**Title:** BUCCAL COMPOSITION CONTAINING S(+) FLURBIPROFEN OR KETOPROFEN

**Abstract**

A composition for the treatment of disorders associated with periodontal disease affecting soft tissue and bone of the oral cavity, and a composition useful in the method. The method comprises applying to buccal membranes a therapeutically effective quantity of at least one S enantiomer, generally an S(+) enantiomer, of a nonsteroidal anti-inflammatory drug, such as S(+) flurbiprofen or S(+) ketoprofen. The composition is a formulation which is a toothpaste or which is a mouthwash.
DESIGNATIONS OF "DE"

Until further notice, any designation of "DE" in any international application whose international filing date is prior to October 3, 1990, shall have effect in the territory of the Federal Republic of Germany with the exception of the territory of the former German Democratic Republic.

FOR THE PURPOSES OF INFORMATION ONLY

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BUCCAL COMPOSITION CONTAINING S (+) FLURBIPROFEN OR KETOPROFEN

Description

Background
5 Periodontal disease, which includes any abnormality, whether inflammatory or degenerative, of tissue around a tooth, is very common worldwide. For example, the World Health Organization has estimated that even if there were no new periodontal disease, it would take 45 years to treat those people who are affected. In addition, the Journal of Public Health Dentistry concluded in 1985 that "more than two out of three patients were affected by periodontal disease." Moos, W.F., Medical Marketing & Media, 52-54 (1985). Chronic gingivitis (i.e., inflammation of the gingiva or gums) and chronic destructive periodontitis (i.e., a disease of the connective tissue which attaches a tooth to the alveolar bone, which results in alveolar bone resorption, increasing mobility of the tooth and, ultimately, tooth loss) are two common types of periodontal disease.

Although chronic periodontal disease is so common and known to be caused ultimately by bacteria accumulated on the teeth and under the gingiva, progress in its prevention and treatment has been limited and therapy is still largely unsuccessful.
Preventive techniques rely heavily on establishing and maintaining good oral hygiene and therapy of existing periodontal disease includes expensive and ongoing treatments, such as periodontal surgery, which, in many cases, must be carried out often and has not been clearly shown to be effective in arresting alveolar bone loss and preserving teeth. Alveolar bone loss or resorption, which occurs after tooth extraction, is also a serious dental problem which cannot, to date, be successfully treated. A more effective method of preventing or treating alveolar bone loss would be of great value, particularly because of the prevalence of its occurrence.

15 **Summary of the Invention**

The present invention is a method of reducing (decreasing or preventing) bone loss and/or promoting bone regrowth, to replace previously destroyed or lost bone, as well as a composition useful in the method. The present method and composition are particularly useful in the case of alveolar bone loss associated with periodontal disease, bone loss associated with osteoporosis and fracture repair. In the method of the present invention, at least one S enantiomer of a nonsteroidal anti-inflammatory drug, such as S(+)-flurbiprofen or S(+)-ketoprofen, is administered by application to the buccal membranes to an individual, in whom bone loss is to be prevented, reduced or reversed, in sufficient quantities to produce a systemic effect (adequate blood levels of
the drug). In the case in which an individual with periodontal disease is being treated, the present method is also useful in reducing (decreasing or preventing) inflammation or gingivitis.

Particularly suitable for use in the present method is a composition which can be used to provide a means by which the S enantiomer of one or more nonsteroidal anti-inflammatory drugs can be applied to make sufficient contact with an individual's buccal membranes to result in adequate blood levels of the drug to produce the desired effect.

Typically, the composition will be a formulation, referred to as a toothpaste, but which can be any form (gel, powder, foam) or a mouthwash. The toothpaste is used as is any other toothpaste (typically, it is applied by brushing), as is the mouthwash, with which an individual gargles, rinses his or her mouth, etc.

The composition of the present invention includes at least one S enantiomer, typically the S(+)enantiomer(s), of the nonsteroidal anti-inflammatory drug(s), either in highly purified form (i.e., substantially free of its R(-) form) or in combination with a small quantity of the R(-) form.

In addition, the composition includes a flavoring agent or agents and other components typically present in toothpastes (gels, powders, foams, etc.). Because the S(+) enantiomer, which is readily absorbed and is likely to have enhanced bioavailability, is used in the composition, a lower concentration is needed than would be the case if the typically-used racemic mixture were included in the
composition. Typically, the nonsteroidal anti-inflammatory drug(s) will be present in the composition in a concentration of approximately 0.1 to approximately 5.0% and preferably in a concentration of approximately 0.25% to approximately 1.0%, although the level can be altered as needed. In the case in which two or more such enantiomers are present, the total concentration falls within this range. The present composition and the method of using it in preventing or treating bone resorption and inflammation secondary to periodontitis and in promoting bone regrowth once it has occurred have several advantages over other formulations or methods of treating this condition. For example, because the active component of the composition is the highly purified S(+) enantiomer of the nonsteroidal anti-inflammatory drug, a relatively low concentration is needed and, thus, the problems of unpleasant or bitter taste and irritation to tissues of the mouth and/or other areas of the gastrointestinal tract associated with consumption of such drugs can be avoided. In addition, because the S(+) enantiomer is well absorbed, it is possible, using such formulations, to produce adequate blood levels (i.e., levels high enough to reduce bone resorption, such as that associated with periodontal disease), reduce inflammation associated with periodontal disease and/or promote regrowth of bone once loss has occurred.
Detailed Description of the Invention

The present invention is based on the use of the S enantiomer of at least one nonsteroidal anti-inflammatory agent, typically the S(+) of nonsteroidal anti-inflammatory drugs such as flurbiprofen or ketoprofen, in a composition for oral administration for the treatment and/or prevention of bone resorption.

In one embodiment of the present invention, the S(+) enantiomer of flurbiprofen, of ketoprofen or of another nonsteroidal anti-inflammatory drug which is an aryl propionic acid of sufficient activity to have the desired effect is administered by application to an individual's buccal membranes in order to reduce (decrease or prevent) inflammation and alveolar bone loss associated with periodontal disease and/or to promote bone regrowth associated with the disease. As used herein, the term periodontal disease refers to any disease which affects the periodontia and, typically includes periodontitis, gingivitis and/or periodontosis. The present method can also be used to reduce bone loss associated with other conditions, such as osteoporosis as well as to promote bone regrowth, once loss has occurred. It can also be used in conjunction with fracture repair. In the method of the present invention, the S enantiomer of at least one nonsteroidal anti-inflammatory drug is administered in a highly purified form (i.e., essentially free of its R form or in combination with a small quantity of its R form). The S enantiomer is typically the
dextrorotatory enantiomer and is designated S(+) using standard chemical notation. Further description of the present method and composition used therein will refer to the S(+) enantiomer, although it is not to be construed as limiting (i.e., the active enantiomer is what is intended).

In the case in which the S(+) enantiomer-containing composition is administered to treat or prevent alveolar bone loss and/or to promote alveolar bone regrowth associated with periodontal disease, the composition is a formulation, referred to for convenience as a toothpaste, although it may take other forms which can be applied to the gum area by brushing or other means of topical application, or is a mouthwash. The toothpaste may be, for example, a gel, powder, or a foam which is applied to the gums and then removed (e.g., by further or continued brushing with a toothbrush which does not contain the formulation or by rinsing with water). In general, the toothpaste formulation of the present invention contains from approximately 0.1% to 5.0% of the S(+) enantiomer and, preferably, from approximately 0.25% to approximately 1.0% of the S(+) enantiomer in highly purified form, although this concentration can be varied as needed in a particular instance. The toothpaste is applied in sufficient quantity (e.g., 1-2 grams toothpaste, twice daily) and for sufficient time to produce adequate blood levels (an adequate systemic level) to result in the desired effect. It also appears that this results in localized tissue levels which are of value in producing the desired effect.
The S(+) enantiomer of flurbiprofen and the S(+) enantiomer of ketoprofen have been shown to be readily absorbed when taken orally. In general, because these drugs are themselves acids, the composition (toothpaste, mouthwash) should be acidic (e.g., pH of 5.0 to 6.5) to enhance the absorption of the drug(s). The selected S(+) enantiomer can be incorporated into an existing toothpaste formulation, simply by mixing, or can be included with other components as they are combined. An important consideration in terms of user acceptance and willingness to comply with a use regimen is inclusion in the formulation of a flavoring material (e.g., menthol, spearmint, peppermint) sufficiently strong to cover or reduce the flavor of the S(+) enantiomer, which is generally regarded as unpleasant because it is bitter, as well as to reduce the burning sensation it can cause. Because the S(+) enantiomer is used, however, masking or reducing the unpleasant flavor is not as difficult as would be the case if the racemic mixture were used because of the considerably smaller quantity of the S(+) enantiomer used (e.g., approximately one half that of the racemic mixture) and, thus, the lower intensity of the unpleasant flavor. Other aryl propionic acids can be used such as: carprofen, naproxin, indoprofen, pierprofen, pranoprofen, microprofen, thiaoxa and aminoprofen.

In the present method, the S(+) enantiomer-containing formulation is applied in sufficient quantity (e.g., generally 1-2 grams of a 0.25% to 1.0% toothpaste), twice a day. Thus, the amount of
S(+) enantiomer that is applied twice daily can range from 1-50mg, but usually ranges from 2.5-20mg. Because the S(+) enantiomer of flurbiprofen or of ketoprofen is used and can be incorporated into a formulation which is acceptable to an individual and convenient for self administration/home use, the present method and composition avoid an important limitation of previously-described methods, in which using racemic mixtures (S(+), R(-)) of either or both compound(s) were used and must be administered in tablet or other form which did not remain in the mouth for any length of time. A particular advantage of the present method and formulation is that it can easily be administered on an on-going basis and user compliance will be high.

The ability of a particular (selected) formulation to have the desired effect (i.e., reduce inflammation, reduce bone loss, promote regrowth) can be assessed using standard techniques. For example, its effect on inflammation is determined by observation, to determine whether the redness and/or puffiness or edema characteristic of inflammation has decreased. Bone loss reduction can be assessed using the method of Jeffcoat and co-workers.

bone height is determined using standardized radiography and alveolar bone metabolism is assessed using 99m-Tc uptake prior to administration of the selected S(+) enantiomer and 2 months after administration begins. A reduction in radiopharmaceutical (99m-Tc) uptake, after S(+) enantiomer administration, in the alveolar bone of teeth shown initially (prior to administration) to be undergoing active bone loss is interpreted as an indication that the S(+) enantiomer used has a beneficial effect (i.e., reduces alveolar bone loss in individuals with periodontal disease). Bone regrowth can be assessed using a standard method, such as digital subtractive radiography (see Jeffcoat et al.).

In the embodiment of the present method in which S(+) flurbiprofen or S(+) ketoprofen is administered orally to reduce bone resorption and/or promote bone growth associated with conditions or diseases other than periodontal disease, such as osteoporosis and fracture repair, the selected S(+) enantiomer is applied in a similar manner, resulting in the desired systemic effect (i.e., blood levels appropriate for affecting bone metabolism).

The S enantiomer used in the method and composition of the present invention can be produced by any appropriate method. For example, it can be produced by the method described in WO 89/09765. This patent teaches a combination of organic synthesis and enzymatic treatment to produce the desired enantiomer of drugs such as flurbiprofen or ketoprofen. Alternatively, the S(+) enantiomer of
flurbiprofen can be produced by the method described in Example 1 herein.

The following Examples detail the protocols for producing the S(+) enantiomer of flurbiprofen, for formulating a toothpaste as a vehicle for administrering S(+) flurbiprofen, and for assessing the bioavailability of toothpastes containing various levels of S(+) flurbiprofen. The bioavailability of S(+) ketoprofen and other S(+) enantiomers can also be determined using this protocol. These Examples are not intended to be limiting of the invention.

EXAMPLES

EXAMPLE 1 Preparation of S(+) Flurbiprofen

The following is a description of the resolution of flurbiprofen by an enzymatic process. Included is a description of the synthesis of the water-soluble ester used (a two step procedure), as well as the actual enzymatic resolution, subsequent base hydrolysis of the non-substrate ester, and the recovery of both enantiomers of flurbiprofen acid.

A. Synthesis of Flurbiprofen Dimethylthanolamine Ester

0.5 moles (122g) BP grade racemic flurbiprofen was added to 1.0 moles (73 mls) of SOCl₂ in a flask fitted with a drying tube. 250μl of dimethylformamide was added to the reaction mixture as a catalyst. The reaction mixture was then stirred and warmed gently until the flurbiprofen dissolved and gas evolution commenced. The heat was then
removed, and the reaction mixture allowed to stir at 20°C-22°C for 18 hours, after which time the excess SOCl₂ was removed under reduced pressure. The remaining material was a liquid which slowly solidified. IR analysis of the liquid indicated total conversion of the carboxylic acid to the acid chloride. 131.0 g of flurbiprofen acid chloride were recovered, indicating a 99.7% conversion. This material was carried on to the next step without any further purification.

The entire quantity of acid chloride was then dissolved in 125 mls of THF, and added dropwise to a solution of 1.0 moles (100.5 mls) of N,N-dimethylethanolamine dissolved in 500 mls of THF in a flask fitted with a drying tube. The addition of the acid chloride solution was made over approximately 60 minutes during which time the reaction mixture was cooled to 0°C by an ice/water bath. When addition was complete, the ice bath was removed, and the entire mixture allowed to stir at 20°C-22°C for 18 hours. The reaction was then worked-up by the careful addition of 500 mls of saturated aqueous K₂CO₃ solution. The resulting organic layer was separated, and remaining aqueous layer extracted twice with 250 mls of diethyl ether. The organic layers were combined, back-washed with saturated NaCl solution, dried over anhydrous K₂CO₃, and evaporated under reduced pressure to leave a colourless, viscous oil. 112.0 g of material
were recovered, giving a 71% yield. IR analysis of the product indicated only an ester carbonyl function.

B. Quaternization of the N,N-Dimethylethanolamine Ester

The entire quantity of the N,N-Dimethyl-ethanolamine ester (0.355 moles) was dissolved in 500 mls of diethyl ether and stirred in a flask cooled to 0°C by an ice/water bath. To this solution was added dropwise a solution of 1.0 equivalents (0.355 moles, 33.6 mls) of dimethyl sulphate, dissolved in 100 mls diethyl ether over approximately 60 minutes. The ice bath was then removed, and the reaction mixture allowed to stir at 20°C-22°C for 18 hours. The resulting solid material was removed by filtration, washed with diethyl ether and dried under vacuum at 20-22°C to leave 156.9g (100% yield in quaternization step, 70% yield from racemic flurbiprofen acid) of the N,N,N-trimethyl ethanolammonium ester (also known as the choline ester) of flurbiprofen.

C. Enzymatic Hydrolysis of the Racemic Flurbiprofen Choline Ester

75 mmols of the racemic choline ester were dissolved in 1L of 200 mM sodium phosphate buffer at pH 7.0. To this solution was added 2.0g of a protease derived from Aspergillus oryzae, which is available commercially from the Amano Enzyme Company under the name Prozyme
6. The reaction was allowed to stir gently at 20°C-22°C for 48 hours. The entire enzymatic reaction mixture was then acidified to a pH of 2 to 3 by the careful addition of concentrated HCl, and the resulting mixture was extracted 3 times with 150 mls of diethyl ether. The ether layers were combined, dried over anhydrous K₂CO₃, and evaporated under reduced pressure to leave crude (R)-flurbiprofen acid, which was dried under vacuum, and an acidic aqueous solution containing (S)-flurbiprofen choline ester.

The remaining acidic aqueous mixture was then made basic, by the careful addition of NaOH, until the pH had risen to 12.5. The resulting mixture was allowed to stir at 20°C-22°C for approximately two hours, after which time the pH was again brought to approximately pH 2 by the careful addition of concentrated HCl in order to precipitate the flurbiprofen acid produced by the base hydrolysis of the choline ester. The resulting mixture was extracted 3 times with 150 mls of diethyl ether. The ether layers were combined, dried over anhydrous K₂CO₃, and filtered into a clean flask. This solution was chilled to approximately -10°C in order to crystallize the (S)-flurbiprofen acid. The resulting crystals were collected by filtration, and dried under vacuum.

The enantiomeric excess of each isomer was determined by polarimetry, assuming an [α]₀.
value of +42.7° (c = 1.0, CHCl₃) for (S)-flurbiprofen acid of 100% ee.

In order to prepare a reasonable amount of resolved flurbiprofen, the procedures outlined immediately above for the enzymatic hydrolysis of the racemic choline ester substrate, and the subsequent recovery of both the (R)- and (S)-flurbiprofen acid, were repeated exactly as described four times. The (R)- and (S)-acid products were combined to give the following yields of materials:

(R)-flurbiprofen 18.0g, [α]₀ = -31.2°, ee = 73%
(S)-flurbiprofen 18.0g, [α]₀ = +36.7°, ee = 86%

Subsequent re-crystallization of the (S)-acid material from ether gave (S)-flurbiprofen of 95% enantiomeric excess.

EXAMPLE 2 Toothpaste Composition

S(+) Flurbiprofen 1.0%
Magnesium aluminum silicate 1.0%
Dicalcium phosphate 47.0%
Sodium carboxymethylcellulose 0.5%
Mint flavor 4.0%
Sodium lauryl sulfate 2.0%
Benzoic acid 0.1%
Water 44.4%
The nonaqueous ingredients are slowly added to the water with stirring. The resultant mixture is then passed through a roller mill.

**EXAMPLE 3**  
**Evaluation of Bioavailability of S(+) Flurbiprofen in Toothpaste**

The purpose of this study is to show how well subjects tolerate three strengths of S(+) flurbiprofen toothpaste (1%, 0.5% and 0.25%), as well as the relationship between dose and blood level of the active isomer in comparison with an identical formulation of racemic flurbiprofen (1%). A toothpaste containing one of the three concentrations of S(+) flurbiprofen or 1% racemic flurbiprofen is used in the study.

The drug is an acid and, therefore, the formulation is adjusted to be on the acid side, in order to improve buccal absorption. Any standard formulation of appropriate pH can be used. The formulation can also contain menthol or wintergreen in order to mask the slight bitter taste of the drug. Standard formulation techniques are used.

Subjects are selected as follows: Seven males, all of whom are in good health (age 21) are recruited in order to allow for one dropout during the course of the study. Individuals with allergies to aspirin or nonsteroidal anti-inflammatory drugs; asthma; a history of valvular heart disease; or a history of ulcer disease or chronic dyspepsia are excluded.

A 7 ml. sample of blood is drawn from each subject and serves as the time zero reading (prior
to any brushing) for serum flurbiprofen. Over a period of four days, following an initial oral examination, six subjects brush their teeth twice daily with one of the four toothpaste formulations. The subjects keep a daily diary recording the times of their morning and evening brushings and any observed effects.

After their morning brushing on the fourth day, a single 7 ml sample of blood is drawn from each subject immediately after brushing, then again at .25 hours, 1 hour, 8 hours, 18 hours and 24 hours. Blood samples are centrifuged and the serum frozen at approximately -10°C prior to delivery to a designated analytical laboratory.

Serum samples are analyzed to determine the concentration of flurbiprofen stereoisomers.

This same process is repeated after three days through three additional cycles until all subjects have received all four treatments. The dosage strengths are randomized throughout the four experimental cycles.

At completion of the four treatments the subjects are again examined in order to evaluate effects on the subjects' oral cavities (i.e., as described previously, effects on inflammation, side effects).
CLAIMS

1. A composition for application to buccal membranes, comprising a highly purified S enantiomer of at least one nonsteroidal anti-inflammatory drug which is an aryl propionic acid.

2. A composition for application to buccal membranes, comprising a highly purified S(+) enantiomer of at least one nonsteroidal anti-inflammatory drug.

3. A composition of Claim 2 wherein the nonsteroidal anti-inflammatory drug is selected from the group consisting of S(+) flurbiprofen and S(+) ketoprofen.

4. A composition of Claim 3 wherein the composition includes from approximately 0.1% to approximately 5.0% of the nonsteroidal anti-inflammatory drug.

5. A toothpaste comprising a highly purified S(+) enantiomer of at least one nonsteroidal anti-inflammatory drug.

6. A toothpaste of Claim 5 wherein the nonsteroidal anti-inflammatory drug is selected from the group consisting of S(+) flurbiprofen and S(+) ketoprofen.
7. A toothpaste of Claim 6 comprising from approximately 0.1% to approximately 5.0% nonsteroidal anti-inflammatory drug.

8. A mouthwash comprising a highly purified S enantiomer of at least one nonsteroidal anti-inflammatory drug.

9. A mouthwash of Claim 8 wherein the nonsteroidal anti-inflammatory drug is selected from the group consisting of S(+) flurbiprofen and S(+) ketoprofen.

10. Use of a highly-purified S enantiomer of at least one aryl propionic acid for the preparation of the topical medicament or mouthwash for the treatment of disorders associated with periodontal disease affecting soft tissue and bone of the oral cavity.

11. The use of Claim 10 wherein the S enantiomer is an S(+) enantiomer.

12. The use of Claim 11 wherein the S(+) enantiomer is selected from the group consisting of S(+) flurbiprofen and S(+) ketoprofen.
INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 90/04623

I. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC: A 61 K 7/16, 7/18, 31/19

II. FIELDS SEARCHED

Classification System | Classification Symbols
----------------------|---------------------
IPC | A 61 K

Documentation Search other than Minimum Documentation to the extent that such documents are included in the fields searched.

III. DOCUMENTS CONSIDERED TO BE RELEVANT

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* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underling the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "Z" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search
29th November 1990

Date of Mailing of this International Search Report
20. 12. 90

International Searching Authority
EUROPEAN PATENT OFFICE

Signature of Authorized Officer
R.J. Earnisse

Form PCT/ISA/210 (second sheet) (January 1985)
V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers .........., because they relate to subject matter not required to be searched by this Authority, namely:

   Claims searched incompletely: 1, 2, 5, 8, 10, 11, 12
   Reason: Aryl propionic acid is a broad concept. Therefore the search has been restricted to compositions containing flurbiprofen and ketoprofen.
   (Art. 6 PCT)

2. ☐ Claim numbers .........., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers .........., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☒ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest
☐ The additional search fees were accompanied by applicant’s protest.
☐ No protest accompanied the payment of additional search fees.

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ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 9004623
SA 39450

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