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A B O G A D O S

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO DIVISIÓN DE NUEVAS CREACIONES

E. S. D.

Ref.: Expediente No. 00-041.828
Solicitud de Patente a nombre de
McNeil-PPC, Inc.

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00341828 00000005 Folios: 2
Fecha (AMD): 2002-06-25 14:21:36
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 A No. 94-76 Of. 305, obrando como apoderada de la sociedad McNeil-PPC, Inc., domiciliada en Skillman, New Jersey, Estados Unidos de América, solicitante de la patente de la referencia, pido a usted que se proceda a examinar si la invención, cuya patente se tramita en el expediente de la referencia, es patentable.

Adjunto al presente memorial el recibo No. 02 - 41,045 de junio 21, 2002, por la suma de \$318.000.00, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio.

Señor Superintendente,



JIMENA ESCOBAR URIBE

C.C. 39.779.452 de usaquén

T.P. 68.228

Cod. 5376

JEU/ra.

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NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 02 - 41,045
FECHA : JUNIO 21 DE 2002

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ESCOBAR URIBE ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	4063113	21/06/2002	4,786,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		85 EXAMEN DE PATENTABILIDAD DE INVEN	318,000.00
		TOTAL :	\$ 318,000.00

SON: TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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2005-08-25
375.

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Doctor
JIMENA ESCOBAR URIBE
(Apoderado)

ASUNTO	Radicación	00041828
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	7296
	Folios	022

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados:

Los textos estudiados fueron la descripción (Folios: 2 a 17) y las reivindicaciones 1 a 17 (Folios: 62 a 64).

La presente solicitud reivindica prioridad americana N° US9.329900 de 10 de junio de 1999 y cumple con lo establecido en los artículos 9, 10 y 11 de la Decisión 486 de la Comisión de la Comunidad Andina.

Objeto de invención:

La presente solicitud se titula: "Método para proveer absorción incrementada de una amina farmacéuticamente aceptable en la sangre de un humano y composición que comprende una amina farmacéuticamente aceptable y un fármaco antiinflamatorio no esteroidal".

El objeto de la presente solicitud se refiere a medicamentos que contienen una combinación de un compuesto ácido analgésico/antiinflamatorio y una amina farmacológicamente activa. En una modalidad preferida, la presente solicitud se refiere a la combinación de materiales en una forma líquida de dosificación.

De acuerdo con la presente solicitud, productos que combinan ingredientes múltiples farmacéuticamente activos están disponibles comercialmente en todo el mundo. Los consumidores adquieren estos medicamentos en vista de que alivian varios síntomas al mismo tiempo. Por ejemplo, el ibuprofeno y la pseudoefedrina se comercializan en combinación en formas sólidas tales como tabletas, cápsulas y polvos para reconstitución. El ibuprofeno es un agente analgésico/antipirético efectivo, mientras que la pseudoefedrina es un descongestionante efectivo. Aunque se sabe que estos productos son efectivos, los consumidores quienes los usan buscan un alivio más rápido a los síntomas. Por consiguiente, continúa habiendo una gran necesidad de desarrollar productos que den rápido alivio al consumidor.

El Nivel Inventivo se evaluó por comparación entre lo solicitado y encontrado en el estado de la técnica y que se relaciona con el objeto reivindicado y de acuerdo con la definición de nivel inventivo del Artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina.

La respuesta al problema técnico que se pretendía resolver, resulta obvia partiendo de las anterioridades WO 92/15332, WO 98/24414, WO 92/17171 y WO 95/19759. Como se observa, el objeto de esta solicitud podría resultar obvio para una persona del oficio normalmente versada en la materia y derivarse de manera evidente del estado de la técnica.

Evaluación de la Aplicación Industrial:

El artículo 19 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Se considerará que una invención es susceptible de aplicación industrial, cuando su objeto pueda ser producido o utilizado en cualquier tipo de industria, entendiéndose por industria la referida a cualquier actividad productiva, incluidos los servicios".

El objeto de la presente solicitud cumple con el requisito de Aplicación Industrial.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	WO 92/15332	1 a 17	Novedad y Nivel Inventivo
2	WO 95/19759	1 a 17	Novedad y Nivel Inventivo
3	WO 92/17171	1 a 17	Novedad y Nivel Inventivo
4	WO 98/24414	1 a 17	Novedad y Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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 CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 25 AGO. 2005

CONCEPTO TÉCNICO Nº: 1212	EXAMINADOR TÉCNICO Código N°: 202005	EXAMINADOR JURÍDICO Código N°:
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 45/06, 31/60, 31/62 A61K 31/19, 31/445, 31/55 // (A61K 31/19, 31:135) (A61K 31/60 A61K 31:135, 31:34, 31:415 A61K 31:445, 31:55, 31:19)	A1	(11) International Publication Number: WO 92/15332 (43) International Publication Date: 17 September 1992 (17.09.92)
(21) International Application Number: PCT/US92/00164 (22) International Filing Date: 10 January 1992 (10.01.92) (30) Priority data: 664,018 4 March 1991 (04.03.91) US (71) Applicant: WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US). (72) Inventors: FAWZI, Mahdi, B. ; 11 Timberline Drive, Flanders, NJ 07836 (US). MAHJOUR, Majid ; 82 Koclas Drive, Netcong, NJ 07857 (US). (74) Agents: BELL, Craig, M. et al.; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US).	(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: NOVEL SALTS/ION PAIRS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN VARIOUS DOSAGE FORMS (57) Abstract Novel pharmaceutical compositions are comprised of the salt or ion pair formation of a non-steroidal anti-inflammatory drug and an antihistamine or other decongestant. The physico-chemical characteristics of these compositions show them to be substantially different from their parent acid or base and will enable the preparation of dual action sustained or enhanced relief therapy regimens. The compositions also possess enhanced stability and therefore the multi-symptom relief can be incorporated into a number of dosage forms such as capsules, tablets, elixirs, ointments and the like.		

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What We Claim is:

- 5 1) An improved pharmaceutical composition comprising a non-steroidal anti-inflammatory drug/antihistamine salt/ion pair.
- 10 2) The pharmaceutical composition of claim 1 wherein said non-steroidal anti-inflammatory drug is selected from the group consisting of Meclofenamic acid, Salicylic acid, Sulindac, Ibuprofen, Naproxen, Dichlofinac and mixtures thereof.
- 15 3) The pharmaceutical composition of claim 2 wherein said antihistamine is selected from the group consisting of Diphenhydramine, Pseudoephedrine, Ranitidine, Loratidine, Cimetidine, Hismanal, Terfenadine and mixtures thereof.
- 20 4) The pharmaceutical composition of claim 3 wherein the ratio of the non-steroidal anti-inflammatory drug to the antihistamine is 1:1.
- 25 5) The pharmaceutical composition of claim 4 further comprising excipients and a pharmaceutically acceptable non-toxic carrier material.
- 30 6) The pharmaceutical composition of claim 5 wherein said composition is incorporated into a therapeutic dosage form selected from the group consisting of capsules, tablets, elixirs, parenterals, transdermal patches, suppositories and topical ointments.
- 35 7) An improved pharmaceutical composition comprising the salt/ion pair of a non-steroidal anti-inflammatory drug and sympathomimetic drug combination.
- 8) The pharmaceutical composition of claim 7 wherein said non-steroidal anti-inflammatory drug is

selected from the group consisting of Meclofenamic acid, Salicylic acid, Sulindac, Ibuprofen, Naproxen, Dichlofinac and mixtures thereof.

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- 9) The pharmaceutical composition of claim 8 wherein said sympathomimetic drug is selected from the group consisting of nasal decongestants and bronchodilators.

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- 10) The pharmaceutical composition of claim 9 wherein said non-steroidal anti-inflammatory drug is combined with said sympathomimetic drug in a 1:1 ratio.

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- 11) The pharmaceutical composition of claim 10 further comprising pharmaceutically acceptable excipients and non-toxic carrier materials.

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- 12) The pharmaceutical composition of claim 11 wherein said composition is incorporated into a therapeutic dosage form selected from the group consisting of capsules, tablets, elixirs, parenterals, suspensions, saches, transdermal patches, suppositories, and topical ointments.

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- 13) An improved pharmaceutical composition comprising the salt formed by the acid-base reaction of a non-steroidal anti-inflammatory drug and an antihistamine.

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- 14) An improved pharmaceutical composition comprising an ion pair formed by the acid base reaction of a non-steroidal anti-inflammatory drug and an antihistamine.

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- 15) The pharmaceutical composition of claim 13 or 14 wherein said non-steroidal anti-inflammatory drug is selected from the group consisting of Meclofenamic

acid, Salicylic acid, Sulindac, Ibuprofen, Naproxen, Dichlofinac and mixtures thereof.

- 5 16) The pharmaceutical composition of claim 15 wherein said antihistamine is selected from the group consisting of Diphenhydramine, Pseudoephedrine, Ranitidine, Loratidine, Cimetidine, Hismanal, Terfenadine and mixtures thereof.
- 10
- 17) The pharmaceutical composition of claim 16 wherein said non-steroidal anti-inflammatory drug is mixed with said antihistamine in a 1:1 ratio.
- 15 18) The pharmaceutical composition of claim 17 further comprising the addition of pharmaceutically acceptable excipients and non-toxic carrier materials.
- 20 19) The pharmaceutical composition of claim 18 wherein said composition is incorporated into a therapeutic dosage form selected from the group consisting of capsules, tablets, elixirs, parenterals, suspensions, saches, transdermal patches, 25 suppositories and topical ointments.
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/10, 47/38, 47/36, 31/44, 31/135, 31/09, 31/485, 31/19, 31/165	A1	(11) International Publication Number: WO 98/24414 (43) International Publication Date: 11 June 1998 (11.06.98)
(21) International Application Number: PCT/US97/21935 (22) International Filing Date: 2 December 1997 (02.12.97) (30) Priority Data: 08/702,777 5 December 1996 (05.12.96) US (71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940 (US). (72) Inventors: SINGH, Kiran, Pal; 117 Steeplechase Court, Deptford, NJ 08096 (US). POPLI, Shankar, D.; 31 Pelham Road, Marlton, NJ 08053 (US). (74) Agents: ALICE, Ronald, W.; American Home Products Corporation, One Campus Drive, Parsippany, NJ 07054 (US) et al.		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: PHARMACEUTICAL SUSPENSION SYSTEMS		
(57) Abstract A pharmaceutically acceptable liquid suspension system is provided for solid finely divided pharmaceutical actives incompletely soluble in water, the suspension system comprising water, xanthan gum and hydroxypropyl methylcellulose.		

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CLAIMS

1. A pharmaceutically acceptable liquid excipient suspending base for homogeneously suspending solid pharmaceutically active compounds without excessive foam formation which liquid excipient base comprises water and per 100 milliliters of said base a) about 0.3 to about 0.5 grams of xanthan gum and b) about 0.3 to about 0.5 grams of hydroxypropyl methylcellulose, the weight ratio of said xanthan gum to said hydroxypropyl methylcellulose being about 0.88 to about 1.1:1.
2. The pharmaceutically acceptable liquid excipient suspending base of Claim 1 wherein the hydroxypropyl methyl cellulose has a methoxyl content of 19 - 24 %, a hydroxypropoxyl content of 7 - 12%, and a molecular weight of approximately 86,000.
3. The pharmaceutically acceptable liquid excipient base of Claim 2 wherein the pH is about 4 to about 6.0
4. A pharmaceutically acceptable composition comprising (1) a liquid excipient suspending base comprising water and per 100 milliliters of said base (a) about 0.3 to about 0.5 grams of xanthan gum and (b) about 0.3 to about 0.5 grams of hydroxypropyl methyl cellulose, the weight ratio of said xanthan gum to said hydroxypropyl methyl cellulose being about 0.88 to about 1.1:1, and (2) at least one finely divided solid pharmaceutically active compound selected from the group consisting of antihistamines, decongestants, antitussives, expectorants, non-steroidal anti-inflammatory drugs (NSAIDS) and analgesic drugs, said finely, divided solid pharmaceutically active compound being suspended in the liquid excipient suspending base.
5. The composition of Claim 4 wherein the pharmaceutically active compound is an antihistamine selected from the group consisting of chlorpheniramine, brompheniramine, dexchlorpheniramine, dexbrompheniramine, triprolidine, diphenhydramine, doxylamine, tripeleminamine, cyproheptadine, bromodiphenhydramine, phenindamine, pyrilamine and azatadine.

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6. The composition of Claim 5 wherein the antihistamine is brompheniramine maleate in an amount of about 0.5 to about 4 milligrams per 5 milliliters of the excipient base.
7. The composition of Claim 4 wherein the pharmaceutically active compound is a decongestant selected from the group consisting of pseudoephedrine HCl, phenylpropanolamine and phenylephrine.
8. The composition of Claim 7 wherein the pharmaceutically active compound is pseudoephedrine HCl in an amount of about 10 to about 60 milligrams per 5 milliliters of the excipient base.
9. The composition of claim 8 wherein the pharmaceutically active compound is pseudoephedrine HCl in an amount of about 15 to about 30 milligrams per 5 milliliters of the excipient base.
10. The composition of Claim 4 wherein the pharmaceutically active compound is an expectorant selected from the group consisting of oterpin hydrate, guaifenesin, potassium iodide, potassium citrate and potassium guaicol sulfonate.
11. The composition of Claim 10 wherein the expectorant is guaifenesin in an amount up to about 300 milligrams per 5 milliliters of the excipient base.
12. The composition of Claim 11 wherein the guaifenesin is present in an amount of about 100 to about 200 milligrams per 5 milliliters of the excipient base.
13. The composition of Claim 4 wherein the pharmaceutically active compound is an antitussive selected from the group consisting of caramiphen, dextromethorphan HBr, codeine phosphate and codeine sulfate.
14. The composition of Claim 13 wherein the antitussive is dextromethorphan HBr in an amount of between about 5 and about 20 milligrams per 5 milliliters of excipient base.
15. The composition of Claim 14 wherein the antitussive is dextromethorphan HBr in an amount of between about 10 and about 15 milligrams per 5 milliliters of excipient base.
16. The composition of Claim 4 wherein the NSAID is selected from the group consisting of propionic acid derivatives, acetic acid derivatives, fenamic acid

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derivatives, biphenylcarboxylic acid derivatives and oxicams.

17. The composition of Claim 16 wherein the NSAID is selected from the group consisting of ibuprofen, ketoprofen and naproxen.
18. The composition of Claim 17 wherein ibuprofen is present in an amount ranging from about 50 to about 150 milligrams per 5 milliliters of excipient base.
19. The composition of Claim 18 wherein ibuprofen is present in an amount ranging from about 100 to about 150 milligrams per 5 milliliters of excipient base.
20. The composition of Claim 17 wherein naproxen is present in an amount ranging from about 50 to about 250 milligrams per 5 milliliters of excipient base.
21. The composition of Claim 20 wherein naproxen is present in an amount ranging from about 100 to about 150 milligrams per 5 milliliters of excipient base.
22. The composition of Claim 4 wherein the analgesic is acetaminophen.
23. The composition of Claim 22 wherein acetaminophen is present in an amount up to about 600 milligrams per 5 milliliters of the excipient base.
24. The composition of Claim 23 wherein acetaminophen is present in an amount of about 150 to about 175 milligrams per 5 milliliters of the excipient base.

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 31/19	A1	(11) International Publication Number: WO 92/17171 (43) International Publication Date: 15 October 1992 (15.10.92)
(21) International Application Number: PCT/US92/02388 (22) International Filing Date: 24 March 1992 (24.03.92) (30) Priority data: 678,773 1 April 1991 (01.04.91) US 812,523 20 December 1991 (20.12.91) US (60) Parent Applications or Grants (63) Related by Continuation US 678,773 (CON) Filed on 1 April 1991 (01.04.91) US 812,523 (CON) Filed on 20 December 1991 (20.12.91) (71) Applicants (for all designated States except US): MERCK & CO., INC. [US/US]; 126 E. Lincoln Avenue, Rahway, NJ 07065 (US). McNEIL-PPC, INC. [US/US]; Van Liew Avenue, Milltown, NJ 08850 (US).		(72) Inventors; and (75) Inventors/Applicants (for US only): SIMS, Robert, T. [US/US]; 5080 Anderson Road, Holicong, PA 18928 (US). SLIVKA, William [US/US]; 9425 Meadowbrook Lane, Philadelphia, PA 19118 (US). (74) Agent: WINOKUR, Melvin; 126 E. Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KR, LK, LU (European patent), MC (European patent), MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL (European patent), NO, PL, RO, RU, SD, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent), US. Published With international search report.
(54) Title: IBUPROFEN-DECONGESTANT COMBINATIONS (57) Abstract This invention relates to pharmaceutical compositions for use in the treatment of pain and inflammation and the relief of nasal congestion and sinus pressure in a mammalian organism, said composition comprising: (i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen, or a salt thereof, substantially free of (R)-ibuprofen; and (ii) a sympathomimetically effective amount of at least one of the sympathomimetic amines selected from phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, levo-desoxyephedrine or a therapeutically active stereoisomer thereof substantially free of its other stereoisomers or a pharmaceutically acceptable salt thereof.		

this invention are any diastereomers and/or enantiomers of each decongestant. Where a particular therapeutically active stereoisomer is not commercially available it may be prepared following
5 standard resolution chemistry from the available racemic mixture.

The amount of the decongestant useful in the practice of the present invention may vary from about 1 mg to 100 mg depending on the specific
10 decongestant. The amount of a salt, such as pseudoephedrine hydrochloride, is determined based on the amount of active decongestant, such as pseudoephedrine, contained therein.

The present compositions may be administered
15 in the form of tablets, capsules, elixirs, syrups, drops, granules, liquids, nasal spray inhaler, or a suspension. For oral administration the active components may be admixed with a pharmaceutically acceptable diluent such as lactose, starch, sucrose,
20 cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol and in a liquid composition, ethyl alcohol. Acceptable binders such as PVP, starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium
25 alginate, carboxymethylcellulose, polyethylene glycol and waxes, may also be admixed with the active components. Where necessary lubricants such as magnesium stearic acid talc, and disintegrators such as starch, methylcellulose, agar, bentonite and guar
30 gum and super disintegrators such as docusate sodium, sodium starch glycollate or cross linked PVP may also be included.

The active components may also be formulated in sustained release formulations. These

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EXAMPLE 3

(S)-ibuprofen, Decongestant Sustained Release

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(S)-ibuprofen	400 mg
Pseudoephedrine HCl	60 mg
PVP	30 mg
Avicel PH101	80 mg
10 Magnesium Stearate	8 mg
Methocel E10MCR	66 mg
Methocel K100MLV	200 mg

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EXAMPLE 4

(S)-ibuprofen-(S)-lysine/decongestant Solution

20 {	(S)-ibuprofen-(S)-lysine	342 mg
	Pseudoephedrine HCl	15 mg
	q.s. syrup	5 ml

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WHAT IS CLAIMED IS:

1. A pharmaceutical composition for use in the treatment of pain and inflammation and the relief of nasal congestion and sinus pressure in a mammalian organism and adapted for unit dosage oral administration said composition comprising:

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen, or a salt thereof, substantially free of (R)-ibuprofen; and

(ii) a sympathomimetically effective amount of at least one of the sympathomimetic amines phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, levo-desoxyephedrine or a therapeutically active stereoisomer thereof substantially free of its other stereoisomers or a pharmaceutically acceptable salt thereof.

2. A composition of Claim 1 where the ibuprofen is present as the salt (S)-ibuprofen-(S)-lysine, or (S)-ibuprofen-(R)-lysine.

3. A composition of Claim 1 comprising at least 50 mg of (S)-ibuprofen.

4. A composition of Claim 3 wherein the sympathomimetic amine is selected from: phenylephrine, phenylpropanolamine, pseudoephedrine, or a therapeutically active stereoisomer thereof substantially free of its other stereoisomers, or a pharmaceutically acceptable salt.

5. A method of treating pain and inflammation and the relief of allergy and cold symptoms in a mammalian organism in need of such treatment comprising administering to such organism:

5 (i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen, or a salt thereof, substantially free of (R)-ibuprofen;

(ii) a sympathomimetically effective amount of at least one of the sympathomimetic amines
10 phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, levo-desoxyephedrine or a therapeutically active stereoisomer thereof substantially free of its other stereoisomers or a
15 pharmaceutically acceptable salt thereof.

6. A method of eliciting an onset hastened and enhanced response for the treatment of pain and inflammation and the relief of allergy and cold
20 symptoms in a mammalian organism in need of such treatment comprising administering to such organism.

(i) an analgesically and anti-inflammatory effective amount of (S)-ibuprofen, or a salt thereof, substantially free (R)-ibuprofen; and

25 (ii) a sympathomimetically effective amount of at least one of the sympathomimetic amines phenylephrine, phenylpropanolamine, pseudoephedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, levo-desoxyephedrine
30 or a therapeutically active stereoisomer thereof substantially free of its other stereoisomers or a pharmaceutically acceptable salt thereof.

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(21) International Application Number: PCT/US95/01018 (22) International Filing Date: 24 January 1995 (24.01.95) (30) Priority Data: 08/185,576 24 January 1994 (24.01.94) US (71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US). (72) Inventor: DHABHAR, Dadi, Jamshed; 10127 Bennington Drive, Cincinnati, OH 45241 (US). (74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US).	(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: PROCESS FOR SOLUBILIZING DIFFICULTLY SOLUBLE PHARMACEUTICAL ACTIVES (57) Abstract A process for improving the solubility of difficultly soluble pharmaceutical actives in a mixture of polyethylene glycol and propylene glycol by using a polyvinylpyrrolidone with a specific viscosity average molecular weight of from about 5,000 to about 25,000.		

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Jimerson, "Softgel (Soft Gelatin Capsule) Update", Drug Development and Industrial Pharmacy (Interphex '86 Conference), vol. 12, no. 8 & 9, pp. 1133-1144 (1986); and W.R. Ebert, "Soft Elastic Gelatin Capsules: A Unique Dosage Form", Pharmaceutical Technology, vol. 1, no. 5, pp. 44-50 (1977); these references are incorporated by reference herein in their entirety. Methods for tempering soft gelatin capsules are described in U.S. Patent 5,200,191 to Steele et al., herein incorporated by reference. The resulting soft gelatin capsule is soluble in water and in gastrointestinal fluids. Upon swallowing the capsule, the gelatin shell rapidly dissolves or ruptures in the gastrointestinal tract thereby introducing the pharmaceutical actives into the physiological system.

EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

EXAMPLE I

Solubilized Pharmaceutical Composition

A highly concentrated solution containing acetaminophen in combination with other pharmaceutical actives is prepared from the following ingredients:

	<u>Ingredients</u>	<u>Weight %</u>
	Acetaminophen	31.25
	Pseudoephedrine HCl	2.88
	Dextromethorphan HBr	1.44
25	Doxylamine Succinate	0.60
	Polyethylene Glycol 600	24.38
	Polyethylene Glycol 1000	22.14
	Propylene Glycol	4.33
	Polyvinylpyrrolidone ¹	8.17
30	<u>Water Purified</u>	4.81

¹ Available as Kollidon K-17 PF from BASF Chem.Co. (Viscosity average molecular weight $\approx$ 10,000)

A solution of the polyethylene glycols, propylene glycol, and polyvinylpyrrolidone is prepared by mixing and warming these compositions to 70°C. Acetaminophen is then dissolved into this solution, stirring and heating the solution to 120°C in the presence of

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nitrogen. Once the acetaminophen is dissolved the solution is removed from the heat. In a separate container, pseudoephedrine HCl, dextromethorphan HBr and doxylamine succinate are dissolved in water at room temperature by stirring. Finally, this separate admixture is combined with the original batch solution and mixed until uniform.

5 Examples II-III are further examples of concentrated solutions containing acetaminophen in combination with other pharmaceutical actives and are manufactured in a manner substantially similar to Example I

EXAMPLE II

Solubilized Pharmaceutical Composition

10	<u>Ingredients</u>	<u>Weight %</u>
	Acetaminophen	31.25
	Pseudoephedrine HCl	2.88
	Dextromethorphan HBr	1.44
	Doxylamine Succinate	0.60
15	Polyethylene Glycol 600	24.38
	Polyethylene Glycol 1000	22.14
	Propylene Glycol	4.33
	Polyvinylpyrrolidone ¹	8.17
	Water Purified	4.81

20 ¹ Available as Kollidon K-12 PF from BASF Chem.Co. (Viscosity average molecular weight $\approx$ 5,000)

EXAMPLE III

Solubilized Pharmaceutical Composition

	<u>Ingredients</u>	<u>Weight %</u>
25	Acetaminophen	31.25
	Pseudoephedrine HCl	2.88
	Dextromethorphan HBr	1.44
	Chlorpheniramine Maleate	0.19
	Polyethylene Glycol 600	24.52
30	Polyethylene Glycol 1000	22.40
	Propylene Glycol	4.33
	Polyvinylpyrrolidone ¹	8.17
	Water Purified	4.82

35 ¹ Available as Kollidon K-17 PF from BASF Chem.Co. (Viscosity average molecular weight $\approx$ 10,000)

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WHAT IS CLAIMED IS:

1. A process to enhance solubility of difficultly soluble pharmaceutical actives by combining and mixing until dissolved from 1% to 40%, preferably from 20% to 40%, more preferably from 25% to 35%, of at least one difficultly soluble pharmaceutical active in a solution comprising:
 - i) from 20% to 70%, preferably from 30% to 65%, more preferably from 40% to 60%, of a polyethylene glycol;
 - ii) from 4% to 20% of a polyvinylpyrrolidone having a viscosity average molecular weight from 5,000 to 25,000, preferably from 5,000 to 15,000, more preferably from 5,000 to 10,000; and
 - iii) from 1% to 10% of a propylene glycol.
2. A process according to Claim 1 further comprising the step of combining and mixing until dissolved the composition of Claim 1 with from 1% to 50% of an aqueous phases, preferably water.
3. A process according to any one of the preceeding claims wherein the ratio of polyethylene glycol to said difficultly soluble pharmaceutical active and said polyvinylpyrrolidone is from 1:0.3 to 1:0.9 and from 1:0.09 to 1:0.3 respectively.
4. A process according to any one of the preceeding claims wherein said difficultly soluble pharmaceutical active is selected from the group consisting of acetaminophen, acetylsalicylic acid, ibuprofen, fenbuprofen, fenoprofen, flubiprofen, indomethacin, naproxen, and mixtures thereof, preferably acetaminophen.
5. A process according to any one of the preceeding claims wherein said polyethylene glycol is selected from a group consisting of PEG-6, PEG-8, PEG-9, PEG-10, PEG-12, PEG-14, PEG-16, PEG-18, PEG-20, and mixtures thereof.

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6. A process according to any one of the preceeding claims wherein said polyethylene glycol is a mixture of PEG-12 and PEG-20, preferably in a ratio of 1:1.
7. A process according to any one of the preceeding claims wherein one or more additional pharmaceutical actives are added to said aqueous phase and wherein said active is selected from the group of pharmaceutical actives consisting of dextromethorphan, HBr, doxylamine succinate, pseudoephedrine HCl, chlorpheniramine maleate, guaifenesin, triprolidine HCl, diphenhydramine HCl, and mixtures thereof.