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(72) Inventeurs/Inventors:
Geisslinger, Gerd, DE;
Brune, Kay, DE

(73) Propriétaire/Owner:
PAZ Arzneimittelentwicklungsgesellschaft GmbH, DE

(74) Agent: MARKS & CLERK

(54) Titre : TRAITEMENT DE LA DOULEUR ET DE L'INFLAMMATION CHEZ LES MAMMIFERES AVEC LE FLURBIPROFENE

(54) Title: TREATMENT WITH FLURBIPROFEN OF PAIN AND INFLAMMATION IN MAMMALS

(57) Abrégé/Abstract:
Described are drugs for the treatment of painful and/or inflammatory conditions with flurbiprofen, the previously separated enantiomers of flurbiprofen being combined in the ratio 99.5-0.5% to 0.5-99.5% and processed with the usual pharmaceutical vehicles and additives to give drugs. For pain, or chronic conditions in which pain is a dominant factor, the mixture of enantiomers contains 50-99.5%, preferably 60-95%, of R(-)-fluorbiprofen and for inflammations, or chronic conditions in which inflammation is a dominant factor, the mixture contains 50-99.5%, preferably 60-95%, of S(+)-flurbiprofen.

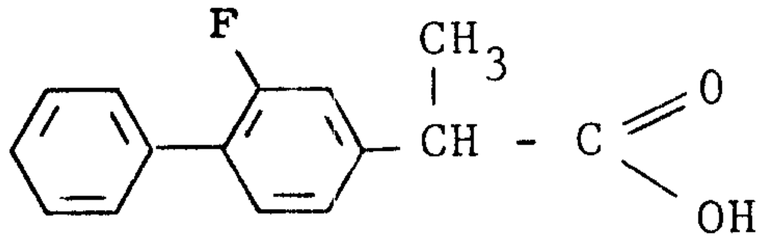
ABSTRACT OF THE DISCLOSURE

Described are drugs for the treatment of painful and/or inflammatory conditions with flurbiprofen, the previously separated enantiomers of flurbiprofen being combined in the ratio 99.5-0.5% to 0.5-99.5% and processed with the usual pharmaceutical vehicles and additives to give drugs. For pain, or chronic conditions in which pain is a dominant factor, the mixture of enantiomers contains 50-99.5%, preferably 60-95%, of R(-)-fluorbiprofen and for inflammations, or chronic conditions in which inflammation is a dominant factor, the mixture contains 50-99.5%, preferably 60-95%, of S(+)-flurbiprofen.

TREATMENT WITH FLURBIPROFEN OF PAIN AND INFLAMMATION IN MAMMALS

The subject of the present invention are flurbiprofen-containing medicaments and their use in the combating of pains and/or inflammations in humans and animals which, in the case of pains, preponderantly contain R(-)-flurbiprofen and in the case of inflammations preponderantly S(+)-flurbiprofen. The active material can consist of the previously separated flurbiprofen enantiomers in the desired ratio.

Flurbiprofen (2-(2-fluoro-4-biphenylyl)-propionic acid) of the following structure I



is a long since known medicament (DE-C-1518528) which, because of its anti-inflammatory, antipyretic and analgesic action, is used to a wide extent (Martindale, The Extra Pharmacopeia, 20th ed., page 18, 1989).

In the case of the chemical synthesis, flurbiprofen is normally obtained as racemate and is also used in this form in various medicaments. Furthermore, it is known that this material, especially in the case of long-term treatment of painful and inflammatory processes, shows considerable undesired side effects, especially gastro-intestinal irritations and damages,

such as ulcers, perforations (cf. Martindale, see above).

Since it is known that, in the case of many pharmacologically active 2-arylpropionic acids, the biological in vitro activity (prostaglandin synthesis inhibition, thrombocyte aggregation inhibition) of one enantiomer is greater than that of the other, whereas the side effects in many cases are attributed to both enantiomers or even to the pharmacologically less effective enantiomers, in DE-A 28 09 794 a process is suggested to increase a portion of the pharmacologically-active enantiomers in comparison with the racemate. For this purpose, a solution which contains the racemic active material or an active material already partly enriched in one of the enantiomers is reacted in a non-polar solvent with an optically-active alkylamine, preferably α-phenylethylamine, to give a diastereomeric salt mixture, whereby the amount of solvent does not suffice in order completely to dissolve this salt. Therefore, the sparingly soluble component enriches in the precipitate. Depending upon the optically-active base used and the solvent employed, in this way, inter alia, there can also be prepared the two-optically-active enantiomers of flurbiprofen. However, pharmacological effectivenésses of the enantiomers are not given in the literature.

From Sunshine, A. et al., Clin. Pharmakol. Ther. 41(2), 162, 1987, it is known to use S(+)-flurbiprofen

as analgesic in the case of post-episiotomy pains. In a double blind study, it was thereby found that S-flurbiprofen, compared with the racemate, is, in the case of half dosage, already more effective so that it was assumed that the enantiomer is alone responsible for the analgesic action.

Surprisingly, it was now found that, contrary to this knowledge, not the S(+)- but rather the R(-)-flurbiprofen in recognised pain models is outstandingly analgesically effective. This unexpected result was verified by investigation on two animal models (mouse and rat). Not only in the cramp pain test in the mouse but also in the interleukin 1-induced pain test in the case of the rat, the R-enantiomer, as follows from Figures 1 and 2, is approximately one third to one half as effective. In the case of the rat, other than in the case of other known arylpropionic acids, these results are also clearly to be ascribed to the enantiomers since not only after R- but also after S-flurbiprofen administration, no or only a small inversion took place.

Furthermore, S(+)-flurbiprofen, contrary to the published state of knowledge (see above), is, in the case of administration after episiotomy, preferably anti-phlogistically and not preferably analgesically effective. This also surprising test result was tested on two inflammation models selected independently of

one another. Thus, it was demonstrated on macrophages (peritoneum of the mouse) that S(+)-flurbiprofen inhibits the prostaglandin liberation more markedly than the R(-)-form (Figure 3).

In the case of the carrageenin paw oedema of the rat, S(+)-flurbiprofen is superior in its inflammation-inhibiting action to the R(-)-form, as Figures 3 and 4 demonstrate.

According to the present state of knowledge of the action mechanism of medicaments, in the case of the successful combating of pains of different genesis, one must differentiate as follows.

In the case of analgesics, the rapid onset of action has an outstanding value. In the case of oral, topical and other non-parenteral forms of administration, this presupposes first an accelerated liberation, as well as a sufficiently good bioavailability of the active material or active materials. Furthermore, such pain agents block because the transmission of apprec-iations of pain takes place via a transmission system ascending from the periphery to the central nervous system (CNS), in which control mechanisms present on different levels of the CNS participate on their receptors with chiral structures.

Furthermore, it is assumed that the inhibition of the prostaglandin biosynthesis acts as common feature of the action mechanism in the case of analgesics and

antiphlogistics (Vane, J.R., Nature 231 et seq., 1971, Higgs, G.A., Brit J. Clin. Pharmacol. 10, 233 et seq., 1980). Thus, this action is to be understood as connecting member between the pain alleviation and the inflammation inhibition. However, all effects cannot be explained with this mechanism alone. Thus, in the case of acidic analgesics and/or antiphlogistics, such as flurbiprofen, neurophysiological effects are also probable as a result of inclusion of such active materials in cell membranes.

Prostaglandins participate in the triggering of classical symptoms in the case of inflammations, such as reddening, swelling, oedema and thus of pain. Such inflammatory changes can be weakened by inflammation-inhibiting active materials, whereby the patient simultaneously experiences an alleviation of pain. At present, this is the main field of use of the non-steroidal inflammation inhibitors (antiphlogistics). Of the antiphlogistics, only few representatives can be used for the differentiated or pure treatment of pain. To these belong e.g. indomethacin, naproxen or ibuprofen which are also analgesically effective in the case of spasms of the smooth musculature. The by far the greater number of non-steroidal antiphlogistics is withheld from anti-rheumatic therapy because of the insufficient analgesic action and because of a series of undesired actions.

Accordingly, it is an object of the present invention to provide a readily administratable and problem-free, parenterally-administratable medicament which is effective in the case of pains and/or inflammations and possesses the smallest possible side effect quotient. Furthermore, such medicaments are to be simple to produce, should flow in quickly and controllably, be characterised by good bioavailability, and be adaptable, in the case of diseases with different analgestic and/or antiphlogistic requirements, by simple variation to the frequently occurring disease manifestation.

Summary of the Invention

The present invention provides a medicament for the treatment of painful or inflammatory diseases with flurbiprofen, wherein the flurbiprofen, in the case of pains, or in the case of chronic disease pictures with dominating states of pain, comprises 60 to 99.5% R(-)-flurbiprofen, remainder S(+)-flurbiprofen, or wherein the flurbiprofen, in the case of inflammations, or in the case of chronic disease pictures with dominating inflammations, comprises 60 to 99.5% S(+)-flurbiprofen, remainder R(-)-flurbiprofen.

The present invention also provides a medicament for the effective treatment of painful diseases, the medicament comprising 2-(2-fluoro-4-biphenylyl)-propionic acid ("flurbiprofen") and a pharmaceutical carrier, an adjuvant material, or both, wherein the medicament comprises R(-)-flurbiprofen which is substantially free from S(+)-flurbiprofen.

The present invention also provides a medicament for the effective treatment of painful and inflammatory diseases, the medicament comprising 2-(2-fluoro-4-biphenylyl)-propionic acid ("flurbiprofen") and a pharmaceutical carrier, an adjuvant, or both, wherein the medicament comprises R(-)-flurbiprofen which is substantially free from S(+)-flurbiprofen.

The present invention also provides a medicament effective for the treatment of a disease characterized by pain or inflammation, which medicament comprises (a) a mixture of previously-separated R(-) and S(+) enantiomers of flurbiprofen; and (b) a pharmaceutically acceptable carrier, wherein the ratio of the R(-) and S(+) enantiomers of flurbiprofen is from about 99.5:0.5% to 0.5:99.5%, and

wherein the medicament further comprises 2-10% of a release agent.

The enantiomers are, in a ratio adapted to the particular use, worked up together with suitable pharmacologically compatible adjuvant and carrier materials, to give the medicaments according to the invention.

Brief Description of the Drawings

The invention may be more readily understood by referring to the accompanying drawings by which:

Figs. 1 to 4 are graphs of tests in rats for cramp pain, interleukin-1-induced pain, prostaglandin production and carrageenin-induced paw oedema for the R(-) and S(+) enantiomers of flurbiprofen;

Fig. 5 is a graph showing the speed of dissolving for a racemate and pseudoracemate (i.e., mixture of previously-separated enantiomers) of flurbiprofen;

Fig. 6 is a plot of a writhing test in mice using the flurbiprofen enantiomers; and

Fig. 7 is a plot of intestinal lesion occurrence in rats using the flurbiprofen enantiomers.

Known, undesired side effects, such as e.g. stomach-intestine complaints, are, in the case of non-steroidal inflammation inhibitors, substantially coupled with the action mechanism. In medicine, these are taken into account in the case of the administration in the case of diseases of the rheumatic type. However, in the case of patients who primarily require a pain alleviation, the quota of undesired actions is to be minimal. In the case of flurbiprofen administration, according to the invention this can be achieved in that the proportion of R(-)-flurbiprofen is increased in the enantiomer combination or the R(-)-flurbiprofen is administered in pure form since the R(-)-flurbiprofen, on the one hand, as stated above, has a stronger pain-alleviating action in the acute case than the S-enantiomer and, on the other hand, also manifests a lower grade toxicity on the gastrointestinal tract than the racemate or the S-enantiomer. A content of 60 - 99.5%, preferably of 60 - 95%, of R(-)-flurbiprofen and 40 - 0.5%, preferably 40 - 5% of S(+)-flurbiprofen in the active material is provided for the alleviation of pain.

On the other hand, for the treatment of inflammatory diseases, S(+)-flurbiprofen is preponderantly desired so that the active material thereby consists of 60 - 99.5%, preferably 40 - 95% of S(+)-flurbiprofen and of 40 - 0.5%, preferably 40 - 5% of R(-)-flurbiprofen.

The enantiomers are either isolated from flurbiprofen racemate in per se known manner or prepared by stereospecific synthesis.

Surprisingly, it is shown that the enantiomers previously separated according to the invention and then again mixed together again in the desired mixing ratio in the final medicament display substantially quicker active material liberation than the racemate. This finding is important for the therapeutic use since the quicker active material liberation also results in a correspondingly quicker inflow of the active material into the body, which precisely in the case of pain agents is extraordinarily important.

The speed of dissolving was thereby determined according to the procedure of USP XXII, p. 683 for ibuprofen tablets (0.9 l of phosphate buffer pH 7.2, stirrer speed 150 r.p.m., concentration determination by UV absorption measurement at 220 nm, determination via 10 tablets). Flurbiprofen tablets with 100 mg active material according to Example on page 13 were used. The results are reproduced in the graph according to Figure 5.

Medicaments with flurbiprofen are usually administered to humans and animals in the form of tablets, coated tablets or powder, granulate, suppositories, as well as sterile solution parenterally or non-sterile solutions or suspensions orally. Usually, a rapid commencement of action is desired but forms of administration with delayed liberation can also be produced by means of which a longer-lasting action is ensured. Such forms of administration with delayed liberation are preferably those which first liberate

in the distal intestinal section, such as in the colon, i.e. delayed after taking, but then spontaneously. The patient with rheumatic complaints, such as morning stiffness, can take such an "evening before pill" in order, according to the invention, to wake up the next morning free of complaint. The known formulations for racemic flurbiprofen can, without further change, also be used directly for the enantiomer mixture according to the invention.

An oral administration in the form of tablets, coated tablets or capsules or possibly also chewing tablets or chewing masses is especially preferred, whereby the powdered active materials are mixed in the usual way with suitable particle division with the known pharmaceutical adjuvant and carrier materials and further pressed into tablets or coated tablets or filled into gelatine capsules.

Depending upon the form of administration, the flurbiprofen enantiomers are contained in the medicaments according to the invention in an amount of 2 to 60% of the formulation.

Solid forms of administration contain 20 to 80% of filling materials. As such, there can, inter alia, be used starch, lactose, glucose, mannitol, calcium carbonate, calcium phosphate, cellulose and the like products known in the technology for this purpose. In order to accelerate the liberation and thus to improve the availability, a disintegration agent is added to the formulation in an amount of 2 to 10%. As disintegration agents, there have proved to be useful especially carboxymethyl starch, carboxymethyl cellulose, polyvinylpyrrolidone and silica gel. Furthermore, the formulation can also contain lubricating agents in an amount of 0 to 5%, whereby talc, magnesium or calcium stearate or other adjuvant materials with lubricating properties can be added to the powder in order to simplify the working up.

The powders are usually mixed dry and subsequently moist granulated with a usual binding agent, for example starch paste or also water, and dried. The granulate can then subsequently be pressed into tablets, possibly with the addition of further lubricants, or filled into capsules. It is advantageous subsequently to coat tablets with a sugar coating or to lacquer with a soluble film former, whereby, for the improvement of the administration, this coating can also contain flavouring and sweetening materials. Besides the coating agents usual in pharmaceutical technology (sugars, such as saccharose or lactose, various types of cellulose, such as methyl cellulose or cellulose acetate phthalate, polyacrylates, polymethacrylates or polyvinyl acetate phthalate), carnauba wax can preferably be used as polishing agent.

The filling into capsules can take place either as dry powder or granulate or pellets or as suspension in a vegetable oil or other pharmaceutically compatible liquid carrier material. The active materials, relatively sparingly soluble in water, can also be suspended in water in the presence of a suitable suspension agent, such as tragacanth, methyl cellulose etc.

Also known is the use of flubiprofen active materials in the form of suppositories for the rectal or vaginal administration, whereby, besides the active

material, fats or polyglycols can be used as carrier materials, the melting points of which either lie in the body temperature range or also dissolve after the administration.

Furthermore, the speed of dissolving can also be altered in that, instead of flurbiprofen, its salts are used. Alkali metal, alkaline earth metal, ammonium or amino acid salts which are water-soluble are thereby preferred. Complex salts with basic amino acids can be used directly, mixed salts with neutral or acidic amino acids are previously converted into the alkali metal, alkaline earth metal or ammonium salts. The methods also known for the other medicaments of applying the active material to aluminium oxide gels can also be carried out with the flurbiprofens according to the invention. The prepared flurbiprofen salts can then be further worked up in known manner as described above. The flurbiprofen salts are preferably prepared indirectly in that one adds the bases needed for the salt formation to the binding agent solution serving for the granulation so that the corresponding salts form during the granulation process.

For the treatment of pain with the flurbiprofen medicaments according to the invention, about 0.25 to 5 mg of active material per kg of body weight are necessary which, for example, can be taken in 2 to 5 portions spread out over the day. Retard forms were

especially used in order to reduce the administrations to 1 or 2 dosages. Therefore, the single dose should contain between 10 and 100 mg of active material.

Pharmacological experiments

Analgesic action in the writhing test (cf. Domer, Animal Exp. in Pharm. Analysis, 1971, p. 312)

In each case, in equal numbers, male and female NMRI mice (defined strain) with an average body weight (BW) of about 20 g receive per dosage group either 1.0 mg S(+)- or 1.0 mg R(-)-flurbiprofen per kg BW or an adequate amount of placebo (N = 6) p.o. About 30 min. after administration of the test preparation, the experimental animals receive an i.p. injection of an aqueous acetic acid solution administered in usual concentration. There is observed the appearance or non-appearance of typical dragging movements in the sequential process during an observation time of 30 min. The results are reproduced in Figure 6, whereby, in the ordinate there is plotted the number of dragging movements. In comparison with the control, the result is significant in the case of R administration ($p < 0.05$ Student's test two-sided).

Action on the carrageenin-induced paw oedema of the rat (cf. Domer, Animal Exp. in Pharm. Analysis, 1971, p. 303).

To male Sprague-Dawley rats of, in each case, 120 - 150 g BW were administered the test substances

(0.3 mg/kg BW) per os with a stomach probe. Immediately thereafter, 0.1 ml of a 1% carrageenin solution was injected subplantary in the left rear paw in order to provoke oedema. After 3 hours p.a., the paw volumes (modified method according to Hofrichter) were determined by means of a plethysmometer. By means of S(+)-flurbiprofen, the oedema is inhibited by 64% and by R(-)-flurbiprofen by only 18% (cf. Figure 4).

Gastrointestinal toxicity on the rat (cf. Beck et al., Arch. Toxicology, 1990, pp. 210-217).

R(-)-Flurbiprofen causes considerably less gastric ulcerations after oral administration of 25 mg of test substance per kg BW in the investigated fasting rat collective (N = 9) than S(+) or racemic flurbiprofen. In the small intestine, after oral administration of 25 mg R(-) amounts per kg of BW, no lesions were observed after the taking of food, as is to be seen from the results of Figure 7.

The test groups are sacrificed after 24 hours, stomach and intestine removed and the stomach opened and cleaned with salt solution. The number of ulcerations multiplied by their diameter in mm is given as "gastric ulcer index". The small intestine is investigated unopened for white and brown colour changes. The appropriate sections are cut out and their weight plotted in % in the ratio of the total weight as "intestinal ulcer". The results are significant in the

t-test in comparison with the control.

Medicament compositions

Tablets

One thousand tablets with, in each case, a content of 100 mg flurbiprofen as pseudoracemate are produced as follows:

R(-)-flurbuprofen	50 g
S(+)-flurbiprofen	50 g
lactose	75 g
maize starch	50 g
magnesium stearate	4 g
silicon dioxide	5 g

The enantiomers are finely ground (air jet mill), mixed with the adjuvant materials and pre-compressed. From this, a granulate is produced in known manner which is pressed into tablets of about 235 mg.

With reference to this production procedure, there can also be produced tablets with other enantiomer proportions per tablet in the claimed ratio. Furthermore, on the basis of this composition, there can also be produced tablets with, for example, a total active material proportion of 25 or 50 mg.

Injection solution

A sterile aqueous solution for parenteral administration which, per litre, contains 350 mg of the enantiomer mixture, is prepared, for example, as sodium salt as follows:

R(-)-flurbiprofen sodium salt +)	266 mg
S(-)-flurbiprofen sodium salt +)	87 mg
water p.i.; q.s.	1000 ml

+) 99.5% purity.

Instead of the sodium salts, there can also be used other salts which are obtained after neutralisation of the enantiomer-pure active materials with, for example, ammonia, amino acids, such as lysine, etc., and having regard to the equivalent weights in question. The solutions are filtered into sterile containers and closed.

Hard gelatine capsules

About 1000 hard gelatine capsules with 50 mg R(-)-flurbiprofen for oral administration are produced as follows:

R(-)-flurbiprofen	50 g
lactose	100 g
maize starch	20 g
talc	20 g
magnesium stearate	2 g

The finely ground R(-)-flurbiprofen is mixed homogeneously with the other ingredients and filled in known manner into capsules. Capsules with 25, 75 or 100 mg R(-)-flurbiprofen but also with flurbiprofen enantiomer mixtures in the claimed ratio can also be produced analogously.

Suspension for taking orally

In order to produce 1000 ml of an aqueous suspension, whereby one oral dosage unit (1 teaspoon = 5 ml) contains 5 mg R(-)- as well as 95 mg S(+)-flurbiprofen as aluminium salt, use is made of the following composition:

R(-)-flurbiprofen	1 g
S(+)-flurbiprofen	19 g
citric acid	2 g
benzoic acid	1 g
sugar	700 g
tragacanth	5 g
lemon oil	2 g
water, desalinated; q.s.	1000 ml

Citric acid, benzoic acid, sugar, tragacanth and lemon oil are first suspended with so much water in order that about 800 to 900 ml of suspension are obtained. Thereafter, the micronised flurbiprofen enantiomers are homogeneously stirred in, as well as made up with water to 1000 ml.

Suppositories

A suppository which, as active material, can contain 10 to 100 mg of the enantiomer mixture and weighs about 2 g, is composed as follows:

R(-)-flurbiprofen	90 mg
S(+)-flurbiprofen	10 mg
hard fat	1890 mg
tocopherol	10 mg

If the amount of active material(s) is/are to be reduced, the proportion of hard fat is to be increased to the same extent.

Cream

The production of a cream with 4% flurbiprofen enantiomers takes place in per se known manner, whereby the following components give a typical formulation:

R(-)-flurbiprofen	1.0 g
S(+)-flurbiprofen	3.0 g
triglycerides; average chain	35.0 g
glycerine monostearate-polyoxy-ethylene stearate mixture	6.0 g
polyoxyethylene-fatty acid ester	4.0 g
1,2-propanediol	4.0 g
4-hydroxybenzoic acid methyl ester sodium	0.1 g
xanthan gum	0.2 g
water, desalinated; q.s.	100.0 g

The active materials are dissolved in the oily phase warmed to about 60°C, the also pre-warmed aqueous phase is thereafter stirred in and uniformly further stirred up to cooling. A length of about 2.5 cm contains about 100 mg of the active material mixture.

Film tablet

Examples for a flurbiprofen tablet formulation

38.5 kg flurbiprofen lysinate were dry mixed with 7.5 kg microcryst. cellulose, granulated with 3 kg gelatine (10% in water) and dried, mixed with 0.5 kg

Mg stearate, 1 kg talc and 2 kg Na carboxymethyl cellulose and pressed to give round tablets with a diameter of 6 mm and a weight (residual moisture: 0.8 - 1.5%) of 260 mg. The finished tablets are coated with a lacquer coating of a solution of 0.7% glycerol, 4% methyl cellulose, 0.7% polyglycol 6000, 58% water and 36.6% acetone and dried.

There was thereby used:

R(-)-flurbiprofen substantially free from S(+)-flurbiprofen,

S(+)-flurbiprofen substantially free from R(-)-flurbiprofen and a pseudoracemate of 50% S(+)- and 50% R(-)-flurbiprofen.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A medicament for the treatment of painful or inflammatory diseases with flurbiprofen, wherein the flurbiprofen, in the case of pains or in the case of chronic disease pictures with dominating states of pain, comprises 60 to 99.5% R(-)-flurbiprofen, remainder S(+)-flurbiprofen, or wherein the flurbiprofen, in the case of inflammations or in the case of chronic disease pictures with dominating inflammations, comprises 60 to 99.5% S(+)-flurbiprofen, remainder R(-)-flurbiprofen.

2. A medicament according to claim 1, which comprises 60 to 99.5% R(-)-flurbiprofen.

3. A medicament according to claim 2, which comprises 60 to 95% R(-)-flurbiprofen.

4. A medicament according to claim 1, which comprises 60 to 99.5% S(+)-flurbiprofen.

5. A medicament according to claim 4, which comprises 60 to 95% S(+)-flurbiprofen.

6. A medicament according to any one of claims 1 to 5, wherein the medicament is formulated for administration either orally as tablets, coated tablets, chewing masses or suspensions, anally as suppositories, or parenterally intramuscularly as suspensions.

7. A medicament according to any one of claims 1 to 6, wherein the flurbiprofen is an alkali metal, alkaline earth metal, ammonium or amino acid salt, or is an aluminium compound, or a mixture thereof.

8. A medicament according to claim 7, wherein the amino acid salt is a lysinate.

9. A medicament according to claims 1 to 8, wherein the medicament further comprises retarding-acting additives or coatings.

10. A medicament according to any one of claims 1 to 9, wherein the R-enantiomer is present in rapidly inflowing form and the S-enantiomer in retarded form.

11. A medicament according to any one of claims 1 to 10, wherein previously separated enantiomers of the flurbiprofen are recombined in a desired ratio, and worked

up with a pharmaceutical carrier, an adjuvant material, or both.

12. A medicament for the effective treatment of painful diseases, the medicament comprising 2-(2-fluoro-4-biphenylyl)-propionic acid ("flurbiprofen") and a pharmaceutical carrier, an adjuvant material, or both, wherein the medicament comprises R(-)-flurbiprofen which is substantially free from S(+)-flurbiprofen.

13. A medicament according to claim 12, wherein the flurbiprofen is present as an alkali metal, alkaline earth metal, amino acid salt or aluminium salt.

14. A medicament according to claim 13, wherein the amino acid salt is a lysinate.

15. A medicament for the effective treatment of painful and inflammatory diseases, the medicament comprising 2-(2-fluoro-4-biphenylyl)-propionic acid ("flurbiprofen") and a pharmaceutical carrier, an adjuvant, or both, wherein the medicament comprises R(-)-flurbiprofen which is substantially free from S(+)-flurbiprofen.

16. A medicament according to claim 15, wherein the flurbiprofen is present as an alkali metal, alkaline earth metal, ammonium, amino acid salt or aluminium salt.

17. A medicament according to claim 16, wherein the amino acid salt is a lysinate.

18. A medicament according to any one of claims 12 to 17, wherein R(-)-flurbiprofen is present in rapidly inflowing form, and S(+)-flurbiprofen, if present, is in retarded form.

19. A medicament effective for the treatment of a disease characterized by pain or inflammation, which medicament comprises:

(a) a mixture of previously-separated R(-) and S(+) enantiomers of flurbiprofen; and

(b) a pharmaceutically-acceptable carrier, wherein the ratio of said R(-) and S(+) enantiomers of flurbiprofen is from about 99.5:0.5% to 0.5:99.5%, and wherein the medicament further comprises 2-10% of a release agent.

20. A medicament as claimed in claim 19, further comprising an adjuvant.

21. A medicament as claimed in claim 19 or 20, wherein said ratio is from about 95:5% to 5:95%.

22. A medicament as claimed in claim 19 or 20, which is effective for the treatment of pain, or of chronic diseases with a predominant state of pain, wherein said ratio is from 99.5:0.5% to 50:50%.

23. A medicament as claimed in claim 22, wherein said ratio is from 95:5% to 60:40%.

24. A medicament as claimed in claim 19 or 20, which is effective for the treatment of inflammation, or of diseases with predominant inflammation, wherein said ratio is from 50:50% to 0.5:99.5%.

25. A medicament as claimed in claim 24, wherein said ratio is from 40:60% to 5:95%.

26. A medicament as claimed in any one of claims 19 to 25, in the form of a tablet, dragee, capsule, chewable mass, cream, suppository, suspension or solution.

27. A medicament as claimed in any one of claims 19 to 26, comprising 2 to 60 wt.% of the enantiomers based on the total weight of the medicament.

28. A medicament as claimed in any one of claims 19 to 27, wherein said flurbiprofen enantiomers are in the form of flurbiprofen salts or aluminum compounds.

29. A medicament as claimed in claim 28, wherein said salts are selected from the group consisting of alkali metal, alkaline earth metal, ammonium and amino acid salts.

30. A medicament as claimed in claim 28, wherein said salts are lysinate salts.

31. A medicament as claimed in any one of claims 19 to 30, further comprising a retarding additive or coating in an amount effective to delay the liberation of the enantiomers.

32. A medicament as claimed in claim 31, wherein said R(-)-enantiomer is present in rapidly inflowing form and said S(+)-enantiomer is present in retarded form, and wherein the retarded form does not contain a release agent.

33. A medicament according to claim 19, which is produced by a method which comprises the steps of:

(a) providing substantially pure R(-) and S(+) enantiomers of flurbiprofen;

(b) combining said R(-) and S(+) enantiomers of flurbiprofen in a ratio from about 99.5:0.5% to 0.5:99.5% to form a mixture; and

(c) combining said mixture with a pharmaceutically-acceptable carrier.

34. A medicament as claimed in claim 33, wherein step (a) comprises isolating said R(-) and S(+) enantiomers of flurbiprofen from flurbiprofen racemate.

35. A medicament as claimed in claim 33, wherein step (a) comprises stereospecifically synthesizing said R(-) and S(+) enantiomers of flurbiprofen.

36. Use of a medicament for treating a human or animal patient suffering from a disease characterized by pain, the medicament comprising:

(a) an analgesically-effective amount of a mixture of the previously separated R(-) and S(+) enantiomers of flurbiprofen, and mixture containing 50 to 99.5% R(-)-flurbiprofen and 50 to 0.5% S(+)-flurbiprofen; and

(b) a pharmaceutically-acceptable carrier wherein the medicament further comprises 2-10% of a release agent.

37. A use as claimed in claim 36, wherein said mixture contains 60 to 95% R(-)-flurbiprofen and 40 to 5% S(+)-flurbiprofen.

38. Use of a medicament for treating a human or animal patient suffering from a disease characterized by inflammation, the medicament comprising:

(a) an antiphlogistically-effective amount of a mixture of the previously separated R(-) and S(+) enantiomers of flurbiprofen, said mixture containing 50 to 99.5% S(+)-flurbiprofen and 50 to 0.5% R(-)-flurbiprofen; and

(b) a pharmaceutically-acceptable carrier wherein the medicament further comprises 2-10% of a release agent.

39. A use as claimed in claim 38, wherein said mixture contains 60 to 95% S(+)-flurbiprofen and 40 to 5% R(-)-flurbiprofen.

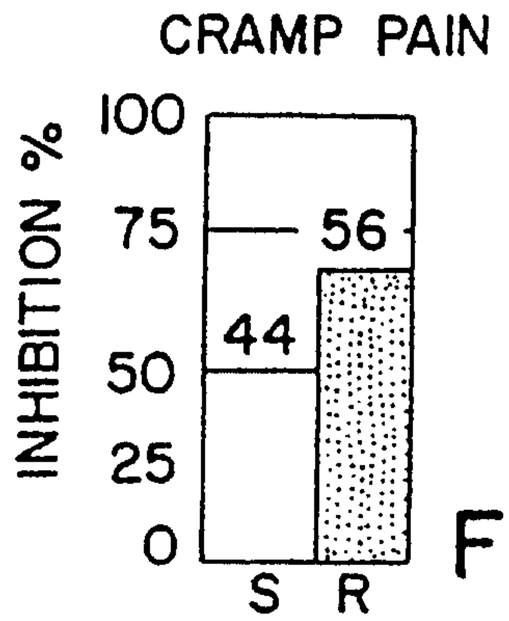


FIG.1

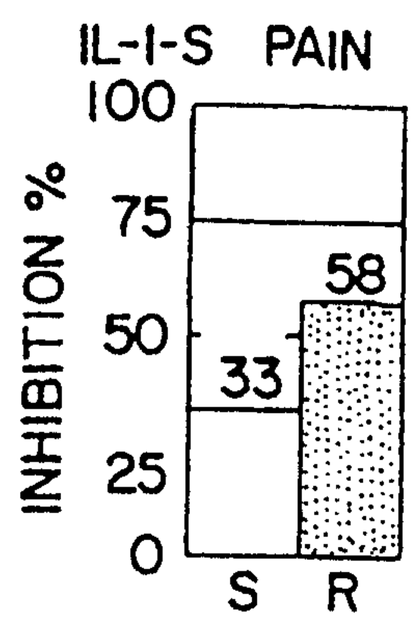


FIG.2

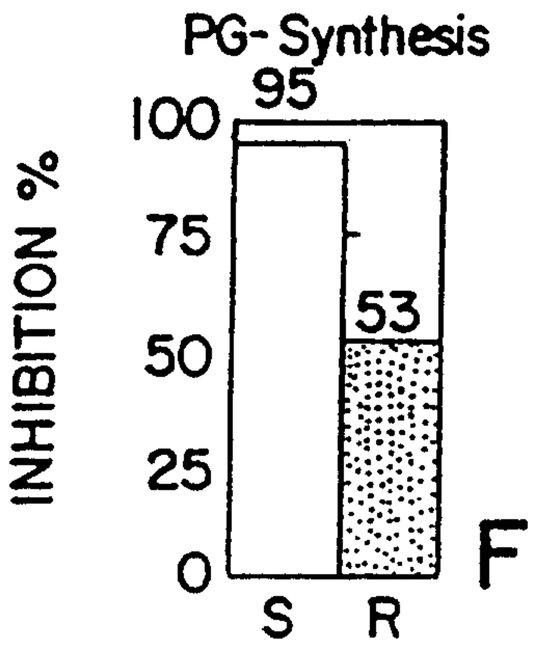


FIG.3

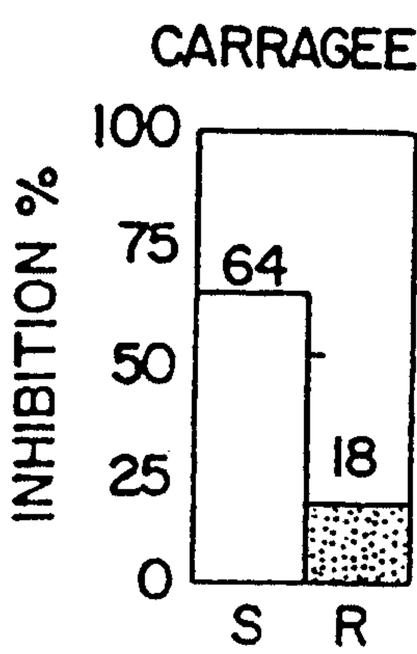


FIG.4

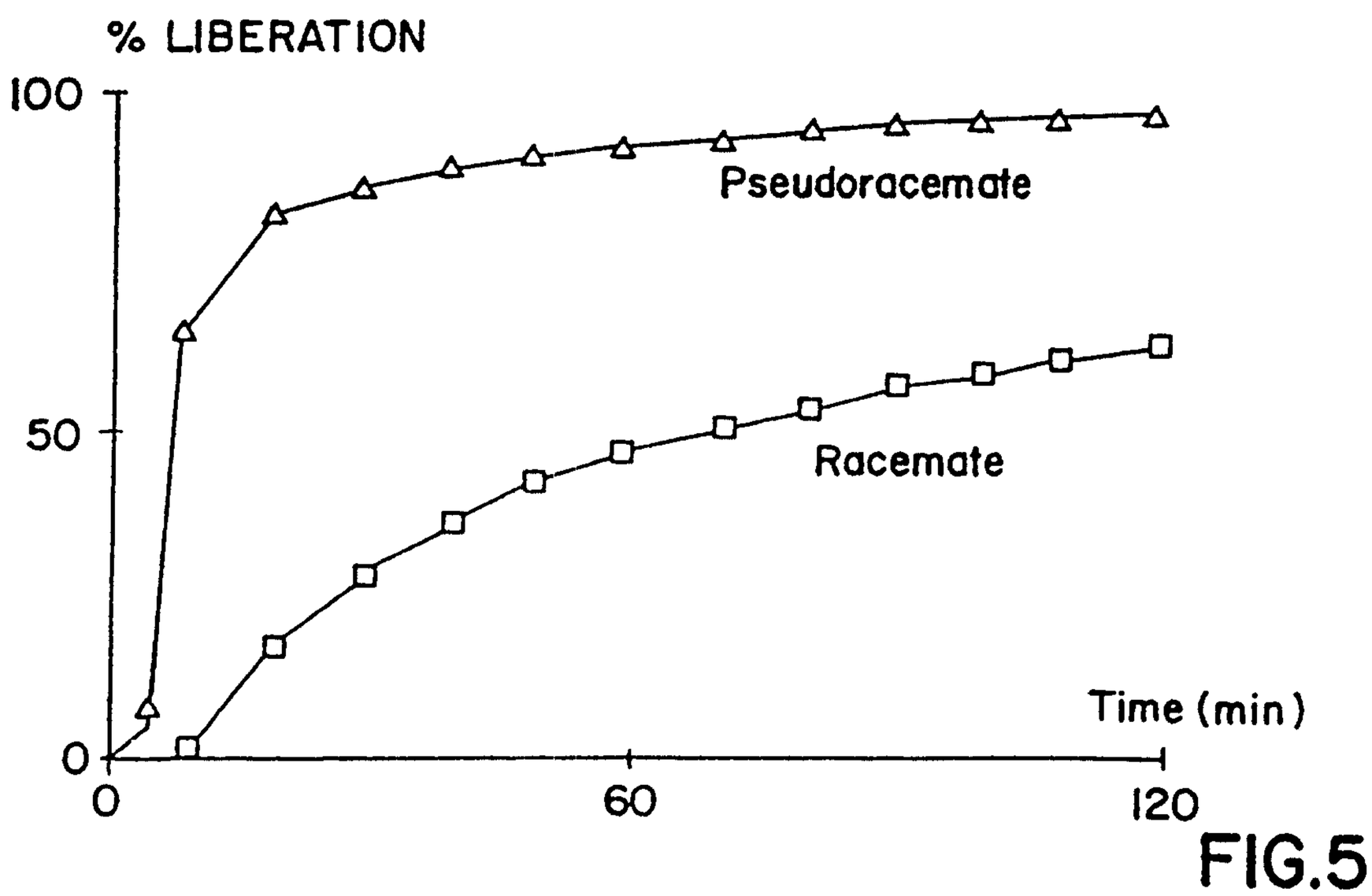


FIG.5

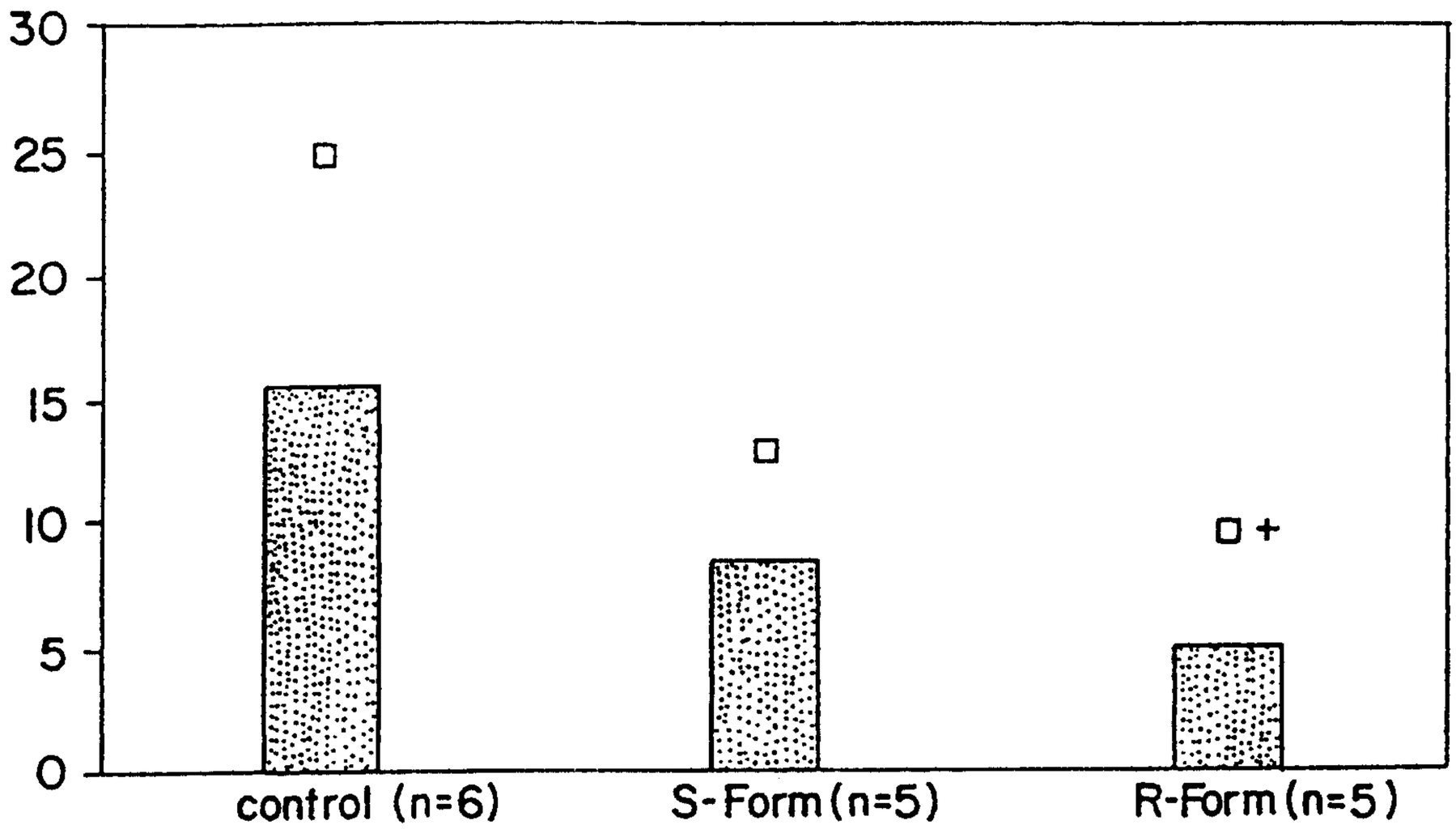

30
25
20
15
10
5
0
control (n=6)
S-Form (n=5)
R-Form (n=5)
+

FIG.6

GASTRIC ULCER INDEX
INTESTINAL ULCERS %g/g
2
1,6
1,2
0,8
0,4
0
12
9
6
3
0
ns
1%
1%
5%
5%
rac
S
R
rac
S
R

FIG.7