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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 06-127716- -00002-0000
DIVISION NUEVAS CREACIONES
FOLIOS FASE NACIONAL

AS: 102.629

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

REF.: Expediente No. 06 127716 - Solicitud de Patente FASE NACIONAL
Corresp. a la Solicitud Internacional PCT/US2005/019415
a nombre de **COLGATE-PALMOLIVE COMPANY**
Titulada: DENTÍFRICO ANTIBACTERIANO ANTIMANCHAS

**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. 08-28.735 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, 28 de abril de 2008
MEV/JCN/aac

US005294431A

# United States Patent [19]

Gaffar et al.

[11] Patent Number: 5,294,431

[45] Date of Patent: * Mar. 15, 1994

[54] ANTIBACTERIAL ANTIPLAQUE ORAL COMPOSITION MOUTHWASH OR LIQUID DENTIFRICE

[75] Inventors: **Abdul Gaffar**, Princeton; **Nuran Nabi**, Brunswick; **John Afflitto**, Brookside, all of N.J.; **Orum Stringer**, Yardley, Pa.

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

[ * ] Notice: The portion of the term of this patent subsequent to Jul. 16, 2008 has been disclaimed.

[21] Appl. No.: **961,976**

[22] Filed: **Oct. 16, 1992**

**Related U.S. Application Data**

[60] Division of Ser. No. 398,592, Aug. 28, 1989, Pat. No. 5,188,821, 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.

[51] **Int. Cl.**[5] ..... **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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*Primary Examiner*—Shep K. Rose

*Attorney, Agent, or Firm*—Robert L. Stone; Murray M. Grill

[57] **ABSTRACT**

An oral composition mouthwash or liquid dentifrice containing an aqueous vehicle acceptable vehicle, a substantially water-insoluble noncationic antibacterial antiplaque agent, such as 2,4,4'-trichloro-2'-hydroxy-diphenyl ether (triclosan) and an antibacterial-enhancing agent which enhances delivery of said antibacterial agent to, and retention thereof on, oral surfaces.

**25 Claims, No Drawings**

# ANTIBACTERIAL ANTIPLAQUE ORAL COMPOSITION MOUTHWASH OR LIQUID DENTIFRICE

This is a division, of application Ser. No. 07/398,592, filed Aug. 28, 1989, now U.S. Pat. No. 5,188,821 granted Feb. 23, 1993, which is a continuation-in-part of application Ser. No. 07/291,712 filed Dec. 29, 1988, and now U.S. Pat. No. 4,894,220, and of application Ser. No. 07/346,258 filed May 1, 1989, and now U.S. Pat. No. 5,043,154 which are respectively a continuation-in-part and a continuation of application Ser. No. 07/008901, filed Jan. 30, 1987 now abandoned.

This invention relates to an antibacterial antiplaque oral composition mouthwash or liquid dentifrice. More particularly, it relates to an oral composition mouthwash or liquid 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. Also, in European Patent Publication 0271,332 to Davis, mouthwash containing triclosan and in a carrier system containing a solubilizing agent such as propylene glycol is disclosed.

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 antiplaque agents may have limited antiplaque effectiveness with commonly employed materials such as polyphosphate anticalculus agents which are disclosed together in British Patent Publication 2200551 of Gaffar et al and EP 0251591 of Jackson et al. In commonly assigned Ser. No. 398,605 filed Aug. 25, 1989, titled "Antibacterial, Antiplaque Anticalculus Oral Composition", it is shown that 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 ratios of polyphosphate and AEA.

Further, even when polyposphate anticalculus agent is not present as shown in patent applications commonly assigned Ser. No. 398,606; 398,566; and 399,699 each filed on Aug. 25, 1989, antiplaque effectiveness on soft oral tissue is optimized in dentifrices containing the noncationic antibacterial agent and said AEA.

It is an advantage of this invention that an oral composition mouthwash or liquid dentifrice is obtained in which substantially water-insoluble noncationic antibacterial agent is solubilized to provide substantial antiplaque effectiveness in the presence of said AEA.

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

It is a further advantage of this invention that an antiplaque oral composition is provided which is directly or indirectly 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, an effective antiplaque amount of a substantially water insoluble noncationic antibacterial agent, and about 0.05–4% by weight of said AEA, wherein said oral composition comprises a solubilizing material for said antibacterial agent in amount sufficient to dissolve said antibacterial agent in saliva. 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
3,3,3',5-tetrachlorosalicylanilide
3,5-dibromo-3'-trifluoromethyl salicylanilide
5-n-octanoyl-3'-trifluoromethyl salicylanilide
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 polyalkyl and aromatichalo (e.g. F, Cl, Br, I)-phenols, resor-

cinol and catechol and their derivatives and bisphenolic compounds). Such compounds include 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-Chlorphenol |
| 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-dimethyl phenol | |
| 3,4,5,6-tetrabromo-2-methyl-phenol | |

-continued

| | |
|---|---|
| 5-methyl-2-pentylphenol | |
| 4-isopropyl-3-methylphenol | |
| 5-chloro-2-hydroxydiphenyl methane | |

| 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 |

## Bisphenol 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, typically about 0.01–5% by weight although in a mouthwash or liquid dentifrice the amount is generally about 0.01–0.3%, preferably about 0.03–0.3% and more preferably about 0.03–0.1%. 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, 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 desensitizing agent containing a source of potassium ion. 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 mm 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 charactrized as having utility as dentifrice adhesives or fixatives or dental cements. For example, U.S. Pat. Nos. 4,521,551 and 4,375,036, each to Chang et al, describe commercially available copolymer of methylvinyl ether-maleic anhydride (Gantrez) as a denture fixture. 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 Change, 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 prophylatic 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 I 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.

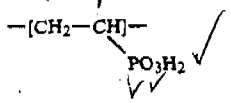
| n | X | $-(X)_nR$ |
|---|---|---|
| 0 | — | methyl, ethyl, propyl, butyl, isobutyl, t-butyl, cyclohexyl, allyl, benzyl, phenyl, chlorophenyl, xylyl, pyridyl, furanyl, acetyl, benzoyl, butyryl, terephthaloyl, etc. |
| 1 | 0 | ethoxy, benzyloxy, thioacetoxy, phenoxy, carboethoxy, carbobenzyloxy, etc. |
| | 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, methylbenzyphosphinoxy, 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, attachs 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.

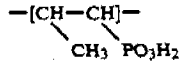
It will be understood that any examples or illustrations of AEA's disclosed herein which do not contain both delivery-enhancing groups and retention enhancing groups may and preferably should be chemically modified in known manner to obtain the preferred AEA's containing both such groups and preferably 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:



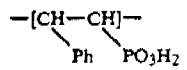
I

which however does not contain a retention-enhancing group. A group of the latter type would however be present in poly (1-phosphonopropene) with units of the formula:



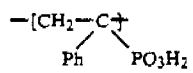
II

A preferred phosphonic acid-containing AF-A for use herein is poly (beta styrene phosphonic acid) containing units of the formula:



III

wherein Ph is phenyl, the phosphonic delivery-enhancing group and the phenyl retention-enhancing group being bonded on vicinal carbon atoms in the chain, or a copolymer of beta styrene phosphonic acid with vinyl phosphonyl chloride having the units of the foregoing formula III alternating or in random association with units of formula I above, or poly (alpha styrene phosphonic acid) containing units of the formula:

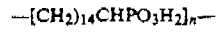


IV

in which the delivery - and retention - enhancing groups are geminally bonded to the chain.

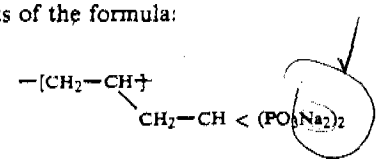
These styrene phosphonic acid polymers and their copolymers with other inert ethylenically unsaturated monomers generally have molecular weights in the range of about 2,000 to about 30,000, preferably about 2,500 to about 10,000, and are, with their methods of preparation disclosed and claimed in concurrently filed application Ser. No. 398,606, which disclosure is incorporated here. Such "inert" monomers do not significantly interfere with the intended function of any copolmyer employed as an AEA herein.

Other phosphonic-containing polymers include, for example, phosphonated ethylene having units of the formula.



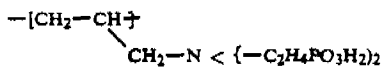
V

where n may for example be an integer or have a value giving the polymer a molecular weight of about 3,000; and sodium poly (butene-4,4-diphosphonate) having units of the formula:



VI

poly (allyl bis (phosphonoethyl) amine) having units of the formula:



VII

Other phosphonated polymers, for example poly (allyl phosphono acetate), phosphonated polymethacrylate, etc. and the geminal diphosphonate polymers disclosed in EP Publication 0321233 may be employed herein as AEA's, provided of course that they contain or are modified to contain the above-defined organic retention-enhancing groups.

Although not used in the present invention to coact with polyphosphate anticalculus agent, synthetic anionic Polymeric polycarboxylate having a molecular weight of about 1,000 to about 1,000,000, preferably about 30,000 to about 500,000, have been used as an inhibitor of alkaline phosphate enzyme in optimizing anticalculus effectiveness of linear molecularly dehydrated Polyphosphate salts, as disclosed in U.S. Pat. No. 4,627,977 to Gaffar et al. Indeed, in published British Patent Publication 22 00551, the polymeric polycarboxylate is dislosed as an optional ingredient in oral compositions containing linear molecularly dehydrated polyphosphate salts and substantially water-insoluble noncationic antibacterial agent. It is further observed, in the context of the present invention that such polycarboxylate is markedly effective to enhance delivery and retention of the noncationic antibacterial, antiplaque agent to dental surfaces even when another ingredient with which the polymeric polycarboxylate would coact (that is, molecularly dehydrated polyphosphate) is absent; for instance, when the ingredient with which the polymeric polycarboxylate coacts is especially the noncationic antibacterial agent.

Synthetic anionic polymeric polycarboxylates and their complexes with various cationic germicides, zinc and magnesium have been previously disclosed as anticalculus agents per se in, for example U.S. Pat. No. 3,429,963 to Shedlovsky; U.S. Pat. No 4,152,420 to Gaffar; U.S. Pat. No. 3,956,480 to Dichter et al; U.S. Pat. No. 4,138,477 to Gaffar; and U.S. Pat. No. 4,183,914 to Gaffar et al. It is to be understood that the synthetic anionic polymeric polycarboxylates so disclosed in these several patents when containing or modified to contain the said retention-enhancing groups are operative as AEA's in the compositions and methods of this invention and such disclosures are to that extent incorporated herein by reference thereto.

The synthetic anionic polymeric polycarboxylates are often employed in the form of their free acids or preferably partially or more preferably fully neutralized water soluble or water swellable (hydratable, gel forming) alkali metal (e.g. potassium and preferably sodium) or ammonium salts. Preferred are 1:4 to 4:1 copolymers of maleic anhydride or acid with another polymerizable ethylenically unsaturated monomer, preferably methyl vinyl ether (maleic anhydride) having a molecular weight (M.W.) of about 30,000 to about 1,000,000, most preferably about 30,000 to about 500,000. These copolymers are available for example as Gantrez, e.g. AN 139 (M.W. 500,000), A.N. 119 (M.W. 250,000); and preferably S-97 Pharmaceutical Grade (M.W. 70,000), of GAF Corporation.

Other AEA operative polymeric polycarboxylates when containing or modified to contain the said retention-enhancing groups include those disclosed in U.S. Pat. No. 3,956,480 referred to above, such as the 1:1

ally about 6 to 9 microns. A typical grade has the following size distribution:

| Microns | Percent |
|---|---|
| <30 | 94–99 |
| <20 | 85–93 |
| <10 | 56–67 |
| <5 | 28–40 |

Without being bound to a theory whereby the advantages of this invention are achieved, it is believed that an aqueous vehicle, typically including humectant, is normally solubilized in surfactant micelles in a mouthwash or mobile phase (that is, not including gelling agent and possibly a polishing agent in liquid dentifrice). Such solution during use becomes diluted with saliva but triclosan does not substantially precipitate and may be additionally protected against precipitation by presence of a solubilizing material such as propylene glycol. In this regard it is noted that propylene glycol is widely used in drug delivery systems for its strong interaction with biological membranes. It is expected that triclosan is partitioned from aqueous environment into propylene glycol and surfactant emulsions during use and further that propylene glycol in bulk phase allows greater probability of triclosan emergence out of surfactant micelles, thereby rendering triclosan available for delivery into bacterial and soft surfaces as well as onto tooth surfaces. Similar remarks apply to other water-insoluble noncationic antibacterial agents herein described.

The oral composition mouthwash or liquid dentifrice may also contain an anticaries amount of fluoride ion source sufficient to supply 25 ppm. to 5,000 ppm. of fluoride ions. The fluoride ion source may be present even when the polyphosphate anticalculus agent is not, since it also provides anticaries effectiveness.

The sources of fluoride ions, or fluoride-providing component are well known in the art as anticaries agents. These compounds may be slightly soluble in water or may be fully water-soluble. It is characterized by its 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, for 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 monoand 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, 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 500 or 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 e 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 jar of mouthrinse will have a label describing it, in substance, as a mouthrinse or mouthwash and having directions for its use; and a liquid toothpaste will usually be in a collapsible or drip tube, typically aluminum, lined lead or plastic, or other dispenser for metering out the contents, having a label describing it, in substance, as a liquid toothpaste or dentifrice.

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, generally soluble, 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, peppermint, 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% or more of the preparation, each being typically about 0.1–2.5%. Moreover, the flavoring oil is believed to assist in dissolving the antibacterial agent.

In the preferred practice of this invention an oral composition according to this invention such as a mouthwash or liquid dentifrice containing a composition of the present invention is preferably applied regularly to dental enamel 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 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 mouthrinses below are effective in reducing plaque by increasing the uptake and retention of triclosan oral surfaces.

| | A Parts | B Parts | C Parts | D Parts | E Parts |
|---|---|---|---|---|---|
| Gantrez S-97 | 0.25 | 0.25 | 0.25 | 0.25 | 0.25 |
| Glycerine | 15.00 | 10.00 | 15.00 | 10.00 | 15.00 |
| Ethanol | — | — | 12.50 | 12.50 | — |

-continued

| | A Parts | B Parts | C Parts | D Parts | E Parts |
|---|---|---|---|---|---|
| Propylene glycol | — | 5.00 | — | 5.00 | — |
| Pluronic F108-(Polyoxyethylene/ Polyoxypropylene Block Copolymer) | | 2.00 | | | |
| Sodium Lauryl Sulfate | — | — | 0.20 | 0.20 | 0.20 |
| Triclosan | 0.10 | 0.10 | 0.06 | 0.06 | 0.03 |
| Flavoring oil | 0.40 | 0.40 | 0.40 | 0.40 | 0.40 |
| Water | Q.S. to 100.00 | Q.S. to 100.00 | Q.S. to 100.00 | Q.S. to 100.00 | Q.S. to 100.00 |

## EXAMPLE 2

The following liquid dentifrices are also effective in reducing plaque by increasing the uptake and retention of triclosan on oral surfaces:

| | A Parts | B Parts | C Parts |
|---|---|---|---|
| Glycerine | 20.0 | 20.0 | — |
| Gantrez S-97 | 0.3 | 0.3 | 0.3 |
| Polysaccharide of high molecular weight, the molecule containing mannose, glucose, potassium glucuronate and acetyl moieties in the approximate molar ratio of 2:1:1:1 | 0.8 | — | 1.0 |
| Sodium benzoate | 0.5 | 0.5 | 0.5 |
| Saccharine sodium | 0.5 | 0.5 | 0.5 |
| Water | 61.3 | 73.1 | 71.6 |
| Sodium lauryl sulfate | 3.0 | 3.0 | 3.0 |
| Insoluble sodium metal phosphate | 10.0 | — | 10.0 |
| Anhydrous dicalcium phosphate | 1.0 | — | 2.5 |
| Flavoring oil | 2.5 | 2.5 | 2.5 |
| Ethyl alcohol | — | — | 10.0 |
| Triclosan | 0.1 | 0.1 | 0.1 |

In the foregoing Examples improved results are also achievable when triclosan is replaced with each of phenol, 2,2'-methylene bis (4-chloro-6-Bromophenol) , eugenol and thymol, and/or when Gantrez is replaced by other AEA's such as Carbopols (e.g. 934), or styrene phosphonic acid polymers having molecular weights within the range of about 3,000 to 10,000 such as poly (beta-styrenephosphonic acid), copolymers of vinyl phosphonic acid with beta-styrenephosphonic acid, and poly (alpha-styrenephosphonic acid), or sulfoacrylic oligomers, or a 1:1 copolymer of maleic anhydride with ethyl acrylate.

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. Oral composition mouthwash or liquid dentifrice comprising an aqueous vehicle, an effective antiplaque amount of a substantially water insoluble noncationic antibacterial agent, said oral composition comprising at least one of a surface active agent, a flavoring oil and a non-toxic alcohol and about 0.005–4% by weight of an antibacterial-enhancing agent which contains at least one delivery-enhancing functional group and at leas tone 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 or oral tooth and gum surfaces, wherein said oral composition mouthwash or liquid dentifrice is free of polyphosphate anticalculus agent in an effective anticalculus amount.

2. The oral composition claimed in claim 1 wherein said antibacterial agent is selected from the group consisting of halogenated diphenyl ethers, halogenated salicylanides, benzoic esters, halogenated carbanilides and phenolic compounds.

3. The oral composition claimed in claim 2 wherein said antibacterial agent is a halogenated diphenyl ether.

4. The oral composition mouthwash or liquid dentifrice claimed in claim 3 wherein said halogenated diphenyl ether is 2,4,4'-trichloro-2'-hydroxyphenyl ether.

5. The oral composition mouthwash or liquid dentifrice claimed in claim 2 wherein said antibacterial agent is a phenolic compound.

6. The oral composition mouthwash or liquid dentifrice claimed in claim 5 wherein said phenolic compound is selected from the group consisting of phenol, thymol, eugenol and 2,2'-methylene bis (4-chloro-6-bromophenol).

7. The oral composition mouthwash or liquid dentifrice claimed in any of claims 1 to 6 wherein said antibacterial agent is present in amount of about 0.01–5% by weight.

8. The oral composition mouthwash or liquid dentifrice claimed in claim 7 wherein said amount of antibacterial agent is about 0.25–0.5%.

9. The oral composition claimed in any of claims 1 to 6 wherein said composition is a mouthwash and said aqueous vehicle contains a non-toxic alcohol and the weight ratio of water to non-toxic alcohol is from about 1:1 to about 20:1.

10. The oral composition mouthwash claimed in claim 9 wherein said non-toxic alcohol is ethanol.

11. The oral composition claimed in any of claims 1 to 6 wherein said oral composition is a liquid dentifrice.

12. The oral composition liquid dentifrice claimed in claim 11 wherein said said liquid dentifrice contains about 0.3–2.0% by weight of a polysaccharide of high molecular weight in excess of 1,000,000 containing mannose, glucose, potassium glucuronate and acetyl moieties in the approximate ratio of 2:1:1:1, as suspending and thickening agent.

13. The oral composition liquid dentifrice claimed in claim 12 wherein said liquid dentifrice contains about 10–20% by weight of a polishing material.

14. The oral composition mouthwash or liquid dentifrice claims in any of claims 1 or 6 wherein said surface active agent is present in amount of about 0.5–5% by weight.

15. The oral composition mouthwash or liquid dentifrice claims in any of claims 1 to 6 wherein said flavoring oil is present in amount of about 0.1–5% by weight.

16. The oral composition according to any of claims 1 to 6 wherein said antibacterial-enhancing agent has an average molecular weight of about 100 to about 1,000,000.

17. The oral composition according to claim 16 wherein said delivery-enhancing group is acidic.

18. The oral composition according to claim 17 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

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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 occurrence of gingivitis.

[00005] 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 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 and in PCT Publication WD 92/00721 to Read in combination with azacycloalkane diphosphonates.

[00006] 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.

[00007] However, oral compositions typically are mixtures of numerous components and even such typically neutral materials as humectants can affect performance of such compositions.

[00008] 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.

[00009] It is an advantage of this invention that an oral composition is provided comprising a substantially water. insoluble noncationic antibacterial agent wherein polyvinyl phosphonate (PVPA) enhances the antibacterial effect of the antibacterial agent to inhibit plaque formation, wherein the oral composition contains an orally acceptable liquid vehicle effective to enable said antibacterial agent to dissolve in saliva in effective antiplaque amount.

[00010] It is a further advantage of this invention that an antiplaque oral composition is provided which is effective to reduce the occurrence of gingivitis.

[00011] Additional advantages of this invention will be apparent from consideration of the following specification.

[00012] In accordance with certain of its aspects, this invention relates to an oral composition comprising an effective antiplaque amount of a substantially water insoluble noncationic antibacterial agent, at least about 0.005% by weight of polyvinyl phosphonate having recurring groups ##STR1## and average molecular weight of at least about 1,000 and wherein M and M.sub.1 are hydrogen, alkali metal or ammonium and wherein M and M.sub.1 are the same or different and an orally acceptable vehicle comprising at least one of a surface-active agent or a flavoring oil effective to enable said antibacterial agent to dissolve in saliva in effective antiplaque amount.

[00013] Typical examples of water insoluble noncationic antibacterial agents which are particularly desirable from considerations of antiplaque effectiveness, safety and formulation are:

HALOGENATED DIPHENYL ETHERS

[00014] 2,4,4'-trichloro-2'-hydroxy-diphenyl ether (Triclosan)

[00015] 2,2'-dihydroxy-5,5'-dibromo-diphenyl ether

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**
**DIRECCIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado:
**JUAN PABLO CADENA SARMIENTO**

| | | |
|---|---|---|
| ASUNTO: | Radicación No. | 6 127716 |
| | Trámite | 011 |
| | Evento | 378 |
| | Actuación | 430 |
| | Oficio | 005322 |
| | Folios | |

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:

**Documentos estudiados:**

Descripción: Folios 42 a 77 como se radicó inicialmente.

Reivindicaciones: Folios 78 a 81 como se radicó inicialmente.

Prioridad: UK 0402491.5 (2004-02-04); US 60/545.663 (2004-02-17)

**Objeto de la Invención**

Titulo de la invención: "Dentífrico antibacteriano antimanchas."

Problema Técnico Planteado: "Necesidad de una composición dental antimanchas con eficacia antibacteriana"

Solución: "Proveer una composición de acuerdo a las características de la presente solicitud de, que provea eficacia antibacteriana y antimanchas en donde el agente antimanchas no afecte la actividad antibactariana del o de los agentes antibacterianos"

IPC: A61K 31/4196 AC; A61K 31/506 AC; A61P 31/0

**Excepciones a la Patentabilidad** (Art 20 D 486 literal d)

Las reivindicaciones 19 y 20 se refieren a un método de tratamiento, por lo que deben ser retiradas del capitulo reivindicatorio.

**Análisis de la Solicitud de Patente**

**Reivindicaciones** (Art 30 D 486, Art 22 PCT)

Claridad y concisión: El capitulo reivindicatorio presenta rangos definidos por porcentajes aproximados pero no exactos, se recomienda realizar los ajustes para definir concisamente los rangos.

**Determinación del Estado de la Técnica**

El Estado de la Técnica se determinó con base en la fecha de prioridad 2004-02-04 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

| Item | Documento | Título | Fecha de Publicación |
|---|---|---|---|
| D1 | US 5294431 | *Antibacterial antiplaque oral composition mouthwash or liquid dentifrice* | Mz.15.1994 |
| D2 | US 5,296,214 | *Anticalculus composition* | Mz. 22.1994 |

**Análisis de Patentabilidad (Art 14 D486)**

**Nivel Inventivo** (Art18 D486)

La reivindicación 1 se refiere a composiciones dentríficas que comprenden:

i) un polímero o copolímero que contiene fosfonato de acuerdo a la formula I (f.78)
ii) un agente antibacteriano éter difenílico halogenado(f.79)
iii) un mejorador antibacteriano de éter polivinilmetílico/anhídrido maleico

D1 revela una composición oral antiplaca (portada) que revela el uso de fosfonato de etileno (col.7-8), agentes antibacteriales no catiónicos insolubles como éteres difenílicos halogenados, ej. triclosán (col.2-4), y agentes antibacteriales mejoradores como polímeros de metilvinil éter/ anhidro maleico (col.5).

La solicitud se diferencia de D1 en el uso de copolímeros o polímeros de fosfonato como el acido polivinilfosfónico (PVPA).

El Efecto Técnico que logra la diferencia es la obtención de una composición blanqueadora eficaz con una acción antibacterial aumentada como se muestra en la tabla 2, 3 y 4 (f.74 y 77).

El Problema Técnico Objetivo de esta solicitud es proveer composiciones antiplaca alternativas con actividad antibacterial.

D2 revela una composición oral como dentífrico o enjuague bucal, que contienen una cantidad efectiva antiplaca de un agente antibacterial como el triclosan (portada, párrafos 1 y 14) y polivinilfofonato como una mejorador de la actividad antibacterial (párrafos 1 y 9). Enseña que el PVPA mejora la actividad antibacterial de la composición para inhibir la formación de placa.

El experto en la materia habría sido sugerido por D2 compuestos como el PVPA en las composiciones enseñadas por D1 para mejorar la actividad antibacterial sin alterar el efecto blanqueador de la composición y así obtener la composición acá reclamada.

Se concluye que las reivindicaciones 1 a 18 no poseen nivel inventivo.

**Conclusión**

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

| N° | Documento | Reivindicaciones afectadas | Requisito que afecta |
|---|---|---|---|
| D1 | US 5294431 | 1-18 | Nivel inventivo |
| D2 | US 5,296,214 | 1-18 | 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.

**ALIX CARMENZA CÉSPEDES DE VERGEL**
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 23 ABR 2010

| CONCEPTO TECNICO<br>NUMERO: 569 | EXAMINADOR TÉCNICO<br>Código:202092 |
|---|---|