

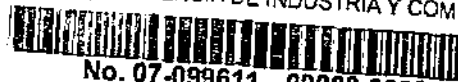
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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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1

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☒ Patente de Invención.☐ Patente de Modelo de Utilidad.☒ Capítulo I.☐ Capítulo II.

2

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3

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Número 80.410.337 TP 57492

4

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DISUSTITUIDOS Y MÉTODOS RELACIONADOS

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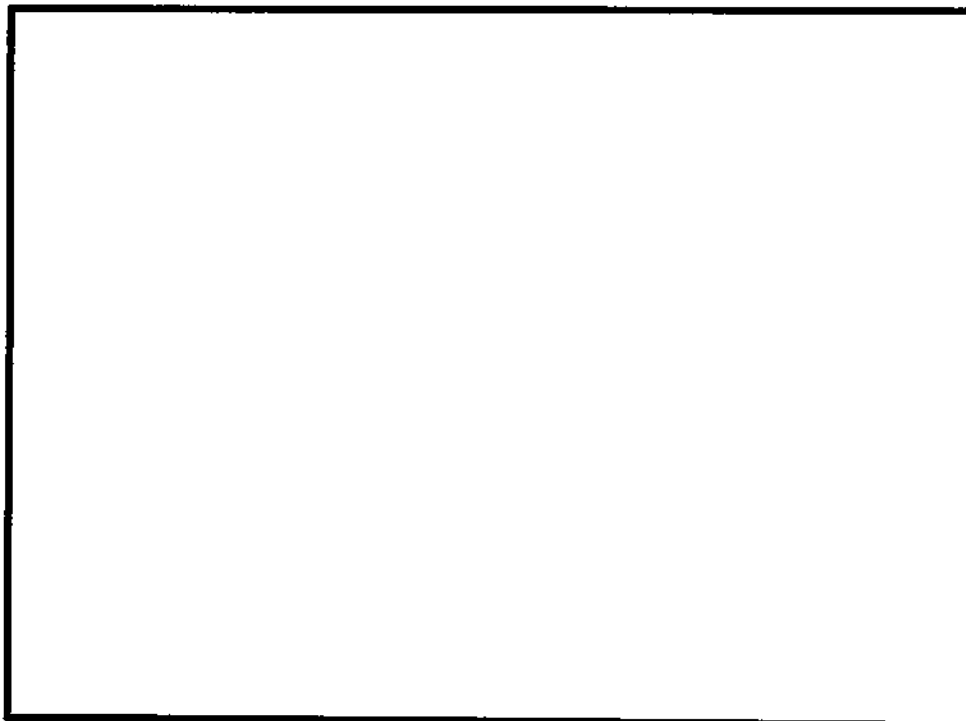
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$482000
 - ☒ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
 - ☒ Poderes, si fuere el caso.
 - ☐ Documento de cesión del inventor al solicitante o a su causante.
 - ☐ Declaraciones
 - ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
 - ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
 - ☐ Copia del examen preliminar efectuado por la IPEA.
 - ☐ Traducción del examen preliminar efectuado por la IPEA.
 - ☐ De ser el caso, copia del contrato de acceso.
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 - ☐ De ser el caso, certificado de depósito del material biológico.
 - ☐ Arte final 12x12
 - ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
 - ☒ Otros Tarjeta de Propietarios
- Documentos PCT

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:

Juan Pablo Cadena

C.C. 80.410.337 de Usaquén TP 57492 del C.S.J.

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DIVISION DE NUEVAS CREACIONES

PATENTE ☒ PCT/US2006/009046

MODELO DE UTILIDAD ☐

DISÑO INDUSTRIAL ☐

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DOMICILIO NUEVA YORK, NUEVA YORK, ESTADOS UNIDOS DE AMERICA

APODERADO JUAN PABLO CADENA SARMIENTO

TITULO COMPUESTOS, DERIVADOS ANTIBACTERIANOS DE 2,4'-DIHIDROXIFENILO 3,5-DISUSTITUIDOS
Y METODOS ...

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VIGENCIA DESDE

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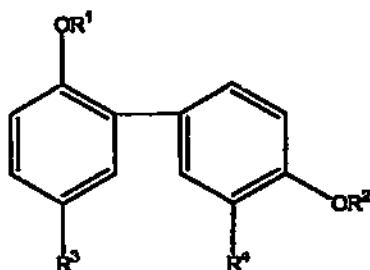
ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: ANTIBACTERIAL 3',5-DISUBSTITUTED 2,4'-DIHYDROXYBIPHENYL COMPOUNDS, DERIVATIVES AND RELATED METHODS



(I)

(57) Abstract: The invention provides an antiplaque oral composition containing an orally acceptable carrier and an antibacterial effective amount of compound (I). In the structure, R¹ and R² are independently a hydrogen atom or a lower C₁₋₄ alkyl group and R³ and R⁴ are independently an alkenyl or alkyl group having from 1 to 20 carbon atoms, with the proviso that R³ and R⁴ are not both 2-propenyl or n-propyl when R¹ and R² are both hydrogen atoms. Also included are oral compositions containing the compound (I).

WO 2006/101818 A1

TITLE OF THE INVENTION

Antibacterial 3',5-disubstituted 2,4'-dihydroxybiphenyl Compounds, Derivatives and Related Methods

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to United States Provisional Patent Application No. 60/662,991, filed March 18, 2005, the contents of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] A number of disease conditions are associated with the action of bacteria in the oral cavity. Dental plaque is a soft deposit that forms on the surface of the teeth as a by-product of bacterial growth. Gingivitis, an inflammation or infection of the gums and alveolar bones, is generally believed to be caused by plaque causing bacteria and the toxins formed as by-products from the bacteria. In addition, plaque provides a locus for calculus or tartar formation. Periodontitis is generally believed to occur where unremoved plaque hardens into calculus (tartar), which effects the periodontal ligaments. As plaque and tartar continue to build up, the gums begin to recede, which can lead to continued infection and potentially the loss of teeth.

[0003] To prevent or treat these diseased conditions, antibacterial agents are incorporated into oral care compositions such as toothpaste and mouthwashes or rinses. Application of antibacterial compositions in the oral cavity tends to retard plaque formation and related oral infections.

[0004] The antiplaque efficacy of antibacterial compounds in a dentifrice composition depends on a number of factors, including the presence of other ingredients that may interfere with its action. For example, certain cationic antibacterial compounds and certain nonionic antibacterial compounds lose their effectiveness when formulated with certain anionic surfactants or other anionic active ingredients, such as tartar control phosphates. In many instances, it is preferred to use antibacterial compounds that do not show the adverse interactions with such anionic components.

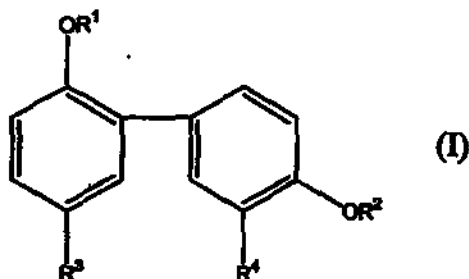
[0005] Extracts from *Magnolia officinalis* (hereinafter "magnolia"), and especially from the bark, contain biphenol antibacterial compounds that include honokiol and tetrahydrohonokiol. The extracts have been found to have antibacterial effectiveness when formulated into, for example, toothpaste formulations.

[0006] Extracts prepared from natural sources such as magnolia are variable in composition and contain many compounds other than the particular actives for which the extract is prepared. The mode of activity of the extract compounds is not well characterized, so that it is unpredictable how alterations in structure of any of the extract compounds would affect its antibacterial effectiveness. In addition, the composition of the extracts can vary from season to season and between different geographical regions. As a result, the antibacterial activity of the extracts in vivo is far from optimal.

DESCRIPTION OF THE INVENTION

[0007] A class of 3',5'-disubstituted 2,4'-dihydroxy- and -dialkoxy-1,1'-biphenyl compounds exhibits inhibitory action against a variety of bacteria commonly found in the oral cavity. The compounds are used as antiplaque and/or antibacterial components of dentifrices and other oral compositions. The invention provides various oral compositions containing the compounds and an orally acceptable carrier. In various embodiments, antibacterial and antiplaque oral compositions are provided in the form of a toothpaste or gel, a tooth powder, a mouthwash or mouth rinse, a lozenge, chewing gum, an edible strip, and the like. The antibacterial compounds are conveniently synthesized using conventional coupling, alkylation, reduction, and demethylation steps, although any means of synthesis known or developed in the art can be used.

[0008] The invention provides disubstituted 2,4'-diphenols and derivatives represented by the structure:



and exclusive of honokiol and tetrahydrohonokiol. R^1 and R^2 are independently H or a lower C_{14} alkyl group and R^3 and R^4 are independently an alkenyl or alkyl group having from 1 to 20 carbon atoms, with the proviso that R^3 and R^4 are not both 2-propenyl or n-propyl when R^1 and R^2 are both H. Preferably, R contains 1 to 8 carbon atoms.

[0009] Antiplaque oral compositions are provided that contain an orally acceptable carrier and an antibacterial effective amount of at least one compound of structure

(I). In various embodiments, the compositions contain from about 0.001% to about 10% by weight of (I). Without limitation, the orally acceptable carrier may be a liquid carrier; a powder carrier; or a carrier that dissolves upon contact with saliva and other components of an oral environment. In other embodiments, the carrier can comprise a gum base. The oral compositions are provided variously in the form of a toothpaste or gel, a tooth powder, a mouth rinse, a lozenge, chewing gum, and an edible strip. Other forms of the composition include without limitation a liquid suitable for painting a dental surface, a wafer, a wipe or towelette, an implant, a dental floss, and forms that are edible or chewable by smaller mammals, such as dogs or cats.

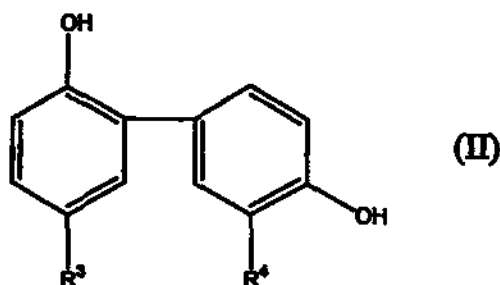
[0010] In other embodiments, the invention provides toothpaste or gel compositions that contain at least one humectant, at least one abrasive material, and an antibacterial effective amount of at least one compound of structure (I). In various embodiments, the toothpaste or gel compositions further comprise an anticalculus agent such as a phosphate compound, alternatively combined with synthetic anionic polycarboxylates. In an exemplary embodiment, the toothpaste or gel composition comprises

- 0.001- 5% by weight of compound (I);
- 1-70% by weight humectant;
- 1-70% by weight abrasive compounds;
- 0.5-2.5% by weight tetrasodium pyrophosphate (TSPP); and
- 1-10% by weight sodium tripolyphosphate (STPP).

[0011] In other embodiments, the invention provides a method for inhibiting bacterial growth in the oral cavity of a subject animal, human or non-human, comprising applying to the oral surfaces of the subject animal an antibacterial composition comprising at least one compound of structure (I). In various embodiments, the method involves brushing the teeth and rinsing with compositions containing compound (I). As above, the method can be practiced by applying the antibacterial composition in a wide variety of forms such as toothpastes, tooth gels, tooth powder, mouth rinse, paint on gels, dissolvable or edible strips, chewing gum, lozenges, and the like. In various embodiments, treatment of oral surfaces with antibacterial compositions containing compound (I) leads to reduction or elimination of plaque, to prevention or treatment of gingivitis, to amelioration of oral malodor, and prevention of periodontal disease.

[0012] In various embodiments, the antibacterial compounds are selected from a

class of 3',5'-disubstituted-2,4'-dihydroxy-1,1'-biphenyls, represented by the structure:

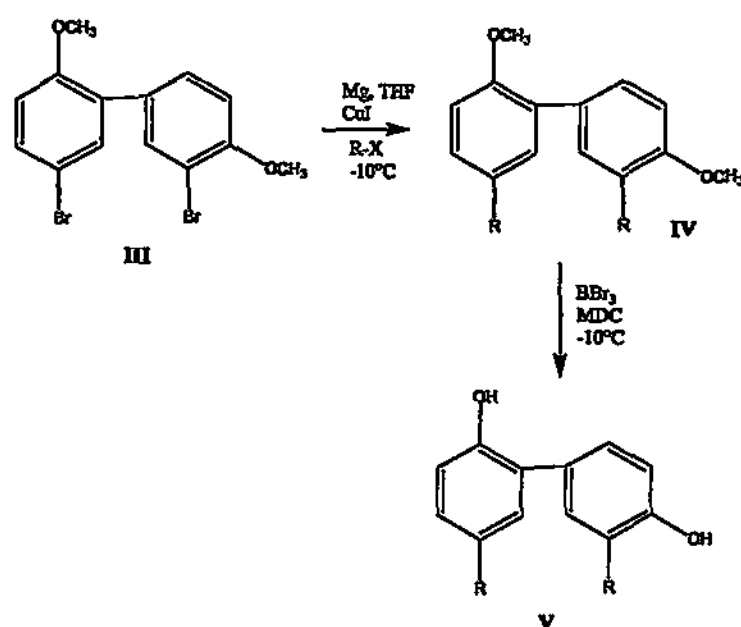


where R^3 and R^4 independently represent an alkenyl or alkyl group of 1 to 20 carbon atoms, with the proviso that R^3 and R^4 are not simultaneously 2-propenyl or n-propyl. Structure (II) corresponds to structure (I) where R^1 and R^2 are both hydrogen.

[0013] In some embodiments of structures (I) and (II), both R^3 and R^4 are alkyl groups. In other embodiments, both R^3 and R^4 are alkenyl groups. In yet other embodiments, one of the groups R^3 and R^4 is an alkyl group and the other is an alkenyl group. In various embodiments, the groups R^3 and R^4 are the same. In various embodiments, oral compositions containing compounds (I) and/or (II) exhibit antibacterial efficacy comparable to compositions containing triclosan.

[0014] The size and nature of the alkyl or alkenyl groups R^3 and R^4 are selected to achieve a desired combination of solubility and bioavailability in the compounds of structures (I) and (II). The compounds of structure (I) and (II) tend to be lipid soluble; distribution of the compounds between a lipid and water phase is reflected in a value of log P well known to those of skill in the art. In various embodiments, a log P value of 3 to 5 is preferred. In general, the larger the groups R^3 and R^4 (i.e., the higher the number of carbon atoms in the alkyl or alkenyl groups), the higher the solubility in lipid and the lower the solubility in water. The size of the groups R^3 and R^4 also affects the molecular weight and thus the molar amount of compounds (I) or (II) delivered by a unit dose. In a preferred embodiment, the groups R^3 and R^4 are selected such that the solubility of the compound (I) in water is 1 ppm or greater, preferably 5 ppm or greater, and more preferably 10 ppm or greater.

[0015] The compounds described herein may be synthesized via any means known or to be developed in the art. An exemplary synthesis of compounds (I) and (II) for the embodiment where R^1 and R^2 are either H or methyl is illustrated in the following scheme



A dibromo intermediate (III) is alkylated to a dimethyl intermediate (IV), which is demethylated to arrive at compounds (V). Compounds (IV) and (V) of the reaction scheme correspond to embodiments of structure (I) and (II), respectively, of the invention. The dibromo intermediate can be alkylated, for example, under conventional Grignard reaction conditions as shown. R-X represents an alkyl or alkenyl halide, with R as defined above for R³ and R⁴ and X representing a halogen, preferably bromine. When a single halide is used in the Grignard reaction, an embodiment of compounds (I) and (II) is synthesized wherein R³ and R⁴ are the same. If desired, a mixture of halides can be used to prepare embodiments of compounds (I) and (II) wherein R³ and R⁴ are different. In various embodiments complete or partial dealkylation (shown as complete demethylation) of the resulting structure (IV) proceeds according to known procedures, illustrated in the scheme by stirring with boron tribromide in dimethylene chloride at -10°C. Starting materials (III) can be readily synthesized. In a non-limiting example, p-iodoanisole is coupled to 2-methoxyphenylboronic acid to give an intermediate that is brominated to form (III). In an exemplary embodiment, the coupling reaction is carried out in the presence of palladium tetraphenyl phosphate, potassium carbonate and a phase transfer catalyst such as tetrabutyl ammonium bromide. Bromination of the coupling reaction product proceeds readily, for example at 0°C in Br₂ and ethylene dichloride.

[0016] Other non-limiting synthetic routes to alkyl and alkenyl compounds of structures (I) and (II) are given in Figure 1. In one alternative synthetic pathway, a dibromo

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X

intermediate 10 is reacted with an alkenyl bromide (illustrated in the alternative embodiments of 2-bromopropene 20a and crotyl bromide 20b) to make alkenyl compounds 30a and 30b where R^1 and R^2 are methyl. As shown, the alkenyl compounds 30a and 30b can be reduced to form corresponding alkyl compounds 40a and 40b, with optional subsequent dealkylation (illustrated as a demethylation) to a diol 50. In another pathway, the dibromo intermediate 10 is converted to a dialdehyde intermediate 60, followed by Claisen-type condensation with a ketone (exemplified by acetone) to form another intermediate 70 with a 4 carbon chain. Other ketones can be used to provide chains longer than 4. The double bond and the oxo group of the intermediate side chain are then reduced to form compound 80 with a saturated alkyl chain for R^3 and R^4 . The alkyl groups (illustrated as methyl groups) can be removed to form the 2, 4'-dihydroxy compounds 40b.

[0017] The antibacterial compound of the invention is formulated together with an orally acceptable carrier to provide oral compositions having a variety of forms such as referred to above. Depending on the form of the composition, the orally acceptable carrier can be a liquid carrier, a powder carrier, a dissolvable solid carrier, a gum base, a film forming polymer or polymers, and so on.

[0018] Various compositions of the invention contain an orally acceptable carrier and an antibacterial effective amount of compound (I). The effective amount is in the form of either a single compound or a mixture of compounds represented by structure (I). A mixture of compounds can result for example from intentional addition of separately synthesized compounds or from addition of a reaction product containing a mixture of substitution patterns of the groups R^1 , R^2 , R^3 , and R^4 .

[0019] As used herein, the "carrier" refers to components of the individual oral compositions in which the antibacterial compound or compounds of structure (I) are formulated as an active ingredient. In various embodiments, the carrier embraces all of the components of the oral composition except for the antibacterial compound (I). In other aspects, the term refers to components such as inactive ingredients, carriers, vehicles, and the like, that are commonly understood to persons of skill in the art to function as a carrier, filler or other relatively inert ingredient. In other words, the term carrier is used in different ways depending on context. Depending on the context, the oral compositions comprise other components in addition to the active compound (I) and the carrier. However, in all contexts, the components of the oral compositions of the invention can be divided into carrier

components and the antibacterial compounds (I).

[0020] To illustrate in a non-limiting example for the case of toothpastes, the carrier can be said to be the water/humectant system that provides a large fraction by weight of the composition. Alternatively, the carrier component of a toothpaste composition may be considered as the water, humectant, and other functional components other than the antibacterial system. Whatever the context, the person of skill in the art recognizes that the toothpaste composition contains both antibacterial compounds (I) and an orally acceptable carrier for the compound.

[0021] To illustrate further, in a mouth rinse, the carrier is generally considered to be the water/alcohol liquid component in which the antibacterial compounds (I) are dissolved or dispersed. In a dissolvable lozenge, the carrier is generally understood to comprise the solid matrix material that dissolves slowly in the mouth to the oral surfaces in the mouth. In chewing gums, the carrier comprises a gum base, while in an edible strip, the carrier comprises one or more film forming polymers.

[0022] In all of the above examples, the oral composition, in whatever form, includes antibacterial compounds (I), a suitable carrier in an appropriate form, and other actives or functional materials needed to provide the oral compositions with desired properties. Additional active materials and functional materials are described below.

[0023] In addition to a biologically acceptable carrier, oral compositions of the invention contain an antibacterial effective amount of compound (I). In various embodiments, an antibacterial effective amount is from about 0.001% to about 10%, based on the total weight of the oral composition, for example from 0.01% to about 5% or about 0.1% to about 2%. The effective amount will vary depending on the form of the oral composition. For example, in toothpastes, tooth gels, and tooth powders, an effective amount is usually at least about 0.01% and more preferably at least about 0.05%. In some preferred embodiments, compound (I) is present in a toothpaste, gel, or powder at a level of 0.1% or more, to achieve a desired level of antibacterial activity. Normally, compound (I) is formulated at 5% or less, preferably about 2% or less, and more preferably about 1% or less. Concentrations in the upper end of these limits can be used, but are sometimes less preferred for economic reasons. In various embodiments, optimum effectiveness is achieved at from about 0.1% to about 1%, especially from about 0.1% to about 0.5% or about 0.1% to about 0.3%, wherein all percentages are based on the total weight of the oral composition.

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Amounts used in tooth gels, tooth powders, gums, edible strips, and the like are comparable to those used in toothpastes.

[0024] In mouth washes and rinses, an antibacterial effective amount of (I) is normally on the lower side of the above ranges. Typically, compound (I) is used at a level of about 0.001% (or 10 ppm) up to about 1% or less. Preferably, compound (I) is at about 0.5% or less or about 0.2% or less. Preferably it is about 0.01% (100 ppm) or greater. In various embodiments, compound (I) is present at from 0.03 to 0.12% by weight.

[0025] The statements herein for structure (I) also apply to structure (II), which illustrates an embodiment or species of structure (I) where R^1 and R^2 are both a hydrogen atom. In addition to the antibacterial compound (I), a number of active ingredients and functional materials are included in various compositions of the invention. Such materials include, without limitation, abrasives, humectants, surfactants, anticalculus agents, thickeners, viscosity modifiers, anticaries agents, flavorants, colorants, additional antibacterial agents, antioxidants, anti-inflammation components, and so on. They are added to the pastes, gels, rinses, gums, lozenges, strips, and other forms of the oral compositions of the invention according to known methods.

[0026] In various embodiments of the present invention, where the carrier of the oral care composition is solid or a paste, the oral composition preferably comprises a dentally acceptable abrasive material, which serves to either polish the tooth enamel or provide a whitening effect. Non-limiting examples include silica abrasives such as silica gels and precipitated silicas. Commercial embodiments include ZEODENT[®] 115, marketed by J. M. Huber and SYLODENT[®] XWA, SYLODENT[®] 783 or SYLODENT[®] 650 XWA of the Davison Chemical Division of W. R. Grace & Co. Other useful dentifrice abrasives include, without limitation, sodium metaphosphate, potassium metaphosphate, tricalcium phosphate, dihydrated dicalcium phosphate, aluminum silicate, calcined alumina, bentonite or other siliceous materials, or combinations thereof.

[0027] The abrasive is present in an effective amount. In embodiments where the oral composition is in a solid or paste form, the abrasive material is generally present at about 10% to about 99% of the oral composition. In certain embodiments, the polishing material is present in amounts ranging from about 10% to about 75% (for example about 10% to about 40% or about 15% to about 30%) in toothpaste, and from about 70% to about 99% in toothpowder.

[0028] In a still further embodiment a composition of the invention comprises at least one humectant, useful for example to prevent hardening of a toothpaste upon exposure to air. Any orally acceptable humectant can be used, including without limitation polyhydric alcohols such as glycerin, sorbitol, xylitol and low molecular weight PEGs. Most humectants also function as sweeteners. One or more humectants are optionally present in a total amount of about 1% to about 70%, for example about 1% to about 50%, about 2% to about 25%, or about 5% to about 15% by weight of the composition.

[0029] In a still further embodiment a composition of the invention comprises at least one surfactant, useful for example to compatibilize other components of the composition and thereby provide enhanced stability, to help in cleaning the dental surface through detergency, and to provide foam upon agitation, e.g., during brushing with a dentifrice composition of the invention. Any orally acceptable surfactant, most of which are anionic, nonionic or amphoteric, can be used. Suitable anionic surfactants include without limitation water-soluble salts of C₈₋₂₀ alkyl sulfates, sulfonated monoglycerides of C₈₋₂₀ fatty acids, sarcosinates, taurates and the like. Illustrative examples of these and other classes include sodium lauryl sulfate, sodium coconut monoglyceride sulfonate, sodium lauryl sarcosinate, sodium lauryl isethionate, sodium laureth carboxylate and sodium dodecyl benzenesulfonate. Suitable nonionic surfactants include without limitation poloxamers, polyoxyethylene sorbitan esters, fatty alcohol ethoxylates, alkylphenol ethoxylates, tertiary amine oxides, tertiary phosphine oxides, dialkyl sulfoxides, and the like. Suitable amphoteric surfactants include without limitation derivatives of C₈₋₂₀ aliphatic secondary and tertiary amines having an anionic group such as carboxylate, sulfate, sulfonate, phosphate or phosphonate. A suitable example is cocoamidopropyl betaine. One or more surfactants are optionally present in a total amount of about 0.01% to about 10%, for example about 0.05% to about 5% or about 0.1% to about 2% by weight of the composition.

[0030] In another embodiment the composition comprises an orally acceptable anticalculus agent. One or more such agents can be present. Suitable anticalculus agents include without limitation phosphates and polyphosphates (for example pyrophosphates), polyaminopropanesulfonic acid (AMPS), zinc citrate trihydrate, polypeptides such as polyaspartic and polyglutamic acids, polyolefin sulfonates, polyolefin phosphates, diphosphonates such as azacycloalkane-2,2-diphosphonates (e.g., azacycloheptane-2,2-diphosphonic acid), N-methyl azacyclopentane-2,3-diphosphonic acid, ethane-1-hydroxy-