

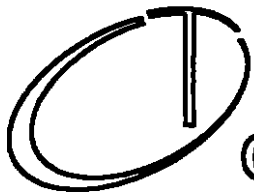
Doctor,
JAIRO RUBIO ESCOBAR
Superintendente de Industria y Comercio
E. S. D.

SUPERINDUSTRIA Y COMERCIO
Radicación : 00090142 00000006 Folios: 02
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Trámite : 002 PATENTES 3 1 REGISTRAR/ 329 COMPLETAR
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Referencia : Expediente N° 00-90142
Asunto : Remisión de información a la solicitud de patente de Invención titulada "MÉTODOS PARA TRATAR SÍNTOMAS DE MIGRAÑA CON IBUPROFENO Y SALES DEL MISMO".
Solicitante: McNEIL-PPC, INC.

Yo, Luis Fernando Rincón Cuellar, abogado con tarjeta profesional N° 113438 del consejo superior de la judicatura, en mi condición de apoderado de la sociedad PROCAPS S.A. conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que por orden expresa de mi representada, con el animo de colaborar con esa Entidad en la decisión que sobre la patentabilidad de la solicitud de la referencia se tomará, me permito solicitarle, muy respetuosamente, dar curso a la siguiente información relativa al arte anterior relevante para que sea tomado en cuenta en el estudio de patentabilidad de la solicitud de patente de Invención de la referencia.

1. PETICIÓN.

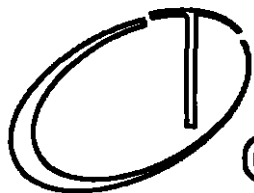


Ruego al Señor Superintendente, NEGAR, en los términos de artículo 48 de la Decisión 486 de 2000 de la CAN, la Solicitud de Patente de Invención denominada "MÉTODOS PARA TRATAR SÍNTOMAS DE MIGRAÑA CON IBUPROFENO Y SALES DEL MISMO", cuyo solicitante es McNEIL-PPC, INC, con base en los siguientes hechos y fundamentos de derecho, relacionados con el incumplimiento de los requisitos fundamentales exigidos para la concesión de Patentes de Invención, según la legislación vigente.

2. FUNDAMENTOS DE HECHOS

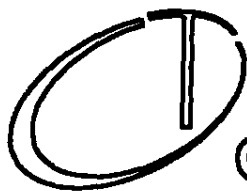
2.1. La solicitud objeto de la presente fue presentada el 24 de noviembre de 2000, reivindicando prioridad bajo las solicitudes US 09/449124 del 24 de noviembre de 1999 y la US 09/709069 del 9 de noviembre de 2000 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 525.

2.2. La solicitud colombiana 00-90142 tiene como objeto presentado en la reivindicación número 1 una cantidad efectiva de ibuprofeno, una sal farmacéuticamente aceptable del mismo, un isómero del mismo o una mezcla de los mismos, como único ingrediente farmacéuticamente efectivo, usados en un método para calmar o tratar la fofobia asociada con migraña en un paciente; en las siguientes reivindicaciones se describe que la cantidad efectiva de ibuprofeno, el isómero del mismo o la mezcla de los mismos de entre 100 a 800 miligramos por dosificación o entre 200 a 600 miligramos, únicamente de 200 miligramos por dosis o de 400 miligramos por dosis. En la reivindicación número 11 se indica que la sal farmacéuticamente aceptable de ibuprofeno se selecciona del grupo que consiste de a) sales de cationes inorgánicos; b) sales orgánicas d ibuprofeno con aminas primarias, secundarias, terciarias y cuaternarias farmacéuticamente aceptables y mezclas de los mismos. En la reivindicación 12 se especifica que las



sales de cationes inorgánicos son de sodio, potasio, litio, magnesio, calcio, cesio, amoníaco, ferroso, zinc, manganeso, aluminio, férrico y mangánico. Las sales orgánicas de ibuprofeno con aminas se seleccionan del grupo de trietilamina, tripropilamina, 2-dimetilaminoctanol, 2-dietilaminoctanol, lisina, arginina, histidina, cafeína, procaína, N-etilpiperidina, hidrabamina, colina, betaína, etilendiamina, glucosamina, TRIS(hidroximetil aminoctano, metilglucamina, teobromina, pruiná, piperazina, piperidina, y resinas de poliamina mezclas de las mismas. En la reivindicación número 13 se indica que la mezcla aceptable es una mezcla de ibuprofeno y su sal de sodio. En la reivindicación 14 se indica que el isómero de ibuprofeno se selecciona del grupo que consiste de R-ibuprofeno, S-ibuprofeno y mezclas de los mismos. En las reivindicaciones 19, 20, 21, y 23 se menciona que la cantidad de la sal farmacéuticamente aceptable de ibuprofeno es de 100 a 1700 miligramos por dosis, y en la 22 y 24 se habla de 200 a 1300 miligramos por dosis.

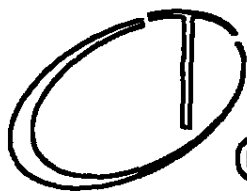
2.3. Lo primero que hay que decir es que esta solicitud de patente esta incurso en los impedimentos que consagra el artículo 21 de la Decisión 486 de la CAN, el cual indica: *"los productos o procedimientos ya patentados, comprendidos en el estado de la técnica de conformidad con el artículo 16 de la presente decisión, no serán objeto de nueva patente, por el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial"*. Esto significa que en Colombia a la fecha no se conceden patente para los segundos usos. El ibuprofeno como tal es una sustancia activa que fue patentada en 1964 y cuya primera indicación fue como antiinflamatorio. Ahora lo que pretende reclamar la presente solicitud no es más que un uso diferente del ibuprofeno para tratar la fobia asociada con la migraña.



2.4. Por otra parte se está también tratando de reivindicar un método de tratamiento para calmar o tratar la fotofobia con una cantidad efectiva de ibuprofeno, una sal farmacéuticamente aceptable del mismo, un isomero del mismo o una mezcla de los mismos, como único ingrediente farmacéuticamente efectivo, usados en un método para calmar o tratar la fotofobia asociada con migraña en un paciente. La decisión 486 de la CAN establece claramente en su artículo número 20: "No serán patentables: ...d) Los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o animales". De aquí se deduce claramente que el objeto de la presente solicitud no puede ser objeto de patente en Colombia.

2.5. El artículo 14 de la Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: "Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial. La presente solicitud carece de aplicación Industrial ya que como se demostró en el apartado interior lo que se está reclamando es un método de tratamiento. Estos no son aplicables industrialmente porque primero no se obtiene un resultado mediante el empleo de materias o fuerzas de la naturaleza; y segundo no es repetible ya que usados los medios previstos no se obtiene siempre el mismo resultado. Por lo tanto el objeto de la presente invención no cumple con el requisito de la aplicación industrial.

2.6. Ese mismo artículo 14 se refiere a que las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afectan la novedad y el nivel inventivo de la presente solicitud:



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- D1 WO 9730699 (1997-08-28)
- D2 US 5696165 (1997-12-09)
- D3 US 5914 129 (1999-06-22)
- D4 US 5538959 (1996-07-23)

2.7. Los documentos D1, D2, D4, revelan el ibuprofeno como un analgésico que se puede usar en la terapia para tratar la migraña y composiciones que lo contienen. Las composiciones reveladas contienen ibuprofeno como único ingrediente activo, el cual puede tener sales de cationes inorgánicos tales como el sodio o magnesio, en varias dosis que van desde 256 hasta 342 mg, estos se puede apreciar claramente en el documento D1, página 29, desde la línea 4 hasta la línea 11 de la página 30, igualmente se pueden apreciar los ejemplos 1 a 27. También se pueden encontrar dosis de 160, 430, 680, 512 y 769 mg como las mostradas en el documento D2 en los ejemplos 12, 19 y 30; también en el documento D4 en las reivindicaciones 1, 2, 4, 5, 9-12 y 16. Por lo tanto el objeto presentado en las reivindicaciones 1-10 y 19-24 no es nuevo porque para la fecha de prioridad más antigua reclamada en la presente solicitud que es el 24 de noviembre de 1999 el objeto reclamado en las mencionadas cláusulas no era nuevo porque ya hacía parte del estado de la técnica en los documentos D1, D2 y D4.

2.8 El documento D4, revela el empleo de sales de magnesio de ibuprofeno como el único ingrediente activo para calmar o tratar la fotofobia y la fonofobia asociada con la migraña tal y como se aprecia en la columna 3 líneas 57 a 61 y en las reivindicaciones 2, 4, 9, 10, 12 y 16. Por lo tanto las reivindicaciones 1-10 y 19-24 no son nuevas respecto del mencionado documento.

2.9. En cuanto al nivel inventivo, este se ve fuertemente afectado por la combinación de los documentos D1, D3 y D4, ya que estas parentes revelan al ibuprofeno y sus sales de magnesio para tratar la fotofobia y la fonofobia. Lo único que diferencia a la presente solicitud es que los compuestos usados sean sales inorgánicas como el sodio o sales orgánicas de ibuprofeno con amina tales como la lisina. El problema a ser resuelto por una persona medianamente versada en el arte es el de encontrar un tratamiento alternativo para la fotofobia asociada con la migraña. El documento D1 revela las sales de amina y en particular las sales de lisina de ibuprofeno actuando como analgésicos, esto se revela claramente en la página 30 del mencionado documento. Sería obvio para una persona medianamente versada en el arte usar una sal de ibuprofeno tal como una sal de sodio o su sal de la lisina para tratar la fotofobia en un paciente con migraña, sabiendo que el ibuprofeno de por sí es efectivo contra estos síntomas y que sus sales de sodio y de amina también son usadas en terapia analgésica.

2.10. El documento D3 revela que ya se ha usado el ibuprofeno para tratar la migraña. La presente solicitud sólo se diferencia por el hecho de que se trata un síntoma específico como es la fotofobia con el mismo compuesto. El documento D3 revela el empleo de ibuprofeno asociado con cafeína en una dosis que va desde 650 hasta 1300 mg, para tratar los síntomas de la migraña como son la fotofobia y la fonofobia, esto se puede constatar en la columna 3, líneas 50 a 67 y en los ejemplos 4 a 7 del mismo documento. Este conocimiento proveniente del estado del arte refiriéndose a que el ibuprofeno es eficiente contra los síntomas de la fotofobia y la fonofobia en asociación con la cafeína, motivaría lógicamente a una persona medianamente versada en el arte para tratar con solamente con ibuprofeno los síntomas de fonofobia y fotofobia asociados con la migraña. Si, además se considera que en el documento D4 ya se revelaba que la migraña es

frecuentemente asociada con síntomas de fonofobia y fotofobia, sería lógico entonces para una persona medianamente versada en la materia usar un compuesto bien conocido como el ibuprofeno para tratar la migraña y emplearlo para aminorar los síntomas asociados tales como la fonofobia y la fotofobia. Por todo lo anterior se ha demostrado que la presente solicitud no cumple con el requisito de nivel inventivo contemplado en el artículo 14 de la Decisión 486 de la CAN.

3. PRUEBAS

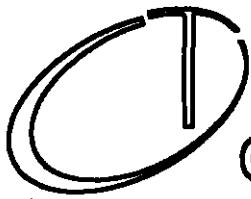
De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- D1 WO 9730699 (1997-08-28)
- D2 US 5696165 (1997-12-09)
- D3 US 5914 129 (199-06-22)
- D4 US 5538959 (1996-07-23)

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 48 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.



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5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

- D1 WO 9730699 (1997-08-28)
- D2 US 5696165 (1997-12-09)
- D3 US 5914 129 (199-06-22)
- D4 US 5538959 (1996-07-23)

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas de abogado situadas en la calle 119ª N° 53-99 de esta ciudad de Bogotá.

Señor Superintendente,


C.C. 79532186.

**DILIGENCIA DE RECONOCIMIENTO
Y PRESENTACION PERSONAL**

Ante el Notario Once del Circulo de Bogotá, compareció

Quien exhibió la C.C. No.

expedida en

y declaró que la firma y huella que aparecen en
el presente memorial son suyas y que el conte-
nido del mismo es cierto.

Memorial dirigido a

Rematado de Bogotá, D.C.

16 SET 2004

Firma del Declarante

HUELLA

Autorizó la anterior Diligencia

NOTARIO ONCE DEL CIRCULO DE BOGOTA

REPUBLICA DE COLOMBIA
DEL CIRCULO DE
BOGOTA, D.C.

ZULIA NAVARRO DE SANTISTA
NOTARIA ONCE



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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/20	A2	(11) International Publication Number: WO 97/30699 (43) International Publication Date: 28 August 1997 (28.08.97)
(21) International Application Number: PCT/EP97/00841 (22) International Filing Date: 19 February 1997 (19.02.97) (30) Priority Data: 9603699.1 21 February 1996 (21.02.96) GB (71) Applicant (for all designated States except US): THE BOOTS COMPANY PLC (GB/GB); 1 Thame Road West, Nottingham NG2 3AA (GB). (72) Inventor; and (73) Inventor/Applicant (for US only): PRICE, Ian, Ashley (GB/GB); The Boots Company plc, 1 Thame Road West, Nottingham NG2 3AA (GB). (74) Agent: SMITH, Elizabeth, Jane; The Boots Company plc, Group Patents Dept., Building D31, 1 Thame Road West, Nottingham NG2 3AA (GB).		(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, 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, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UO), 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>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: DOSAGE FORM OF IBUPROFEN (57) Abstract A solid non-effervescent compressed dosage form comprising an ibuprofen medicament and a carrier material comprising a compressible filler component combined with a disintegrating component wherein the ibuprofen medicament is present to an extent of 35 % or more by weight of the dosage form, characterised in that the carrier material further includes an alkali metal carbonate or bicarbonate in an amount such that the dosage form has a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes. Such rapidly disintegrating compositions are particularly valuable in the treatment of pain and fever.		

DOSAGE FORM OF IBUPROFEN

This invention relates to a non-effervescent compressed solid dosage form for oral administration, to a process to make said dosage form and to its therapeutic utility.

Ibuprofen, namely 2-(4-isobutylphenyl)propionic acid, is a well known medicament with analgesic, anti-inflammatory and anti-pyretic properties. It is usually sold in the form of racemic ibuprofen (equal amounts of the S(+)-ibuprofen and R(-)-ibuprofen enantiomers). It may also be in the form of the purified form of either enantiomer, especially S(+)-ibuprofen which is acknowledged to be the active form of racemic ibuprofen. Ibuprofen is also available in salt form, for example the sodium salt of ibuprofen. Ibuprofen is available under prescription in the UK (eg Brufen (RTM)), primarily for the treatment of painful and anti-inflammatory disorders including rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, postoperative pain, post partum pain and soft tissue injuries, generally at doses up to 3200mg per day. Ibuprofen is also available as a non-prescription drug in the UK (eg Nurofen (RTM)), primarily for the treatment of symptoms of pain and fever including headache, migraine, rheumatic pain, muscular pain, backache, neuralgia, dysmenorrhoea, dental pain and colds and flu, generally at doses up to 1200mg per day. A unit dose of ibuprofen or derivative thereof is generally equivalent to 200mg, 400mg, 600mg or 800mg racemic ibuprofen.

A major issue in connection with the above disorders is to improve the onset of action of ibuprofen, particularly in the treatment of pain. It is believed that rapid disintegration of a formulation releases the drug into the body quickly leading to a more rapid onset of therapeutic action compared with a standard dosage form. Accordingly, it is desired to produce a solid dosage form for oral administration adapted to disintegrate quickly in the gastro-intestinal tract. It is also preferred that the dosage form is manufactured by compression on standard tableting machines with granulation and drying stages prior to tableting optional. However, there are a number of formulation problems associated with providing a rapidly disintegrating

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solid dosage form containing an ibuprofen medicament. One problem is that, in order to achieve a therapeutic dose, solid compositions generally contain a high dose of drug, eg 200-800mg ibuprofen, which thus forms a considerable proportion of the dosage form, is greater than 35% by weight. Thus, there is a problem to include the ibuprofen medicament, together with the excipients useful to formulate the tablet into a dosage form and the excipients useful to ensure rapid disintegration, but also to provide a tablet that is both not too large for patient consumption and can be manufactured according to standard processes. Furthermore, the solid dosage form must be sufficiently hard to withstand the rigours of the manufacturing process, for example as encountered during the stage of film coating in a perforated rotating drum, and packaging etc, but must have appropriate disintegration characteristics to ensure rapid release of the drug from the formulation. Another desirable feature is that a composition comprising a mixture of the desired ingredients is capable of being compressed without sticking to the punches of the tableting machine.

Previously, it has been found that a slight increase in the tableting compaction pressure, in order to improve the hardness properties, led to a significant increase in the disintegration time of the resulting tablet. Thus, when compressing ingredients, it was difficult to use standard tableting machine compaction pressures to arrive at an appropriate tablet disintegration time and maintain an acceptably sized tablet of sufficient hardness.

German Patent Application 3922441A seeks to improve the tablettability of ibuprofen compositions and discloses that this may be achieved by converting ibuprofen wholly or partially into its calcium salt and using these for tableting. It is said that the compositions may optionally contain ibuprofen, S(+)-ibuprofen or their ammonium, sodium or potassium salts. The calcium salt and the optional other ibuprofen actives may be incorporated into the tablet as separately produced compounds or the salts may be formed in-situ during the tablet preparation method through the reaction between ibuprofen (an acidic drug) with a solution or suspension of a reactant comprising one or more of CaO, Ca(OH)₂, CaCO₃, NaOH, KOH, NH₄OH, Na₂CO₃, NaHCO₃, K₂CO₃, KHCO₃, (NH₄)₂CO₃, NH₄HCO₃ (in an amount of 25% to 110% of the equivalent quantity of ibuprofen). The mixture obtained is then granulated, dried if appropriate, and then tabletted after the optional incorporation of

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other excipients. The specification comments that depending on the proportions of other salts used with the calcium salt, the ammonium and alkali salts improve the solubility of the calcium salt-containing compositions and thus control the bioavailability, but they also increase the hygroscopicity and stickiness. These are both undesirable characteristics for optimum tableting. This disclosure does not seek to improve the disintegration time.

We have now found that by incorporating an alkali metal carbonate or bicarbonate in the composition for compression, a solid dosage form of acceptable size containing an ibuprofen medicament can be produced which has a rapid disintegration time and satisfactory hardness. The present invention is based on the discovery that the addition of an alkali metal carbonate or bicarbonate enhances the compressibility of a composition containing a compressible filler in combination with a disintegrant component leading to a solid dosage form with valuable hardness and disintegration characteristics. The disclosure in German Patent Application 3922441A of compositions containing the calcium salt optionally with an ibuprofen sodium or potassium salt, formed in-situ in the presence of a liquid during tablet formation, are outside the scope of the present invention.

Accordingly, the present invention provides a solid non-effervescent compressed dosage form comprising an ibuprofen medicament and a carrier material comprising a compressible filler component combined with a disintegrating component wherein the ibuprofen medicament is present to an extent of 35% or more by weight of the dosage form, characterised in that the carrier material includes an alkali metal carbonate or bicarbonate in an amount such that the dosage form has a crushing strength in the range 8.5-15Kp and a disintegration time of less than 10 minutes, provided that the ibuprofen medicament does not include a calcium salt of ibuprofen in combination with an alkali metal salt of ibuprofen.

The term "ibuprofen medicament" covers ibuprofen, its S(+) and R(-)-enantiomers and mixtures thereof, salts, hydrates and other derivatives.

Crushing strength is a measure of the hardness of a compressed dosage form. It represents the pressure required to break the tablet. The crushing strength of the

solid dosage form may be measured by any machine adapted for this purpose, ie by squeezing the dosage form between two jaws and measuring the force required to break the tablet diametrically. Suitable Crushing Strength Testers are available from Monsanto, Erweka and Schleuniger (manual or automatic operation). The
5 disintegration time represents the time taken for the tablet to disintegrate in an aqueous medium under the test defined in the European Pharmacopoeia 1986 Ref V.5.1.1 (updated 1995).

Alkali metal carbonates and bicarbonates are not normally used as compressible materials. It was not expected that replacing a proportion of a compressible filler
10 component in the composition with a portion of substantially incompressible alkali metal carbonate or bicarbonate would lead to a solid dosage form having both good crushing strength properties and good disintegration properties. It was also found that other soluble materials such as lactose, sucrose, mannitol, sodium citrate and sodium chloride did not yield tablets having the combination of satisfactory
15 compressibility, crushing strength and disintegration properties and acceptable size, as is achieved by the use of the alkali metal carbonates or bicarbonates in a dosage form according to the present invention.

Alkali metal carbonates and bicarbonates are soluble materials which have
20 previously been proposed for use in effervescent tablets, for example to react with the acid component in an effervescent couple (see for example WO 94/10994) or to prevent initiation of the effervescent reaction eg during storage. Effervescent tablets disintegrate by means of the reaction between acid and base particularly in the presence of water leading to the production of carbon dioxide. The system of
25 disintegration of non-effervescent dosage forms according to the present invention, which are arranged to be swallowed and for which an effervescent reaction is not desired, is different to that of effervescent systems. The present dosage form does not contain any soluble acidic component with which the alkali metal carbonate or bicarbonate could react in an effervescent reaction.

30 Sodium bicarbonate is also known for use as an antacid and has previously been combined with ibuprofen in a tablet formulation for its antacid properties, eg Japanese Patent Application 63198620A. However, this document does not provide a

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disclosure relating to the incorporation of ibuprofen and sodium bicarbonate in a tablet with a compressible filler component combined with a disintegrating component or the formation of solid dosage forms having the crushing strength and disintegration properties that are characteristic of the present invention.

- 5 Sodium bicarbonate has also been proposed for use in a water-soluble composition which forms an acceptably-tasting drink product comprising ibuprofen (33-46% w/w), L-arginine (34-51%) and sodium bicarbonate (9-29%) (US 4834986). However, this disclosure does not disclose the other formulation ingredients useful to provide the crushing strength and disintegration characteristics of the present invention.
- 10 US 4873231 relates to decreasing the toxicity of an ibuprofen salt by combining the salt with from one to five molar excess of a bicarbonate or carbonate. Example 13 discloses that sodium ibuprofen is pressed into a tablet with one equivalent of sodium or potassium bicarbonate to provide a dosage of 200 or 400mg ibuprofen. It gives no further details of the formulation and therefore does not provide an enabling
- 15 disclosure concerning the production a solid dosage form having the crushing strength and disintegration properties which characterizes the present invention.

- European Patent Application 418043A discloses that although the compounds selected from alkali metal bicarbonates, alkali metal monohydrogen phosphates and alkali metal tribasic citrates can be used to mask the taste of a water-soluble
- 20 ibuprofen salt in solution, other materials including alkali metal carbonates cannot be used, because, in potential taste-masking amounts, the resultant aqueous solution has an unacceptably high pH for oral administration. The compositions used therein will usually be in the form of a free-flowing powder suitably contained in unit dose sachets. However, it is also disclosed that the composition could be in any other form
- 25 such as a water-soluble tablet suitable for dissolution in water which can include a small amount of an effervescent couple to assist dispersion of the tablet on addition to water. However, there is no disclosure of a non-effervescent solid dosage form characterized by the crushing strength and disintegration properties according to the present invention.

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The present invention allows any ibuprofen medicament to be formulated into a solid dosage form using a carrier material common to all ibuprofen medicaments. Due to the different properties of the different ibuprofen medicaments, such as the melting point, the crystal form, particle size, the yield pressure etc, it is difficult to find
5 a common carrier material which allows all forms of ibuprofen to be compressed into a solid dosage form. Accordingly, where prior art disclosures particularly relate to formulation characteristics required of an ibuprofen dosage form and/or to compression into a solid dosage form, in many cases the disclosure relates particularly either to ibuprofen or to an ibuprofen salt. For example, European Patent
10 Application 298666A, WO 90/08542, WO 89/02266 and US Patent 4809875, all relate to directly compressible formulations containing ibuprofen as the active ingredient, but do not extend their disclosures to salts. Thus, it is a particular advantage that the dosage form according to the invention may include both ibuprofen and salts thereof, particularly salts such as the sodium salt, where compression into a dosage form is
15 particularly difficult.

The alkali metal carbonate or bicarbonate enhances the compressibility of the compressible filler in combination with the ibuprofen medicament. Thus, the use of an alkali metal carbonate or bicarbonate allows a reduction in the amount of compressible filler component that would normally be required in a composition to
20 achieve satisfactory compressibility. This is of advantage as ibuprofen medicaments are usually administered in large doses. Thus minimising the amount of formulation excipients is valuable as it allows an acceptably sized dosage form to be produced. In accordance with the invention, the total amount of the compressible filler and alkali metal carbonate or bicarbonate that can be used is less than the amount of
25 compressible filler component combined with a disintegrating component that would be required in the absence of the alkali metal carbonate or bicarbonate to achieve a dosage form with satisfactory hardness and disintegration characteristics.

The solid dosage forms according to the invention are adapted for direct
30 administration to a patient to obtain the desired therapeutic effect. They are not intended to be dissolved or dispersed in water prior to administration. Furthermore, the compressed dosage forms according to the present invention need no further

processing after compression of a composition comprising a mixture of the ingredients to produce a solid dosage form.

The ibuprofen molecule exists in two enantiomeric forms and the term ibuprofen medicament as used herein is intended to embrace the individual enantiomers, especially S(+)-ibuprofen, and mixtures thereof in any proportion including a 1:1 mixture which is herein referred to as racemic ibuprofen. The ibuprofen medicament may be also present in the form of any salt or other derivative of ibuprofen or its enantiomers. If necessary, the ibuprofen medicament may comprise one or more ibuprofen active ingredients such as racemic ibuprofen and S(+)-ibuprofen in combination. However, we prefer that the ibuprofen medicament comprises a single ibuprofen active ingredient. The ibuprofen medicament may also be present in different degrees of hydration. The present invention applies to both anhydrous and hydrated forms, for example the monohydrate or the dihydrate. The most stable anhydrous or hydrated form will generally be used. Preferably, the ibuprofen medicament is in the form of a salt of racemic or S(+)-ibuprofen. Representative examples include alkali metal salts, for example the sodium or potassium salts of ibuprofen; alkaline earth metal salts, eg the calcium or magnesium salts of ibuprofen; metal salts, eg the aluminium salt of ibuprofen; amino acid salts for example the lysine or arginine salts of ibuprofen; or amine salts, eg the meglumine salt of ibuprofen. Preferably the ibuprofen medicament is a single salt selected from alkali metal salts, amino acid salts and amine salts. Greater advantages are obtained in accordance with the present invention by the use of soluble salts of ibuprofen, for example the alkali metal salts such as sodium and potassium, as these materials are poorly compressible. For example, the sodium salt is a flaky, soft and sticky material. It does not lend itself to formulation into a dosage form as it is particularly difficult to compress. It is also difficult to pre-granulate the sodium salt prior to compression with other excipients into tablets. It thus usually requires an initial treatment stage such as milling, in order to form satisfactory tablets. However, no such pre-treatment of the sodium salt is required in accordance with the present invention. It is thus a further advantage to use sodium ibuprofen taken from a bulk production process to produce the raw material. These soluble ibuprofen salts also have the advantage that, as they are more soluble in an aqueous medium, on release from the formulation they have improved absorption, thus leading to an improved

onset of action compared to the substantially insoluble forms of ibuprofen. The sodium salt of ibuprofen is particularly preferred, especially the sodium salt of racemic ibuprofen. It has been found that the dihydrate of the sodium salt of racemic ibuprofen is a particularly stable hydrated form, accordingly we prefer to use the sodium salt dihydrate in a compressed dosage form according to the present invention.

The particle size of the ibuprofen medicament should be such as to facilitate the manufacturing process, for example to permit flow during the manufacturing process and thus aid the compression process. Accordingly, preferably it has a median particle size in the range 25-600µm, preferably 50-300µm, most preferably 150-250µm.

It is generally desired to have as high a proportion of ibuprofen medicament in the dosage form as possible to reduce the size of the solid dosage form. Representative dosage forms generally comprise ibuprofen medicament to an extent to give 35-90% ibuprofen by weight of the formulation, preferably 35-75% by weight, more preferably 40-60% by weight and most preferably 45-55% by weight. Unit dosages may comprise ibuprofen medicament to an extent of 50mg, 100mg, 150mg, 200mg, 250mg, 300mg, 350mg, 400mg, 500mg, 600mg and 800mg. Where salts or other derivatives are employed, usually the precise unit doses are chosen to give the equivalent ibuprofen doses set out above, for example 256mg of the sodium salt dihydrate or 342mg of the dl lysine salt provides an equivalent dose to 200mg ibuprofen.

The alkali metal carbonate or bicarbonate aids the formation of a solid dosage form having the crushing strength and disintegration characteristics outlined above. The alkali metal carbonate or bicarbonate is suitably included in the dosage form in solid form. It is not necessary to dissolve it in a solvent, eg water, for a granulation step before compression into a solid dosage form. The properties of crushing strength and disintegration of the dosage form are achieved by the presence of the solid alkali metal carbonate or bicarbonate in homogenous admixture with the ibuprofen medicament and compressible filler with disintegrating component. It is

particularly desired that the particles of the ibuprofen medicament and alkali metal carbonate or bicarbonate are intimately mixed.

The alkali metal carbonate or bicarbonate used in accordance with the present invention may suitably comprise sodium carbonate or bicarbonate or potassium carbonate or bicarbonate either alone or mixed together. Preferably, the alkali metal comprises sodium, thus sodium bicarbonate and sodium carbonate are preferred ingredients. The alkali metal carbonates may be supplied anhydrous or in varying degrees of hydration for example the monohydrate and decahydrate. Both these forms may be used. However, we prefer to use the anhydrous form. The preferred alkali carbonate for use in accordance with the present invention is thus anhydrous sodium carbonate.

The alkali metal carbonate or bicarbonate is present to aid the formation of the ibuprofen medicament dosage form and to provide a solid dosage form having a crushing strength in the range 8.5-15Kp and a disintegration time of less than 10 minutes. Suitably, the alkali metal carbonate or bicarbonate is present in an amount of 3-20% by weight of the dosage form, preferably 4-18% by weight, more preferably 5-15% by weight and most preferably 6-10% by weight of the dosage form. The alkali metal carbonate or bicarbonate preferably has a particle size in the range of 25-600µm, more preferably 50-100µm. In preferred dosage forms the weight of sodium carbonate or bicarbonate to ibuprofen medicament is in the range 1:2 to 1:10 parts by weight. In a particularly preferred aspect of the invention the dosage form is in the form of a directly compressed tablet comprising 40-85% w/w sodium salt of ibuprofen and 5-15% w/w sodium carbonate or bicarbonate.

The carrier material forms suitably up to 85% by weight of the dosage form. Preferred dosage forms include 25-85% by weight carrier material, more preferably 40-80% by weight and most preferably 45-55% by weight carrier material. In a more preferred dosage form, the ratio of ibuprofen medicament to the carrier material is in the range 2:1 to 1:2 parts by weight and the carrier material comprises 5-20% w/w sodium carbonate or bicarbonate.

A13
105

The carrier material comprises a compressible filler component which is used in a sufficient amount together with the alkali metal carbonate or bicarbonate to ensure that the composition containing the ibuprofen medicament is capable of being formed, preferably by direct compression, into a solid dosage form having a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes. The ingredients are usually compressed from a dry powder mixture. The mixture may contain a pre-granulated product, eg formed by wet or dry granulation and optionally containing the ibuprofen medicament, and the dry granule produced may be combined with other dry powder ingredients, as necessary, and compressed into a solid dosage form. Usually, in any wet pre-granulation stage, the ibuprofen medicament would be present in the granule. The alkali metal carbonate or bicarbonate would be added to the formed granule with optional other excipients, such as a lubricant, prior to compression. However, preferably no liquid (ie water) is added to the formulation in any optional pre-granulation stage or prior to compression. It will also be appreciated that a directly compressible formulation has advantages as it represents a more efficient tableting process, namely just mixing the ingredients and then compressing them, thus alleviating the need for the intermediate granulation and drying steps necessary in other tableting procedures.

The compressible filler component is suitably present to an extent of 10-50% by weight of the dosage form, preferably 20-50% by weight of the dosage form, more preferably 27-45% by weight, most preferably 30-40% by weight of the dosage form. The ratio of alkali metal carbonate or bicarbonate to compressible filler component is preferably in the range 2:1 to 1:10 parts by weight.

Examples of the compressible filler component include one or more of cellulose derivatives, starch and derivatives thereof (eg pre-gelatinised starch), soluble sugars (eg lactose, sucrose, dextrin), sodium chloride, calcium phosphate, calcium sulphate, mannitol, sorbitol, cyclodextrin and maltodextrin. Preferably the compressible filler component comprises a cellulose derivative. Examples of suitable cellulose derivatives include methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose phthalate and micro-crystalline cellulose. The preferred cellulose derivative used in accordance with the present invention is micro-crystalline cellulose. Further

preferably, the cellulose derivative has a particle size above 100µm, preferably in the range 100-150µm.

In preferred dosage forms the cellulose derivative forms 50-100% by weight of the compressible filler component, more preferably 70-100% and most preferably 90-100% by weight of the compressible filler component. The remainder of the compressible filler component may be formed by other fillers known in the art including those listed above. Preferred compressible filler components comprise one or more of microcrystalline cellulose, lactose and mannitol. In a preferred aspect of the present invention, where the compressible filler component comprises 50-100% by weight of a cellulose derivative, the ratio of alkali metal carbonate or bicarbonate to cellulose derivative is suitably in the range of 2:1 to 1:10, more preferably 1:1 to 1:9 and especially 1:3 to 1:8 parts by weight. In a further preferred aspect the combined weight ratio of the cellulose derivative and alkali metal carbonate or bicarbonate to the ibuprofen medicament is 1:10 to 2:1 parts by weight, more preferably 1:4 to 2:1 parts by weight, most preferably 1:1 to 1:2 parts by weight.

The compressible filler component is combined with a disintegrating component. Examples of disintegrating components include one or more of wheat starch, maize starch, potato starch, sodium starch glycollate, low-substituted hydroxypropylcellulose, alginic acid, cross-linked polyvinylpyrrolidone, magnesium aluminium silicate and croscarmellose sodium. Preferred disintegrants comprise one or more of croscarmellose sodium and sodium starch glycollate. Such disintegrating agents, if used, may form up to 15% by weight of the dosage form, for example 1-10% by weight, preferably 5-15% by weight of the dosage form. Some compressible filler components have disintegrant properties, for example microcrystalline cellulose and/or hydroxypropylmethyl cellulose and therefore a discrete disintegrant material is not necessary as the compressible filler component is thus combined with a disintegrating component. However, we prefer to use a compressible filler component (which may have disintegrant properties) and a discrete disintegrant component which are separate components mixed into the composition.

AS
107

In a particularly preferred dosage form the carrier material comprises 8-80% by weight compressible filler component (more preferably 50-75% by weight), 8-40% by weight alkali metal carbonate or bicarbonate (more preferably 10-20% by weight), 10-20% by weight disintegrant (more preferably 12-18% by weight). Especially preferred is a carrier material comprising 50-75% microcrystalline cellulose, 12-18% croscarmellose sodium and 8-20% sodium carbonate or bicarbonate. Desirably the ratio of the compressible filler to the alkali metal carbonate or bicarbonate to the disintegrant component is 1-9:1:0.5-2 parts by weight, preferably 2.5-8:1:0.8-1.4 parts by weight.

The compressed dosage form may also comprise one or more inert diluents (which are not characterised by the property of compressibility) as desired by the person skilled in the art. The inert diluent may be present up to an extent of 20% by weight of the formulation, suitably 0-10% by weight.

The solid dosage form may also include a flow aid such as talc or colloidal silicon dioxide, which may preferably be used to an extent of up to 4% by weight of the formulation, for example 0.5-2.0% by weight of the formulation. Lubricants such as stearic acid, sodium lauryl sulphate, polyethylene glycol, hydrogenated vegetable oil, calcium stearate, sodium stearyl fumarate or magnesium stearate may also be included in the dosage form. These may be used to an extent of up to 4% by weight of the dosage form, for example 0.5-2% by weight of the dosage form. Anti-adherents such as talc may further be included in an amount of up to 4% by weight of the dosage form, for example 0.5-2% by weight of the dosage form.

A solid dosage of the invention may be coated, eg with a sugar or film coating which has minimal effect on the disintegration time. A preferred solid dosage form of the present invention, ie a tablet, is film coated, such as by spraying tablets with a solution comprising hydroxypropylmethylcellulose and a plasticiser such as propylene glycol, polyethylene glycol and/or talc in one or more coatings.

A preferred dosage form comprises:-

(a) 40-60% by weight sodium salt of ibuprofen (more preferably 45-55% by weight);

- (b) 20-50% by weight of a compressible filler, eg micro-crystalline cellulose (more preferably 30-40% by weight);
- (c) 4-16% by weight sodium carbonate or sodium bicarbonate (more preferably 5-10% by weight);
- 5 (d) Up to 10% by weight of a disintegrant, eg croscarmellose sodium or sodium starch glycolate (more preferably 5-10% by weight);
- (e) Up to 4% by weight of a lubricant, eg stearic acid (more preferably 0.5-2.0% by weight); and
- 10 (f) Up to 2% by weight of a flow aid, eg colloidal silicon dioxide (more preferably 0.5-1% by weight).

In a further preferred dosage form the ratio of ibuprofen medicament to carrier material is in the range 1:2 to 2:1 parts by weight, preferably 2:3 to 3:2 parts by weight, and the ratio of the cellulose derivative compressible filler component to alkali metal carbonate or bicarbonate is 9:1 to 1:1, preferably 5:1 to 3:1 parts by weight.

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A solid dosage form produced in accordance with the present invention may be compressed, preferably directly compressed, to have a crushing strength in the range of 8.5-15Kp, more preferably 8-12Kp. This can be achieved, for example, using standard single punch or rotary tableting machines having a compression force in the range 100-140MPa.

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It will be appreciated by the person skilled in the art that due to the different excipients used in the formulation and varying amounts thereof that for any compression pressure, different formulations will have different crushing strengths and disintegration times. Preferred dosage forms exhibit a crushing strength of 8.5-15Kp and a disintegration time of less than 10 minutes at a compression force above 80MPa. More preferred formulations exhibit a crushing strength of 8.5-15Kp

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447
109

and a disintegration time of less than 10 minutes when compressed at a compression force in the range 100-140MPa such as by a standard tableting machine, eg a rotary tableting machine. Such compression pressures include, 110MPa, 120MPa and 130MPa. Especially preferred dosage forms exhibit a crushing strength of 6.5-15Kp and a disintegration time of less than 10 minutes when compressed at all pressures in the range 100-140MPa.

As disclosed hereinabove, it is necessary to have a dosage form of appropriate crushing strength. This is necessary so that the dosage form retains its integrity and does not crumble and/or break-up during the manufacturing process, the packaging process and transit of the packaged product. However, it is also necessary to ensure that the dosage form is not too hard that the drug cannot be released from the formulation quickly. Preferred dosage forms have a crushing strength in the range 7-12Kp, more preferably 8-12Kp. Preferably the dosage form has a crushing strength in the range 8-12Kp at a compression force in the range 100-140MPa.

The disintegration time of the tablet formed in accordance with the present invention is less than 10 minutes as measured by the method described in the European Pharmacopoeia 1986, Ref V.5.1.1 (updated 1995) (A. Disintegration Test for Tablets and Capsules). Preferred disintegration times are less than 6 minutes (eg 1-6 minutes), more preferably less than 5 minutes (eg 1-5 minutes) and most preferably 3 minutes or less (eg 1-3 minutes).

The dosage forms according to the present invention may or may not be water-soluble. We have found that water-solubility of the dosage form is not crucial. Some of the materials found to be most useful in accordance with the present invention are insoluble. Accordingly, if one or more materials is insoluble, the dosage form is water-insoluble and this represents a preferred dosage form.

The dosage forms formed in accordance with the present invention are prepared by compression. The carrier material is combined with the ibuprofen medicament and compressed (preferably directly compressed) into a solid dosage form. The final stage of producing the solid dosage form (eg compression) may be preceded by a pre-granulation stage such as initial wet-granulation or initial dry granulation. In the

wet granulation stage the ibuprofen medicament is generally pre-granulated with a binder, such as polyvinylpyrrolidone in a solvent, such as water or a hydrocarbon solvent and then the granules are dried. The granulated material is then mixed with other excipients as necessary and formed into a solid dosage form according to the invention. In any initial pre-granulation stage however, there is no requirement to add a solvent (eg water) at any stage during the manufacturing process and therefore, in a preferred embodiment of the invention, no drying stage is necessary. In a dry pre-granulation stage, certain of the components may be compressed together such as by roller compaction or slugging, and the granules are then mixed with the remaining excipients and compressed into a solid dosage form. The dosage forms may also be formed by sieving powdered ingredients into a container and then blending all of the ingredients to prepare a homogeneous mixture. The mixture may then be directly compressed to form tablets. This process forms a further aspect of the invention.

Thus, there is provided a process to prepare a non-effervescent solid dosage form comprising an ibuprofen medicament present to an extent of 35% or more by weight of the dosage form and a carrier material comprising a compressible filler component combined with a disintegrating component, characterised by combining the carrier material incorporating an alkali metal carbonate or bicarbonate with the ibuprofen medicament to form a homogeneous solid mixture under substantially dry conditions, optionally with other tableting excipients, and compressing the mixture into one or more solid dosage forms having a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes.

In a more preferred process, the dosage form is prepared by direct compression of a powder mixture of the ingredients and does not include any pre-granulation stage. In such a process the ibuprofen medicament may be combined with the compressible filler component, a discrete disintegrant component and the alkali metal carbonate or bicarbonate. The other optional carrier excipients, such as a flow aid and a lubricant, may also be added and mixed so that all the powder particles are in intimate admixture, and finally the mixture is directly compressed into a solid dosage form according to the present invention.

449
111

In a preferred process, there is provided a dosage form comprising the sodium salt of ibuprofen together with a carrier material comprising microcrystalline cellulose and sodium carbonate or bicarbonate.

5 In therapeutic use the dosage forms of the present invention are administered orally, thus the therapeutic dosage forms are presented in solid dosage form, preferably as a tablet. The dosage forms may be coated with a sugar or film coating, which dissolves substantially immediately the dosage form comes into contact with an aqueous medium. The composition may also be compressed onto a solid core of another material to form a solid formulation with an quick release outer coating.
10 Alternatively, the compressed composition may be present in one or more layers of a multi-layer solid dosage form. In such formulations the remaining layers or core may comprise standard excipients to provide conventional, fast or slow release and are well within the knowledge of a person skilled in the art (eg. see Remington's Pharmaceutical Sciences, 17th Edition, Ed Gennaro et al).

15 Thus, in a further preferred aspect the invention also provides a solid formulation having a layer comprising a composition comprising an ibuprofen medicament together with a carrier material, the ibuprofen medicament being present to an extent of 35% or more by weight of the composition and the carrier material comprising a compressible filler component combined with a disintegrating component
20 characterised in that the carrier material comprises an alkali metal carbonate or bicarbonate in an amount such that the composition is capable of compression to provide a layer having a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes.

25 The dosage forms of the present invention may, if desired, include other compatible pharmacologically active ingredients (for example centrally acting analgesics, eg codeine) and/or enhancing agents. Thus, for example, the dosage form may include any ingredient commonly used in a cough, cold or 'flu remedy, for example caffeine or another xanthine derivative, and/or another analgesic, and/or a skeletal muscle relaxant, and/or an antihistamine, and/or a decongestant, and/or a
30 cough suppressant and/or an expectorant.

A20
112

Suitable antihistamines include acrivastine, astemizole, azatadine, azelastine, bromodiphenhydramine, brompheniramine, carbinoxamine, cetirizine, chlorpheniramine, cyproheptadine, dextbromopheniramine, dexchlorpheniramine, diphenhydramine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, mequitazine, oxatomide, phenindamine, phenyltoloxamine, pyrilamine, setastine, taziflyline, temelastine, terfenadine, tripeleminamine or triprolidine. Preferably non-sedating antihistamines are employed. Suitable cough suppressants include caramiphen, codeine or dextromethorphan. Suitable decongestants include pseudoephedrine, phenylpropanolamine and phenylephrine. Suitable expectorants include guaifenesin, potassium citrate, potassium guaiacolsulphonate, potassium sulphate and terpin hydrate.

Ibuprofen and its derivatives are primarily anti-inflammatory, analgesic and anti-pyretic agents but have also been proposed for other therapeutic uses, including the treatment of periodontal bone loss, pruritus and Alzheimer's disease. The dosage forms of the present invention are therefore indicated for use in the treatment of all therapeutic uses for which ibuprofen is effective, including rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, seronegative arthropathies, periaricular disorders and soft tissue injuries. They may also be used in the treatment of postoperative pain, postpartum pain, dental pain, dysmenorrhoea, headache, migraine, rheumatic pain, muscular pain, backache, neuralgia and/or musculoskeletal pain or the pain or discomfort associated with the following: respiratory infections, colds or influenza, gout or morning stiffness.

In a further aspect the present invention provides a method of obtaining an onset-hastened analgesic and/or anti-pyretic response comprising the administration of a non-effervescent compressed solid dosage form comprising 35% or more by weight of an ibuprofen medicament together with a carrier material comprising a compressible filler component combined with a disintegrating component and an alkali metal carbonate or bicarbonate, the dosage form having a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes, provided that the ibuprofen medicament does not include a calcium salt of ibuprofen in combination with an alkali metal salt of ibuprofen.

In yet a further preferred aspect, the invention provides the use of an alkali metal carbonate or bicarbonate in a carrier material including a compressible filler component combined with a disintegrating component, said carrier material being arranged for admixture with an ibuprofen medicament under substantially dry conditions and then for compression into a solid non-effervescent dosage form wherein the ibuprofen medicament comprises 35% or more by weight of the dosage form, the dosage form having a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes.

The preparation of compressed tablets from formulations of the present invention is illustrated by the following Examples. In the Examples the racemic ibuprofen and racemic/S(+)-ibuprofen sodium salt is available from Knoll Pharma, Nottingham, GB; the grades of microcrystalline cellulose are available from the FMC Corporation, Brussels, BE under the tradenames Avicel PH101 and PH102; Croscarmellose sodium is available from the FMC Corporation, Brussels, BE under the tradename Ac-Di-Sol; colloidal silicon dioxide is available from Degussa, Frankfurt, DE under the tradename Aerosil 200; hydrogenated vegetable oil is available from Karlshamn, SE under the tradename Sterotex; hydroxypropylmethyl cellulose 2910 (50CPs) is available from Colorcon, Kent, GB; hydroxypropylmethyl cellulose 2910 (6CPs) is available from Shin-etsu, Japan and the Opaspray is available from Colorcon, Kent, GB; sodium starch glycolate is available from Edward Mendell, Reigate, GB, under the tradename Explotab; sodium stearyl fumarate is available from Forum Chemicals, Surrey, GB, under the tradename Pruv; mannitol is available from Roquette Freres, Lestrem, France, under the tradename Pearlitol, cross-linked polyvinylpyrrolidone is available from BASF, Ludwigshaven, Germany under the tradename Kollidon CL.

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A. Method of Preparation of Tablets in the Examples

The tablets were prepared by screening all the ingredients and blending until an homogenous mixture was obtained using a conventional blending machine. The formulation was then fed into and compressed on a single punch tableting machine (Manesty F) using a compression force in the range 100 to 140 MPa. In some Examples, (Examples 1-9, 22) the compositions were compressed at particular compression forces, eg 100, 120, 140 MPa. In other Examples (Examples 10-21, 23-27) the compositions were compressed at an appropriate compression force within the range 100-140 MPa having regard to the ingredients used and the crushing strength and dissolution time required of the finished tablet.

B. Measurement of the Properties of the Tablets Prepared in the Examples

1. Crushing Strength (Ko)

The crushing strength is a measure of the hardness of a tablet. It was measured by recording the diametrical crushing strength when the tablet was broken between the motorised jaws of a Schleuniger crushing strength tester. The range of crushing strengths of five tablets prepared with each Example formulation is given and the mean crushing strengths for Examples 10-27 are also given.

2. Disintegration Time (Minutes)

The disintegration time was measured using the disintegration method described in the European Pharmacopoeia 1986, Ref V.5.1.1 (updated 1995) using tap water (pH approximately 7) as the liquid. The method provides the time by which six tablets prepared with each Example formulation had all disintegrated.

C. Example Tablets and Properties Thereof

% are given in weight

Ibuprofen is racemic ibuprofen except where indicated

Examples 1-3

Ingredients	Example 1	Example 2	Example 3
Content of drug per tablet (mg)	256mg	256mg	256mg
Ibuprofen sodium salt dihydrate	51.2%	53.1%	51.2%
Microcrystalline cellulose (PH 101)	-	13.3%	12.8%
Microcrystalline cellulose (PH 102)	35.4%	-	-
Lactose NF (Spray Dried)	-	14.9%	8.0%
Anhydrous sodium carbonate	5.0%	10.4%	20.0%
Croscarmellose sodium	7.2%	7.5%	7.2%
Colloidal silicon dioxide	0.2%	-	-
Stearic acid	0.5%	0.8%	0.8%
Magnesium stearate	0.5%	-	-

Properties of Tablet	Example 1		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	10.4-10.7	10.7-11.5	10.3-11.2
Disintegration Time (min)	5.8	5.4	5.0

Properties of Tablet	Example 2		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	8.8-9.2	7.2-10.8	9.3-11.0
Disintegration Time (min)	3.5	3.5	4.5

Properties of Tablet	Example 3		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	8.5-9.5	9.3-10.4	11.1-11.7
Disintegration Time (min)	4.3	4.7	4.9

124
116**Examples 4-6**

Ingredients	Example 4	Example 5	Example 6
Content of drug per tablet (mg)	256mg	256mg	256mg
Ibuprofen sodium salt dihydrate	53.1%	53.1%	51.2%
Microcrystalline cellulose (PH 101)	13.3%	13.3%	12.8%
Lactose NF (Spray Dried)	14.9%	14.9%	14.4%
Anhydrous sodium carbonate	10.4%	10.4%	10.0%
Croscarmellose sodium	7.5%	7.5%	7.2%
Stearic acid	-	-	0.8%
Magnesium stearate	0.8%	-	-
Hydrogenated Vegetable Oil	-	0.8%	-
Talc	-	-	3.6%

Properties of Tablet	Example 4		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	6.6-7.2	8.3-10.2	8.8-10.1
Disintegration Time (min)	4.7	5.4	5.3

Properties of Tablet	Example 5		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	6.6-6.9	8.5-9.1	9.0-10.7
Disintegration Time (min)	2.9	3.2	3.7

Properties of Tablet	Example 6		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	8.1-8.6	9.7-10.5	10.7-11.6
Disintegration Time (min)	3.5	3.9	4.5

128
117**Examples 7-9**

Ingredients	Example 7	Example 8	Example 9
Content of drug per tablet (mg)	256mg	256mg	256mg
Ibuprofen sodium salt dihydrate	51.2%	51.2%	51.2%
Microcrystalline cellulose (PH 101)	27.2%	-	-
Microcrystalline cellulose (PH 102)	-	35.4%	29.6%
Anhydrous sodium carbonate	10.0%	5.0%	10.0%
Croscarmellose sodium	7.2%	7.2%	7.2%
Colloidal silicon dioxide	-	0.2%	1.0%
Stearic acid	1.0%	1.0%	0.5%
Magnesium stearate	-	-	0.5%
Talc	3.4%	-	-

Properties of Tablet	Example 7		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	7.0-7.4	8.1-9.1	7.9-10.4
Disintegration Time (min)	3	3.8	4.5

Properties of Tablet	Example 8		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	8.4-9.1	10.1-10.6	12.2-12.7
Disintegration Time (min)	3.1	4.1	4.8

Properties of Tablet	Example 9		
Compression force (MPa)	100	120	140
Crushing Strength Range (Kp)	5.8-6.2	7.3-7.9	9.2-9.8
Disintegration Time (min)	2.2	3.3	4.7

Examples 10 and 11

Ingredients	Example 10	Example 11
Content of drug per tablet (mg)	256mg	256mg
Ibuprofen sodium salt dihydrate	49.7%	51.2%
Microcrystalline cellulose (PH 101)	-	12.8%
Microcrystalline cellulose (PH 102)	34.3%	-
Lactose	-	8.0%
Anhydrous sodium carbonate	7.8%	-
Sodium bicarbonate BP	-	20.0%
Croscarmellose sodium	7.0%	7.2%
Colloidal silicon dioxide	0.2%	-
Stearic acid	1.0%	0.8%

Properties of Tablet	Example 10	Example 11
Compression force (MPa)	100-140	100-140
Crushing Strength Range (Kp)	7.1-8.0	8.2-9.2
Mean Crushing Strength (Kp)	7.5	8.8
Disintegration Time (min)	4.3	6.0

The tablet core of Example 10 was coated with the following coatings (% are given of core weight):-

5 First coat: hydroxypropylmethyl cellulose 2910 (6Cps) (1.016%), talc (0.204%), Opaspray White M-I-7111B (0.336%).

Outer coat: hydroxypropylmethylcellulose 2910 (5-0Cps) (0.437%), Polyethylene Glycol 8000 (0.049%), calcium stearate (0.002%).

The disintegration time of the coated tablet of Example 10 was 5.5 minutes.

Examples 12-14

Ingredients	Example 12	Example 13	Example 14
Content of drug per tablet (mg)	250mg	250mg	250mg
Ibuprofen sodium salt dihydrate	51.7%	49.7%	48.7%
Microcrystalline cellulose (PH 102)	35.7%	34.3%	34.3%
Anhydrous sodium carbonate	4.0%	-	7.8%
Sodium bicarbonate - BP	-	7.8%	-
Croscarmellose sodium	7.3%	7.0%	-
Sodium starch glycolate	-	-	7.0%
Colloidal silicon dioxide	0.3%	0.2%	0.2%
Stearic acid	1.0%	1.0%	1.0%

Properties of Tablet	Example 12	Example 13	Example 14
Compression force (MPa)	100-140	100-140	100-140
Crushing Strength range (Kp)	7.7-9.1	8.7-9.6	5.7-7.1
Mean Crushing Strength (Kp)	8.7	9.1	6.0
Disintegration Time (min)	3.5	4.5	5.8

The tablet cores of Examples 12-14 had the same coatings applied as described in Example 10. The disintegration times were 5.1 min, 5.5 min and 7.5 mins respectively for Examples 12, 13 and 14.

128
120Examples 15-17

Ingredients	Example 15	Example 16	Example 17
Content of drug per tablet (mg)	256mg	256mg	256mg
Ibuprofen sodium salt dihydrate	51.7%	49.7%	51.2%
Microcrystalline cellulose (PH 102)	35.7%	34.3%	35.4%
Anhydrous sodium bicarbonate	4.0%	-	5.0%
Sodium bicarbonate	-	7.8%	-
Croscarmellose sodium	-	-	7.2%
Sodium starch glycolate	7.3%	7.0%	-
Colloidal silicon dioxide	0.3%	0.2%	0.2%
Stearic acid	1.0%	1.0%	-
Sodium stearyl fumarate	-	-	1.0%

Properties of Tablet	Example 15	Example 16	Example 17
Compression force (MPa)	100-140	100-140	100-140
Crushing Strength Range (Kp)	6.2-8.1	6.4-7.2	10.0-11.6
Mean Crushing Strength (Kp)	6.9	6.7	10.7
Disintegration Time (min)	5.5	4.9	4.8

129
121Examples 18-20

Ingredients	Example 18	Example 19	Example 20
Content of drug per tablet (mg)	258mg	258mg	258mg
Ibuprofen sodium salt dihydrate	50.7%	51.2%	51.2%
Microcrystalline cellulose (PH 101)	-	12.8%	12.8%
Microcrystalline cellulose (PH 102)	35.0%	-	-
Lactose NF (Spray Dried)	-	14.4%	14.4%
Anhydrous sodium carbonate	5.9%	10.0%	10.0%
Croscarmellose sodium	7.1%	7.2%	7.2%
Colloidal silicon dioxide	0.3%	-	-
Stearic acid	1.0%	-	-
Hydrogenated Vegetable Oil	-	1.8%	1.0%
Talc	-	2.8%	3.4%

Properties of Tablet	Example 18	Example 19	Example 20
Compression force (MPa)	100-140	100-140	100-140
Crushing Strength Range (Kp)	8.5-9.4	10.0-10.8	9.1-10.3
Mean Crushing Strength (Kp)	8.9	10.4	9.7
Disintegration Time (min)	4.8	3.9	5.7

130
122**Examples 21-23**

Ingredients	Example 21	Example 22	Example 23
Content of drug per tablet (mg)	256mg	256mg	200mg
Ibuprofen sodium salt dihydrate	51.2%	49.7%	-
Ibuprofen	-	-	49.7%
Microcrystalline cellulose (PH 101)	12.8%	-	-
Microcrystalline cellulose (PH 102)	-	34.3%	34.3%
Mannitol 300	14.4%	-	-
Anhydrous sodium carbonate	10.0%	7.7%	7.8%
Croscarmellose sodium	7.2%	7.0%	7.0%
Colloidal silicon dioxide	-	0.3%	0.2%
Stearic acid	1.0%	0.5%	1.0%
Magnesium stearate	-	0.5%	-
Talc	3.4%	-	-

* 50µm crystal size

Properties of Tablet	Example 21
Compression force (MPa)	100-140
Crushing Strength Range (Kp)	8.9-9.7
Mean Crushing Strength (Kp)	9.4
Disintegration Time (min)	4.0

Properties of Tablet	Example 22		
Compression force (MPa)	100	120	140
Mean Crushing Strength (Kp)	10.2	10.5	10.5
Disintegration Time (min)	4.8	5.5	6.0

Properties of Tablet	Example 23
Compression force (MPa)	100-140
Crushing Strength Range (Kp)	6.6-7.0
Mean Crushing Strength (Kp)	6.8
Disintegration Time (min)	0.6

Examples may also be prepared in a similar way to Examples 1-22 above containing the sodium salt of racemic ibuprofen in an amount of 64mg, 128mg, 192mg, 384mg, 512mg using the same proportions of ingredients as given in Examples 1-22.

Examples 24-26

Ingredients	Example 24	Example 25	Example 26
Content of drug per tablet (mg)	342.0g	342.0g	342.0g
Ibuprofen (dl lysine salt)	68.4%	49.7%	49.7%
Microcrystalline cellulose (PH 102)	20.35%	-	-
Hydroxypropylmethylcellulose	-	34.3%	-
Tricalcium phosphate	-	-	34.3%
Anhydrous sodium carbonate	5.0%	7.8%	7.8%
Croscarmellose sodium	5.0%	-	-
Cross-linked polyvinyl pyrrolidone	-	7.0%	7.0%
Colloidal silicon dioxide	0.25%	0.2%	0.2%
Stearic acid	1.0%	1.0%	1.0%

Properties of Tablet	Example 24		
Compression force (MPa)	100	120	140
Crushing Strength (Kp)	8.0	7.0	8.0
Disintegration Time (min)	4.0	4.5	4.8

Properties of Tablet	Example 25	Example 26
Compression force (MPa)	100-140	100-140
Crushing Strength Range (Kp)	9.0-13.8	10.5-10.8
Mean Crushing Strength (Kp)	11.3	10.6
Disintegration Time (min)	8.0	7.5

Tablets may also be prepared in a similar manner to Examples 24-26 above containing the ibuprofen dl lysine salt in an amount of 171.0mg, 256.5mg and
5 513.0mg using the same proportions of ingredients as given in Examples 24-26.

132
124

Example 27

Ingredients	Example 27
Content of drug per tablet (mg)	256g
S(+)-Ibuprofen sodium salt dihydrate	49.7%
Microcrystalline cellulose (PH 102)	34.3%
Anhydrous sodium carbonate	7.8%
Croscarmellose sodium	7.0%
Colloidal silicon dioxide	0.2%
Stearic acid	1.0%

Properties of Tablet	Example 27
Compression force (MPa)	100-140
Crushing Strength Range (Kp)	7.3-8.7
Mean Crushing Strength (Kp)	7.9
Disintegration Time (min)	4.3

Comparative Examples

A. Tablets containing 256mg racemic ibuprofen sodium salt
(Ibuprofen equivalent 200mg)

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Comparative Formulation A
(without (b) carbonate component)

Ingredient	% (wt)
Ibuprofen sodium salt dihydrate	53.9%
Microcrystalline cellulose (PH102)	37.2%
10 Croscarmellose sodium	7.6%
Colloidal silicon dioxide	0.3%
Stearic acid	0.5%
Magnesium stearate	0.5%

B. Tablets containing 342.0mg racemic ibuprofen lysine salt
(ibuprofen equivalent 200mg)

<u>Comparative Formulation B</u>		
<u>(without (bi)carbonate component)</u>		
5	<u>Ingredient</u>	<u>% (wt)</u>
	Ibuprofen (dl lysine salt)	69.9
	Microcrystalline cellulose (PH102)	23.4
	Croscarmellose sodium	5.3
	Colloidal silicon dioxide	0.4
10	Stearic acid	1.0

In the Figures, Figure 1 shows a comparison of the disintegration times of:-

- (a) a compressed dosage form of the present invention containing the sodium salt of ibuprofen (Example 22) with comparative Example A (without a (bi)carbonate component); and
- 15 (b) a compressed dosage form of the present invention containing the lysine salt of ibuprofen (Example 24) with comparative Example B (without a (bi)carbonate component).

The disintegration times are shown as a function of compaction pressure.

- Figure 2 shows a comparison of the disintegration properties of the tablets having
- 20 the following components with no sodium carbonate (Comparative Formulation A) and varying amounts of sodium carbonate additionally included in that Example (as shown below). The disintegration time is shown as a function of the compaction pressure.

Ingredient	Comparative Formulation A wt (mg)	Ex 28 wt (mg)
Ibuprofen sodium salt dihydrate	256.00	256.00
Microcrystalline cellulose (PH 102)	176.75	176.75
Anhydrous sodium carbonate	-	12.50
Croscarmellose sodium	36.00	36.00
Colloidal silicon dioxide	1.25	1.25
Stearic acid	2.50	2.50
Magnesium stearate	2.50	2.50

Ingredient	Ex 29 wt (mg)	Ex 30 wt (mg)	Ex 31 wt (mg)
Ibuprofen sodium salt dihydrate	256.00	256.00	256.00
Microcrystalline cellulose (PH 102)	176.75	176.75	176.75
Anhydrous sodium carbonate	25.00	37.50	50.00
Croscarmellose sodium	36.00	36.00	36.00
Colloidal silicon dioxide	1.25	1.25	1.25
Stearic acid	2.50	2.50	2.50
Magnesium stearate	2.50	2.50	2.50

- 5 It can be seen from Figures 1 and 2 that at standard operating compaction pressures in the range 100-140MPa, the disintegration time of the tablet without sodium carbonate steeply rises reflecting a sharp increase in disintegration time for only a small increase in compaction pressure. The disintegration time vs compaction force gradient for tablets containing sodium carbonate is unexpectedly much more shallow which leads to the processing advantages described herein. In Figure 2 it can be seen that the disintegration times at 100MPa for tablets containing sodium carbonate are less than 300 seconds, whereas omitting this component provides a disintegration time greater than 420 seconds.

135
127Claims

1. A solid non-effervescent compressed dosage form comprising an ibuprofen medicament and a carrier material comprising a compressible filler component combined with a disintegrating component wherein the ibuprofen medicament is present to an extent of 35% or more by weight of the dosage form, characterised in that the carrier material includes an alkali metal carbonate or bicarbonate in an amount such that the dosage form has a crushing strength in the range 8.5-15Kp and a disintegration time of less than 10 minutes, provided that the ibuprofen medicament does not contain a calcium salt of ibuprofen in combination with an alkali metal salt of ibuprofen.
2. A dosage form according to claim 1 wherein the ibuprofen medicament is in the form of a salt of ibuprofen.
3. A dosage form according to claim 2 wherein the ibuprofen medicament is the sodium salt of racemic ibuprofen.
4. A dosage form according to any one of claims 1 to 3 comprising a filler component and a discrete disintegrant component.
5. A dosage form according to any one of claims 1 to 4 comprising 5-15% w/w alkali metal carbonate or bicarbonate.
6. A dosage form according to any one of claims 1 to 5 wherein the alkali metal carbonate or bicarbonate comprises sodium carbonate or sodium bicarbonate.
7. A dosage form according to claim 6 comprising sodium carbonate or bicarbonate in a weight ratio to the ibuprofen medicament of 1:2 to 1:10.
8. A dosage form according to any one of claims 1 to 7 wherein the compressible filler component comprises one or more of microcrystalline cellulose, lactose and mannitol.

136
128

9. A dosage form according to any one of claims 1 to 8 wherein the disintegrant comprises one or more of croscarmellose sodium and sodium starch glycolate.
10. A dosage form according to any one of claims 1 to 9 in the form of a compressed tablet.
- 5 11. The use of an alkali metal carbonate or bicarbonate in a carrier material including a compressible filler component combined with a disintegrating component, said carrier material being arranged for admixture with an ibuprofen medicament under substantially dry conditions and then for compression into a solid non-effervescent dosage form wherein the ibuprofen medicament comprises 35% or more by weight of
- 10 the dosage form, the dosage form having a crushing strength in the range 8.5-15Kp and a disintegration time of less than 10 minutes.
12. The use according to claim 11 wherein the ibuprofen medicament is in the form of the sodium salt.
13. The use according to either one of claims 11 and 12 wherein the carrier material
- 15 is adapted for direct compression with the ibuprofen medicament into a tablet.
14. The use according to any one of claims 11 to 13 wherein the solid dosage form comprises the sodium salt of ibuprofen together with a carrier material comprising microcrystalline cellulose and sodium carbonate or bicarbonate.
15. The use according to anyone of claims 11 to 14 wherein carrier material
- 20 comprises 45-60% microcrystalline cellulose, 2-10% croscarmellose sodium and 2-20% sodium carbonate or bicarbonate.
16. A method of obtaining an onset-hastened analgesic and/or anti-pyretic response comprising the administration of a non-effervescent compressed solid dosage form comprising 35% or more by weight of an ibuprofen medicament together with a
- 25 carrier material comprising a compressible filler component combined with a disintegrating component and an alkali metal carbonate or bicarbonate, the dosage form having a crushing strength in the range 8.5-15Kp and a disintegration time of
-

less than 10 minutes, provided that the ibuprofen medicament does not include a calcium salt of ibuprofen in combination with an alkali metal salt of ibuprofen.

17. A method according to claim 16 wherein the dosage form has a crushing strength in the range 8-12Kp, at a compression force in the range 100-140MPa.

5 18. A method according to either one of claims 15 and 16 wherein the solid dosage form has a disintegration time in the range 1-5 minutes.

19. A method according to any one of 18 to 19 wherein the dosage form is in the form of a directly compressed tablet comprising 40-85% w/w sodium salt of ibuprofen and 5-15% w/w sodium carbonate or bicarbonate.

10 20. A process to prepare a non-effervescent solid dosage form comprising an ibuprofen medicament present to an extent of 35% or more by weight of the dosage form and a carrier material comprising a compressible filler component combined with a disintegrating component, characterised by combining the carrier material incorporating an alkali metal carbonate or bicarbonate with the ibuprofen medicament
15 to form a homogeneous solid mixture under substantially dry conditions optionally with other tableting excipients and compressing the mixture into one or more solid dosage forms having a crushing strength in the range 8.5-15Kp and a disintegration time of less than 10 minutes.

20 21. A process according to claim 20 wherein the ibuprofen medicament is a salt of racemic ibuprofen.

22. A process according to either one of claims 20 and 21 wherein the carrier material comprises a inert diluent component.

25 23. A process according to any one of claims 20-22 wherein the dosage form is prepared by direct compression of a powder mixture of the ingredients and does not include any pre-granulation stage.

24. A process according to any one of claims 20-23 wherein the ratio of the alkali metal carbonate or bicarbonate to compressible filler component is in the range 2:1 to 1:10 parts by weight.

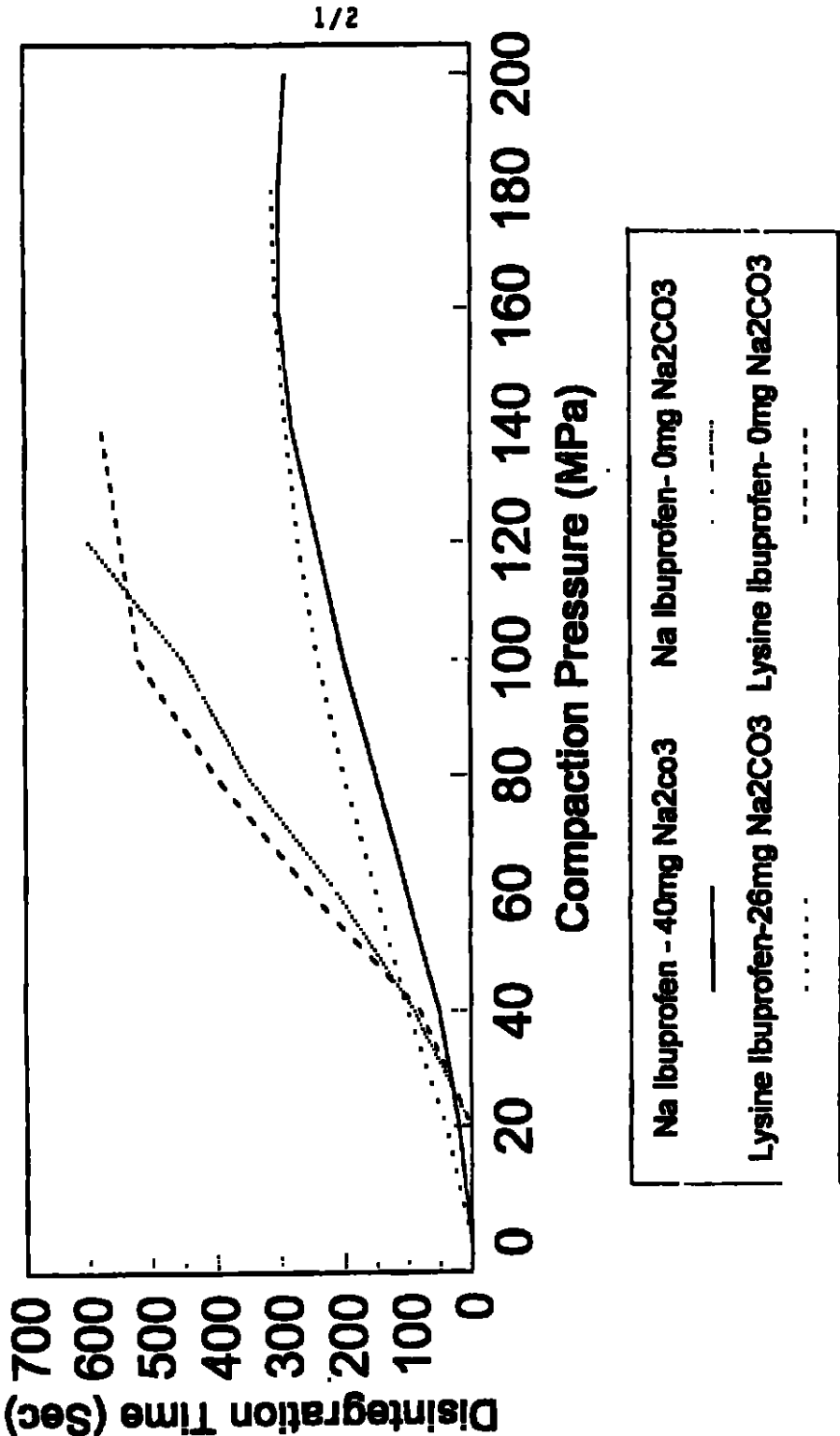
5 25. A process according to any one of claims 19-24 wherein the ratio of ibuprofen medicament to the carrier material is in the range 2:1 to 1:2 parts by weight and the carrier material comprises 5-20% w/w sodium carbonate or bicarbonate.

10 26. A solid formulation having a layer comprising a composition comprising an ibuprofen medicament together with a carrier material, the ibuprofen medicament being present to an extent of 35% or more by weight of the composition and the carrier material comprising a compressible filler component combined with a disintegrating component characterised in that the carrier material comprises an alkali metal carbonate or bicarbonate in an amount such that the composition is capable of compression to provide a layer having a crushing strength in the range 6.5-15Kp and a disintegration time of less than 10 minutes.

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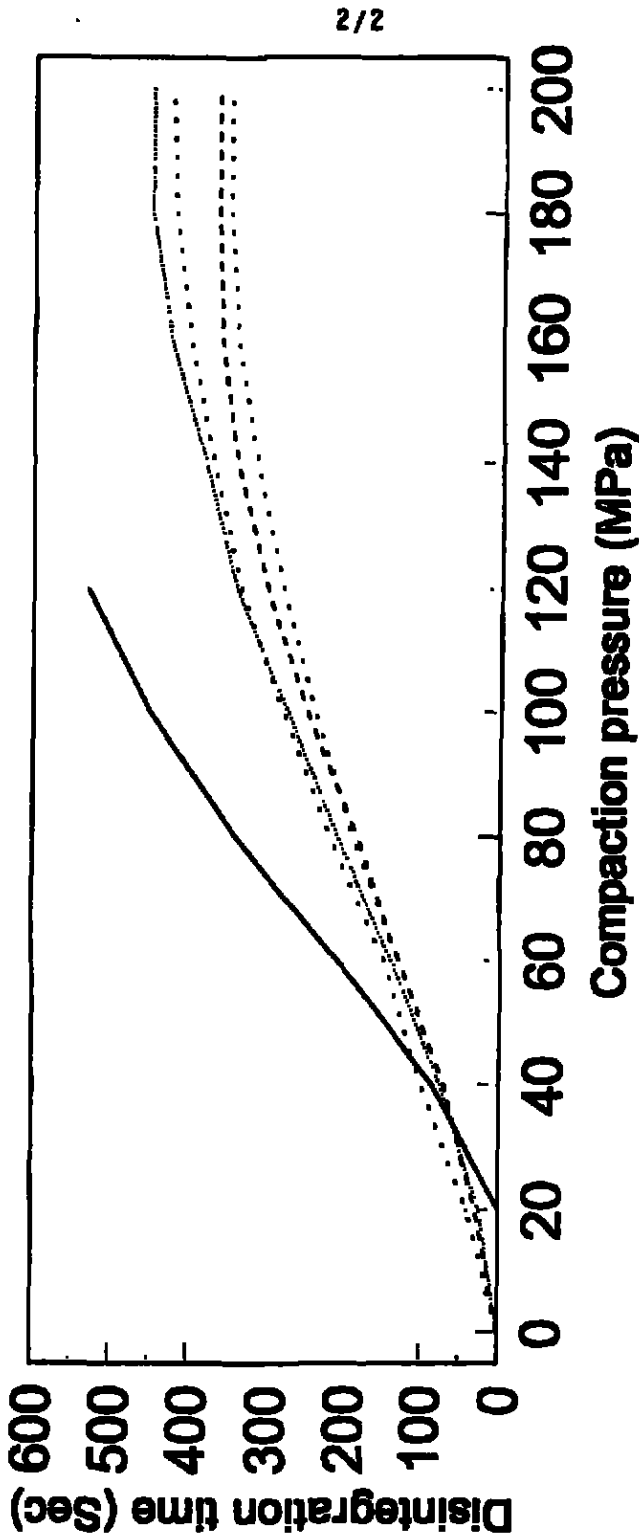
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Figure 1
Ibuprofen Salts
Effect of sodium carbonate on disintegration time



440

Figure 2
Ibuprofen sodium salt
Effect of sodium carbonate level on disintegration time



0 mg sodium carbonate	12.5mg sodium carbonate	25mg sodium carbonate
37.5mg sodium carbonate	50mg sodium carbonate	



US005696165A

442
133**United States Patent** [19]
Armitage et al.[11] **Patent Number:** 5,696,165
[45] **Date of Patent:** Dec. 9, 1997**[54] COMPOSITION OF S(-) SODIUM
IBUPROFEN****[75] Inventors:** Bernard John Armitage; John Francis
Lampard; Alan Smith, all of
Nottinghamshire, United Kingdom**[73] Assignee:** The Boots Company PLC,
Nottingham, United Kingdom**[21] Appl. No.:** 557,565**[22] Filed:** Nov. 14, 1995**Related U.S. Application Data****[62] Division of Ser. No. 137,092, filed as PCT/EP92/01025,
May 4, 1992.****[30] Foreign Application Priority Data**May 13, 1991 [GB] United Kingdom 9110342
Jan. 5, 1991 [GB] United Kingdom 9112058**[51] Int. Cl.⁶ A61K 31/19****[52] U.S. Cl. 514/570****[58] Field of Search 562/401; 514/570****[56] References Cited****U.S. PATENT DOCUMENTS**

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[57] ABSTRACT

The use of S(-)-sodium 2-(4-isobutylphenyl)propionate (the sodium salt of S(+)-ibuprofen) in pharmaceutical compositions for the treatment of inflammation, pain and pyrexia is described. Preferred compositions comprise S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate. Processes to prepare S(-)-sodium 2-(4-isobutylphenyl)propionate and its use in a process to prepare S(+)-2-(4-isobutylphenyl)propionic acid of high enantiomeric purity are also described.

15 Claims, No Drawings

1

COMPOSITION OF S(-) SODIUM IBUPROFEN

This is a division of application Ser. No. 08/137,092 filed Oct. 26, 1993. This application also claims priority to PCT/EP92/01025 filed May 4, 1992.

This invention relates to a salt of S(+)-ibuprofen, to its anti-inflammatory, anti-pyretic and analgesic activity, to pharmaceutical compositions containing the salt, to its use as an intermediate in a process to prepare S(+)-ibuprofen of high enantiomeric purity and to a novel form of the salt.

(±)-2-(4-isobutyphenyl)propionic acid, ibuprofen, is a potent and well tolerated anti-inflammatory, analgesic and anti-pyretic compound. The racemic mixture consists of two enantiomers, namely S(+)-2-(4-isobutyphenyl)propionic acid or S(+)-ibuprofen and R(-)-2-(4-isobutyphenyl)propionic acid or R(-)-ibuprofen. It is known that S(+)-ibuprofen is the active agent and that R(-)-ibuprofen is partially converted into S(+)-ibuprofen in humans. The drug has been previously marketed as the racemic mixture, however, in certain circumstances it may be advantageous to administer S(+)-ibuprofen. Problems arise, however, when attempting to formulate S(+)-ibuprofen into pharmaceutical compositions due to its low melting point of 51° C.

DE 3922441 considers the formulation problems associated with the low melting point of S(+)-ibuprofen and proposes a solution to the problem by using the calcium salt of S(+)-ibuprofen on its own or in admixture with a compound selected from the group comprising the sodium-, potassium- or ammonium-S(+)-ibuprofen salt, ibuprofen or S(-)-ibuprofen. It is disclosed that the pharmaceutical composition must contain the calcium salt as an essential component as alkali metal salts of S(+)-ibuprofen per se, for example the sodium salt, are too hygroscopic to allow satisfactory tableting.

We have now prepared and characterized the sodium salt of S(+)-ibuprofen and surprisingly we have found that it possesses advantageous formulation properties. The sodium salt of S(+)-ibuprofen has a negative optical rotation of -4.3° and is thus correctly named as S(-)-sodium 2-(4-isobutyphenyl)propionate.

The preparation of the sodium salt of S(+)-ibuprofen in anhydrous form for use as a base, as an alternative to the use of pyridine, in a process to racemise S(+)-ibuprofen, is described in U.S. Pat. No. 4,946,997. In this reference no details are given of the physical properties of the material obtained and there is no suggestion that the material is suitable for pharmaceutical use.

The administration of S(+)-ibuprofen as a solution in dilute sodium hydroxide to a normal subject in a volunteer study has been reported (Lee et al, J. Pharm Sci. Vol. 73, No.11, 1984, pp 1542-44). However, the taste of such a preparation would be unacceptable to the vast majority of patients.

The present invention provides pharmaceutical compositions comprising S(-)-sodium 2-(4-isobutyphenyl)propionate having an enantiomeric purity of at least 90%, together with a pharmaceutically acceptable carrier, with the exception of (a) compositions consisting of a solution of S(-)-sodium 2-(4-isobutyphenyl)propionate in water with no additional pharmaceutical excipient and (b) compositions comprising the calcium salt of S(+)-ibuprofen.

S(-)-sodium 2-(4-isobutyphenyl)propionate possesses a number of formulation advantages over S(+)-ibuprofen. S(-)-sodium 2-(4-isobutyphenyl)propionate may be easily compressed into tablets even on long compressing runs during which the temperature of the tablet tooling will rise.

2

Under similar circumstances S(+)-ibuprofen would tend to stick and generally display poor flow characteristics. S(-)-sodium 2-(4-isobutyphenyl)propionate may also be easily milled to the most appropriate particle size. These advantages would not be expected from consideration of the prior art (DE 3922441) referred to earlier.

The high melting point of S(-)-sodium 2-(4-isobutyphenyl)propionate, 220°-222° C., allows higher temperatures to be used in drying intermediates in formulation processes, for example granules, compared to the corresponding intermediates containing S(+)-ibuprofen. The high melting point also gives increased physical stability to final formulations containing S(-)-sodium 2-(4-isobutyphenyl)propionate during storage for example in hot climates compared to final formulations containing S(+)-ibuprofen which may deteriorate when stored at temperatures close to the melting point of S(+)-ibuprofen.

S(-)-sodium 2-(4-isobutyphenyl)propionate has a higher water solubility than S(+)-ibuprofen and is thus very useful in the formulation of pharmaceutical compositions containing water. Such compositions may be formulated to have a bright, clear, aesthetically-appealing appearance.

An additional formulation advantage is that S(-)-sodium 2-(4-isobutyphenyl)propionate will resist esterification with excipients which contain a hydroxyl group for example mono-, di-, tri- or poly-hydric alcohols. For example this is a problem encountered when formulating S(+)-ibuprofen with liquid fill excipients, for example, esterified natural vegetable oils which may contain alcohols.

The enantiomeric purity of S(-)-sodium 2-(4-isobutyphenyl)propionate used in the pharmaceutical compositions of the invention is in the range of 90-100%. Preferably the enantiomeric purity of the S(-)-sodium 2-(4-isobutyphenyl)propionate used greater than 95%, more preferably the enantiomeric purity is greater than 98% and most preferably the enantiomeric purity is greater than 99%. In an especially preferred embodiment of the present invention the enantiomeric purity is greater than 99.5% e.g. greater than 99.9%. We have found that S(-)-sodium 1-(4-isobutyphenyl)propionate can exist in the form of a stable dihydrate which is a novel and valuable compound for use in preparing pharmaceutical compositions. In the following detailed description of compositions of the invention the term S(-)-sodium 2-(4-isobutyphenyl)propionate includes the anhydrous form and hydrated forms. Preferably the dihydrate is used.

S(-)-sodium 2-(4-isobutyphenyl)propionate dihydrate may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof.

In therapeutic use, S(-)-sodium 2-(4-isobutyphenyl)propionate may be administered orally, rectally, parenterally or topically, preferably orally or topically. Suitably the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for oral, rectal, parenteral or topical administration. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention may contain 1-99% by weight of S(-)-sodium 2-(4-isobutyphenyl)propionate. The compositions of the invention are generally prepared in unit dosage form. Preferably the unit dosage of S(-)-sodium 2-(4-isobutyphenyl)propionate is in the range of 10-1200 mg in a precalculated amount to provide doses which are equivalent by weight to doses of for example 100 mg, 200 mg, 400 mg or 800 mg of S(+)-ibuprofen.

Solid compositions for oral administration are preferred compositions of the invention and there are known pharma-

3

ceutical forms for such administration, for example tablets and capsules. Suitably tablets may be prepared by mixing S(-)-sodium 2-(4-isobutyphenyl)propionate with an inert diluent such as calcium phosphate in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and tableting the mixture by known methods. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing S(-)-sodium 2-(4-isobutyphenyl)propionate with or without added excipients, may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. The tablets may be formulated in a manner known to those skilled in the art so as to give a controlled release of the compound of the present invention. Other compositions for oral administration include oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil.

Preferably, a solid composition comprises a) 10-99% S(-)-sodium 2-(4-isobutyphenyl)propionate; b) 1-90% of a diluent and c) 0.1-10% of a lubricating agent, d) 0.1-15% of a disintegrating agent and optionally e) 0.1-15% of a binder. Optionally 0.1-10% of a flow aid may be added.

Preferably the diluent includes lactose, calcium phosphate, dextrin, microcrystalline cellulose, sucrose, starch, calcium sulphate or mixtures thereof. More preferably the diluent is lactose or calcium phosphate. Preferably the lubricating agent includes magnesium stearate, stearic acid, calcium stearate or mixtures thereof. More preferably the lubricating agent is magnesium stearate or stearic acid. Preferably the disintegrating agent includes microcrystalline cellulose, maize starch, sodium starch glycolate, low substituted hydroxypropyl cellulose, alginate acid or croscarmellose sodium or mixtures thereof. Preferably the binder includes polyvinyl pyrrolidone, gelatin, hydroxypropylmethyl cellulose, starch or mixtures thereof. More preferably the binder is polyvinylpyrrolidone. Suitable flow aids include talc and colloidal silicon dioxide. It will be appreciated by those skilled in the art that a particular excipient may perform more than one function for example maize starch may act as a diluent, a binder or as a disintegrating agent.

Controlled release forms of S(-)-sodium 2-(4-isobutyphenyl)propionate include rapid release formulations such as soluble granules or melt filled fast release capsules, delayed release formulations such as tablets provided with enteric coatings, for example, of cellulose acetate phthalate and, in particular, sustained release formulations. Numerous types of sustained release formulations are known to those skilled in the art. Typically, S(-)-sodium 2-(4-isobutyphenyl)propionate may be encapsulated within a release retarding coating, for example, a copolymer of cellulose ether and acrylate, or may be bound to small particles such as, for example, ion exchange resin beads. Alternatively, S(-)-sodium 2-(4-isobutyphenyl)propionate may be incorporated into a matrix containing a release retarding agent such as a hydrophilic gum e.g. xanthan gum, a cellulose derivative e.g. hydroxypropyl methylcellulose, or a polysaccharide, wax or plastics material. Such techniques may provide sustained blood levels of S(+)-ibuprofen by controlling, for example, erosion, swelling, disintegration and dissolution of the composition within the gastrointestinal tract.

Liquid fill compositions for example viscous liquid fills, liquid paste fills or thixotropic liquid fills are also suitable for oral administration. Melt filled compositions may be

4

obtained by mixing S(-)-sodium 2-(4-isobutyphenyl)propionate with certain esters of natural vegetable oil fatty acids, for example, the Gelucire (Trademark) range available from Gattefosse to provide a variety of release rates. Suitably a melt-filled capsule comprises a) 10-80% S(-)-sodium 2-(4-isobutyphenyl)propionate and b) 20-90% of a fatty acid ester excipient which comprises one or more polyol esters and triglycerides of natural vegetable oil fatty acids.

Solid compositions designed to effervesce when added to water to form an effervescent solution or suspension are also suitable for oral administration. Suitably an effervescent composition comprises a) 1-50% of S(-)-sodium 2-(4-isobutyphenyl)propionate and b) a pharmaceutically acceptable effervescent couple. Such a composition may be presented in the form of tablets or granules. Although S(-)-sodium 2-(4-isobutyphenyl)propionate may have advantageous organoleptic properties compared to the sodium salt of racemic ibuprofen preferably the effervescent compositions additionally comprise a taste masking component for example a sweetener, a flavouring agent, arginine, sodium carbonate or sodium bicarbonate.

Solid non-effervescent compositions are preferred compositions of the present invention. Preferably such compositions comprise S(-)-sodium 2-(4-isobutyphenyl)propionate as the dihydrate.

Preferably oral liquid compositions comprise a) 0.1-10% S(-)-sodium 2-(4-isobutyphenyl)propionate b) 1-50% of a diluent c) water to 100%. Optionally the composition may contain alcohol and/or include a preservative. Suitable diluents include sweetening agents for example sorbitol, xylitol, sucrose, or LYCASIN® (registered trademark of Roquette). Flavourings or other taste-masking agents known to those skilled in the art for example saccharin, sodium saccharin may be added. The use of S(-)-sodium 2-(4-isobutyphenyl)propionate in aqueous liquid compositions is particularly advantageous as it provides clear, homogeneous, bright formulations which are aesthetically appealing to the consumer in addition to the beneficial pharmacological effect provided.

Compositions for topical administration are also preferred compositions of the invention. Suitably the S(-)-sodium 2-(4-isobutyphenyl)propionate may be dispersed in a pharmaceutically acceptable cream, ointment or gel. A suitable cream may be prepared by incorporating S(-)-sodium 2-(4-isobutyphenyl)propionate in a topical vehicle such as petrolatum and/or light liquid paraffin, dispersed in an aqueous medium using surfactants. An ointment may be prepared by mixing S(-)-sodium 2-(4-isobutyphenyl)propionate with a topical vehicle such as a mineral oil, petrolatum and/or a wax e.g. paraffin wax or beeswax. A gel may be prepared by mixing S(-)-sodium 2-(4-isobutyphenyl)propionate with a topical vehicle comprising a gelling agent e.g. basified Carbomer BP, in the presence of water.

Suitable topically administrable compositions may also comprise a matrix in which the pharmaceutically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally for example in a patch or poultice. A suitable transdermal composition may be prepared by mixing S(-)-sodium 2-(4-isobutyphenyl)propionate with a topical vehicle, such as described above, together with a potential transdermal accelerant such as dimethyl sulphoxide, propylene glycol or peppermint oil.

Semi-solid compositions are preferred for topical use for example compositions in the form of a cream, an ointment

or a gel. Suitable gels comprise a) 1-15% S(-)-sodium 2-(4-isobutyphenyl)propionate; b) 1-20% of a gelling agent c) 0.01-10% of a preservative and d) water to 100%. Preferably the gelling agent comprises 0.1-10% of a carbomer and a neutralizing agent. It is a particular advantage of the present invention that as a result of the high water solubility of S(-)-sodium 2-(4-isobutyphenyl)propionate clear gels are obtained which have an acceptable cosmetic appearance and texture in addition to their pharmacological activity.

A suitable cream comprises a) 1-15% S(-)-sodium 2-(4-isobutyphenyl)propionate; b) 5-40% of an oily phase; c) 5-15% of an emulsifier; d) 30-85% of water. Suitable oily phases comprise petrolatum and/or light liquid paraffin.

Alternatively, S(-)-sodium 2-(4-isobutyphenyl)propionate may be distributed in a base comprising a) 10-40% of a self-emulsifying base b) 60-90% of water to form a cream. LABRAPILL and GELLOT (both trademarks of Gattefossé) are examples of self-emulsifying bases.

A suitable ointment comprises a) 1-15% S(-)-sodium 2-(4-isobutyphenyl)propionate and b) a topical vehicle to 100%. Suitable topical vehicles include mineral oil, petrolatum and/or a wax.

Compositions of the invention suitable for rectal administration are known pharmaceutical forms for such administration, for example suppositories with polyethylene glycol bases or semi-synthetic glycerides. Preferably the composition in the form of a suppository comprises 10-30% S(-)-sodium 2-(4-isobutyphenyl)propionate and 70-90% of a carrier wherein the carrier is selected from a base which comprises polyethylene glycol or a semi-synthetic glyceride.

Compositions of the invention suitable for parenteral administration are known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

In some formulations it may be beneficial to use S(-)-sodium 2-(4-isobutyphenyl)propionate in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the S(-)-sodium 2-(4-isobutyphenyl)propionate may, if desired, be associated with other compatible pharmacologically active ingredients and/or enhancing agents. Thus, for example, S(-)-sodium 2-(4-isobutyphenyl)propionate may be combined with any ingredient commonly used in a cough or cold remedy, for example, an antihistamine, caffeine or another xanthine derivative, a cough suppressant, a decongestant, an expectorant, a muscle relaxant, or combinations thereof.

Suitable antihistamines which are preferably non-sedating include acrivastine, astemizole, azatadine, azelastine, bromodiphenhydramine, brompheniramine, carbinoxamine, cetirizine, chlorpheniramine, cyproheptadine, dexbrompheniramine, dexchlorpheniramine, diphenhydramine, ebastine, ketotifen, lodoxamide, loratadine, levocabastine, mequitazine, oxatomide, phenindamine, phenyltoloxamine, pyrrolamine, setastine, tazafylline, temclastine, terfenadine, tripelemamine or triprolidine. Suitable cough suppressants include caramiphen, codeine or dextromethorphan. Suitable decongestants include pseudoephedrine, phenylpropanolamine and phenylephrine. Suitable expectorants include guaifenesin, potassium citrate, potassium guaiacolsulphonate, potassium sulphate and terpin hydrate.

S(-)-sodium 2-(4-isobutyphenyl)propionate is an anti-inflammatory, analgesic and anti-pyretic agent. It is, therefore, indicated for use in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, seronegative

arthropathies, periarthritic disorders and soft tissue injuries. S(-)-sodium 2-(4-isobutyphenyl)propionate may also be used in the treatment of postoperative pain, postpartum pain, dental pain, dysmenorrhoea, headache, musculoskeletal pain or the pain or discomfort associated with the following: respiratory infections, colds or influenza, gout or morning stiffness.

In another aspect the present invention provides a pharmaceutical composition comprising S(-)-sodium 2-(4-isobutyphenyl)propionate having an enantiomeric purity of at least 90% together with a pharmaceutically acceptable carrier for use in the treatment of inflammation, pain and pyrexia. Preferably the S(-)-sodium 2-(4-isobutyphenyl)propionate is present as the dihydrate.

In a further aspect the present invention provides the use of a pharmaceutical composition comprising S(-)-sodium 2-(4-isobutyphenyl)propionate having an enantiomeric purity of at least 90% together with a pharmaceutically acceptable carrier for the manufacture of a medicament for use as an anti-inflammatory, analgesic and anti-pyretic agent. Preferably the S(-)-sodium 2-(4-isobutyphenyl)propionate is present as the dihydrate.

It will be appreciated that the present invention provides a method of treating inflammation, pain and pyrexia by administration of a pharmaceutical composition comprising S(-)-sodium 2-(4-isobutyphenyl)propionate having an enantiomeric purity of at least 90% together with a pharmaceutically acceptable carrier to a mammal, e.g. a human, in need thereof. Preferably the S(-)-sodium 2-(4-isobutyphenyl)propionate is present as the dihydrate.

S(-)-sodium 2-(4-isobutyphenyl)propionate may be absorbed more quickly from the gastrointestinal tract in humans than S(+)-ibuprofen thus giving therapeutically acceptable plasma levels in a shorter period of time. This effect offers the possibility of eliciting an onset-hastened and/or enhanced therapeutic response, by use of S(-)-sodium 2-(4-isobutyphenyl)propionate compared to S(+)-ibuprofen, which is especially important in cases where analgesia is required, for example, in headache or dental pain. Thus the present invention includes a method of eliciting an onset-hastened and/or enhanced analgesic response compared to the use of an equivalent dose of S(+)-ibuprofen in a mammal, e.g. a human, comprising the administration of S(-)-sodium 2-(4-isobutyphenyl)propionate to a mammal in need thereof.

This surprising effect occurs not only when S(-)-sodium 2-(4-isobutyphenyl)propionate is administered in solution but also when administered in other formulations, for example, solid formulations for oral use (for example tablets or capsules) or suppositories.

In another aspect the present invention provides a method of preparing a pharmaceutical composition comprising S(-)-sodium 2-(4-isobutyphenyl)propionate together with a diluent or carrier characterised in that S(-)-sodium 2-(4-isobutyphenyl)propionate dihydrate is used as the source of S(-)-sodium 2-(4-isobutyphenyl)propionate.

In a further aspect the present invention provides a process to prepare a pharmaceutical composition comprising S(-)-sodium 2-(4-isobutyphenyl)propionate having an enantiomeric purity of at least 90% together with a pharmaceutically acceptable carrier comprising combining S(-)-sodium 2-(4-isobutyphenyl)propionate having an enantiomeric purity of at least 90% in solid form with a pharmaceutically acceptable carrier and formulating into a dosage form.

A preferred process for preparing a solid composition in tablet form comprises combining 10-90% of S(-)-sodium 2-(4-isobutyphenyl)propionate having an enantiomeric

purity of at least 90% with 1-90% of a diluent, optionally adding other pharmaceutically acceptable excipients selected from lubricating agents, disintegrating agents, binders, flow aids, oils, fats and waxes, mixing the ingredients with one another to form a uniform mixture, and compressing the mixture thus obtained to form tablets which may be optionally coated with a film coat or a sugar-coat.

Processes for the preparation of S(-)-sodium 2-(4-isobutyphenyl)propionate will now be described. These processes form another aspect of the present invention. In the following description of these processes the term S(-)-sodium 2-(4-isobutyphenyl)propionate includes the anhydrous form and hydrated forms for example the dihydrate.

S(-)-sodium 2-(4-isobutyphenyl)propionate may be prepared by neutralising S(+)-2-(4-isobutyphenyl) propionic acid with a sodium-containing base. It would be expected that in order to prepare S(-)-sodium 2-(4-isobutyphenyl) propionate in an enantiomerically pure form, for example greater than 90%, then the S(+)-2-(4-isobutyphenyl) propionic acid employed would be required to be greater than 90%. While this procedure may be used, it is time-consuming and costly to prepare S(+)-2-(4-isobutyphenyl) propionic acid of greater than 90% enantiomeric purity. Typically racemic ibuprofen is resolved using S(-)-1-phenylethylamine as described in the Journal of Pharmaceutical Sciences, 1976, page 26. The intermediate S(-)-1-phenylethylammonium S(+)-2-(4-isobutyphenyl) propionate salt requires several recrystallisations to raise the enantiomeric purity of the S(+)-ibuprofen produced, after hydrolysis of the salt, to above 90%. The amine employed is expensive and in theory the yield of S(+)-ibuprofen obtained cannot exceed 50%. The unwanted R(-)-ibuprofen may be racemised and the resolution procedure repeated to produce more S(+)-ibuprofen but overall the whole process is costly in terms of manpower, materials and plant equipment.

It is known that ibuprofen crystallises as a racemic compound rather than a mixture of enantiomers and that consequently preferential crystallisation is not an efficient process for the removal of small amounts of R(-)-ibuprofen from a sample of S(+)-ibuprofen.

Unexpectedly in preparing solid S(-)-sodium 2-(4-isobutyphenyl)propionate we have discovered that this salt may be purified enantiomerically by crystallisation and that this surprising property may be utilised industrially to provide a simple, efficient and very cheap process to prepare S(-)-sodium 2-(4-isobutyphenyl)propionate of high enantiomeric purity and to provide a process to prepare S(+)-ibuprofen of high enantiomeric purity. The process may be adapted to provide R(+)-sodium 2-(4-isobutyphenyl) propionate of high enantiomeric purity and optionally to prepare R(-)-ibuprofen of high enantiomeric purity.

Accordingly, the present invention provides a process for preparing a sodium salt of a desired enantiomer of 2-(4-isobutyphenyl)propionic acid said sodium salt having an enantiomeric purity of greater than 90% that is 90-100% comprising the steps of:

- neutralising 2-(4-isobutyphenyl)propionic acid containing 50% or more of the desired enantiomer with a sodium-containing base in the presence of a solvent system;
- crystallising to produce the solid sodium salt of the desired enantiomer; and
- separating said solid from the solvent system; and either
- recrystallising said solid

or

- converting said solid into 2-(4-isobutyphenyl) propionic acid and repeating steps a, b and c.

This process is surprising since it is known in the art that pure enantiomers of arylpropionic acids may be racemised when heated in the presence of a base.

Suitably the 2-(4-isobutyphenyl)propionic acid used contains 70% or more of the desired enantiomer, preferably 80% or more of the desired enantiomer and more preferably 85% or more of the desired enantiomer.

In a more preferred embodiment the present invention provides a process for preparing S(-)-sodium 2-(4-isobutyphenyl)propionate having an enantiomeric purity of greater than 90% comprising the steps of:

- neutralising 2-(4-isobutyphenyl)propionic acid containing 85% or more of the S(+)-enantiomer with a sodium-containing base in the presence of a solvent system;
- crystallising to produce solid S(-)-sodium 2-(4-isobutyphenyl)propionate and
- separating said solid from the solvent system.

Optionally the S(-)-sodium 2-(4-isobutyphenyl)propionate may be recrystallised. Optionally, the S(-)-sodium 2-(4-isobutyphenyl)propionate may be acidified to produce S(+)-2-(4-isobutyphenyl)propionic acid of higher enantiomeric purity than the acid used as starting material.

Preferably the process provides S(-)-sodium 2-(4-isobutyphenyl)propionate having an enantiomeric purity of greater than 95%. More preferably the process provides S(-)-sodium 2-(4-isobutyphenyl)propionate having an enantiomeric purity of greater than 98%. Most preferably the process provides S(-)-sodium 2-(4-isobutyphenyl) propionate having an enantiomeric purity of greater than 99%. In an especially preferred process the enantiomeric purity is greater than 99.5% e.g. greater than 99.9%.

In a most preferred embodiment the present invention provides a process for preparing S(-)-sodium 2-(4-isobutyphenyl)propionate having an enantiomeric of greater than 99% comprising the steps of:

- neutralising 2-(4-isobutyphenyl)propionic acid containing 95% or more of the S(+)-enantiomer with a sodium-containing base in the presence of a solvent system;
- crystallising to produce solid S(-)-sodium 2-(4-isobutyphenyl)propionate and
- separating said solid from the solvent system.

2-(4-isobutyphenyl)propionic acid containing 50% of a desired enantiomer i.e. racemic ibuprofen may be prepared by methods known to those skilled in the art. 2-(4-isobutyphenyl)propionic acid containing more than 50% of a desired enantiomer for example 70%, 80%, 85%, 90%, 95% and 98% may be prepared by the partial resolution of racemic ibuprofen via salt formation with an optionally active amine for example S(-)-1-phenylethylamine followed by separation and hydrolysis as is well known in the art. Alternatively starting material for use in the process containing more than 50% of a desired enantiomer 2-(4-isobutyphenyl)propionic acid may be prepared by asymmetric synthesis using chemical techniques for example asymmetric hydrogenation, or biochemical techniques, for example stereoselective enzymatic ester hydrolysis.

The term neutralisation as used above means that substantially a molar equivalent of base is used within acceptable experimental error of around 10%. It will be appreciated by a person skilled in the art that the sodium salt of 2-(4-isobutyphenyl)propionic acid will give a pH value of

greater than 7 in aqueous solution. In practice we have found that best results are achieved by neutralisation in the range 90-98% for example 96% of the calculated amount of 2-(4-isobutylphenyl)propionic acid and then measuring the pH of the solution to confirm that it is into the range of pH 8-9.9 prior to crystallisation. If necessary the pH may be adjusted to the required value by the addition of more acid or base. It will be appreciated that if the solution is heated at a pH greater than 10 for any length of time that there is a possibility of racemisation occurring.

The formation of the sodium salt of S(+)-2-(4-isobutylphenyl)propionic acid may be carried out in numerous ways. Typically the acid is reacted with an equivalent of a sodium-containing base in a solvent system. Suitable sodium-containing bases are sodium hydroxide, sodium carbonate, sodium bicarbonate, a sodium alkoxide, for example sodium methoxide or sodium ethoxide, sodium hydride or sodamide. Preferably the sodium-containing base is sodium hydroxide or a sodium alkoxide. Most preferably the sodium-containing base is sodium hydroxide.

The solvent system employed depends on the sodium-containing base used and may be a single solvent or a mixture of solvents. The solvent system may contain water when a hydrolytically-stable, sodium-containing base is used, for example sodium hydroxide, or the solvent system may be substantially anhydrous when a hydrolytically-unstable, sodium-containing base, for example a sodium alkoxide or sodium hydride, is used. The purpose of the solvent system is to allow contact between the acid and sodium-containing base to permit formation of the sodium salt of the acid and to provide a medium from which this salt will crystallise or precipitate. Any solvent system in which these purposes are achieved may be used.

Suitably the solvent system contains water. When the solvent system employed contains water in at least twice the stoichiometric amount of the 2-(4-isobutylphenyl)propionic acid used as the starting material then the S(-)-sodium 2-(4-isobutylphenyl)propionate initially obtained is in the dihydrate form which may be dried by heating, optionally under vacuum to produce the anhydrous form. When the solvent system employed is anhydrous the initially formed S(-)-sodium 2-(4-isobutylphenyl)propionate is anhydrous.

Suitable solvent systems for hydrolytically-stable, sodium-containing bases are water or mixtures of water and at least one water-miscible organic solvent for example acetone or a C₁₋₄ alcohol for example methanol, ethanol, propan-1-ol, propan-2-ol or butan-1-ol. Also suitable are mixtures of water and a partially water-miscible organic solvent for example methyl ethyl ketone. Preferably the solvent system comprises a mixture of water and acetone.

Alternatively the solvent system may comprise a mixture of water and a water-immiscible organic solvent in a two phase solvent system wherein the 2-(4-isobutylphenyl)propionic acid is dissolved in the organic phase and the base is dissolved in the aqueous phase. The mixture may be agitated for example by stirring or shaking to form the sodium salt of the acid in the aqueous layer. The sodium salt may be recovered from the aqueous layer, optionally after separating the two layers, by crystallisation optionally after the addition of a water miscible organic solvent, for example acetone. Suitable water-immiscible solvents are for example aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons, ethers or esters. Preferably the water immiscible solvent is toluene.

When a hydrolytically-unstable, sodium-containing base is employed for example a sodium alkoxide such as sodium methoxide, a suitable solvent system comprises a substan-

tially anhydrous inert organic solvent, for example toluene or methanol, which is compatible with the base employed.

Suitably the formation of the sodium salt is carried out at a temperature in the range of 0°-150° C., although lower temperatures may be used, preferably in the range 5°-120° C. and most preferably in the range 10°-80° C. In a particularly preferred embodiment the formation of the sodium salt is carried out in the range from ambient temperature to 50° C. at atmospheric pressure.

Suitably the crystallisation of the sodium salt is carried out at a temperature in the range between the boiling point of the solvent system employed and the freezing point of the solvent system. Suitably the crystallisation may be carried out at a temperature in the range from -50° C. to +50° C., preferably in the range -20° C. to ambient temperature and most preferably from -10° C. to +10° C. at atmospheric pressure. It will be appreciated by those skilled in the art that the crystal size of the product obtained, may be varied by adjusting the crystallisation temperature, and by varying the rate of cooling.

In a preferred process according to the present invention S(+)-2-(4-isobutylphenyl)propionic acid is converted into the sodium salt by reaction with sodium hydroxide in the presence of a solvent system comprising a mixture of water and acetone. Suitably the process is carried out in the range 0°-80° C., preferably between 40° C. and 60° C. Suitably the volume ratio of acetone to water is in the range from 50:1 to 1:10 preferably the ratio is in the range 20:1 to 1:1 and most preferably in the range 15:1 to 2:1.

The sodium salt may be crystallised from the solvent system by methods for encouraging crystallisation known to those skilled in the art. For example the solvent system may be cooled, concentrated, seeded with the desired material or diluted with a solvent in which the sodium salt is less soluble or any combination of these methods may be employed. Preferably the solvent system is selected so that the sodium salt crystallises immediately after it is formed or on cooling of the solvent system.

The crystallised sodium salt may be separated from the solvent system by methods known to those skilled in the art for example by filtration or centrifugation.

In another aspect the present invention provides a process for preparing a sodium salt of a desired enantiomer of 2-(4-isobutylphenyl)propionic acid said sodium salt having an enantiomeric purity of greater than 90% comprising the steps of:

- dissolving sodium 2-(4-isobutylphenyl)propionate containing 50% or more of the desired enantiomer in a solvent to form a saturated solution;
- seeding said solution with the desired enantiomer of sodium 2-(4-isobutylphenyl)propionate;
- cooling said solution in a controlled manner to cause crystallisation of the solid sodium salt;
- separating said solid sodium salt from the solvent;
- repeating steps a) to d) until the desired level of enantiomeric purity is achieved.

The crystallisation mother liquors which contain a higher proportion of the undesired enantiomer may be racemised by known methods, for example heating in the presence of a base e.g. sodium hydroxide, and the racemic salt obtained optionally by crystallisation or by evaporation, recycled by carrying out steps a) to e) above.

Suitably racemic sodium 2-(4-isobutylphenyl)propionate is used in the process. It may be prepared by hydrolysis of an ester of 2-(4-isobutylphenyl)propionic acid or by hydrolysis of 2-(4-isobutylphenyl)propionitrile or by

447
138

139
448

hydrolysis of a 2-(4-isobutylphenyl) propionamide derivative or by other methods known to those skilled in the art.

Suitably any solvent or mixture of solvents, in which sodium 2-(4-isobutylphenyl)propionate is soluble and from which the salt may be recovered by crystallisation, may be employed. Suitably a mixture of water and a partially water miscible organic solvent for example methyl ethyl ketone may be used. Preferably, the solvent is a mixture of water and at least one water-miscible solvent selected from acetone or a C₁₋₄ alcohol for example methanol, ethanol, propan-1-ol, propan-2-ol or butan-1-ol. Most preferably the solvent comprises a mixture of water and acetone.

In a further aspect of the present invention the S(-)sodium 2-(4-isobutylphenyl)propionate obtained by any of the above processes may be acidified to produce S(+)-ibuprofen having an increased enantiomeric purity compared to that of the 2-(4-isobutylphenyl)-propionic acid used initially. This process is commercially extremely useful since S(+)-ibuprofen may be prepared by resolution of the racemic acid as described earlier or by asymmetric synthesis using chemical techniques, for example asymmetric hydrogenation, or biochemical techniques, for example stereoselective enzymatic ester hydrolysis. In such methods the final purification step is often a problem if the enantiomeric purity of the material obtained is not of the required standard. Previously an expensive resolution would have been required to upgrade the enantiomeric purity to an acceptable level, for example to greater than 99% purity. The process herein described provides a cheap and efficient method of increasing the enantiomeric purity of S(+)-ibuprofen to produce S(+)-ibuprofen of 99% or greater enantiomeric purity.

In a similar manner we have found that the enantiomeric purity of R(-)-ibuprofen may be increased by conversion into R(+)-sodium 2-(4-isobutylphenyl)propionate using the same process.

As mentioned previously when the solvent system employed contains water in at least twice the stoichiometric amount of the 2-(4-isobutylphenyl)propionic acid used as the starting material, S(-)sodium 2-(4-isobutylphenyl)propionate dihydrate is produced, which is novel.

Accordingly, the present invention provides S(-)sodium 2-(4-isobutylphenyl)propionate dihydrate having an enantiomeric purity of at least 90%. Preferably the enantiomeric purity of the S(-)sodium 2-(4-isobutylphenyl)propionate dihydrate is greater than 95% (that is 95-100%), more preferably the enantiomeric purity is greater than 98% and most preferably the enantiomeric purity of the S(-)sodium 2-(4-isobutylphenyl)propionate dihydrate is greater than 99%. In an especially preferred embodiment of the present invention the enantiomeric purity of the S(-)sodium 2-(4-isobutylphenyl)propionate dihydrate is greater than 99.5% e.g. greater than 99.9%.

The solid dihydrate compound flows freely and does not absorb further water. A particularly preferred embodiment of the present invention comprises solid S(-)sodium 2-(4-isobutylphenyl)propionate dihydrate in which two molecules of water are present for each molecule of S(-)sodium 2-(4-isobutylphenyl)propionate.

In another aspect the present invention provides S(-)sodium 2-(4-isobutylphenyl)propionate for use in the treatment of inflammation, pain and pyrexia.

The invention is illustrated by the following non-limitative Examples.

The samples of S(+)-2-(4-isobutylphenyl)propionic acid used as the starting materials in the examples were prepared by resolving racemic ibuprofen using S(-)-1-phenylethylamine in a similar manner to that described in J.

Pharm. Sci. 65 (1976) p.269-273. Acidification of the S(-)-1-phenylethylammonium S(+)-2-(4-isobutylphenyl)propionate salt initially produced gave S(+)-2-(4-isobutylphenyl)propionic acid of enantiomeric purity in the range 85-88%. Recrystallisation of the initially produced salt from propan-2-ol gave S(+)-2-(4-isobutylphenyl)propionic acid of enantiomeric purity in the range 95-99% after acidification.

The sample of R(-)-2-(4-isobutylphenyl)propionic acid used as a starting material was prepared by resolving racemic ibuprofen using R(+)-1-phenylethylamine in a similar manner to that described in J. Chromatography 99, (1974), p.541-551.

Enantiomeric Purity Determinations

The enantiomeric purity of samples of S(-)sodium 2-(4-isobutylphenyl)propionate was determined as follows. The S(-)sodium 2-(4-isobutylphenyl)propionate was acidified with 5M hydrochloric acid and the mixture extracted with ether. The combined ether extracts were washed with water, dried and evaporated to give S(+)-2-(4-isobutylphenyl)propionic acid.

This sample of S(+)-2-(4-isobutylphenyl)propionic acid was reacted with thionyl chloride and acetyl chloride to form S(+)-2-(4-isobutylphenyl)propionyl chloride which was then reacted with (-)-1-phenylethylamine to form N(-)-1-phenylethyl-S(+)-2-(4-isobutylphenyl)propionamide. The amount of the diastereoisomeric amide formed from the R(-)-2-(4-isobutylphenyl)propionic present in each sample was determined using HPLC.

EXAMPLE 1

A solution of sodium hydroxide (6.4 g) in water (50 ml) was added over two minutes to a stirred solution of S(+)-2-(4-isobutylphenyl)propionic acid (41.2 g, enantiomeric purity 98.9%) in acetone (2 l) at ambient temperature. After standing for 30 minutes the precipitated salt was collected, washed with acetone and dried. The salt was taken up in warm water (45 ml) at 50°-60° C. and stirred whilst acetone (300 ml) was added slowly over 5 minutes. The warm solution was decanted from the residue and whilst still warm was mixed with acetone (650 ml). The material which crystallised out on cooling was collected by filtration to give S(-)sodium 2-(4-isobutylphenyl)propionate dihydrate m.p. 220°-222° C., $[\alpha]_D^{25} = -4.3^\circ$ (c 0.94). A sample converted back into S(+)-2-(4-isobutylphenyl)propionic acid as described above had $[\alpha]_D^{25} = +58.7^\circ$ (c 1.116). The enantiomeric purity was found to be at least 99.9%.

EXAMPLE 2

A mixture of S(+)-2-(4-isobutylphenyl)propionic acid (10.3 g, enantiomeric purity 95.9%), acetone (80 ml) and water (8 ml) was warmed to 50° C. A solution of sodium hydroxide (2.2 g) in water (4 ml) was added and the solution cooled. The solid formed was collected by filtration, washed with acetone and dried in air to give S(-)sodium 2-(4-isobutylphenyl)propionate dihydrate (yield 89%). Enantiomeric purity 99%.

EXAMPLE 3

A mixture of S(+)-2-(4-isobutylphenyl)propionic acid (20.6 g, enantiomeric purity 98.6%) and propan-2-ol (100 ml) was heated to 35° C. A solution of sodium hydroxide flakes (4.0 g) in water (15 ml) was added. After cooling to 2° C., the salt which crystallised out was collected by filtration.

13

washed with propan-2-ol (10 ml containing 10% water) then dried in air and finally under vacuum. The S(-)-sodium 2-(4-isobutyphenyl)propionate obtained (yield 74%) was converted into S(+)-2-(4-isobutyphenyl)propionic acid and assayed as described previously. Enantiomeric purity 99.9%.

EXAMPLE 4

A mixture of S(+)-2-(4-isobutyphenyl)propionic acid (20.6 g, enantiomeric purity 98.6%), water (50 ml) and caustic soda flake (4.0 g) was stirred and heated at 60° C. until a solution was obtained. The solution was cooled to 5° C. and the S(-)-sodium 2-(4-isobutyphenyl)propionate dihydrate which crystallised out was collected by filtration and dried under vacuum at 30° C. to give the anhydrous form (yield 53%). The salt was converted into S(+)-2-(4-isobutyphenyl)propionic acid and assayed as described in previously. Enantiomeric purity 99.9%.

EXAMPLE 5

A solution of sodium hydroxide (2.0 g) in water (7 ml) was added to a solution of S(+)-2-(4-isobutyphenyl)propionic acid (10.3 g, enantiomeric purity 98.6%) in acetone (60 ml). Immediate precipitation occurred. The mixture was cooled to 5° C. and the S(-)-sodium 2-(4-isobutyphenyl)propionate dihydrate collected by filtration, washed with acetone (5 ml) then dried in air and finally under vacuum at 35° C. to give the anhydrous form (yield 83%). The salt was converted into S(+)-2-(4-isobutyphenyl)propionic acid and assayed as described previously. Enantiomeric purity 99.8%.

EXAMPLE 6

A mixture of S(+)-2-(4-isobutyphenyl)propionic acid (10.3 g, enantiomeric purity 88%), acetone (80 ml) and water (8 ml) was heated to 50° C. A solution of sodium hydroxide flake (2.5 g) in water (4 ml) was added and the mixture cooled to ambient temperature. The material which crystallised out was collected by filtration and washed with acetone to give S(-)-sodium 2-(4-isobutyphenyl)propionate dihydrate (yield 53.7%). Enantiomeric purity 98.2%.

EXAMPLE 7

A mixture of S(+)-2-(4-isobutyphenyl)propionic acid (10.3 g, enantiomeric purity 98.6%), toluene (25 ml), water (7 ml) and sodium hydroxide (2.0 g) was heated to 80° C. More water (5 ml) was added. The mixture gradually separated into two layers. The lower aqueous layer was separated off and heated to 65° C. Acetone (80 ml) was added dropwise to the stirred warm aqueous layer and the mixture cooled to 5° C. More acetone (20 ml) was added and the mixture stirred at 2°-5° C. for 1 hour. The S(-) sodium 2-(4-isobutyl phenyl) propionate dihydrate formed was collected by filtration, washed with acetone and dried in air to constant weight (yield 78%). The salt was converted into the acid and assayed as described previously. Enantiomeric purity 99.9%.

EXAMPLE 8

A solution of sodium methoxide formed by dissolving sodium (2.3 g) in methanol (30 ml) under reflux was added to a stirred solution of S(+)-2-(4-isobutyphenyl)propionic acid (20.6 g, enantiomeric purity 98.6%) in toluene (150 ml). After the addition more S(+)-2-(4-isobutyphenyl)propionic acid (0.8 g, optical purity 98.6%) was added to adjust the pH to 8. Methanol was removed by distillation

14

until the still head temperature reached 100° C. and then the mixture was cooled to ambient temperature and filtered to give S(-)-sodium 2-(4-isobutyphenyl)propionate (22.4 g, yield 94.5%). The salt was converted into the acid and assayed as described previously. Enantiomeric purity 99.3%.

EXAMPLE 9

Acetone (1080 l) was added to a solution of S(+)-2-(4-isobutyphenyl)propionic acid (211 kg, enantiomeric purity 98.2%) in toluene (850 kg) and the solution filtered. Caustic soda solution (80 kg, SG 1.5) was added over 30 minutes at 50°-55° C. followed by water (77 l). The mixture was cooled to 5° C. and the precipitated solid was collected by filtration, washed with filtered acetone (2x200 l) and dried under vacuum at 50° C. to give S(-) sodium 2-(4-isobutyphenyl)propionate (84.4%, enantiomeric purity 99.95%).

EXAMPLE 10

Caustic soda solution (40 l, SG 1.5) and water (155 l) were added to a solution of S(+)-2-(4-isobutyphenyl)propionic acid (151 kg, enantiomeric purity 97.6%) in toluene (331 kg) and the mixture heated at 50° C. for 0.5 h with stirring. The aqueous phase was separated off and filtered. The organic phase was washed with water (50 l). The combined aqueous phases were heated to reflux and a mixture of residual toluene and water (120 l) was removed by distillation. The aqueous solution was cooled to below 40° C. and filtered acetone (1451 l) was added. The resulting slurry was heated at 55°-60° C. for 0.5 h with stirring. The solution obtained was cooled to 1.5° C. and stirred at this temperature for 1 hour. The mixture was filtered and the residue washed with filtered acetone (2x200 l) and dried under vacuum at 50° C. to remove acetone to give S(-) sodium 2-(4-isobutyphenyl)propionate dihydrate (88.7% yield, enantiomeric purity 99.9%).

The acetone mother liquors (1570 kg) were treated with hydrochloric acid (5 l, SG 1.17) and water (300 l) and heated to 70° C. where acetone (1393 kg) was recovered by distillation. Water (300 l) was added to the residue and a water/acetone azeotrope (107 kg) was removed by distillation at 100° C. The aqueous residues were cooled to 57° C. and then hydrochloric acid (5 l, SG 1.17) and toluene (150 l) were added. The aqueous phase was removed by separation and the toluene phase was washed with water (300 l) at 60° C. The toluene phase containing crude S(+)-2-(4-isobutyphenyl)propionic acid was then reworked to produce more S(-) sodium 2-(4-isobutyphenyl)propionate.

EXAMPLE 11

Hydrochloric acid (76 l, SG 1.18) was added over 15 minutes to a mixture of S(-) sodium 2-(4-isobutyphenyl)propionate (203 kg, enantiomeric purity 99.4%), water (450 ml) and heptane (159 l). The aqueous phase was removed by separation and the heptane solution was washed with de-ionised water (2x200 l) at 30° C. The heptane solution was filtered and added to chilled heptane (159 l) over approximately 1.75 h. The mixture was kept at below -10° C. for 2 hours and the solid collected by filtration and dried under vacuum to give S(+)-2-(4-isobutyphenyl)propionic acid (121.3 kg, 76%, enantiomeric purity, 99.4%).

450
141

15

EXAMPLE 12

Tablets are prepared from the following ingredients:

	mg/tablet	% w/w
Core		
S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate	680	75.2
methocel E30	12	1.3
lactose spray dried	137	15.2
croscarmellose sodium	33	3.7
low substituted hydroxypropyl cellulose	33	3.7
magnesium stearate	9	1.0
Film Coat		
hydroxypropylmethylcellulose	20	
white colouring agent	6	
tin	4	

The drug is granulated with an aqueous solution of methocel. The dried granules are blended with the lactose, croscarmellose sodium, hydroxypropyl cellulose and magnesium stearate. The blend is compressed and then coated using an aqueous solution of the film-coating ingredients.

EXAMPLE 13

(Tablet)

	mg/tablet	% w/w
S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate	512	57.7
tricalcium phosphate	180	20.3
microcrystalline cellulose	60	6.8
polyvinylpyrrolidone	36	4.1
croscarmellose sodium	96	10.8
magnesium stearate	4	0.4

The drug, tricalcium phosphate and microcrystalline cellulose are granulated with a solution of polyvinylpyrrolidone in alcohol. The granules are dried and blended with croscarmellose sodium and magnesium stearate. The blend is compressed using capsule shaped tooling.

EXAMPLE 14

(Tablet)

	mg/tablet	% w/w
Core		
S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate	160	33.2
maize starch	128	44.2
stearic acid	1.6	0.6
Sugar Coat		
varnish layer	1.3	
saccharin powdered	1.3	
refined sugar	112	
calcium sulphate dihydrate	36	
sodium carboxymethylcellulose	0.8	
colouring agent	2.0	
carnauba wax powder	0.2	

The drug and a portion of the maize starch are granulated with a portion of the maize starch as a gel. The mixture is dried and blended with the remaining maize starch and is

16

compressed. The cores are sugar-coated by serial application of varnish, build-up, smoothing and colouring syrups. The tablets are polished with carnauba wax.

EXAMPLE 15

(Melt Filled Capsules)

	mg/capsule	% w/w
S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate	160	32.0
GELUCIRE 44/14	340	68.0

(GELUCIRE is the trademark of Gattefossé)

The drug is dispersed in the molten (GELUCIRE) and filled into hard gelatin capsules.

EXAMPLE 16

(Suppository)

	mg/suppository	% w/w
S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate	430	20.3
WITTEPSOL N 185 (WITTEPSOL is the Trade-mark of Dynamit Nobel)	1000	47.6
WITTEPSOL N 15 (WITTEPSOL is the Trade-mark of Dynamit Nobel)	670	31.9

The drug is dispersed in a mixture of the molten carriers. The mixture is poured into cavities to give a suppository of 2.1 g.

EXAMPLE 17

(Effervescent Tablet)

	mg/tablet	% w/w
S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate	128	11.3
sodium bicarbonate	800	70.7
citric acid	200	17.7
sodium lauryl sulphate	4	0.35

All ingredients are blended together and the resultant mix is compressed. A binding agent and/or a taste-masking component and/or flavouring may optionally be added.

EXAMPLE 18

(Effervescent Granule)

	mg/tablet	% w/w
S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate	512	16.5
pulverised sugar	1000	32.2
malic acid	330	11.3
sodium saccharin	25	0.8
sodium bicarbonate	476	15.3
sodium carbonate	143	4.6
flavour	100	3.2
β -cyclodextrin	300	16.1

All ingredients are dry blended together and are packed into foil sachets to give a dose of 400 mg of S(+)-ibuprofen.

AST
142

17
EXAMPLE 19

(Cold Relief Tablet)

	mg/tablet	% w/w
Core		
S(-)-sodium 2-(4-isobutyloxyphenyl)propionate dihydrate	160	90.6
pseudoephedrine hydrochloride	30	2.9
microcrystalline cellulose	20	6.3
croscarmellose sodium	32	10.1
polyvinylpyrrolidone	12	3.8
tricalcium phosphate	60	19.0
magnesium stearate	2	0.6
Film Coat		
hydroxypropylmethylcellulose	9	
talc	1.6	
yellow colouring agent	3.5	

The sodium salt of S(+)-ibuprofen, tricalcium phosphate, microcrystalline cellulose and croscarmellose sodium are granulated with a solution of polyvinylpyrrolidone in alcohol. The dried granules are blended with the pseudoephedrine hydrochloride and magnesium stearate. The blend is compressed and the cores film-coated using an aqueous solution of the film-former.

EXAMPLE 20

(Topical Gel)

	% w/w
S(-)-sodium 2-(4-isobutyloxyphenyl)propionate dihydrate	3.25
Carbopol 980 NF (1)	2.0
polyethylene glycol 300	10.0
2-phenoxyethanol	1.0
Propylene glycol	5.0
Sodium hydroxide	0.72
Purified water	to 100

(1) CARBOPOL is the registered trademark of B.F. Goodrich.

The polyethylene glycol was mixed with about 25% of the required purified water and the Carbopol® dispersed in this mixture. About 56% of the required purified water was added with rapid stirring until the CARBOPOL® was well dispersed and appeared hydrated. The sodium hydroxide was dissolved in a minimum of purified water and added to the bulk with stirring. The S(+)-ibuprofen sodium salt dihydrate was dissolved in a mixture of phenoxyethanol, propylene glycol and remaining purified water and added to the Carbopol® gel with rapid stirring.

A clear gel of a viscosity suitable for use as a topical rub was produced. The inclusion of the free S(+)-ibuprofen acid in the above formulation gave an opaque product of a high viscosity not suitable for use as a topical rub.

The inclusion of a dose equivalent amount of the sodium salt of ibuprofen racemate in the formulation produced a totally unsatisfactory product that separated into a clear upper liquid and a cloudy viscous lower layer.

18
EXAMPLE 21

(Topical Gel)

	%
S(-)-sodium 2-(4-isobutyloxyphenyl)propionate dihydrate	4.27
polyethylene glycol 300	10
carboxamer	1
2-phenoxyethanol	1
triethanolamine	1.35
propylene glycol	5
purified water	to 100

Polyethylene glycol, phenoxyethanol and propylene glycol are added to a portion of water and mixed. The drug is added and then the carboxamer is dispersed. The carboxamer is gelled by addition of triethanolamine in the remaining water.

EXAMPLE 22

(Sustained Release Tablet)

	mg/tablet	% w/w
S(-)-sodium 2-(4-isobutyloxyphenyl)propionate dihydrate	641	52.1
xanthan gum	227	18.45
polyvinylpyrrolidone	20	1.6
stearic acid	9	0.7
colloidal silicon dioxide	3	0.2

The sodium salt and a portion of the xanthan gum are granulated with a solution of the polyvinylpyrrolidone in isopropanol. The other ingredients and the remainder of the xanthan gum are blended into the mixture which is then compressed into tablets. The tablets may optionally be film-coated.

EXAMPLE 23

(Oral Liquid Low Strength)

	% w/w
S(-)-sodium 2-(4-isobutyloxyphenyl)propionate dihydrate	1.30
LYCASIN® 80/55 (1)	40.0
glycerin	20.0
dimiphen bromide	0.005
alcohol 96%	2.0
purified water	to 100

(1) LYCASIN is the registered trademark of Roquette.

The LYCASIN® and glycerin were mixed together. The dimiphen bromide was dissolved in the alcohol. The sodium salt was added to this alcoholic solution along with sufficient purified water to produce a solution. The aqueous alcoholic solution was added to the LYCASIN®/glycerin mixture and mixed well. Optional flavourings may be added to the above formulation.

S(+)-ibuprofen free acid, when included in the above formulation, gave a poor product with a significant proportion of the S(+)-ibuprofen floating on the surface of the product. The sodium salt gave a bright clear product.

AS7
143

19
EXAMPLE 24

(Oral Liquid (Low Strength))

	%
S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate	1.6
xylytol	35
glycerin	20
xanthan gum	0.35
dexamphen bromide	0.005
alcohol 96%	2.0
flavour	0.1
menthol	0.01
purified water	to 100

The xylytol is dissolved in half of the water, the xanthan gum is dispersed and allowed to hydrate, then the glycerin, the sodium salt of S-(+)-ibuprofen, the dexamphen bromide and the saccharin sodium are added. The menthol and flavour are dissolved in alcohol and added to bulk. Water is added to make up the volume.

EXAMPLE 25

(Higher Strength Oral Liquid)

	% w/w
S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate	2.6
LYCAsIN ® 80/55 (1)	40.0
glycerin	20.0
dexamphen bromide	0.005
alcohol 96%	2.0
purified water	to 100

(1) LYCAsIN is the registered trademark of Roquette.

The LYCAsIN® and glycerin were mixed together and diluted with a suitable volume of water. The sodium salt was dispersed and dissolved in the mixture. The dexamphen bromide was dissolved in the alcohol and this solution added slowly with stirring to the bulk. The formulation was made up to volume and mixed well. Optional flavourings may be added to the formulation.

The inclusion of S-(+)-ibuprofen free acid in the above formulation gave an unpalatable product with the drug floating on the surface. The sodium salt produced a clear bright liquid.

EXAMPLE 26

(Oral Liquid (High Strength))

	%
S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate	3.2
LYCAsIN ®	40
glycerin	20
dexamphen bromide	0.005
flavour	0.2
alcohol 96%	2.0
purified water to	100

This is prepared in a similar manner to Example 24.

20
EXAMPLE 27

(Cold Relief Powder (Hot Drink))

	mg/sachet	% w/w
S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate	130	6.3
β -cyclodextrin	441	22.0
paracetamol hydrochloride	30	1.5
sodium saccharin	20	1.0
powdered sugar	to 2000	to 100

The powders were sieved through a 30 mesh sieve and blended together, then filled into sachets containing 2000 mg of powder. Optional flavourings may be added to the above mixture. On addition to hot water (70° C. or greater) a clear solution is produced which can be drunk by the patient.

In the same formulation base S-(+)-ibuprofen produced an unpalatable oily layer on the surface of the hot water.

EXAMPLE 28

(Cold Relief (Hot Water Drink))

	mg/sachet	% w/w
S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate	160	4.6
paracetamol hydrochloride	30	0.9
sodium saccharin	20	0.6
β -cyclodextrin	1000	28.4
powdered sugar	2000	57.0
flavour	300	8.6

The ingredients are dry blended together and packed into sachets.

In Examples 12-28, S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate may be replaced by the anhydrous form or other hydrated forms.

EXAMPLE 29

A solution of sodium hydroxide (0.65 g) in water (5 ml) was added to a stirred solution of R(-)-2-(4-isobutylphenyl)propionic acid (4.1 g) in acetone (200 ml). The mixture was stirred at ambient temperature for 30 minutes and the solid which crystallised was collected by filtration, washed with acetone and dried in air. This material was dissolved in hot water (6 ml) and stirred while acetone (200 ml) was added. The material which crystallised was collected by filtration and dried in air to give R(+)-sodium 2-(4-isobutylphenyl)propionate dihydrate mp. 220°-221° C. $[\alpha]_D^{25} +4.0^\circ$ (c 0.934).

EXAMPLE 30

(Tablet)

	mg/tablet	% w/w
S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate	760	66.0
microcrystalline cellulose	200	18.9
croscarmellose sodium	32	2.9
lactose	84	7.6

143
144

21

-continued

	mg/tablet	% w/w
colloidal silicon dioxide	1	0.1
magnesium stearate	6	0.6

All the ingredients were blended together and the resultant mixture compressed into tablets (Tablet A).

The properties of the above tablets were compared with tablets containing the same excipients in the same amounts as indicated above, but replacing the S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate with 600 mg S(+) 2-(4-isobutylphenyl)propionic acid (comparative Tablet A).

The pressure at which the tablets were compressed is indicated in the table below. The hardness of the resultant tablets was measured. The disintegration time was measured by the method of the British Pharmacopoeia 1980 and the dissolution time was measured using Apparatus 2 described in US Pharmacopoeia XXII, section 711, p1578, with 900 ml of a phosphate buffer of the pH's indicated and a paddle speed of 50 revolutions per minute.

	Pressure (KN)	Hardness (Kg)	Disinte- gration Time	Dissolution Time (minutes)			
				pH 7.2	pH 6.0	pH 7.2	pH 6.0
Tablet A	11.0	4.72	10 m	9.1	16.0	—	—
	17.2	5.98	—	—	—	8.7	13.8
Comparative Tablet A	11.0	2.65	18 s	6.3	19.0	—	—
	16.4	3.15	—	—	—	34.1	NA

s = seconds
m = minutes
NA = not obtained
T₅₀ = time taken for 50% of active ingredient to be released from the tablet
T₉₀ = time taken for 90% of active ingredient to be released from the tablet

From the results obtained it can be seen that Tablet A gave harder tablets than comparative Tablet A when compressed at the same pressure, and that Tablet A had a longer disintegration time and comparable dissolution at pH 7.2 but superior dissolution at pH 6.0.

EXAMPLE 31
(Tablet)

	mg/tablet	% w/w
S(-)-sodium 2-(4-isobutylphenyl)- propionate dihydrate	600	61.3
tricalcium phosphate	180	18.4
microcrystalline cellulose	60	6.1
croscarmellose sodium	96	9.8
povidone	36	3.7
stearic acid	6	0.6

The povidone was dissolved in a mixture of isopropanol and water (1:1 parts by volume). The S(-) sodium 2-(4-isobutylphenyl)propionate dihydrate was blended with the tricalcium phosphate, microcrystalline cellulose and croscarmellose sodium and then granulated with the solution of povidone. The granules were dried, sized, blended with the stearic acid and then compressed into tablets (Tablet B).

The properties of the above tablets were compared with tablets containing the same excipients in the same amounts

22

as indicated above, but replacing the S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate with 600 mg S(+) 2-(4-isobutylphenyl)propionic acid (comparative Tablet B).

The dissolution time of the resultant tablets was measured at pH 6 using the method described in Example 30.

	Dissolution time (minutes)	
	T ₅₀	T ₉₀
Tablet B	9.1	34.1
Comparative Tablet B	21.4	NA

NA = not obtained
T₅₀ = time taken for 50% of active ingredient to be released
T₉₀ = time taken for 90% of active ingredient to be released

It can be seen that Tablet B shows a superior dissolution performance compared with comparative Example B.

We claim:

1. A solid or semi-solid pharmaceutical composition comprising S(-) sodium 2-(4-isobutylphenyl)-propionate salt having an enantiomeric purity of at least 90% as the sole form of 2-(4-isobutylphenyl)-propionate together with a pharmaceutically acceptable carrier.
2. A composition as claimed in claim 1 wherein the S(-)-sodium 2-(4-isobutylphenyl)propionate is present as the dihydrate.
3. A solid composition according to claim comprising:
 - (a) 10-99% w/w S(-)-sodium 2-(4-isobutylphenyl)propionate;
 - (b) 1-90% w/w of a diluent;
 - (c) 0.1-10% w/w of a lubricating agent;
 - (d) 0.1-15% w/w of a disintegrating agent and optionally
 - (e) 0.1-15% w/w of a binder.
4. A composition according to claim 3 in the form of a tablet or granules.
5. A composition according to claim 1 in the form of a capsule comprising:
 - a) 10-80% w/w S(-) sodium 2-(4-isobutylphenyl)propionate, and
 - b) 20-90% w/w of a fatty acid ester excipient which comprises one or more polyol esters and glycerides of natural vegetable oil fatty acids.
6. An effervescent composition according to claim 1 comprising a) 1-30% w/w S(-) sodium 2-(4-isobutylphenyl)propionate and b) an effervescent couple.
7. A composition according to claim 6 in the form of granules or tablet.
8. A semi-solid composition according to claim 1 in the form of a cream, an ointment or a gel.
9. A gel according to claim 8 comprising:
 - a) 1-15% w/w S(-) sodium 2-(4-isobutylphenyl)propionate;
 - b) 1-20% w/w of a gelling agent;
 - c) 0.01-10% w/w of a preservative; and
 - d) water to 100% w/w.
10. A topical composition according to claim 1 in the form of a poultice or a patch.
11. A composition according to claim 1 in the form of a suppository comprising 10-30% w/w S(-) sodium 2-(4-isobutylphenyl)propionate and 70-90% w/w of a carrier.
12. A process to prepare a composition according to claim 1 comprising combining S(-)-sodium 2-(4-isobutylphenyl)propionate having an enantiomeric purity of at least 90% in solid form with a pharmaceutically acceptable carrier and formulating into a dosage form.

1574
145

23

13. A pharmaceutical composition according to claim 1 for use in the treatment of pain comprising S(-)-sodium 2-(4-isobutyphenyl)propionate having an enantiomeric purity of at least 90% and at least one further pharmacologically active ingredient.

14. A pharmaceutical composition according to claim 1 comprising S(-)-sodium 2-(4-isobutyphenyl)propionate having an enantiomeric purity of at least 90% and at least

24

one pharmacologically active ingredient selected from an antihistamine, a cough suppressant, a decongestant, an expectorant and a muscle relaxant.

15. The pharmaceutical composition of claim 1 in the form of a unit dose.

* * * * *



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United States Patent [19]
Mauskop

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[54] **ANALGESIC COMPOSITION FOR TREATMENT OF MIGRAINE HEADACHES**

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[58] **Field of Search** 424/44, 682, 692, 424/464.5; 514/165, 224.5, 350, 568, 728, 812

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[57] **ABSTRACT**

Magnesium-containing analgesic compositions used for the alleviation of pain, in particular, migraine headache pain, and methods for using the same are described herein. The compositions consist essentially of an analgesic agent, a magnesium salt, a stimulant, optionally an effervescing agent, and a pharmaceutically acceptable carrier or vehicle. The symptoms of migraine headache intended to be alleviated include nausea, unilateral pain, dizziness, pulsatile pain, worsening of pain by light physical activity, photophobia and phonophobia.

28 Claims, No Drawings

ANALGESIC COMPOSITION FOR TREATMENT OF MIGRAINE HEADACHES

FIELD OF THE INVENTION

This invention relates to magnesium-based analgesic compositions for treating migraine headaches, and methods for using the same.

BACKGROUND OF THE INVENTION

Analgesic compositions comprising magnesium salts have been used to treat a variety of ailments as well as reduce the gastric irritancy often accompanying the oral administration of such analgesic compositions. U.S. Pat. 2,801,951 to Cooper, Jr. discloses the use of an analgesic composition comprising acetylsalicylic acid, citric acid, p-ethoxyacetanilide, caffeine and $MgCO_3$ or $Mg(OH)_2/Al(OH)_3$. U.S. Pat. No. 3,865,933 to Mudge teaches the use of a mixture comprising magnesium gluconate, stramonium extract and 3-(2-methylphenoxy)-1,2-propanediol to relieve headache pain. U.S. Pat. No. 3,759,980 to Rosen et al. teaches the use of a mixture of magnesium salicylate and choline salicylate as an analgesic, anti-pyretic, anti-inflammatory and anti-rheumatic agent. U.S. Pat. No. 3,385,886 to Nicholson et al. teaches the use of phenylpropionic acid magnesium salts for the relief of pain, fever and inflammation. U.S. Pat. No. 3,359,166 to McClure teaches the use of magnesium 4-thiazolidinecarboxylate as an analgesic agent. U.S. Pat. No. 4,083,951 to Goudie et al. teaches the use of magnesium acetylsalicylate in conjunction with sodium bicarbonate as an analgesic having reduced gastric irritancy properties. U.S. Pat. No. 4,217,340 to Tobert discloses the use of a phenylbenzoic acid compound and magnesium hydroxide for treating pain and inflammation. Such compositions have employed magnesium salts for their solubility, absorption properties and buffering effects.

A deficiency of magnesium, i.e., hypomagnesemia, has been suggested to play a role in migraine headaches (B.A.

Altura, *Magnesium*, 4:169 (1985); A. Mauskop et al., *Cephalalgia*, 14:241 (1994)). It had been shown that low serum ionized magnesium (IMg^{2+}) levels were found in 42 % of patients suffering migraine headaches (A. Mauskop et al., *Headache*, 33(3):135 (1993)). The magnesium salt of pyrrolidone carboxylic acid has been used to treat women with premenstrual migraine headache (F. Facchinetti et al., *Headache*, 31(5):298 (1991)). Amino-chelated magnesium compounds have been used to treat patients with classic migraine headache (K. Weaver in "Letter to the Editor," *Headache*, 30(2):168 (1990)). In addition, Mg^{2+} has been known to regulate the function of N-methyl-D-aspartate receptors (A. C. Foster et al., *Nature* (London), 329:395 (1987)), which are essential for pain transmission.

When some magnesium-based compositions are administered to patients having migraines, severe headaches or other painful conditions, the slowing of gastric motility which often accompanies these conditions delays the absorption of any medication taken orally. Such a delay in absorption is often more pronounced with tablet than with liquid medicaments. As a result, the onset of action associated with such compositions administered to migraine patients is undesirably delayed, resulting in the prolongation of pain and discomfort to the patient. Thus, there remains a need for compositions which can be used for treating migraine headaches and which are rapidly absorbed and provide rapid onset of action.

In addition, because migraine headache is believed to be, at least in part, stress-induced, patients who suffer from

migraine headaches often experience other secondary pain, e.g., muscle ache, joint stiffness, eye strain and jaw problems, associated with stress-related muscle tension. Where the patient is elderly or has still other painful health conditions, the combination with migraine and such secondary pain described above can be overwhelming. Thus there is a need for compositions which can be used for treating migraine headaches which contain analgesics or other compounds known to relieve pain.

Moreover, oral administration of compositions comprising magnesium salts often results in the unwanted side effect of constipation, a feeling of bloatedness and short-term loss of appetite. Thus there is a need for compositions which can be used for treating migraine headaches which contain magnesium salts and do not give produce the above-described side effects following administration.

Citation or identification of any reference in this section shall not be construed as an admission that such reference is available as prior art to the present application.

SUMMARY OF THE INVENTION

The present invention relates to a method for treatment of migraine headaches which comprises orally administering to a person in need of such treatment a rapidly absorbed magnesium- and effervescent agent-containing analgesic composition in an amount effective to relieve at least some symptoms of such headaches. Such compositions include various proportions of an analgesic agent, a magnesium salt and an effervescent agent.

Prior to ingestion, such compositions are admixed with or dissolved in water, preferably in about 2-10 ounces of water. Such compositions are ingested as their aqueous admixture or solution, preferably within 1-2 minutes of admixture or dissolution.

The invention further relates to pharmaceutical compositions for alleviating pain, consisting essentially of a therapeutically effective amount of one or more magnesium salt, stimulant, and analgesic agent; and a pharmaceutically acceptable carrier or vehicle, wherein the composition is rapidly absorbed when orally administered.

The invention still further relates to pharmaceutical compositions for alleviating pain, consisting essentially of a therapeutically effective amount of one or more magnesium salt, stimulant, analgesic agent and effervescent agent; and a pharmaceutically acceptable carrier or vehicle, wherein the composition is rapidly absorbed when orally administered.

The present invention may be understood more fully by reference to the following detailed description and illustrative examples which are intended to exemplify non-limiting embodiments of the invention.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, improved absorption and hence improved onset of action, as well as improved analgesia, of a preparation for treating a patient with a migraine headache can be achieved by administering to a patient with a migraine headache a magnesium-containing analgesic composition.

Such analgesic agents which can be included in the magnesium-containing analgesic compositions of the present invention include, but are not limited to, at least one or more non-opioid analgesic agent such as acetylsalicylic acid acetaminophen, paracetamol, ibuprofen, ketoprofen, ketoclonazole, indomethacin, diflunisal, naproxen, ketorolac,

3

dichlophenac, tolmetin, sulindac, phenacetin, piroxicam, mefenamic acid, dextromethorphan, other non-steroidal anti-inflammatory drugs including salicylates, pharmaceutically acceptable salts thereof and mixtures thereof; or at least one or more opioid analgesic agent such as codeine, morphine, hydromorphone, levorphanol, meperidine, meptazinol, propoxyphene, propiram, buprenorphine, pentazocine, nalbuphine, butorphanol, tramadol, hydrocodone, oxycodone, methadone, pharmaceutically acceptable salts thereof and mixtures thereof. Such pharmaceutically acceptable salts include, but are not limited to hydrochloride, hydrobromide, phosphate, sulfate, acetate, succinate, ascorbate, tartrate, gluconate, benzoate, malate, fumarate, and the like. In addition, the present compositions can contain a combination of a non-opioid analgesic agent and an opioid analgesic agent, i.e., a mixture of at least one or more non-opioid analgesic agent, and at least one or more opioid analgesic agent.

The analgesic agent(s) of the magnesium-containing analgesic compositions of the present invention are useful for relieving pain, in particular pain associated with migraine symptoms, as well as pain associated with non-migraine illnesses aggravated by migraine pain. In the former instance, it is believed that the combination of a magnesium salt and the analgesic agent(s) exert(s) a synergistic effect for relieving pain and related migraine symptoms. In addition, the analgesic agent(s) can relieve pain associated with non-migraine illnesses. Common examples include muscle aches, joint stiffness, eye strain and jaw problems associated with stress-related muscle tension, as well as pain derived from non-stress related conditions. Where the pain is less than severe, non-opioid analgesics are preferred. Preferably, the non-opioid analgesics used in the present magnesium-containing analgesic compositions are acetaminophen or ibuprofen, or mixtures thereof.

Where the patient suffering from an illness, particularly a migraine headache, has particularly severe pain, or has additional pain from a non-migraine illness such that the combination of pain is judged to be severe, it may be necessary that the analgesic component of the magnesium-containing analgesic composition include an opioid analgesic capable of provided relief from severe pain. Such a regimen is also useful where the patient has a terminal illness such that liabilities resulting from long-term administration of an opioid are outweighed by the interest in the patient's short-term comfort.

In a particular embodiment of the invention, the magnesium-containing analgesic compositions include more than one analgesic agent, i.e., at least two different non-opioid analgesic agents, at least two different opioid analgesic agents, or at least one non-opioid analgesic agent and at least one opioid analgesic agent. It is believed that combinations of non-opioid analgesic agents, or opioid analgesic agents, or both, act synergistically to relieve pain.

The magnesium component of the magnesium-containing analgesic compositions of the present invention is ionic magnesium (i.e., Mg^{2+}). Suitable sources of Mg^{2+} are magnesium salts which include, but are not limited to magnesium chloride, magnesium citrate, magnesium tartrate, magnesium oxide, magnesium carbonate, magnesium sulfate, magnesium hydroxide and mixtures thereof. It is to be understood that the present compositions can include one or more magnesium salt. Where an analgesic agent to be included in the magnesium-containing compositions is a carboxylic acid, the magnesium salt can be a magnesium salt of that analgesic agent carboxylic acid. For example, if the analgesic agent is acetylsalicylic acid, the magnesium salt

4

can be magnesium acetylsalicylate. This is convenient in combining both important components within a single compound. When a magnesium salt of an analgesic is included in the magnesium-containing analgesic composition of the present invention, an additional analgesic may or may not be included.

It is advantageous for the compositions to be rapidly absorbed by the subject or patient following oral administration. By "rapidly absorbed" is meant that the present compositions are absorbed through the gastrointestinal tract within about 5 to about 20 minutes following ingestion.

There are a number of ways to formulate such compositions to achieve rapid absorption, and one of ordinary skill in the art would be aware of such ways. Generally, encapsulating the active ingredient or employing other forms of delaying the release of the agent into the subject should be avoided, except when such means to delay release are included in combination with a rapidly absorbed form of such agent. This could be used, for example, when the composition is intended to provide both a rapidly absorbed initial administration of the analgesic agent, followed by a delayed release of longer duration administered for continued relief of headache symptoms.

In one embodiment of a rapidly absorbable magnesium-containing analgesic composition, one or more effervescent agent is included. By "effervescent agent" is meant any compound which, upon dissolution in water, provides effervescence to the aqueous mixture or solution upon release of carbon dioxide. Such effervescent agents include, but are not limited to, alkali or alkaline earth metal carbonates, bicarbonates or mixtures thereof, including, but not limited to sodium carbonate, sodium bicarbonate, sodium glycine carbonate, calcium carbonate and magnesium carbonate. Preferably, at least one of the effervescent agents is sodium bicarbonate.

In another embodiment of the invention, the magnesium-containing compositions include one or more stimulant, such as methamphetamine, dexamphetamine, methylphenidate, pemoline and preferably, caffeine, and mixtures thereof. Inclusion of a stimulant, inter alia, allows the present compositions to be rapidly absorbed. Without being bound to any particular theory, it is believed that such stimulants, particularly caffeine, stimulate gastric secretion and accordingly enhance absorption through the small intestine. In the case of caffeine, it is believed that magnesium cation forms a relatively stable chelate therewith, such that the caffeine serves to rapidly deliver the magnesium to the small intestine and increase its rate of absorption. Thus, the stimulant component serves to confer rapid absorption properties to the present compositions. In addition, it is believed that caffeine itself has analgesic properties (see Federal Register, 42(131):35482-35485 (1977)) which can serve to diminish the discomfort of pain, particularly pain associated with migraine headaches.

In addition to serving as a means to enhance the absorption of the present magnesium-containing analgesic compositions, the inclusion of a stimulant also serves to diminish the discomfort of constipation or a feeling of bloatedness, or relieve the temporary loss of appetite often following ingestion of opioids, which are known to be binding and are known to produce the aforementioned side effects, and counteract the gastric stasis associated with migraine headaches. In this regard, a stimulant diminishes or relieves the discomfort of these side effects by moderately stimulating peristalsis. It is within the purview of one skilled in the art to tailor the present compositions so as to provide the optimal dosage of stimulant.

5

Moreover, the inclusion of a stimulant serves to counteract the sedative, or in extreme cases where an analgesic is an opioid analgesic, hallucinatory effects of the analgesic. In other words, the incorporation of a stimulant improves the patient's motor coordination, alertness and overall sense of well being.

It is to be understood that the present magnesium-containing analgesic compositions can include both an effervescing agent and a stimulant, so as to further enhance the absorbability of the present compositions.

The magnesium-containing analgesic compositions further include a pharmaceutically acceptable carrier or vehicle. Such carriers or vehicles are known to those skilled in the art and are found, for example, in *Remington's Pharmaceutical Sciences*, 14th Ed. (1970). Examples of such carriers or vehicles include lactose, starch, dicalcium phosphate, calcium sulfate, kaolin, mannitol and powdered sugar. Additionally, when required, suitable binders, lubricants, disintegrating agents and coloring agents can be included. If desired, dyes, as well as sweetening or flavoring agents can be included.

The magnesium-containing analgesic compositions may optionally include accessory ingredients including, but not limited to dispersing agents such as microcrystalline cellulose, starch, cross-linked poly(vinyl pyrrolidone), and sodium carboxymethyl cellulose; flavoring agents; coloring agents; binders; preservatives; surfactant and the like.

The non-opioid analgesic agent(s) is (are) advantageously present in the magnesium-containing compositions at levels ranging from about 10 to about 90 wt. %, preferably about 10 to about 75 wt. %.

The opioid analgesic agent(s) is (are) present in the magnesium-containing compositions at levels ranging from about 0.5 to about 20 wt. %, preferably from about 1 to about 15 wt. %.

It is to be understood that the present compositions can contain an analgesic agent such that the analgesic agent is a mixture of one or more non-opioid analgesic agent and one or more non-analgesic agent. In such a case, the non-opiate analgesic agent(s) is (are) present in the magnesium-containing compositions at levels ranging from about 10 to about 90 wt. %, preferably about 10 to about 75 wt. %; and the opioid analgesic agent(s) is (are) present in the magnesium-containing compositions at levels ranging from about 0.5 to about 20 wt. %, preferably from about 1 to about 15 wt. %.

When added as a separate component, i.e., not as a magnesium salt of an analgesic agent, the magnesium salt(s) is (are) present in the magnesium-containing compositions at levels ranging from about 5 to about 30 wt. %, preferably from about 10 to about 30 wt. %. When a single compound of a magnesium salt of the analgesic agent is used, the amounts of such a single compound would be between about 20 and 95 wt. % of the composition.

When present, the effervescing agent(s) is (are) present in the magnesium-containing compositions at levels ranging from about 20 to about 80 wt. %, preferably from about 25 to about 75 wt. %.

The stimulant(s) is (are) present in the magnesium-containing analgesic compositions at levels ranging from about 1 to about 25%, preferably from about 5 to about 20 wt. %.

Of course, the total amounts of these components would be 100 wt. %, and those of ordinary skill in the art can vary the amounts within the stated ranges to achieve useful compositions.

6

The intended route of administration of the magnesium-containing analgesic compositions of the present invention is oral, wherein the composition including an effervescing agent is admixed with or dissolved in a pre-determined amount of an aqueous vehicle, such as for example water, prior to ingestion. The present compositions not including effervescing agents are not admixed with or dissolved in water prior to administration.

Compositions of the present invention which are suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets, as a powder or granules; as a solution or a suspension in an aqueous liquid or non-aqueous liquid; or an oil-in-water or water-in-oil liquid emulsion. Preferably, the compositions of the present invention is presented in liquid, capsule, or most preferably, tablet form. Such tablets may be conventionally formed by compression or molding. Compressed tablets may be prepared by compressing in a suitable machine the mixture of one or more analgesic, magnesium salt, stimulant, optionally an effervescing agent, and a pharmaceutically acceptable carrier or vehicle described above. Molded tablets may be made by molding in a suitable machine the above mixture which can optionally be moistened with an inert liquid diluent. The tablets may optionally be coated or scored, having indicia inscribed thereupon, and may be so formulated as to provide slow or controlled release of the analgesic, magnesium or effervescing compounds therein.

Such tablets can range in weight from 25-2000 mg., preferably from 100-1000 mg., and most preferably from 250-1500 mg.

Prior to ingestion, compositions comprising effervescing agents are admixed or dissolved in about 2-10 ounces of an aqueous carrier such as water, preferably about 4-8 ounces of water. The compositions of the present invention are ingested as their aqueous admixture or solution within 2 minutes, preferably within 1 minute, of their admixture with or dissolution in water, so as to maximize their effervescence and hence absorptive properties.

Compositions not comprising effervescent agents are ingested, in the case of liquid compositions, neat (undiluted), and in the case of capsules or tablets, swallowed whole, preferably with water.

The compositions of the present invention are administered shortly after the onset of migraine symptoms. Such symptoms include nausea, unilateral pain, dizziness, pulsatile pain, worsening of pain by light activity, photophobia and phonophobia.

Administration can continue every 2-6 hours, preferably every 4 hours until migraine symptoms have subsided. In patients who suffer from chronic migraine headaches, a daily administration of 1000 mg. of the magnesium-containing compositions four times per day of the present invention is advantageous.

The following series of examples are presented by way of illustration and not by way of limitation on the scope of the invention.

160
150

7
EXAMPLES OF MAGNESIUM-CONTAINING
ANALGESIC COMPOSITIONS

EXAMPLE 1

Magnesium-Containing Analgesic Composition A

Ingredient	mg./Tablet
Acetylsalicylic Acid	800
Magnesium Chloride	250
Sodium Bicarbonate	500
Poly(ethylene Glycol) 4000	50

EXAMPLE 2

Magnesium-Containing Analgesic Composition B

Ingredient	mg./Tablet
Magnesium Acetylsalicylic Acid	1000
Sodium Bicarbonate	350
Citric Acid	75

EXAMPLE 3

Magnesium-Containing Analgesic Composition C

Ingredient	mg./Tablet
Acetaminophen Na Salt	1000
Magnesium Trisilicate	200
Magnesium Carbonate	200

EXAMPLE 4

Magnesium-Containing Analgesic Composition D

Ingredient	mg./Tablet
Ibuprofen	400
Magnesium Chloride	225
Caffeine	80
Carboxymethyl cellulose	50

EXAMPLE 5

Magnesium-Containing Analgesic Composition E

Ingredient	mg./Tablet
Magnesium Acetylsalicylic Acid	1000
Methamphetamine	75
Starch	75

8
EXAMPLE 6

Magnesium-Containing Analgesic Composition F

Ingredient	mg./Tablet
Acetaminophen Na Salt	1000
Magnesium Trisilicate	200
Magnesium Carbonate	200
Caffeine	100
Codeine Sulfate	45

EXAMPLE 7

Magnesium-Containing Analgesic Composition G

Ingredient	mg./Tablet
Ibuprofen	500
Magnesium Chloride	225
Caffeine	80
Carboxymethyl cellulose	50
Sodium Bicarbonate	500

EXAMPLE 8

Magnesium-Containing Analgesic Cocktail

The tablet of Examples 1-3, 6 or 7 is added to 8 ounces of tap water. The resulting cocktail is ingested within 1 minute of admixture with or dissolution in water.

EXAMPLE 9

Results of Administration of Magnesium-Containing Analgesic Cocktail to Patients with Migraine Headaches

Methods

Five subjects were selected to participate in this study. Included were patients who had daily, but not necessarily continuous migraine headaches. Patients could have had headache-free periods lasting for hours and on a rare occasion for a day. Average severity of headaches prior to and two hours following administration of the magnesium-containing analgesic cocktail described below were assessed on a 1 to 10 verbal scale. Patients taking acetaminophen or non-steroidal anti-inflammatory drugs were excluded from this study.

Magnesium-Containing Analgesic Cocktail

Three tablets each having the following formulation:

Ingredient	mg./Tablet
Acetylsalicylic acid	325
Sodium Bicarbonate	1916

were dissolved in a solution of 500 mg of magnesium sulfate in 7 ounces of water and administered to each of five patients suffering migraine headache by ingestion of the resulting cocktail within 1 minute of dissolution of each of the three tablets. The results, compiled from a survey of each patient taken 2 hours following ingestion of the cocktail are shown below in Table 1:

TABLE I

RESULTS				
N	Age	Sex	Severity Prior to Administration	Severity Following Administration
1	33	F	10	4
2	35	F	7	2
3	14	F	8	3
4	59	F	7	1
5	30	M	8	2

Thus for all patients included in this study, the administration of the above-described magnesium-containing analgesic composition significantly reduced the severity of migraine headaches.

EXAMPLE 10

Reduction of Migraine Symptoms Following Intravenous Administration of MgSO₄

Methods

Forty consecutive patients (3 men and 37 women) who presented with an acute migraine but did not have renal, cardiac or other medical problems were administered with 1 g. of MgSO₄ in a 10% saline solution intravenously, over 5 minutes. Patients remained in a recumbent position during the infusion and for 5 minutes after the infusion. Headache intensity was measured on a verbal 1 to 10 scale before, and 15 minutes after, the infusion. The recurrence or worsening of a headache within the following 24h was determined using the verbal 1 to 10 scale in a telephone interview. A greater than 50% reduction of pain intensity lasting at least 24h was considered a positive response.

Results

Of the 40 patients, 35 (87.5%) had a reduction of pain of 50% or more 15 minutes after the infusion. This included 9 patients who experienced complete relief. In 21 of these 35 patients, at least this degree of improvement or complete relief persisted for 24h or more (positive response).

Thus, the administration of magnesium salt is effective at relieving the symptoms of migraine headache.

The magnesium-containing analgesic compositions of the present invention can be used to treat patients with migraine headaches. It is to be understood that such uses are not limited to treating the symptoms of migraine headaches but rather include treating other maladies including non-migraine headache pain, muscular pain, fever associated with viral or bacterial infection, thrombotic diathesis, magnesium deficiency and gastric discomfort.

The present invention is not be limited in scope by the specific embodiments disclosed in these examples which are intended to illustrate the most preferred embodiments of the invention. Indeed, various modifications of the invention or other embodiments which are functionally equivalent to those shown and described herein will become apparent to those skilled in the art and are intended to be covered by the appended claims.

A number of references have been cited, the entire disclosures of which are incorporated herein by reference.

What is claimed:

1. A pharmaceutical composition for the alleviation of pain, associated with migraine headache consisting essentially of a therapeutically effective amount of one or more

magnesium salt, one or more stimulant selected from the group consisting of methamphetamine, dexamphetamine, methylphenidate, pemoline, caffeine and mixtures thereof, and one or more analgesic agent selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, ketoprofen, ketoconazole, indomethacin, diflunisol, naproxen, ketorolac, dichlophenac, tolmetin, sulindac, phenacetin, piroxicam, mefamanic acid, dextromethorphan, codeine, morphine, hydromorphone, levophanol, meperidine, meptazinol, propoxyphene, yopiram, buprenorphine, pentazocine, nalbuphine, butorphanol, tramadol, hydrocodone, oxycodone and methadone, pharmaceutically acceptable salts thereof, and mixtures thereof; and a pharmaceutically acceptable carrier or vehicle, wherein the composition is orally administered.

2. The composition of claim 1, wherein at least one of the one or more analgesic agent is a non-opioid analgesic agent.

3. The composition of claim 2, wherein the non-opioid analgesic agent is selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, ketoprofen, ketoconazole, indomethacin, diflunisol, naproxen, ketorolac, dichlophenac, tolmetin, sulindac, phenacetin, piroxicam, mefamanic acid, dextromethorphan, salicylates, pharmaceutically acceptable salts thereof, and mixtures thereof.

4. A pharmaceutical composition for the alleviation of pain, associated with migraine headache consisting essentially of a therapeutically effective amount of one or more magnesium salt, one or more stimulant, and one or more analgesic agent selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, ketoprofen, ketoconazole, indomethacin, diflunisol, naproxen, ketorolac, dichlophenac, tolmetin, sulindac, phenacetin, piroxicam, mefamanic acid, dextromethorphan, codeine, morphine, hydromorphone, levophanol, meperidine, meptazinol, propoxyphene, propiram, buprenorphine, pentazocine, nalbuphine, butorphanol, tramadol, hydrocodone, oxycodone and methadone, pharmaceutically acceptable salts thereof, and mixtures thereof, wherein at least one of the one or more analgesic agent is an opioid analgesic agent; and a pharmaceutically acceptable carrier or vehicle, wherein the composition is orally administered.

5. The composition of claim 4, wherein the opioid analgesic agent is selected from the group consisting of codeine, morphine, hydromorphone, levophanol, meperidine, meptazinol, propoxyphene, propiram, buprenorphine, pentazocine, nalbuphine, butorphanol, tramadol, hydrocodone, oxycodone and methadone, pharmaceutically acceptable salts thereof, and mixtures thereof.

6. A pharmaceutical composition for the alleviation of pain, associated with migraine headache consisting essentially of a therapeutically effective amount of one or more magnesium salt, one or more stimulant, and one or more analgesic agent selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, ketoprofen, ketoconazole, indomethacin, diflunisol, naproxen, ketorolac, dichlophenac, tolmetin, sulindac, phenacetin, piroxicam, mefamanic acid, dextromethorphan, codeine, morphine, hydromorphone, levophanol, meperidine, meptazinol, propoxyphene, propiram, buprenorphine, pentazocine, nalbuphine, butorphanol, tramadol, hydrocodone, oxycodone and methadone, pharmaceutically acceptable salts thereof, and mixtures thereof, wherein the one or more analgesic agent is a combination of a non-opioid analgesic agent and an opioid analgesic agent;

11

and a pharmaceutically acceptable carrier or vehicle, wherein the composition is orally administered.

7. The composition of claim 1, wherein at least one of the one or more magnesium salt is a magnesium salt of an analgesic agent.

8. The composition of claim 7, wherein the magnesium salt of the analgesic agent is magnesium acetylsalicylate.

9. The composition of claim 1, wherein the one or more magnesium salt is present at a level ranging from about 5 to about 30 wt. %, and the one or more stimulant is present at a level ranging from about 1 to about 25%.

10. The composition of claim 1, wherein at least one of the one or more analgesic agent is a non-opioid analgesic agent and is present at a level ranging from about 10 to about 90 wt. %.

11. The composition of claim 4, wherein the opioid analgesic agent is present at a level ranging from about 0.5 to about 20 wt. %.

12. The composition of claim 6, wherein the non-opioid analgesic agent is present at a level ranging from about 10 to about 90 wt. %, and the opioid analgesic agent that is present at a level ranging from about 0.5 to about 20 wt. %.

13. A pharmaceutical composition for the alleviation of pain, associated with migraine headache consisting essentially of a therapeutically effective amount of one or more magnesium salt, one or more stimulant selected from the group consisting of methamphetamine, dexamphetamine, methylphenidate, pemoline, caffeine and mixtures thereof, one or more analgesic agent selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, ketoprofen, ketoconazole, indomethacin, diflunisol, naproxen, ketorolac, dichlophenac, tolmetin, sulindac, phenacetin, piroxicam, mefamanic acid, dextromethorphan, codeine, morphine, hydromorphone, levophanol, meperidine, meptazinol, propoxyphene, propiram, buprenorphine, pentazocine, nalbuphine, butorphanol, tramadol, hydrocodone, oxycodone and methadone, pharmaceutically acceptable salts thereof, and mixtures thereof and one or more effervescing agent; and a pharmaceutically acceptable carrier or vehicle, wherein the composition is orally administered.

14. The composition of claim 13, wherein at least one of the one or more analgesic agent is a non-opioid analgesic agent.

15. The composition of claim 14, wherein the non-opioid analgesic agent is selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, ketoprofen, ketoconazole, indomethacin, diflunisol, naproxen, ketorolac, dichlophenac, tolmetin, sulindac, phenacetin, piroxicam, mefamanic acid, dextromethorphan, salicylates, pharmaceutically acceptable salts thereof, and mixtures thereof.

16. A pharmaceutical composition for the alleviation of pain, associated with migraine headache consisting essentially of a therapeutically effective amount of one or more magnesium salt; one or more stimulant; one or more analgesic agent selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, ketoprofen, ketoconazole, indomethacin, diflunisol, naproxen, ketorolac, dichlophenac, tolmetin, sulindac, phenacetin, piroxicam, mefamanic acid, dextromethorphan, codeine, morphine, hydromorphone, levophanol, meperidine, meptazinol, propoxyphene, propiram, buprenorphine, pentazocine, nalbuphine, butorphanol, tramadol, hydrocodone, oxycodone and methadone, pharmaceutically acceptable salts thereof, and mixtures thereof, wherein at least one of the one or more analgesic agent is an

12

opioid analgesic agent; one or more effervescing agent; and a pharmaceutically acceptable carrier or vehicle, wherein the composition is orally administered.

17. The composition of claim 16, wherein the opioid analgesic agent is selected from the group consisting of codeine, morphine, hydromorphone, levophanol, meperidine, meptazinol, propoxyphene, propiram, buprenorphine, pentazocine, nalbuphine, butorphanol, tramadol, hydrocodone, oxycodone and methadone, pharmaceutically acceptable salts thereof, and mixtures thereof.

18. A pharmaceutical composition for the alleviation of pain, associated with migraine headache consisting essentially of a therapeutically effective amount of one or more magnesium salt; one or more stimulant; one or more analgesic agent selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, ketoprofen, ketoconazole, indomethacin, diflunisol, naproxen, ketorolac, dichlophenac, tolmetin, sulindac, phenacetin, piroxicam, mefamanic acid, dextromethorphan, codeine, morphine, hydromorphone, levophanol, meperidine, meptazinol, propoxyphene, propiram, buprenorphine, pentazocine, nalbuphine, butorphanol, tramadol, hydrocodone, oxycodone and methadone, pharmaceutically acceptable salts thereof, and mixtures thereof, wherein at least one of the one or more analgesic agent is a non-opioid analgesic agent, and at least one of the one or more analgesic agent is an opioid analgesic agent; one or more effervescing agent; and a pharmaceutically acceptable carrier or vehicle, wherein the composition is orally administered.

19. The composition of claim 13, wherein at least one of the one or more magnesium salt is a magnesium salt of an analgesic agent.

20. The composition of claim 19, wherein the magnesium salt of the analgesic agent is magnesium acetylsalicylate.

21. The composition of claim 13, wherein the one or more effervescing agent is selected from the group consisting of alkali or alkaline earth metal carbonates, bicarbonates and mixtures thereof.

22. The composition of claim 13, wherein at least one of the one or more magnesium salt is present at a level ranging from about 5 to about 30 wt. %, and the one or more stimulant is present at a level ranging from about 1 to about 25 wt. %.

23. The composition of claim 13, wherein at least one of the one or more analgesic agent is a non-opioid analgesic agent and is present at a level ranging from about 10 to about 90 wt. %.

24. The composition of claim 16, wherein the opioid analgesic agent is present at a level ranging from about 0.5 to about 20 wt. %.

25. The composition of claim 18, wherein the non-opioid analgesic agent is present at a level ranging from about 10 to about 90 wt. %, and the opioid analgesic agent is present at a level ranging from about 0.5 to about 20 wt. %.

26. The composition of claim 13, wherein the one or more effervescing agent is present at a level ranging from about 20 to about 80 wt. %.

27. A pharmaceutical composition for the alleviation of pain, associated with migraine headache consisting essentially of from about 5 to about 30 wt. % of one or more magnesium salt, from about 1 to about 25 wt. % of one or more stimulant selected from the group consisting of methamphetamine, dexamphetamine, methylphenidate, pemoline, caffeine and mixtures thereof, and analgesic agent selected from the group consisting of an opioid analgesic agent, a non-opioid analgesic agent and mixtures thereof.

the non-opioid analgesic agent being selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, ketoprofen, ketoconazole, indomethacin, diflunisol, naproxen, ketorolac, dichlophenac, tolmetin, sulindac, phenacetin, piroxicam, mefamanic acid and dextromethorphan, and pharmaceutically acceptable salts thereof; and the opioid analgesic agent being selected from the group consisting of codeine, morphine, hydromorphone, levophanol, meperidine, meptazinol, propoxyphene, propiram, buprenorphine, pentazocine, nalbuphine, butorphanol, tramadol, hydrocodone, oxycodone and methadone, and pharmaceutically acceptable salts thereof, wherein the opioid analgesic agent is present in an amount of from about 0.5 to about 20 wt. %, and the non-opioid analgesic agent is present in an amount from about 10 to about 90 wt. %; and a pharmaceutically acceptable carrier or vehicle, wherein the composition is orally administered.

28. A pharmaceutical composition for the alleviation of pain, associated with migraine headache consisting essentially of from about 5 to about 30 wt. % of one or more magnesium salt, from about 1 to about 25 wt. % of one or more stimulant selected from the group consisting of methamphetamine, dextamphetamine, methylphenidate,

pemoline, caffeine and mixtures thereof, from about 20 to about 80 wt. % of one or more effervescent agent, and analgesic agent selected from the group consisting of an opioid analgesic agent, a non-opioid analgesic agent and mixtures thereof, the non-opioid analgesic agent being selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, ketoprofen, ketoconazole, indomethacin, diflunisol, naproxen, ketorolac, dichlophenac, tolmetin, sulindac, phenacetin, piroxicam, mefamanic acid and dextromethorphan, and pharmaceutically acceptable salts thereof; the opioid analgesic agent being selected from the group consisting of codeine, morphine, hydromorphone, levophanol, meperidine, meptazinol, propoxyphene, propiram, buprenorphine, pentazocine, nalbuphine, butorphanol, tramadol, hydrocodone, oxycodone and methadone, and pharmaceutically acceptable salts thereof, wherein the opioid analgesic agent is present in an amount of from about 0.5 to about 20 wt. %, and the non-opioid analgesic agent is present in an amount from about 10 to about 90 wt. % and a pharmaceutically acceptable carrier or vehicle, wherein the composition is orally administered.

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154

United States Patent [19]
Mauskop

[11] Patent Number: 5,538,959
[45] Date of Patent: Jul. 23, 1996

[54] ANALGESIC COMPOSITION FOR
TREATMENT OF MIGRAINE HEADACHES
[76] Inventor: Alexander Mauskop, 17A Lafayette
Rd., Larchmont, N.Y. 10538
[21] Appl. No.: 378,423
[22] Filed: Jan. 26, 1995
[51] Int. Cl.⁴ A61K 31/615; A61K 31/335
[52] U.S. Cl. 514/165; 514/224.5; 514/300;
514/728; 514/812; 424/44; 424/682; 424/689
[58] Field of Search 424/44, 682, 692;
514/165, 300, 728, 568, 224.5, 812

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Primary Examiner—John W. Rollins

Attorney, Agent, or Firm—Pennis & Edmonds

[57] ABSTRACT

A magnesium-containing analgesic composition used for treating migraine headaches and methods for using the same are described herein. The composition comprises an analgesic, a magnesium salt and an effervescent agent and is admixed with or dissolved in water prior to ingestion. The symptoms of migraine headache intended to be alleviated include nausea, unilateral pain, dizziness, pulsatile pain, worsening of pain by light physical activity, photophobia and phonophobia.

18 Claims, No Drawings

1

ANALGESIC COMPOSITION FOR TREATMENT OF MIGRAINE HEADACHES

FIELD OF THE INVENTION

This invention relates to magnesium-based compositions for treating migraine headaches, and methods for using the same.

BACKGROUND OF THE INVENTION

Analgesic compositions comprising magnesium salts have been used to treat a variety of ailments as well as reduce the gastric irritancy often accompanying the oral administration of such analgesic compositions. U.S. Pat. No. 3,865,933 to Mudge teaches the use of a mixture comprising magnesium gluconate, stramonium extract and 3-(2-methylphenoxy)-1,2-propanediol to relieve headache pain. U.S. Pat. No. 3,759,980 to Rosen et al. teaches the use of a mixture of magnesium salicylate and choline salicylate as an analgesic, anti-pyretic, anti-inflammatory and anti-rheumatic agent. U.S. Pat. No. 3,385,886 to Nicholson et al. teaches the use of phenylpropionic acid magnesium salts for the relief of pain, fever and inflammation. U.S. Pat. No. 3,359,166 to McClure teaches the use of magnesium 4-thiazolidinecarboxylate as an analgesic agent. U.S. Pat. No. 4,083,951 to Goudie et al. teaches the use of magnesium acetylsalicylate in conjunction with sodium bicarbonate as an analgesic having reduced gastric irritancy properties. Such compositions have employed magnesium salts for their

A deficiency of magnesium, i.e., hypomagnesemia, has been suggested to play a role in migraine headaches (B. A. Altura, *Magnesium*, 4:169 (1985); A. Mauskop et al., *Cephalalgia*, 14:241 (1994)). It had been shown that low serum ionized magnesium (IMg^{2+}) levels were found in 42% of patients suffering migraine headaches (A. Mauskop et al., *Headache*, 33(3):135 (1993)). The magnesium salt of pyrrolidone carboxylic acid has been used to treat women with premenstrual migraine headache (F. Facchinetti et al., *Headache*, 31(5):298 (1991)). Amino-chelated magnesium compounds have been used to treat patients with classic migraine headache (K. Weaver in "Letter to the Editor," *Headache*, 30(2):168 (1990)).

When some magnesium-based compositions are administered to patients having migraines, severe headaches or other painful conditions, the slowing of gastric motility which often accompanies these conditions delays the absorption of any medication taken orally. Such a delay in absorption is often more pronounced with tablet than with liquid medicaments. As a result, the onset of action associated with such compositions administered to migraine patients is undesirably delayed, resulting in the prolongation of pain and discomfort to the patient. Thus, there remains a need for compositions which can be used for treating migraine headaches and which are rapidly absorbed and provide rapid onset of action.

SUMMARY OF THE INVENTION

The present invention relates to a method for treatment of migraine headaches which comprises orally administering to a person in need of such treatment a rapidly absorbed magnesium-containing analgesic composition in an amount effective to relieve at least some symptoms of such headaches. Such compositions include various proportions of an analgesic agent, a magnesium salt and an effervescent agent.

2

Prior to ingestion, such compositions are admixed with or dissolved in water, preferably in about 2-10 ounces of water. Such compositions are ingested as their aqueous admixture or solution, preferably within 1-2 minutes of admixture or dissolution.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, improved absorption and hence improved onset of action of a preparation for treating a patient with a migraine headache can be achieved by administering to a patient with a migraine headache a magnesium-containing analgesic composition.

Such analgesic agents which can comprise the magnesium-containing analgesic composition of the present invention include, but are not limited to, acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, non-steroidal anti-inflammatory drugs, opiates such as codeine and morphine, pharmaceutically acceptable salts thereof, and mixtures thereof. Such pharmaceutically acceptable salts include, but are not limited to hydrochloride, hydrobromide, phosphate, sulfate, acetate, succinate, ascorbate, tartrate, gluconate, benzoate, malate, fumarate, and the like.

The magnesium component of the magnesium-containing analgesic composition of the present invention is ionic magnesium (i.e., Mg^{2+}). Suitable sources of Mg^{2+} are magnesium salts which include, but are not limited to magnesium chloride, magnesium citrate, magnesium tartrate, magnesium oxide, magnesium carbonate, magnesium sulfate and the like. Where the analgesic to be included in the magnesium-containing composition is a carboxylic acid, such as for example acetylsalicylic acid, the magnesium salt can be magnesium acetylsalicylate. This is convenient in combining both important components within a single compound. When the magnesium salt of the analgesic is included in the magnesium-containing analgesic composition of the present invention, an additional analgesic may or may not be included.

It is advantageous for the composition to be rapidly absorbed by the subject following oral administration. There are a number of ways to formulate such compositions to achieve rapid absorption, and one of ordinary skill in the art would be aware of such ways. Generally, encapsulating the active ingredient or employing other forms of delaying the release of the agent into the subject should be avoided, except when such means to delay release are included in combination with a rapidly absorbed form of such agent. This could be used, for example, when the composition is intended to provide both a rapidly absorbed initial administration of the analgesic agent, followed by a delayed release of longer duration administered for continued relief of headache symptoms.

In the preferred form of a rapidly absorbable magnesium-containing analgesic composition, an effervescent agent is included. By "effervescent agent" is meant any compound which, upon dissolution in water, provides effervescence to the aqueous mixture or solution upon release of carbon dioxide. Such effervescent agents include, but are not limited to, alkali or alkaline earth metal carbonates or bicarbonates, including, but not limited to sodium carbonate, sodium bicarbonate, sodium glycine carbonate, calcium carbonate and magnesium carbonate. Preferably, the effervescent agent is sodium bicarbonate.

The magnesium-containing analgesic composition may optionally comprise accessory ingredients including, but not

limited to dispersing agents such as microcrystalline cellulose, starch, cross-linked poly(vinyl pyrrolidone), and sodium carboxymethyl cellulose; flavoring agents; coloring agents; binders; preservatives; surfactants and the like.

The analgesic agent is advantageously present in the magnesium-containing composition at levels ranging from 10-90 wt. %, preferably 10-75 wt. %.

When added as a separate component, the magnesium salt is present in the magnesium-containing composition at levels ranging from 5-30 wt. %, preferably 10-30 wt. %. When a single compound of a magnesium salt of the analgesic agent is used, the amounts of such a single compound would be between about 20 and 95 wt. % of the composition.

The effervescing agent is present in the magnesium-containing composition at levels ranging from 20-80 wt. %, preferably 25-75 wt. %.

Of course, the total amounts of these components would be 100 wt. %, and those of ordinary skill in the art can vary the amounts within the stated ranges to achieve useful compositions.

The intended route of administration of the magnesium-containing analgesic compositions of the present invention is oral, wherein the composition is admixed with or dissolved in a pre-determined amount of water prior to ingestion.

Compositions of the present invention which are suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets, as a powder or granules; as a solution or a suspension in an aqueous liquid or non-aqueous liquid; or an oil-in-water or water-in-oil liquid emulsion. Preferably, the composition of the present invention is presented in tablet form.

Such tablets may be conventionally formed by compression or molding. Compressed tablets may be prepared by compressing in a suitable machine the mixture of one or more analgesic(s), magnesium salt(s), and effervescing agent(s) and optionally one or more accessory ingredients listed above. Molded tablets may be made by molding in a suitable machine the above mixture which can optionally be moistened with an inert liquid diluent. The tablets may optionally be coated or scored, having indicia inscribed thereupon, and may be so formulated as to provide slow or controlled release of the analgesic, magnesium or effervescing compounds therein.

Such tablets can range in weight from 25-2000 mg., preferably from 100-1000 mg., and most preferably from 250-1000 mg.

Prior to ingestion, such compositions are admixed or dissolved in about 2-10 ounces of water, preferably about 4-8 ounces of water. The compositions of the present invention are ingested as their aqueous admixture or solution within 2 minutes, preferably within 1 minute, of their admixture with or dissolution in water, so as to maximize their effervescence and hence absorptive properties.

The compositions are administered shortly after the onset of migraine symptoms. Such symptoms include nausea, unilateral pain, dizziness, pulsatile pain, worsening of pain by light activity, photophobia and phonophobia.

Administration can continue every 2-6 hours, preferably every 4 hours until migraine symptoms have subsided. In patients who suffer from chronic migraine headaches, a daily administration of 1000 mg. of the magnesium-containing composition four times per day of the present invention is advantageous.

EXAMPLE 1

Magnesium-Containing Analgesic Composition A

Ingredient	mg./Tablet
Acetylsalicylic Acid	800
Magnesium Chloride	250
Sodium Bicarbonate	300
Poly(methylene Glycol) 4000	50

EXAMPLE 2

Magnesium-Containing Analgesic Composition B

Ingredient	mg./Tablet
Magnesium Acetylsalicylic Acid	1000
Sodium Bicarbonate	350
Citric Acid	75

EXAMPLE 3

Magnesium-Containing Analgesic Composition C

Ingredient	mg./Tablet
Acetaminophen Na Salt	1000
Magnesium Trisilicate	200
Magnesium Carbonate	200

EXAMPLE 4

Magnesium-Containing Analgesic Cocktail

The tablet of Examples 1, 2 or 3 is added to 8 ounces of tap water. The resulting cocktail is ingested within 1 minute of admixture with or dissolution in water.

EXAMPLE 5

Results of Administration of Magnesium-Containing Analgesic Cocktail to Patients with Migraine Headaches

Methods

Five subjects were selected to participate in this study. Included were patients who had daily, but not necessarily continuous migraine headaches. Patients could have had headache-free periods lasting for hours and on a rare occasion for a day. Average severity of headaches prior to and two hours following administration of the magnesium-containing analgesic cocktail described below were assessed on a 1 to 10 verbal scale. Patients taking acetaminophen or non-steroidal anti-inflammatory drugs were excluded from this study.

Magnesium-Containing Analgesic Cocktail
Three tablets each having the following formulation:

Ingredient	mg./Tablet
Acetylsalicylic acid	325
Sodium Bicarbonate	1916

were dissolved in a solution of 500 mg of magnesium sulfate in 7 ounces of water and administered to each of five patients suffering migraine headache by ingestion of the resulting cocktail within 1 minute of dissolution of each of the three tablets. The results, compiled from a survey of each patient taken 2 hours following ingestion of the cocktail are shown below in Table 1:

RESULTS

TABLE 1

N	Age	Sex	Severity Prior to Administration	Severity Following Administration
1	33	F	10	4
2	35	F	7	2
3	14	F	8	3
4	59	F	7	1
5	30	M	8	2

Thus for all patients included in this study, the administration of the above-described magnesium-containing analgesic composition significantly reduced the severity of migraine headaches.

The magnesium-containing analgesic compositions of the present invention can be used to treat patients with migraine headaches. It is to be understood that such uses are not limited to treating the symptoms of migraine headaches but rather include treating other maladies including non-migraine headache pain, muscular pain, fever associated with viral or bacterial infection, thrombotic diathesis, magnesium deficiency and gastric discomfort.

The present invention is not to be limited in scope by the specific embodiments disclosed in these examples which are intended to illustrate the most preferred embodiments of the invention. Indeed, various modifications of the invention or other embodiments which are functionally equivalent to those shown and described herein will become apparent to those skilled in the art and are intended to be covered by the appended claims.

What is claimed:

1. A method for treatment of migraine headaches which comprises orally administering to a person in need of such treatment a rapidly absorbed composition in an amount effective to relieve at least some symptoms of such headaches, said composition consisting essentially of an analgesic agent, a magnesium salt and an effervescing agent.

2. The method of claim 1 wherein the analgesic agent is in the form of a magnesium salt of the analgesic agent.

3. The method of claim 2 wherein the magnesium salt of the analgesic agent is present in an amount of 20-95 wt. % of the composition.

4. The method of claim 2 wherein the analgesic agent is selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, a non-steroidal anti-inflammatory drug, an opiate or mixtures thereof.

5. The method of claim 1 wherein the analgesic agent is

present in an amount of about 10-90 wt. %, the magnesium compound is present in an amount of 5-30 wt. % and the effervescing agent is present in an amount of 20-80 wt. %.

6. The method of claim 1 wherein the analgesic agent is selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, a non-steroidal anti-inflammatory drug, an opiate, pharmaceutically acceptable salts or mixtures thereof.

7. The method of claim 1 wherein the composition is administered to a person having a deficiency of ionic magnesium.

8. The method of claim 1 wherein the symptoms to be relieved are selected from the group consisting of unilateral pain, nausea, dizziness, pulsatile pain, worsening of pain by light physical activity, photophobia and phonophobia.

9. A method for treatment of migraine headaches which comprises orally administering to a person in need of such treatment a rapidly absorbed composition in an amount effective to relieve at least some symptoms of such headaches, said composition consisting essentially of an analgesic agent and a magnesium salt.

10. The method of claim 9 wherein the analgesic agent is in the form of a magnesium salt of the analgesic agent.

11. The method of claim 10 wherein the magnesium salt of the analgesic agent is present in an amount of 20-95 wt. % of the composition.

12. The method of claim 10 wherein the analgesic agent is selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, a non-steroidal anti-inflammatory drug, an opiate or mixtures thereof.

13. The method of claim 9 wherein the analgesic agent is present in an amount of about 10-90 wt. % and the magnesium compound is present in an amount of 5-30 wt. %.

14. The method of claim 9 wherein the analgesic agent is selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, a non-steroidal anti-inflammatory drug, an opiate, pharmaceutically acceptable salts or mixtures thereof.

15. The method of claim 9 wherein the composition is administered to a person having a deficiency of ionic magnesium.

16. The method of claim 9 wherein the symptoms to be relieved are selected from the group consisting of unilateral pain, nausea, dizziness, pulsatile pain, worsening of pain by light physical activity, photophobia and phonophobia.

17. A method for treatment of migraine headaches which comprises orally administering to a person in need of such treatment a rapidly absorbed composition in an amount effective to relieve at least some symptoms of such headaches, said composition consisting essentially of a magnesium salt.

18. The method of claim 17 wherein the symptoms to be relieved are selected from the group consisting of unilateral pain, nausea, dizziness, pulsatile pain, worsening of pain by light physical activity, photophobia and phonophobia.

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

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PATENT NO. : 5,538,959
DATED : July 23, 1996
INVENTOR(S) : Alexander Mauskop

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1, line 31, please delete the incomplete sentence: "Such compositions have employed magnesium salts for their"

Signed and Sealed this

Eighteenth Day of February, 1997

Attest:



BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks



Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

Ciudad

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Referencia: Poder- Remisión de información a la solicitud de patente N° 00-90142.

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad, identificado con la cédula de ciudadanía No. 16.251.923 expedida en Palmira (Valle), domiciliado y residente en la ciudad de Barranquilla, actuando en nombre y representación de la sociedad **PROCAPS S.A.**, con NIT 890.106.527-5, manifiesto que confiero poder especial, amplio y suficiente al doctor **LUIS FERNANDO RINCÓN CUELLAR**, abogado en ejercicio, identificado con la cédula de ciudadanía número 79.532.186 de Bogotá y con tarjeta profesional número 113.438 expedida por el Consejo Superior de la Judicatura, para que adelante y lleve hasta su culminación una remisión de información en relación a la patentabilidad de la solicitud de la referencia titulada **"MÉTODOS PARA TRATAR SÍNTOMAS DE MIGRAÑA CON IBUPROFENO Y SALES DEL MISMO"**, cuyo solicitante es **McNEIL-PPC, INC.**

Mi apoderado cuenta con amplias facultades para el ejercicio del presente poder, en especial las de recibir, transigir, sustituir, reasumir y desistir.

Atentamente.


WALTER TANAKA TATEKAWA
REPRESENTANTE LEGAL
PROCAPS S.A.
C.C. 16.251.923 de Palmira

Acepto,


LUIS FERNANDO RINCON CUELLAR
C.C. 79.532.186 de Bogotá
T.P. 113.438 del C.S.J.

DILIGENCIA DE PRESENTACION PERSONAL

DECRETO 960 DE 1970 - ART. 68

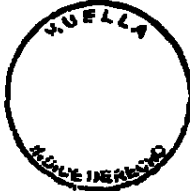
MARIA DEL S. ROMAN DE ARTETA - NOTARIA SEGUNDA DE BARRANQUILLA

CERTIFICA

En Barranquilla a los 13 días del mes de Mayo de 2010 ✓ Firmaron esta
diligencia en su presencia: WALTER FERNANDEZ TOTERANUS

Portadoras de las cédulas

16 251 923



Expedidas en

Palmita

y dieron fe de su contenido el contenido del documento
que ante mí se presentó y está autorizado con sus firmas



Comparecientes

WALTER FERNANDEZ TOTERANUS

REPUBLICA DE COLOMBIA
LA NOTARIA NOTARIA SEGUNDA DEL CANTON
DE BARRANQUILLA

Maria del S. Roman de Arteta

MARIA DEL S. ROMAN DE ARTETA

127
160



***** Pag.01
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
06*****
CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA,

C E R T I F I C A

Que por Escritura Publica Nro. 1190 del 22 de Julio de 1,976,
ot rgada en la Notaria Tercera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 28 de Julio de 1,976 bajo
el No. 6,070 del libro respectivo, fue constituida la sociedad
limitada denominada "PRODUCTORA DE CAPSULAS DE GELATINAS LIMITADA
"PROCAPS LIMITADA".-----

C E R T I F I C A

Que por Escritura Publica Nro. 1307 del 28 de Junio de 1,979,
ot rgada en la Notaria Tercera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 23 de Julio de 1,979 bajo
el No. 10,039 del libro respectivo, la sociedad antes mencionada
se transformo en sociedad anonima bajo la denominacion social de
"PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Publica Nro. 3810 del 31 de Dic/bre de 1,980,
otorgada en la Notaria Primera de Barranquilla, -----
inscrita en esta Camara de Comercio, el 30 de Enero de 1,981 bajo
el No. 12,705 del libro respectivo, la sociedad antes mencionada
se transformo en sociedad de responsabilidad limitada bajo al razon
social de "PRODUCTORA DE CAPSULAS DE GELATINA LIMITADA "PROCAPS LI -
MITADA".-----

C E R T I F I C A

Que por Escritura Publica Nro. 3755 del 10 de Nov/bre de 1,983,
otorgada en la Notaria Unica de Soledad, -----
inscrita en esta Camara de Comercio, el 22 de Nov/bre de 1,983 bajo
el No. 17,922 del libro respectivo, la sociedad antes mencionada
se transformo en sociedad anonima bajo la denominacion social de
"PRODUCTORA DE CAPSULAS DE GELATINA S.A." PROCAPS S.A.".-----

C E R T I F I C A

Que por Escritura Publica Nro. 3615 del 6 de Dic/bre de 1,996,
otorgada en la Notaria 2a. de Barranquilla -----
inscrita en esta Camara de Comercio, el 20 de Dic/bre de 1,996 bajo

***** C O N T I N U A *****

**CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.**

PROCAPS S.A. -----

el No. 67,218 del libro respectivo, la sociedad antes mencionada
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A

C E R T I F I C A

Que por Escritura Publica Nro. 3775 del 18 de Dic/bre de 1,996,
otorgada en la Notaria 2a. de Barranquilla -----
inscrita en esta Camara de Comercio, el 23 de Enero de 1,997 baj
el No. 67,704 del libro respectivo, la sociedad antes mencionada
cambio de razon social, por la denominacion PROCAPS S.A. -----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras
y/o documentos privados:

Numero	mm/dd/aaaa	Notaria	No.Ins o Reg	mm/dd/aaaa
39	1/18/1979	Notaria 3a. de Barranquilla	9,452	1/24/1979
992	4/30/1981	Notaria 1a. de Barranquilla	13,112	5/ 6/1981
1,464	8/27/1982	Notaria Unica de Soledad	15,533	9/ 8/1982
2,744	8/18/1983	Notaria Unica de Soledad	17,416	8/26/1983
3,826	7/16/1984	Notaria Unica de Soledad	19,554	7/27/1984
3,835	8/26/1985	Notaria Unica de Soledad	22,230	9/ 4/1985
2,260	9/10/1986	Notaria Unica de Soledad.	24,995	9/15/1986
1,849	7/11/1989	Notaria 2a. de Barranquilla	33,909	7/13/1989
444	2/21/1990	Notaria 2a. de Barranquilla	36,101	3/16/1990
3,090	12/17/1991	Notaria 2a. de Barranquilla	43,993	1/28/1992
269	2/ 1/1993	Notaria 2a. de Barranquilla	48,428	2/16/1993
2,342	7/28/1993	Notaria 2a. de Barranquilla	50,582	8/10/1993
3,652	11/ 9/1993	Notaria 2a. de Barranquilla	51,798	11/22/1993
3,615	12/ 6/1996	Notaria 2a. de Barranquilla	67,218	12/20/1996
89	1/16/1997	Notaria 2a. de Barranquilla	67,704	1/23/1997
2,070	7/17/1997	Notaria 2a. de Barranquilla	70,627	7/31/1997
2,281	8/ 4/1997	Notaria 2a. de Barranquilla	70,813	8/14/1997
765	4/22/1999	Notaria 3a. de Barranquilla	80,628	4/23/1999
459	2/21/2001	Notaria 2a. de Barranquilla	91,502	2/23/2001
2,608	10/ 5/2001	Notaria 2a. de Barranquilla	95,771	11/ 8/2001
1,730	7/29/2004	Notaria 2. de Barranquilla	112,999	8/26/2004

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad
se rige por las siguientes disposiciones: -----

DENOMINACION O RAZON SOCIAL: -----

PROCAPS S.A. -----

Sigla: PROCAPS -----

DOMICILIO PRINCIPAL: BARRANQUILLA -----

Nit No. 890,106,527-5 -----

MATRICULA MERCANTIL: 24,802 -----

***** C O N T I N U A *****



***** Pag.02
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----

C E R T I F I C A

Direccion para notificaciones judiciales
CL 80 # 78B -201
de la ciudad de BARRANQUILLA

C E R T I F I C A

DURACION: El termino de duracion de la sociedad se fijo hasta el
18 de Agosto del ano 2,073. -----

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados, d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos, y hospitalarios para la salud humana y animal. e)La compra, venta, exportacion y distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, de-

***** C O N T I N U A *****

**CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.**

PROCAPS S.A. -----

sarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podra garantizar el cumplimiento de obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.-----

C E R T I F I C A

CAPITAL:	Nro.Acciones	Valor Accion
AUTORIZADO:		
\$*****2,000,000,000.00	2,000,000.00	1,000.00
SUSCRITO:		
\$*****1,212,449,000.00	1,212,449.00	1,000.00
PAGADO:		
\$*****1,212,449,000.00	1,212,449.00	1,000.00

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad correspondera a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente, quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion Legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con

***** C O N T I N U A *****

A23
162

***** Pag.03
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----

1 previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de intereses inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendra (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para

***** C O N T I N U A *****

**CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.**

PROCAPS S.A. -----

ello acreditar la ausencia del principal. La sociedad tendra un gerente general con su respectivo suplente, quienes tambien ejerceran la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el presidente y el vicepresidente. El gerente general, tendra las siguientes facultades entre otras: Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o superior al equivalente en pesos colombianos cincuenta mil dolares de los estados unidos de America (US\$50.000) liquidados a la tasa de cambio representativa del mercado vigente el dia en que surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del presidente. Las demas funciones que les correspondan como representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El gerente lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades.-----

C E R T I F I C A

Que segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----

PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo,

y por Acta No. 127 del 22 de Marzo de 2,000, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----

PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 29 de Mayo de 2,000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos: -----

J U N T A D I R E C T I V A

Principales

1. Minski Gontovnik Ruben
2. Minski Gontovnik Meyer
3. Minski Gontovnik Jose

Suplentes

- Minski Zilberblum Elliot
Minski Deitel Daniel
Minski Sharon

C E R T I F I C A

Que segun Acta No. 116 del 27 de Junio de 1,997, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----

PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 15 de Agosto de 1,997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo

Nombre

Identificacion

***** C O N T I N U A *****



***** Pag.04
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----

Presidente.	Minski Gontovnik Ruben	C.*****7,463,982=
Suplente del Presidente	Minski Minski Abraham	C.*****802,575=
Vicepresidente	Minski Gontovnik Meyer	C.*****7,461,324=
Suplente del vicepresidente	Minski Gontovnik Jose	C.*****8,671,834=

C E R T I F I C A

Que segun Acta No. 124 del 29 de Marzo de 1,999, correspondiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 4 de Agosto de 1,999 bajo el No. 82,226 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Revisor Fiscal Ppal.	Vargas Pertuz Ana Isabel	C.****32,696,645=

C E R T I F I C A

Que segun Acta No. 127 del 22 de Marzo de 2,000, corresp ndiente a la Asamblea de Accionistas en Barranquilla de la sociedad: -----
PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 29 de Mayo de 2,000 bajo el No. 87,250 del libro respectivo, fuer n hech s los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Suplente del Revisor Fiscal.	Lozada Villareal Milena	C.****32,748,111=

C E R T I F I C A

Que segun Acta No. 11 del 1 de Febrero de 2,001, correspondiente a la Junta Directiva en Barranquilla de la sociedad: -----
PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 12 de Febrero de 2,001 bajo el No. 91,273 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Gerente General.	Uribe Ochoa Guillermo Luis	C.****70,073,754=

C E R T I F I C A

***** C O N T I N U A *****

~~CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL~~
~~O DE INSCRIPCION DE DOCUMENTOS.~~

PROCAPS S.A. -----

Que segun Acta No. 406 del 2 de Sep/bre de 2,004, correspondiente a la Junta Directiva en Barranquilla de la sociedad: -----

PROCAPS S.A. -----

cuya parte pertinente se inscribio en esta Camara de Comercio, el 9 de Sep/bre de 2,004 bajo el No.113,263 del libro respectivo, fueron hechos los siguientes nombramientos: -----

Cargo	Nombre	Identificacion
Suplente del Gerente.	Tanaka Walter	C.****16,251,923=

C E R T I F I C A

Que por escritura publica No. 2.608 del 5 de Octubre del 2.001, otorgada en la Notaria 2a. de Barranquilla, inscrita en esta Camara de Comercio el 8 de Noviembre del 2.001, bajo los Nos. 95.771, 2.056, 2.057, 2.058, 2.059, 2.060, 2.061, 2.062 y 2.064 del libro respectivo, se reforma totalmente el articulo 65, contenido en la escritura publica No. 3.705 de Noviembre 6 de 1.998, de la Notaria Segunda del Circuito de Barranquilla, y se constituyen los siguientes Apoderados Generales, quienes tendran las funciones que a continuacion se indican en razon de su cargo en la sociedad: 1.-Se confiere Poder Especial, Amplio y Suficiente a los senores: WALTER TANAKA TATEKAWA, C.C. No. 16.251.923; WILLIAM ALBERTO BARROS CERRA, C.C. No. 8.715.941, para que cada uno en forma independiente en nombre y representacion de PROCAPS S.A., suscriba todas las declaraciones tributarias, aduaneras y cambiarias a que este obligada la sociedad, asi como para que responda todo tipo de requerimiento o solicitudes de informacion de las autoridades tributarias, aduaneras o cambiarias, en los ordenes Distrital, Departamental y Nacional. 2.-Se confiere Poder Especial, amplio y suficiente, a los siguientes senores que conforman el Grupo A y el Grupo B para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta por la suma de US\$800.000.00 (OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA), liquidados a la tasa representativa del mercado vigente en el dia que se realice la respectiva transaccion. GRUPO A: GUILLERMO LUIS URIBE OCHO C.C. No. 70.073.754, LINO LAZALA SILVA VARGAS C.C. No. 19.260.410, JAIRO MOLINA MEJIA C.C. No. 8.706.380, CLAUDIA TANGARIFE CASTILLO C.C. No. 41.660.293. GRUPO B: WALTER TANAKA TATEKAWA C.C. No. 16.251.923, HENRY CARO DIAZ C.C. No. 19.395.298, CARMEN ALICIA FLOREZ C.C. No. 22.434.044, CARMEN ALICIA HERRERA DIAZ GRANADOS C.C. No. 22.377.540. Para el ejercicio de estas facultades se requerira por lo menos la firma de uno (1) de los apoderados especiales del Grupo A y uno de los apoderados especiales del Grupo B; 3.-Se otorga Poder General, Amplio y Suficiente a la Doctora JOSEFINA MIELES BUELVAS C.C. No. 33.138.497, a la Doctora MARCELA CARVAJALINO PAGANO C.C. No. 22.579.748, y al Doctor DANIEL MORENO VILLALBA, C.C. No. 19.113.210; para que cada uno representen a PROCAPS S.A., ante todo tipo de autoridades administrativas y judiciales, en asuntos de naturaleza cambiaria y fiscal, tales como: Contestar e interponer demandas y requerimientos, com-

***** C O N T I N U A *****



***** Pag.05
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL
O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----

parecer en juicios, pedir la practica de pruebas, recibir notificaciones, interponer recursos y ejercer acciones contencioso administrativas y de tutela, transigir, conciliar, recibir en nombre de la sociedad desistir, sustituir y reasumir este mandato. Para la celebracion de cualquier acuerdo conciliatorio o transaccional, judicial o extrajudicial, cualquiera que sea su cuantia, los Apoderados deberan aportar la autorizacion escrita del Representante Legal de la sociedad. Los Apoderados podran presentar solicitudes de devolucion y/o compensacion de impuestos y recibir los pagos por devoluciones de impuestos, firmar, notificarse y realizar todo acto necesario para cumplir con el mandato encomendado.-----

C E R T I F I C A

Que segun documento privado de fecha 7 de junio de 2000, inscrito en esta Camara de Comercio el 8 de junio de 2000, bajo el No.1.786 del libro respectivo, consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982 de Barranquilla, actuando como Presidente y Representante Legal de la sociedad PROCAPS S.A, confiere poder especial, amplio y suficiente a KAREN FIGUEROA GARCIA, C.C.No.32.732.070 de Barranquilla, para que en su nombre y representacion de la sociedad suscriba todas declaraciones cambiarias a que este obligada PROCAPS S.A, en el giro normal de sus negocios y operaciones sociales.--

C E R T I F I C A

Que segun Documento Privado del 13 de diciembre del 2.002, inscrito en esta Camara de Comercio el 15 de enero del 2.003 bajo el No.2.290 del libro respectivo, el señor RUBEN MINSKI GONTOVNIK, C.C.No.7.463.982, en calidad de REPRESENTANTE LEGAL, y en condicion de PRESIDENTE de PROCAPS S.A., mediante el presente documento otorgo PODER ESPECIAL al Sr. MARLON TATIS PAREDES, C.C.No.72.176.874, para que en representacion de PROCAPS S.A., suscriba declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces. En consecuencia, el Sr. MARLON TATIS PAREDES, podra suscribir en representacion de PROCAPS S.A. declaraciones, reportes y cualquier tipo de documentos relacionados con tramites o registros de Comercio Exterior ante el Ministerio de Comercio Exterior y/o cualquier entidad del Estado que haga sus veces.-----

C E R T I F I C A

Que en esta Camara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolucion, liquidacion o nombramientos de representantes legales de la expresada sociedad.-----

***** C O N T I N U A *****

~~CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL~~
O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----

C E R T I F I C A

Que su ultima Renovacion fue el: 31 de Marzo de 2,004. -----

La informacion sobre embargos de establecimientos se suministra en
Certificados de Matricula, la de contratos sujetos a registro, en
Certificados Especiales.

C E R T I F I C A

Que los actos de registro aqui certificados quedan en firme cinco dias
habiles despues de la fecha de la publicacion en la noticia de la
correspondiente inscripcion, siempre que, dentro de dicho termino, no
sean objeto de los recursos de reposicion ante esta entidad, y/o de
apelacion para ante la Superintendencia de Industria y Comercio.--

NO CAUSA IMPUESTO DE TIMBRE


EL SECRETARIO
MARIBEL REYES OVIEDO

176/65

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

2020
Bogotá, D.C.,

Doctora
JIMENA ESCOBAR URIBE
(Apoderado)

ASUNTO	Radicación	00090142
	Trámite	002
	Evento	001
	Actuación	430
	Oficio.-	1 4.05
	Folios	006

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: 3 a 11) y las reivindicaciones 1 a 14 (Folios: 48 a 52).

La presente solicitud reivindica prioridad americana N° US9.449.124 de 24 de noviembre 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 tratar síntomas de migraña".

El objeto de la presente solicitud se refiere a al tratamiento de síntomas de migraña mediante la administración de una cantidad efectiva de acetaminofén; más específicamente, la presente solicitud se refiere al tratamiento de fonofobia y fotofobia con acetaminofén, sales farmacéuticamente aceptables del mismo o mezclas de los mismos.

Según la descripción, la migraña produce una amplia variedad de dolor y síntomas y trastornos asociados en quienes sufren de la enfermedad. Entre estos síntomas están incluidos: náusea, dolor de cabeza, dolor moderado a severo, así como también dolor incapacitante e inhabilitación total en un porcentaje de pacientes. Algunos pacientes también relatan síntomas más específicos tales como fotofobia, sensibilidad dolorosa a la luz, o fonofobia, sensibilidad dolorosa al ruido.

El tratamiento del dolor de migraña incluye tanto medicamentos para venta con receta, como medicamentos para venta sin receta o de libre acceso. Entre los medicamentos de libre acceso que están disponibles actualmente está una combinación de acetaminofén/aspirina/cafeína, como que se indica en la patente de EUA N° 5972916. La combinación de ingredientes activos pueden ocasionar efectos

secundarios indeseables. Por ejemplo, es bien conocido que la aspirina ocasiona irritación estomacal y la cafeína puede ocasionar ansiedad e insomnio. Por lo tanto, existe la necesidad continua de tratamiento de migraña y de alternativas de tratamiento para los síntomas específicos de la migraña.

Lo que se reivindica como novedoso es lo siguiente: Una cantidad efectiva de ibuprofeno, una sal farmacéuticamente aceptable del mismo, un isómero del mismo o una mezcla de los mismos, como único ingrediente farmacéuticamente efectivo, usados en un método para calmar o tratar la fotofobia asociada con migraña en un paciente.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/19.

Claridad de la solicitud:

El artículo 28 de la Decisión 486 de la Comisión de la Comunidad Andina establece "La descripción deberá divulgar la invención de manera suficientemente clara y completa para su comprensión y para que una persona capacitada en la materia técnica correspondiente pueda ejecutarla."

De acuerdo con lo anterior, la solicitud se relaciona con un método de tratamiento y el título, pero el capítulo reivindicatorio se encuentra encabezado en función del fármaco ibuprofeno que se encuentra en una cantidad efectiva.

El artículo 30 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: "Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción."

Las reivindicaciones podrán ser independientes o dependientes. Una reivindicación será independiente cuando defina la materia que se desea proteger sin referencia a otra reivindicación anterior. Una reivindicación será dependiente cuando defina la materia que se desea proteger refiriéndose a una reivindicación anterior. Una reivindicación que se refiera a dos o más reivindicaciones anteriores se considerará una reivindicación dependiente múltiple."

De acuerdo con lo anterior, las reivindicaciones están encabezadas como una cantidad efectiva de ibuprofeno, lo cual no es claro si se está reclamando una cantidad de fármaco que, por lo demás, no se dice el valor de dicha cantidad, o es el fármaco en sí que se encuentra en esa cantidad. De otro lado, no se comprende si lo que se trata de reclamar es una formulación farmacéutica que contiene ibuprofeno como principio activo; si este es el caso, debería decirse el vehículo en el cual se encuentra formulado dicho fármaco y no debe caracterizarse por un uso que se le va a dar a dicho fármaco.

Las reivindicaciones 11, 12, 15 a 17 (folios: 28 a 30) que se relacionan con las sales de ibuprofeno, no son claras, puesto que no se comprende la forma de unión o enlace entre por ejemplo: cafeína con el ibuprofeno para formar la sal, o colina con ibuprofeno, o la histidina con el ibuprofeno; además, a lo largo de la solicitud no aparecen ejemplos de dichas sales que aclaren como se encuentran formadas. Se solicita que se explique en qué consisten tales reacciones y cuál es el producto de ellas (estructura química).

En las reivindicaciones aparecen términos que son bastante subjetivo y conllevan a ambigüedad, por lo cual le restan claridad a lo que se pretende proteger. Por ejemplo: "aproximadamente", "cantidad efectiva", "sal farmacéuticamente aceptable", etc.

Evaluación de la Unidad de Invención:

El artículo 25 de la Decisión 486 de la Comisión de la Comunidad Andina establece: "La solicitud de patente sólo podrá comprender una invención o un grupo de invenciones relacionadas entre sí, de manera que conformen un único concepto inventivo."

Según lo anterior la (s) reivindicación (es) 11,12, 15 a 17 (folios: 28 a 30), que se refiere(n) a una cantidad efectiva de ibuprofeno, una sal farmacéuticamente aceptable del mismo,... caracterizado porque la sal se selecciona del grupo...: sales inorgánicas,... sales orgánicas,..., mezclas de las mismas, no guarda(n) unidad de invención con las reivindicaciones precedentes, que se relacionan con con una cantidad efectiva de ibuprofeno, una sal farmacéuticamente aceptable,... usados en un método para calmar o tratar la fotofobia asociada con migraña.

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de Patente o, en su caso, de la prioridad reconocida."

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ésta se publique o hubiese transcurrido el plazo previsto en el artículo 40".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 24/11/1999, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se hizo la búsqueda de documentos relevantes en el estado de la técnica, entendiendo como estado de la técnica la definición provista en el artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina y las excepciones fijadas en el artículo 17 de la misma.

Se encontró como anterioridades (documentos cuya fecha de publicación es anterior a la fecha de presentación de la primera solicitud de patente sobre la cual se reivindica prioridad o de la fecha de presentación de esta solicitud) que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
1	WO 97/30699	Dosage form of ibuprofen	28 de agosto de 1997
2	US 5696165	Composition of S(-) sodium ibuprofen	9 de diciembre de 1997
3	US5914129	Analgesic composition for treatment of migraine headaches	22 de junio de 1999
4	US 5538959	Analgesic composition for treatment of migraine headaches	23 de Julio de 1996

Evaluación de los requisitos de Patentabilidad:

El Artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina el cual establece: "Los Países Miembros otorgarán Patentes para las invenciones, sean de producto o de procedimiento en todos los campos de la tecnología siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial".

Se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación Industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de Novedad:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Una invención se considerará nueva cuando no esté comprendida en el estado de la técnica". "El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".

Esta se evaluó por comparación entre lo solicitado y los documentos encontrados en el estado de la técnica y que se relacionan con el objeto reivindicado y de acuerdo con la definición de novedad del Artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina.

Comparando elemento por elemento el objeto de esta solicitud con lo mencionado en las anterioridades, tenemos que:

La Solicitud de Patente Colombiana No. 00080142, se refiere a:

Una cantidad efectiva de ibuprofeno, una sal farmacéuticamente aceptable del mismo, un isómero del mismo o una mezcla de los mismos, como único ingrediente farmacéuticamente efectivo, usados en un método para calmar o tratar la fotofobia asociada con migraña en un paciente.

La anterioridad WO 97/30699 (folios: 103 a 140) menciona una forma farmacéutica sólida no-efervescente cuyo principio activo es ibuprofeno; además, menciona composiciones con la sal de sodio de ibuprofeno. Las cantidades de ibuprofeno pueden estar entre 256 mg y 342 mg.

El documento US 5696165 (folios: 142 a 154) menciona composiciones de ibuprofeno sódico para el tratamiento del dolor y de la inflamación.

El documento US 5914129 (folios: 157 a 162) menciona composiciones para tratar la migraña, que contienen un analgésico tal como ibuprofeno.

La anterioridad US 5538959 (folios: 165 a 169) menciona composiciones que comprende un agente analgésico entre los cuales está el ibuprofeno, para tratar la fotofobia y fonofobia asociadas a migraña.

Estos documentos revelan formulaciones que contienen ibuprofeno o derivados del mismo y que pueden estar en una forma de administración sólida, tal como tabletas.

Como se observa, el objeto de esta solicitud puede ser idéntico a lo comprendido en el estado de la técnica, con lo cual se considera que podría no cumplir con el requisito de Novedad.

Evaluación de Nivel Inventivo:

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica".

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.

Los documentos WO 97/30699, US 5914129 y US 5538959 mencionan composiciones de sales de ibuprofeno, donde pueden estar las de magnesio y de sodio—como lo indica el documento WO 97/30699—, y mencionan sales con lisina. No obstante, en tales documentos no se encuentren todas las posibilidades de sales que menciona la actual solicitud, puede observarse que el problema a resolverse es encontrar una composición para el tratamiento de fotofobia y fonofobia en eventos de migraña y, pues, con los documentos encontrados en el estado de la técnica, una persona medianamente versada en la materia puede llegar a la solución planteada en la presente solicitud.

En cuanto a la actividad, ya era conocido en el estado de la técnica el empleo de analgésicos tal como el ibuprofeno para el tratamiento de la migraña (ver documentos US 5914129, folio: 157 y US 5538959, folio: 168); por lo anterior puede decirse nuevamente que la solución al problema planteado ya había sido dada con antelación a la fecha de prioridad de la actual solicitud de patente.

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.

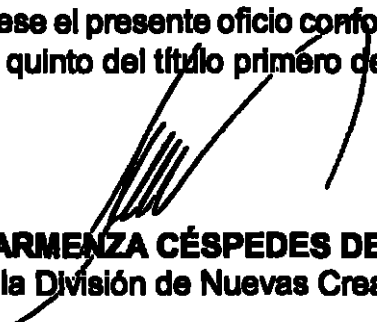
En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

170
187

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	WO 97/30699	1 a 24	Novedad y Nivel Inventivo
2	US 5696165	1 a 24	Novedad
3	US5914129	1 a 24	Novedad y Nivel Inventivo
4	US 5538959	1 a 24	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 _____ i 09 FEB. 2008

CONCEPTO TÉCNICO Nº: 134	EXAMINADOR TÉCNICO Código N°: 202005	EXAMINADOR JURÍDICO Código N°:
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

171

RADICACIÓN: 6-00142

EDICTO No. 8872

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió Resolución No. 13307 de 26-MAY-2006. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "METODO PARA TRATAR SINTOMAS DE MIGRAÑA CON IBUPROFENO Y SALES DEL MISMO".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución a la doctora Jimena Escobar Uribe, o a quien haga sus veces, en su calidad de apoderada de McNeil - Ppc, Inc., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los 25 MAY 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JIMENA ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaría General Ad-Hoc 12-JUN-2006
Secretaría General Ad-Hoc
EDICTO No. 8872

Este edicto se desfila hoy 27-JUN-2006 a las cinco (5:00 p.m.)

AVISO DE NOTIFICACION

CORREO CERTIFICADO

Radicación : 0-90142- -10-0 Fecha: 2006-05-26 08:04:19
Trámite : 2 PATENTES
Evento : 1 REGDEPOSITO
Actuación : 432 COMUNICACTOADM
Destinatario : JIMENA ESCOBAR URIBE Folios 1

Señor (a) (es)
JIMENA ESCOBAR URIBE
CARRERA 11A NO. 94 - 76 OF. 305
BOGOTA D.C.

8872

REF.RESOLUCION :13307

FECHA : 25/05/2006
Expediente : 0-90142
Trámite : 2 PATENTES DE INVENCION
Evento : 1 REGISTRO/DEPOSITO/CONCESION/DEPOSITO
Actuación : 432 COMUNICACION ACTO ADMINISTRATIVO

Comendidamente le solicito presentarse a este Despacho ubicado en la Carrera 13 No. 27 - 00 Piso Quinto (5), de la ciudad de Bogotá D.C., dentro del término de cinco (5) días hábiles contados a partir del envío de la presente citación, en horario de 8:30 a.m. a 5:00 p.m. Jornada continua, con el fin de notificarle personalmente el contenido de la resolución de la referencia proferida dentro del expediente tramitado con el número de radicación citado en el asunto.

De no hacerse presente en el término indicado anteriormente, la providencia en mención se notificará por edicto, el cual se fijará por el término de diez (10) días en el Centro de Documentación e Información.

Para su comodidad el texto completo de la resolución se encontrará disponible en la página web de la Entidad desde el día hábil siguiente al de su notificación, la cual podrá ser consultada desde un computador con acceso a Internet, en la página www.sic.gov.co, con el número de resolución a través de la opción servicios en línea - caracter general - consulta actos administrativos.

Secretaría General
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



173

Industria y Comercio
SUPERINTENDENCIA

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 13307

Por la cual se niega una patente de invención

Rad. N° 00-90142

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
en ejercicio de sus facultades legales, en especial de las que se confirieron en el artículo
4, numeral 5 del decreto 2153 de 1992, y

CONSIDERANDO:

PRIMERO: Que mediante escrito radicado en esta Superintendencia el 24 de noviembre del 2000, bajo el número 00090142, se presentó la solicitud de patente para la invención denominada: "METODO PARA TRATAR SINTOMAS DE MIGRAÑA CON IBUPROFENO Y SALES DEL MISMO", contenida en el expediente de la referencia.

SEGUNDO: Que efectuado el examen de forma en cuanto a los requisitos que debe llenar la solicitud y cumplidas las exigencias legales, se ordenó publicar el extracto sin que se hubieran presentado oposiciones por parte de terceros.

TERCERO: Que el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: "Si la oficina nacional competente encontrara que la invención no es patentable o que no cumple con alguno de los requisitos establecidos en esta Decisión para la concesión de la patente, lo notificará al solicitante. Este deberá responder a la notificación dentro del plazo de sesenta días contados a partir de la fecha de la notificación. Este plazo podrá ser prorrogado por una sola vez por un período de treinta días adicionales... si el solicitante no respondiera a la notificación dentro del plazo señalado, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, la oficina nacional competente denegará la patente".

CUARTO: Que realizado el examen de fondo, se requirió al solicitante en los términos del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, para que presentara respuesta a las observaciones de carácter técnico visibles a folios 176 a 181 del cuaderno administrativo, relacionadas con la patentabilidad o cumplimiento de los requisitos establecidos por esta Decisión para la concesión de la patente. Frente a dicho requerimiento no hubo pronunciamiento alguno por parte del mismo, motivo por el cual es procedente negar el privilegio de patente solicitado con fundamento en lo dispuesto en el artículo 45 de la Decisión 486.

RESUELVE:

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "METODO PARA TRATAR SINTOMAS DE MIGRAÑA CON IBUPROFENO Y SALES DEL MISMO".

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Sede CAN: Tr. 40A No. 38-50 Conmutador: 3820840
Fax: 382 26 96. Línea 9800-910 165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia

13307



124

Industria y Comercio
SUPERINTENDENCIA

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 13307

Por la cual se niega una patente de invención

Rad. N° 00-90142

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución a la doctora Jimena Escobar Uribe, o a quien haga sus veces, en su calidad de apoderada de McNeil – Ppc, Inc., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE

Dada en Bogotá, D.C., a los **25 MAYO 2006**

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

JAIR RUBIO ESCOBAR

Doctora

JIMENA ESCOBAR URIBE

Carrera 11 A N° 94 - 76 Of. 305

Bogotá D.C. (p.m.)

202021

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Sede CAN: Tr. 40A No. 38-50 Conmutador: 3820840
Fax: 382 28 95. Línea 9800-910 165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia

175

EXAMEN TÉCNICO DE FONDO			
Nº Radicación	00090142	Fecha de presentación	24-11-2000
Nº Prioridad	US09/449124, US09/709069	Fecha de Prioridad	24-11-1999, 9-11-2000

Palabras clave	
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CLASIFICACIONES INTERNACIONALES DE BÚSQUEDA
A61K 31/19

DOCUMENTOS CORRESPONDIENTES EN OTROS PAÍSES	
EP1129710 A2	05-09-2001
Patente Original	

BASES DE DATOS CONSULTADAS
EPOLINE ESPACENET

INFORMES DE EXÁMENES EN OTRAS OFICINAS		
Oficina	Fecha	Reivindicaciones
EUROPEA		

ANTERIORIDADES ENCONTRADAS		
Documento	Relevancia	Reivindicaciones afectadas
GB1514225 A [X]; US3987170 A [X]; US5914129 A [A]; US5538959 A [A]; WO9838883 A2 [X]; WO 97/30899 US 5898185 US 5538959	_____ _____ Novedad y Nivel Inventivo _____ _____ Novedad y Nivel Inventivo Novedad Novedad y Nivel Inventivo	_____ _____ 1 a 24 _____ _____ 1 a 24 1 a 24 1 a 24

LITERATURA NO PATENTES		
Documento no Patentes	Relevancia	Reiv. afectadas

Observaciones	
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Fecha del examen	Art. 45: 3-02-2008
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No hay Rta y
17/05/06.