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CARRERA 7 # 71 – 21 TORRE B – PISO 4
BOGOTÁ – COLOMBIA
TEL: (571) 744 22 00
FAX: (571) 742 22 00 – (571) 3214045
www.bc.com.co

AS. 104.422

Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

REF.: Expediente No. 07 063.493 - Solicitud de Patente FASE NACIONAL
Corresp. a la Solicitud Internacional PCT/US2005/046514.
a nombre de: **COLGATE-PALMOLIVE COMPANY.**
Titulada: COMPOSICIONES ORALES QUE CONTIENEN *CAMELLIA* OXIDADA.

JUAN PABLO CADENA SARMIENTO, vecino de Bogotá, portador de la tarjeta profesional No. 57492 del Consejo Superior de la Judicatura, obrando como apoderado de la Sociedad **COLGATE-PALMOLIVE COMPANY**, según lo acredita el documento de poder presentado en esa División, de acuerdo con el Artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito solicitar que se examine si la invención contenida en la solicitud en referencia es patentable.

De acuerdo con lo anterior, me permito anexar el recibo oficial de caja No. 08-53,446 por valor de $420.000.

De la Señora Jefe atentamente,

JUAN PABLO CADENA SARMIENTO
C.C. No. 80.410.337 de Usaquén
T.P. No. 57492 del C.S.J.
Cra 7 No. 71-21 Torre B, Piso 4

Bogotá, 04 de agosto de 2008
MEV/CAG/jpg

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SPINARD & CASTRO LTDA	CONSIGNACION	BANCO DE BOGOTA	062754387	3249794	07/07/2008	17,750,000.00

**** C O N C E P T O ****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
		TOTAL : $	420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-63493

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **589** DE

FECHA **29 DE FEBRERO DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **03 DE JUNIO DE 2008**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO ____X____

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(71) 出願人 (米国を除く全ての指定国について): サントリー株式会社 (SUNTORY LIMITED) [JP/JP]; 〒530-8203 大阪府 大阪市 北区 堂島浜２丁目１番４０号 Osaka (JP)

(72) 発明者; および
(75) 発明者/出願人 (米国についてのみ): 前田 満 (MAEDA,Mitsuru) [JP/JP]; 〒520-0244 滋賀県 大津市 衣川２－１５－５ Shiga (JP).

(74) 代理人: 杜本 一夫, 外 (SHAMOTO,Ichio et al.): 〒100-0004 東京都 千代田区 大手町二丁目２番１号 新大手町ビル２０６区 ユアサハラ法律特許事務所 Tokyo (JP).

(81) 指定国 (国内): AU, CA, CN, JP, KR, US.

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国際調査報告書

２文字コード及び他の略語については、定期発行される各PCTガゼットの巻頭に掲載されている「コードと略語のガイダンスノート」を参照。

(54) Title: GALLOCATECHIN GALLATE-CONTAINING COMPOSITION

(54) 発明の名称: ガロカテキンガレート含有組成物

(57) **Abstract:** It is intended to provide a safe and highly efficacious antibacterial composition which is to be used in products mainly taken into the human or animal body or employed in the oral cavity such as foods and oral hygienic preparations without damaging the tastes of foods and drinks. The above composition contains gallocatechin gallate as a potentiator for antibacterial catechins. In particular, the antibacterial effects of the antibacterial catechins on bacteria causative of human decay such as *Streptococcus mutans* are enhanced thereby. The composition can be produced by mixing antibacterial catechins with gallocatechin gallate. Alternatively, it can be produced as a composition containing as the main component an adsorption fraction which is obtained by subjecting a solvent extract of tea leaves to adsorption by a synthetic adsorbent selected from among aromatic synthetic adsorbents and methacrylic synthetic adsorbents.

(57) 要約: 本発明は、食品および口腔衛生剤などの、主としてヒトや動物の体内に摂取されまたは口腔内で使用される製品に使用する、飲食物の味を損なうことなく、安全で、効果の高い抗菌組成物を提供する。 本発明の組成物は、ガロカテキンガレートを抗菌性カテキン類の作用増強剤として含有し、特にストレプトコッカス・ミュータンス等の虫歯菌に対して、抗菌性カテキン類の抗菌性が増強されている。本発明の組成物は、抗菌性カテキン類とガロカテキンガレートを混合して製造することができ、あるいは茶葉の溶媒抽出物を芳香族系合成吸着剤またはメタクリル系合成吸着剤から選ばれた合成吸着剤を用いる吸着処理に付して得られる合成吸着剤吸着画分を主成分とする組成物として製造することもできる。

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(19) **United States**

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Maeda (43) **Pub. Date: Jun. 22, 2006**

(54) **GALLOCATECHIN GALLATE-CONTAINING COMPOSITION**

(75) Inventor: **Mitsuru Maeda**, Shiga (JP)

Correspondence Address:
BUCHANAN INGERSOLL PC
(INCLUDING BURNS, DOANE, SWECKER & MATHIS)
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404 (US)

(73) Assignee: **Suntory Limited**, Osaka-shi, Osaka (JP)

(21) Appl. No.: **10/513,914**

(22) PCT Filed: **May 12, 2003**

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(30) **Foreign Application Priority Data**

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Publication Classification

(51) **Int. Cl.**
A23L 3/3463 (2006.01)

(52) **U.S. Cl.** **426/335**

(57) **ABSTRACT**

The present invention provides a safe and highly effective antibacterial composition without impairing the flavor of foods or drinks, which composition is used in products such as foods and oral care goods which are mainly to be taken into human or animal bodies or mainly to be used in the oral cavity.

The composition according to the present invention contains gallocatechin gallate as an agent for enhancing the activity of antibacterial catechins in which the antibacterial activity of the antibacterial catechins against *Streptococcus mutans* is particularly enhanced. The composition according to the present invention can be produced by mixing the antibacterial catechins with gallocatechin gallate. Alternatively, it can be produced as a composition comprising a synthetic adsorbent-adsorbed fraction as the main component, which is obtained by subjecting a solvent-extract from tea leaves to an adsorption treatment with the use of a synthetic adsorbent selected from among aromatic compound-based synthetic adsorbents and methacrylic compound-based synthetic adsorbents.

DETAILED DESCRIPTION OF THE INVENTION

[0009] To search for a highly safe antibacterial agent with the use of the effect on *Streptococcus mutans* as an indication, the present inventers have conducted intensive studies and, as a result, surprisingly found that GCG (gallocatechin gallate) has an activity of enhancing the antibacterial activity of green tea catechins such as EGCG, thereby completing the present invention.

[0010] Accordingly, the present invention relates to a composition comprising catechins mixed with an antibacterial effect enhancer gallocatechin gallate.

[0011] The present invention also relates to an antibacterial composition against *Streptococcus mutans* and the like, containing an antibacterial-active fraction containing gallocatechin gallate and green tea catechins obtained by extracting tea leaves with a solvent, adsorbing the solvent-extract from the tea leaves on synthetic adsorbent selected from among aromatic compound-based synthetic adsorbents and methacrylic compound-based synthetic adsorbents and then eluting the adsorbed components from the adsorbent, where the antibacterial activity of the green tea catechins is enhanced by the coexisting gallocatechin gallate.

[0012] The term "green tea catechins" as used in the present invention means green tea polyphenol catechins known as a composition having very safe cariostatic and anti periodontal disease activity based on the antibacterial activity, and includes for example, C, EC, GC, EGC, ECG, EGCG, etc., or a mixture thereof. It is preferable that the green tea catechins contain at least EGCG.

[0013] The term "antibacterial catechins" as used in the present invention means catechins at least containing EGCG and having an antibacterial effect.

[0014] The composition according to the present invention is an antibacterial composition that is expected to be applicable in the fields of quasi drugs or foods, that exerts a highly safe, antibacterial, cariostatic, and anti periodontal disease effects, and that is aimed at improving the storage stability of drinks or processed foods.

[0015] Although the composition according to the present invention may be produced from any starting materials without restriction, preferably it derives from tea in view of stable supply. The "tea" as used herein includes, but is not limited to, unfermented tea products of green tea such as Sen-cha (Japanese green tea), Houji-cha (roasted green tea), gyokuro tea, Kabuse-cha (semi sun shaded tea), and Mushi-seicha (steamed tea); unfermented tea products of various Chinese type green tea (Kamairi-cha, pan fired tea), such as Ureshino-cha, Aoyagi-cha, semi-fermented tea products such as Hoshu-tea and oolong tea, fermented tea products such as black tea, Awa-bancha, Goishi-cha and Pu-er tea, Mate-tea and so on. Considering the presence of an epimer and the synergistic effect on catechins, oolong tea produced from *Camellia* leaves is preferably employed as a supply source.

[0016] The composition according to the present invention may be produced by mixing GCG with catechins having an antibacterial effect, such as EGCG. Alternatively, it can be obtained using any of the tea materials described above as a starting material, according to a conventional extraction method. An extract from oolong tea using hot water or water-containing ethanol, etc., or an eluate which is obtained, as will be described in greater detail hereinafter, by dissolving or suspending said extract in water and then subjecting it to column chromatography using adsorptive resin such as DIAION HP-21 (manufactured by Mitsubishi Chemical Corporation) may be used.

[0017] The solvent used for extraction may be water alone, or an arbitrary mixture of water with one or more of polar solvents such as lower alcohols including methanol, ethanol, etc., and acetone. However, since the active ingredients according to the present invention cannot be efficiently extracted with a polar solvent alone, it is preferable to use a mixture of a polar solvent with water. Further, in such a solvent mixture, the content of the polar solvent is preferably not more than 90% by volume. Among these solvents, it is preferable to use water, ethanol or a mixture thereof from the viewpoint of safety, since the extract is to be finally formulated in oral care products or foods.

[0018] In the extraction step, the ratio of the tea leaves to the solvent is not particularly restricted. However, it is preferable to employ the solvent in an amount of 2 to 1,000 times by weight of the tea leaves, and in view of extraction procedure and efficiency, still preferably 5 to 100 times by weight of the tea leaves. It is convenient to carry out the extraction at a temperature of from room temperature to the boiling point of the solvent under atmospheric pressure. The extraction is preferably continued for a period of 10 minutes to 24 hours, though the extraction time varies depending on the extraction temperature.

[0019] To obtain an antibacterial fraction from the tea leaf extract thus obtained, the extract can be treated with a synthetic adsorbent. The synthetic adsorbent to be used in separating the tea leaf extract is, e.g., an aromatic compound-based synthetic adsorbent produced by polymerizing styrene and divinyl benzene or a methacrylic compound-based synthetic adsorbent produced by polymerizing methacrylic acid. Examples of commercially available aromatic compound-based synthetic adsorbents include DIAION HP20 and DIAION HP21 (manufactured by Mitsubishi Chemical Corporation), AMBERLITE XAD2 and AMBERLITE XAD 4 (manufactured by Rohm and Haas Company, USA) and so on, while examples of commercially available methacrylic compound-based synthetic adsorbents include DIAION HP1MG and DIAION HP2MG (manufactured by Mitsubishi Chemical Corporation), AMBERLITE XAD7 and AMBERLITE XAD 8 (manufactured by Rohm and Haas Company, USA) and so on.

[0020] It is preferable to carry out the synthetic adsorbent treatment by packing the synthetic adsorbent into a column, passing the tea leaf extract through the column and then washing the resin with water. When treating the tea leaf extract with the synthetic adsorbents, it is preferable to perform a pretreatment such as concentration under reduced pressure, to eliminate organic solvent from the extract, or sufficient dilution with water, to achieve complete fractionation of the extract. The gallocatechin gallate can be eluted from the adsorbent with the use of, for example, a 30% aqueous methanol solution, though the invention is not restricted thereto.

[0021] It is still preferable to further purify the eluate using DIAION HP-21 (manufactured by Mitsubishi Chemi-

cal Corporation) having a smaller pore size as a column packing. In this way, high-molecular weight substances such as polyphenols having molecular weight of 2000 or more, which were adsorbed together with the antibacterial components on an adsorbent in the case of HP-20, are not adsorbed and pass as such, and therefore, catechins and their epimers with lower molecular weights can be selectively adsorbed and collected. If necessary, the eluate is further treated with DIAION HP-21 or SEPHADEX LH-20 (manufactured by Amersham-Pharmacia) and eluted with a water-containing alcohol, e.g., a 30% aqueous methanol solution or water-containing acetone, e.g., a 50% aqueous acetone solution. In this way, substances not contributing to the antibacterial activity, e.g., caffeine, can be removed, and the catechins, EGCG and its epimer gallocatechin gallate, can be obtained at elevated concentration. The catechins, EGCG and its epimer gallocatechin gallate according to the present invention, can be determined by the colorimetry using the phenol reagent (Folin-Ciocalteu reagent). However, it is advisable to use high-performance liquid chromatography (HPLC) to determine the composition in detail.

[0022] According to the above-described method, a composition is provided, wherein the antibacterial effect of EGCG is enhanced by GCG, and wherein the ratio EGCG:GCG ranges from 1.0:0.01 to 1.0:10.0, preferably from 1.0:0.05 to 1.0:2.0. From the fraction separated by the above-described method, a favorable GCG composition ratio can be determined using the antibacterial activity as an indication.

[0023] The tea leaf extract thus obtained may be used in any form, for example, a product as extracted or a product as eluted from the synthetic adsorbent, a concentrate thereof or a dried product obtained by removing solvents from the eluate. From the viewpoints of storage stability and safety for organic solvents, it is advisable to use the extract in the form of a dried product.

[0024] The composition according to the present invention may be used to reduce or prevent the onset of dental caries, by being added alone or together with various components already employed in the art, to drinks and foods of various purposes. To reduce or prevent the onset of dental caries means both to use the composition according to the present invention as oral care goods to suppress or prevent the onset of dental caries, and to regularly or intermittently take foods or drinks containing the composition according to the present invention over a certain period of time to reduce or prevent the onset of dental caries.

[0025] Preferred embodiments of the present invention include dental care goods such as toothpastes, mouth wash and troches, as well as additives to foods such as sweeteners such as sucrose, sweetened bean pastes, Castella cakes, mizu-yokan (soft adzuki-bean jelly), dorayaki (bean-jelly pancake) coating, sponge cakes, butter cakes, bavarois, custard cream, butter cream, custard pudding, cookies, sweet buns, steamed buns, jams, lactic acid bacteria drinks, carbonated drinks, coffee drinks, coffee jelly, caramel, candies, ice creams, chewing gums, juice, candies and chocolates.

[0026] To produce these oral care goods or foods containing the cariostatic agents, components commonly employed in the art can be selected and used appropriately depending on the product types. For example, oral care goods may optionally contain calcium carbonate, dibasic calcium phosphate, silicic anhydride, magnesium carbonate, glycerine, sorbitol, propylene glycol, polyethylene glycol, carboxymethylcellulose, methyl cellulose, sodium alginate, carrageenan, carboxyvinyl polymer, sodium dioctylsulfosuccinate, sodium lauryl sulfate, sodium dodecylbenzenesulfonate, butyl parahydroxybenzoate, hinokitiol, allantoin, glycyrrhizin, alcohols, gum arabic, starch, corn starch, saccharin sodium, stevioside, glucose, lactose, magnesium stearate, monopotassium phosphate, dipotassium phosphate, menthol, eucalyptus oil, peppermint, spearmint, colorants, as well as fluorides such as sodium fluoride and sodium monofluorophosphate, anti-inflammatory agents such as lysozyme chloride and azulene, sodium chloride and so on.

[0027] On the other hand, foods may be produced by optionally blending commonly employed food materials such as glucose, fructose, sucrose, maltose, sorbitol, stevioside, corn syrup, lactose, citric acid, tartaric acid, malic acid, succinic acid, lactic acid, L-ascorbic acid, dl-a-tocopherol, sodium erythorbate, glycerine, propylene glycol, glycerine fatty acid esters, polyglycerine fatty acid esters, sucrose fatty acid esters, sorbitan fatty acid esters, propylene glycol fatty acid esters, gum arabic, carrageenan, casein, gelatin, pectin, agar, vitamin B family, nicotinic acid amide, calcium pantothenate, amino acids, calcium salts, colorants, flavoring agents and preservatives.

[0028] In the case of adding sugar together with a cariostatic agent to give, e.g., a cariostatic food, as will be shown in EXAMPLES by adding the composition according to the present invention to a food, a cariostatic sugar can be used as a substrate, as will be shown in EXAMPLES 6 to 8.

[0029] Since tea has been widely consumed all over the world from ancient times, there is no trouble with the fraction obtained from tea leaf extract in terms of safety. However, considering the flavor, smell, color tone, etc. of the product, it is preferred to add the composition according to the present invention (including the cariostatic composition) to the food and drink of the present invention at a concentration of 0.0001 to 0.5%, still preferably 0.01 to 0.2%, on a dry weight basis. It is also preferable to control the concentration in a food within the range as specified above, in use. Further, according to the present invention, it is also possible to reduce an amount of antibacterial catechins owing to the effect of gallocatechin gallate.

ADVANTAGES OF THE INVENTION

[0030] The composition according to the present invention shows a strong antibacterial activity against *Streptococcus mutans* which is the major causative bacterium of dental plaque formation inducing dental caries and periodontal diseases. The component employed in the present invention is extremely safe and the composition can be supplied in a large amount as cariostatic and anti periodontal disease composition, because the ingredients of the composition originate in tea, which has been widely consumed from ancient times. Accordingly, the present invention appears to contribute to improvement in oral hygiene and, furthermore, is expected to be applicable to the field of general foods, and therefore, industrially very useful.

[0031] Next, the present invention will be illustrated in greater detail by reference to the following EXAMPLES. However, it is needless to say that the present invention is not restricted to these EXAMPLES.

EXAMPLE 1

Enhancement of Antibacterial Effect by Mixing EGCG and GCG

[0032] *Streptococcus mutans* (MT8148R) was cultured in a brain heart infusion medium (BHI, manufactured by Difco) at 37° C. for 18 hours. After collection of the cells by centrifugation, the precipitate was washed three times with a phosphate buffer solution (PBS, pH 6.8). Then the cells were suspended to give an absorbance of 0.5 at 550 nm. Thus, about 2×10^7 colonies per mL (expressed in colony forming unit: CFU) were formed. Next, an equal amount of a previously prepared sample solution was added to the suspension and the resultant mixture was allowed to stand at 37° C. for 1 hour. 0.1 mL of this liquid mixture or the same mixture seriously 10-fold diluted was sowed on a Mitis salivarius agar medium (MS agar medium, manufactured by Difco). After culturing at 37° C. for 2 days, the colonies thus formed were counted. The antibacterial activity was indicated in the logarithm of CFU of test group CFU of control lot (i.e., the reducing ratio).

[0033] The mixing ratio of EGCG to GCG (manufactured by Sigma) was varied so as to adjust the final concentration of the sample to 1 mg/mL and thus the antibacterial activity was examined. Compared with the samples containing EGCG or GCG alone, the mixtures of them showed enhanced antibacterial activities. In particular, the sample having an EGCG:GCG ratio of 1.00:0.45 showed an activity $10^{2.23}$ times higher (about 15-fold) than that of the sample containing EGCG alone. Table 1 summarizes the results.

TABLE 1

Ratio		Antibacterial activity
EGCG	GCG	
	2.5	−3.1
1.0		3.8
1.0	0.5	−4.07
1.00	0.45	−4.21
1.0	0.5	−4.58
1.00	0.45	−4.73
1.0	1	−4.55
1.00	2	−4.22

EXAMPLE 2

Fractionation of Oolong Tea Extract

[0034] To oolong tea leaves was added 10 volumes of a 45% (w/w) aqueous ethanol solution. After immersion of the tea leaves at room temperature for 1 day, the mixture was filtered and the extract thus obtained was powdered by concentration under reduced pressure and freeze-drying. To the powder thus obtained, 100 volumes of deionized water were added and the resultant suspension was passed through a DIAION HP-21 column (manufactured by Mitsubishi Chemical Corporation). After washing with deionized water, elution was carried out with the use of a 30% aqueous methanol solution (passing speed: SV=3, passing volume: 5-bed volumes each time). The eluate obtained using the 30% aqueous methanol solution was concentrated under reduced pressure and freeze-dried to give a powder.

[0035] Using the obtained powder, a 50% DMSO solution was prepared and analyzed by high-performance liquid chromatography (analyzer: Alliance Photodiode Array System, manufactured by Waters, column: Develosil C30-UG-5, 4.6×150 mm, manufactured by Nomura Kagaku Co., Ltd.; mobile phase and elution conditions: linear gradient from Solution A (0.05% trifluoroacetic acid) to Solution B (50% acetonitrile-0.05% trifluoroacetic acid) within 20 minutes; flow rate: 1 mL/min; column temperature: 40° C.). C, CG, EC, GC, EGC, EGCG, GCG and ECG (manufactured by Sigma) were used as standards and the weights of the catechins contained were determined from the respective calibration curves. The composition ratio is shown in Table 2, with the major component EGCG being taken as 1.00.

TABLE 2

Composition ratio of catechins: Composition ratio of catechins by weight							
EGCG	EGC	GCG	ECG	C	EC	GC	CG
1.0	0.4	0.2	0.16	0.1	Tr	Tr	Tr

In this Table, "Tr" means a trace amount which is too small to indicate numerically.

EXAMPLE 3

[0036] Toothpaste

component	parts by weight
Dibasic Calcium phosphate	40
Glycerine	20
Carrageenan	1.0
[illegible]	1.2
Saccharin Sodium	0.09
[illegible]	0.015
Tea leaf extract*	1.0
Foaming agent	1.5
Water	the balance
Total	100

* The tea leaf extract was prepared in accordance with [illegible] of JAMP 5.2. The same [illegible]

EXAMPLE 4

[0037] Mouth wash

component	parts by weight
[illegible]	0.5
Glycerine	10
Ethanol	5.0
[illegible]	0.5
Tea leaf extract	0.2
[illegible]	0.5
Perfuming agent	0.4
[illegible]	1
Water	the balance
Total	100

D2 → T30
100


US005776435A

United States Patent [19]

Gaffar et al.

[11] **Patent Number: 5,776,435**

[45] **Date of Patent: *Jul. 7, 1998**

[54] **ANTIPLAQUE ANTIBACTERIAL ORAL COMPOSITION**

[75] Inventors: **Abdul Gaffar**, Princeton; **Nuran Nabi**, No. Brunswick; **John Affilitto**, Brookside, all of N.J.; **Orum Stringer**, Yardley, Pa.

[73] Assignee: **Colgate-Palmolive Company**, New York, N.Y.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. Nos. 5,037,635, 5,192,531 and 5,288,480.

[21] Appl. No.: **176,926**

[22] Filed: **Feb. 22, 1994**

Related U.S. Application Data

[62] Division of Ser. No. 964,247, Oct. 21, 1992, Pat. No. 5,288,480, which is a division of Ser. No. 655,571, Feb. 19, 1991, Pat. No. 5,178,851, which is a continuation of Ser. No. 398,566, Aug. 25, 1989, Pat. No. 5,032,386, which is a continuation-in-part of Ser. No. 291,712, Dec. 29, 1988, Pat. No. 4,894,220, and Ser. No. 346,258, May 1, 1989, Pat. No. 5,043,154, said Ser. No. 291,712, is a continuation-in-part of Ser. No. 8,901, Jan. 30, 1987, abandoned, said Ser. No. 346,258, is a continuation of Ser. No. 8,901, Jan. 30, 1987, abandoned.

[51] **Int. Cl.**[6] **A61K 7/16**; A61K 7/18

[52] **U.S. Cl.** **424/49**; 424/52

[58] **Field of Search** 424/49–58

[56] **References Cited**

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5,192,531	3/1993	Gaffar et al.	424/52
5,288,480	2/1994	Gaffar et al.	424/52
5,294,431	3/1994	Gaffar et al.	424/52

Primary Examiner—Shep K. Rose
Attorney, Agent, or Firm—Henry S. Goldfine

[57] **ABSTRACT**

An oral composition dentifrice comprising an orally acceptable vehicle, about 5–30% by weight of a siliceous polishing agent, about 0.25–0.35% by weight of a substantially water-insoluble noncationic antibacterial antiplaque agent, such as 2,4,4'-trichloro-2'-hydroxydiphenyl ether (triclosan) and an antibacterial-enhancing agent which enhances the delivery of said antibacterial agent to, and retention thereof on, oral surfaces.

19 Claims, No Drawings

ANTIPLAQUE ANTIBACTERIAL ORAL COMPOSITION

This is a division of application Ser. No. 07/964,247, filed Oct. 21, 1992, now U.S. Pat. No. 5,288,480, which is a division of application Ser. No. 07/655,571, Feb. 19, 1991, now U.S. Pat. No. 5,178,851, granted Jan. 12, 1993, which is a continuation of application Ser. No. 07/398,566, filed Aug. 25, 1989, now U.S. Pat. No. 5,032,386, granted Jul. 16, 1991, which is a continuation-in-part of application Ser. No. 07/291,712, filed Dec. 29, 1988, now U.S. Pat. No. 4,894,220, granted Jan. 16, 1990, and of application Ser. No. 07/346,258, filed May 1, 1989, now U.S. Pat. No. 5,043,154, granted Aug. 27, 1991, which are respectively a continuation-in-part and a continuation of application Ser. No. 07/008,901, filed Jan. 30, 1987, now abandoned.

This invention relates to an antibacterial antiplaque oral composition dentifrice. More particularly, it relates to an oral composition dentifrice containing a substantially water-insoluble noncationic antibacterial agent effective to inhibit plaque.

Dental plaque is a soft deposit which forms on teeth as opposed to calculus which is a hard calcified deposit on teeth. Unlike calculus, plaque may form on any part of the tooth surface, particularly including at the gingival margin. Hence, besides being unsightly, it is implicated in the occurence of gingivitis.

Accordingly, it is highly desirable to include antimicrobial agents which have been known to reduce plaque in oral compositions. Frequently, cationic antibacterial agents have been suggested. Moreover, in U.S. Pat. No. 4,022,880 to Vinson et al, a compound providing zinc ions as an anticalculus agent is admixed with an antibacterial agent effective to retard the growth of plaque bacteria. A wide variety of antibacterial agents are described with the zinc compounds including cationic materials such as guanides and quaternary ammonium compounds as well as non-cationic compounds such as halogenated salicylanilides and halogenated hydroxydiphenyl ethers. The noncationic antibacterial antiplaque halogenated hydroxydiphenyl ether, triclosan, has also been described in combination with zinc citrate trihydrate in European Patent Publication 0161,899 to Saxton et al. Triclosan is also disclosed in European Patent Publication 0271,332 to Davis as a toothpaste component, containing a solubilizing agent such as propylene glycol.

The cationic antibacterial materials such as chlorhexidine, benzthonium chloride and cetyl pyridinium chloride have been the subject of greatest investigation as antibacterial antiplaque agents. However, they are generally not effective when used with anionic materials. Noncationic antibacterial materials, on the other hand, can be compatible with anionic components in an oral composition.

However, oral compositions typically are mixtures of numerous components and even such typically neutral materials as humectants can affect performance of such compositions.

Moreover, even noncationic antibacterial agents may have limited antiplaque effectiveness with commonly used materials such as polyphosphate anticalculus agents which are disclosed together in British Patent Publication 22 00551 of Gaffar et al and in EP 0251591 of Jackson et al. In commonly assigned Ser. No. 398,605 filed on even date herewith, titled "Antibacterial, Antiplaque Anticalculus Oral Composition", it is shown the antiplaque effectiveness is greatly enhanced by including an antibacterial-enhancing agent (AEA) which enhances the delivery of said antibacterial agent to, and retention thereof on, oral surfaces and providing optimized amounts and ratio of polyphosphate and AEA.

Further, even when polyphosphate anticalculus agent is not present as in commonly assigned Ser. No. 398,606 filed on even date herewith, titled "Antibacterial Antiplaque Oral Composition", antiplaque effectiveness on soft oral tissue is optimized by including with the AEA a solubilizing material which dissolves the noncationic antibacterial agent in saliva when the polishing agent is a siliceous polishing agent present in amount of about 5–30%. When the amount of polishing material is about 30–75% by weight, the special solubilizing material is not required, as in commonly assigned Ser. No. 398,699, filed on even date herewith, titled "Antibacterial Antiplaque Oral Composition".

It is an advantage of this invention that an oral composition dentifrice containing a siliceous polishing agent, a small but effective antiplaque amount of a substantially water-insoluble noncationic antibacterial agent and an AEA is provided to inhibit plaque formation, even without requiring the presence of special solubilizing agent.

It is an advantage of this invention that the AEA enhances the delivery and retention of small but effective antiplaque amount of the antibacterial agent on teeth and on soft oral tissues.

It is a further advantage of this invention that an antiplaque oral composition is provided which is effective to reduce the occurrence of gingivitis.

Additional advantages of this invention will be apparent from consideration of the following specification.

In accordance with certain of its aspects, this invention relates to an oral composition dentifrice comprising in an orally acceptable vehicle, about 5–30% by weight of a siliceous polishing agent, about 0.25–0.35% by weight of a substantially water insoluble noncationic antibacterial agent, said oral composition dentifrice comprising at least one of a surface active-agent and a flavoring oil, and about 0.05–4% by weight of said AEA, said oral composition dentifrice being substantially free of polyphosphate anticalculus agent.

Typical examples of water insoluble noncationic antibacterial agents which are particularly desirable from considerations of antiplaque effectiveness, safety and formulation are:

Halogenated Diphenyl Ethers
2',4,4'-trichloro-2-hydroxy-diphenyl ether (Triclosan)
2,2'-dihydroxy-5,5'-dibromo-diphenyl ether.
Halogenated Salicylanilides
4'5-dibromosalicylanilide
3,4',5-trichlorosalcylanilide
3,4',5-tribromosalicylanilide
2,3,3',5-tetrachlorosalicylanilide
3,3',5-tetrachlorosalicylanilide
3,5-dibromo-3'-trifluoromethyl salicylanilide
5-n-octanoyl-3'-trifluoromethyl salicylanilide
3,5-dibromo-4'-trifluoromethyl salicylanilide
3,5-dibromo-3'-trifluoro methyl salicylanilide (Fluorophene)
Benzoic Esters
Methyl-p-Hydroxybenzoic Ester
Ethyl-p-Hydroxybenzoic Ester
Propyl-p-Hydroxybenzoic Ester
Butyl-p-Hydroxybenzoic Ester
Halogenated Carbanilides
3,4,4'-trichlorocarbanilide
3-trifluoromethyl-4,4'-dichlorocarbanilide
3,3',4-trichlorocarbanilide

Phenolic Compounds (including phenol and its homologs, mono- and poly-alkyl and aromatic halo (e.g. F,Cl,Br,I)-phenols, resorcinol and catechol and their derivatives and bisphenolic compounds). Such phenolic compounds includes inter alia:

Phenol and its Homologs
Phenol
2 Methyl-Phenol
3 Methyl-Phenol
4 Methyl-Phenol
4 Ethyl-Phenol
2,4-Dimethyl-Phenol
2,5-Dimethyl-Phenol
3,4-Dimethyl-Phenol
2,6-Dimethyl-Phenol
4-n-Propyl-Phenol
4-n-Butyl-Phenol
4-n-Amyl-Phenol
4-tert-Amyl-Phenol
4-n-Hexyl-Phenol
4-n-Heptyl-Phenol
2-Methoxy-4-(2-Propenyl)-Phenol (Eugenol)
2-Isopropyl-5-Methyl-Phenol (Thymol)
Mono- and Poly-Alkyl and Aralkyl Halophenols
Methyl-p-Chlorophenol
Ethyl-p-Chlorophenol
n-Propyl-p-Chlorophenol
n-Butyl-p-Chlorophenol
n-Amyl-p-Chlorophenol
sec-Amyl-p-Chlorophenol
n-Hexyl-p-Chlorophenol
Cyclohexyl-p-Chlorophenol
n-Heptyl-p-Chlorophenol
n-Octyl-p-Chlorophenol
O-Chlorophenol
Methyl-o-Chlorophenol
Ethyl-o-Chlorophenol
n-Propyl-o-Chlorophenol
n-Butyl-o-Chlorophenol
n-Amyl-o-Chlorophenol
tert-Amyl-o-Chlorophenol
n-Hexyl-o-Chlorophenol
n-Heptyl-o-Chlorophenol
p-Chlorophenol
o-Benzyl-p-Chlorophenol
o-Benzyl-m-methyl-p-Chlorophenol
o-Benzyl-m, m-dimethyl-p-Chlorophenol
o-Phenylethyl-p-Chlorophenol
o-Phenylethyl-m-methyl-p-Chlorophenol
3-Methyl-p-Chlorophenol
3,5-Dimethyl-p-Chlorophenol
6-Ethyl-3-methyl-p-Chlorophenol
6-n-Propyl-3-methyl-p-Chlorophenol
6-iso-Propyl-3-methyl-p-Chlorophenol
2-Ethyl-3,5-dimethyl-p-Chlorophenol
6-sec Butyl-3-methyl-p-Chlorophenol
2-iso-Propyl-3,5-dimethyl-p-Chlorophenol
6-Diethylmethyl-3-methyl-p-Chlorophenol
6-iso-Propyl-2-ethyl-3-methyl-p-Chlorophenol
2-sec Amyl-3,5-dimethyl-p-Chlorophenol
2-Diethylmethyl-3,5-dimethyl-p-Chlorophenol
6-sec Octyl-3-methyl-p-Chlorophenol
p-Bromophenol
Methyl-p-Bromophenol
Ethyl-p-Bromophenol
n-Propyl-p-Bromophenol
n-Butyl-p-Bromophenol
n-Amyl-p-Bromophenol
sec-Amyl-p-Bromophenol
n-Hexyl-p-Bromophenol
cyclohexyl-p-Bromophenol
o-Bromophenol
tert-Amyl-o-Bromophenol
n-Hexyl-o-Bromophenol
n-Propyl-m,m-Dimethyl-o-Bromophenol
2-Phenyl Phenol
4-chloro-2-methyl phenol
4-chloro-3-methyl phenol
4-chloro-3,5-dimethyl phenol
2,4-dichloro-3,5-dimethylphenol
3,4,5,6-terabromo-2-methylphenol
5-methyl-2-pentylphenol
4-isopropyl-3-methylphenol
5-chloro-2-hydroxydiphenylemthane
Resorcinol and its Derivatives
Resorcinol
Methyl-Resorcinol
Ethyl-Resorcinol
n-Propyl-Resorcinol
n-Butyl-Resorcinol
n-Amyl-Resorcinol
n-Hexyl-Resorcinol
n-Heptyl-Resorcinol
n-Octyl-Resorcinol
n-Nonyl-Resorcinol
Phenyl-Resorcinol
Benzyl-Resorcinol
Phenylethyl-Resorcinol
Phenylpropyl-Resorcinol
p-Chlorobenzyl-Resorcinol
5-Chloro-2,4-Dihydroxydiphenyl Methane
4'-Chloro-2,4-Dihydroxydiphenyl Methane
5-Bromo-2,4-Dihydroxydiphenyl Methane
4'-Bromo-2,4-Dihydroxydiphenyl Methane
Bisphenolic Compounds
Bisphenol A
2,2'-methylene bis (4-chlorophenol)
2,2'-methylene bis (3,4,6-trichlorophenol) (hexachlorophene)
2,2'-methylene bis (4-chloro-6-bromophenol)
bis (2-hydroxy-3,5-dichlorophenyl) sulfide
bis (2-hydroxy-5-chlorobenzyl) sulfide

The noncationic antibacterial agent is present in the oral composition in an effective antiplaque amount of about 0.25–0.35% by weight, preferably about 0.3%. The antibacterial agent is substantially water-insoluble, meaning that its solubility is less than about 1% by weight in water at 25° C. and may be even less than about 0.1%.

The preferred halogenated diphenyl ether is triclosan. The preferred phenolic compounds are phenol, thymol, eugenol, hexyl resorcinol and 2,2'-methylene bis(4-chloro-6-bromophenol). The most preferred antibacterial antiplaque compound is triclosan. Triclosan is disclosed in aforementioned U.S. Pat. No. 4,022,880 as an antibacterial agent in combination with an anticalculus agent which provides zinc ions, and in German Patent Disclosure 3532860 in combination with a copper compound. In European Patent Disclosure 0278744 it is disclosed in combination with a tooth densitizing agent containing a source of potassium ions. It is also disclosed as an antiplaque agent in a dentifrice formulated to contain a lamellar liquid crystal surfactant phase having a lamellar spacing of less than 6.0 nm and which may optionally contain a zinc salt in published European Patent Application 0161898 of Lane et al and in a dentifrice containing zinc citrate trihydrate in published European Patent Application 0161899 to Saxton et al.

The antibacterial-enhancing agent (AEA) which enhances delivery of said antibacterial agent to, and retention thereof on, oral surfaces, is employed in amounts effective to

achieve such enhancement within the range in the oral composition of about 0.05%, to about 4%, preferably about 0.1% to about 3%, more preferably about 0.5% to about 2.5% by weight.

AEA polymeric materials of the present invention include those which can be characterized as having utility as dentifrice adhesives or fixatives or dental cements. For example, U.S. Pat. Nos. 4,521,551 and 4,373,036 each to Chang et al. describe commercially available copolymer of methylvinyl ether-maleic anhydride (Gantrez) as a denture fixative. However, there has not been recognition in the prior art that adhesives, fixatives or cements when applied in water-soluble or water-swellable form together with substantially water-insoluble non-cationic antibacterial antiplaque agents could enhance the antibacterial activity of such agents. Further, in U.S. Pat. No. 4,485,090 to Chang, Gantrez AN copolymer is mentioned among polymeric anionic membrane-forming materials which attach to a tooth surface to form a hydrophobic barrier which reduces elution of a previously applied therapeutic caries prophylactic fluoride compound. Again, there is no recognition that such polymeric material could enhance the antibacterial activity of substantially water-insoluble non-cationic antibacterial antiplaque agents.

This AEA may be a simple compound, preferably a polymerizable monomer, more preferably a polymer, which latter term is entirely generic, including for example oligomers, homopolymers, copolymers of two or more monomers, ionomers, block copolymers, graft copolymers, cross-linked polymers and copolymers, and the like. The AEA may be natural or synthetic, and water insoluble or preferably water (saliva) soluble or swellable (hydratable, hydrogel forming). It has an (weight) average molecular weight of about 100 to about 1,000,000, preferably about 1,000 to about 1,000,000, more preferably about 2,000 or 2,500 to about 250,000 or 500,000.

The AEA ordinarily contains at least one delivery-enhancing group, which is preferably acidic such as sulfonic, phosphinic, or more preferably phosphonic or carboxylic, or salt thereof, e.g. alkali metal or ammonium, and at least one organic retention-enhancing group, preferably a plurality of both the delivery-enhancing and retention-enhancing groups, which latter groups preferably have the formula $—(X)_n—R$ wherein X is O, N, S, SO, SO_2, P, PO or Si or the like. R is hydrophobic alkyl, alkenyl, acyl, aryl, alkaryl, aralkyl, heterocyclic or their inert-substituted derivatives, and n is zero or 1 or more. The aforesaid "inert-substituted derivatives", are intended to include substituents on R which are generally non-hydrophilic and do not significantly interfere with the desired functions of the AEA as enhancing the delivery of the antibacterial agent to, and retention thereof on, oral surfaces such as halo, e.g. Cl, Br, I, and carbo and the like. Illustrations of such retention-enhancing groups are tabulated below.

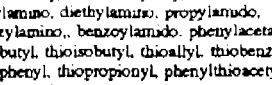
n	X	$—(X)_nR$
0	—	methyl, ethyl, propyl, butyl, isobutyl, t-butyl, cyclohexyl, allyl, benzyl, phenyl, chlorophenyl, xylyl, pyridyl, furanyl, aceryl, benzoyl, butyryl, terephthaloyl, etc
1	O	ethoxy, benzyloxy, thioacetoxy, phenoxy, carboethoxy, carbobenzyloxy, etc.
	N	ethylamino, diethylamino, propylamido, benzylamino,, benzoylamido, phenylacetamido, etc.
	S	thiobutyl, thioisobutyl, thioallyl, thiobenzyl, thiophenyl, thiopropionyl, phenylthioacetyl, thiobenzoyl, etc.
	SO	butylsulfoxy, allylsulfoxy, benzylsulfoxy, phenylsulfoxy, etc.
	SO_2	butylsulfonyl, allysulfonyl, benzylsulfonyl, phenylsulfonyl, etc.
	P	diethyphosphinyl, ethylvinylphosphinyl, ethylallylphosphinyl, ethylbenzylphosphinyl, ethylphenylphosphinyl, etc.
	PO	diethylphosphinoxy, ethylvinylphosphinoxy, methylallylphosphinoxy, methylbenzylphosphinoxy, methylphenylphosphinoxy, etc.
	Si	trimethysilyl, dimethylbutylsilyl, dimethylbenzylsilyl, dimethylvinylsilyl, dimethylallylsilyl, etc.

As employed herein, the delivery-enhancing group refers to one which attaches or substantively, adhesively, cohesively or otherwise bonds the AEA (carrying the antibacterial agent) to oral (e.g. tooth and gum) surfaces, thereby "delivering" the antibacterial agent to such surfaces. The organic retention-enhancing group, generally hydrophobic, attaches or otherwise bonds the antibacterial agent to the AEA, thereby promoting retention of the antibacterial agent to the AEA and indirectly on the oral surfaces. In some instances, attachment of the antibacterial agent occurs through physical entrapment thereof by the AEA, especially when the AEA is a cross-linked polymer, the structure of which inherently provides increased sites for such entrapment. The presence of a higher molecular weight, more hydrophobic cross-linking moiety in the cross-linked polymer still further promotes the physical entrapment of the antibacterial agent to or by the cross-linked AEA polymer.

Preferably, the AEA is an anionic polymer comprising a chain or backbone containing repeating units each preferably containing at least one carbon atom and preferably at least one directly or indirectly pendant, monovalent delivery-enhancing group and at least one directly or indirectly pendant monovalent retention-enhancing group geminally, vicinally or less preferably otherwise bonded to atoms, preferably carbon, in the chain. Less preferably, the polymer may contain delivery-enhancing groups and/or retention-enhancing groups and/or other divalent atoms or groups as links in the polymer chain instead of or in addition to carbon atoms, or as cross-linking moieties.

It will be understood that any examples or illustrations of AEA's disclosed herein which do not contain both delivery-enhancing groups and retention enhancing groups may and preferably should be chemically modified in known manner to obtain the preferred AEA's containing both such groups and preferably a plurality of each such groups. In the case of the preferred polymeric AEA's, it is desirable, for maximizing substantivity and delivery of the antibacterial agent to oral surfaces, that the repeating units in the polymer chain or backbone containing the acidic delivery enhancing groups constitute at least about 10%, preferably at least about 50%, more preferably at least about 80% up to 95% or 100% by weight of the polymer.

According to a preferred embodiment of this invention, the AEA comprises a polymer containing repeating units in which one or more phosphonic acid delivery-enhancing groups are bonded to one or more carbon atoms in the polymer chain. An example of such an AEA is poly (vinyl phosphonic acid) containing units of the formula:



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which however does not contain a retention-enhancing group. A group of the latter type would however be present

readily functions in polymerization because of its presence in the monomer molecule either in the alpha-beta position with respect to a carboxyl group or as part of a terminal methylene grouping. Illustrative of such acids are acrylic, methacrylic, ethacrylic, alpha-chloroacrylic, crotonic, beta-acryloxy propionic, sorbic, alpha-chlorsorbic, cinnamic, beta-styrylacrylic, muconic, itaconic, citraconic, mesaconic, glutaconic, aconitic, alpha-phenylacrylic, 2-benzyl acrylic, 2-cyclohexylacrylic, angelic, umbellic, fumaric, maleic acids and anhydrides. Other different olefinic monomers copolymerizable with such carboxylic monomers include vinylacetate, vinyl chloride, dimethyl maleate and the like. Copolymers ordinarily contain sufficient carboxylic salt groups for water-solubility.

Also useful herein are so-called carboxyvinyl polymers disclosed as toothpaste components in U.S. Pat. No. 3,980,767 to Chown et al; U.S. Pat. No. 3,935,306 to Roberts et al; U.S. Pat. No. 3,919,409 to Perla et al; U.S. Pat. No. 3,911,904 to Harrison, and U.S. Pat. No. 3,711,604 to Colodney et al. They are commercially available for example under the trademarks Carbopol 934, 940 and 941 of B. F. Goodrich, these products consisting essentially of a colloidally water-soluble polymer of polyacrylic acid crosslinked with from about 0.75% to about 2.0% of polyallyl sucrose or polyallyl pentaerythritol as cross linking agent, the cross-linked structure and cross-linkages providing the desired retention enhancement by hydrophobicity and/or physical entrapment of the antibacterial agent or the like. Polycarbophil is somewhat similar, being poly acrylic acid cross-linked with less than 0.2% of divinyl glycol, the lower proportion, molecular weight and/or hydrophobicity of this cross-linking agent tending to provide little or no retention enhancement. 2,5-dimethyl-1,5-hexadiene exemplifies a more effective retention-enhancing cross-linking agent.

The synthetic anionic polymeric polycarboxylate component is mainly a hydrocarbon with optional halogen and O-containing substituents and linkages as present in for example ester, ether and OH groups, and is employed in the instant compositions in approximate weight amounts of 0.05 to 4%, preferably 0.05 to 3%, more preferably 0.1 to 2%.

The AEA may also comprise natural anionic polymeric polycarboxylates containing retention-enhancing groups. Carboxymethyl cellulose and other binding agents gums and film-formers devoid of the above-defined delivery-enhancing and/or retention-enhancing groups are ineffective as AEA's.

As illustrative of AEA's containing phosphinic acid and/or sulfonic acid delivery enhancing groups, there may be mentioned polymers and copolymers containing units or moieties derived from the polymerization of vinyl or allyl phosphinic and/or sulfonic acids substituted as needed on the 1 or 2 (or 3) carbon atom by an organic retention-enhancing group, for example having the formula $-(X)_n-R$ defined above. Mixtures of these monomers may be employed, and copolymers thereof with one or more inert polymerizable ethylenically unsaturated monomers such as those described above with respect to the operative synthetic anionic polymeric polycarboxylates. As will be noted, in these and other polymeric AEA's operative herein, usually only one acidic delivery-enhancing group is bonded to any given carbon or other atom in the polymer backbone or branch thereon. Polysiloxanes containing pendant delivery-enhancing groups and retention enhancing groups may also be employed as AEA's herein. Also effective as AEA's herein are ionomers containing or modified to contain delivery- and retention-enhancing groups. Ionomers are described on pages 546–573 of the Kirk-Othmer Encyclopedia of Chemical Technology, third edition, Supplement Volume, John Wiley & Sons, Inc. copyright 1984, which description is incorporated herein by reference. Also effective as AEA's herein, provided they contain or are modified to certain retention-enhancing groups, are polyesters, polyurethanes and synthetic and natural polyamides including proteins and proteinaceous materials such as collagen, poly (argenine) and other polymerized amino acids.

Without being bound to a theory, it is believed that the AEA, especially polymeric AEA, is generally an anionic film forming material and is thought to attach to tooth surfaces and form a continuous film over the surfaces, thereby preventing bacterial attachment to tooth surfaces. It is possible that the noncationic antibacterial agent forms a complex or other form of association with the AEA, thus forming a film of a complex or the like over tooth surfaces. The film forming property of the AEA and the enhanced delivery property of the AEA and the enhanced delivery and retention of the antibacterial agent on tooth surfaces due to the AEA appears to make tooth surfaces unfavourable for bacterial accumulation particularly since the direct bacteriostatic action of the antibacterial agent controls bacterial growth. Therefore, through the combination of three modes of actions: 1) enhanced delivery, 2) long retention time on tooth surfaces, and 3) prevention of bacterial attachment to tooth surfaces, the oral composition is made efficacious for reducing plaque. Similar antiplaque effectiveness is attained on soft oral tissue at or near the gum line.

In aforementioned application Ser. No. 398,606, filed on even date herewith, titled "Antibacterial Antiplaque Oral Compositions" wherein the dentifrices thereof contain about 5–30% by weight of a siliceous polishing agent, a material which solubilizes the noncationic antibacterial agent to render it effective in delivery to soft oral tissues at the gum line is employed. In the present invention, when the amount of the noncationic antibacterial agent is optimized at about 0.25–0.35% by weight, it is found that the solubilizing agent is not required; but is rather optional.

In the oral preparation dentifrice, an orally acceptable vehicle including a water-phase with humectant is present. Water is present typically in amount of at least about 3% by weight, generally about 3–35% and humectant, preferably glycerine and/or sorbitol, typically total about 6.5–75% or 80% by weight of the oral preparation dentifrice, more typically about 10–75%. Reference hereto to sorbitol refers to the material typically as available commercially in 70% aqueous solutions. Although not required in the present invention wherein about 0–25–0.35% of the water insoluble non-cationic antibacterial agent is present optionally, an additional ingredient which assists solubilization of the antibacterial agent in saliva may be incorporated in the water-humectant vehicle. Such optional solubilizing agents include humectant polyols such as propylene glycol, dipropylene glycol, and hexylene glycol, cellosolves such as methyl cellosolve and ethyl cellosolve, vegetable oils and waxes containing at least about 12 carbons in a straight chain such as olive oil, castor oil and petrolatum and esters such as amyl acetate, ethyl acetate and benzyl benzoate. As used herein "propylene glycol" includes 1,2-propylene glycol and 1,3-propylene glycol. Significant amounts of polyethylene glycol particularly of molecular weight of 600 or more should be avoided since polyethylene glycol effectively inhibits the antibacterial activity of the noncationic antibacterial agent. For instance, polyethylene glycol (PEG) 600 when present with triclosan in a weight ratio of 25 triclosan:1 PEG 600 reduces the antibacterial activity of tri-

closan by a factor of about 16 from that prevailing in the absence of the polyethylene glycol.

The pH of such oral preparation dentifrice of the invention is generally in the rental range of about 4.5 to about 9 or 10 and not preferably about 6.5 to about 7.5. It is noteworthy that the compositions of the invention may be applied orally at a pH below 5 without substantially decalcifying or otherwise damaging dental enamel. The pH can be controlled with acid (e.g. citric acid or benzoic acid) or base (e.g. sodium hydroxide) or buffered (as with sodium citrate, benzoate, carbonate, or bicarbonate, disodium hydrogen phosphate, sodium dihydrogen phosphate, etc.).

In this invention, the oral composition dentifrice may be substantially gel in character, such as a gel dentifrice. Such gel oral preparations contain siliceous dentally polishing material. Preferred polishing materials include crystalline silica having particle sized of up to about 5 microns, a mean particle size of up to about 1.1 microns, and a surface area of up to about 50,000 $cm.^2/gm.$, silica gel or colloidal silica and complex amorphous alkali metal aluminosilicate.

When visually clear or opacified gels are employed, a polishing agent of colloidal silica, such as those sold under the trademark SYLOID as Syloid 72 and Syloid 74 or under the trademark SANTOCEL as Santocel 100 or alkali metal almuinosilicate complexes (that is, silica containing alumina combined in its matrix) are particularly useful, since they are consistent with gel-like texture and have refractive indices close to the refractive indices of gelling agent-liquid (including water and/or humectant)systems commonly used in dentifices.

The polishing material is generally present in the oral composition dentifrices such as toothpaste or gel compositions in weight concentrations of about 5% to about 30%.

In a gel toothpaste, the liquid vehicle may typically comprise about 3–35% by weight of water, such as about 10–35%, and humectant in an amount ranging from about 6.5% to about 80%, such as about 10% to about 80% by weight of the preparation. In clear gels where the refractive index is an important consideration, about 3–30% of water, 0 to about 70% of glycerine and about 20–25% of sorbitol are preferably employed.

The oral composition dentifrices typically contain a natural or synthetic thickener or gelling agent in proportions of about 0.1 to about 10%, preferably about 0.5 to about 5%. A suitable thickener is synthetic hectorite, a synthetic colloidal magnesium alkali metal silicate complex clay available for example as Laponite (e.g. CP, SP 2002,D) marketed by Laporte Industries Limited. Laponite D analysis shows, approximately by weight, 58.00% SiO_2, 25.40% MgO, 3.05% Na_2O, 0.98% Li_2O, and some water and trace metals. Its true specific gravity is 2.53 and it has an apparent bulk density (g./ml. at 8% moisture) of 1.0.

Other suitable gelling agents or thickeners include Irish moss, i-carrageenan, gum tragacanth, starch, polyvinylpyrrolidone, hydroxyethypropyl-cellulose, hydroxybutyl methyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose (e.g. available as Natrosol), sodium carboxymethyl cellulose, and colloidal silica such those available as finely ground Syloid 244 and Sylodent 15.

There may be a tendency for the dentifrice to separate into liquid and solid portions when about 5% by weight or more of the optional solubilizing material such as propylene glycol is present. Furthermore, in the present invention excellent antiplaque effects can be obtained with small amounts of antibacterial agent which do not even require solubilizing agent. In the present invention, a preferred dentifrice contains about 0.3% by weight of the antibacterial agent and about 1.5–2% by weight of the polycarboxylate.

Without being bound to a theory whereby the advantages of this invention are achieved, it is believed that an aqueous, humectant vehicle is normally solubilized in surfactant micelles in the mobile phase (that is, not including gelling agent and polishing agent) of a dentfrice formula. The mobile phase solution of dentifrice during use can become diluted with saliva which causes triclosan to precipitate. However, in the present invention, it is found that even in the absence of a special solubilizing material for triclosan, when the amount of triclosan is about 0.25%–0.35% by weight and the polycarboxylate is present, sufficient triclosan is present to exert an excellent antiplaque effect on the soft tissues at the gum line. Similar remarks apply to other water-insoluble noncationic antibacterial agents herein described.

The oral composition dentifrice may also contain a source of fluoride ions, or fluorine-providing component, as anticaries agent, in an amount sufficient to supply about 25 ppm to 5,000 ppm of fluoride ions. These compounds may be slightly soluble in water or may be fully water-soluble. They are characterized by their ability to release fluoride ions in water and by substantial freedom from undesired reaction with other compounds of the oral preparation. Among these materials are inorganic fluoride salts, such as soluble alkali metal, alkaline earth metal salts, or example, sodium fluoride, potassium fluoride, ammonium fluoride, calcium fluoride, a copper fluoride such as cuprous fluoride, zinc fluoride, barium fluoride, sodium flourosilicate, ammonium flourosilicate, sodium fluorozirconate, ammonium fluorozirconate, sodium monofluorophosphate, aluminum mono-and di-fluorophosphate, and fluorinated sodium calcium pyrophosphate. Alkali metal and tin fluorides, such as sodium and stannous fluorides, sodium monofluorophosphate (MFP) and mixtures thereof, are preferred.

The amount of fluorine-providing compound is dependent to some extent upon the type of compound, its solubility, and the type of oral preparation, but it must be a non-toxic amount, generally about 0.0005 to about 3.0% in the preparation. In a dentifrice preparation, e.g. dental gel and an amount of such compound which releases up to about 5,000 ppm of F ion by weight of the preparation is considered satisfactory. Any suitable minimum amount of such compound may be used, but it is preferable to employ sufficient compound to release about 300 to 2,000 ppm, more preferably about 800 to about 1,500 ppm of fluoride ion.

Typically, in the cases of alkali metal fluorides, this component is present in an amount up to about 2% by weight, based on the weight of the preparation, and preferably in the range of about 0.05% to 1%. In the case of sodium monofluorophosphate, the compound may be present in an amount of about 0.1–3%, more typically about 0.76%.

It will be understood that, as is conventional, the oral preparations are to be sold or otherwise distributed in suitable labelled packages. Thus a dentifrice gel will usually be in a collapsible tube, typically aluminum, lined lead or plastic, or other squeeze, pump or pressurized dispenser for metering out the contents, having a label describing it, in substance, as a dentifrice gel or the like.

Organic surface-active agents are used in the compositions of the present invention to achieve increased prophylactic action. Moreover, they assist in achieving thorough and complete dispersion of the antiplaque antibacterial agent throughout the oral cavity, and render the instant compositions more cosmetically acceptable. Indeed, at least one of

surface-active agent or flavoring oil is present to effect desired the solubilization of the antibacterial agent. The organic surface-active material is preferably anionic, nonionic or ampholytic in nature, and it is preferred to employ as the surface-active agent a detersive material which imparts to the composition detersive and foaming properties. Suitable examples of anionic surfactants are water-soluble salts of higher fatty acid monoglyceride monosulfates, such as the sodium salt of the monosulfated monoglyceride of hydrogenated coconut oil fatty acids, higher alkyl sulfates such as sodium lauryl sulfate, alkyl aryl sulfonates such as sodium dodecyl benzene sulfonate, higher alkyl sulfoacetates, higher fatty acid esters of 1,2-dihydroxy propane sulfonate, and the substantially saturated higher aliphatic acyl amides of lower aliphatic amino carboxylic acid compounds, such as those having 12 to 16 carbons in the fatty acid, alkyl or acyl radicals, and the like. Examples of the last mentioned amides are N-lauroyl sarcosine, and the sodium, potassium, and ethanolamine salts of N-lauroyl, N-myristoyl, or N-palmitoyl sarcosine which should be substantially free from soap or similar higher fatty acid material. The use of these sarcosinate compounds in the oral compositions of the present invention is particularly advantageous since these materials exhibit a prolonged and marked effect in the inhibition of acid formation in the oral cavity due to carbohydrate breakdown in addition to exerting some reduction in the solubility of tooth enamel in acid solutions. Examples of water-soluble nonionic surfactants are condensation products of ethylene oxide with various reactive hydrogen-containing compounds reactive therewith having long hydrophobic chains (e.g. aliphatic chains of about 12 to 20 carbon atoms), which condensation products ("ethoxamers") contain hydrophilic polyoxyethylene moieties, such as condensation products of poly(ethylene oxide) with fatty acids, fatty alcohols, fatty amides, polyhydric alcohols (e.g. sorbitan monosterate) and polypropyleneoxide (e.g. Pluronic materials).

Surface active agent is typically present in amount of about 0.5–5% by weight, prefereably about 1–2.5%. As indicated, surface-active agent is believed to assist in dissolving the noncationic antibacterial agent.

Various other materials may be incorporated in the oral preparations of this invention such as whitening agents, preservatives, silicones, chlorophyll compounds and/or ammoniated material such as urea, diammonium phosphate, and mixtures thereof. These adjuvants, where present, are incorporated in the preparations in amounts which do not substantially adversely affect the properties and characteristics desired. Significant amounts of zinc, magnesium and other metal salts and materials, which are generally soluble and which would complex with active components of the instant invention are to be avoided.

Any suitable flavoring or sweetening material may also be employed. Examples of suitable flavoring constituents are flavoring oils, e.g. oil of spearmint, pepperment, wintergreen, sassafras, clove, sage, eucalyptus, marjoram, cinnamon, lemon, and orange, and methyl salicylate. Suitable sweetening agents include sucrose, lactose, maltose, xylitol, sodium cyclamate, perillartine, AMP (aspartyl phenyl alanine, methyl ester), saccharine and the like. Suitably, flavor and sweetening agents may each or together comprise from about 0.1% to 5% more of the preparation. Moreover, flavoring oil is believed to aid the dissolving of the antibacterial agent, together with or even in the absence of surface-active agent.

In the preferred practice of this invention an oral composition dentifrice containing the composition of the present invention is preferably applied regularly to dental enamel and soft oral tissues, particularly at or near the gum line, such as every day or every second or third day or preferably from 1 to 3 times daily, at a pH of about 4.5 to about 9, generally about 5.5 to about 8, preferably about 6 to 8, for at least 2 weeks up to 8 weeks or more up to lifetime.

The compositions of this invention can be incorporated in lozenges, or in chewing gum or other products, e.g. by stirring into a warm gum base or coating the outer surface of a gum base, illustrative of which may be mentioned jelutong, rubber latex, vinylite resins, etc., desirably with conventional plasticizers or softeners, sugar or other sweeteners or carbohydrates such as glucose, sorbitol and the like.

The following examples are further illustrative of the nature of the present invention, but it is understood that the invention is not limited thereto. All amounts and proportions referred to herein and in the appended claims are by weight, unless otherwise indicated.

EXAMPLE 1

The following dentifrice is prepared:

	Parts	
	A	B
Glycerine	10.00	—
Propylene Glycol	—	10.00
Sorbitol (70%)	25.00	25.00
Iota carrageenan	0.60	0.60
Gantrez S-97	2.00	2.00
Sodium Saccharin	0.40	0.40
Sodium Fluoride	0.243	0.243
Sodium Hydroxide (50%)	1.00	1.00
Titanium Oxide	0.50	0.50
Silica Polishing Agent (Zeodent 113)	20.00	20.00
Silica Thickener (Sylox 15)	5.50	5.50
Sodium Lauryl Sulfate	2.00	2.00
Water	31.507	31.507
Tricolosan	0.30	0.30
Flavor Oil	0.95	0.95

The above dentifrice A delivers Triclosan to the teeth and soft gum tissue essentially as well as dentifrices B containing a special solubilizing agent for Triclosan. In other words, a special solubilizing agent is not required for the dentifrice of the present invention to be effective. Further, a corresponding dentifrice in which the Gantrez polycarboxylate is absent is substantially poorer in delivering Triclosan.

In the foregoing example, improved results may also be obtained by replacing triclosan with other antibacterial agents herein described such as phenol, thymol, eugenol and 2,2'-methylene bis (4-chloro-6-bromophenol) and/or by replacing Gantrez with other AEA's such as a 1:1 copolymer of maleic anhyride and ethyl acrylate, sulfoacrylic oligomers, Carbopols (e.g. 934), and polymers of alpha or beta-styrenephosphonic acid monomers and copolymers of these monomers with each or with other ethylenically unsaturated polymerizable monomers such as vinyl phosphonic acid.

EXAMPLE 2

The following liquid phase dentifrice solutions are tested for uptake and retention of triclosan on saliva coated HA disks following the test procedures described in Example 1 with the indicated results:

Ingredients	Parts A	B	C	D
Sorbitol (70% solution)	30.0	30.0	30.0	30.0
Glycerol	9.5	9.5	9.5	9.5
Propylene Glycol	0.5	0.5	0.5	0.5
SLS	20.0	20.0	20.0	20.0
NaF	0.243	0.243	0.243	0.243
Flavor Oil	0.95	0.95	0.95	0.95
Triclosan	0.3	0.3	0.3	0.3
Water	56.507	54.507	54.507	54.507
Poly (beta-styrenephosphonic acid)		2.0		
Poly (alpha-styrenephosphonic acid)			2.0	
Polyvinyl Alcohol				2.0
Adjusted to pH 6.5 with NaOH	31.0	174.0	86.0	36.0
Triclosan Uptake in Micrograms on Saliva Coated Disks				
Retention of Triclosan on Saliva Coated HA Disks After:				
Initial	183.0			
30 minutes	136.0			
1 hour	105.0			
3 hours	83.0			

The above results show that solution (D) containing polyvinyl alcohol, not an AEA hereunder, produced a triclosan uptake of only 36.0, quite similar to the 31.0 uptake of the control solution (A) without additive. In contrast, solution (C) with poly (alpha-styrenephosphonic acid) produces an uptake of 86.0, more than double that of solutions (A) and (D), and solution (B) with poly (beta- styrenephosphonic acid) produces an uptake about 5 times that of solutions (A) and (D), tending to indicate further that vicinal substitution of the delivery-enhancing group yields superior results. The above results also show the surprisingly good retention of triclosan on the HA disks over time obtained with solution (B) containing poly (beta-styrenephosphonic acid (M.W's about 3,000 to 10,000).

This invention has been described with respect to certain preferred embodiments and it will be understood that modifications and variations thereof obvious to those skilled in the art are to be included within the purview of this application and the scope of the appended claims.

We claim:

1. An oral composition dentifrice for attaching, adhering or bonding a plaque-inhibiting antibacterial agent to oral tooth and gum surfaces comprising in an orally acceptable aqueous humectant vehicle, about 5–30% by weight of a siliceous polishing agent and about 0.25%–0.35% by weight of a substantially water insoluble noncationic antibacterial agent, said oral composition comprising at least one of a surface active agent and a flavoring oil and also containing about 0.05–4% by weight of a water soluble or water swellable antibacterial enhancing agent having an average material weight of about 100 to 1,000,000 which contains at least one carboxylic delivery enhancing group and at least one organic retention-enhancing group, which delivery enhancing group enhances delivery of said antibacterial agent to oral tooth and gum surfaces and said retention-enhancing group enhances attachment, adherence or bonding of said antibacterial agent on oral tooth and gum surfaces, wherein said oral composition is free of polyphosphate anticalculus agent in an effective anticalculus amount and said vehicle is other than polyethylene glycol which reduces the antibacterial activity of said antibacterial agent.

2. An oral composition dentifrice for attaching adhering or bonding a plaque-inhibiting antibacterial agent to oral tooth and gum surfaces comprising in an orally acceptable aqueous humectant vehicle, about 5–30% by weight of a siliceous polishing agent and about 0.25%–0.35% by weight of a substantially water insoluble noncationic antibacterial agent, said oral composition comprising at least one of a surface active agent and a flavoring oil and also containing about 0.05–4% by weight of an anionic copolymer of maleic acid or anhydride with another ethylenically unsaturated polymerizable monomer, which copolymer enhances delivery and attachment, adherence or bonding of said antibacterial agent on oral tooth and gum surfaces, wherein said oral composition is free of polyphosphate anticalculus agent in an effective anticalculus amount and said vehicle is other than polyethylene glycol which reduces the antibacterial activity of said antibacterial agent.

3. The oral composition according to either of claim 1 or claim 2 wherein said antibacterial agent is selected from the group consisting of halogenated diphenyl ethers, halogenated salicylanilides, benzoic esters, halogenated carbonilides and phenolic compounds.

4. The oral composition according to claim 2 wherein said other monomer of said copolymer is methyl vinyl ether in a 4:1 to 1:4 molar ratio with the maleic acid or anhydride.

5. The oral composition according to claim 4 wherein said copolymer has a molecular weight of about 30,000–1,000,000.

6. The oral composition according to claim 5 wherein the copolymer has an average molecular weight of about 70,000.

7. An oral composition according to claim 3 wherein said antibacterial agent is triclosan.

8. An oral composition dentifrice for attaching, adhering or bonding a plaque-inhibiting agent to oral tooth and gum surfaces comprising in an orally acceptable aqueous humectant vehicle, about 5–30% by weight of a siliceous polishing agent, about 0.25%–0.35% by weight of a substantially water insoluble noncationic phenolic antibacterial agent, said oral composition comprising at least one of a surface active agent and a flavoring oil and about 0.05–4% by weight of an antibacterial-enhancing agent which contains at least one delivery-enhancing functional group and at least one organic retention-enhancing group, wherein said delivery-enhancing group enhances delivery of said antibacterial agent to oral tooth and gum surfaces and said retention-enhancing group enhances attachment, adherence or bonding of said antibacterial agent on oral tooth and gum surfaces, wherein said oral composition is free of polyphosphate anticalculus agent in an effective anticalculus amount and said vehicle is other than polyethylene glycol which reduces the antibacterial activity of said antibacterial agent.

9. The oral composition claimed in claim 8 wherein said phenolic compound is selected from the group consisting of phenol, thymol, eugenol and 2,2'-methylene bis (4-chloro-6-bromophenol).

10. The oral composition claims in any of claims 1, 2, 4–6, 8 or 9 wherein said surface active agent is present in amount of about 0.5–5% by weight.

11. The oral composition claims in any of claims 1, 2, 4–6, 8 or 9 wherein said flavoring oil is present in amount of about 0.1–5% by weight.

12. The oral composition according to either of claims 8–9 wherein said antibacterial-enhancing agent has an average molecular weight of about 100 to 1,000,000.

13. The oral composition according to claim 12 wherein said delivery-enhancing group is acidic.

14. The oral composition according to claim 13 wherein said delivery-enhancing group is selected from the group consisting of carboxylic, phosphoric, phosphinic, and sulfonic acids, and salts, and mixtures thereof and wherein said organic retention-enhancing group comprises the formula $-(X)_n-R$ wherein X is O, N, S, SO, SO_2, P, PO or Si, R is hydrophobic alkyl, aryl, alkaryl, alkenyl, acyl, aralkyl, heterocyclic, or inert-substituted derivatives thereof, and n is zero or 1 or more and wherein said antibacterial-enhancing agent is a natural or synthetic monomer or a polymer selected from the group consisting of oligomers, homopolymers, copolymers of two or more monomers, ionomers, block copolymers, graft copolymers and cross-linked polymers and monomers.

15. The oral composition according to claim 14 wherein said antibacterial-enhancing agent is an anionic polymer containing a plurality of said delivery-enhancing and retention-enhancing groups.

16. The oral composition according to claim 15 wherein said anionic polymer comprises a chain containing repeating units each containing at least one carbon atom.

17. The oral composition according to claim 16 wherein the unit contains at least one delivery-enhancing group and at least one retention-enhancing group bonded to the same, vicinal, or other atoms in the chain.

18. An oral composition comprising in an orally acceptable aqueous humectant vehicle, about 5–30% of a siliceous polishing agent, about 0.25%–0.35% of triclosan, at least one of a surface active agent and a flavoring oil, and about 0.05–4% of a copolymer of maleic acid or anhydride with methyl vinyl ether.

19. The oral composition according to any of claims 1, 2, 4–6, 8, 9 or 18 containing a fluoride-providing source.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado: **JUAN PABLO CADENA SARMIENTO**

ASUNTO:

Radicación No.	07-63493
Trámite	002
Evento	378
Actuación	519
Oficio	0401
Folios	017

Patente de Invención
Vía Nacional
Vía PCT (fase nacional) ☒ Cap.I ■ Cap. II ☐

No. Solicitud Internacional: PCT/US2005/046514
Fecha de Presentación Internacional: 2005-12-21

Como resultado del Examen de Fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción: Folios 32 a 48 como se radicó inicialmente.

Reivindicaciones: Folios 49 a 51como se radicó inicialmente.
Folios 59 a 62 modificada en fase Internacional
Folios 86 a 89 modificada en fase Internacional

Prioridad: US2004 60639169 (2004-12-23) - folio 1
US2005 11256776 (2005-10-24) - folio 1

2. Modificaciones
Esta oficina acepta el nuevo capitulo reivindicatorio modificado que corresponde a los folios 59 a 62, el cual es igual a la modificación presente en los folios 86 a 89.

3. Objeto de la invención

Titulo de la invención: "Composiciones orales que contienen *camellia* oxidada"

El problema planteado en esta solicitud es la necesidad de composiciones orales para prevenir o remover la placa dental.

Para resolver este problema técnico la solicitud en estudio proporciona una composición oral para remover la placa o inhibir su formación que contiene extracto de camelia semi oxidada.

Clasificación Internacional de Patentes (CIP): A61K36/82; A61K47/30; A61K8/00; A61P1/02

4. De la Solicitud de Patente

4.1. Reivindicaciones (Art 30 D 486, Art 22 PCT)

El capitulo reivindicatorio carece de claridad y concisión en cuanto a:

Las reivindicaciones 1 y 25 reclaman una composición que comprende un extracto de tejido "semi oxidado" dicha expresión no es clara pues el carácter de "semi" no define el estado de oxidación, es ambigua y no permite la comparación con el estado de la técnica; de igual manera la expresión un "agente acrecentador", no es claro pues no establece a que tipo de sustancia se refiere y no define la invención. Se sugiere modificar dichas reivindicaciones definiendo de mejor manera la invención.

La reivindicación 5 reclama una composición la cual esta definida por un resultado a alcanzar. Se sugiere modificar o eliminar esta del capitulo reivindicatorio.

La reivindicación 1 reclama una composición que comprende "entre 0.001 y 10% en peso de un extracto de camelia"; este rango de peso es muy amplio por lo cual la reivindicación carece de concisión. Se sugiere que se limite el objeto de esta reivindicación teniendo en cuenta una generalización razonable de lo mostrado en la memoria descriptiva.

Las reivindicaciones 6, 7 y 25 hace referencia a una composición que contiene un agente polimérico de peso molecular promedio de 100 a 1000000, este rango de peso molecular es muy amplio y puede representar cualquier tipo de polímero, por lo cual la reivindicación carece de concisión. Se sugiere que se limite el objeto de estas reivindicaciones teniendo en cuenta una generalización razonable de lo mostrado en la memoria descriptiva.

La reivindicación 10 dice: "una cantidad antiplaca efectiva de un agente antibacterial". A partir de lo anterior se evidencia:

- la expresión "una cantidad efectiva" no es clara ya que no se establece un valor especifico y no limita la invención.
- se puede suponer que el solicitante pretendía decir que dicha composición comprende una cantidad "antibacterial" efectiva de un agente antibacterial.

Se sugiere modificar dicha reivindicación.

La reivindicación 25 dice: "una composición oral para al menos una de inhibir y remover la placa dental" lo anterior no es claro y se sugiere eliminar la expresión "al menos una" que quita sentido a la oración.

La reivindicación 27 reclama una composición dependiente de la 25, donde se habla de un agente antibacterial sin embargo no se puede hacer una dependencia debido a que la reivindicación 25 no hace referencia a la presencia de un agente antibacterial. Se sugiere eliminar dicha reivindicación.

5. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de la solicitud prioritaria 2004-12-23 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	WO03-094878*	Gallocatechin Gallate-Containing Composition	2003-11-20
D2	US5776435	Antiplaque, antibacterial oral composition	1998-07-07

(*) Este documento se encuentra en idioma chino por lo cual se utiliza el documento US2006/0134286 que corresponde a la misma solicitud pero en idioma ingles.

D1- Composición antibacteriana que contiene el galato del gallocatequina proveniente del te de oolong como agente antibacteriano. La composición puede tener una fracción del extracto de te absorbido en un compuesto de tipo polímero metacrilato.
D2-Composicion antiplaca y antibacterial que comprende un agente antibacterial como triclosan, una fuente de sílice y una agente acrecentador del agente antibacterial que permite mayor retención de los en los dientes.

6. Análisis de Patentabilidad (Art 14 D486)

Comparación de las características técnicas **esenciales**, con las del estado de la Técnica:

Características esenciales	D1	D2
Composición oral	√	√
- Extracto de Camellia semi oxidado(0.001%-10%)	√	-
- Agente acrecentador	-	√

6.1. Nivel Inventivo (Art18 D486)

La **reivindicación 1** consiste en: "una composición oral que comprende entre 0.001% y 10% en peso de un extracto de *Camellia* de tejido semi oxidado, y un agente acrecentador".

Estado de la Técnica más cercano es **D1** que divulga una composición oral que contiene extracto de ***camellia* semi fermentado** (el termino fermentado corresponde a una expresión de la oxidación de la planta como se describe en los folios 34 a 36) específicamente extracto de hojas de te de oolong (párrafo 0015, Ejemplos 1 a 5) como agente antibacterial, para la prevención de la caries y la formación de placa bacteriana, dicho agente antibacterial se encuentra en concentraciones entre **0.0001 y 0.5%** (párrafo 0029, ejemplos 3 a 5) y dicha composición contiene además excipientes que dan estabilidad a la formulación entre los que se encuentran **copolimeros aniónicos** que se hinchan como polietilen glicol, polímeros de carboxivinil, gomas, carragenina, entre otros (Párrafo 0026, ejemplos 3 y 4). Adicionalmente es importante mencionar que D1 traslapa el rango de concentración de extracto de camellia semioxidado reivindicado en la solicitud, mostrando el mismo efecto antibacterial a concentraciones menores (párrafo 0014; ejemplos 1 y 2), siendo esto indicativo de una ventaja de la formulación de D1 con la de la solicitud.

La solicitud se diferencia de D1 en una concentración mayor de extracto de camelia de tejido semioxidado en la composición (0.001% y 10% en peso) y que contiene un agente acrecentador.

Es importante mencionar que la composición de extracto de camellia semioxidado divulgada en D1 muestra el mismo efecto antibacterial, a concentraciones menores, (párrafo 0014; ejemplos 1 y 2) que la reivindicada en la presente solicitud; siendo esto indicativo de una ventaja de la composición de D1 con respecto a la de la solicitud.

El hecho de incluir un agente acrecentador en la composición que se daba a conocer en D1, causa que las composiciones, tengan mayor retención del extracto de camellia de tejido semioxidado en los dientes y el tejido oral.

Por tanto, el Problema Técnico Objetivo es: "cómo modificar al composición conocida según D1 para que tenga mayor retención del extracto de *camellia* en los dientes y el tejido oral".

> Por su lado **D2** describe una manera de solucionar el problema técnico mediante la adición de un agente acrecentador ó de retención (columna 1 líneas 62 a 66); dicho agente es un **copolimero de ácido maléico o anhídrido con metilvinil éter** (columna 4, línea 65; columna 5, reivindicación 4) el cual permite una mejor retención de componentes antibacteriales (columna 10, línea 24 a 30; reivindicaciones 2 y 8) a la superficie del diente.

La reivindicación es obvia, porque el Experto en la Materia enfrentado al problema de obtener mayor retención de los componentes del extracto de camellia en los dientes y el tejido oral, incluiría el agente acrecentador (copolímero de ácido malénico o anhídrido con metilvinil éter) que se revela en D2, dentro de las composiciones que se enseñan en D1, logrando de esta forma la composición objeto de esta solicitud, por lo cual la composición de la reivindicación 1 carece de Nivel Inventivo.

Puesto que las reivindicaciones dependientes 11-12 no mencionan características inventivas adicionales, tampoco pueden ser consideradas inventivas.

6.2. Aplicación industrial (Art 19 D 486)

Las reivindicaciones 14 a 24 hacen referencia a un método para remover la placa e inhibir el depósito de placa. Teniendo en cuenta que este método tiene que ser aplicado a un individuo (humano) no se considera que tenga aplicación industrial.

7. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO03-094878	1,2,6,7,9,10	Nivel inventivo
D2	US5776435	8, 11,12	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

CONCEPTO TÉCNICO	EXAMINADOR TÉCNICO
No.0037	Código No.20293