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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.

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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 6.5-15Kp 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 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.

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 16 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 6.5-15Kp 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.

Figure 1

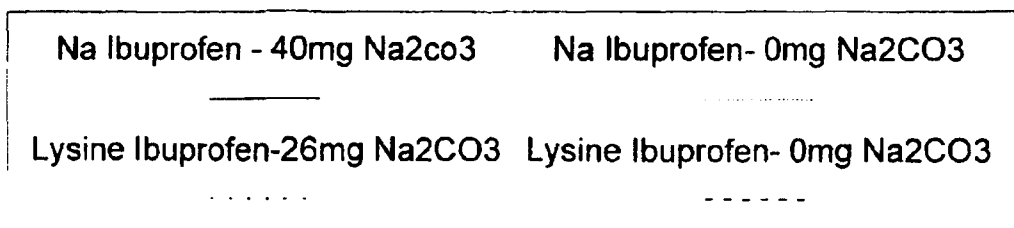
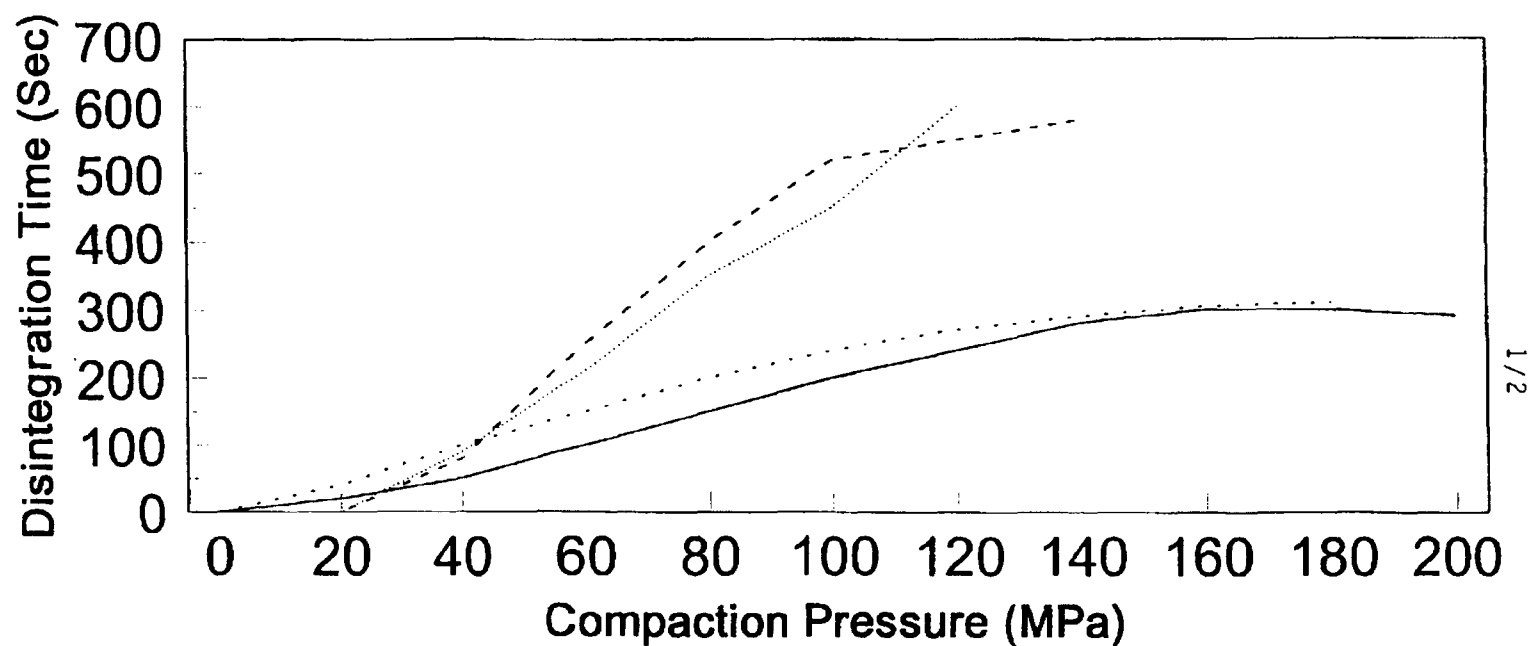
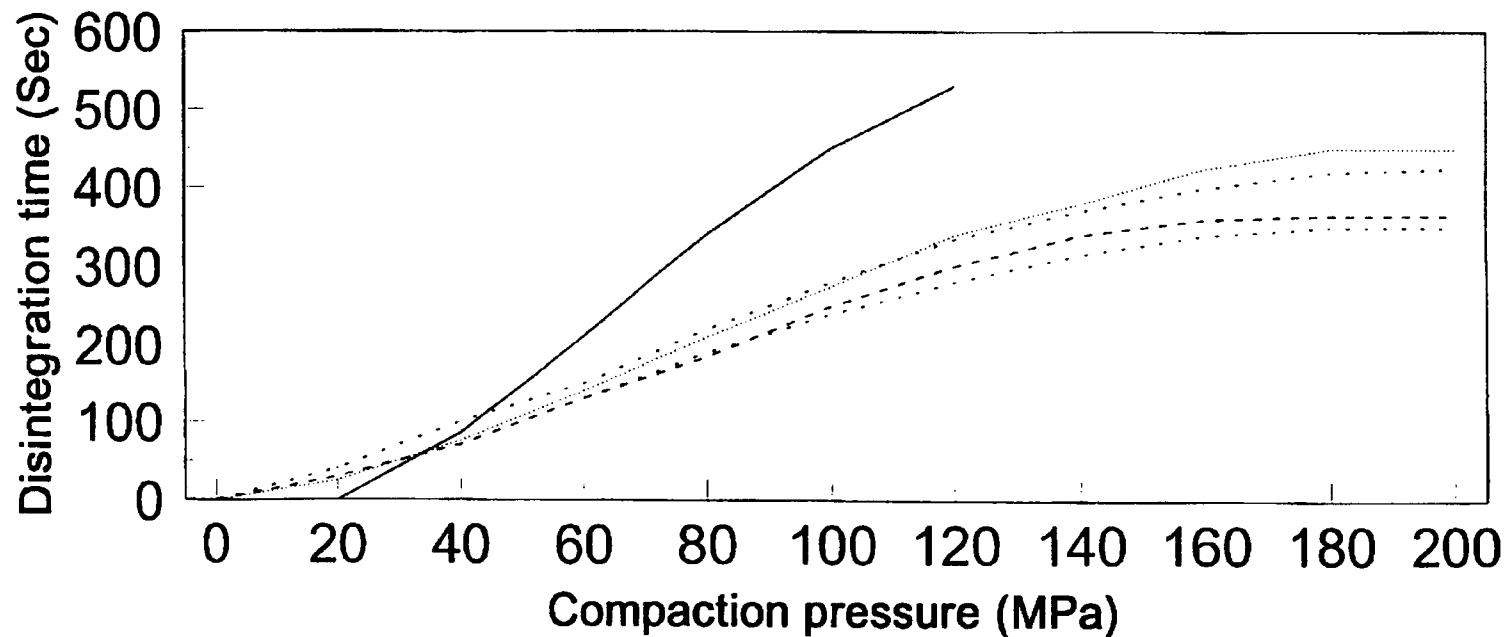
Ibuprofen SaltsEffect of sodium carbonate on disintegration time

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

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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**5,278,337 1/1994 Manimaran et al. .... 562/401  
5,302,751 4/1994 Manimaran et al. .... 562/401[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  
Jun. 5, 1991 [GB] United Kingdom ..... 9112058[51] **Int. Cl.<sup>6</sup>** ..... **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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**Attorney, Agent, or Firm**—Nikaido, Marmelstein, Murray & Oram LLP

[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-isobutyl-phenyl)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-Isobutylphenyl)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-isobutylphenyl)propionic acid or S(+)-ibuprofen and R(-)-2-(4-isobutylphenyl)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 characterised 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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate in water with no additional pharmaceutical excipient and (b) compositions comprising the calcium salt of S(+)-ibuprofen.

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

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Under similar circumstances S(+)-ibuprofen would tend to stick and generally display poor flow characteristics. S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate includes the anhydrous form and hydrated forms. Preferably the dihydrate is used.

S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate. The compositions of the invention are generally prepared in unit dosage form. Preferably the unit dosage of S(-)-sodium 2-(4-isobutylphenyl)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-

ceutical forms for such administration, for example tablets and capsules. Suitably tablets may be prepared by mixing S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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, alginic 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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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

obtained by mixing S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate as the dihydrate.

Preferably oral liquid compositions comprise a) 0.1-10% S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate may be dispersed in a pharmaceutically acceptable cream, ointment or gel. A suitable cream may be prepared by incorporating S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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 neutralising agent. It is a particular advantage of the present invention that as a result of the high water solubility of S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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. LABRAFILL and GELOT (both tradenames of Gattefosse) are examples of self-emulsifying bases.

A suitable ointment comprises a) 1-15% S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate may, if desired, be associated with other compatible pharmacologically active ingredients and/or enhancing agents. Thus, for example, S(-)-sodium 2-(4-isobutylphenyl)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, cypheptadine, dexbrompheniramine, dexchlorpheniramine, diphenhydramine, ebastine, ketotifen, lodoxamide, loratidine, levocubastine, mequitazine, oxatomide, phenindamine, phenyltoloxamine, pyrilamine, setastine, tazifylline, temelastine, terfenadine, tripelemine or triprolidine. Suitable cough suppressants include caramiphen, codeine or dextromethorphan. Suitable decongestants include pseudoephedrine, phenylpropanolamine and phenylephrine. Suitable expectorants include guaifensin, potassium citrate, potassium guaiacolsulphonate, potassium sulphate and terpin hydrate.

S(-)-sodium 2-(4-isobutylphenyl)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, periarticular disorders and soft tissue injuries. S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate in present as the dihydrate.

In a further aspect the present invention provides the use of a pharmaceutical composition comprising S(-)-sodium 2-(4-isobutylphenyl)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 antiinflammatory, analgesic and anti-pyretic agent. Preferably the S(-)-sodium 2-(4-isobutylphenyl)propionate in 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-isobutylphenyl)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-isobutylphenyl)propionate in present as the dihydrate.

S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate to a mammal in need thereof.

This surprising effect occurs not only when S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)propionate together with a diluent or carrier characterised in that S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate is used as the source of S(-)-sodium 2-(4-isobutylphenyl)propionate.

In a further aspect the present invention provides a process to prepare a pharmaceutical composition comprising S(-)-sodium 2-(4-isobutylphenyl)propionate having an enantiomeric purity of at least 90% together with a pharmaceutically acceptable carrier 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.

A preferred process for preparing a solid composition in tablet form comprises combining 10-90% of S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate includes the anhydrous form and hydrated forms for example the dihydrate.

S(-)-sodium 2-(4-isobutylphenyl)propionate may be prepared by neutralising S(+)-2-(4-isobutylphenyl) propionic acid with a sodium-containing base. It would be expected that in order to prepare S(-)-sodium 2-(4-isobutylphenyl) propionate in an enantiomerically pure form, for example greater than 90%, then the S(+)-2-(4-isobutylphenyl) 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-isobutylphenyl) 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-isobutylphenyl) 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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl) 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-isobutylphenyl)propionic acid said sodium salt having an enantiomeric purity of greater than 90% that is 90-100% comprising the steps of:

- neutralising 2-(4-isobutylphenyl)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

e) converting said solid into 2-(4-isobutylphenyl) 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-isobutylphenyl)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-isobutylphenyl)propionate having an enantiomeric purity of greater than 90% comprising the steps of:

- neutralising 2-(4-isobutylphenyl)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-isobutylphenyl)propionate and
- separating said solid from the solvent system.

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

Preferably the process provides S(-)-sodium 2-(4-isobutylphenyl)propionate having an enantiomeric purity of greater than 95%. More preferably the process provides S(-)-sodium 2-(4-isobutylphenyl)propionate having an enantiomeric purity of greater than 98%. Most preferably the process provides S(-)-sodium 2-(4-isobutylphenyl) 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-isobutylphenyl)propionate having an enantiomeric of greater than 99% comprising the steps of:

- neutralising 2-(4-isobutylphenyl)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-isobutylphenyl)propionate and
- separating said solid from the solvent system.

2-(4-Isobutylphenyl)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-Isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionic acid will give a pH value of

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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 C<sub>1-4</sub> 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

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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 C<sub>1-4</sub> 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.,  $[\alpha]_D^{22} = -4.3^\circ$  (c 0.94). A sample converted back into S(+)-2-(4-isobutylphenyl)propionic acid as described above had  $[\alpha]_D^{22} = +58.7^\circ$  (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 flake (4.0 g) in water (15 ml) was added. After cooling to 2° C., the salt which crystallised out was collected by filtration.

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

## EXAMPLE 4

A mixture of S(+)-2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionic acid and assayed as described previously. Enantiomeric purity 99.8%.

## EXAMPLE 6

A mixture of S(+)-2-(4-isobutylphenyl)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-isobutylphenyl)propionate dihydrate (yield 53.7%). Enantiomeric purity 98.2%.

## EXAMPLE 7

A mixture of S(+)-2-(4-isobutylphenyl)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-isobutylphenyl)propionic acid (20.6 g, enantiomeric purity 98.6%) in toluene (150 ml). After the addition more S(+)-2-(4-isobutylphenyl)propionic acid (0.8 g, optical purity 98.6%) was added to adjust the pH to 8. Methanol was removed by distillation

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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionic acid (151 kg, enantiomeric purity 97.6%) in toluene (531 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-isobutylphenyl)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-isobutylphenyl)propionic acid was then reworked to produce more S(-) sodium 2-(4-isobutylphenyl)propionate.

## EXAMPLE 11

Hydrochloric acid (76 l, SG 1.18) was added over 15 minutes to a mixture of S(-) sodium 2-(4-isobutylphenyl)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-isobutylphenyl)propionic acid (121.3 kg, 76%, enantiomeric purity, 99.4%).

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## EXAMPLE 12

Tablets are prepared from the following ingredients:

|                                                     | mg/tablet | % w/w |
|-----------------------------------------------------|-----------|-------|
| <b>Core</b>                                         |           |       |
| S(-)sodium 2-(4-isobutylphenyl)propionate dihydrate | 680       | 75.2  |
| methocel E50                                        | 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   |
| <b>Film Coat</b>                                    |           |       |
| hydroxypropylmethylcellulose                        | 20        |       |
| white colouring agent                               | 6         |       |
| talc                                                | 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 |
|-----------------------------------------------------|-----------|-------|
| <b>Core</b>                                         |           |       |
| S(-)sodium 2-(4-isobutylphenyl)propionate dihydrate | 160       | 55.2  |
| maize starch                                        | 128       | 44.2  |
| stearic acid                                        | 1.6       | 0.6   |
| <b>Sugar Coat</b>                                   |           |       |
| varnish layer                                       | 1.3       |       |
| acacia 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

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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            | 20.5  |
| WITEPSOL H 185 (WITEPSOL is the Trade-mark of Dynamit Nobel) | 1000           | 47.6  |
| WITEPSOL H 15 (WITEPSOL 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/sachet | % w/w |
|-----------------------------------------------------|-----------|-------|
| S(-)sodium 2-(4-isobutylphenyl)propionate dihydrate | 512       | 16.5  |
| pulverised sugar                                    | 1000      | 32.2  |
| malic acid                                          | 350       | 11.3  |
| sodium saccharin                                    | 25        | 0.8   |
| sodium bicarbonate                                  | 476       | 15.3  |
| sodium carbonate                                    | 143       | 4.6   |
| flavour                                             | 100       | 3.2   |
| $\beta$ -cyclodextrin                               | 500       | 16.1  |

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

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 fotofobia 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 de 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-dimetilaminoetanol, 2-dietilaminoetanol, lisina, arginina, histidina, cafeína, procaína, N-etilpiperidina, hidrabamina, colina, betaina, etilendiamina, glucosamina, TRIS(hidroximetil aminoetano, metilglucamina, teobromina, pruinas, 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 fotofobia 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. Éstos 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:

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 patentes 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

- 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)

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.

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.

## 5. ANEXOS

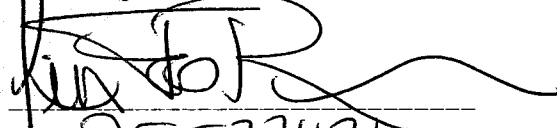
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

- 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 Secretaria 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. 79732186.

**DILIGENCIA DE RECONOCIMIENTO  
Y PRESENTACION PERSONAL**

Ante el Notario Once del Circulo de Santa Fe de  
Bogotá, compareció

Quién exhibió la C.C. No. 79532786

expedida en Bogotá T.P. 71398  
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 \_\_\_\_\_

Santafé de Bogotá, D.C.

**16 SET 2004**

Firma del Declarante

HUELLA

Autorizó la anterior Diligencia

REPUBLICA DE COLOMBIA  
NOTARIO ONCE DEL CIRCULO DE SANTA FE DE BOGOTA, D.C.

**ZULMA NAVARRO DE BAPTISTA**  
NOTARIA ONCE

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



95 103

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>(51) International Patent Classification <sup>6</sup> :</b><br><b>A61K 9/20</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | <b>A2</b> | <b>(11) International Publication Number:</b> <b>WO 97/30699</b><br><b>(43) International Publication Date:</b> 28 August 1997 (28.08.97)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>(21) International Application Number:</b> PCT/EP97/00841<br><b>(22) International Filing Date:</b> 19 February 1997 (19.02.97)<br><b>(30) Priority Data:</b><br>9603699.1 21 February 1996 (21.02.96) GB<br><b>(71) Applicant (for all designated States except US):</b> THE BOOTS COMPANY PLC [GB/GB]; 1 Thane Road West, Nottingham NG2 3AA (GB).<br><b>(72) Inventor; and</b><br><b>(75) Inventor/Applicant (for US only):</b> PRICE, Ian, Ashley [GB/GB]; The Boots Company plc, 1 Thane Road West, Nottingham NG2 3AA (GB).<br><b>(74) Agent:</b> SMITH, Elizabeth, Jane; The Boots Company plc, Group Patents Dept., Building D31, 1 Thane Road West, Nottingham NG2 3AA (GB).                                                  |           | <b>(81) Designated States:</b> 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, UG), 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).<br><br><b>Published</b><br><i>Without international search report and to be republished upon receipt of that report.</i> |
| <b>(54) Title:</b> DOSAGE FORM OF IBUPROFEN<br><br><b>(57) Abstract</b><br><br>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 a 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, ie greater than 35% by weight. Thus, there is a problem to include the  
5 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  
10 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.

15 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  
20 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  
25 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)<sub>2</sub>, CaCO<sub>3</sub>, NaOH, KOH,  
30 NH<sub>4</sub>OH, Na<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, KHCO<sub>3</sub>, (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub>, NH<sub>4</sub>HCO<sub>3</sub> (in an amount of 25% to 110% of the equivalent quantity of ibuprofen). The mixture obtained is then granulated, dried if appropriate, and then tableted 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 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.

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 4834966). 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 characterises 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 characterised 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 4609675, 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

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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  
5 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  
10 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 6.5-15Kp and a disintegration time of less than 10  
15 minutes. Suitably, the alkali metal carbonate or bicarbonate is present in an amount of 3-20% by weight of the dosage form, preferably 4-16% 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  
20 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 65% by weight of the dosage form.  
25 Preferred dosage forms include 25-65% by weight carrier material, more preferably 40-60% 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.

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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

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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  
5 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%  
10 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  
15 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  
20 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  
25 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  
30 composition.

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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 2.5-6:1:0.8-1.4 parts by weight.

10 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.

15 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.

25 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).

15 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.

20 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 6.5-15Kp, 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.

25 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 6.5-15Kp and a disintegration time of less than 10 minutes at a compression force above 80MPa. More preferred formulations exhibit a crushing strength of 6.5-15Kp

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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

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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 an 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.

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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.

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. 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).

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 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.

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 cough suppressant and/or an expectorant.

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Suitable antihistamines include acrivastine, astemizole, azatadine, azelastine, bromodiphenhydramine, brompheniramine, carbinoxamine, cetirizine, chlorpheniramine, cyproheptadine, dexbromopheniramine, dexchlorpheniramine, diphenhydramine, ebastine, ketotifen, lodoxamide, loratidine, levocabastine, 5 mequitazine, oxatomide, phenindamine, phenyltoloxamine, pyrilamine, setastine, tazifylline, temelastine, terfenadine, tripelennamine 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 10 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 15 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, periarticular disorders and soft tissue injuries. They may also be used in the treatment of postoperative pain, postpartum pain, dental pain, dysmenorrhoea, headache, 20 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 25 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 30 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 glycollate 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 (Kp)

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.

A23  
115C. 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       |

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## 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       |

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117Examples 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     |

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118Examples 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 6000 (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)     | 256mg      | 256mg      | 256mg      |
| Ibuprofen sodium salt dihydrate     | 51.7%      | 49.7%      | 49.7%      |
| 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.

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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 glycollate            | 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        |

Examples 18-20

| Ingredients                         | Example 18 | Example 19 | Example 20 |
|-------------------------------------|------------|------------|------------|
| Content of drug per tablet (mg)     | 256mg      | 256mg      | 256mg      |
| 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          | -          | 1.6%       | 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        |

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)    | 6.0        | 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 513.0mg using the same proportions of ingredients as given in Examples 24-26.

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124Example 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 ExamplesA. Tablets containing 256mg racemic ibuprofen sodium salt

(Ibuprofen equivalent 200mg)

5

Comparative Formulation A(without (bi)carbonate component)

| <u>Ingredient</u>                  | <u>% (wt)</u> |
|------------------------------------|---------------|
| 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%          |

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

|    |                                    | <u>Comparative Formulation B</u><br><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.

- 20 Figure 2 shows a comparison of the disintegration properties of the tablets having 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<br>wt (mg) | Ex 28<br>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<br>wt (mg) | Ex 30<br>wt (mg) | Ex 31<br>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             |

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.

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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 6.5-15Kp 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.

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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 glycollate.
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 6.5-15Kp 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.
- 15 13. The use according to either one of claims 11 and 12 wherein the carrier material 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.
- 20 15. The use according to anyone of claims 11 to 14 wherein carrier material comprises 45-60% microcrystalline cellulose, 2-10% croscarmellose sodium and 2-20% sodium carbonate or bicarbonate.
- 25 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 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.

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 16 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 6.5-15Kp 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.

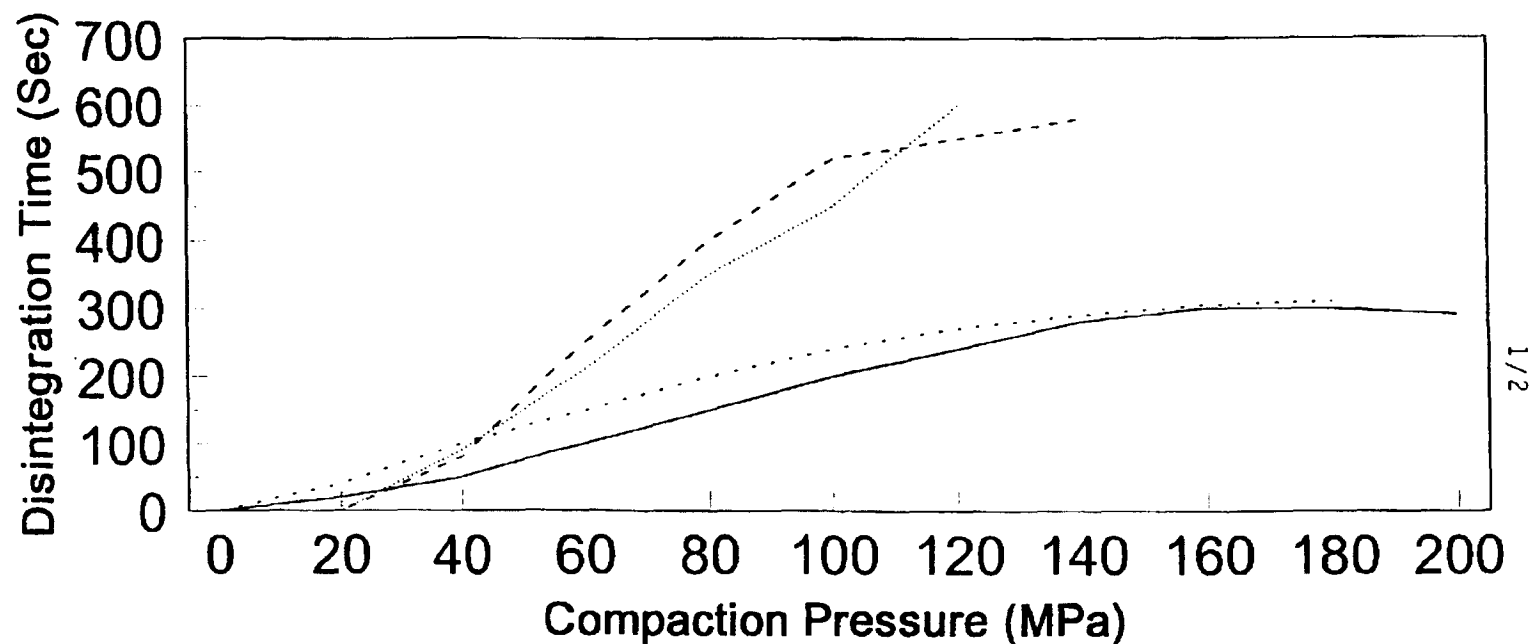
10 26. A solid formulation having a layer comprising a composition comprising an ibuprofen medicament together with a carrier material, the ibuprofen medicament being present to an extent of 35% or more by weight of the composition and the carrier material comprising a compressible filler component combined 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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Figure 1

## Ibuprofen Salts

Effect of sodium carbonate on disintegration time



Na Ibuprofen - 40mg Na<sub>2</sub>CO<sub>3</sub>

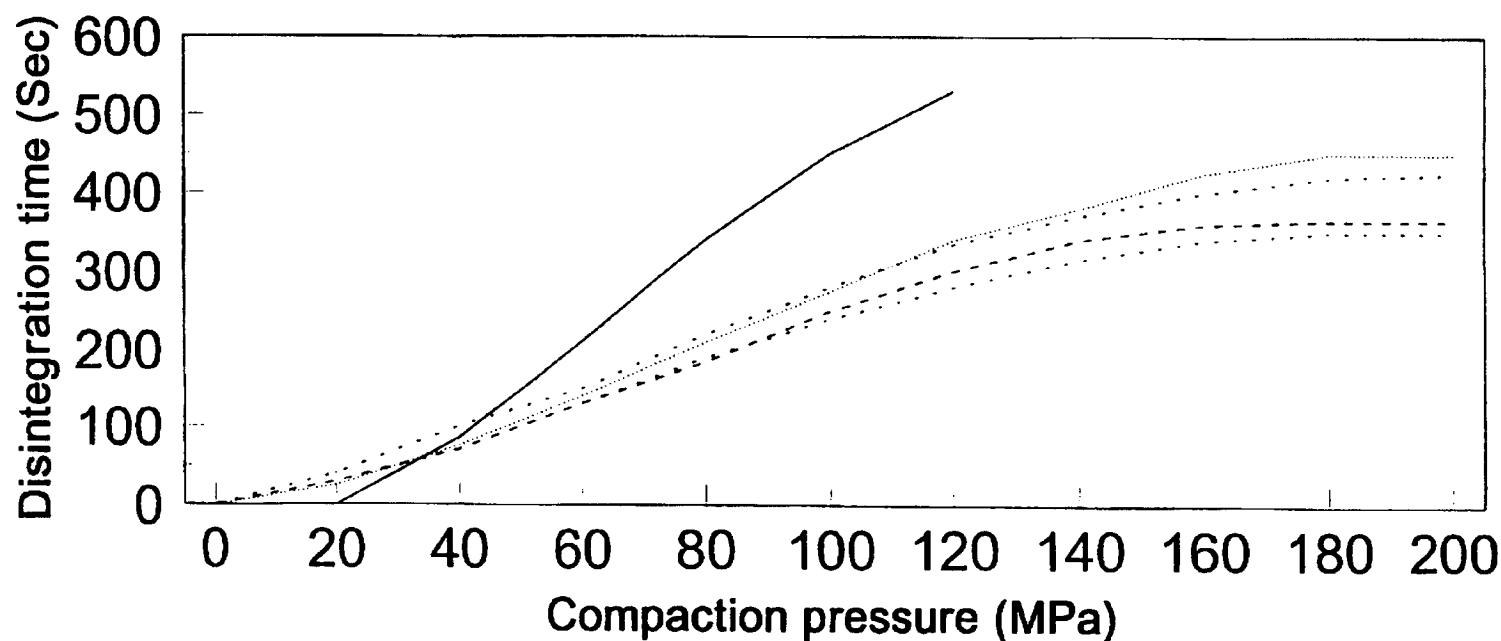
Na Ibuprofen - 0mg Na<sub>2</sub>CO<sub>3</sub>

Lysine Ibuprofen - 26mg Na<sub>2</sub>CO<sub>3</sub>

Lysine Ibuprofen - 0mg Na<sub>2</sub>CO<sub>3</sub>

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Figure 2

Ibuprofen sodium saltEffect 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

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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**5,278,337 1/1994 Manimaran et al. .... 562/401  
5,302,751 4/1994 Manimaran et al. .... 562/401[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  
Jun. 5, 1991 [GB] United Kingdom ..... 9112058[51] **Int. Cl.<sup>6</sup>** ..... **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**

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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-Isobutylphenyl)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-isobutylphenyl)propionic acid or S(+)-ibuprofen and R(-)-2-(4-isobutylphenyl)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 characterised 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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate in water with no additional pharmaceutical excipient and (b) compositions comprising the calcium salt of S(+)-ibuprofen.

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

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Under similar circumstances S(+)-ibuprofen would tend to stick and generally display poor flow characteristics. S(-) sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate includes the anhydrous form and hydrated forms. Preferably the dihydrate is used.

S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate. The compositions of the invention are generally prepared in unit dosage form. Preferably the unit dosage of S(-)-sodium 2-(4-isobutylphenyl)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-

ceutical forms for such administration, for example tablets and capsules. Suitably tablets may be prepared by mixing S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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, alginic 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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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

obtained by mixing S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate as the dihydrate.

Preferably oral liquid compositions comprise a) 0.1-10% S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate may be dispersed in a pharmaceutically acceptable cream, ointment or gel. A suitable cream may be prepared by incorporating S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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 neutralising agent. It is a particular advantage of the present invention that as a result of the high water solubility of S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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. LABRAFIL and GELOT (both tradenames of Gattefosse) are examples of self-emulsifying bases.

A suitable ointment comprises a) 1-15% S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate may, if desired, be associated with other compatible pharmacologically active ingredients and/or enhancing agents. Thus, for example, S(-)-sodium 2-(4-isobutylphenyl)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, loratidine, levocubastine, mequitazine, oxatomide, phenindamine, phenyltoloxamine, pyrilamine, setastine, tazifylline, temclastine, terfenadine, tripelenamine or triprolidine. Suitable cough suppressants include caramiphen, codeine or dextromethorphan. Suitable decongestants include pseudoephedrine, phenylpropanolamine and phenylephrine. Suitable expectorants include guaifensin, potassium citrate, potassium guaiacolsulphonate, potassium sulphate and terpin hydrate.

S(-)-sodium 2-(4-isobutylphenyl)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, periarticular disorders and soft tissue injuries. S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate is present as the dihydrate.

S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate to a mammal in need thereof.

This surprising effect occurs not only when S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)propionate together with a diluent or carrier characterised in that S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate is used as the source of S(-)-sodium 2-(4-isobutylphenyl)propionate.

In a further aspect the present invention provides a process to prepare a pharmaceutical composition comprising S(-)-sodium 2-(4-isobutylphenyl)propionate having an enantiomeric purity of at least 90% together with a pharmaceutically acceptable carrier 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.

A preferred process for preparing a solid composition in tablet form comprises combining 10-90% of S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate includes the anhydrous form and hydrated forms for example the dihydrate.

S(-)-sodium 2-(4-isobutylphenyl)propionate may be prepared by neutralising S(+)-2-(4-isobutylphenyl) propionic acid with a sodium-containing base. It would be expected that in order to prepare S(-)-sodium 2-(4-isobutylphenyl) propionate in an enantiomerically pure form, for example greater than 90%, then the S(+)-2-(4-isobutylphenyl) 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-isobutylphenyl) 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-isobutylphenyl) 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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl) 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-isobutylphenyl)propionic acid said sodium salt having an enantiomeric purity of greater than 90% that is 90-100% comprising the steps of:

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

or

e) converting said solid into 2-(4-isobutylphenyl) 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-isobutylphenyl)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-isobutylphenyl)propionate having an enantiomeric purity of greater than 90% comprising the steps of:

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

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

Preferably the process provides S(-)-sodium 2-(4-isobutylphenyl)propionate having an enantiomeric purity of greater than 95%. More preferably the process provides S(-)-sodium 2-(4-isobutylphenyl)propionate having an enantiomeric purity of greater than 98%. Most preferably the process provides S(-)-sodium 2-(4-isobutylphenyl) 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-isobutylphenyl)propionate having an enantiomeric of greater than 99% comprising the steps of:

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

2-(4-Isobutylphenyl)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-Isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionic acid will give a pH value of

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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 C<sub>1-4</sub> 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

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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 C<sub>1-4</sub> 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.,  $[\alpha]_D^{22} = -4.3^\circ$  (c 0.94). A sample converted back into S(+)-2-(4-isobutylphenyl)propionic acid as described above had  $[\alpha]_D^{22} = +58.7^\circ$  (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 flake (4.0 g) in water (15 ml) was added. After cooling to 2° C., the salt which crystallised out was collected by filtration.

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

## EXAMPLE 4

A mixture of S(+)-2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionic acid and assayed as described previously. Enantiomeric purity 99.8%.

## EXAMPLE 6

A mixture of S(+)-2-(4-isobutylphenyl)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-isobutylphenyl)propionate dihydrate (yield 53.7%). Enantiomeric purity 98.2%.

## EXAMPLE 7

A mixture of S(+)-2-(4-isobutylphenyl)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-isobutylphenyl)propionic acid (20.6 g, enantiomeric purity 98.6%) in toluene (150 ml). After the addition more S(+)-2-(4-isobutylphenyl)propionic acid (0.8 g, optical purity 98.6%) was added to adjust the pH to 8. Methanol was removed by distillation

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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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionic acid (151 kg, enantiomeric purity 97.6%) in toluene (531 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-isobutylphenyl)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-isobutylphenyl)propionic acid was then reworked to produce more S(-) sodium 2-(4-isobutylphenyl)propionate.

## EXAMPLE 11

Hydrochloric acid (76 l, SG 1.18) was added over 15 minutes to a mixture of S(-) sodium 2-(4-isobutylphenyl)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-isobutylphenyl)propionic acid (121.3 kg, 76%, enantiomeric purity, 99.4%).

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## EXAMPLE 12

Tablets are prepared from the following ingredients:

|                                                     | mg/tablet | % w/w |
|-----------------------------------------------------|-----------|-------|
| <b>Core</b>                                         |           |       |
| S(-)sodium 2-(4-isobutylphenyl)propionate dihydrate | 680       | 75.2  |
| methocel E50                                        | 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   |
| <b>Film Coat</b>                                    |           |       |
| hydroxypropylmethylcellulose                        | 20        |       |
| white colouring agent                               | 6         |       |
| talc                                                | 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 |
|-----------------------------------------------------|-----------|-------|
| <b>Core</b>                                         |           |       |
| S(-)sodium 2-(4-isobutylphenyl)propionate dihydrate | 160       | 55.2  |
| maize starch                                        | 128       | 44.2  |
| stearic acid                                        | 1.6       | 0.6   |
| <b>Sugar Coat</b>                                   |           |       |
| varnish layer                                       | 1.3       |       |
| acacia 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

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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 Gattefosse)

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            | 20.5  |
| WITEPSOL H 185 (WITEPSOL is the Trade-mark of Dynamit Nobel) | 1000           | 47.6  |
| WITEPSOL H 15 (WITEPSOL 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/sachet | % w/w |
|-----------------------------------------------------|-----------|-------|
| S(-)sodium 2-(4-isobutylphenyl)propionate dihydrate | 512       | 16.5  |
| pulverised sugar                                    | 1000      | 32.2  |
| malic acid                                          | 350       | 11.3  |
| sodium saccharin                                    | 25        | 0.8   |
| sodium bicarbonate                                  | 476       | 15.3  |
| sodium carbonate                                    | 143       | 4.6   |
| flavour                                             | 100       | 3.2   |
| $\beta$ -cyclodextrin                               | 500       | 16.1  |

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

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5,696,165

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EXAMPLE 19

(Cold Relief Tablet)

|                                                      | mg/tablet | % w/w |
|------------------------------------------------------|-----------|-------|
| <b>Core</b>                                          |           |       |
| S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate | 160       | 50.6  |
| 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   |
| <b>Film Coat</b>                                     |           |       |
| 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-isobutylphenyl)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.

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EXAMPLE 21

(Topical Gel)

|                                                      | %      |
|------------------------------------------------------|--------|
| S(-)-sodium 2-(4-isobutylphenyl)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-isobutylphenyl)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-isobutylphenyl)propionate dihydrate | 1.30   |
| LYCASIN® 80/55 (1)                                   | 40.0   |
| glycerin                                             | 20.0   |
| domiphen 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 domiphen 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.

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EXAMPLE 24

(Oral Liquid (Low Strength))

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

The xylitol 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 domiphen 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   |
| domiphen 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 domiphen 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 unsuitable 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    |
| domiphen bromide                                     | 0.005 |
| flavour                                              | 0.2   |
| alcohol 96%                                          | 2.0   |
| purified water to                                    | 100   |

This is prepared in a similar manner to Example 24.

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EXAMPLE 27

(Cold Relief Powder (Hot Drink))

|                                                      | mg/sachet | % w/w  |
|------------------------------------------------------|-----------|--------|
| S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate | 130       | 6.5    |
| β-cyclodextrin                                       | 441       | 22.0   |
| pseudoephedrine hydrochloride                        | 30        | 1.5    |
| sodium saccharin                                     | 20        | 1.0    |
| pulverised 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   |
| pseudoephedrine hydrochloride                        | 30        | 0.9   |
| sodium saccharin                                     | 20        | 0.6   |
| β-cyclodextrin                                       | 1000      | 28.4  |
| pulverised 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.  $[\alpha]_D^{22} = +4.0^\circ$  (c 0.934).

EXAMPLE 30

(Tablet)

|                                                      | mg/tablet | % w/w |
|------------------------------------------------------|-----------|-------|
| S(-)-sodium 2-(4-isobutylphenyl)propionate dihydrate | 769       | 69.9  |
| microcrystalline cellulose                           | 208       | 18.9  |
| croscarmellose sodium                                | 32        | 2.9   |
| lactose                                              | 84        | 7.6   |

-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<br>(KN) | Hardness<br>(Kp) | Disinte-<br>gration<br>Time | Dissolution Time (minutes) |                 |                 |                 |
|-------------------------|------------------|------------------|-----------------------------|----------------------------|-----------------|-----------------|-----------------|
|                         |                  |                  |                             | pH 7.2                     |                 | pH 6.0          |                 |
|                         |                  |                  |                             | T <sub>50</sub>            | T <sub>80</sub> | T <sub>50</sub> | T <sub>80</sub> |
| Tablet A                | 11.0             | 4.72             | 10 m                        | 9.1                        | 16.0            | —               | —               |
|                         | 17.2             | 5.38             | —                           | —                          | —               | 8.7             | 15.8            |
| Comparative<br>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 attained

T<sub>50</sub> = time taken for 50% of active ingredient to be released from the tablet

T<sub>80</sub> = time taken for 80% 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)-<br>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

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 <sub>50</sub>            | T <sub>80</sub> |
| Tablet B             | 9.1                        | 24.1            |
| Comparative Tablet B | 21.4                       | NA              |

NA = not attained

T<sub>50</sub> = time taken for 50% of active ingredient to be released

T<sub>80</sub> = time taken for 80% 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.

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

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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.

\* \* \* \* \*