglicol.

[0019] La Patente de los EE.UU. No. 5.474.995 citada anteriormente expone que sus sujetos (metilsulfonil)fenilfuranonas, de las cuales el rofecoxib es un ejemplo, se pueden administrar por vía parenteral en una solución isotónica en 1,3-butanodiol. En la Patente de los EE.UU. No. 5.474.995 también se informan jarabes y elixires para administración oral, formulados con propilenglicol como agente edulcorante.

[0020] Además, una suspensión de celecoxib particulado en un vehículo sin estructura de jugo de manzana se expone en la Patente PCT No. WO 00/32189 co-asignada. En la misma no se provee información sobre la estabilidad química o física de una composición con dichas características.

[0021] Según se indica aquí más adelante, el tratamiento con drogas inhibidoras de COX-2 de baja solubilidad en agua está indicado en un muy amplio espectro de trastornos y condiciones mediados por ciclooxigenasa-2. Por lo tanto, si se pudiese preparar una suspensión acuosa de una droga de baja solubilidad, por ejemplo una droga inhibidora selectiva de COX-2, para administrar en forma oral, física y químicamente estable, y que aún así se pudiese verter fácilmente, se podría realizar un avance significativo en el tratamiento de muchas condiciones y trastornos, en particular donde se

desean formas de dosificación fáciles de tragar de diferentes drogas.

RESUMEN DE LA INVENCIÓN

[0022] A continuación se provee una composición farmacéutica que comprende una droga de baja solubilidad en agua para administrar en forma oral y un vehículo líquido acuoso que comprende (a) un agente humectante aceptable para uso farmacéutico, (b) un agente espesante tixotrópico aceptable para uso farmacéutico, y (c) un agente de suspensión inorgánico aceptable para uso farmacéutico, donde por lo menos una porción sustancial de la droga está suspendida en el vehículo en forma particulada para formar una suspensión y donde el agente humectante, el agente espesante, y el agente de suspensión están presentes en cantidades totales y relativas tales que la suspensión es tixotrópica, sustancialmente desfloculada, y que es físicamente estable de manera sustancial.

[0023] En una forma de realización que se prefiere, la droga es una droga inhibidora selectiva de COX-2 de baja solubilidad en agua.

[0024] Según se utilizan aquí para describir una suspensión, los términos "físicamente estable de manera sustancial" significan que (a) las partículas de droga permanecen suspendidas en el vehículo de la suspensión de manera tal que se puede obtener uniformidad en la dosis, según se determina por ejemplo mediante dos o más alícuotas que se extraen de manera volumétrica, durante un período de almacenamiento estacionario a temperatura ambiente de por lo menos 48 horas después de preparar la suspensión, y/o (b) la suspensión muestra una dispersión de partículas de droga sustancialmente uniforme y sin una separación sustancial de fases durante un período de almacenamiento estacionario a temperatura ambiente

de por lo menos 48 horas después de la preparación.

[0025] Aquí, el término "uniformidad de dosis" significa que, con respecto a dos o más alícuotas que se extraen de manera volumétrica de la misma suspensión, extrayendo ambas en forma simultánea o en diferentes puntos de tiempo y desde la misma posición o desde posiciones diferentes dentro de la suspensión, todas dichas alícuotas contienen cantidades sustancialmente similares (es decir ± aproximadamente 15%) de droga en suspensión y cantidades sustancialmente similares de droga libre. Se puede medir una cantidad de droga en un volumen de suspensión determinado mediante cualquier método apropiado, por ejemplo por cromatografía líquida de alto rendimiento.

[0026] Aquí, una suspensión "tixotrópica" es una suspensión cuya viscosidad disminuye sustancialmente cuando se aplica un esfuerzo de manera continua y/o creciente. Dicha definición incluye las suspensiones que se definen en otros documentos como seudoplásticas o que se licúan ante el esfuerzo.

[0027] Aquí, el término "floculada" se refiere a partículas de droga en suspensión que se coagulan y/o se aglomeran para formar agregados o flóculos con un empaque poco denso. Aquí, una "suspensión floculada" es una suspensión donde por lo menos una porción visible de todas las partículas de droga son partículas de droga floculadas. El término "sustancialmente desfloculadas" se refiere aquí a partículas de droga en suspensión que no se coagulan ni se aglomeran para formar flóculos. Aquí, una "suspensión desfloculada" es una suspensión donde sustancialmente ninguna porción visible de partículas de droga está floculada.

[0028] Típicamente, si se comparan una suspensión floculada y una suspensión desfloculada, manteniendo iguales la distribución de tamaños de las partículas de droga, la forma de las partículas de droga, la densidad de las partículas de droga, y la viscosidad del vehículo; las partículas de droga de la suspensión desfloculada sedimentarán más lentamente que las partículas de droga de la suspensión floculada. Además, cuando se ponen en un vehículo de suspensión de baja viscosidad, por ejemplo en un vehículo sin estructura, en general las partículas de droga desfloculadas sedimentarán para formar una capa de sedimento densamente empacada que no se dispersa fácilmente cuando se la somete a una agitación moderada, mientras que en general las partículas floculadas sedimentarán para formar una capa de sedimento mullida, suelta, que se puede redispersar con agitación moderada.

[0029] Aquí, un "vehículo estructurado" es un vehículo que comprende uno o más agentes de suspensión para conferirle viscosidad que reducen sustancialmente la tasa de sedimentación de las partículas dispersas.

[0030] La presente invención también provee métodos para el uso terapéutico y/o profiláctico de las composiciones de la presente invención, y un método para utilizar una composición de la invención en la fabricación de un medicamento útil para tratar y/o impedir una enfermedad o un trastorno mediado por COX-2.

[0031] Se ha descubierto que las composiciones de la invención resuelven de una manera sorprendentemente efectiva por lo menos algunas de las dificultades que se mencionaron antes. En primer lugar, las composiciones de la invención son físicamente estables de manera sustancial. En segundo lugar, las composiciones de la invención son tixotrópicas y por lo

tanto se vierten y administran fácilmente luego de una agitación suave. En tercer lugar, debido por lo menos en parte a la reducida concentración de droga libre, las composiciones de la invención tienen una estabilidad química mejorada.

[0032] Otras características de la presente invención serán evidentes en parte y en parte se puntualizarán de aquí en adelante.

DESCRIPCIÓN BREVE DE LAS FIGURAS

[0033] La Fig. 1 muestra el volumen de sedimento luego de la centrifugación de las suspensiones de celecoxib S1-S3 del Ejemplo 1 a 1500 RPM durante 5, 10 y 30 minutos, según se describe en el Ejemplo 3.

[0034] La Fig. 2 muestra el volumen de sedimento luego de la centrifugación de las suspensiones de celecoxib S1 y S3 del Ejemplo 1 a 2500 RPM durante 30, 60 y 90 minutos, según se describe en el Ejemplo 3.

[0035] La Fig. 3 muestra el volumen de sedimento luego de la centrifugación de las suspensiones de celecoxib S1-S3 del Ejemplo 1 a 3000 RPM durante 5, 10 y 20 minutos, según se describe en el Ejemplo 3.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

[0036] Las novedosas composiciones farmacéuticas de acuerdo con la presente invención comprenden una o más unidades de dosificación para administrar en forma oral. Aquí, el término "para administrar en forma oral" significa apropiado para administración oral. El término "administración oral" incluye aquí cualquier forma de administración de un agente terapéutico o una composición del mismo a un sujeto, donde el agente o composición se pone en la boca de dicho sujeto, ya sea que el agente o composición se trague o no. Por lo tanto, "administración oral" incluye la administración bucal y

sublingual así como la esofágica. La absorción del agente puede ocurrir en cualquier parte o partes del tracto gastrointestinal, incluso en la boca, esófago, estómago, duodeno, yeyuno, íleon y colon. El término "unidad de dosificación" significa aquí una porción de una composición farmacéutica que contiene una cantidad de un agente terapéutico que es apropiada para para proveer un efecto terapéutico mediante una única administración oral. Típicamente, una unidad de dosificación, o una cantidad reducida de unidades de dosificación (de hasta aproximadamente 4), provee una cantidad del agente suficiente para causar el efecto que se desea.

Droga de baja solubilidad en agua

[0037] Cada unidad de dosificación o cada pequeña cantidad de unidades de dosificación comprende una cantidad total de una droga de baja solubilidad en agua que es efectiva para uso terapéutico y/o para la profilaxis. Aquí, una "droga de baja solubilidad en agua" o "droga con una pobre solubilidad en agua" se refiere a cualquier droga o compuesto con una solubilidad en agua, medida a 37°C no mayor de aproximadamente 10mg/ml, y que preferiblemente no es mayor de aproximadamente 1mg/ml. Se contempla que las composiciones de la invención son especialmente ventajosas para drogas con una solubilidad en agua, medida a 37°C, no mayores de aproximadamente 0,1mg/ml.

[0038] La solubilidad en agua de muchas drogas se puede encontrar fácilmente en libros de referencia farmacéutica que son estándar, por ejemplo The Merck Index, 11va. ed., 1989 (publicado por Merck & Co., Inc., Rahway, NJ); la United States Pharmacopoeia, 24va. ed. (USP 24), 2000; The Extra Pharmacopoeia, 29va. ed., 1989 (publicada por Pharmaceutical Press,

Londres); y la Physicians Desk Reference (PDR), 2001 ed. (publicada por Medical Economics Co., Montvale, NJ), cada de las cuales se incorpora aquí individualmente como referencia.

[0039] Por ejemplo, según se definen aquí, las drogas individuales de baja solubilidad incluyen aquellas drogas dentro de las categorías "ligeramente soluble", "apenas soluble", "prácticamente insoluble" e "insoluble" en la USP 24, páginas 2254-2298; y aquellas drogas dentro de la categoría que requiere 100ml o más de agua para disolver 1g de la droga, según se da en la lista de la USP 24, páginas 2299-2304.

[0040] Las drogas de baja solubilidad en agua apropiadas que sirven como ilustración incluyen, sin limitación, las drogas de las siguientes clases: abortivos, inhibidores ACE, agonistas α- y β-adrenérgicos, bloqueadores α- y β-adrenérgicos, supresores adrenocorticales, hormonas adrenocorticotrópicas, disuasivos del consumo de alcohol, inhibidores de aldosa reductasa, antagonistas de aldosterona, anabólicos, analgésicos (que incluyen analgésicos narcóticos y no narcóticos), andrógenos, antagonistas del receptor de angiotensina II, anoréxicos, antiácidos, antihelmínticos, agentes antiacné, antialérgicos, agentes antialopecia, antiamébicos, antiandrógenos, agentes antianginales, antiarrítmicos, antiarterioescleróticos, agentes antiartríticos/antirreumáticos (que incluyen inhibidores selectivos de COX-2), antiasmáticos, antibacterianos, adjuntos antibacterianos, anticolinérgicos, anticoagulantes, anticonvulsivos, antidepresivos, antidiabéticos, agentes antidiarreicos, antidiuréticos, antídotos de venenos, antidisquinéticos, antieczemas, antieméticos, antiestrógenos, antifibróticos, antiflatulentos, antifúngicos, agentes antiglaucoma, antigonadotropinas, agentes antigotosos,

antihistamínicos, antihiperactivos, antihiperlipoproteinémicos, antihiperfosfatínicos, antihipertensivos, agentes antihipertiroideos, antihipotensivos, agentes antihipotiroideos, antiinflamatorios, agentes antimalaria, antimanícos, antimetemglobinémicos, agentes antimigraña, antimuscarínicos, antimicobacterianos, agentes y adjuntos antineoplásticos, antineutropénicos, antiosteoporóticos, anti Page, agentes anti Parkinson, agentes antifeocromocitoma, agentes antineumocistis, agentes antihipertrofia prostática, antiprotozoarios, antipruríticos, antipsoriáticos, antipsicóticos, antipiréticos, anti-ricktesias, antiseborreicos, antisépticos/desinfectantes, antiespasmódicos, antisifilíticos, antitrombocitémicos, antitrombóticos, antitusivos, antiulcerosos, antiuroliticos, antiveninas, agentes antivirales, ansiolíticos, inhibidores de aromatasa, astringentes, antagonistas de antagonistas de benzodiazepina, inhibidores de la reabsorción de huesos, agentes bradicárdicos, antagonistas de bradiquinina, broncodilatadores, bloqueadores del canal de calcio, reguladores de calcio, inhibidores de la anhidrasa carbónica, cardiotónicos, antagonistas de CCK, agentes quelantes, agentes colelitolíticos, coleréticos, colinérgicos, inhibidores de colinesterasa, reactivadores de colinesterasa, estimulantes del SNC, anticonceptivos, agentes de desbridamiento, descongestivos, despigmentadores, supresores de la dermatitis herpetiforme, coadyuvantes de la digestión, diuréticos, agonistas del receptor de dopamina, antagonistas del receptor de dopamina, ectoparasiticidas, eméticos, inhibidores de encefalinasa, enzimas, cofactores de enzimas, estrógenos, expectorantes, antagonistas del receptor de fibrinógeno, suplementos de flúor, estimulantes de la secreción gástrica y pancreática, citoprotectores gástricos, inhibidores de la bomba de protones

gástrica, secreción gástrica, gastroprocinéticos, glucocorticoides, inhibidores de α-glucosidasa, principios gonado-estimulantes, inhibidores de la hormona de crecimiento, factores de liberación de la hormona de crecimiento, estimulantes del crecimiento, hematínicos, hematopoyéticos, hemolíticos, hemostáticos, antagonistas de heparina, inductores de enzimas hepáticas, hepatoprotectores, antagonistas del receptor de histamina H_2, inhibidores de proteasa de VIH, inhibidores de reductasa HMG CoA, inmunomoduladores, inmunosupresores, sensibilizadores ante insulina, resinas de intercambio iónico, queratolíticos, hormonas estimulantes de la secreción de leche, laxantes/catárticos, antagonistas de leucotrieno, agonistas LH-RH, lipotrópicos, inhibidores de 5-lipooxigenasa, supresores de lupus eritematoso, inhibidores de metalproteinasas de matriz, mineralcorticoides, mióticos, inhibidores de monoamina oxidasa, mucolíticos, relajantes musculares, midriáticos, antagonistas de narcóticos, neuroprotectores, neuroprotectores, nootrópicos, hormonas ováricas, oxitócicos, inhibidores de pepsina, agentes de pigmentación, agentes que aumentan el volumen de plasma, sustancias que activan o abren el canal de potasio, progestógenos, inhibidores de prolactina, prostaglandinas, inhibidores de proteasa, radio-farmacéuticos, inhibidores de 5-α-reductasa, estimulantes respiratorios, inhibidores de transcriptasa inversa, sedantes/hipnóticos, serénicos, inhibidores de reabsorción de serotonina noradrenalina, agonistas del receptor de serotonina, antagonistas del receptor de serotonina, inhibidores de la absorción de serotonina, análogos de somatostatina, trombolíticos, antagonistas del receptor de tromboxano A_2, hormonas tiroideas, hormonas tirotrópicas, tocolíticos, inhibidores de topoisomerasa I y II, uricosúricos, vasomoduladores,

que incluyen vasodilatadores y vasoconstrictores, vasoprotectores, inhibidores de xantina oxidasa, y combinaciones de los mismos.

[0041] Los ejemplos no limitantes de drogas de baja solubilidad en agua apropiadas que sirven como ilustración incluyen acetohexamida, ácido acetilsalicílico, alclofenac, alopurinol, atropinas, benztiazida, carprofeno, celecoxib, clordiazepóxido, clorpromazina, clonidina, codeína, fosfato de codeína, sulfato de codeína, deracoxib, diacereína, diclofenac, diltiazem, estradiol, etodolac, etopósido, etoricoxib, fenbufeno, fenclofenac, fenprofeno, fentiazac, flurbiprofeno, griseofulvina, haloperidol, ibuprofeno, indometacina, indoprofeno, cetoprofeno, lorazepam, acetato de medroxiprogesterona, megestrol, metoxsaleno, metilprednisona, morfina, sulfato de morfina, naproxeno, nicergolina, nifedipina, niflumic, oxaprozina, oxazepam, oxifenbutazona, paclitaxel, fenindiona, fenobarbital, piroxicam, pirprofeno, prednisolona, prednisona, procaína, progesterona, pirimetamina, rofecoxib, sulfadiazina, sulfamerazina, sulfisoxazol, sulindac, suprofeno, temazepam, ácido tiaprofénico, tiomisol, tolmetic, valdecoxib, etc.

[0042] La cantidad de droga que se incorpora en una forma de dosificación de la invención se puede seleccionar de acuerdo con principios de farmacia que se conocen. Se contempla de manera específica una cantidad de droga efectiva para uso terapéutico. Según se usa aquí, los términos "cantidad efectiva para uso terapéutico y/o para la profilaxis" se refieren a una cantidad de droga que es suficiente como para suscitar la respuesta terapéutica y/o profiláctica que se requiere o que se desea. Preferiblemente, el agente terapéutico está presente en la suspensión a una concentración de por lo menos aproximadamente 0,01%, por lo menos aproximadamente 0,1%, por

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lo menos aproximadamente 1% o por lo menos aproximadamente 10% hasta una concentración que preferiblemente no es mayor de aproximadamente un 90% no mayor de aproximadamente 75% no mayor de aproximadamente 50% o no mayor de aproximadamente 35% sobre una base peso/peso. A no ser que se indique de otra manera, todos los valores de los porcentajes que se dan aquí se deben calcular sobre una base peso/peso.

[0043] En una forma de realización que se prefiere en particular, la droga es una droga inhibidora selectiva de COX-2 de baja solubilidad en agua. Se puede utilizar cualquiera de las drogas inhibidoras selectivas de COX-2 que se conocen en el arte, que incluyen sin limitación los compuestos que se dan en las patentes y publicaciones de la lista a continuación.

Patente de los EE.UU. No. 5.344.991 de Reitz & Li.

Patente de los EE.UU. No. 5.380.738 de Nonnan *et al.*

Patente de los EE.UU. No. 5.393.790 de Reitz *et al.*

Patente de los EE.UU. No. 5.401.765 de Lee.

Patente de los EE.UU. No. 5.418.254 de Huang & Reitz.

Patente de los EE.UU. No. 5.420.343 de Koszyk & Weier.

Patente de los EE.UU. No. 5.434.178 de Talley & Rogier.

Patente de los EE.UU. No. 5.436.265 de Black *et al.*

Patente de los EE.UU. No. 5.466.823, citada anteriormente.

Patente de los EE.UU. No. 5.474.995, citada anteriormente.

Patente de los EE.UU. No. 5.475.018 de Lee & Bertenshaw.

Patente de los EE.UU. No. 5.486.534 de Lee *et al.*

Patente de los EE.UU. No. 5.510.368 de Lau *et al.*

Patente de los EE.UU. No. 5.521.213 de Prasit *et al.*

Patente de los EE.UU. No. 5.536.752 de Duchanne *et al.*

Patente de los EE.UU. No. 5.543.297 de Cromlish *et al.*

Patente de los EE.UU. No. 5.547.975 de Talley *et al.*

Patente de los EE.UU. No. 5.550.142 de Duchanne *et al.*

Patente de los EE.UU. No. 5.552.422 de Gauthier *et al.*

Patente de los EE.UU. No. 5.585.504 de Desmond *et al.*

Patente de los EE.UU. No. 5.593.992 de Adams *et al.*

Patente de los EE.UU. No. 5.596.008 de Lee.

Patente de los EE.UU. No. 5.604.253 de Lau *et al.*

Patente de los EE.UU. No. 5.604.260 de Guay & Li.

Patente de los EE.UU. No. 5.616.458 de Lipsky *et al.*

Patente de los EE.UU. No. 5.616.601 de Khanna *et al.*

Patente de los EE.UU. No. 5.620.999 de Weier *et al.*

Patente de los EE.UU. No. 5.633.272, citada anteriormente.

Patente de los EE.UU. No. 5.639.780 de Lau *et al.*

Patente de los EE.UU. No. 5.643.933 de Talley *et al.*

Patente de los EE.UU. No. 5.658.903 de Adams *et al.*

Patente de los EE.UU. No. 5.668.161 de Talley *et al.*

Patente de los EE.UU. No. 5.670.510 de Huang & Reitz.

Patente de los EE.UU. No. 5.677.318 de Lau.

Patente de los EE.UU. No. 5.681.842 de Dellaria & Gane.

Patente de los EE.UU. No. 5.686.460 de Nicolai *et al.*

Patente de los EE.UU. No. 5.686.470 de Weier *et al.*

Patente de los EE.UU. No. 5.696.143 de Talley *et al.*

Patente de los EE.UU. No. 5.710.140 de Ducharme *et al.*

Patente de los EE.UU. No. 5.716.955 de Adams *et al.*

Patente de los EE.UU. No. 5.723.485 de Gungör & Teulon.

Patente de los EE.UU. No. 5.739.166 de Reitz *et al.*

Patente de los EE.UU. No. 5.741.798 de Lazer *et al.*

Patente de los EE.UU. No. 5.756.499 de Adams *et al.*

Patente de los EE.UU. No. 5.756.529 de Isakson & Talley.

Patente de los EE.UU. No. 5.776.967 de Kreft *et al.*

Patente de los EE.UU. No. 5.783.597 de Beers & Wachter.

Patente de los EE.UU. No. 5.789.413 de Black *et al.*

Patente de los EE.UU. No. 5.807.873 de Nicolai & Teulon.

Patente de los EE.UU. No. 5.817.700 de Dube *et al.*

Patente de los EE.UU. No. 5.830.911 de Faillli *et al.*

Patente de los EE.UU. No. 5.849.943 de Atkinson & Wang.

Patente de los EE.UU. No. 5.859.036 de Sartori *et al.*

Patente de los EE.UU. No. 5.861.419, citada anteriormente.

Patente de los EE.UU. No. 5.866.596 de Sartori & Teulon.

Patente de los EE.UU. No. 5.869.524 de Faillli.

Patente de los EE.UU. No. 5.869.660 de Adams *et al.*

Patente de los EE.UU. No. 5.883.267 de Rossen *et al.*

Patente de los EE.UU. No. 5.892.053 de Zhi *et al.*

Patente de los EE.UU. No. 5.922.742 de Black *et al.*

Patente de los EE.UU. No. 5.929.076 de Adams & Garigipati.

Patente de los EE.UU. No. 5.932.598 de Talley *et al.*

Patente de los EE.UU. No. 5.935.990 de Khanna *et al.*

Patente de los EE.UU. No. 5.945.539 de Haruta *et al.*

Patente de los EE.UU. No. 5.958.978 de Yamazaki *et al.*

Patente de los EE.UU. No. 5.968.958 de Guay *et al.*

Patente de los EE.UU. No. 5.972.950 de Nicolai & Teulon.

Patente de los EE.UU. No. 5.973.191 de Marnett & Kalgutkar.

Patente de los EE.UU. No. 5.981.576, citada anteriormente.

Patente de los EE.UU. No. 5.994.3 81 de Harata *et al.*

Patente de los EE.UU. No. 6.002.014 de Harata *et al.*

Patente de los EE.UU. No. 6.004.960 de Li *et al.*

Patente de los EE.UU. No. 6.005.000 de Hopper *et al.*

Patente de los EE.UU. No. 6.020.343 de Belley *et al.*

Patente de los EE.UU. No. 6.020.347 de DeLaszlo & Hagmann.

Patente de los EE.UU. No. 6.034.256, citada anteriormente.

Patente de los EE.UU. No. 6.040.319 de Corley *et al.*

Patente de los EE.UU. No. 6.040.450 de Davies *et al.*

Patente de los EE.UU. No. 6.046.208 de Adams *et al.*

Patente de los EE.UU. No. 6.046.217 de Friesen *et al.*

Patente de los EE.UU. No. 6.057.319 de Black *et al.*

Patente de los EE.UU. No. 6.063.804 de De Nanteuil *et al.*

Patente de los EE.UU. No. 6.063.807 de Chabrier de Lassauniere & Broquet.

Patente de los EE.UU. No. 6.071.954 de LeBlanc *et al.*

Patente de los EE.UU. No. 6.077.868 de Cook *et al.*

Patente de los EE.UU. No. 6.077.869 de Sui & Wachter.

Patente de los EE.UU. No. 6.083.969 de Ferro *et al.*

Patente de los EE.UU. No. 6.096.753 de Spohr *et al.*

Patente de los EE.UU. No. 6.133.292 de Wang *et al.*

Publicación de Patente Internacional No. WO 94/15932.

Publicación de Patente Internacional No. WO 96/19469.

Publicación de Patente Internacional No. WO 96/26921.

Publicación de Patente Internacional No. WO 96/31509.

Publicación de Patente Internacional No. WO 96/36623.

Publicación de Patente Internacional No. WO 96/38418.

Publicación de Patente Internacional No. WO 97/03953.

Publicación de Patente Internacional No. WO 97/10840.

Publicación de Patente Internacional No. WO 97/13755.

Publicación de Patente Internacional No. WO 97/13767.

Publicación de Patente Internacional No. WO 97/25048.

Publicación de Patente Internacional No. WO 97/30030.

Publicación de Patente Internacional No. WO 97/34882.

Publicación de Patente Internacional No. WO 97/46524.

Publicación de Patente Internacional No. WO 98/04527.

Publicación de Patente Internacional No. WO 98/06708.

Publicación de Patente Internacional No. WO 98/07425.

Publicación de Patente Internacional No. WO 98/17292.

Publicación de Patente Internacional No. WO 98/21195.

Publicación de Patente Internacional No. WO 98/22457.

Publicación de Patente Internacional No. WO 98/32732.

Publicación de Patente Internacional No. WO 98/41516.

Publicación de Patente Internacional No. WO 98/43966.

Publicación de Patente Internacional No. WO 98/45294.

Publicación de Patente Internacional No. WO 98/47871.

Publicación de Patente Internacional No. WO 99/01130.

Publicación de Patente Internacional No. WO 99/01131.

Publicación de Patente Internacional No. WO 99/01452.

Publicación de Patente Internacional No. WO 99/01455.

Publicación de Patente Internacional No. WO 99/10331.

Publicación de Patente Internacional No. WO 99/10332.

Publicación de Patente Internacional No. WO 99/11605.

Publicación de Patente Internacional No. WO 99/12930.

Publicación de Patente Internacional No. WO 99/14195.

Publicación de Patente Internacional No. WO 99/14205.

Publicación de Patente Internacional No. WO 99/15505.

Publicación de Patente Internacional No. WO 99/23087.

Publicación de Patente Internacional No. WO 99/24404.

Publicación de Patente Internacional No. WO 99/25695.

Publicación de Patente Internacional No. WO 99/35130.

Publicación de Patente Internacional No. WO 99/61016.

Publicación de Patente Internacional No. WO 99/61436.

Publicación de Patente Internacional No. WO 99/62884.

Publicación de Patente Internacional No. WO 99/64415.

Publicación de Patente Internacional No. WO 00/01380.

Publicación de Patente Internacional No. WO 00/08024.

Publicación de Patente Internacional No. WO 00/10993.

Publicación de Patente Internacional No. WO 00/13684.

Publicación de Patente Internacional No. WO 00/18741.

Publicación de Patente Internacional No. WO 00/18753.

Publicación de Patente Internacional No. WO 00/23426.

Publicación de Patente Internacional No. WO 00/24719, citada anteriormente.

Publicación de Patente Internacional No. WO 00/26216.

Publicación de Patente Internacional No. WO 00/31072.

Publicación de Patente Internacional No. WO 00/40087.

Publicación de Patente Internacional No. WO 00/56348.

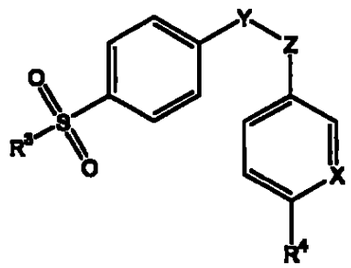
Solicitud de patente Europea No. 0 799 823.

Solicitud de patente Europea No. 0 846 689.

Solicitud de patente Europea No. 0 863 134, citada anteriormente.

Solicitud de patente Europea No. 0 985 666.

[0044] Las composiciones de la invención son especialmente útiles para compuestos con la fórmula (VII):



(VII)

[0045] donde R^3 es un grupo metilo o amino. R^4 es hidrógeno o un grupo alquilo C_{1-4} o alcoxi, X es N o CR^5 donde R^5 es hidrógeno o halógeno, e Y y Z son independientemente átomos de carbono o nitrógeno que definen átomos adyacentes de un anillo de entre cinco y seis miembros que no está sustituido o está sustituido en una o más posiciones con grupos oxo, halo, metilo o halometilo. Se prefiere que los anillos de entre cinco y seis miembros con dichas características sean anillos ciclopentenona, furanona, metilpirazol, isoxazol y piridina que no están sustituidos en más de una posición.

[0046] Como ilustración, en las composiciones de la invención son útiles celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, 2-(3,5-difluorofenil)-3-[4-(metilsulfonil)fenil]-2-ciclopenten-1-ona, ácido (S)-6,8-dicloro-2-(trifluorometil)-2H-1-benzopiran-3-carboxílico y 2-(3,4difluorofenil)-4-(3-hidroxi-3-metil-1-butoxi)-5-[4-(metilsulfonil)fenil]-3(2H)-piridazinona, más en particular celecoxib, valdecoxib, rofecoxib y etoricoxib, y aún más en particular celecoxib y valdecoxib.

[0047] La invención se ilustra aquí haciendo referencia en particular al celecoxib, y se comprenderá que, si se desea, el celecoxib de las composiciones que se describen aquí se puede sustituir por completo o en parte por cualquier otra droga de baja solubilidad en agua.

[0048] Si la droga es celecoxib, la composición comprende típicamente celecoxib en una cantidad total efectiva para uso terapéutico y/o para la profilaxis, de entre aproximadamente 2mg y aproximadamente 1000mg por unidad de dosificación. Si la droga es una droga inhibidora selectiva de COX-2 diferente de celecoxib, la cantidad de droga por unidad de dosificación es el equivalente terapéutico de entre aproximadamente 2mg y aproximadamente 1000mg de celecoxib.

[0049] Se comprenderá que para un sujeto, la cantidad de una droga que es efectiva para uso terapéutico y/o para la profilaxis depende entre otras cosas del peso corporal de dicho sujeto. Aquí, un "sujeto" al que se puede administrar un agente terapéutico o una composición del mismo incluye un sujeto o paciente humano de cualquier sexo y edad, y también incluye cualquier animal no humano, en particular un animal doméstico o de compañía, como ilustración un gato, perro o caballo.

[0050] Si el sujeto es un lactante, un niño o un animal pequeño (por ejemplo, un perro), es probable que, por ejemplo, una cantidad de celecoxib relativamente baja, dentro del rango preferido de entre aproximadamente 2mg y aproximadamente 1000mg, sea consistente con la efectividad terapéutica. Si el sujeto es un humano adulto o un animal grande (por ejemplo, un caballo), es probable que para conseguir la efectividad terapéutica se requieran unidades de dosificación con una cantidad de celecoxib relativamente mayores. Para un humano adulto, una cantidad de celecoxib por unidad de dosificación que es efectiva para uso terapéutico en una composición de la presente invención es típicamente de entre aproximadamente 50mg y aproximadamente 400mg. Las cantidades de celecoxib por unidad de dosificación que se prefieren especialmente son de entre aproximadamente 100mg y aproximadamente 200mg.

[0051] Para otras drogas inhibidoras selectivas de COX-2, la cantidad de droga por unidad de dosificación puede estar dentro del rango que se conoce como efectivo para uso terapéutico para dichas drogas. Preferiblemente, la cantidad por unidad de dosificación está dentro del rango que provee equivalencia terapéutica al celecoxib en los rangos de dosificación que se acaban de indicar.

[0052] Una composición de celecoxib en suspensión de la presente invención comprende preferiblemente entre aproximadamente 0,01 y aproximadamente 15%, más preferiblemente entre aproximadamente 0,01 y aproximadamente 10%, y aún más preferiblemente entre aproximadamente 0,01 y aproximadamente 5% en peso del total, de celecoxib. En general, dichas concentraciones corresponderán al celecoxib en una cantidad entre

aproximadamente 1% y aproximadamente 90%, más preferiblemente entre aproximadamente 1% y aproximadamente 75%, más preferiblemente entre aproximadamente 1% y aproximadamente 50%, y aún más preferiblemente entre aproximadamente 1% y aproximadamente 35% en peso de todos los componentes secos, no líquidos.

[0053] Si la droga inhibidora selectiva de COX-2 no es celecoxib y es efectiva para uso terapéutico a menores dosificaciones que el celecoxib, la mínima cantidad en suspensión de droga inhibidora de COX-2 puede ser menor que las que se acaban de indicar para el celecoxib; por ejemplo, en el caso del valdecoxib, la droga puede estar presente en una cantidad de aproximadamente un 0,1% en peso del total.

[0054] Se prefiere que entre aproximadamente 50% y el 100%, se prefiere más que entre aproximadamente 75% y 100%, se prefiere aún más que entre aproximadamente 85% y 100%, y se prefiere aún más que sustancialmente todo el celecoxib presente en las composiciones de la invención esté suspendido en forma de particulado. En las composiciones de la invención también se prefiere que menos de aproximadamente 25%, se prefiere más que menos de aproximadamente un 10%, se prefiere aún más que menos de aproximadamente un 5%, y se prefiere aún más que sustancialmente ninguna porción del celecoxib esté en la forma disuelta y/o solubilizada.

[0055] El celecoxib particulado presente en las composiciones en suspensión de la invención tiene preferiblemente un tamaño de partícula D_{90} entre aproximadamente 0,5μm y aproximadamente 50μm, más preferiblemente entre aproximadamente 0,5μm y aproximadamente 40μm, y

aún más preferiblemente entre 0,5 μm y aproximadamente 30μm. El D_{90} se define aquí como una medida lineal del diámetro con un valor tal que el 90% en peso de la partículas en la formulación, medidas según su dimensión más alargada, son más pequeñas que dicho diámetro.

Agente humectante

[0056] En las composiciones en suspensión de la invención hay uno o más agentes humectantes presentes. Se cree que dichos uno o más agentes humectantes facilitan la suspensión de las partículas de droga de baja solubilidad en agua, pero pueden tener otras funciones.

[0057] Los tensioactivos, polímeros hidrofílicos y ciertas arcillas pueden ser útiles como agentes humectantes para contribuir a la suspensión de una droga hidrofóbica como por ejemplo el celecoxib. Los agentes humectantes que se prefieren en las composiciones en suspensión de la invención son los tensioactivos, que incluyen tensioactivos no iónicos, aniónicos, catiónicos y dipolares. Los ejemplos no limitantes de tensioactivos que se pueden utilizar como agentes humectantes en las composiciones de la invención incluyen compuestos de amonio cuaternario, por ejemplo cloruro de benzalconio, cloruro de bencetonio y cloruro de cetilpiridinio, dioctilsulfosuccinato sódico, éteres alquilfenílicos de polioxietileno, por ejemplo nonoxinol 9, nonoxinol 10, y octoxinol 9, poloxámeros (copolímeros de bloque polioxietileno y polioxipropileno), glicéridos de polioxietileno ácido graso y aceites, por ejemplo mono- y di-glicéridos caprílicos/cápricos de polioxietileno (8) (por ejemplo, Labrasol™ de Gattefossé), polioxietileno (35) aceite de castor y polioxietileno (40) aceite de castor hidrogenado; éteres alquílicos de polioxietileno, por ejemplo éter cetoestearílico de polioxietileno (20), ésteres de ácido graso

polioxietileno, por ejemplo estearato de polioxietileno (40), ésteres de sorbitan polioxietileno, por ejemplo polisorbato 20 y polisorbato 80 (por ejemplo, Tween™ 80 de ICI), ésteres de ácido graso y propilenglicol, por ejemplo laurato de propilenglicol (por ejemplo, Lauroglicol™ de Gattefossé), laurilsulfato de sodio, ácidos grasos y sales de los mismos, por ejemplo ácido oleico, oleato de sodio y oleato de trietanolamina, ésteres de glicerilo y ácido graso, por ejemplo monoestearato de glicerilo, ésteres de sorbitan, por ejemplo monolaurato de sorbitan, monooleato de sorbitan, monopalmitato de sorbitan y monoestearato de sorbitan, tiloxapol, y mezclas de los mismos. Una clase preferida de agentes humectantes son los ésteres de sorbitan polioxietileno.

[0058] Los agentes humectantes que se prefieren son cloruro de benzalconio, cloruro de bencetonio, cloruro de cetilpiridinio, dioctilsulfosuccinato sódico, nonoxinol 9, nonoxinol 10, octoxinol 9, mono- y di-glicéridos caprílicos/cápricos de polioxietileno (8), polioxietileno (35) aceite de castor, éter cetoestearílico de polioxietileno (20), polioxietileno (40) aceite de castor hidrogenado, oleil éter de polioxietileno (10), estearato de polioxietileno (40), polisorbato 20, polisorbato 40, polisorbato 60, polisorbato 80, laurato de propilenglicol, laurilsulfato de sodio, monolaurato de sorbitan, monooleato de sorbitan, monopalmitato de sorbitan, monoestearato de sorbitan y tiloxapol. Un agente humectante que se prefiere en particular es el polisorbato 80.

[0059] Demasiado agente humectante (por ejemplo un tensioactivo) o una selección inapropiada del mismo, puede no ser deseable debido a varias razones. Una alta concentración de tensioactivo libre puede causar la aparición de partículas de droga floculadas que sedimentan más rápidamente

que las partículas de droga desfloculadas. Una alta concentración de tensioactivo libre también puede hacer que aumente la cantidad de droga disuelta y/o solubilizada que, en comparación con la misma droga en forma de particulado, puede ser más susceptible a la degradación química y puede producir un sabor desagradable. Por lo tanto, en una forma de realización que se prefiere en particular, hay uno o más agentes humectantes presentes en una cantidad total suficiente como para facilitar la suspensión de las partículas de droga, pero en una cantidad que no solubiliza ni disuelve la droga de manera sustancial.

[0060] En otra forma de realización que se prefiere, hay uno o más agentes humectantes presentes en cantidades totales y relativas suficientes como para suspender en forma particulada por lo menos aproximadamente un 75%, más preferiblemente por lo menos aproximadamente un 85%, y se prefiere aún más que a sustancialmente toda la droga, pero en cantidades totales y relativas menores de las que permitan que haya presente en la composición aproximadamente un 25% o más, preferiblemente aproximadamente un 10% o más, y se prefiere más que sustancialmente ninguna porción, de droga solubilizada y/o disuelta.

[0061] Demasiado tensioactivo también puede hacer que quede retenido el aire atrapado dentro de una composición en suspensión de la invención. En general, cuando se homogeneiza una suspensión durante la preparación, queda aire atrapado en la misma. Sin ligarse a una teoría, se cree que los tensioactivos y otros agentes humectantes estabilizan las burbujas de aire por lo menos en parte disminuyendo la tensión superficial en la superficie de la burbuja. Por lo tanto, en comparación con una suspensión

que comprende cantidades relativamente altas de tensioactivo libre, se cree que una suspensión con una menor concentración de tensioactivo libre mostrará burbujas de aire atrapado menos estables y por lo tanto, que mostrará una uniformidad de dosis/volumen mejorada.

[0062] En general, uno o más agentes humectantes(s) constituyen, en total, entre aproximadamente 0,01% y aproximadamente 2%, preferiblemente entre aproximadamente 0,1% y aproximadamente 1,5%, y más preferiblemente entre aproximadamente 0,25% y aproximadamente 0,75%, del peso total de la composición.

Agente espesante tixotrópico

[0063] Las composiciones de la invención comprenden uno o más agentes espesantes tixotrópicos. Los agentes espesantes tixotrópicos que son apropiados son polímeros naturales o sintéticos que, cuando se agregan a un medio acuoso, le confieren características tixotrópicas. Los agentes espesantes tixotrópicos que se prefieren son polímeros celulósicos, como por ejemplo metilcelulosa, celulosa microcristalina (por ejemplo *Avicel de* FMC Corp.), polivinilpirrolidona, hidroxipropilmetilcelulosa, *etc.* Más preferiblemente, los agentes espesantes tixotrópicos en las composiciones de la invención son gomas de polisacáridos. Las gomas de polisacáridos que son apropiadas incluyen, como ilustración de ninguna manera limitante, las gomas xántica, guar, de acacia, y tragacanto.

[0064] Los agentes espesantes tixotrópicos en las composiciones de la invención están presentes preferiblemente en una cantidad total entre aproximadamente 0,25% y aproximadamente 2%, preferiblemente entre aproximadamente 0,3% y aproximadamente 2%, y más preferiblemente entre

aproximadamente 0,4% y aproximadamente 2%, sobre una base peso/peso. Aunque el término goma de polisacárido se utiliza a veces aquí para referirse a un agente espesante tixotrópico, dichos agentes no se limitan a las gomas de polisacáridos.

Agente de suspensión inorgánico

[0065] En las composiciones de la invención se puede utilizar cualquier agente de suspensión inorgánico aceptable para uso farmacéutico. Los ejemplos no limitantes que sirven como ilustración de los agentes de suspensión inorgánicos que son apropiados incluyen dióxido de silicio, bentonita, silicato de aluminio hidratado (por ejemplo caolín) y mezclas de los mismos. El dióxido de silicio es un agente de suspensión inorgánico que se prefiere en particular. Aunque aquí a veces se utiliza el término dióxido de silicio coloidal para referirse a un agente de suspensión inorgánico, los agentes de suspensión inorgánicos no se limitan al dióxido de silicio coloidal.

[0066] Aunque se sabe que en ciertas preparaciones en gel y semisólidas, a concentraciones relativamente altas *(por ejemplo* entre aproximadamente 5 y aproximadamente 15%) el dióxido de silicio coloidal confiere características tixotrópicas, los inventores han descubierto de manera inesperada que una pequeña cantidad de dióxido de silicio coloidal (por ejemplo de aproximadamente 2% o menos) tiene un efecto sinergético con la goma de polisacáridos, mejorando las características tixotrópicas de las composiciones de la invención. De manera específica, la presencia de ambos, dióxido de silicio coloidal y goma de polisacárido, en las composiciones de la invención mejora las características tixotrópicas más de lo que se podría esperar de la suma de los respectivos efectos mejoradores de la tixotropía

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individuales de los dos componentes.

[0067] Los inventores también han descubierto que, sorprendentemente, el agregado de una pequeña cantidad de dióxido de silicio coloidal a las composiciones en suspensión de la invención permite obtener una estabilidad química mejorada de la droga presente en la misma. Sin ligarse a una teoría en particular, actualmente se cree que el dióxido de silicio coloidal en las composiciones de la invención adsorbe el agente humectante, disminuyendo la concentración de agente humectante libre en comparación con una composición sin dióxido de silicio coloidal pero similar en todo lo demás; a su vez, se cree que la menor concentración de agente humectante libre causa una reducción de la concentración de droga libre y por lo tanto, un aumento de la proporción de droga presente en forma particulada, que es menos susceptible a la degradación química que la droga libre.

[0068] El dióxido de silicio coloidal en las composiciones de la invención también provee la sorprendente ventaja de reducir la retención de aire atrapado y por lo tanto, mejora la uniformidad de la dosis. Como se describió antes, el agente humectante libre puede estabilizar las burbujas de aire atrapadas dentro de una suspensión. Sin ligarse a una teoría, se cree que la adsorción de agente humectante libre por el dióxido de silicio coloidal presente en las composiciones de la invención hace que disminuya la concentración del agente humectante libre y, por lo tanto, las burbujas de aire atrapadas se vuelven más inestables.

[0069] En las composiciones de la invención se puede utilizar cualquier fuente de dióxido de silicio coloidal aceptable para uso farmacéutico. Los sinónimos no limitantes para dióxidos de silicio coloidales que son apropiados

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y los ejemplos de los mismos, incluyen *Aerosil*™ de Degussa, *Cab-O-Sil*™ de Cabot Corp., sílice ahumada, ácido silícico anhidro liviano, anhídrido silícico, dióxido de silicio ahumado, sílice coloidal, etc.

[0070] En una forma de realización que se prefiere actualmente, el dióxido de silicio coloidal tiene un área superficial específica entre aproximadamente 50 y aproximadamente 400, más preferiblemente entre aproximadamente 100 y aproximadamente 400, y aún más preferiblemente entre aproximadamente 150 y aproximadamente 400m^2/g. Los dióxidos de silicio coloidales que se prefieren también tienen un promedio ponderado de diámetros de partícula entre aproximadamente 7 y aproximadamente 40nm, y más preferiblemente entre aproximadamente 10 y aproximadamente 25nm. Un dióxido de silicio coloidal que se prefiere en particular para utilizar en las composiciones de la invención es *Cab-O-Sil*™.

[0071] En general, en las composiciones de la invención hay uno o más agentes de suspensión inorgánicos presentes, en una cantidad total entre aproximadamente 0,01% y aproximadamente 3,0%, preferiblemente entre aproximadamente 0,1% y aproximadamente 2,0%, y más preferiblemente entre aproximadamente 0,25% y aproximadamente 1,0% en peso.

Características tixotrópicas

[0072] Una característica benéfica de las composiciones de la invención es que en el estado estacionario son físicamente estables de manera sustancial y aún luego de una agitación suave se pueden verter fácilmente. El término "que se puede verter fácilmente" significa aquí que la composición se podrá verter fácilmente desde un envase apropiado, como por ejemplo un frasco o botella. El límite de fluencia relativamente alto de las composiciones

de la invención favorece la estabilidad física. Aquí, "límite de fluencia" (que aquí también se denomina viscosidad máxima) es una medida de la resistencia inicial a fluir bajo esfuerzo de una suspensión.

[0073] Alguien con experiencia en el arte puede optimizar fácilmente las cantidades totales y relativas de agente humectante, del agente de suspensión inorgánico, y de los agentes espesantes tixotrópicos, dentro de los rangos que se dan aquí, para proveer características reológicas apropiadas, desfloculación de las partículas de droga, y una concentración mínima de droga libre. Dicha optimización deberá considerar otros factores relevantes, como por ejemplo la droga en particular, el tamaño de partícula de la droga, su uniformidad y densidad, concentración de droga, excipientes adicionales que estén presentes, vida útil en almacenamiento que se desea, etc.

[0074] Para propósitos prácticos, se puede determinar si una composición en particular es tixotrópica de acuerdo con el Ensayo 1 a continuación.

Ensayo 1:

[0075] Se extrae una muestra de 1ml de una suspensión de ensayo después de dejarla en reposo durante por lo menos 60 minutos, y se pone en una cubeta P45 de un viscosímetro HAAKE CV 100 (equipado con un huso PK30-4) que se mantiene a 25°C durante todo el ensayo.

[0076] Se aplica a la muestra un esfuerzo cortante y se aumenta por incrementos entre 0 y 3seg^{-1} durante un período de 3 minutos y luego se hace disminuir por incrementos entre 3 y 0seg^{-1} durante otro período de 3 minutos. Se mide la viscosidad dinámica a una velocidad de esfuerzo de corte de 2 seg^{-1} donde se obtiene un estado estacionario. Se calcula el límite de

fluencia utilizando una regresión lineal de los datos entre 2 seg^{-1} y 3seg^{-1}.

[0077] Si durante el ensayo la muestra tiene una viscosidad máxima entre aproximadamente 5 y aproximadamente 50 Pa•s y una viscosidad dinámica, medida a 2 seg^{-1}, entre aproximadamente 0,3 y aproximadamente 20 Pa•s, se decide que la composición es tixotrópica.

[0078] Preferiblemente, el agente espesante tixotrópico y el agente de suspensión inorgánico están presentes en cantidades totales y relativas tales que, cuando se analiza una composición de la invención de acuerdo con el Ensayo 1, dicha composición tiene una viscosidad máxima entre aproximadamente 5 y aproximadamente 40, más preferiblemente entre aproximadamente 5 y aproximadamente 30, y aún más preferiblemente entre aproximadamente 5 y aproximadamente 25 Pa•s y, a una velocidad de corte de 2 seg^{-1}, la composición tiene una viscosidad dinámica entre aproximadamente 0,3 y aproximadamente 20, preferiblemente entre aproximadamente 0,4 y aproximadamente 15, y aún más preferiblemente entre aproximadamente 0,5 y aproximadamente 7 Pa•s.

[0079] En general, el agente espesante tixotrópico y el agente de suspensión inorgánico estarán presentes en una proporción en peso entre aproximadamente 10:1 y aproximadamente 1:10, preferiblemente entre aproximadamente 5:1 y aproximadamente 1:5, y más preferiblemente entre aproximadamente 2:1 y aproximadamente 1:2.

[0080] Es importante que, como las composiciones de la invención están sustancialmente desfloculadas y físicamente son estables de manera sustancial, no se requiere agitación para volver a dispersar las partículas de droga o para mezclar la suspensión antes de la administración. La agitación

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moderada facilitará el vertido de las composiciones en suspensión de la invención.

Excipientes farmacéuticos

[0081] Las composiciones de la invención pueden comprender cualquier excipiente adicional aceptable para uso farmacéutico. El término "excipiente" significa aquí cualquier sustancia, que en sí misma no es un agente terapéutico, que se utiliza como vehículo para administrar un agente terapéutico a un sujeto o que se agrega a una composición farmacéutica para mejorar sus propiedades de manipulación, almacenamiento, desintegración, dispersión, disolución, de liberación u organolépticas o para permitir o facilitar la formación de un artículo discreto como por ejemplo una cápsula apropiada para administración oral con una unidad de dosificación de la composición. Como ilustración, y no como limitación, los excipientes pueden incluir diluyentes, polímeros, sustancias que se agregan para enmascarar o contrarrestar un sabor u olor desagradables, sabores, tinturas, conservantes, fragancias, y sustancias que se agregan para mejorar el aspecto de la composición.

[0082] Las composiciones de la invención se pueden preparar mediante cualquier proceso apropiado, sin limitarse a los procesos que se describen aquí. Un proceso que sirve como ilustración comprende mezclar celecoxib, uno o más agentes humectantes, una goma de polisacárido, y dióxido de silicio junto con cualquier otro excipiente que se desee para formar una mezcla en polvo, y homogeneizar dicha mezcla en polvo junto con agua para formar una suspensión.

Utilidad de las composiciones de la invención

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[0083] Si las composiciones de la invención comprenden una droga inhibidora de COX-2 de baja solubilidad en agua, las mismas son útiles en el tratamiento y la prevención de un muy amplio espectro de trastornos mediados por COX-2, incluyendo pero sin restringirse a los trastornos que se caracterizan por inflamación, dolor y/o fiebre. Dichas composiciones son especialmente útiles como agentes antiinflamatorios, como por ejemplo en el tratamiento de la artritis, con el beneficio adicional de tener efectos secundarios significativamente menos dañinos que las composiciones de drogas antiinflamatorias no esteroides (NSAIDs) convencionales que carecen de selectividad por COX-2 con respecto a COX-1. En particular, las composiciones de la invención tienen un reducido potencial de toxicidad gastrointestinal y de irritación gastrointestinal incluyendo la ulceración y hemorragia del tracto gastrointestinal superior, un reducido potencial de efectos secundarios renales como por ejemplo de reducción de la función renal que causa retención de fluidos y exacerbación de la hipertensión, un efecto reducido de los tiempos de hemorragia que incluyen la inhibición de la función de plaquetas, y posiblemente una disminución de la capacidad de inducir ataques de asma en sujetos asmáticos sensibles a la aspirina, en comparación con las composiciones de NSAIDs convencionales. Por lo tanto, las composiciones de la invención son útiles en particular como alternativa a los NSAIDs convencionales donde dichos NSAIDs estén contraindicados, por ejemplo en pacientes con úlceras pépticas, gastritis, enteritis regional, colitis ulcerativa, diverticulitis o con historial de lesiones gastrointestinales recurrentes; hemorragia gastrointestinal, trastornos de coagulación que incluyen anemia como por ejemplo hipoprotrombinemia, hemofilia u otros

problemas de hemorragias; enfermedad renal; o en pacientes antes de cirugía o en pacientes que toman anticoagulantes.

[0084] Las composiciones que se contemplan son útiles para tratar una variedad de trastornos artríticos, que incluyen pero sin limitarse a, artritis reumatoide, espondiloartropatías, artritis gotosa, osteoartritis, lupus eritematoso sistémico y artritis juvenil.

[0085] Las composiciones con dichas características son útiles en el tratamiento de asma, bronquitis, calambres menstruales, trabajo de parto prematuro, tendinitis, bursitis, neuritis alérgica, infectividad por citomegalovirus, apoptosis que incluyen la apoptosis inducida por VIH, lumbago, enfermedad hepática incluyendo hepatitis, condiciones relacionadas con la piel como por ejemplo psoriasis, eczema, acné, quemaduras, dermatitis y daño por radiación ultravioleta incluyendo quemaduras de sol, e inflamaciones del postoperatorio que incluyen las posteriores a una cirugía oftálmica como por ejemplo a una cirugía de cataratas o a una cirugía refractiva.

[0086] Las composiciones con dichas características son útiles para tratar condiciones gastrointestinales como por ejemplo enfermedad inflamatoria del intestino, enfermedad de Crohn, gastritis, síndrome del intestino irritable y colitis ulcerativa.

[0087] Las composiciones con dichas características son útiles para tratar la inflamación en enfermedades tales como dolores de cabeza del tipo migraña, periarteritis nodosa, tiroiditis, anemia aplástica, enfermedad de Hodgkin, esclerodoma, fiebre reumática, diabetes de tipo 1, enfermedad de acoplamiento neuromuscular que incluye miastenia gravis, enfermedades de

la materia blanca que incluyen esclerosis múltiple, sarcoidosis, síndrome nefrótico, síndrome de Behcet, polimiositis, gingivitis, nefritis, hipersensibilidad, hinchazón posterior a heridas que incluyen edema cerebral, isquemia del miocardio, etcétera.

[0088] Las composiciones con dichas características son útiles en el tratamiento de enfermedades oftálmicas, como por ejemplo retinitis, conjuntivitis, retinopatías, uveitis, fotofobia ocular, y de heridas agudas al tejido ocular.

[0089] Las composiciones con dichas características son útiles en el tratamiento de la inflamación pulmonar, como por ejemplo aquellas que se asocian con infecciones virales y fibrosis quística, y en la reabsorción de huesos como por ejemplo aquellas que se asocian con la osteoporosis.

[0090] Las composiciones con dichas características son útiles para el tratamiento de ciertos trastornos del sistema nervioso central, como por ejemplo demencias corticales que incluyen la enfermedad de Alzheimer, neurodegeneración, y daño al sistema nervioso central posterior a una apoplejía, isquemia y trauma. En el contexto de la presente, el término "tratamiento" incluye la inhibición parcial o total de demencias, que incluyen la enfermedad de Alzheimer, demencia vascular, demencia por multi-infarto, demencia pre-senil, demencia alcohólica y demencia senil.

[0091] Las composiciones con dichas características son útiles en el tratamiento de la rinitis alérgica, síndrome de insuficiencia respiratoria, síndrome de shock por endotoxinas y enfermedad hepática.

[0092] Las composiciones con dichas características son útiles en el tratamiento del dolor, que incluyen pero sin limitarse: dolor del postoperatorio,

dolor dental, dolor muscular, y dolor causado por cáncer. Por ejemplo, dichas composiciones son útiles para aliviar el dolor, la fiebre y la inflamación en una variedad de condiciones que incluyen fiebre reumática, gripe y otras infecciones virales que incluyen resfrío común, dolor de cintura y cuello, dismenorrea, dolor de cabeza, dolor dental, esguinces y desgarros, miositis, neuralgia, sinovitis, artritis, que incluyen artritis reumatoide, enfermedades degenerativas de las articulaciones (osteoartritis), gota y espondilitis anquilosante, bursitis, quemaduras, y trauma posterior a procedimientos quirúrgicos y dentales.

[0093] Las composiciones con dichas características son útiles para tratar e impedir trastornos cardiovasculares relacionados con inflamación, que incluyen enfermedades vasculares, enfermedad de las arterias coronarias, aneurisma, rechazo vascular, ateroesclerosis, ateroesclerosis que incluye ateroesclerosis por transplante cardíaco, infarto de miocardio, embolia, apoplejía, trombosis que incluyen trombosis venosa, anginas que incluyen angina inestable, inflamación coronaria por placas, inflamación inducida por bacterias incluyendo inflamación inducida por Chlamydia, inflamación inducida por virus, e inflamación asociada con procedimientos quirúrgicos como por ejemplo implante vascular incluyendo cirugía de bypass de arteria coronaria, procedimientos de revascularización que incluyen angioplastia, implantación de un Stent, endarterectomía, u otros procedimientos invasivos que incluyen arterias, venas y capilares.

[0094] Las composiciones con dichas características son útiles en el tratamiento de trastornos relacionados con la angiogénesis en un sujeto, por ejemplo para inhibir la angiogénesis de un tumor. Dichas composiciones son

útiles en el tratamiento de neoplasias, que incluyen metástasis; condiciones oftalmológicas como por ejemplo rechazo de implante de córnea, neovascularización ocular, neovascularización de la retina que incluye neovascularización posterior a heridas o infección, retinopatía diabética, degeneración macular, fibroplasia retrolental y glaucoma neovascular; enfermedades ulcerativas como por ejemplo úlcera gástrica; condiciones patológicas pero no malignas, como por ejemplo hemanglomas, que incluyen hemagiomas infantiles, angiofibroma de la nasofaringe y necrosis avascular del hueso; y trastornos del sistema reproductor femenino como por ejemplo endometriosis.

[0095] Las composiciones con dichas características son útiles en la prevención y tratamiento de tumores benignos y malignos y neoplasia que incluyen cáncer, como por ejemplo cáncer colorrectal, cáncer del cerebro, cáncer de huesos, neoplasia derivada de células epiteliales (carcinoma epitelial) como por ejemplo carcinoma de célula basal, adenocarcinoma, cáncer gastrointestinal como por ejemplo cáncer de labios, cáncer de boca, cáncer esofágico, cáncer de intestino delgado, cáncer de estómago, cáncer de colon, cáncer de hígado, cáncer de vejiga, cáncer de páncreas, cáncer de ovarios, cáncer cervical, cáncer de pulmón, cáncer de mamas, cáncer de piel como por ejemplo cánceres de células escamosas y de células basales, cáncer de próstata, carcinoma de células renales, y otros cánceres conocidos que afectan las células epiteliales de todo el cuerpo. Las neoplasias para las cuales se contempla que las composiciones de la invención son útiles en particular son cáncer gastrointestinal, esófago de Barrett, cáncer hepático, cáncer de vejiga, cáncer pancreático, cáncer de ovarios, cáncer de próstata,

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cáncer cervical, cáncer de pulmón, cáncer de mamas y cáncer de piel. Dichas composiciones también se pueden utilizar para tratar las fibrosis que ocurren a causa de la terapia por radiaciones. Dichas composiciones se pueden utilizar para tratar sujetos con pólipos adenomatosos, incluyendo aquellas con poliposis adenomatosa familiar (FAP). Además, dichas composiciones se pueden utilizar para impedir que se formen pólipos en pacientes en riesgo de contraer FAP.

[0096] Las composiciones con dichas características inhiben la contracción del músculo liso inducida por prostanoides inhibiendo la síntesis de prostanoides contráctiles y por lo tanto se puede utilizar en el tratamiento de dismenorrea, trabajo de parto prematuro, asma y trastornos relacionados con eosinófilos. Las mismas también se pueden utilizar para disminuir la pérdida ósea, en particular en mujeres postmenopáusicas (es decir, para el tratamiento de osteoporosis), y para el tratamiento de glaucoma.

[0097] Los usos preferidos para las composiciones de la invención son el tratamiento de artritis reumatoide y osteoartritis, para gestión del dolor en general (en particular dolor posterior a cirugía oral, dolor posterior a cirugía general, dolor posterior a cirugía ortopédica, y exacerbaciones agudas de la osteoartritis), para el tratamiento de la enfermedad de Alzheimer, y para quimioprevención del cáncer de colon.

[0098] En el tratamiento de la artritis reumatoide o de la osteoartritis se pueden utilizar las composiciones de la invención para proveer una dosificación diaria de celecoxib de entre aproximadamente 50mg y aproximadamente 1000mg, preferiblemente entre aproximadamente 100mg y aproximadamente 600mg, más preferiblemente entre aproximadamente

150mg y aproximadamente 500mg, aún más preferiblemente entre aproximadamente 175mg y aproximadamente 400mg, por ejemplo aproximadamente 200mg. Cuando se administra en una composición de la invención, en general es apropiada una dosis diaria de celecoxib de entre aproximadamente 0,7 y aproximadamente 13mg/kg de peso corporal, preferiblemente entre aproximadamente 1,3 y aproximadamente 8mg/kg de peso corporal, más preferiblemente entre aproximadamente 2 y aproximadamente 6,7mg/kg de peso corporal, y aún más preferiblemente entre aproximadamente 2,3 y aproximadamente 5,3mg/kg de peso corporal, por ejemplo de aproximadamente 2,7mg/kg de peso corporal. Dicha dosis diaria se puede administrar en entre una y aproximadamente cuatro dosis por día, preferiblemente una o dos dosis por día.

[0099] En el tratamiento de la enfermedad de Alzheimer o de cáncer, se pueden utilizar las composiciones de la invención para proveer una dosificación diaria de celecoxib de entre aproximadamente 50mg y aproximadamente 1000mg, preferiblemente entre aproximadamente 100mg y aproximadamente 800mg, más preferiblemente entre aproximadamente 150mg y aproximadamente 600mg, y aún más preferiblemente entre aproximadamente 175mg y aproximadamente 400mg, por ejemplo de aproximadamente 400mg. Cuando se administra en una composición de la invención, en general es apropiada una dosis diaria entre aproximadamente 0,7 y aproximadamente 13mg/kg de peso corporal, preferiblemente entre aproximadamente 1,3 y aproximadamente 10,7mg/kg de peso corporal, más preferiblemente entre aproximadamente 2 y aproximadamente 8mg/kg de peso corporal, y aún más preferiblemente entre aproximadamente 2,3 y

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aproximadamente 5,3mg/kg de peso corporal, por ejemplo de aproximadamente 5,3mg/kg de peso corporal. La dosis diaria se puede administrar en entre una y aproximadamente cuatro dosis por día, preferiblemente en una o dos dosis por día.

[00100] Para la gestión del dolor se pueden utilizar las composiciones de la invención para proveer una dosificación diaria de celecoxib de entre aproximadamente 50mg y aproximadamente 1000mg, preferiblemente entre aproximadamente 100mg y aproximadamente 600mg, más preferiblemente entre aproximadamente 150mg y aproximadamente 500mg, y aún más preferiblemente entre aproximadamente 175mg y aproximadamente 400mg, por ejemplo, de aproximadamente 200mg. Cuando se administra en una composición de la invención, en general es apropiada una dosis diaria de celecoxib de entre aproximadamente 0,7 y aproximadamente 13mg/kg de peso corporal, preferiblemente entre aproximadamente 1,3 y aproximadamente 8mg/kg de peso corporal, más preferiblemente entre aproximadamente 2 y aproximadamente 6,7mg/kg de peso corporal, y aún más preferiblemente entre aproximadamente 2,3 y aproximadamente 5,3mg/kg de peso corporal, por ejemplo de aproximadamente 2,7mg/kg de peso corporal. La dosis diaria se puede administrar en entre una y aproximadamente cuatro dosis por día. Se prefiere la administración a una tasa de una unidad de dosificación de 50mg cuatro veces por día, una unidad de dosificación de 100mg o dos unidades de dosificación de 50mg dos veces al día o una unidad de dosificación de 200mg, dos unidades de dosificación de 100mg o cuatro unidades de dosificación de 50mg una vez al día.

[00101] Para drogas inhibidoras selectivas de COX-2 diferentes del

celecoxib, se puede seleccionar la dosis apropiada refiriéndose a la literatura de patentes que se citó aquí anteriormente.

[00102] Además de ser útiles para el tratamiento de humanos, las composiciones de la invención son útiles para el tratamiento veterinario de animales de compañía, animales exóticos, animales de granja, etcétera, en particular de mamíferos. Más en particular, las composiciones de la invención son útiles para el tratamiento de trastornos mediados por COX-2 en caballos, perros y gatos.

[00103] La presente invención se dirige además a un método terapéutico para tratar una condición o trastorno donde se indica el tratamiento con una droga inhibidora de COX-2, donde dicho método comprende la administración oral de una composición de la invención a un sujeto que la necesita. El régimen de dosificación para impedir, aliviar, o mejorar la condición o trastorno corresponde preferiblemente a un tratamiento de una vez diaria o dos veces al día, pero se puede modificar de acuerdo con varios de factores. Dichos factores incluyen el tipo, edad, peso, sexo, dieta y la condición médica del sujeto y la naturaleza y gravedad del trastorno. Por lo tanto, el régimen de dosificación que se emplee en efecto puede variar ampliamente y por lo tanto se puede desviar de los regímenes de dosificación preferidos que se establecieron antes.

[00104] El tratamiento inicial puede comenzar con un régimen de dosificación según se indicó anteriormente. En general, el tratamiento se continúa según sea necesario durante un período de entre varias semanas y varios meses o años hasta que la condición o el trastorno sean controlados o eliminados. Para determinar la efectividad de la terapia, los sujetos sometidos

a tratamiento con una composición de la invención se pueden monitorear de manera rutinaria mediante cualquiera de los métodos que se conocen bien en el arte. El análisis continuo de los datos de dichos monitoreos permite modificar el régimen de tratamiento durante la terapia, de manera de administrar la dosis óptimamente efectiva en cualquier punto del tiempo, y de manera que se pueda determinar la duración de dicho tratamiento. De esa manera, se pueden modificar racionalmente el régimen de tratamiento y el calendario de dosificación durante el transcurso de la terapia, para administrar la menor cantidad de la composición que muestre una efectividad satisfactoria, y para continuar la administración solamente durante tanto tiempo como sea necesario para tratar con éxito la condición o el trastorno.

[00105] Las presentes composiciones se pueden utilizar en terapias de combinación con opioides y otros analgésicos, que incluyen analgésicos narcóticos, antagonistas del receptor Mu, antagonistas del receptor Kappa, analgésicos no narcóticos (es decir no adictivos), inhibidores de la absorción de monoamina, agentes reguladores de adenosina, derivados canabinoides, antagonistas de la sustancia P, antagonistas del receptor de neuroquinina-1 y bloqueadores de canal de sodio, entre otros. Las terapias de combinación que se prefieren comprenden el uso de una composición de la invención con uno o más compuestos que se seleccionan entre el grupo que consiste en aceclofenac, acemetacina, ácido e-acetamidocaproico, acetaminofeno, acetaminosalol, acetanilida, ácido acetilsalicílico (aspirina), *S*-adenosilmetionina, alclofenac, alfentanil, alilprodine, alminoprofeno, aloxiprin, alfaprodine, bis(acetilsalicilato) de aluminio, amfenac, aminoclortenoxazina, ácido 3-amino-4-hidroxibutírico, 2-amino-4-picolina, aminopropilon,

aminopirina, amixetrina, salicilato de amonio, ampiroxicam, amtolmetin guacilo, anileridina, antipirina, salicilato de antipirina, antrafenina, apazona, bendazac, benorilato, benoxaprofeno, benzpiperilon, bencidamina, bencilmorfina, bermoprofeno, bezitramida, *α*-bisabolol, bromfenac, *p*-bromoacetanilida, acetato del ácido 5-bromosalicílico, bromosaligenina, bucetin, ácido buclóxico, bucolome, bufexamac, bumadizon, buprenorfina, butacetin, butibufen, butofanol, acetilsalicilato de calcio, carbamazepina, carbifeno, carprofeno, carsalam, clorobutanol, clortenoxazina, salicilato de colina, cinchofen, cinmetacina, ciramadol, clidanac, clometacina, clonitazeno, clonixin, clopirac, clove, codeína, metil bromuro de codeína, fosfato de codeína, sulfato de codeína, cropropamida, crotetamida, desomorfina, dexoxadrol, dextromoramida, dezocine, diampromide, diclofenac sódico, difenamizol, difenpiramida, diflunisal, dihidrocodeína, enol acetato de dihidrocodeinona, dihidromorfina, acetilsalicilato de dihidroxialumino, dimenoxadol, dimepheptanol, dimetiltiambuteno, butirato de dioxafetil, dipipanona, diprocetilo, dipirona, ditazol, droxicam, emorfazona, ácido enfenámico, epirizol, eptazocine, etersalate, etenzamida, etoheptazina, etoxazeno, etilmetiltiambuteno, etilmorfina, etodolac, etofenamato, etonitazeno, eugenol, felbinac, fenbufen, ácido fenclózico, fendosal, fenoprofeno, fentanil, fentiazac, fepradinol, feprazona, floctafenina, ácido flufenámico, flunoxaprofeno, fluoresona, flupirtina, fluprocuazona, flurbiprofeno, fosfosal, ácido gentísico, glafenina, glucametacina, salicilato de glicol, guayazuleno, hidrocodona, hidromorfona, hidroxipetidina, ibufenac, ibuprofeno, ibuproxam, salicilato de imidazol, indometacina, indoprofeno, isofezolac, isoladol, isometadona, isonixin, isoxepac, isoxicam, cetobemidona,

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cetoprofeno, cetorolac, *p*-lactofenetide, lefetamina, levorfanol, lofentanil, lonazolac, lomoxicam, loxoprofeno, acetilsalicilato de lisina, acetilsalicilato de magnesio, ácido meclofenámico, ácido mefenámico, meperidina, meptazinol, mesalamina, metazocine, clorhidrato de metazocine, metotrimeprazina, ácido metiazínico, metofoline, metopon, mofebutazona, mofezolac, morazone, morfina, clorhidrato de morfina, sulfato de morfina, salicilato de morfolina, mirofina, nabumetone, nalbufina, salicilato de 1-naftilo, naproxeno, narceína, nefopam, nicomorfina, nifenazona, ácido niflumico, nimesulide, 5'-nitro-2'-propoxiacetanilida, norlevorfanol, normetadona, normorfina, norpipanona, olsalazina, opio, oxaceprol, oxametacina, oxaprozin, oxicodona, oximorfona, oxifenbutazona, papaveretum, paranilina, parsalmide, pentazocina, perisoxal, fenacetín, fenadoxona, fenazocine, clorhidrato de fenazopiridina, phenocoll, fenoperidina, fenopirazona, acetilsalicilato de fenilo, fenilbutazona, salicilato de fenilo, feniramidol, picetoprofeno, piminodine, pipebuzone, piperilona, piprofeno, pirazolac, piritramida, piroxicam, pranoprofeno, proglumetacina, proheptazina, promedol, propacetamol, propiram, propoxifeno, propifenazona, procuazona, ácido protizínico, ramifenazona, remifentanil, metilsulfato de rimazolio, salacetamida, salicina, salicilamida, ácido o-salicilamida acético, ácido salicilsulfúrico, salsalte, salverine, simetride, salicilato de sodio, sufentanil, sulfasalazina, sulindac, superóxido dismutasa, suprofeno, suxibuzone, talniflumato, tenidap, tenoxicam, terofenamato, tetrandrine, tiazolinobutazona, ácido tiaprofenoico, tiaramida, tilidina, tinoridina, ácido tolfenámico, tolmetín, tramadol, tropesin, viminol, xenbucin, ximoprofeno, zaltoprofeno y zomepirac (véanse en The Merck Index, 12va Edición (1996), Therapeutic Category and Biological Activity Index, las listas tituladas

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"Analgesic" [Analgésico], "Anti-inflammatory" [Antiinflamatorio] y "Antipyretic" [Antipirético]").

[00106] Las terapias de combinación que se prefieren en particular comprenden el uso de una composición de la invención con un compuesto opioide, más en particular donde el compuesto opioide es codeína, meperidina, morfina o un derivado de las mismas.

[00107] El compuesto que se va a administrar en combinación con una droga inhibidora selectiva de COX-2 se puede formular separado de la droga o se puede co-formular con la droga en una composición de la invención. Si se co-formula una droga inhibidora selectiva de COX-2 con una segunda droga, por ejemplo una droga opioide, dicha segunda droga se puede formular en una forma de liberación inmediata, de efecto rápido, de liberación sostenida o de liberación dual.

EJEMPLOS

[00108] Los siguientes ejemplos se dan solamente con el propósito de servir como ilustración y no se deben interpretar como limitantes del alcance de la presente invención. Los ejemplos permitirán comprender mejor la invención y percibir mejor sus ventajas.

Ejemplo 1

[00109] Se prepararon seis suspensiones de celecoxib que comprendían los componentes que se muestran en la Tabla 1. Todos los componentes se mezclaron, y las suspensiones se homogeneizaron durante 5 minutos utilizando un emulsionador Silverson Laboratory Mixer Emulsifier.

Tabla 1. Composición (%) de las suspensiones de celecoxib S1-S6

Componente	S1	S2	S3	S4	S5	S6

Celecoxib	2	2	2	2	2	2
Goma xántica	0,5	-	0,5	0,5	0,5	-
Sílice coloidal	-	0,5	0,5	1,0	2,0	1,0
Polisorbato 80	0,5	0,5	0,5	0,5	0,5	0,5
Sacarosa	30	30	30	30	30	30
Ácido cítrico	1,31	1,31	1,31	1,31	1,31	1,31
Citrato de sodio	1,11	1,11	1,11	1,11	1,11	1,11
Tutti fruti	0,1	0,1	0,1	0,1	0,1	0,1
Benzoato de sodio	0,2	0,2	0,2	0,2	0,2	0,2
Rojo FD&C #40	0,1	0,1	0,1	0,1	0,1	0,1
Agua	c.s.p. 100	c.s.p. 100	c.s.p. 100	c.s.p. 100	c.s.p. 100	c.s.p. 100

Ejemplo 2

[00110] Se mantuvieron las suspensiones de celecoxib S1-S6 del Ejemplo 1 a temperatura ambiente durante 24 horas antes del muestreo. Luego se extrajo una muestra de 1,5ml de cada suspensión y se centrifugaron individualmente a 15.800g durante 60 minutos o a 43.000g durante 10 minutos. Después de la centrifugación, se extrajeron alícuotas de entre 0,1 y 0,5ml del sobrenadante de cada suspensión con una pipeta; cada alícuota se diluyó individualmente con metanol (desde 1:2 hasta 2:10) para precipitar la goma xántica. Luego se centrifugaron las muestras diluidas a 15.800g durante 15 minutos. Se determinó la concentración de droga libre, que se muestra en la Tabla 2, para las suspensiones S1 y S3-S5 mediante un análisis por cromatografía líquida de alto rendimiento (HPLC) del sobrenadante diluido.

Tabla 2. Concentración de droga libre (mg/ml) en suspensiones de celecoxib

S1 y S3-S5.

Suspensión de celecoxib	Concentración de droga libre
S1	0,311
S3	0,187
S4	0,009
S5	0,010

[00111] Según se muestra en la Tabla 2, las suspensiones de celecoxib que comprendían dióxido de silicio coloidal (S3-S5) tuvieron una pequeña concentración de droga libre en comparación con la suspensión de celecoxib S1 que no comprendía dióxido de silicio coloidal. Dichos datos sugieren que las drogas en suspensiones de celecoxib que comprenden dióxido de silicio coloidal son menos susceptibles a la degradación química que las suspensiones sin dióxido de silicio coloidal.

Ejemplo 3

[00112] Para estimar los efectos de dióxido de silicio coloidal sobre la sedimentación y la estabilidad física, se centrifugaron individualmente alícuotas de 10ml de las suspensiones de celecoxib S1-S3 a tres diferentes velocidades. Se cuantificaron los volúmenes de sedimento obtenidos en varios puntos de tiempo durante la centrifugación (Figs. 1-3). Como se muestra en la Fig. 1, después de centrifugar a 1500 RPM durante 5, 15 y 30 minutos, la suspensión de celecoxib S2 (que comprendía dióxido de silicio coloidal pero no comprendía goma xántica) dio un volumen de sedimento de 0,0375ml, mientras que no se observó sedimento en los recipientes que contenían las suspensiones de celecoxib S1 (con goma xántica pero sin dióxido de silicio coloidal) y S3 (con goma xántica y dióxido de silicio coloidal).

[00113] Según se muestra en la Fig. 2, la suspensión de celecoxib S1 mostró un mayor volumen de sedimento que la suspensión de celecoxib S3 después de centrifugarlas a 2500 RPM durante 30, 60 y 90 minutos. Además, según se muestra en la Fig. 3, la centrifugación a 3.000 RPM durante 5, 10 y 20 minutos de las suspensiones de celecoxib S1 y S2 produjo un mayor volumen de sedimento que la centrifugación de la suspensión de celecoxib S3 en las mismas condiciones.

[00114] Dichos datos indican que la presencia de goma xántica y dióxido de silicio coloidal juntos aumenta mucho las propiedades anti-sedimentación de las suspensiones de celecoxib en comparación con las suspensiones que comprenden tanto goma xántica como dióxido de silicio coloidal solos. Dicho efecto anti-sedimentación indica un aumento de la estabilidad física de la suspensión de celecoxib.

Ejemplo 4

[00115] Se determinó la reología de las suspensiones de celecoxib S1-S4 y S6 de acuerdo con el Ensayo 1 que se describió anteriormente. En la Tabla 3 se muestran las viscosidades dinámicas que se obtuvieron, medidas a 2 seg^{-1}, y el límite de fluencia.

Tabla 3. Reología de las suspensiones de celecoxib S1-S4 y S6.

Suspensión de Celecoxib	Viscosidad dinámica (Pa•s) (a velocidad de corte de 2 seg^{-1})	Límite de fluencia (Pa)
S1	3,21	5,3
S2	0,08	0,14
S3	3,58	6,2

S4	5,49	8,5
S6	0,13	0,16

[00116] Según se muestra en la Tabla 3, la presencia de goma xántica y dióxido de silicio coloidal juntos (suspensiones de celecoxib S3 y S4) tuvo un efecto sinergético sobre el límite de fluencia en comparación con la suspensión de celecoxib con dióxido de silicio coloidal pero sin goma xántica (S2 y S6) y con la suspensión de celecoxib con goma xántica pero sin dióxido de silicio coloidal (S1). Dicho aumento del límite de fluencia indica la presencia de una resistencia a fluir relativamente alta a bajos esfuerzos, por ejemplo ante los esfuerzos gravitacionales que actúan en la sedimentación de las partículas. A pesar del alto límite de fluencia que mostraron las suspensiones de celecoxib S3 y S4, las viscosidades dinámicas, medidas a una velocidad de corte de 2 seg^{-1}, fueron aún relativamente bajas, indicando una buena fluidez de las suspensiones después de alcanzar el límite de fluencia. Dichos datos indican que las suspensiones de celecoxib S3 y S4 son espesas en reposo pero fluidas luego de una agitación moderada. Dicho aumento de la viscosidad en reposo dará como resultado un aumento de la estabilidad física.

Ejemplo 5

[00117] Se prepararon cinco suspensiones de celecoxib, S7- S11, con los componentes que se muestran en la Tabla 4. Se mezclaron todos los componentes, y las suspensiones se homogeneizaron durante 5 minutos utilizando un emulsionador Silverson Laboratory Mixer Emulsifier.

Tabla 4. Composición (%) de las suspensiones de celecoxib S7-811.

Componente	S7	S8	S9	S10	S11

Celecoxib	2	2	2	2	2
Goma xántica	0,5	0,1	0,1	0,2	0,5
Sílice coloidal	0,5	0,5	-	0,5	0,5
Polisorbato 80	0,25	0,25	0,25	0,25	0,25
Sacarosa	38,25	30	30	30	30
Ácido cítrico	1,31	1,31	1,31	1,31	1,31
Citrato de sodio	1,11	1,11	1,11	1,11	1,11
Tutti fruti	0,05	0,1	0,1	0,1	0,1
Benzoato de sodio	0,2	0,2	0,2	0,2	0,2
Rojo FD&C #40	0,015	0,015	0,015	0,015	0,015
Solución de sorbitol al 70%	45	-	-	-	-
Agua	c.s.p. 100	c.s.p. 100	c.s.p. 100	c.s.p. 100	c.s.p. 100

Ejemplo 6

[00118] Se determinó la reología de las suspensiones de celecoxib S7-S11 de acuerdo con el Ensayo 1 que se describió anteriormente. En la Tabla 5 se muestran las viscosidades dinámicas, medidas a 2 seg^{-1}, y el límite de fluencia.

Tabla 5. Reología de las suspensiones de celecoxib S7-811.

Suspensión de celecoxib	Viscosidad dinámica (Pa•s) (a velocidad de corte de 2 seg^{-1})	Límite de fluencia (Pa)
S7	22,04	19
S8	0,612	0,75
S9	0,184	0,19

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S10	0,855	1,2
S11	3,566	5,9

[00119] Según se muestra en la Tabla 5, la presencia de una cantidad muy pequeña de goma xántica (0,2% o menos) en las suspensiones de celecoxib S8, S9 y S10 fue insuficiente para conferir una estabilidad física apropiada y características tixotrópicas a las suspensiones, aún si había dióxido de silicio presente (S8 y S10). En contraste, un 0,5% de goma xántica confirió características reológicas apropiadas a la suspensión de celecoxib S11. Los resultados para la suspensión de celecoxib S7 sugieren que altas concentraciones de azúcar en las composiciones de la invención aumentan mucho tanto el límite de fluencia como la viscosidad dinámica, de tal manera que la suspensión no se puede verter fácilmente aún después de una agitación suave.

[00120] Todas las referencias que se citan en la presente memoria descriptiva se incorporan aquí como referencia. La exposición de las referencias que se hace aquí es solamente para resumir lo que afirman sus autores y no se admite que ninguna referencia constituya arte anterior relevante con respecto a la posibilidad de patentar la presente. Los inventores se reservan el derecho a objetar la precisión y pertinencia de las referencias que se citan.

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REIVINDICACIONES

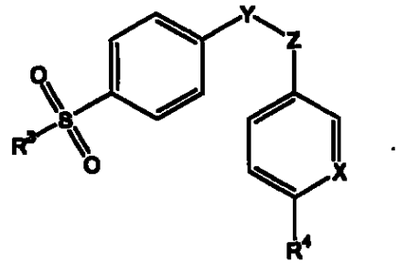
1. Una composición farmacéutica que comprende una droga de baja solubilidad en agua para administrar en forma oral y un vehículo líquido acuoso que comprende (a) un agente humectante aceptable para uso farmacéutico, (b) un agente espesante tixotrópico aceptable para uso farmacéutico, y (c) un agente de suspensión inorgánico aceptable para uso farmacéutico.

2. La composición de la reivindicación 1 donde se suspende en el vehículo por lo menos una porción sustancial de la droga en forma particulada para formar una suspensión y donde el agente humectante, el agente espesante y agente de suspensión están presentes en cantidades totales y relativas tales que la suspensión es tixotrópica, sustancialmente desfloculada, y que es físicamente estable de manera sustancial.

3. La composición de la reivindicación 1 donde la droga está presente en una cantidad total efectiva para uso terapéutico y/o para la profilaxis.

4. La composición de la reivindicación 1 donde la droga es una droga inhibidora selectiva de ciclooxigenasa-2 de baja solubilidad en agua.

5. La composición de la reivindicación 4 donde la droga inhibidora selectiva de ciclooxigenasa-2 es un compuesto de fórmula:



donde R^3 es un grupo metilo o amino, R^4 es hidrógeno o un grupo

alquilo C_{1-4} o alcoxi, X es N o CR^5 donde R^5 es hidrógeno o halógeno, e Y y Z son independientemente átomos de carbono o de nitrógeno que definen átomos adyacentes de un anillo de entre cinco y seis miembros que no está sustituido o está sustituido en una o más posiciones con grupos oxo, halo, metilo o halometilo.

6. La composición de la reivindicación 5 donde el anillo de entre cinco y seis miembros se selecciona entre el grupo que consiste en anillos ciclopentenona, furanona, metilpirazol, isoxazol y piridina que no están sustituidos en más de una posición.

7. La composición de la reivindicación 4 donde la droga inhibidora selectiva de ciclooxigenasa-2 se selecciona entre el grupo que consiste en celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, 2-(3,5-difluorofenil)-3-[4-(metilsulfonil)fenil]-2-ciclopenten-1-ona y ácido (S)-6,8-dicloro-2-(trifluorometil)-2H-1-benzopiran-3-carboxílico.

8. La composición de la reivindicación 4 donde la droga inhibidora selectiva de ciclooxigenasa-2 es celecoxib.

9. La composición de la reivindicación 1 donde la droga está presente en una cantidad entre aproximadamente 0,01% y aproximadamente 15% del peso total de la composición.

10. La composición de la reivindicación 1 donde la droga está presente en una cantidad entre aproximadamente 0,01% y aproximadamente 5% del peso total de la composición.

11. La composición de la reivindicación 1 donde el agente humectante se selecciona entre el grupo que consiste en compuestos de amonio cuaternario, dioctilsulfosuccinato sódico, éteres alquilfenílicos de polioxietileno,

poloxámeros, glicéridos de polioxietileno ácido graso y aceites, éteres alquílicos de polioxietileno, ésteres de ácido graso polioxietileno, ésteres de sorbitan polioxietileno, ésteres de ácido graso y propilenglicol, laurilsulfato de sodio, ácidos grasos y sales de los mismos, ésteres de glicerilo y ácido graso, ésteres de sorbitan, tiloxapol y mezclas de los mismos.

12. La composición de la reivindicación 1 donde el agente humectante se selecciona entre el grupo que consiste en cloruro de benzalconio, cloruro de bencetonio, cloruro de cetilpiridinio, dioctilsulfosuccinato sódico, nonoxinol 9, nonoxinol 10, octoxinol 9, polioxietileno 8 mono- y di-glicéridos caprílicos/cápricos, polioxietileno 35 aceite de castor, éter cetoestearílico de polioxietileno 20, polioxietileno 40 aceite de castor hidrogenado, éter oleílico de polioxietileno 10, estearato de polioxietileno 40, polisorbato 20, polisorbato 40, polisorbato 60, polisorbato 80, laurato de propilenglicol, laurilsulfato de sodio, monolaurato de sorbitan, monooleato de sorbitan, monopalmitato de sorbitan, monoestearato de sorbitan, tiloxapol y combinaciones de los mismos.

13. La composición de la reivindicación 1 donde el agente humectante es polisorbato 80.

14. La composición de la reivindicación 1 donde el agente humectante está presente en una cantidad entre aproximadamente 0,01% y aproximadamente 2% en peso.

15. La composición de la reivindicación 1 donde el agente humectante está presente en una cantidad entre aproximadamente 0,25% y aproximadamente 0,75% en peso.

16. La composición de la reivindicación 1 donde el agente espesante tixotrópico es un polímero celulósico.

17. La composición de la reivindicación 16 donde el agente espesante tixotrópico se selecciona entre el grupo que consiste en metilcelulosa, celulosa microcristalina, polivinilpirrolidona, e hidroxipropilmetilcelulosa.

18. La composición de la reivindicación 1 donde el agente espesante tixotrópico es una goma de polisacáridos.

19. La composición de la reivindicación 18 donde la goma de polisacárido se selecciona entre el grupo que consiste en gomas xántica, guar, de acacia, y tragacanto.

20. La composición de la reivindicación 18 donde la goma de polisacárido es goma xántica.

21. La composición de la reivindicación 1 donde el agente espesante tixotrópico está presente en una cantidad entre aproximadamente 0,25% y aproximadamente 2% en peso.

22. La composición de la reivindicación 1 donde el agente espesante tixotrópico está presente en una cantidad entre aproximadamente 0,4% y aproximadamente 2% en peso.

23. La composición de la reivindicación 1 donde el agente de suspensión inorgánico se selecciona entre el grupo que consiste en dióxido de silicio coloidal, bentonita y caolín.

24. La composición de la reivindicación 1 donde el agente de suspensión inorgánico es dióxido de silicio coloidal.

25. La composición de la reivindicación 24 donde el dióxido de silicio coloidal tiene un área superficial específica entre aproximadamente 50 y aproximadamente 400m^2/g.

26. La composición de la reivindicación 24 donde el dióxido de silicio

coloidal tiene un área superficial específica entre aproximadamente 150 y aproximadamente 400m^2/g.

27. La composición de la reivindicación 24 donde el dióxido de silicio coloidal tiene un promedio ponderado de diámetros de partícula entre aproximadamente 7 y aproximadamente 40nm.

28. La composición de la reivindicación 24 donde el dióxido de silicio coloidal tiene un promedio ponderado de diámetros de partícula entre aproximadamente 10 y aproximadamente 25nm.

29. La composición de la reivindicación 1 donde el agente de suspensión inorgánico está presente en una cantidad entre aproximadamente 0,01% y aproximadamente 3% en peso.

30. La composición de la reivindicación 24 donde el agente de suspensión inorgánico está presente en una cantidad entre aproximadamente 0,25% y aproximadamente 1% en peso.

31. La composición de la reivindicación 1 donde el agente espesante tixotrópico y el agente de suspensión inorgánico están presentes en una proporción en peso entre aproximadamente 10:1 y aproximadamente 1:10.

32. La composición de la reivindicación 1 donde el agente espesante tixotrópico y el agente de suspensión inorgánico están presentes en una proporción en peso entre aproximadamente 2:1 y aproximadamente 1:2.

33. La composición de la reivindicación 1 donde aproximadamente entre un 75% y el 100% de la droga está suspendida en forma de particulado.

34. La composición de la reivindicación 1 donde sustancialmente toda la droga está suspendida en forma de particulado.

35. La composición de la reivindicación 1 donde menos de

aproximadamente un 25% de la droga está disuelta y/o solubilizada.

36. La composición de la reivindicación 1 donde sustancialmente ninguna porción de la droga está disuelta ni solubilizada.

37. La composición de la reivindicación 1 la cual, cuando se analiza de acuerdo con el Ensayo 1, tiene una viscosidad máxima entre aproximadamente 5 y aproximadamente 50 Pa•s y una viscosidad dinámica medida a 2 seg^{-1} de entre aproximadamente 0,3 y aproximadamente 20 Pa•s.

38. La composición de la reivindicación 1 la cual, cuando se analiza de acuerdo con el Ensayo 1, tiene una viscosidad máxima entre aproximadamente 5 y aproximadamente 25 Pa•s y una viscosidad dinámica medida a 2 seg^{-1} de entre aproximadamente 0,5 y aproximadamente 7 Pa•s.

39. Un método para aumentar la estabilidad física de una composición farmacéutica de una droga de baja solubilidad en agua, donde dicho método comprende agregar a la composición un agente tixotrópico aceptable para uso farmacéutico y un agente de suspensión inorgánico aceptable para uso farmacéutico en cantidades que actúan en forma sinergética para aumentar la estabilidad física de la composición.

40. El método de la reivindicación 39 donde la composición comprende además un agente humectante.

41. El método de la reivindicación 40 donde una porción sustancial de la droga se suspende en forma particulada en el vehículo para formar una suspensión.

42. El método de la reivindicación 41 donde la composición está sustancialmente desfloculada.

43. El método de la reivindicación 39 donde el agente espesante

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tixotrópico es un polímero celulósico.

44. El método de la reivindicación 43 donde el agente espesante tixotrópico se selecciona entre el grupo que consiste en metilcelulosa, celulosa microcristalina, polivinilpirrolidona, e hidroxipropilmetilcelulosa.

45. El método de la reivindicación 39 donde el agente espesante tixotrópico es una goma de polisacáridos.

46. El método de la reivindicación 45 donde la goma de polisacárido se selecciona entre el grupo que consiste en gomas xántica, guar, de acacia, y tragacanto.

47. El método de la reivindicación 45 donde la goma de polisacárido es goma xántica.

48. El método de la reivindicación 39 donde el agente espesante tixotrópico está presente en una cantidad entre aproximadamente 0,25% y aproximadamente 2% en peso.

49. El método de la reivindicación 39 donde el agente espesante tixotrópico está presente en una cantidad entre aproximadamente 0,4% y aproximadamente 2% en peso.

50. El método de la reivindicación 39 donde el agente de suspensión inorgánico se selecciona entre el grupo que consiste en dióxido de silicio coloidal, bentonita y caolín.

51. El método de la reivindicación 39 donde el agente de suspensión inorgánico es dióxido de silicio coloidal.

52. El método de la reivindicación 51 donde el dióxido de silicio coloidal tiene un área superficial específica entre aproximadamente 50 y aproximadamente 400m^2/g.

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53. El método de la reivindicación 51 donde el dióxido de silicio coloidal tiene un área superficial específica entre aproximadamente 150 y aproximadamente 400m^2/g.

54. El método de la reivindicación 51 donde el dióxido de silicio coloidal tiene un promedio ponderado de diámetros de partícula entre aproximadamente 7 y aproximadamente 40nm.

55. El método de la reivindicación 51 donde el dióxido de silicio coloidal tiene un promedio ponderado de diámetros de partícula entre aproximadamente 10 y aproximadamente 25nm.

56. El método de la reivindicación 39 donde el agente de suspensión inorgánico está presente en una cantidad entre aproximadamente 0,01% y aproximadamente 3% en peso.

57. El método de la reivindicación 56 donde el agente de suspensión inorgánico está presente en una cantidad entre aproximadamente 0,25% y aproximadamente 1% en peso.

58. El método de la reivindicación 39 donde el agente espesante tixotrópico y el agente de suspensión inorgánico están presentes en una proporción en peso entre aproximadamente 10:1 y aproximadamente 1:10.

59. El método de la reivindicación 39 donde el agente espesante tixotrópico y el agente de suspensión inorgánico están presentes en una proporción en peso entre aproximadamente 2:1 y aproximadamente 1:2.

60. El método de la reivindicación 40 donde el agente humectante se selecciona entre el grupo que consiste en compuestos de amonio cuaternario, dioctilsulfosuccinato sódico, éteres alquilfenílicos de polioxietileno, poloxámeros, glicéridos de polioxietileno ácido graso y aceites, éteres

alquílicos de polioxietileno, ésteres de ácido graso polioxietileno, ésteres de sorbitan polioxietileno, ésteres de ácido graso y propilenglicol, laurilsulfato de sodio, ácidos grasos y sales de los mismos, ésteres de glicerilo y ácido graso, ésteres de sorbitan, tiloxapol y mezclas de los mismos

61. El método de la reivindicación 40 donde el agente humectante se selecciona entre el grupo que consiste en cloruro de benzalconio, cloruro de bencetonio, cloruro de cetilpiridinio, dioctilsulfosuccinato sódico, nonoxinol 9, nonoxinol 10, octoxinol 9, polioxietileno 8 mono- y di-glicéridos caprílicos/cápricos, polioxietileno 35 aceite de castor, éter cetoestearílico de polioxietileno 20, polioxietileno 40 aceite de castor hidrogenado, éter oleílico de polioxietileno 10, estearato de polioxietileno 40, polisorbato 20, polisorbato 40, polisorbato 60, polisorbato 80, laurato de propilenglicol, laurilsulfato de sodio, monolaurato de sorbitan, monooleato de sorbitan, monopalmitato de sorbitan, monoestearato de sorbitan, tiloxapol y combinaciones de los mismos.

62. El método de la reivindicación 40 donde el agente humectante es polisorbato 80.

63. El método de la reivindicación 40 donde el agente humectante está presente en una cantidad entre aproximadamente 0,01% y aproximadamente 2% en peso.

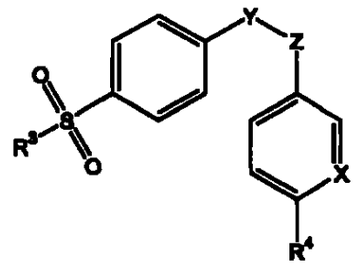
64. El método de la reivindicación 40 donde el agente humectante está presente en una cantidad entre aproximadamente 0,25% y aproximadamente 0,75% en peso.

65. El método de la reivindicación 39 donde la droga está presente en una cantidad total efectiva para uso terapéutico y/o para la profilaxis.

66. El método de la reivindicación 39 donde la droga es una droga

inhibidora selectiva de ciclooxigenasa-2 de baja solubilidad en agua.

67. El método de la reivindicación 66 donde la droga inhibidora selectiva de ciclooxigenasa-2 es un compuesto de fórmula:



donde R^3 es un grupo metilo o amino, R^4 es hidrógeno o un grupo alquilo C_{1-4} o alcoxi, X es N o CR^5 donde R^5 es hidrógeno o halógeno, e Y y Z son independientemente átomos de carbono o nitrógeno que definen átomos adyacentes de un anillo de entre cinco y seis miembros que no está sustituido o está sustituido en una o más posiciones con grupos oxo, halo, metilo o halometilo.

68. El método de la reivindicación 67 donde el anillo de entre cinco y seis miembros se selecciona entre el grupo que consiste en anillos ciclopentenona, furanona, metilpirazol, isoxazol y piridina que no están sustituidos en más de una posición.

69. El método de la reivindicación 68 donde la droga inhibidora selectiva de ciclooxigenasa-2 se selecciona entre el grupo que consiste en celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, 2-(3,5-difluorofenil)-3-[4-(metilsulfonil)fenil]-2ciclopenten-1-ona y ácido (S)-6,8-dicloro-2-(trifluorometil)-2H-1-benzopiran-3-carboxílico.

70. El método de la reivindicación 69 donde la droga inhibidora selectiva de ciclooxigenasa-2 es celecoxib.

71. El método de la reivindicación 39 donde la droga está presente en una cantidad entre aproximadamente 0,01% y aproximadamente 15% del peso total de la composición.

72. El método de la reivindicación 39 donde la droga está presente en una cantidad entre aproximadamente 0,01% y aproximadamente 5% del peso total de la composición.

73. El método de la reivindicación 41 donde entre aproximadamente un 75% y el 100% de la droga está suspendida en forma de particulado.

74. El método de la reivindicación 73 donde sustancialmente toda la droga está suspendida en forma de particulado.

75. El método de la reivindicación 39 donde menos de aproximadamente un 25% de la droga está disuelta y/o solubilizada.

76. El método de la reivindicación 39 donde sustancialmente ninguna porción de la droga está disuelta ni solubilizada.

77. El método de la reivindicación 39 donde la composición tiene una viscosidad máxima entre aproximadamente 5 y aproximadamente 50 Pa•s y una viscosidad dinámica medida a 2 seg^{-1} entre aproximadamente 0,3 y aproximadamente 20 Pa•s cuando se analiza de acuerdo con el Ensayo 1.

78. El método de la reivindicación 39 donde la composición tiene una viscosidad máxima entre aproximadamente 5 y aproximadamente 25 Pa•s y una viscosidad dinámica medida a 2 seg^{-1} entre aproximadamente 0,5 y aproximadamente 7 Pa•s cuando se analiza de acuerdo con el Ensayo 1.

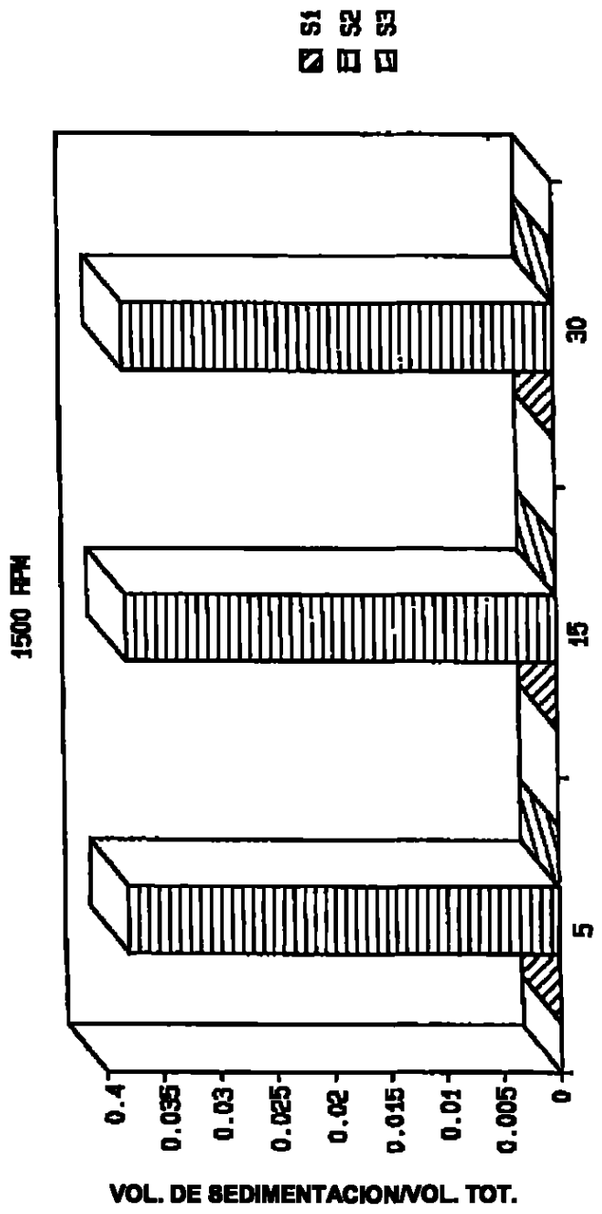


FIG. 1

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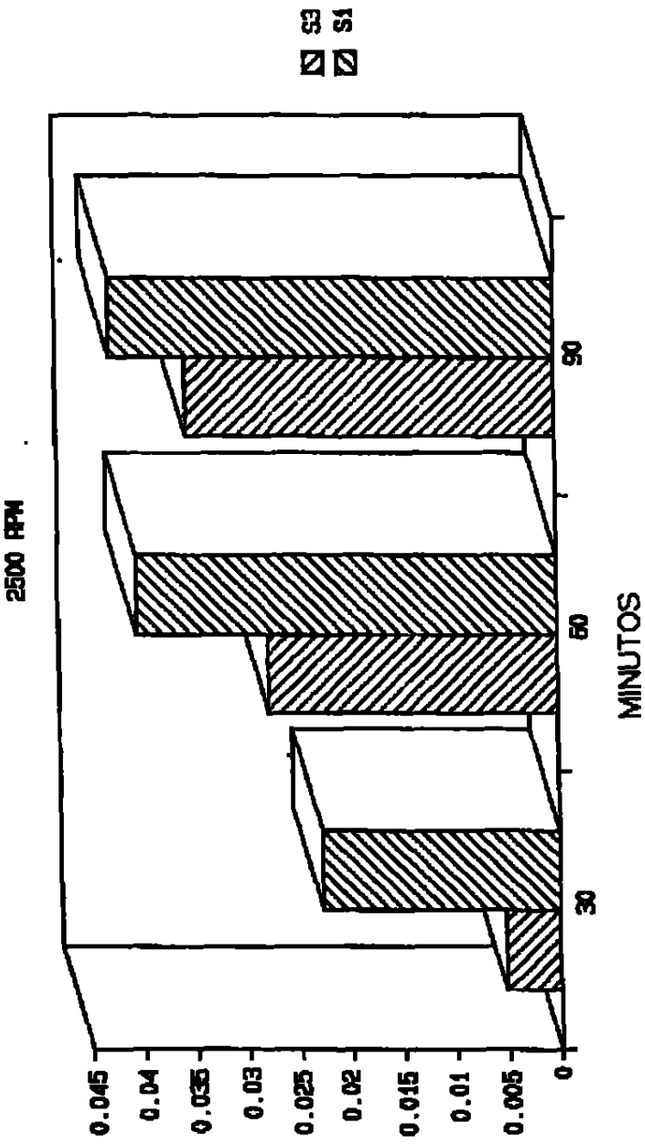
S3
S1
2500 RPM
90
60
30
MINUTOS
0.045
0.04
0.035
0.03
0.025
0.02
0.015
0.01
0.005
0
VOL. DE SEDIMENTACION/VOL. TOT.

FIG. 2

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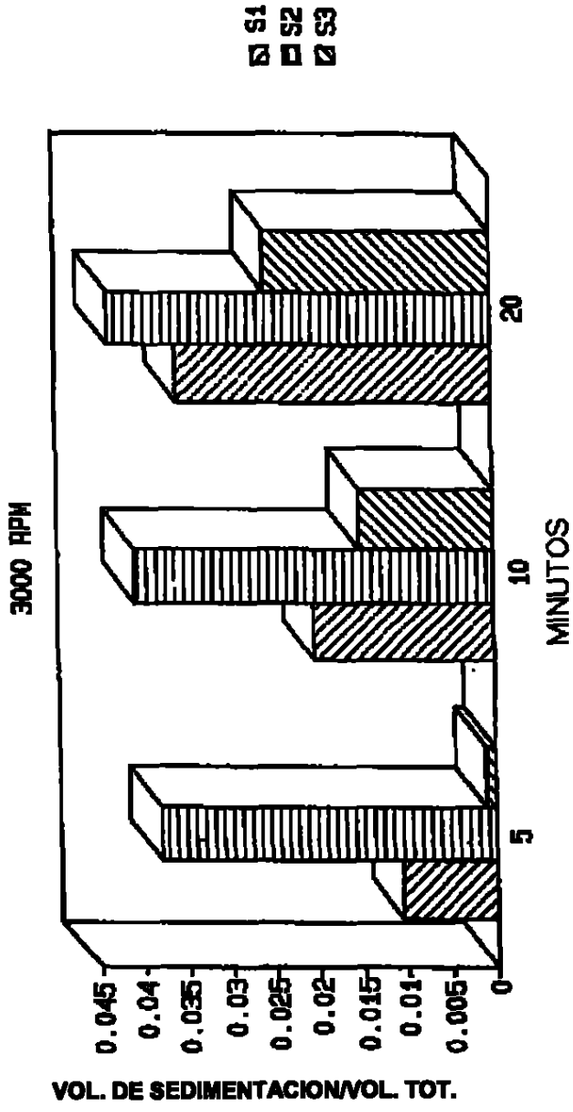

FIG. 3

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TRADUCCIÓN

(Al pie): Formulario PCT/ISA/210 (segunda hoja) (julio de 1992)

INFORME DE BÚSQUEDA INTERNACIONAL

Solicitud Internacional Nº: PCT/US 02/24746

A. Clasificación del objeto:

IPC 7 A61K9/10 A61K31/415 A61K31/635

Conforme a la Clasificación Internacional de Patentes (IPC) o a la clasificación nacional e IPC.

B: Campos investigados:

Documentación mínima investigada (sistema de clasificación seguido de símbolos de clasificación)

IPC 7 A61K

Base de datos electrónica consultada durante la búsqueda internacional (nombre de la base de datos y, si fuera conveniente, términos de búsqueda utilizados)

EPO-Internal, PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTOS CONSIDERADOS PERTINENTES

Categoría	Mención del documento con indicación, si fuera necesario, de las partes pertinentes	Pertinente a la reivindicación Nº
X	WO 93 20798 A (RIKER LABORATORIES INC) 28 octubre 1993 (1993-10-28)	1-3, 9-12,14, 15,18, 19,23, 24,31, 39-42, 45-47, 50,51, 56-58, 60,61, 71,72

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Y	página 1, línea 5 - línea 8 página 2, línea 21 - línea 29 página 2, línea 35 -página 3, línea 33 página 10; tabla 1 página 12; tabla 3 reivindicación 1	4-8,13, 16,17,

Se enumeran listados adicionales en la continuación del casillero C	Los miembros de la familia de patentes están enumerados en el anexo.
° Categorías especiales de los documentos citados 'A' documento que define el estado general de la técnica que no se considera de especial relevancia 'E' documento previo pero publicado en coincidencia o con posterioridad a la fecha de publicación internacional. 'L' documento que puede arrojar dudas respecto de la o las prioridades reivindicadas, o que se cita para establecer la fecha de publicación de otra cita u otra razòn especial (según se indica) 'O' documento que se refiere a la revelación oral, uso, exhibición u otras formas 'P' documento publicado antes de la fecha de presentación internacional pero después que la fecha de la prioridad reivindicada	'T' documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y que no representa un conflicto con la solicitud pero que se cita para comprender el principio o teoría subyacente de la invención. 'X' documento de especial relevancia; la invención reivindicada no puede considerarse novedosa ni que comprende un paso inventivo si el documetno se toma por sí solo 'Y' documento de especial relevancia; la invención reivindicada no puede considerarse que contenga un paso inventivo cuando el documento se combina con uno o más de dichos documentos, siendo dicha combinación obvia para para un especialista. '&' documento miembro de la misma familia de patentes
Fecha de la finalización real de la búsqueda internacional: 15 de octubre de 2002	Fecha de envío por correo del informe de búsqueda internacional: 28/10/2002
Nombre y dirección comercial de la ISA Oficina Europea de Patentes (sigue texto en otro idioma)	Funcionario autorizado: Von Eggelkraut, S

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Página 2 de 5

(Al pie): Formulario PCT/ISA/210 (continuación de la segunda hoja) (julio de 1992)

INFORME DE BÚSQUEDA INTERNACIONAL.

C.(Continuación) Documentos considerados relevantes		
Categoría	Cita del documento, con indicación, cuando corresponde, de las partes relevantes	Relevante a la reiv. Nro.
		21,22, 25-28, 33-36, 43,44, 52-55, 62-64, 66,73-76
	& US 5 112 604 A 12 mayo 1992 (1992-05-12) citada en la solicitud	
X	WO 91 08734 A (ABBOTT LAB) 27 junio 1991 (1991-06-27)	39-41, 50,51, 60-63, 65,71-76
	página 1, párrafo 2 página 3, línea 11,12 página 3, último párrafo -página 4, línea 10 página 9; ejemplo 10	
X	EP 0 257 288 A (ORATECH PHARM DEV CORP) 2 marzo 1988 (1988-03-02)	39,43, 44,50, 58,59
	página 1, línea 4 - línea 8 página 3, línea 28 - línea 44 página 5; ejemplo 3	
Y	WO 00 32189 A (GAO DANCHEN ;SEARLE & CO(US); MAZHARY AHMAD M (US); HLINAK ANTHON) 8 de Junio de 2000 (2000-06-08) citada en la solicitud	4-8,13, 16,17, 21,22, 25-28, 33-36, 43,44, 52-55, 62-64, 66,73-76
	página 47, línea 3-5	

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A	página 61, línea 7 - línea 9 WO 01 30342 A (CHEN YANG LING LING;TRUSTEES OF SOUTHERN ILLINOIS (US); LEE TONY) 3 de mayo de 2001 (2001-05-03) página 32, línea 9 - línea 13	
P,A	WO 02 05799 A (HASSAN FRED ;FORBES JAMES C(US); PHARMACIA CORP (US)) 24 enero 2002 (2002-01-24) página 101, línea 8 -página 102, línea 6 página 113, línea 10 -página 114, línea 17	

(Al pie): Formulario PCT/ISA/210 (continuación de la primera hoja (1)) (julio de 1998)

INFORME DE BÚSQUEDA INTERNACIONAL

Casillero I. Observaciones por imposibilidad de búsqueda de determinadas reivindicaciones (Continuación del ítem 1 de la primera hoja)

El presente Informe de la Búsqueda Internacional no fue realizado respecto de determinadas reivindicaciones bajo el Artículo 17(2)(a) por las siguientes causas:

2.Reiv. Nros.: porque se relacionan con partes de la Solicitud Internacional que no cumplen con los requisitos prestablecidos en una medida tal que no se puede efectuar una búsqueda internacional significativa, concretamente: ver INFORMACIÓN ADICIONAL del formulario PCT/ISA/210

INFORMACIÓN ADICIONAL del formulario PCT/ISA/210

Continuación del casillero I.2

Las reivindicaciones actuales 1 y 39 se relacionan con una cantidad extremadamente grande de compuestos posibles, caracterizados porque tienen una baja solubilidad en agua. En efecto, las reivindicaciones contienen tantas opciones que surge una falta de claridad según se

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establece en el Artículo 6 de PCT, en una medida tal que se hace imposible una búsqueda significativa de las mismas. En consecuencia, la búsqueda se ha efectuado para dichas partes de la solicitud que parecer ser claras, específicamente de los compuestos definidos en las reivindicaciones 4-8 y 66-70.

Se llama la atención del solicitante sobre el hecho de que no es necesario que las reivindicaciones, o las partes de las reivindicaciones, relacionadas con invenciones respecto de las cuales no se ha emitido un informe de la búsqueda internacional sean objeto de un examen preliminar internacional (Regla 66.1(e) PCT). Se informa al solicitante que la política de la OPE cuando actúa como Autoridad a Cargo del Examen Preliminar Internacional normalmente es no efectuar un examen preliminar de un objeto que no haya sido buscado. Este es así sin tener en cuenta si las reivindicaciones fueron modificadas despues de recibir el informe de la búsqueda o durante cualquier procedimiento del Capítulo II.

Página 5 de 5

(Al pie): Formulario PCT/ISA/210 (anexo de familia de patentes) (julio de 1992)

INFORME DE BÚSQUEDA INTERNACIONAL

Información sobre miembros de la familia de patentes.

Nro. de solicitud internacional: PCT/EP 02/24746.

Documento de patente citado en el informe de búsqueda	Fecha de publicación	Miembros de la familia de patentes			Fecha de publicación
WO 9320798 A	28-10-1993	US	5112804	A	12-05-1992
		AU	2397492	A	18-11-1993
		EP	0637235	A1	08-02-1995
		WO	9320798	A1	28-10-1993
WO 9108734 A	27-06-1991	AU	639004	B2	15-07-1993

			AU	5934290	A	18-07-1991
			CA	2060501	A1	14-12-1990
			EP	0477289	A1	01-04-1992
			GR	90100441	A,B	15-11-1991
			IE	902109	A1	02-01-1991
			IL	94710	A	26-05-1995
			JP	4506216	T	29-10-1992
			PT	94372	A	08-02-1991
			WO	9108734	A1	27-06-1991
EP 0257288	A	02-03-1988	US	4684666	A	04-08-1987
			AU	7567287	A	25-02-1988
			DK	321187	A	20-02-1988
			EP	0257288	A1	02-03-1988
			JP	63051325	A	04-03-1988
WO 0032189	A	08-06-2000	AU	748851	B2	13-06-2002
			AU	1838100	A	19-06-2000
			BG	104680	A	28-02-2001
			BR	9908030	A	28-11-2000
			CA	2319201	A1	08-06-2000
			CN	1288378	T	21-03-2001
			EE	200000437	A	15-06-2001
			EP	1049467	A1	08-11-2000
			HR	20000434	A1	31-08-2000
			HU	0100867	A2	28-03-2002
			NO	20003815	A	29-09-2000
			NZ	505762	A	28-06-2002
			PL	341372	A1	09-04-2001
			SK	11062000	A3	12-03-2001
			TR	200002207	T1	21-12-2000
			WO	0032189	A1	08-06-2000
			ZA	200002722	A	29-11-2000
WO 0130342	A	03-05-2001	AU	2298301	A	08-05-2001
			WO	0130342	A1	03-05-2001
WO 0205799	A	24-01-2002	AU	5754701	A	30-01-2002
			AU	7590801	A	30-01-2002
			AU	8288601	A	30-01-2002
			WO	0205848	A2	24-01-2002
			WO	0205815	A1	24-01-2002
			WO	0205799	A2	24-01-2002
			US	2002128267	A1	12-09-2002
			US	2002035264	A1	21-03-2002
			US	2002077328	A1	20-06-2002

PATENT COOPERATION TREATY

6794S-000009/POA

(4)

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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NOV 18 2003
HARNESS, DICKEY & PIERCE
ST. LOUIS, MISSOURI

PCT

137

To:

Holland, Donald R.
HARNESS, DICKEY & PIERCE P.L.C.
7700 Bonhomme Avenue, Suite 400
St. Louis, Missouri 63105
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	14.11.2003
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
6794S-000009	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US02/24746	05.08.2002	06.08.2001

Applicant
PHARMACIA CORPORATION et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Janzing, M Tel. +31 70 340-4140

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US02/24743

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I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Claims, Numbers

1-90 received on 19.08.2003 with letter of 19.08.2003

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/US02/24746

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☐ claims Nos.

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1,39, as far as the search has been restricted to those parts of the application which do appear to be clear, namely the compounds specified in claims 4-8 and 66-70.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-38,40-42,45-49,51-57,60-76,79-82,85,87-89
	No:	Claims	39,43,44,50,58,59, 77,78,83,84,86,90
Inventive step (IS)	Yes:	Claims	5-8,13, 16,17,20-22,25-30,32-38,48,49,52-55,62-65,67-70,73-76
	No:	Claims	1-4, 9-12, 14, 15, 18, 19, 23, 24, 31, 39-47, 50, 51, 56-61, 66, 71, 72 , 77-90
Industrial applicability (IA)	Yes:	Claims	1-90
	No:	Claims	

2. Citations and explanations

see separate sheet

I. Re Item I

Basis of the report

This report has been established as if the amendments of claims 37,38,77,78 had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c) PCT). Said claims are interpreted as encompassing the Test I specified in the description.

V. Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:

D1: WO 93 20798 A (RIKER LABORATORIES INC) 28 October 1993 (1993-10-28) & US 5 112 604 A 12 May 1992 (1992-05-12) cited in the application
D2: WO 91 08734 A (ABBOTT LAB) 27 June 1991 (1991-06-27)
D3: EP-A-0 257 288 (ORATECH PHARM DEV CORP) 2 March 1988 (1988-03-02)
D4: WO 00 32189 A (GAO DANCHEN ;SEARLE & CO (US); MAZHARY AHMAD M (US); HLINAK ANTHON) 8 June 2000 (2000-06-08) cited in the application

2 NOVELTY (Art. 33(2) PCT)

2.1 D3 discloses a stable liquid syrup comprising ibuprofen in suspension, bentonite and PVP (D3, page 28-44; page 5, example 3). The viscosity is claimed in the range of 1 to 3 Pa*s. The terms "physically stable, thixotropic, orally deliverable pharmaceutical composition" and "thixotropic amount" of an thixotropic thickening agent are not technical features in the sense that they do not provide a technical difference over the teaching of D3. Furthermore D3 teaches that stabilizing agents such as bentonite provide functions such as "aiding in dispersing and suspending the ibuprofen particles and then forming a protective molecular or fine particle coat around the suspended drug". "Aiding in dispersing and suspending" being encompassed by the term " physically stable. As bentonite is a thixotropic agent. Even if D3 does directly disclose the thixotropicity of the syrup and the absence of

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other distinguishing technical features, the presence of the thixotropic agent bentonit suggests that D3 falls within the scope of claims 39,43,44,50,58,59, 77,78,83,84,86,90.

2.2 The present application does not meet the requirements of Article 33(2) PCT because the subject-matter of claims 39,43,44,50,58,59, 77,78,83,84,86,90 is not new.

2.3 In view of the prior art cited, claims 1-38,40-42,45-49,51-57,60-76,79-82,85,87-89 appear to be novel and meet therefore the requirements of Art. 33(2) PCT.

3 **INVENTIVE STEP** (Art. 33(3) PCT)

3.1 Claims 39,43,44,50,58,59,77,78,83,84,86,90 are not new and therefore not inventive.

3.2 D1 discloses oral suspensions comprising a drug of low water solubility (D1, theophylline, salicylsalicylic acid), polysorbate, xanthan gum and silicium dioxide (D1, page 10, table 1; page 12, table 3). The suspensions are stable for a prolonged period of time (D1, page 2, lines 21-29). The difference between the present invention and the prior art is the amount of thickening agent in the composition. In the present invention an amount of at least 0.25 % of a thixotropic agent is used whereas D1 discloses 0.02 % -0.1 % in D1. The combination of xanthan gum and colloidal dioxide being known and there ability to form thixotropic compositions being state of the art knowledge, it is considered to be a matter of standard experimentation to arrive at the desired viscosity by combining the specific compounds subsummarized under the terms of "thixotropic thickening agent" and inorganic suspending agent" in appropriate amounts. Consequently, claims 1-4, 9-12, 14, 15, 18, 19, 23, 24, 31, 39-42, 45-47, 50, 51, 56-58, 60, 61, 66, 71, 72,79-82,85,87-89 are not inventive towards D1. The selection of specific compounds such as polysorbate 80, colloidal silica of a specific surface area and xanthan gum is considered to be inventive.

3.3 Consequently, claims 1-4, 9-12, 14, 15, 18, 19, 23, 24, 31, 39-47, 50, 51, 56- 61, 66, 71, 72 , 77-90 are not inventive (Art. 33(3) PCT).

3.4 Claims 5-8,13,16,17,20-22,25-30,32-38,48,49,52-55,62-65,67-70,73-76 are

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considered to be inventive.

4 Certain defects

4.1 It is clear from the description of the present application that a wetting agent is essential to the performance of the invention. Since independent claim 39 does not contain this feature it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3 (b)(i),(ii) PCT that any independent claim must contain all the technical features essential to the invention.

4.2 The claimed subject-matter of independent claims 1 and 39 is not adequate to provide a solution to the underlying problem of the invention as stated in paragraphs [0059] and [0067] of the present invention. Said claims are merely a statement of the problem stated in the description. As the solution to the problem lies in the selection of appropriate excipients such as the wetting agent, the polysaccharide gum and the active agent in an appropriate quantity, claims 1 and 39 lack of clarity and support (Art. 6 PCT).

WHAT IS CLAIMED IS:

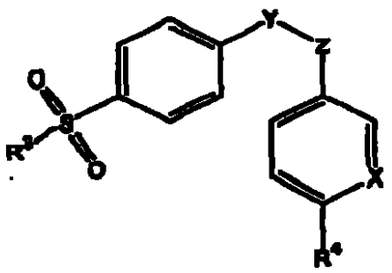
1. A physically stable, thixotropic, orally deliverable pharmaceutical composition comprising a drug of low water solubility and an aqueous liquid vehicle that comprises (a) a pharmaceutically acceptable wetting agent, (b) a pharmaceutically acceptable thixotropic thickening agent present in a thixotropic amount of at least about 0.25%, and (c) a pharmaceutically acceptable inorganic suspending agent.

2. The composition of Claim 1 wherein at least a substantial portion of the drug is suspended in particulate form in the vehicle to form a suspension that is substantially deflocculated.

3. The composition of Claim 1 wherein the drug is present in an amount of at least about 0.01%.

4. The composition of Claim 1 wherein the drug is a selective cyclooxygenase-2 inhibitory drug of low water solubility.

5. The composition of Claim 4 wherein the selective cyclooxygenase-2 inhibitory drug is a compound of formula



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups.

6. The composition of Claim 5 wherein the five- to six-membered ring is selected from the group consisting of cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

28. The composition of Claim 24 wherein the colloidal silicon dioxide has a weight average particle diameter of about 10 to about 25 nm.

29. The composition of Claim 1 wherein the inorganic suspending agent is present in an amount of about 0.01% to about 3%, by weight.

30. The composition of Claim 24 wherein the inorganic suspending agent is present in an amount of about 0.25% to about 1%, by weight.

31. The composition of Claim 1 wherein the thixotropic thickening agent and the inorganic suspending agent are present in a weight ratio of about 10:1 to about 1:10.

32. The composition of Claim 1 wherein the thixotropic thickening agent and the inorganic suspending agent are present in a weight ratio of about 2:1 to about 1:2.

33. The composition of Claim 1 wherein about 75% to 100% of the drug is suspended in particulate form.

34. The composition of Claim 1 wherein about 85% to 100% of the drug is suspended in particulate form.

35. The composition of Claim 1 wherein less than about 25% of the drug is dissolved and/or solubilized.

36. The composition of Claim 1 wherein less than about 10% of the drug is dissolved and/or solubilized.

37. The composition of Claim 1 wherein the composition has a maximum viscosity of about 5 to about 50 Pa-s and a dynamic viscosity measured at 2 sec^{-1} of about 0.3 to about 20 Pa-s.

38. The composition of Claim 1 wherein the composition has a maximum viscosity of about 5 to about 25 Pa-s and a dynamic viscosity measured at 2 sec^{-1} of about 0.5 to about 7 Pa-s.

39. A method for increasing the physical stability of an aqueous, thixotropic pharmaceutical composition of a drug of low water solubility, the method comprising adding to the composition a pharmaceutically acceptable thixotropic thickening agent in a thixotropic amount of at least about 0.25%,

and a pharmaceutically acceptable inorganic suspending agent in amounts which act synergistically to increase physical stability of the composition.

40. The method of Claim 39 wherein the composition further comprises a wetting agent.

41. The method of Claim 40 wherein a substantial portion of the drug is suspended in particulate form in a vehicle to form a suspension.

42. The method of Claim 41 wherein the composition is substantially deflocculated.

43. The method of Claim 39 wherein the thixotropic thickening agent is a cellulosic polymer.

44. The method of Claim 39 wherein the thixotropic thickening agent is selected from the group consisting of methylcellulose, microcrystalline cellulose, polyvinylpyrrolidone, and hydroxypropyl methycellulose.

45. The method of Claim 39 wherein the thixotropic thickening agent is a polysaccharide gum.

46. The method of Claim 45 wherein the polysaccharide gum is selected from the group consisting of xanthan, guar, acacia, and tragacanth gums.

47. The method of Claim 45 wherein the polysaccharide gum is xanthan gum.

48. The method of Claim 39 wherein the thixotropic thickening agent is present in an amount of about 0.25% to about 2%, by weight.

49. The method of Claim 39 wherein the thixotropic thickening agent is present in an amount of about 0.4% to about 2%, by weight.

50. The method of Claim 39 wherein the inorganic suspending agent is selected from the group consisting of colloidal silicon dioxide, bentonite and kaolin.

51. The method of Claim 39 wherein the inorganic suspending agent is colloidal silicon dioxide.

52. The method of Claim 51 wherein the colloidal silicon dioxide has a specific surface area of about 50 to about 400 m^2/g.

53. The method of Claim 51 wherein the colloidal silicon dioxide has a specific surface area of about 150 to about 400 m^2/g.

54. The method of Claim 51 wherein the colloidal silicon dioxide has a weight average particle diameter of about 7 to about 40 nm.

55. The method of Claim 51 wherein the colloidal silicon dioxide has a weight average particle diameter of about 10 to about 25 nm.

56. The method of Claim 39 wherein the inorganic suspending agent is present in an amount of about 0.01% to about 3%, by weight.

57. The method of Claim 56 wherein the inorganic suspending agent is present in an amount of about 0.25% to about 1%, by weight.

58. The method of Claim 39 wherein the thixotropic thickening agent and the inorganic suspending agent are present in a weight ratio of about 10:1 to about 1:10.

59. The method of Claim 39 wherein the thixotropic thickening agent and the inorganic suspending agent are present in a weight ratio of about 2:1 to about 1:2.

60. The method of Claim 40 wherein the wetting agent is selected from the group consisting of quaternary ammonium compounds, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, poloxamers, polyoxyethylene fatty acid glycerides and oils, polyoxyethylene alkyl ethers, polyoxyethylene fatty acid esters, polyoxyethylene sorbitan esters, propylene glycol fatty acid esters, sodium lauryl sulfate, fatty acids and salts thereof, glyceryl fatty acid esters, sorbitan esters, tyloxapol and mixtures thereof.

61. The method of Claim 40 wherein the wetting agent is selected from the group consisting of benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, dioctyl sodium sulfosuccinate, nonoxynol 9, nonoxynol 10, octoxynol 9, polyoxyethylene 8 caprylic/capric mono- and diglycerides, polyoxyethylene 35 castor oil, polyoxyethylene 20 cetostearyl ether, polyoxyethylene 40 hydrogenated castor oil, polyoxyethylene 10 oleyl ether, polyoxyethylene 40 stearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, propylene glycol laurate, sodium lauryl sulfate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, tyloxapol and combinations thereof.

62. The method of Claim 40 wherein the wetting agent is polysorbate 80.

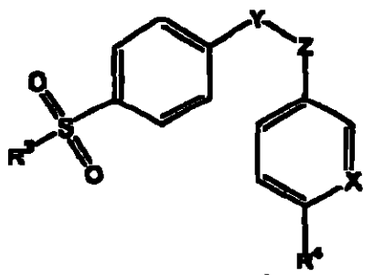
63. The method of Claim 40 wherein the wetting agent is present in an amount of about 0.01% to about 2%, by weight.

64. The method of Claim 40 wherein the wetting agent is present in an amount of about 0.25% to about 0.75%, by weight.

65. The method of Claim 39 wherein the drug is present in an amount of at least about 0.01%, on a weight per weight basis.

66. The method of Claim 39 wherein the drug is a selective cyclooxygenase-2 inhibitory drug.

67. The method of Claim 66 wherein the selective cyclooxygenase-2 inhibitory drug is a compound of formula



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups.

68. The method of Claim 67 wherein the five- to six-membered ring is selected from the group consisting of cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

69. The method of Claim 68 wherein the selective cyclooxygenase-2 inhibitory drug is selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

70. The method of Claim 69 wherein the selective cyclooxygenase-2 inhibitory drug is celecoxib.

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71. The method of Claim 39 wherein the drug is present in an amount of about 0.01% to about 15%, by total weight of the composition.

72. The method of Claim 39 wherein the drug is present in an amount of about 0.01% to about 5%, by total weight of the composition.

73. The method of Claim 41 wherein about 75% to 100% of the drug is suspended in particulate form.

74. The method of Claim 73 wherein about 85% to 100% of the drug is suspended in particulate form.

75. The method of Claim 39 wherein less than about 25% of the drug is dissolved and/or solubilized.

76. The method of Claim 39 wherein less than about 10% of the drug is dissolved and/or solubilized.

77. The method of Claim 39 wherein the composition has a maximum viscosity of about 5 to about 50 Pa•s and a dynamic viscosity measured at 2 sec^{-1} of about 0.3 to about 20 Pa•s.

78. The method of Claim 39 wherein the composition has a maximum viscosity of about 5 to about 25 Pa•s and a dynamic viscosity measured at 2 sec^{-1} of about 0.5 to about 7 Pa•s.

79. The composition of Claim 1, wherein the drug of low water solubility has a solubility in water, measured at 37°C, not greater than about 1 mg/ml.

80. The composition of Claim 1, wherein the drug of low water solubility has a solubility in water, measured at 37°C, not greater than about 0.1 mg/ml.

81. The composition of Claim 4, wherein the selective cyclooxygenase-2 inhibitory drug has a solubility in water, measured at 37°C, not greater than about 1 mg/ml.

82. The composition of Claim 4, wherein the selective cyclooxygenase-2 inhibitory drug has a solubility in water, measured at 37°C, not greater than about 0.1 mg/ml.

83. The method of Claim 39, wherein the drug of low water solubility has a solubility in water, measured at 37°C, not greater than about 1 mg/ml.

84. The method of Claim 39, wherein the drug of low water solubility has a solubility in water, measured at 37°C, not greater than about 0.1 mg/ml.

85. The composition of Claim 1 wherein the drug is present in an amount of no more than about 90%, on a weight per weight basis.

86. The method of Claim 39 wherein the drug is present in an amount of no more than about 90%, on a weight per weight basis.

87. The composition of Claim 1 wherein about 50% to 100% of the drug is suspended in particulate form.

88. The composition of Claim 1 wherein less than about 5% of the drug is dissolved and/or solubilized.

89. The method of Claim 41 wherein about 50% to 100% of the drug is suspended in particulate form.

90. The method of Claim 39 wherein less than about 5% of the drug is dissolved and/or solubilized.

TRADUCCIÓN

(Al pie): Formulario PCT/IPEA/416 (julio 1992)

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES (PCT)

NOTIFICACIÓN DE LA TRANSMISIÓN DEL EXAMEN PRELIMINAR INTERNACIONAL

(PCT Regla 71.1)

De: la Administración encargada del examen preliminar internacional

A: Holland, Donald R. HARNESS, DICKEY & PIERCE P.L.C. 770 Bonhomme Avenue, Suite 400, St. Louis, Missouri 63105, Estados Unidos de América

Fecha de envío: 14/11/2003

Referencia del expediente del solicitante o del agente: 6794S-000009.

NOTIFICACIÓN IMPORTANTE

Solicitud Internacional N° PCT/US02/24746

Fecha de presentación internacional: 05/08/2002

Fecha de prioridad: 06/08/2001

Solicitante: PHARMACIA CORPORATION y otros

1. Por la presente se notifica al solicitante que la Administración Encargada del Examen Preliminar envía junto con la presente el informe del examen preliminar internacional y sus anexos, si los hubiere, respecto de la solicitud internacional.

2. Se envía a la Oficina Internacional para que se informe a todas las Oficinas seleccionadas.

3. A solicitud de cualquiera de las Oficinas seleccionadas, la Oficina Internacional preparará una traducción al inglés del informe (pero no de los anexos) y enviará dicha traducción a las oficinas mencionadas.

4. Recordatorio

El solicitante debe ingresar en la fase nacional ante cada Oficina seleccionada efectuando diversos trámites (presentación de traducciones y pago de tasas nacionales) dentro de los 30 meses de la fecha de prioridad (o más adelante en algunas Oficinas) (Artículo 39 (1)) (véase también el recordatorio enviado por la Oficina Internacional con el Formulario PCT/IB/301).

Cuando se debe presentar una traducción de la solicitud internacional a una Oficina seleccionada, dicha traducción debe contener una traducción de todos los anexos del informe del examen preliminar internacional. Es responsabilidad del solicitante preparar y suministrar dicha traducción en forma directa a cada Oficina respectiva.

Para obtener más detalles sobre los plazos y otros requisitos aplicables en las Oficinas seleccionadas, véase el Volumen II de la Guía del Solicitante de PCT.

Se llama la atención del solicitante respecto del Artículo 33 (5) el cual provee los criterios de novedad, actividad inventiva y aplicabilidad industrial descritos en el Artículo 33(2) a (4) los cuales se establecen al solo efecto del examen preliminar internacional y que "cualquier país contratante puede aplicar criterios adicionales o diferentes a los efectos de decidir si, en dicho Estado, las invenciones reivindicadas son patentables o no" (véase también el Artículo 27(5)). Dichos criterios adicionales se pueden relacionar, por ejemplo, con excepciones a la patentabilidad, requisitos para permitir la revelación, claridad, y sustento de las reivindicaciones.

Nombre y dirección postal de la IPEA:

Oficina europea de patentes

P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk- Países Bajos

(siguen datos de teléfono, télex y fax).

Funcionario autorizado: JANZING, M.

Tel: +31 70 340-4140

(Página siguiente)

(Página siguiente)

(Al pie): Formulario PCT/IPEA/409 (carátula) (enero de 1994)

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES (PCT)

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

(PCT artículo 36 y Regla 70)

Referencia del expediente del solicitante o del agente: 6794S-000009.

Para realizar trámites posteriores: Ver la notificación de transmisión del Informe de Examen Preliminar Internacional (Formulario PCT/IPEA/416)

Publicación Internacional Nº PCT/US02/24746

Fecha de presentación internacional: 05/08/2002

Fecha de prioridad: 06/08/2001

Clasificación internacional de patentes (IPC) o clasificación nacional e IPC: A61K9/10

Solicitante: PHARMACIA CORPORATION y otros

1. Este informe de examen preliminar internacional ha sido preparado por esta Autoridad del examen preliminar Internacional y es comunicado al solicitante de acuerdo al artículo 36.

2. Este INFORME consta de un total de 6 hojas, incluyendo esta carátula.

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Este informe también incluye ANEXOS, es decir, páginas de la memoria, las reivindicaciones y/o los dibujos que han sido modificado y que son la base de este informe y/o páginas que contienen rectificaciones realizadas ente esta Autoridad (véase Regla 70.16 y Artículo 607 de las Instrucciones Administrativas bajo el TCP).

Dichos anexos constan de un total de 7 páginas.

3. Este informe contiene indicaciones relativas a los siguientes puntos:

I -Fundamento del informe

III- No se emite un dictamen con respecto la novedad, actividad inventiva y aplicación industrial.

V- Declaración justificada conforme al Artículo 66(2)(a)(ii) con respecto a la novedad, actividad inventiva y aplicabilidad industrial; citas y explicaciones que apoyen tal declaración.

Fecha de presentación de la solicitud: 7 de febrero de 2003.

Fecha de finalización de este informe: 14/11/2003

Nombre y dirección postal de la IPEA:

Oficina europea de patentes

P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk- Países Bajos

(siguen datos de teléfono, télex y fax).

Funcionario autorizado: VON EGGELKRAUT-GOTTA.

Tel: +31 70 340-4732

(Adjuntos):

(Al pie): Formulario PCT/IPEA/409 (julio 1999)

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional Nº **PCT/US02/24746**

I. Base del informe

1. Con respecto a los **elementos** de la solicitud internacional (Las hojas de reemplazo que han sido suministradas a la Oficina Receptora en respuesta a una invitación conforme al Artículo 14, se mencionan en este informe como "conforme a su presentación original" y no se anexan a este informe dado que no contienen modificaciones (Reglas 70.16 y 70.17):

Reivindicaciones, Nº:

1-90, recibido el 19/08/2003 con carta del 19/08/2003

2. Con respecto al **idioma**, todos los elementos marcados precedentemente fueron proporcionados a esta Autoridad en el idioma en que se presentó la solicitud internacional, salvo indicación en contrario en este item.(en blanco)

3. Con respecto a cualquier **secuencia de nucleótidos y/o aminoácidos** descripta en la solicitud internacional, el examen preliminar internacional se llevó a cabo en base al listado de secuencias: (en blanco).

4. Las modificaciones han ocasionado la anulación de:

(en blanco)

5. El presente informe ha sido formulado como si no se hubiesen presentado (algunas) de las modificaciones, que se ha considerado que iban más allá de la exposición de la invención tal como fue presentada, como se indica en el recuadro suplementario (Regla 70.2.c)).

(Cualquier hoja de reemplazo que contenga dichas modificaciones debe ser mencionada bajo el punto 1 y adjuntarse a este informe)

ver hoja adicional

6. Observaciones adicionales, si son necesarias: (en blanco)

III. No se emite dictamen con respecto a la novedad, actividad inventiva y

aplicabilidad industrial.

1. Las preguntas sobre si la invención reivindicada parece ser novedosa, implicar actividad inventiva (no ser obvia) o ser aplicable para uso industrial no han sido examinadas con respecto a:

No se ha efectuado la búsqueda internacional respecto de dichas reivindicaciones Nros. 1,39, ya que la búsqueda se restringe a las partes de la solicitud que son claras, es decir los compuestos de las reivindicaciones 4-8 y 66-70. 2. No se puede efectuar un examen preliminar internacional significativo debido a que el listado de secuencias de nucleòtidos y/o aminoácidos no cumple con las normas establecidas en el Anexo C de las Instrucciones Administrativas: (en blanco)

V. Declaración justificada conforme al Artículo 35(2) con respecto a novedad, actividad inventiva o aplicabilidad industrial; citas y explicaciones que sustentan esta declaración.

1. Declaración

Novedad (N) SI: Reivindicaciones: 1-38,40-42,45-49,51-57,60-76,79-82,85,87-89

No: Reivindicaciones 39,43,44,50,58,59,77,78,83,84,86,90

Actividad Inventiva: (IS) SI: Reivindicaciones: 5-8,13,16,17,20-22,25-30,32-38,48,49,52-55,62-65,67-70,73-76

No: Reivindicaciones: 1-4,9-12,14,15,18,19,23,24,31,39-47,50,51,56-61,66,71,72,77-90

Aplicabilidad Industrial (IA): SI: Reivindicaciones 1-90

2. Citas y explicaciones: ver hoja adicional.

(Al pie): Formulario PCT/Hoja adicional/409 (Hoja 1) (EPO abril 1997)

Informe del examen preliminar internacional – Hoja Adicional

Solicitud Internacional Nº PCT/US02/24746

I. En relación al Punto I

Base del Informe

Este informe ha sido efectuado como si las modificaciones a las reivindicaciones 37,38,77,78 no se hubieran efectuado, ya que se ha considerado que exceden la invención tal como fuera presentada (Regla 70.2(c) PCT). Dichas reivindicaciones se interpretan como abarcando la Prueba I descrita en la memoria.

V. En relación al Punto V

Declaración justificada conforme a la Regla 66(a)(ii) con respecto a novedad, actividad inventiva o aplicabilidad industrial; citas y explicaciones que sustentan esta declaración.

1. Se hace referencia a los siguientes documentos:

D1: WO 93 20798 A (RIKER LABORATORIES INC) 28 de octubre de 1993 (1993-10-28) & US 5 112 604 A 12 de mayo de 1992 (1992-05-12) citada en la solicitud

D2: WO 91 08734 A (ABBOTT LAB) 27 de junio de 1991 (1991-06-27)

D3: EP-A-0 257 288 (ORATECH PHARM DEV CORP) 2 de marzo de 1988 (1988-03-02)

D4: WO 00 32189 A (GAO DANCHEN ;SEARLE & CO (US); MAZHARY AHMAD M (US); HLINAK ANTHON) 8 de junio de 2000 (2000-06-08) citada en la solicitud

2 NOVEDAD (Art.33(2) PCT)

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2.1 El D3 describe un jarabe líquido estable que comprende ibuprofeno en suspensión, bentonita y PVP (D3, páginas 28-44; página 5, ejemplo 3). Se dice que la viscosidad está dentro del rango entre 1 y 3 Pa•s. Los términos "físicamente estable, tixotrópico, composición farmacéutica para administrar en forma oral" y "cantidad tixotrópica" de un agente espesante tixotrópico no son características técnicas en el sentido que no proveen una diferencia técnica con respecto a la descripción de D3. Además, el D3 describe que los agentes estabilizantes como por ejemplo la bentonita proveen funciones tales como "coadyuvar para dispersar y suspender las partículas de ibuprofeno y por lo tanto para formar un recubrimiento protector molecular o de partículas finas alrededor de la droga suspendida". El término "físicamente estable" abarca "coadyuvar para dispersar y suspender", porque la bentonita es un agente tixotrópico. Aunque D3 expone directamente la tixotropicidad del jarabe y la ausencia de otras características técnicas distintivas, la presencia del agente tixotrópico bentonita sugiere que el D3 queda dentro del alcance de las reivindicaciones 39, 43, 44, 50, 58, 59, 77, 78, 83, 84, 86, 90.

2.2 La presente solicitud no cumple los requisitos del Artículo 33(2) del TCP porque el objeto de las reivindicaciones 39, 43, 44, 50, 58, 59, 77, 78, 83, 84, 86, 90 no es novedoso.

2.3 En vista del arte anterior que se citó, las reivindicaciones 1-38, 40-42, 45-49, 51-57, 60-76, 79-82, 85, 87-89 parecen ser novedosas y por lo tanto cumplen con los requisitos del Art. 33(2) PCT.

3 ACTIVIDAD INVENTIVA Art. 33(3)PCT)

3.1 Las reivindicaciones 39, 43, 44, 50, 58, 59, 77, 78, 83, 84, 86, 90 no son novedosas y por lo tanto no presentan actividad inventiva.

3.2 El D1 describe suspensiones orales que comprenden una droga de baja solubilidad en agua (D1, teofilinas, ácido salicilsalicílico), polisorbato, goma xántica y dióxido de silicio (D1, página 10, tabla 1; página 12, tabla 3). Las suspensiones son estables durante un período de tiempo prolongado (D1, página 2, líneas 21-29). La diferencia entre la presente invención y el arte anterior es la cantidad de agente espesante en la composición. En la presente invención se utiliza una cantidad de un agente tixotrópico de por lo menos 0,25% mientras que en el D1 se indica 0,02% - 0,1%. Como la combinación de goma xántica y dióxido coloidal es conocida y su capacidad de formar composiciones tixotrópicas es un conocimiento del estado actual de la técnica, se considera que llegar a la viscosidad que se desea combinando los compuestos específicos que se incluyen en los términos "agente espesante tixotrópico" y "agente de suspensión inorgánico" en las cantidades apropiadas es cuestión de experimentación estándar. En consecuencia, las reivindicaciones 1-4, 9-12, 14, 15, 18, 19, 23, 24, 31, 39-42, 45-47, 50, 51, 56-58, 60, 61, 66, 71, 72, 79-82, 85, 87-89 no presentan actividad inventiva con respecto al D1. Se considera que la selección de compuestos específicos tales como polisorbato 80, sílice coloidal de un área superficial específica y goma xántica constituye una invención.

3.3 En consecuencia, las reivindicaciones 1-4, 9-12, 14, 15, 18, 19, 23, 24, 31, 39-47, 50, 51, 56-61, 66, 71, 72, 77-90, no presentan actividad inventiva (Art. 33(3) TCP).

3.4 Se considera que las reivindicaciones 5-8, 13, 16, 17, 20-22, 25-30, 32-38, 48, 49, 52-55, 62-65, 67-70, 73-76 presentan actividad inventiva.

4. DEFECTOS PUNTUALES

4.1 De la descripción de la presente solicitud surge claramente que para

cumplir con la función de la invención es esencial un agente humectante. Como la reivindicación independiente 39 no contiene dicha característica, la misma no satisface el requerimiento que se desprende al tomar el Artículo 6 TCP en combinación con la Regla 6.3 (b) (i), (ii) TCP de que cualquier reivindicación independiente debe contener todas las características técnicas que son esenciales para la invención.

4.2 El objeto de las reivindicaciones independientes 1 y 39 no es adecuado para proveer una solución al problema que subyace a la invención según se especifica en los párrafos [0059] y [0067] de la presente invención. Dichas reivindicaciones son solamente una exposición del problema que se especifica en la descripción. Como la solución a dicho problema se basa en la selección de los excipientes apropiados tales como el agente humectante, la goma de polisacárido y el agente activo en una cantidad apropiada, las reivindicaciones 1 y 39 carecen de claridad y sustento (Art. 6 PCT).

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PÁGINAS MODIFICADAS

REIVINDICACIONES

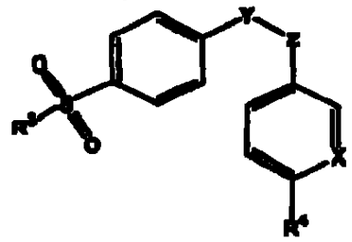
1. Una composición farmacéutica físicamente estable, tixotrópica, que comprende una droga de baja solubilidad en agua, para administrar en forma oral y un vehículo líquido acuoso que comprende (a) un agente humectante aceptable para uso farmacéutico, (b) un agente espesante tixotrópico aceptable para uso farmacéutico presente en una cantidad tixotrópica de por lo menos aproximadamente 0,25%, y (c) un agente de suspensión inorgánico aceptable para uso farmacéutico.

2. La composición de la reivindicación 1 donde por lo menos una porción sustancial de la droga está suspendida en el vehículo en forma particulada para formar una suspensión que está sustancialmente desfloculada.

3. La composición de la reivindicación 1 donde la droga está presente en una cantidad de por lo menos aproximadamente 0,01%.

4. La composición de la reivindicación 1 donde la droga es una droga inhibidora selectiva de ciclooxigenasa-2 de baja solubilidad en agua.

5. La composición de la reivindicación 4 donde la droga inhibidora selectiva de ciclooxigenasa-2 es un compuesto de fórmula:



donde R^3 es un grupo metilo o amino, R^4 es hidrógeno o un grupo alquilo C_{1-4} o alcoxi, X es N o CR^5 donde R^5 es hidrógeno o halógeno e Y y Z son

independientemente átomos de carbono o nitrógeno que definen átomos adyacentes de un anillo de entre cinco y seis miembros que no está sustituido o está sustituido en una o más posiciones con grupos oxo, halo, metilo o halometilo.

6. La composición de la reivindicación 5 donde el anillo de entre cinco y seis miembros se selecciona entre el grupo que consiste en anillos ciclopentenona, furanona, metilpirazol, isoxazol y piridina que no están sustituidos en más de una posición.

28. La composición de la reivindicación 24 donde el dióxido de silicio coloidal tiene un promedio ponderado de diámetros de partícula entre aproximadamente 10 y aproximadamente 25mm.

29. La composición de la reivindicación 1 donde el agente de suspensión inorgánico está presente en una cantidad entre aproximadamente 0,01% y aproximadamente 3% en peso

30. La composición de la reivindicación 24 donde el agente de suspensión inorgánico está presente es una cantidad entre aproximadamente 0,25% y aproximadamente 1% en peso

31. La composición de la reivindicación 1 donde el agente espesante tixotrópico y el agente de suspensión inorgánico están presentes en una proporción en peso entre aproximadamente 10:1 y aproximadamente 1:10.

32. La composición de la reivindicación 1 donde el agente espesante tixotrópico y el agente de suspensión inorgánico están presentes en una proporción en peso entre aproximadamente 2:1 y aproximadamente 1:2

33. La composición de la reivindicación 1 donde entre aproximadamente un 75% y el 100% de la droga está suspendida en forma de particulado.

34. La composición de la reivindicación 1 donde entre aproximadamente un 85% y el 100% de dicha droga está suspendida en forma de particulado.

35. La composición de la reivindicación 1 donde menos de aproximadamente un 25% de la droga está disuelta y/o solubilizada.

36. La composición de la reivindicación 1 donde menos de aproximadamente un 10% de la droga está disuelta y/o solubilizada.

37. La composición de la reivindicación 1 donde la composición tiene una viscosidad entre aproximadamente 5 y aproximadamente 50 Pa•s y una

viscosidad dinámica medida a 2 seg^{-1} entre aproximadamente 0,3 y aproximadamente 20 Pa•s.

38. La composición de la reivindicación 1 donde la composición tiene una viscosidad máxima entre aproximadamente 5 y aproximadamente 25 Pa•s y una viscosidad dinámica medida a 2 seg^{-1} entre aproximadamente 0,5 y aproximadamente 7 Pa•s.

39. Un método para aumentar la estabilidad física de una composición farmacéutica acuosa, tixotrópica de una droga de baja solubilidad en agua, donde el método comprende agregar a la composición un agente espesante tixotrópico aceptable para uso farmacéutico en una cantidad tixotrópica de por lo menos aproximadamente 0,25%, y un agente de suspensión inorgánico aceptable para uso farmacéutico en cantidades que actúan en forma sinergética para aumentar la estabilidad física de la composición.

40. El método de la reivindicación 39 donde la composición comprende además un agente humectante.

41. El método de la reivindicación 40 donde una porción sustancial de la droga está suspendida en forma particulada en un vehículo para formar una suspensión.

42. El método de la reivindicación 41 donde la composición está sustancialmente desfloculada.

43. El método de la reivindicación 39 donde el agente espesante tixotrópico es un polímero celulósico.

44. El método de la reivindicación 39 donde el agente espesante tixotrópico se selecciona entre el grupo que consiste en metilcelulosa, celulosa microcristalina, polivinilpirrolidona, e hidroxipropilmetilcelulosa.

45. El método de la reivindicación 39 donde el agente espesante tixotrópico es una goma de polisacáridos.

46. El método de la reivindicación 45 donde la goma de polisacárido se selecciona entre el grupo que consiste en gomas xántica, guar, de acacia, y tragacanto.

47. El método de la reivindicación 45 donde la goma de polisacárido es goma xántica.

49. El método de la reivindicación 39 donde el agente espesante tixotrópico está presente en una cantidad entre aproximadamente 0,25% y aproximadamente 2% en peso.

49 El método de la reivindicación 39 donde el agente espesante tixotrópico está presente en una cantidad entre aproximadamente 0,4% y aproximadamente 2% en peso.

50. El método de la reivindicación 39 donde el agente de suspensión inorgánico se selecciona entre el grupo que consiste en dióxido de silicio coloidal, bentonita y caolín.

51. El método de la reivindicación 39 donde el agente de suspensión inorgánico es dióxido de silicio coloidal.

52. El método de la reivindicación 51 donde el dióxido de silicio coloidal tiene un área superficial específica entre aproximadamente 50 y aproximadamente 400 m^2/g.

53. El método de la reivindicación 51 donde el dióxido de silicio coloidal tiene un área superficial específica entre aproximadamente 150 y aproximadamente 400 m^2/g.

54. El método de la reivindicación 51 donde el dióxido de silicio coloidal

tiene un promedio ponderado de diámetros de partícula entre aproximadamente 7 y aproximadamente 40nm.

55. El método de la reivindicación 51 donde el dióxido de silicio coloidal tiene un promedio ponderado de diámetros de partícula entre aproximadamente 10 y aproximadamente 25nm.

56. El método de la reivindicación 39 donde el agente de suspensión inorgánico está presente en una cantidad entre aproximadamente 0,01% y aproximadamente 3% en peso.

57. El método de la reivindicación 56 donde el agente de suspensión inorgánico está presente en una cantidad entre aproximadamente 0,25% y aproximadamente 1% en peso

58. El método de la reivindicación 39 donde el agente espesante tixotrópico y el agente de suspensión inorgánico están presentes en una proporción en peso entre aproximadamente 10:1 y aproximadamente 1:10.

59. El método de la reivindicación 39 donde el agente espesante tixotrópico y el agente de suspensión inorgánico están presentes en una proporción en peso entre aproximadamente 2:1 y aproximadamente 1:2.

60. El método de la reivindicación 40 donde el agente humectante se selecciona entre el grupo que consiste en compuestos de amonio cuaternario, dioctilsulfosuccinato sódico, éteres alquilfenílicos de polioxietileno, poloxámeros, glicéridos de polioxietileno ácido graso y aceites, éteres alquílicos de polioxietileno, ésteres de ácido graso polioxietileno, ésteres de sorbitan polioxietileno, ésteres de ácido graso y propilenglicol, laurilsulfato de sodio, ácidos grasos y sales de los mismos ésteres de glicerilo y ácido graso, ésteres de sorbitan, tiloxapol y mezclas de los mismos.

61. El método de la reivindicación 40 donde el agente humectante se selecciona entre el grupo que consiste en cloruro de benzalconio, cloruro de bencetonio, cloruro de cetilpiridinio, dioctilsulfosuccinato sódico, nonoxinol 9, nonoxinol 10, octoxinol 9, polioxietileno 8 mono- y di-glicéridos caprílicos/cápricos, polioxietileno 35 aceite de castor, éter cetoestearílico de polioxietileno 20, polioxietileno 40 aceite de castor hidrogenado, éter oleílico de polioxietileno 10, estearato de polioxietileno 40, polisorbato 20, polisorbato 40, polisorbato 60, polisorbato 80, laurato de propilenglicol, laurilsulfato de sodio, monolaurato de sorbitan, monooleato de sorbitan, monopalmitato de sorbitan, monoestearato de sorbitan, tiloxapol y combinaciones de los mismos.

62. El método de la reivindicación 40 donde el agente humectante es polisorbato 80.

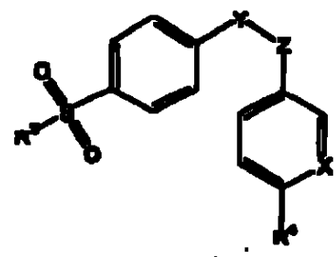
63. El método de la reivindicación 40 donde el agente humectante está presente en una cantidad entre aproximadamente 0,01% y aproximadamente 2% en peso.

64. El método de la reivindicación 40 donde el agente humectante está presente en una cantidad entre aproximadamente 025% y aproximadamente 0,75% en peso.

65. El método de la reivindicación 39 donde la droga está presente en una cantidad de por lo menos aproximadamente 0,01% peso en peso.

66. El método de la reivindicación 39 donde la droga es una droga inhibidora selectiva de ciclooxigenasa-2.

67. El método de la reivindicación 66 donde la droga inhibidora selectiva de ciclooxigenasa-2 es un compuesto de fórmula



donde R^3 es un grupo metilo o amino, R^4 es hidrógeno o un grupo alquilo C_{1-4} o alcoxi, X es N o CR^5 donde R^5 es hidrógeno o halógeno, e Y y Z son independientemente átomos de carbono o nitrógeno que definen átomos adyacentes de un anillo de entre cinco y seis miembros que no está sustituido o está sustituido en una o más posiciones con grupos oxo, halo, metilo o halometilo.

68. El método de la reivindicación 67 donde el anillo de entre cinco y seis miembros se selecciona entre el grupo que consiste en anillos ciclopentenona, furanona, metilpirazol, isoxazol y piridina que no está sustituidos en más de una posición.

69. El método de la reivindicación 68 donde la droga inhibidora selectiva de ciclooxigenasa-2 se selecciona entre el grupo que consiste en celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, 2-(3,5-difluorofenil)-3-[4-(metilsulfonil)fenil]-2-ciclopenten-1-ona y ácido (S)-6,8-dicloro-2-(trifluorometil)-2H-1-benxopiran-3-carboxílico.

70. El método de la reivindicación 69 donde la droga inhibidora selectiva de ciclooxigenasa-2 es celecoxib.

71. El método de la reivindicación 39 donde la droga está presente en una cantidad entre aproximadamente 0,01% y aproximadamente 15% del peso total de la composición.

72. El método de la reivindicación 39 donde la droga está presente en

una cantidad entre aproximadamente 0,01% y aproximadamente 5% del peso total de la composición.

73. El método de la reivindicación 41 donde entre aproximadamente un 75% y el 100% de la droga está suspendida en forma de particulado.

74. El método de la reivindicación 73 donde entre aproximadamente un 85% y el 100% de la droga está suspendida en forma de particulado.

75. El método de la reivindicación 39 donde menos de aproximadamente un 25% de la droga está disuelta y/o solubilizada.

76. El método de la reivindicación 39 donde menos de aproximadamente un 10% de la droga está disuelta y/o solubilizada.

77. El método de la reivindicación 39 donde la composición tiene una viscosidad máxima entre aproximadamente 5 y aproximadamente 50 Pa•s y una viscosidad dinámica medida a 2 seg^{-1} entre aproximadamente 0,3 y aproximadamente 20 Pa•s.

78. El método de la reivindicación 39 donde la composición tiene una viscosidad máxima entre aproximadamente 5 y aproximadamente 25 Pa•s y una viscosidad dinámica medida a 2 seg^{-1} entre aproximadamente 0,5 y aproximadamente 7 Pa•s.

79. La composición de la reivindicación 1, donde la droga de baja solubilidad en agua tiene una solubilidad en agua, medida a 37°C no mayor de aproximadamente 1mg/ml.

80. La composición de la reivindicación 1, donde la droga de baja solubilidad en agua tiene una solubilidad es agua, medida a 37°C no mayor de aproximadamente 0,1mg/ml.

81. La composición de la reivindicación 4 donde la droga inhibidora

selectiva de ciclooxigenasa-2 tiene una solubilidad en agua, medida a 37°C no mayor de aproximadamente 1mg/ml

82. La composición de la reivindicación 4, donde la droga inhibidora selectiva de ciclooxigenasa-2 tiene una solubilidad es agua, medida a 37°C no mayor de aproximadamente 0,1mg/ml

83. El método de la reivindicación 39, donde la droga de baja solubilidad en agua tiene una solubilidad en agua, medida a 37°C no mayor de aproximadamente 1mg/ml.

84. El método de la reivindicación 39, donde la droga de baja solubilidad en agua tiene una solubilidad en agua, medida a 37°C no mayor de aproximadamente 0,1mg/ml.

85. La composición de la reivindicación 1 donde la droga está presente en una cantidad no mayor de aproximadamente un 90% peso en peso.

86. El método de la reivindicación 39 donde la droga está presente en una cantidad no mayor de aproximadamente un 90% peso en peso.

87. La composición de la reivindicación 1 donde entre aproximadamente un 50% y el 100% de la droga está suspendida en forma de particulado.

88. La composición de la reivindicación 1 donde menos de aproximadamente un 5% de la droga está disuelta y/o solubilizada.

89. El método de la reivindicación 41 donde entre aproximadamente un 50% y el 100%, de la droga está suspendida en forma de particulado.

90. El método de la reivindicación 39 donde menos de aproximadamente un 5% de la droga está disuelta y/o solubilizada.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 6794S-000009/POA

Box No. I TITLE OF INVENTION

STABILIZED ORAL SUSPENSION FORMULATION

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

PHARMACIA CORPORATION & UPJOHN
301 Henrietta
Kalamazoo, Michigan 49007
United States of America

Telephone No. 616-833-4000

Facsimile No. 269-833-8897

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

GUANG WEI LU
3172 Birchwood Court
Ann Arbor, MI 48015
United States of America

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: CN

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HOLLAND, DONALD R.
Harness, Dickey & Pierce, P.L.C.
7700 Bonhomme, Suite 400
St. Louis, MO 63105
United States of America

Telephone No. 314-726-7500

Facsimile No. 314-726-7501

Teleprinter No.

Agent's registration No. with the Office 35,197

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

Regional Patent

☒ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT *(If other kind of protection or treatment desired, specify on dotted line)* .....

☒ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** AT Austria, BE Belgium, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, SK Slovakia, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(If other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(If other kind of protection or treatment desired, specify on dotted line)*:

☒ AE United Arab Emirates	☒ GM Gambia	☒ NZ New Zealand
☒ AG Antigua and Barbuda	☒ HR Croatia	☒ OM Oman
☒ AL Albania	☒ HU Hungary	☒ PH Philippines
☒ AM Armenia	☒ ID Indonesia	☒ PL Poland
☒ AT Austria	☒ IL Israel	☒ PT Portugal
☒ AU Australia	☒ IN India	☒ RO Romania
☒ AZ Azerbaijan	☒ IS Iceland	☒ RU Russian Federation
☒ BA Bosnia and Herzegovina	☒ JP Japan	
☒ BB Barbados	☒ KE Kenya	☒ SD Sudan
☒ BG Bulgaria	☒ KG Kyrgyzstan	☒ SE Sweden
☒ BR Brazil	☒ KP Democratic People's Republic of Korea	☒ SG Singapore
☒ BY Belarus		☒ SI Slovenia
☒ BZ Belize	☒ KR Republic of Korea	☒ SK Slovakia
☒ CA Canada	☒ KZ Kazakhstan	☒ SL Sierra Leone
☒ CH & LI Switzerland and Liechtenstein	☒ LC Saint Lucia	☒ TJ Tajikistan
☒ CN China	☒ LK Sri Lanka	☒ TM Turkmenistan
☒ CO Colombia	☒ LR Liberia	☒ TN Tunisia
☒ CR Costa Rica	☒ LS Lesotho	☒ TR Turkey
☒ CU Cuba	☒ LT Lithuania	☒ TT Trinidad and Tobago
☒ CZ Czech Republic	☒ LU Luxembourg	
☒ DE Germany	☒ LV Latvia	☒ TZ United Republic of Tanzania
☒ DK Denmark	☒ MA Morocco	☒ UA Ukraine
☒ DM Dominica	☒ MD Republic of Moldova	☒ UG Uganda
☒ DZ Algeria		☒ US United States of America
☒ EC Ecuador	☒ MG Madagascar	
☒ EE Estonia	☒ MK The former Yugoslav Republic of Macedonia	☒ UZ Uzbekistan
☒ ES Spain		☒ VN Viet Nam
☒ FI Finland	☒ MN Mongolia	☒ YU Yugoslavia
☒ GB United Kingdom	☒ MW Malawi	☒ ZA South Africa
☒ GD Grenada	☒ MX Mexico	☒ ZM Zambia
☒ GE Georgia	☒ MZ Mozambique	☒ ZW Zimbabwe
☒ GH Ghana	☒ NO Norway	

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☐	☒ All other countries included in the PCT	☐
☐	☐	☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No...." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

(i) If more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;

(ii) If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

(iii) If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

(iv) If, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) If, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;

(vi) If, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

Continuation of Box No. IV

TELSCHER, Rudolph A.
WHEELOCK, Bryan K.
WALSH, Joseph E.
GRYTE, David M.
SOTIRIOU, Evan R.
ODELL, Elizabeth D.
BURRIS, Kelly K.
HOLLAND, Donald R.
CASSEL, Alan L.
CUTLER, Matthew L.
GRAY, Scott T.
FUSSNER, Anthony G.

FORBES, James C.
FUZAIL, Kalim S.
KEANE, J. Timothy
KING, Karen B.
WARNER, James M.
WILLIAMS, Scott A.
FOURNIER, David B.

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 08 August 2001	60/310,372	US		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☒ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* *Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* ....

.....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / EP .....

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*: Number of declarations

☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:			This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:	Number of items
(a) the following number of sheets in paper form:				
request (including declaration sheets)	:	5	1. ☒ fee calculation sheet	:
description (excluding sequence listing part)	:	38	2. ☐ original separate power of attorney	:
claims	:	8	3. ☐ original general power of attorney	:
abstract	:	1	4. ☐ copy of general power of attorney; reference number, if any:	:
drawings	:	3	5. ☐ statement explaining lack of signature	:
Sub-total number of sheets	:	55	6. ☐ priority document(s) identified in Box No. VI as item(s):	:
sequence listing part of description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)*	:		7. ☐ translation of international application into *(language)*:	:
Total number of sheets	:	55	8. ☐ separate indications concerning deposited microorganism or other biological material	:
(b) sequence listing part of description filed in computer readable form			9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))	
(i) ☐ only (under Section 801(a)(i))			(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:
(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))			(ii) ☒ *(only where check-box (b)(i) or (b)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:
Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained *(additional copies to be indicated under item 9(ii), in right column)*:			(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	:
			10. ☒ other *(specify)*: Transmittal to USPTO.	:
Figure of the drawings which should accompany the abstract: 3			**Language of filing of the international application:** English	

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Donald R. Holland

HOLLAND, DONALD R. (Agent)
Reg. No. 35, 197

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	☐ not received:
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below.

IPEA/ EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: 6794S-000009POA

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/US02/24746	05/08/02	06/08/2001

Title of invention: STABILIZED ORAL SUSPENSION FORMULATION

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PHARMACIA CORPORATION
301 Henrietta
Kalamazoo, Michigan 49007
United States of America

Telephone No.: 616-833-4000
Facsimile No.: 269-833-8897
Teleprinter No.:
Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US
State *(that is, country)* of residence: US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GUANG WEI LU
3172 Birchwood Court
Ann Arbor, MI 48015
United States of America

State *(that is, country)* of nationality: CN
State *(that is, country)* of residence: US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:
State *(that is, country)* of residence:

☐ Further applicants are indicated on a continuation sheet.

International application No.
PCT/US02/24746

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HOLLAND, DONALD R.
Harness, Dickey & Pierce, P.L.C.
7700 Bonhomme, Suite 400
St. Louis, MO 63105
United States of America

Telephone No.
314-726-7500

Facsimile No.
314-726-7501

Teleprinter No.

Agent's registration No. with the Office
35,197

[ ] Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

[X] the international application as originally filed

the description
- [X] as originally filed
- [ ] as amended under Article 34

the claims
- [X] as originally filed
- [ ] as amended under Article 19 (together with any accompanying statement)
- [ ] as amended under Article 34

the drawings
- [X] as originally filed
- [ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

- [X] which is the language in which the international application was filed.
- [ ] which is the language of a translation furnished for the purposes of international search.
- [ ] which is the language of publication of the international application.
- [ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

International application No.
PCT/US02/24746

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listings in computer readable form
7. ☐ tables in computer readable form related to sequence listings
8. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Donald R Holland

HOLLAND, DONALD R. (Agent)
Reg. No. 35,197

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

67945-000009/WO/POA
2 mo Search Report due
12/28/02
Protest? Neg

PATENT COOPERATION TREATY

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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

HARNESS, DICKEY & PIERCE P.L.C.
Attn. Holland, Donald R.
7700 Bonhomme Avenue, Suite 400
St. Louis, Missouri 63105
UNITED STATES OF AMERICA

RECEIVED
OCT 31 2002
HARNESS, DICKEY & PIERCE
ST. LOUIS, MISSOURI

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing (day/month/year) 28/10/2002
Applicant's or agent's file reference 6794S-000009	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US 02/24746	International filing date (day/month/year) 05/08/2002
Applicant PHARMACIA CORPORATION & UPJOHN	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO
   34, chemin des Colombettes
   1211 Geneva 20, Switzerland
   Facsimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

   Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

   Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Petronella Vaassen-Elsackers

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

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The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
6794S-000009		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 02/24746	05/08/2002	06/08/2001
Applicant		
PHARMACIA CORPORATION & UPJOHN		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readable form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] Certain claims were found unsearchable (See Box I).

3. [ ] Unity of invention is lacking (see Box II).

4. With regard to the title,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the abstract,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. 3

   [X] as suggested by the applicant.

   [ ] None of the figures.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/24746

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/10 A61K31/415 A61K31/635

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 20798 A (RIKER LABORATORIES INC) 28 October 1993 (1993-10-28) page 1, line 5 - line 8 page 2, line 21 - line 29 page 2, line 35 -page 3, line 33 page 10; table 1 page 12; table 3 claim 1	1-3, 9-12,14, 15,18, 19,23, 24,31, 39-42, 45-47, 50,51, 56-58, 60,61, 71,72
Y		4-8,13, 16,17,

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 October 2002	28/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	VON EGGELKRAUT, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
		21,22, 25-28, 33-36, 43,44, 52-55, 62-64, 66,73-76
	& US 5 112 604 A 12 May 1992 (1992-05-12) cited in the application	
X	WO 91 08734 A (ABBOTT LAB) 27 June 1991 (1991-06-27)	39-41, 50,51, 60-63, 65,71-76
	page 1, paragraph 2 page 3, line 11,12 page 3, last paragraph -page 4, line 10 page 9; example 10	
X	EP 0 257 288 A (ORATECH PHARM DEV CORP) 2 March 1988 (1988-03-02)	39,43, 44,50, 58,59
	page 1, line 4 - line 8 page 3, line 28 - line 44 page 5; example 3	
Y	WO 00 32189 A (GAO DANCHEN ;SEARLE & CO (US); MAZHARY AHMAD M (US); HLINAK ANTHON) 8 June 2000 (2000-06-08) cited in the application	4-8,13, 16,17, 21,22, 25-28, 33-36, 43,44, 52-55, 62-64, 66,73-76
	page 47, line 3-5 page 61, line 7 - line 9	
A	WO 01 30342 A (CHEN YANG LING LING ;TRUSTEES OF SOUTHERN ILLINOIS (US); LEE TONY) 3 May 2001 (2001-05-03) page 32, line 9 - line 13	
P,A	WO 02 05799 A (HASSAN FRED ;FORBES JAMES C (US); PHARMACIA CORP (US)) 24 January 2002 (2002-01-24) page 101, line 8 -page 102, line 6 page 113, line 10 -page 114, line 17	

Continuation of Box I.2

Present claims 1 and 39 relate to an extremely large number of possible compounds, characterised by having a low water solubility. In fact, the claims contain so many options that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear, namely the compounds specified in claims 4-8 and 66-70.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/24746

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/24746

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9320798	A	28-10-1993	US	5112604 A	12-05-1992
			AU	2397492 A	18-11-1993
			EP	0637235 A1	08-02-1995
			WO	9320798 A1	28-10-1993
WO 9108734	A	27-06-1991	AU	639004 B2	15-07-1993
			AU	5934290 A	18-07-1991
			CA	2060501 A1	14-12-1990
			EP	0477289 A1	01-04-1992
			GR	90100441 A ,B	15-11-1991
			IE	902109 A1	02-01-1991
			IL	94710 A	26-05-1995
			JP	4506216 T	29-10-1992
			PT	94372 A	08-02-1991
			WO	9108734 A1	27-06-1991
EP 0257288	A	02-03-1988	US	4684666 A	04-08-1987
			AU	7567287 A	25-02-1988
			DK	321187 A	20-02-1988
			EP	0257288 A1	02-03-1988
			JP	63051325 A	04-03-1988
WO 0032189	A	08-06-2000	AU	748851 B2	13-06-2002
			AU	1838100 A	19-06-2000
			BG	104680 A	28-02-2001
			BR	9908030 A	28-11-2000
			CA	2319201 A1	08-06-2000
			CN	1288378 T	21-03-2001
			EE	200000437 A	15-06-2001
			EP	1049467 A1	08-11-2000
			HR	20000434 A1	31-08-2000
			HU	0100867 A2	28-03-2002
			NO	20003815 A	29-09-2000
			NZ	505762 A	28-06-2002
			PL	341372 A1	09-04-2001
			SK	11062000 A3	12-03-2001
			TR	200002207 T1	21-12-2000
			WO	0032189 A1	08-06-2000
			ZA	200002722 A	29-11-2000
WO 0130342	A	03-05-2001	AU	2298301 A	08-05-2001
			WO	0130342 A1	03-05-2001
WO 0205799	A	24-01-2002	AU	5754701 A	30-01-2002
			AU	7590801 A	30-01-2002
			AU	8288601 A	30-01-2002
			WO	0205848 A2	24-01-2002
			WO	0205815 A1	24-01-2002
			WO	0205799 A2	24-01-2002
			US	2002128267 A1	12-09-2002
			US	2002035264 A1	21-03-2002
			US	2002077328 A1	20-06-2002

67945-000009/FOA

2 month response due 4/25/03

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
Holland, Donald R.
HARNESS, DICKEY & PIERCE P.L.C.
7700 Bonhomme Avenue, Suite 400
St. Louis, Missouri 63105
ETATS-UNIS D'AMERIQUE

RECEIVED
MAR 03 2003
HARNESS, DICKEY & PIERCE
ST. LOUIS, MISSOURI

WRITTEN OPINION
(PCT Rule 66)

Date of mailing (day/month/year)	25/02/2003
Applicant's or agent's file reference: 67948-000009	REPLY DUE: within 2 / 00 months/days from the above date of mailing
International application No.: PCT/US 02/ 24746	International filing date (day/month/year): 05/08/2002
Priority date (day/month/year): 06/08/2001	
International Patent Classification (IPC) or both national classification and IPC: A61K9/10	
Applicant: PHARMACIA CORPORATION et al	

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [X] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4*bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 06/12/2003.

Name and mailing address of the IPEA/
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Netherlands
Tel.: (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer
Examiner

Formalities officer
(incl. extension of time limits)
Tel. (+49-89) 2399 2828

Form PCT/IPEA/408 (cover sheet) (march 2002)

I. Basis of the opinion

The basis of this written opinion is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been and will not be the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT; see also international search report).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

1. To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

2. In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

3. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

NB: Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.

IN THE EUROPEAN PATENT OFFICE
AS INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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International Application No.: PCT/US02/24746

International Filing Date: 05 August 2002

Applicant: Pharmacia Corporation

Title: STABILIZED ORAL SUSPENSION FORMULATION

Attorney Docket: 6794S-000009/WO/POA

AMENDMENT AND RESPONSE TO WRITTEN OPINION

This paper is filed in response to the Written Opinion under PCT rule 66, dated 25/02/2003. Applicants hereby request detailed substantive examination and the issuance of a second written opinion based upon the amendment of the claims and the remarks below.

Please amend claims 1 and 39 as indicated below, wherein underlining indicates insertions and bracketing indicates deletions to the claims as originally filed. Applicants include herewith substitute sheets including the amended claims.

IN THE CLAIMS

1. An orally deliverable pharmaceutical composition comprising a drug of low water solubility and an aqueous liquid vehicle that comprises (a) a pharmaceutically acceptable wetting agent, (b) a pharmaceutically acceptable thixotropic thickening agent **present in an amount of at least about 0.25%**, and (c) a pharmaceutically acceptable inorganic suspending agent.

39. A method for increasing the physical stability of [a] **an aqueous** pharmaceutical composition of a drug of low water solubility, the method comprising adding to the composition a pharmaceutically acceptable thixotropic agent **present in an amount of at least about 0.25%,** and a pharmaceutically acceptable inorganic

suspending agent in amounts which act synergistically to increase physical stability of the composition.

REMARKS

Claims 1-78 are pending in this application. This paper amends claims 1 and 39. It is believed that the claim amendments add no new matter to this application. Support for the amendments can be found as follows.

In claim 1, support can be found in claim 1 as originally filed. In addition, support for a pharmaceutically acceptable thixotropic thickening agent present in an amount of at least about 0.25% can be found at least on page 21, lines 25-28.

In claim 39, support can be found in claim 39 as originally filed. In addition, support for a pharmaceutically acceptable thixotropic thickening agent present in an amount of at least about 0.25% can be found at least on page 21, lines 25-28; support for an aqueous pharmaceutical composition of a drug of low water solubility can be found at least on page 6, lines 18-26.

In the Written Opinion, claims 1-3, 9-12, 14, 15, 18, 19, 23, 24, 31, 39-42, 45-47, 50, 51, 56-58, 60, 61, 71 and 72 are categorized by an "X" indicating that the claimed invention cannot be considered novel or involve an inventive step over patent application WO 93 20798 to Riker Laboratories Inc. ("Riker"). Reconsideration and withdrawal of this assessment is respectfully requested in view of the amendments to claim 1 and claim 39. These amendments add the recitation that the thixotropic agent is "present in an amount of at least about 0.25%". In comparison to this, Riker discloses, on page 3 lines 14-15, a gum (which can be a thixotropic agent) present in an amount of from about 0.02% to about 0.10%, which is less than the 0.25% now recited in the claims. The amendments, therefore, remove Riker as a reference regarding novelty or inventive step in claims 1-3, 9-12, 14, 15, 18, 19, 23, 24, 31, 39-42, 45-47, 50, 51, 56-58, 60, 61, 71 and 72.

Claims 4-8, 13, 16, 17, 21, 22, 25-28, 33-36, 43, 44, 52-55, 62-64, 66, and 73-76 are also categorized by a "Y" indicating that the claimed invention cannot be considered to involve an inventive step over Riker. Reconsideration and withdrawal of this assessment is respectfully requested in view of the amendments to claim 1 and claim 39. These amendments add the recitation that the thixotropic agent is "present in an amount of at least about 0.25%". In comparison to this, Riker discloses, on page 3

lines 14-15, a gum (which can be a thixotropic agent) present in an amount of from about 0.02% to about 0.10%, which is less than the 0.25% now recited in the claims. The amendments, therefore, remove Riker as a reference regarding inventive step in claims 4-8, 13, 16, 17, 21, 22, 25-28, 33-36, 43, 44, 52-55, 62-64, 66, and 73-76.

In the Written Opinion, claims 39-41, 50, 51, 60-63, 65, and 71-76 are categorized by an "X" indicating that the claimed invention cannot be considered novel or involve an inventive step over patent application WO 91 08734 to Abbott Laboratories ("Abbott"). Reconsideration and withdrawal of this assesament is respectfully requested because Abbott teaches non-aqueous, oil-based liquid suspension drug delivery vehicles. In contrast, claims 39-41, 50, 51, 60-63, 65, and 71-76 as amended are drawn to an aqueous pharmaceutical composition of a drug of low water solubility. The amendment, therefore, removes Abbott as a reference regarding novelty or inventive step in claims 39-41, 50, 51, 60-63, 65 and 71-76.

In the Written Opinion, claims 39, 43, 44, 50, 58 and 59 are categorized by an "X" indicating that the claimed invention cannot be considered novel or involve an inventive step over patent application EP 0 257 288 A1 to Oratech Pharmaceutical Development Corporation. Reconsideration and withdrawal of this assessment is respectfully requested because Oratech does not teach the use of a thixotropic agent. In contrast, all of claims 39, 43, 44, 50, 58 and 59 include the recitation of "adding to the composition a pharmaceutically acceptable thixotropic agent". Oratech, therefore, does not negate novelty or inventive step of claims 39, 43, 44, 50, 58 and 59.

In the Written Opinion, claims 4-8, 13, 16, 17, 21, 22, 25-28, 33-36, 43, 44, 52-55, 62-64, 66, and 73-76 categorized by a "Y" indicating that the claimed invention cannot be considered to involve an inventive step over WO 00 32189 to G.D. Searle & Co. ("Searle"). Reconsideration and withdrawal of this assessment is respectfully requested because Searle does not teach the use of inorganic suspending agents. In the present application, however, all of claims 4-8, 13, 16, 17, 21, 22, 25-28, 33-36, 43, 44, 52-55, 62-64, 66, and 73-76 recite (by dependence) "a pharmaceutically acceptable inorganic suspending agent." This recitation removes Searle as a reference regarding inventive step in claims 4-8, 13, 16, 17, 21, 22, 25-28, 33-36, 43, 44, 52-55, 62-64, 66, and 73-76.

Because all of the art cited by the IPEA regarding novelty and/or inventive step are removed as references, Applicant requests detailed examination and a new International Preliminary Examining Opinion from the IPEA.

Should any questions arise, the International Preliminary Examining Authority is requested to contact the undersigned attorney.

Respectfully submitted,

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WHAT IS CLAIMED IS:

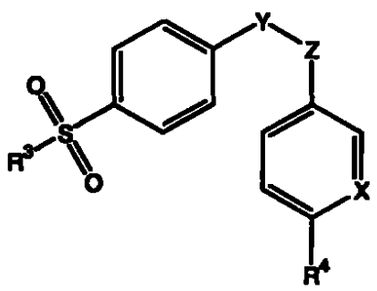
1. An orally deliverable pharmaceutical composition comprising a drug of low water solubility and an aqueous liquid vehicle that comprises (a) a pharmaceutically acceptable wetting agent, (b) a pharmaceutically acceptable thixotropic thickening agent present in an amount of at least about 0.25%, and (c) a pharmaceutically acceptable inorganic suspending agent.

2. The composition of Claim 1 wherein at least a substantial portion of the drug is suspended in particulate form in the vehicle to form a suspension and wherein the wetting agent, thickening agent and suspending agent are present in total and relative amounts such that the suspension is thixotropic, substantially deflocculated, and substantially physically stable.

3. The composition of Claim 1 wherein the drug is present in a therapeutically and/or prophylactically effective total amount.

4. The composition of Claim 1 wherein the drug is a selective cyclooxygenase-2 inhibitory drug of low water solubility.

5. The composition of Claim 4 wherein the selective cyclooxygenase-2 inhibitory drug is a compound of formula



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups.

6. The composition of Claim 5 wherein the five- to six-membered ring is selected from the group consisting of cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

28. The composition of Claim 24 wherein the colloidal silicon dioxide has a weight average particle diameter of about 10 to about 25 nm.

29. The composition of Claim 1 wherein the inorganic suspending agent is present in an amount of about 0.01% to about 3%, by weight.

30. The composition of Claim 24 wherein the inorganic suspending agent is present in an amount of about 0.25% to about 1%, by weight.

31. The composition of Claim 1 wherein the thixotropic thickening agent and the inorganic suspending agent are present in a weight ratio of about 10:1 to about 1:10.

32. The composition of Claim 1 wherein the thixotropic thickening agent and the inorganic suspending agent are present in a weight ratio of about 2:1 to about 1:2.

33. The composition of Claim 1 wherein about 75% to 100% of the drug is suspended in particulate form.

34. The composition of Claim 1 wherein substantially all of the drug is suspended in particulate form.

35. The composition of Claim 1 wherein less than about 25% of the drug is dissolved and/or solubilized.

36. The composition of Claim 1 wherein substantially no portion of the drug is dissolved and/or solubilized.

37. The composition of Claim 1 which, when analyzed according to Test I, has a maximum viscosity of about 5 to about 50 Pa•s and a dynamic viscosity measured at 2 sec^{-1} of about 0.3 to about 20 Pa•s.

38. The composition of Claim 1 which, when analyzed according to Test I, has a maximum viscosity of about 5 to about 25 Pa•s and a dynamic viscosity measured at 2 sec^{-1} of about 0.5 to about 7 Pa•s.

39. A method for increasing the physical stability of an aqueous pharmaceutical composition of a drug of low water solubility, the method comprising adding to the composition a pharmaceutically acceptable thixotropic agent

present in an amount of at least about 0.25%, and a pharmaceutically acceptable inorganic suspending agent in amounts which act synergistically to increase physical stability of the composition.

40. The method of Claim 39 wherein the composition further comprises a wetting agent.

41. The method of Claim 40 wherein a substantial portion of the drug is suspended in particulate form in the vehicle to form a suspension.

42. The method of Claim 41 wherein the composition is substantially deflocculated.

43. The method of Claim 39 wherein the thixotropic thickening agent is a cellulosic polymer.

44. The method of Claim 43 wherein the thixotropic thickening agent is selected from the group consisting of methylcellulose, microcrystalline cellulose, polyvinylpyrrolidone, and hydroxypropyl methycellulose.

45. The method of Claim 39 wherein the thixotropic thickening agent is a polysaccharide gum.

46. The method of Claim 45 wherein the polysaccharide gum is selected from the group consisting of xanthan, guar, acacia, and tragacanth gums.

47. The method of Claim 45 wherein the polysaccharide gum is xanthan gum.

48. The method of Claim 39 wherein the thixotropic thickening agent is present in an amount of about 0.25% to about 2%, by weight.

49. The method of Claim 39 wherein the thixotropic thickening agent is present in an amount of about 0.4% to about 2%, by weight.

50. The method of Claim 39 wherein the inorganic suspending agent is selected from the group consisting of colloidal silicon dioxide, bentonite and kaolin.

51. The method of Claim 39 wherein the inorganic suspending agent is colloidal silicon dioxide.

52. The method of Claim 51 wherein the colloidal silicon dioxide has a specific surface area of about 50 to about 400 m^2/g.

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Holland, Donald R.
HARNESS, DICKEY & PIERCE P.L.C.
7700 Bonhomme Avenue, Suite 400
St. Louis, Missouri 63105
ETATS-UNIS D'AMERIQUE

JUN 02 2003

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	26.05.2003
Applicant's or agent's file reference: 6794S-000009	REPLY DUE: within 3 month(s) from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US02/24746	05/08/2002	06/08/2001

International Patent Classification (IPC) or both national classification and IPC
A61K9/10

Applicant
PHARMACIA CORPORATION et al

1. This written opinion is the second drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain document cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 06/12/2003.

Name and mailing address of the international preliminary examining authority:
European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
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Authorized officer / Examiner
von Eggelkraut-Gotta

Formalities officer (incl. extension of time limits)
Lafitte-de Jong, S
Telephone No. +31 70 340 4827

I. Basis of the opinion

1. With regard to the elements of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, pages:

1-38	as originally filed				

Claims, No.:

7-27,53-78	as originally filed				
1-6,28-52	as received on	23/04/2003	with letter of	23/04/2003	

Drawings, sheets:

1/3-3/3	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☐ claims Nos. ,

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1,39, as far as the search has been restricted to those parts of the application which do appear to be clear, namely the compounds specified in claims 4-8 and 66-70..

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

WRITTEN PINION International application No. PCT/US02/24746

1. Statement

Novelty (N)	Claims	39,43,44,50,58,59,77,78
Inventive step (IS)	Claims	1-4, 9-12, 14, 15, 18, 19, 23, 24, 31, 39-47, 50, 51, 56-61, 66, 71, 72 , 77, 78
Industrial applicability (IA)	Claims	

2. Citations and explanations
see separate sheet

V. Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:

D1: WO 93 20798 A (RIKER LABORATORIES INC) 28 October 1993 (1993-10-28) & US 5 112 604 A 12 May 1992 (1992-05-12) cited in the application
D2: WO 91 08734 A (ABBOTT LAB) 27 June 1991 (1991-06-27)
D3: EP-A-0 257 288 (ORATECH PHARM DEV CORP) 2 March 1988 (1988-03-02)
D4: WO 00 32189 A (GAO DANCHEN ;SEARLE & CO (US); MAZHARY AHMAD M (US); HLINAK ANTHON) 8 June 2000 (2000-06-08) cited in the application

2 **AMENDMENTS (Art. 34(2)(b) PCT)**

The amendments of claims 1 and 39 are conform with Art. 34(2)(b) PCT.

3 **NOVELTY** (Art. 33(2) PCT)

3.1 The Applicant's arguments concerning novelty of the amended claims in view of D1, D2 and D4 are acknowledged.

3.2 D3 discloses a stable liquid syrup comprising ibuprofen in suspension, bentonite and PVP (D3, page 28-44; page 5, example 3). The viscosity is claimed in the range of 1 to 3 Pa*s. As bentonite is obviously a thixotropic agent, claims 39,43,44,50,58,59, 77,78 are not new towards D3.

3.3 The present application does not meet the requirements of Article 33(2) PCT because the subject-matter of claims 39,43,44,50,58,59, 77,78 is not new.

3.4 In view of the prior art cited, claims 1-38,40-42,45-49,51-57,60-76 appear to be novel and meet therefore the requirements of Art. 33(2) PCT.

4 INVENTIVE STEP (Art. 33(3) PCT)

4.1 Claims 39,43,44,50,58,59, 77,78 are not new and therefore not inventive.

4.2 Even if novelty of some claims with respect to D1 seems to have been restored by introducing the amount of thickening agent, this amendment seems not to restore inventivity for the following reasons: D1 discloses oral suspensions comprising a drug of low water solubility (D1, theophylline, salicylsalicylic acid), polysorbate, xanthan gum and silicium dioxide (D1, page 10, table 1; page 12, table 3). Salicylsalicylic acid is a COX inhibitory drug and is considered to fall within the scope of claims 4 and 66, as the term "selective COX-2 inhibitory drug" is not clear. The suspensions are stable for a prolonged period of time (D1, page 2, lines 21-29). Even though the amount of thickening agent is claimed to be slightly higher in the present set of claims, this can not be regarded as inventivity establishing feature, as no surprising effect can be expected from this slightly different quantitity of excipient. Consequently, claims 1-4, 9-12, 14, 15, 18, 19, 23, 24, 31, 39-42, 45-47, 50, 51, 56-58, 60, 61, 66, 71, 72 are not inventive towards D1.

4.3 Consequently, claims 1-4, 9-12, 14, 15, 18, 19, 23, 24, 31, 39-47, 50, 51, 56-59, 60, 61, 66, 71, 72 , 77,78 are not inventive (Art. 33(3) PCT).

5 Certain defects

5.1 It is clear from the description of the present application that a wetting agent is essential to the performance of the invention. Since independent claim 39 does not contain this feature it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3 (b)(I),(ii) PCT that any independent claim must contain all the technical features essential to the invention.

5.2 The claimed subject-matter of independent claims 1 and 39 is not adequate to

provide a solution to the underlying problem of the invention as stated in paragraphs [0059] and [0067] of the present invention. Said claims are merely a statement of the problem stated in the description. As the solution to the problem lies in the selection of appropriate excipients such as the wetting agent, the polysaccharide gum and the active agent in an appropriate quantity, claims 1 and 39 lack of clarity and support (Art. 6 PCT).

5.3 Claim 2 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claim attempts to define the subject-matter in terms of the result to be achieved, namely by stating "..agent are present in total and relative amounts such that the suspension is thixotropic, substantially deflocculated and substantially physically stable". This merely amounts to a statement of the underlying problem.

5.4 Claim 39 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined. The claim attempts to define the subject-matter in terms of the result to be achieved. This merely amounts to a statement of the underlying problem.

5.5 Claims 37, 38, 77 and 78 refer to a test in the description on page 24. Claims must not, in respect of the technical features of the invention, rely on references to the description or drawings "except where absolutely necessary (Guidelines C-III, 4.10; Rule 6.2(a) PCT). As a reference to the description does not seem to be absolutely necessary, claims 37, 38, 77 and 78 do not fulfill the requirements of Article 6 PCT.

5.6 The term "low water solubility" used in claims 1, 4, 39 is vague and indefinite and as such renders the scope of the claims 1-4, 9-66, 71-78 unclear; accordingly, the claims require amendment to remove this defect (Article 6 PCT).

5.7 The term "in a therapeutically and/or prophylactically effective total amount" used in claims 3 and 65 is vague and indefinite and as such renders the scope of the claims unclear (Article 6 PCT). Furthermore, a pharmaceutical composition is considered to necessarily comprise the drug an effective amount.

5.8 The term "substantially" used in claims 2,34,36,42,74,76 is vague and indefinite and as such renders the scope of the claims unclear; accordingly, the claims require amendment to remove this defect (Article 6 PCT).

5.9 The term "about" used in claims 9,10,14,15,21,22,25-33,35,37,38,48,49,52-59,63,64,71-73,75,77,78 render the scope of the claims unclear and indefinite (Article 6 PCT).

5.10 It is not clear how polyvinylpyrrolidone could be considered as a cellulosic polymer. Claim 44 is therefore no clear (Article 6 PCT).

5.11 If amendments are filed, it should be by way of replacement pages in the manner stipulated by Rule 66.8(a) PCT. In particular, fair copies of the amendments should be filed preferably in triplicate. Moreover, the applicant's attention is drawn to the fact that, as a consequence of Rule 66.8(a) PCT the examiner is not permitted to carry out any amendments under the PCT procedure, however minor these may be.

5.12 In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT).

IN THE EUROPEAN PATENT OFFICE
AS INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

International Application No.: PCT/US02/24746

International Filing Date: 05 August 2002

Applicant: Pharmacia Corporation

Title: STABILIZED ORAL SUSPENSION FORMULATION

Attorney Docket: 6794S-000009/WO/POA

AMENDMENT AND RESPONSE TO WRITTEN OPINION

This paper is filed in response to the Written Opinion under PCT rule 66, dated 26/05/2003.

Please amend Claims 1-4, 34, 36-39, 41, 44, 65, 66, 74, and 76-78 as indicated below, wherein underlining indicates insertions and bracketing indicates deletions to the claims as originally filed. Please add new Claims 79-90. Applicants include herewith substitute sheets including the amended claims and new claims.

IN THE CLAIMS

1. (Amended) [An] A physically stable, thixotropic, orally deliverable pharmaceutical composition comprising a drug of low water solubility and an aqueous liquid vehicle that comprises (a) a pharmaceutically acceptable wetting agent, (b) a pharmaceutically acceptable thixotropic thickening agent present in [an] a thixotropic amount of at least about 0.25%, and (c) a pharmaceutically acceptable inorganic suspending agent.

2. (Amended) The composition of Claim 1 wherein at least a substantial portion of the drug is suspended in particulate form in the vehicle to form a suspension [and wherein the wetting agent, thickening agent and suspending agent are present in total and relative

amounts such] that [the suspension] is [thixotropic,] substantially deflocculated[, and substantially physically stable].

3. (Amended) The composition of Claim 1 wherein the drug is present in [a therapeutically and/or prophylactically effective total amount] an amount of at least about 0.01%.

34. (Amended) The composition of Claim 1 wherein [substantially all] about 85% to 100% of the drug is suspended in particulate form.

36. (Amended) The composition of Claim 1 wherein [substantially no portion] less than about 10% of the drug is dissolved and/or solubilized.

37. (Amended) The composition of Claim 1 [which, when analyzed according to Test I,] wherein the composition has a maximum viscosity of about 5 to about 50 Pa•s and a dynamic viscosity measured at 2 sec^{-1} of about 0.3 to about 20 Pa•s.

38. (Amended) The composition of Claim 1 [which, when analyzed according to Test I,] wherein the composition has a maximum viscosity of about 5 to about 25 Pa•s and a dynamic viscosity measured at 2 sec^{-1} of about 0.5 to about 7 Pa•s.

39. (Amended) A method for increasing the physical stability of an aqueous, thixotropic pharmaceutical composition of a drug of low water solubility, the method comprising adding to the composition a pharmaceutically acceptable thixotropic thickening agent [present] in [an] a thixotropic amount of at least about 0.25%, and a pharmaceutically acceptable inorganic suspending agent in amounts which act synergistically to increase physical stability of the composition.

41. (Amended) The method of Claim 40 wherein a substantial portion of the drug is suspended in particulate form in [the] a vehicle to form a suspension.

44. (Amended) The method of Claim [43] 39 wherein the thixotropic thickening

agent is selected from the group consisting of methylcellulose, microcrystalline cellulose, polyvinylpyrrolidone, and hydroxypropyl methycellulose.

65. (Amended) The method of Claim 39 wherein the drug is present in [a therapeutically and/or prophylactically effective total amount] an amount of at least about 0.01%, on a weight per weight basis.

66. (Amended) The method of Claim 39 wherein the drug is a selective cyclooxygenase-2 inhibitory drug[of low water solubility].

74. (Amended) The method of Claim 73 wherein [substantially all] about 85% to 100% of the drug is suspended in particulate form.

76. (Amended) The method of Claim 39 wherein [substantially no portion] less than about 10% of the drug is dissolved and/or solubilized.

77. (Amended) The method of Claim 39 wherein the composition has a maximum viscosity of about 5 to about 50 Pa•s and a dynamic viscosity measured at 2 sec^{-1} of about 0.3 to about 20 Pa•s[when analyzed according to Test I].

78. (Amended) The method of Claim 39 wherein the composition has a maximum viscosity of about 5 to about 25 Pa•s and a dynamic viscosity measured at 2 sec^{-1} of about 0.5 to about 7 Pa•s[when analyzed according to Test I].

79. (New) The composition of Claim 1, wherein the drug of low water solubility has a solubility in water, measured at 37°C, not greater than about 1 mg/ml.

80. (New) The composition of Claim 1, wherein the drug of low water solubility has a solubility in water, measured at 37°C, not greater than about 0.1 mg/ml.

81. (New) The composition of Claim 4, wherein the selective cyclooxygenase-2 inhibitory drug has a solubility in water, measured at 37°C, not greater than about 1 mg/ml.

82. (New) The composition of Claim 4, wherein the selective cyclooxygenase-2 inhibitory drug has a solubility in water, measured at 37°C, not greater than about 0.1 mg/ml.

83. (New) The method of Claim 39, wherein the drug of low water solubility has a solubility in water, measured at 37°C, not greater than about 1 mg/ml.

84. (New) The method of Claim 39, wherein the drug of low water solubility has a solubility in water, measured at 37°C, not greater than about 0.1 mg/ml.

85. (New) The composition of Claim 1 wherein the drug is present in an amount of no more than about 90%, on a weight per weight basis.

86. (New) The method of Claim 39 wherein the drug is present in an amount of no more than about 90%, on a weight per weight basis.

87. (New) The composition of Claim 1 wherein about 50% to 100% of the drug is suspended in particulate form.

88. (New) The composition of Claim 1 wherein less than about 5% of the drug is dissolved and/or solubilized.

89. (New) The method of Claim 41 wherein about 50% to 100% of the drug is suspended in particulate form.

90. (New) The method of Claim 39 wherein less than about 5% of the drug is dissolved and/or solubilized.

REMARKS

Claims 1-78 are pending in this application. This paper amends Claims 1-3, 34, 36-39, 41, 44, 65, 66, 74, and 76-78. Also, new Claims 79-90 are added. It is believed that the claim amendments, as well as the new claims, add no new matter to this application. Support for the amendments and new claims can be found as follows.

In claim 1, support can be found in claim 1 as originally filed. In addition, support for a physically stable, thixotropic, orally deliverable pharmaceutical composition comprising a drug of low water solubility and an aqueous liquid vehicle that comprises a pharmaceutically acceptable wetting agent and a pharmaceutically acceptable thixotropic thickening agent can be found at least on page 6, lines 18-26. Support for a thixotropic amount of at least about 0.25% can be found at least on page 21, lines 25-28.

In Claim 2, support can be found at least on Claim 2 as originally filed.

In Claim 3, support for "an amount of at least about 0.01%" can be found at least on page 12, lines 2-7.

In Claim 34, support for "about 85% to 100% of the drug is suspended in particulate form" can be found at least on page 19, lines 4-6.

In Claim 36, support for "less than about 10% of the drug is dissolved and/or solubilized" can be found at least on page 19, lines 6-8.

In Claim 37, support can be found at least on Claim 37 as originally filed.

In Claim 38, support can be found at least on Claim 38 as originally filed.

In Claim 39, support can be found at least on Claim 39 as originally filed. In addition, support for an aqueous, thixotropic pharmaceutical composition of a drug of low water solubility can be found at least on page 6 lines 18-26; support for a pharmaceutically acceptable thixotropic thickening agent in a thixotropic amount of at least about 0.25% can be found at least on page 21, lines 25-28; support for a pharmaceutically acceptable inorganic suspending agent can be found at least on page 22, lines 1-2; support for agents in amounts which act synergistically can be found at least on page 22 lines 8-16.

In Claim 41, support can be found at least on Claim 41 as originally filed.

In Claim 44, support can be found at least on Claim 44 as originally filed.

In Claim 65, support for "an amount of at least about 0.01%" can be found at least on page 12, lines 2-7.

In Claim 66, support can be found at least on Claim 66 as originally filed.

In Claim 74, support for "about 85% to 100% of the drug is suspended in particulate form" can be found at least on page 19, lines 4-6.

In Claim 76, support for "less than about 10% of the drug is dissolved and/or solubilized" can be found at least on page 19, lines 6-8.

In Claim 77, support can be found at least on Claim 77 as originally filed.

In Claim 78, support can be found at least on Claim 78 as originally filed.

In Claim 79, support for a drug of low water solubility can be found at least at least on claim 1 as originally filed. In addition, support for a drug having a solubility no greater than 1 mg/ml at 37°C can be found at least on page 9, lines 13-15.

In Claim 80, support for a drug of low water solubility can be found at least at least on claim 1 as originally filed. In addition, support for a drug having a solubility no greater than 0.1 mg/ml at 37°C can be found at least on page 9, lines 13-17.

In Claim 81, support for the selective cyclooxygenase-2 inhibitor can be found at least on claim 4 as originally filed. In addition, support for a drug having a solubility no greater than 1 mg/ml at 37°C can be found at least on page 9, lines 13-15.

In Claim 82, support for a drug of low water solubility can be found at least on claim 4 as originally filed. In addition, support for a drug having a solubility no greater than 0.1 mg/ml at 37°C can be found at least on page 9, lines 13-17.

In Claim 83, support can be found at least on Claim 39 as originally filed. In addition, support for a drug of low water solubility having a solubility no greater than 1 mg/ml at 37°C can be found at least on page 9, lines 13-15.

In Claim 84, support can be found at least on Claim 39 as originally filed. In addition, support for a drug of low water solubility having a solubility no greater than 0.1 mg/ml at 37°C can be found at least on page 9, lines 13-17.

In Claim 85, support for an amount of no more than about 90%, on a weight per weight basis can be found at least on page 12, lines 2-10.

In Claim 86, support for an amount of no more than about 90%, on a weight per weight basis can be found at least on page 12, lines 2-10.

In Claim 87, support for suspension of about 50% to 100% of the drug in particulate form can be found at least on page 19, lines 3-6.

In Claim 88, support for dissolution or solubilization of less than about 5% of the drug can be found at least on page 19, lines 6-9.

In Claim 89, support for suspension of about 50% to 100% of the drug in particulate form can be found at least on page 19, lines 3-6.

In Claim 90, support for dissolution or solubilization of less than about 5% of the drug can be found at least on page 19, lines 6-9.

In the Written Opinion, paragraph 3.2, the IPEA states that Claims 39, 43, 44, 50, 58, 59, 77, and 78 cannot be considered novel and, in paragraph 4.2, that they are not inventive, over patent application EP 0 257 288 A1 to Oratech Pharmaceutical Development Corporation ("Oratech"). Applicants request reconsideration and withdrawal of these assessments because Oratech does not teach a method for increasing the physical stability of an aqueous, thixotropic pharmaceutical composition, nor does it teach the addition of a thixotropic amount of a thixotropic thickening agent. While some compositions taught by Oratech include bentonite as indicated by the IPEA, bentonite is included by Oratech as a stabilizing agent (Oratech, page 3 lines 28-39). Although Oratech states that stabilizing agents such as bentonite provide "multiple very useful functions" which are specified to be

"aiding in dispersing and suspending the ibuprofen particles and then forming a protective molecular or fine particle coat around the suspended drug," Oratech does not teach a method for increasing the physical stability of an aqueous, thixotropic pharmaceutical composition that includes adding a thixotropic amount of bentonite. In contrast, Claim 39 as amended (and Claims 43, 44, 50, 58, 59, 77, and 78, by dependence) recites a method of increasing the physical stability of an aqueous, thixotropic pharmaceutical composition which includes the provision of a thixotropic amount of a thixotropic thickening agent. Oratech, therefore, does not negate novelty nor inventiveness of Claims 39, 43, 44, 50, 58, 59, 77, and 78, and applicants respectfully request withdrawal of this assessment.

In the Written Opinion, paragraph 4.2, the IPEA states that Claims 1-4, 9-12, 14, 15, 18, 19, 23, 24, 31, 39-42, 45-47, 50, 51, 56-59, 60, 61, 71, 72, 77, and 78 do not involve an inventive step over patent application WO 93 20798 to Riker Laboratories Inc. ("Riker"). Riker discloses, on page 3 lines 14-15, a hydrocolloid gum present in an amount of from about 0.02% to about 0.10% as a suspending agent. Applicants request reconsideration and withdrawal of this assessment. First, the present claims as amended recite an amount of at least about 0.25% of a thixotropic agent. Second, an amount of a gum that provides activity as a suspending agent is not necessarily the same as an amount of a gum that provides activity as a thixotropic agent. In this connection, Riker neither teaches nor suggests the use of a thixotropic amount of a thixotropic agent. Third, Riker neither teaches nor suggests a thixotropic pharmaceutical composition, as recited in the claims as amended. In addition, there is no disclosure in Riker of the synergistic increase in physical stability as recited in Claim 39. Riker, therefore, does not negate novelty or inventive step in Claims 1-3, 9-12, 14, 15, 18, 19, 23, 24, 31, 39-42, 45-47, 50, 51, 56-58, 60, 61, 71 and 72 and applicants respectfully request withdrawal of this assessment by the IPEA.

In the Written Opinion, paragraph 5.1, the IPEA states that Claim 39 does not contain all the features essential to the performance of the invention. Reconsideration and withdrawal of this assessment is respectfully requested in view of the amendment to Claim 39. Based on the amendment, the method comprises the additional recitation of "a pharmaceutically acceptable wetting agent."

In the Written Opinion, paragraph 5.2, the IPEA states that Claims 1 and 39 do not adequately provide a solution to the underlying problem. Applicant request withdrawal of the assessment, because the underlying problem is to provide a physically stable, orally deliverable pharmaceutical composition, and Claims 1 and 39 recite components of such a composition. A skilled artisan, in view of the specification, can select the components and the amounts thereof without undue experimentation in preparing a composition. Applicants, therefore, request withdrawal of the assessment.

In the Written Opinion, paragraph 5.3, the IPEA states that Claim 2 is indefinite. Claim 2 as amended recites the composition of Claim 1 wherein at least a substantial portion of the drug is substantially deflocculated. A skilled artisan turning to the specification will find guidance for preparation of compositions of the present application that are substantially deflocculated (e.g., in the examples disclosed in paragraphs 265-276). Hence, on the basis of the guidance provided by the specification, a skilled artisan can prepare compositions of the invention without undue experimentation, and Applicants, therefore, request withdrawal of the assessment.

In the Written Opinion, paragraph 5.4, the IPEA states that Claim 39 is indefinite, because it attempts to define the subject-matter in terms of the result to be achieved. Applicants request withdrawal of the assessment, because the claim does not merely recite a result to be achieved. Rather, Claim 39 provides procedures of such method, by reciting the addition of components to a composition. Accordingly, Claim 39 provides a solution to the

underlying problem, and Applicants, therefore, respectfully request reconsideration and withdrawal of this assessment.

In the Written Opinion, paragraph 5.5, the IPEA states that Claims 37, 38, 77, and 78 unnecessarily rely on references to the description. Reconsideration and withdrawal of this assessment is respectfully requested in view of the amendments to Claims 37, 38, 77, and 78.

In the Written Opinion, paragraph 5.6, the IPEA states that the term "low water solubility" as used in Claims 1, 4, and 39 is indefinite, rendering the scope of claims 1-4, 9-66, and 71-78 unclear. Reconsideration and withdrawal of this assessment is requested because "low water solubility" is not only a term well recognized in the art, it is further explained and illustrated in the specification. For example, on page 9, lines 13-15 it is stated that a "'drug of low water solubility' or 'poorly water solubility drug' herein refers to any drug or compound having a solubility in water, measured at 37°C, not greater than about 10 mg/ml, and preferably not greater than about 1 mg/ml." In addition, for example, on page 9, lines 25-29, it is stated that "individual drugs of low solubility as defined herein include those drugs categorized as 'slightly soluble', 'very slightly soluble', 'practically insoluble' and 'insoluble' in USP 24, pp. 2254-2298; and those drugs categorized as requiring 100 ml or more of water to dissolve 1 g of the drug, as listed in USP 24, pp. 2299-2304." Because a claim can be understood in view of the specification, the phrase "low water solubility" is not indefinite in claims 1, 4 and 39, and Applicants, therefore, request withdrawal of the assessment.

In the Written Opinion, paragraph 5.7, the IPEA states that the term "in a therapeutically and/or prophylactically effective total amount" as used in Claims 3 and 65 is indefinite. The IPEA further states that a pharmaceutical composition is considered to necessarily comprise the drug in an effective amount. Reconsideration and withdrawal of this

assessment is respectfully requested in view of the amendments to Claims 3 and 65, in which amounts of a drug are recited.

In the Written Opinion, paragraph 5.8, the IPEA states that the term "substantially" as used in Claims 2, 34, 36, 42, 74, and 76 is indefinite. With respect to Claims 2 and 42, "substantially" is used in the phrase "substantially deflocculated." This phrase is defined in the specification, for example on page 7, paragraph 27 ("The term 'substantially deflocculated' herein refers to drug particles in suspension which do not coagulate and/or agglomerate together to form flocs.") Because of this recitation in the specification, withdrawal of the assessment is requested in regard to claims 2 and 42. With respect to Claims 34, 36, 74, and 76, reconsideration and withdrawal of this assessment is respectfully requested in view of the amendments to the Claims, which now recite ranges.

In the Written Opinion, paragraph 5.9, the IPEA states that the word "about" as used in Claims 9, 10, 14, 15, 21, 22, 25-33, 35, 37, 38, 48, 49, 52-59, 63, 64, 71-73, 75, 77, and 78 renders the claims indefinite. Withdrawal of the assessment is requested in view of examination guidelines. According to Guidelines for Examination in the European Patent Office (Part C, Chapter III, 4.5a), "the word 'about' or similar terms such as 'approximately'... may be applied, for example, to a particular value (e.g. 'about 200° C') or to a range (e.g. 'about x to about y'). In each case, the examiner should use his judgment as to whether the meaning is sufficiently clear in the context of the application read as a whole. However, the word can only be permitted if its presence does not prevent the invention from being unambiguously distinguished from the prior art with respect to novelty and inventive step." In this case, Applicants believe that each use of "about" is sufficiently clear in the context of the application read as a whole, and, furthermore, that none of the recited uses of the word "about" prevent the invention from being unambiguously distinguished from the prior art. Applicants, therefore, respectfully request withdrawal of the assessment.

In the Written Opinion, paragraph 5.10, the IPEA states that Claim 44 is not clear because it is not clear how polyvinylpyrrolidone could be considered as a cellulosic polymer. Reconsideration and withdrawal of this assessment is respectfully requested in view of the amendment to Claim 44, which is now dependent on Claim 39.

Should any questions arise, the International Preliminary Examining Authority is requested to contact the undersigned attorney.

Respectfully submitted,

By: _____

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WHAT IS CLAIMED IS:

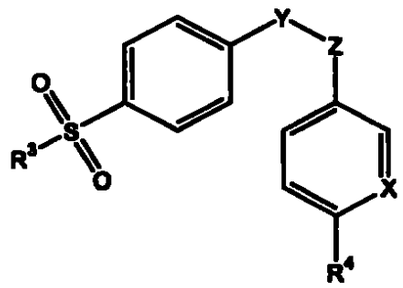
1. A physically stable, thixotropic, orally deliverable pharmaceutical composition comprising a drug of low water solubility and an aqueous liquid vehicle that comprises (a) a pharmaceutically acceptable wetting agent, (b) a pharmaceutically acceptable thixotropic thickening agent present in a thixotropic amount of at least about 0.25%, and (c) a pharmaceutically acceptable inorganic suspending agent.

2. The composition of Claim 1 wherein at least a substantial portion of the drug is suspended in particulate form in the vehicle to form a suspension that is substantially deflocculated.

3. The composition of Claim 1 wherein the drug is present in an amount of at least about 0.01%.

4. The composition of Claim 1 wherein the drug is a selective cyclooxygenase-2 inhibitory drug of low water solubility.

5. The composition of Claim 4 wherein the selective cyclooxygenase-2 inhibitory drug is a compound of formula



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups.

6. The composition of Claim 5 wherein the five- to six-membered ring is selected from the group consisting of cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

28. The composition of Claim 24 wherein the colloidal silicon dioxide has a weight average particle diameter of about 10 to about 25 nm.

29. The composition of Claim 1 wherein the inorganic suspending agent is present in an amount of about 0.01% to about 3%, by weight.

30. The composition of Claim 24 wherein the inorganic suspending agent is present in an amount of about 0.25% to about 1%, by weight.

31. The composition of Claim 1 wherein the thixotropic thickening agent and the inorganic suspending agent are present in a weight ratio of about 10:1 to about 1:10.

32. The composition of Claim 1 wherein the thixotropic thickening agent and the inorganic suspending agent are present in a weight ratio of about 2:1 to about 1:2.

33. The composition of Claim 1 wherein about 75% to 100% of the drug is suspended in particulate form.

34. The composition of Claim 1 wherein about 85% to 100% of the drug is suspended in particulate form.

35. The composition of Claim 1 wherein less than about 25% of the drug is dissolved and/or solubilized.

36. The composition of Claim 1 wherein less than about 10% of the drug is dissolved and/or solubilized.

37. The composition of Claim 1 wherein the composition has a maximum viscosity of about 5 to about 50 Pa•s and a dynamic viscosity measured at 2 sec^{-1} of about 0.3 to about 20 Pa•s.

38. The composition of Claim 1 wherein the composition has a maximum viscosity of about 5 to about 25 Pa•s and a dynamic viscosity measured at 2 sec^{-1} of about 0.5 to about 7 Pa•s.

39. A method for increasing the physical stability of an aqueous, thixotropic pharmaceutical composition of a drug of low water solubility, the method comprising adding to the composition a pharmaceutically acceptable thixotropic thickening agent in a thixotropic amount of at least about 0.25%,

and a pharmaceutically acceptable inorganic suspending agent in amounts which act synergistically to increase physical stability of the composition.

40. The method of Claim 39 wherein the composition further comprises a wetting agent.

41. The method of Claim 40 wherein a substantial portion of the drug is suspended in particulate form in a vehicle to form a suspension.

42. The method of Claim 41 wherein the composition is substantially deflocculated.

43. The method of Claim 39 wherein the thixotropic thickening agent is a cellulosic polymer.

44. The method of Claim 39 wherein the thixotropic thickening agent is selected from the group consisting of methylcellulose, microcrystalline cellulose, polyvinylpyrrolidone, and hydroxypropyl methycellulose.

45. The method of Claim 39 wherein the thixotropic thickening agent is a polysaccharide gum.

46. The method of Claim 45 wherein the polysaccharide gum is selected from the group consisting of xanthan, guar, acacia, and tragacanth gums.

47. The method of Claim 45 wherein the polysaccharide gum is xanthan gum.

48. The method of Claim 39 wherein the thixotropic thickening agent is present in an amount of about 0.25% to about 2%, by weight.

49. The method of Claim 39 wherein the thixotropic thickening agent is present in an amount of about 0.4% to about 2%, by weight.

50. The method of Claim 39 wherein the inorganic suspending agent is selected from the group consisting of colloidal silicon dioxide, bentonite and kaolin.

51. The method of Claim 39 wherein the inorganic suspending agent is colloidal silicon dioxide.

52. The method of Claim 51 wherein the colloidal silicon dioxide has a specific surface area of about 50 to about 400 m^2/g.

53. The method of Claim 51 wherein the colloidal silicon dioxide has a specific surface area of about 150 to about 400 m^2/g.

54. The method of Claim 51 wherein the colloidal silicon dioxide has a weight average particle diameter of about 7 to about 40 nm.

55. The method of Claim 51 wherein the colloidal silicon dioxide has a weight average particle diameter of about 10 to about 25 nm.

56. The method of Claim 39 wherein the inorganic suspending agent is present in an amount of about 0.01% to about 3%, by weight.

57. The method of Claim 56 wherein the inorganic suspending agent is present in an amount of about 0.25% to about 1%, by weight.

58. The method of Claim 39 wherein the thixotropic thickening agent and the inorganic suspending agent are present in a weight ratio of about 10:1 to about 1:10.

59. The method of Claim 39 wherein the thixotropic thickening agent and the inorganic suspending agent are present in a weight ratio of about 2:1 to about 1:2.

60. The method of Claim 40 wherein the wetting agent is selected from the group consisting of quaternary ammonium compounds, dioctyl sodium sulfosuccinate, polyoxyethylene alkylphenyl ethers, poloxamers, polyoxyethylene fatty acid glycerides and oils, polyoxyethylene alkyl ethers, polyoxyethylene fatty acid esters, polyoxyethylene sorbitan esters, propylene glycol fatty acid esters, sodium lauryl sulfate, fatty acids and salts thereof, glyceryl fatty acid esters, sorbitan esters, tyloxapol and mixtures thereof.

61. The method of Claim 40 wherein the wetting agent is selected from the group consisting of benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, dioctyl sodium sulfosuccinate, nonoxynol 9, nonoxynol 10, octoxynol 9, polyoxyethylene 8 caprylic/capric mono- and diglycerides, polyoxyethylene 35 castor oil, polyoxyethylene 20 cetostearyl ether, polyoxyethylene 40 hydrogenated castor oil, polyoxyethylene 10 oleyl ether, polyoxyethylene 40 stearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, propylene glycol laurate, sodium lauryl sulfate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, tyloxapol and combinations thereof.

62. The method of Claim 40 wherein the wetting agent is polysorbate 80.

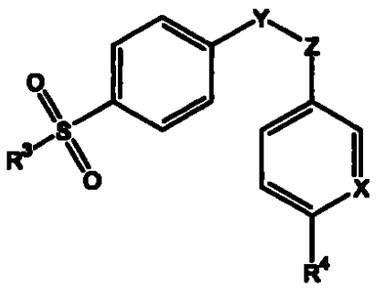
63. The method of Claim 40 wherein the wetting agent is present in an amount of about 0.01% to about 2%, by weight.

64. The method of Claim 40 wherein the wetting agent is present in an amount of about 0.25% to about 0.75%, by weight.

65. The method of Claim 39 wherein the drug is present in an amount of at least about 0.01%, on a weight per weight basis.

66. The method of Claim 39 wherein the drug is a selective cyclooxygenase-2 inhibitory drug.

67. The method of Claim 66 wherein the selective cyclooxygenase-2 inhibitory drug is a compound of formula



where R^3 is a methyl or amino group, R^4 is hydrogen or a C_{1-4} alkyl or alkoxy group, X is N or CR^5 where R^5 is hydrogen or halogen, and Y and Z are independently carbon or nitrogen atoms defining adjacent atoms of a five- to six-membered ring that is unsubstituted or substituted at one or more positions with oxo, halo, methyl or halomethyl groups.

68. The method of Claim 67 wherein the five- to six-membered ring is selected from the group consisting of cyclopentenone, furanone, methylpyrazole, isoxazole and pyridine rings substituted at no more than one position.

69. The method of Claim 68 wherein the selective cyclooxygenase-2 inhibitory drug is selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, etoricoxib, 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

70. The method of Claim 69 wherein the selective cyclooxygenase-2 inhibitory drug is celecoxib.

71. The method of Claim 39 wherein the drug is present in an amount of about 0.01% to about 15%, by total weight of the composition.

72. The method of Claim 39 wherein the drug is present in an amount of about 0.01% to about 5%, by total weight of the composition.

73. The method of Claim 41 wherein about 75% to 100% of the drug is suspended in particulate form.

74. The method of Claim 73 wherein about 85% to 100% of the drug is suspended in particulate form.

75. The method of Claim 39 wherein less than about 25% of the drug is dissolved and/or solubilized.

76. The method of Claim 39 wherein less than about 10% of the drug is dissolved and/or solubilized.

77. The method of Claim 39 wherein the composition has a maximum viscosity of about 5 to about 50 Pa•s and a dynamic viscosity measured at 2 sec^{-1} of about 0.3 to about 20 Pa•s.

78. The method of Claim 39 wherein the composition has a maximum viscosity of about 5 to about 25 Pa•s and a dynamic viscosity measured at 2 sec^{-1} of about 0.5 to about 7 Pa•s.

79. The composition of Claim 1, wherein the drug of low water solubility has a solubility in water, measured at 37°C, not greater than about 1 mg/ml.

80. The composition of Claim 1, wherein the drug of low water solubility has a solubility in water, measured at 37°C, not greater than about 0.1 mg/ml.

81. The composition of Claim 4, wherein the selective cyclooxygenase-2 inhibitory drug has a solubility in water, measured at 37°C, not greater than about 1 mg/ml.

82. The composition of Claim 4, wherein the selective cyclooxygenase-2 inhibitory drug has a solubility in water, measured at 37°C, not greater than about 0.1 mg/ml.

83. The method of Claim 39, wherein the drug of low water solubility has a solubility in water, measured at 37°C, not greater than about 1 mg/ml.

84. The method of Claim 39, wherein the drug of low water solubility has a solubility in water, measured at 37°C, not greater than about 0.1 mg/ml.

85. The composition of Claim 1 wherein the drug is present in an amount of no more than about 90%, on a weight per weight basis.

86. The method of Claim 39 wherein the drug is present in an amount of no more than about 90%, on a weight per weight basis.

87. The composition of Claim 1 wherein about 50% to 100% of the drug is suspended in particulate form.

88. The composition of Claim 1 wherein less than about 5% of the drug is dissolved and/or solubilized.

89. The method of Claim 41 wherein about 50% to 100% of the drug is suspended in particulate form.

90. The method of Claim 39 wherein less than about 5% of the drug is dissolved and/or solubilized.

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

HOLLAND, Donald, R.
Harness, Dickey & Pierce, P.L.C.
Suite 400
7700 Bonhomme
St. Louis, MO 63105
United States of America

Date of mailing (day/month/year)	
12 December 2002 (12.12.02)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
6794S-000009	
International application No.	**International filing date (day/month/year)**
PCT/US02/24746	05 August 2002 (05.08.02)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
PHARMACIA CORPORATION & UPJOHN 301 Henrietta Kalamazoo, MI 49007 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
PHARMACIA CORPORATION 301 Henrietta Kalamazoo, MI 49007 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[ ] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Sean TAYLOR (Fax 338 9090)
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

HOLLAND, Donald, R.
Harness, Dickey & Pierce, P.L.C.
Suite 400
7700 Bonhomme
St. Louis, MO 63105
United States of America

Date of mailing (day/month/year) 09 October 2002 (09.10.02)	
Applicant's or agent's file reference 6794S-000009	**IMPORTANT NOTIFICATION**
International application No. PCT/US02/24746	International filing date (day/month/year) 05 August 2002 (05.08.02)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 06 August 2001 (06.08.01)
Applicant PHARMACIA CORPORATION & UPJOHN et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
06 Augu 2001 (06.08.01)	60/310,372	US	13 Sept 2002 (13.09.02)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Khemais BRAHMI

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

HOLLAND, Donald, R.
Harness, Dickey & Pierce, P.L.C.
Suite 400
7700 Bonhomme
St. Louis, MO 63105
United States of America

Date of mailing (day/month/year): 16 January 2004 (16.01.2004)	
Applicant's or agent's file reference: 6794S-000009	IMPORTANT NOTIFICATION
International application No.: PCT/US2002/024746	International filing date (day/month/year): 05 August 2002 (05.08.2002)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address:
PHARMACIA CORPORATION
301 Henrietta
Kalamazoo, MI 49007
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address:
PHARMACIA CORPORATION
700 Chesterfield Parkway West
Chesterfield, MO 63017-1732
United States of America

State of Nationality: US
State of Residence: US
Telephone No.: 314 694 6812
Facsimile No.: 314 694 7256
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.90.90

Authorized officer: Sean TAYLOR (Fax 338 9090)

Telephone No. (41-22) 338 9811

Form PCT/IB/308 (March 1994) 008058321

PATENT COOPERATION TREATY

226

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

HOLLAND, Donald, R.
Harness, Dickey & Pierce, P.L.C.
Suite 400
7700 Bonhomme
St. Louis, MO 63105
United States of America

Date of mailing (day/month/year)	
20 January 2004 (20.01.2004)	
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
6794S-000009	
International application No.	International filing date (day/month/year)
PCT/US2002/024746	05 August 2002 (05.08.2002)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
GUANG, Wei, Lu 3172 Birchwood Court Ann Arbor, MI 48015 United States of America	CN	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
LU, Guang, Wei 3172 Birchwood Court Ann Arbor MI 48105 United States of America	CH	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Sean TAYLOR (Fax 338 9080)
Facsimile No. (41-22) 338.90.90	Telephone No. (41-22) 338 9811

Form PCT/IB/306 (March 1994) 000000433

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE RECD	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
60/310,372	08/06/2001		150	6794S-000009	3		

CONFIRMATION NO. 8085

Donald R. Holland
Harness, Dickey & Pierce, P.L.C.
Suite 400
7700 Bonhomme
St. Louis, MO 63105

RECEIVED
SEP 10 2001
HARNESS, DICKEY & PIERCE
ST. LOUIS, MISSOURI

FILING RECEIPT

OC000000006813410

FAXED
SEP 11 2001

Date Mailed: 09/05/2001

Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U.S. APPLICATI N NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Guang Wei Lu, Ann Arbor, MI;

If Required, Foreign Filing License Granted 09/05/2001

Projected Publication Date: N/A

Non-Publication Request: No

Early Publication Request: No

Title

Stabilized oral suspension forumlation

Data entry by : TRUONG, LINH **Team : OIPE** **Date: 09/05/2001**

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Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

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PLEASE NOTE the following information about the Filing Receipt:

- The articles such as "a," "an" and "the" are not included as the first words in the title of an application. They are considered to be unnecessary to the understanding of the title.
- The words "new," "improved," "improvements in" or "relating to" are not included as first words in the title of an application because a patent application, by nature, is a new idea or improvement.
- The title may be truncated if it consists of more than 500 characters (letters and spaces combined).
- The docket number allows a maximum of 25 characters.
- If your application was submitted under 37 CFR 1.10, your filing date should be the "date in" found on the Express Mail label. If there is a discrepancy, you should submit a request for a corrected Filing Receipt along with a copy of the Express Mail label showing the "date in."
- The title is recorded in sentence case.

Any corrections that may need to be done to your Filing Receipt should be directed to:

Assistant Commissioner for Patents
Office of Initial Patent Examination
Customer Service Center
Washington, DC 20231

Attorney Docket No. 6794S-000009

ASSIGNMENT

WHEREAS, I/WE, the undersigned, have made certain invention or inventions which are disclosed in patent application(s) and/or provisional patent application(s) entitled:

STABILIZED ORAL SUSPENSION FORMULATION

identified as United States Provisional Patent Application Serial No. 60/310,372 which was filed on August 6, 2001; and

WHEREAS, PHARMACIA CORPORATION, having offices at 100 Route 206 North, Peapack, New Jersey 07977, is desirous of acquiring the entire right, title and interest in and to said invention or inventions and any and all patents to be obtained therefor;

NOW, THEREFORE, FOR GOOD AND VALUABLE CONSIDERATION, the receipt of which is hereby acknowledged, I/WE do hereby sell, assign and transfer to said PHARMACIA CORPORATION, its successors and assigns, the entire right, title and interest in and to said invention or inventions, in any form or embodiment thereof, and in and to said application(s); and in and to any and all applications filed in any country based thereon, including the right to file applications in countries other than the country of priority filing under the provisions of any international convention; also in and to any and all improvements on said invention or inventions now or hereafter made by me/us as employee(s), agent(s) or contractor(s) of said PHARMACIA CORPORATION; also the entire right, title and interest in and to any and all patents, including reissues and extensions thereof, to be obtained in any country upon said invention, inventions or improvements, and any and all continuing applications, including divisional, continuation and continuation-in-part applications, substitute applications, and applications claiming benefit of an earlier filed provisional application, which may be filed upon said invention, inventions or improvements in any country; and

I/WE hereby authorize and request the issuing authority to issue any and all patents on said application or applications to said PHARMACIA CORPORATION, as assignee of the entire interest.

I/WE further agree, without any payment by said PHARMACIA CORPORATION other than in reimbursement of reasonable expenses I/we may incur, to communicate to said PHARMACIA CORPORATION, its representatives or agents, any facts relating to said invention, inventions or improvements, including evidence for purposes of interference, opposition or other legal proceedings, whenever requested; testify in any interference, opposition or other legal proceedings, whenever requested; and execute and deliver, on request, all lawful papers required to make any of the foregoing provisions effective.

IN TESTIMONY WHEREOF, I/WE have hereto set our hands on the dates set after our signatures.

Signature: Guang Wei Lu Date: 2/7/02

Name: Guang Wei Lu

City and state or country of residence: Ann Arbor, Michigan

State of Michigan }
} ss.
County of Kalamazoo }

On this 7th day of February, 2002, before me personally appeared Guang Wei Lu, to me known to be the person who executed the foregoing instrument and acknowledged that he/~~she~~ executed the same as his/~~her~~ free act and deed; in testimony whereof I have hereto set my hand and official seal on the day last above written.

(seal)

Debra J. Marquette
Notary Public or Consular Officer

My Commission Expires: _____

DEBRA J. MARQUETTE
Notary Public, Kalamazoo County, MI
My Commission Expires 9/25/2004

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Radicacion : [illegible]
Fecha (MM): 2004-02-06 15:49:48
Tramite : [illegible]

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN MODELO DE UTILIDAD	( )	(X)
- Indicación de que se solicita la concesión de una patente.	( )	(X)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	(X)
- Descripción de la invención.	( )	(X)
- Dibujos de ser estos pertinentes.	( )	(X)
- Comprobante de Pago de las tasas establecidas.		
COMPLETA ( ) INCOMPLETA	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable:

Edwin Novoa

Fecha: 06-02-2004.

Nº Radicación: 04-9302

232

AS: 93.040

04 009302 00

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

Fecha ENTRADA EN FASE NACIONAL : 06-03-04

1	**SOLICITUD DE:**	
	☒ Patente de Invención.	☐ Patente de Modelo de Utilidad.
	☐ Capítulo I.	☒ Capítulo II.
2 **SOLICITANTE (71)**	Nombre: PHARMACIA CORPORATION Dirección: 700 Chesterfield Parkway West, Chesterfield, MO 63017-1732, Estados Unidos Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual____ Número ____
3 **REPRESENTANTE O APODERADO**	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual____ Número 170.322 TP 1003
4 **INVENTOR (ES) (72)**	Nombre: Guang Wei Lu Dirección: 3172 Birchwood Court, Ann Arbor, MI 48015, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos de América	

5 **PCT (86)**
Solicitud Internacional No. PCT/US02/24746 Fecha 05-08-2002
Publicación Internacional No. WO 03/013473 A1 Fecha 20-02-2003

6 **Título (54):** FORMULACIÓN DE SUSPENSIÓN ORAL ESTABILIZADA

7 **Clasificación Internacional (51)** A61K 41/45.

8 **Prioridad** SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	06-08-2001	60/310,372

9 **Comprobante de pago No.** 04-1.600 Fecha 30-01-2004

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

2020-F08 (01-11-15)

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REIVINDICACIONES

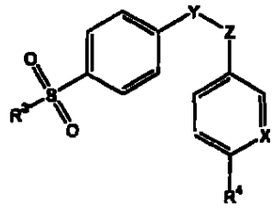
1. Una composición farmacéutica que comprende una droga de baja solubilidad en agua para administrar en forma oral y un vehículo líquido acuoso que comprende (a) un agente humectante aceptable para uso farmacéutico, (b) un agente espesante tixotrópico aceptable para uso farmacéutico, y (c) un agente de suspensión inorgánico aceptable para uso farmacéutico.

2. La composición de la reivindicación 1 donde se suspende en el vehículo por lo menos una porción sustancial de la droga en forma particulada para formar una suspensión y donde el agente humectante, el agente espesante y agente de suspensión están presentes en cantidades totales y relativas tales que la suspensión es tixotrópica, sustancialmente desfloculada, y que es físicamente estable de manera sustancial.

3. La composición de la reivindicación 1 donde la droga está presente en una cantidad total efectiva para uso terapéutico y/o para la profilaxis.

4. La composición de la reivindicación 1 donde la droga es una droga inhibidora selectiva de ciclooxigenasa-2 de baja solubilidad en agua.

5. La composición de la reivindicación 4 donde la droga inhibidora selectiva de ciclooxigenasa-2 es un compuesto de fórmula:



donde R^3 es un grupo metilo o amino, R^4 es hidrógeno o un grupo

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Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Ramiro Castro Duque.
Apoderado
Pharmacia Corporation.

Oficio N° 02166

ASUNTO:

Radicación N°	04-9302
Solicitud Internacional	PCT/US02/24746
Fecha Inicio fase nacional	06/03/2004
Trámite	011
Evento	379
Actuación	430
Folios	001

Como resultado del examen de forma, realizado con fundamento el el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL.
Jefe de la División de Nuevas Creaciones.

27 FEB. 2004

El anterior requerimiento fue notificado por fijación en lista de fecha_____.

202061