

(72) Nabi, Nuran, US

(72) Gaffar, Abdul, US

(73) Colgate-Palmolive Company, US

(51) Int.Cl.⁵ A61K 7/00

(30) 1988/12/29 (291,712) US

(54) **COMPOSE ORAL ANTIBACTERIEN ANTIPLAQUE**

(54) **ANTIBACTERIAL ANTIPLAQUE ORAL COMPOSITION**

(57) An oral composition such as a dentifrice or mouthwash, containing an aqueous phase of water and as humectant propylene glycol, dipropylene glycol, methyl cellosolve, ethyl cellosolve, olive oil, castor oil, amyl acetate, ethyl acetate, glyceryl tristearate or benzyl benzoate mixed with at least one of glycerine and sorbitol, a substantially water-insoluble noncationic antibacterial antiplaque agent, such as 2,4,4' - trichloro-2¹-hydroxydiphenyl ether (triclosan), and a synthetic anionic linear polymeric polycarboxylate having a molecular weight of about 1,000 to about 1,000,000.

2006719

IR 4690

ANTIBACTERIAL ANTIPLAQUE ORAL COMPOSITION

ABSTRACT

An oral composition such as a dentifrice or mouthwash, containing an aqueous phase of water and as humectant propylene glycol, dipropylene glycol, methyl cellosolve, ethyl cellosolve, olive oil, castor oil, amyl acetate, ethyl acetate, glyceryl tristearate or benzyl benzoate mixed with at least one of glycerine and sorbitol, a substantially water-insoluble noncationic antibacterial antiplaque agent, such as 2,4,4' - trichloro-2¹-hydroxydiphenyl ether (triclosan), and a synthetic anionic linear polymeric polycarboxylate having a molecular weight of about 1,000 to about 1,000,000.

This invention relates to an antibacterial antiplaque oral composition. More particularly, it relates to an oral composition 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 occurrence 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. Patent 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 noncationic 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.

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 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 effect performance of such compositions.

62301-1608

It is an advantage of this invention that an oral composition containing a substantially water-insoluble noncationic antibacterial agent and a synthetic anionic linear polymeric polycarboxylate is provided to inhibit plaque
5 formation.

It is an advantage of this invention that the polymeric polycarboxylates enhance the delivery and retention of the antibacterial agent on teeth and on soft oral tissues.

It is a further advantage of this invention that such
10 an oral composition is provided with a humectant which dissolves the noncationic antibacterial agent is an essential component.

It is a further advantage of this invention that an antiplaque oral composition is provided which is effective to
15 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 comprising in an orally acceptable vehicle: a water-humectant phase, in an
20 amount of at least about 10% by weight based on the oral composition, an effective antiplaque amount of a substantially water insoluble noncationic antibacterial agent selected from the group consisting of halogenated diphenyl ethers and
25 phenolic compounds, and about 0.005-4% by weight of a synthetic anionic linear polymeric polycarboxylate having a molecular weight of about 1,000 to about 1,000,000, wherein the humectant includes a solubilizing humectant selected from the group consisting of propylene glycol, dipropylene glycol, methyl
30 cellosolve, ethyl cellosolve, olive oil, castor oil, amyl acetate, ethyl acetate, glyceryl tristearate and benzyl

62301-1608

benzoate mixed with at least one of glycerine and sorbitol, the amount of the solubilizing humectant being sufficient to dissolve the antibacterial agent.

Typical examples of water insoluble noncationic
5 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.

Phenolic Compounds (including phenol and its homologs, mono- and poly-alkyl and aromatic halophenols, resorcinol and its derivatives, bisphenolic compounds and halogenated salicylanilides)

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

Mono- and Poly-Alkyl and Aromatic 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-hydroxydiphenylethane	

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

2,2'-methylene bis (4-chlorophenol)

2,2'-methylene bis (3,4,6-trichlorophenol)

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 preferably about 0.03-1% and most preferably about 0.3-0.5%. 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 hexyl resorcinol, 2,2'-methylene bis(4-chloro-6-bromophenol) and Fluorophene. The most preferred antibacterial antiplaque compound is triclosan. Triclosan is disclosed in aforementioned U.S. Patent 4,022,880 as an antibacterial agent in combination with an anticalculus agent which provides zinc 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.

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 in optimizing anticalculus effectiveness of linear molecularly dehydrated polyphosphate salts, as disclosed in U.S. Patent 4,627,977 to Gaffar et al. It is further observed, in the

context of the present invention that such polycarboxylate is effective to enhance delivery and retention of the nonionic antibacterial, antiplaque agent to dental surfaces.

The synthetic anionic polymeric polycarboxylate is an inhibitor of alkaline phosphatase enzyme. 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. Patent No. 3,429,963 to Shedlovsky; U.S. Patent No 4,152,420 to Gaffar; U.S. Patent No. 3,956,480 to Dichter et al; U.S. Patent No. 4,138,477 to Gaffar; and U.S. Patent 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 are operative 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 employed herein are well known, being often employed in the form of their free acids or preferably partially or more preferably fully neutralized water soluble 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 (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. The term "synthetic" is intended to exclude known thickening or gelling agents comprising carboxymethylcellulose and other derivatives of cellulose and natural gums.

Other operative polymeric polycarboxylates include those disclosed in U.S. Patent No. 3,956,480 referred to above, such as the 1:1 copolymers of maleic anhydride with ethyl acrylate, hydroxyethyl methacrylate, N-vinyl-2-pyrrolidone, or ethylene, the latter being available for example as Monsanto EMA No. 1103, M.W. 10,000 and EMA Grade 61, and 1:1 copolymers of acrylic acid with methyl or hydroxyethyl

methacrylate, methyl or ethyl acrylate, isobutyl vinyl ether or N-vinyl-2-pyrrolidone.

Additional operative polymeric polycarboxylates disclosed in above referred to U.S. Patent No. 4,138,477 and 4,183,914, include copolymers of maleic anhydride with styrene, isobutylene or ethyl vinyl ether, polyacrylic, polyitaconic and polymaleic acids, and sulfoacrylic oligomers of M.W. as low as 1,000, available as Uniroyal ND-2.

Suitable generally are polymerized olefinically or ethylenically unsaturated carboxylic acids containing an activated carbon-to-carbon olefinic double bond and at least one carboxyl group, that is, an acid containing an olefinic double bond which 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 contain sufficient carboxylic salt groups for water-solubility.

Also useful herein are so-called carboxyvinyl polymers disclosed as toothpaste components in U.S. 3,980,767 to Chown et al; U.S. 3,935,306 to Roberts et al; U.S. 3,919,409 to Perla et al; U.S. 3,911,904 to Harrison, and U.S. 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 colloiddally 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.

62301-1608

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 when present is employed in the instant compositions in approximate weight amounts of 0.005 to 4%, preferably 0.05 to 3%, more preferably 0.1 to 2%. Amounts in the upper portions of these ranges are typically employed in dentifrice compositions typically employed in dentifrice compositions typically containing a dental abrasive and used in conjunction with brushing of the teeth, e.g. tooth pastes (including creams), gels, powders and tablets. Amounts in excess of these ranges may be employed for thickening or gelling purposes.

Without being bound to a theory, it is believed that the polymeric polycarboxylate is 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 with the polycarboxylate, thus forming a film of a complex of the two over tooth surfaces. The film forming property of the polycarboxylate and the enhanced delivery and film forming property of the polycarboxylate and the enhanced delivery and retention of the antibacterial agent on tooth surfaces due to the polycarboxylate 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.

62301-1608

In oral preparations such as mouthwashes and dentifrices, and orally acceptable vehicle including a water-phase with humectant is present. In the present invention, the oral preparation contains at least about 10% by weight of the water and humectant liquid phase. Moreover, preferably propylene glycol, typically $\begin{array}{c} \text{CH}_2 - \text{CH} - \text{CH}_3 \\ | \quad | \\ \text{OH} \quad \text{OH} \end{array}$ is present as a portion of the humectant to solubilize the substantially water-insoluble noncationic antibacterial agent. A preferred amount of propylene glycol is about 0.5-50% by weight based on the oral composition. The remainder of the humectant is glycerine and/or sorbitol. Water is present typically in amount of at least about 3% by weight and glycerine and/or sorbitol typically total about 6.5-75% by weight of the oral preparation, more typically about 10-75%, and, together with the solubilizing humectant, the essential humectant components typically amount to about 7-80% by weight of the oral preparation. Reference hereto to sorbitol refers to the material typically as available commercially in 70% aqueous solutions. 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 even when propylene glycol is present to effect its solubilization. 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 triclosan by a factor of about 16 from that prevailing in the absence of the polyethylene glycol.

Besides the preferred solubilizing humectant, propylene glycol, other solubilizing humectants which do not adversely affect the antibacterial activity may be used. These are dipropylene glycol, methyl cellosolve, ethyl cellosolve, olive oil, castor oil, amyl acetate, ethyl acetate, glyceryl

62301-1608

tristearate and benzyl benzoate.

When the amount of substantially water-insoluble noncationic antibacterial agent is low, say up to about 0.3% by weight, as little as about 0.5% by weight of the solubilizing humectant can be sufficient to solubilize the antibacterial agent. When higher amount of antibacterial are present, it is desirable that at least about 5% by weight of the solubilizing humectant be present.

In certain highly preferred forms of the invention the oral composition may be substantially liquid in character, such as a mouthwash or rinse. In such a preparation the vehicle, in addition to the humectant, is typically a water-alcohol mixture. Generally, the weight ratio of water to alcohol is in the range of from about 1:1 to about 20:1, preferably about 3:1 to 10:1 and more preferably about 4:1

to about 6:1. The total amount of water-alcohol mixture in this type of preparation is typically in the range of from about 70 to about 99.9% by weight of the preparation with the humectant typically being about 10-29.9% by weight, preferably about 0.5-15% by weight of propylene glycol and about 9.5-24.9% by weight of glycerine and/or sorbitol. The alcohol being non-toxic in nature is typically ethanol or isopropanol. Ethanol is preferred.

The pH of such liquid and other preparations 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 certain other desirable forms of this invention, the oral composition may be substantially pasty in character, such as a dentifrice, that is a toothpaste (dental cream) or gel dentifrice. The vehicle of such pasty oral preparations generally contains dentally acceptable polishing material. Examples of polishing materials are water-insoluble sodium metaphosphate, potassium metaphosphate, tricalcium phosphate, dihydrated calcium phosphate, anhydrous dicalcium phosphate, calcium pyrophosphate, magnesium orthophosphate, trimagnesium phosphate, calcium carbonate, aluminum silicate, zirconium silicate, silica, bentonite, and mixtures thereof. Other suitable polishing material include the particulate thermosetting resins described in U.S. Pat. No. 3,070,510 of Dec. 15, 1962 such as melamine-, phenolic, and urea-formaldehydes, and cross-linked polyepoxides and polyesters. 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 almuino-silicate complexes are particularly useful, since they are consistant 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 dentifrices.

Many of the so-called "water-insoluble" polishing materials are anionic in character and also include small amounts of soluble material. Thus, insoluble sodium metaphosphate may be formed in any suitable manner as illustrated by Thorpe's Dictionary of Applied Chemistry, Volume 9, 4th Edition, pp. 510-511. The forms of insoluble sodium metaphosphate known as Madrell's salt and Kurrol's salt are further examples of suitable materials. These metaphosphate salts exhibit only a minute solubility in water, and therefore are commonly referred to as insoluble metaphosphates (IMP). There is present therein a minor amount of soluble phosphate material as impurities, usually a few percent such as up to 4% by weight. The amount of soluble phosphate material, which is believed to include a soluble sodium trimetaphosphate in the case of insoluble metaphosphate, may be reduced or eliminated by washing with water if desired. The insoluble alkali metal metaphosphate is typically employed in powder form of a particle size such that no more than 1% of the material is larger than 37 microns.

The polishing material is generally present in the cream paste or gel compositions in weight concentrations of about 10% to about 75%.

In a toothpaste, the liquid vehicle may typically comprise about 10-35% by weight of water and the humectant mixture of solubilizing humectant (e.g. propylene glycol) with glycerine and/or sorbitol in an amount ranging from about 10% to about 80% by weight of the preparation the amount of propylene glycol typically being about 0.5-20% by weight. In clear gels where the refractive index is an important consideration, about 3-30% of water, about 0.5-20% of solubilizing humectant (e.g. propylene glycol), 0 to about 70% of glycerine and about 20-25% of sorbitol are preferably employed.

Toothpastes, creams and gels 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 thickeners include Irish moss, 1-carreageenan, gum tragacanth, starch, polyvinylpyrrolidone, hydroxyethylpropyl-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.

Since there maybe a tendency for the dentifrice to separate into liquid and solid portions when about 5% by weight or more of solubilizing humectant such as propylene glycol is present and since excellent antiplaque and adhesion effects can be obtained with small amounts of antibacterial agent which do not require so much solubilizing humectant to effect solubilization, a preferred dentifrice contains about 0.3% by weight of the antibacterial agent, about 1.5-2% by weight of the polycarboxylate and about 0.5%-1% by weight of the solubilizing humectant.

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 dentifrice formula or in a mouthrinse. The mouthrinse or mobile phase solution of dentifrice during use becomes diluted with saliva and triclosan would precipitate out without the presence of highly solubilizing humectant. On the other hand, propylene glycol being a strong solubilizing humectant for triclosan, appears to prevent such a situation and permit continued humectant presence with triclosan. 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 would apply to other water-insoluble noncationic antibacterial agents herein described.

In accordance with a further aspect of the invention anticalculus properties may also be provided to the oral composition by the inclusion of a molecularly dehydrated polyphosphate salt.

The linear molecularly dehydrated polyphosphate salts operative herein as anticalculus agents are well known, being generally employed in the form of their wholly or partially neutralized water soluble alkali metal (e.g. potassium and preferable sodium) or ammonium salts, and any mixtures thereof. Representative examples include sodium hexametaphosphate, sodium tripolyphosphate, disodium diacid, trisodium monoacid and tetrasodium pyrophosphates and the like. Linear polyphosphates correspond to $(\text{NaPO}_3)_n$ where n is about 2 to about 125. They are generally employed in the instant oral compositions in approximate weight amounts of 0.1 to 7% preferably 1 to 7%, more preferably 2 to 7%. When n is at least 3 in $(\text{NaPO}_3)_n$, the polyphosphates are glassy in character.

Particularly desirable anticalculus agents are tetraalkali metal pyrophosphates, including mixtures thereof, such as tetrasodium pyrophosphate tetrapotassium pyrophosphate and mixtures thereof. An anticalculus agent comprising about 4.3% to about 7% by weight of the oral compositions where in the weight ratio of tetrapotassium pyrophosphate to tetrasodium pyrophosphate is from about 4.3:2.7 to about 6:1 is especially preferred.

In order to optimize the anticalculus effectiveness of the oral composition, inhibitors against enzymatic hydrolysis of the polyphosphate are desirably present. The synthetic anionic polymeric

polycarboxylate as described is one such agent. The other is an amount of a 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 fluorine-providing component, as anti-caries as well as acid phosphatase and pyrophosphatase enzyme inhibitor component, are well known in the art as anti-caries agents. 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 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 fluosilicate, ammonium fluosilicate, sodium fluorozirconate, sodium 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 toothpaste (including cream), 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 preferable 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 jar of mouthrinse will have a label describing it, in substance, as a mouthrinse or mouthwash and having directions for its use; and a toothpaste, cream or 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 toothpaste, gel or dental cream.

Organic surface-active agents are used in the compositions of the present invention to achieve increased prophylactic action, assist in achieving thorough and complete dispersion of the anticalculus agent throughout the oral cavity, and render the instant compositions more cosmetically acceptable. 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 detergent material which imparts to the composition detergent 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 monostearate) and polypropyleneoxide (e.g. Pluronic materials).

Surface active agent is typically present in amount of about 0.5-5% by weight, preferably about 1-2%. It is noteworthy, that surface active agent can assist in the dissolving of the noncationic antibacterial agent and thereby diminish the amount of solubilizing humectant needed.

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 together comprise from about 0.1% to 5% more of the preparation.

In the preferred practice of this invention an oral composition according to this invention such as a mouthwash or dentifrice containing the 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 effect of synthetic anionic linear polycarboxylate on the uptake, retention to and release from tooth surfaces of water-insoluble noncationic antibacterial agent is assessed in vitro on a saliva coated hydroxyapatite disk and on exfoliated buccal epithelial cells. The in vitro assessments are correlatable to in vivo plaque measurements and in vitro reduction is indicative of in vivo reduction.

Dentifrices prepared having the following formulas:

	<u>Parts</u>	
	<u>A</u>	<u>B</u>
Propylene Glycol	10.00	10.00
Iota Carrageenan	0.75	0.75
Gantrez S-97	-	2.00
Titanium Dioxide	0.50	0.50
Sorbitol (70%)	30.00	30.00
Sodium Fluoride	0.332	0.332
Sodium Saccharin	0.40	0.40
Silica Thickener (Sylodent 15)	3.00	3.00
Silica Polishing Agent (Zeodent 113)	20.00	20.00
Triclosan	0.20	0.20
Sodium Lauryl Sulfate	2.00	2.00
Flavor	0.95	9.95
Ethyl Alcohol	1.00	1.00
Sodium Hydroxide (50%)	0.80	0.80
Water	Q.S. to 100.0	Q.S. to 100.0

The uptake of triclosan on the saliva coated hydroxyapatite disk and on buccal epithelial cells with varying levels of the polymeric polycarboxylate, Gantrez S-97, is set forth in Table 1 below:

TABLE 1

<u>Dentifrice</u>	Uptake of Triclosan	
	in micrograms	In Micrograms $\times 10^5$ Buccal
	<u>On Saliva Coated Disk</u>	<u>Epithelial Cells</u>
A	25.0	38.0
B	54.0	96.0

These results reveal that the Gantrez material greatly enhances the delivery and uptake of triclosan to saliva coated hydroxyapatite disk and to the exfoliated buccal epithelial cells.

Similar results are obtained when the dentifrices contain 3% of triclosan.

EXAMPLE 2

In separate tests with saliva coated hydroxapatite disks and exfoliated buccal epithelial cells from those set forth in Example 1 above, dentifrice B containing 2.00% Gantrez S-97 and 0.20% of triclosan, 10.00% of propylene glycol and 2.00% of sodium lauryl sulfate and an equivalently formulated dentifrice, except for the presence of 0.30% of triclosan (Dentifrice B') were compared with a commercially available dentifrice containing (a) 0.2% of triclosan, (b) no Gantrez material, (c) no propylene glycol, (d) 0.5% zinc citrate, (e) 2.5% of surface active agents (f) sodium monofluorophosphate and hydrated alumina polishing agent (Dentifrice C); and the dentifrice formulation below (Dentifrice C') which is similar to commercial Dentifrice C except for the presence of 0.30% of troclosan:

DENTIFRICE C'

	<u>%</u>
Sorbitol (70%)	27.00
Sodium Carboxymethyl Cellulose	0.80
Sodium Monofluorophosphate	0.85
Zinc Citrate	0.50
Sodium Saccharin	0.18
Water	16.47
Hydrated Alumina Polishing Agent	50.00
Ethanol	0.20
Sodium Lauryl Sulfate	1.875
Sodium Dodecyl Benzene Sulfonate	0.625
Triclosan	0.30
Flavor	1.20

Since Dentifrices C and C' contain a total of 2.50% of surface active agent. Thus, more surface active agent is available to dissolve triclosan than in Dentifrices B and B' which contain 2.00%. However, propylene glycol in Dentifrices B and B' insures optimum dissolution of triclosan.

The advantage of Dentifrices B and B' over Dentifrices C and C' in triclosan uptake on saliva coated hydroxyapatite disks and on exfoliated buccal epithelial cells is shown in the Table 2 below:

TABLE 2

	<u>Delivery of Triclosan</u>	
	To Saliva Coated	To Buccal Epithelial
	Hydroxyapatite Disk	Cells
	(in micrograms)	in micrograms
		<u>x 10⁶ Epithelial Cells)</u>
Dentifrice B	41.1	101.6
B'	77.4	142.0
C	20.4	61.0
C'	42.6	100.0

These results indicate that dentifrices containing triclosan, Gantrez material and propylene glycol can provide enhanced delivery of triclosan to tooth surfaces and soft surfaces in the oral cavity, thereby providing improved antiplaque and antibacterial effects.

EXAMPLE 3

For purpose of comparison, Formulas A, B and C, below are prepared:

Formula A is a tartar control dentifrice (containing testrosodium pyrophosphate, sodium fluoride and a Gantrez polycarboxylate, with triclosan as an antibacterial antiplaque agent and with a humectant system of glycerine and sorbitol.

Formula B is a similar type tartar control dentifrice except that in the humectant system, propylene glycol is present with sorbitol.

Formula C is similar to Formula B except principally that the pyrophosphate anticalculus agent is not present.

	<u>Dentifrice</u>		
	<u>A</u>	<u>B</u>	<u>C</u>
	%	%	%
Glycerin	10.00	-	-
Propylene Glycol	-	10.00	10.00
Iota Carrageenan	0.750	0.60	0.60
Sorbitol (70%)	30.00	25.00	25.00
Sodium Saccharin	0.300	0.40	0.40
Sodium Fluoride	0.243	0.243	0.243
Titanium Dioxide	0.500	0.50	0.50
Tetrasodium Pyrophosphate	2.00	2.00	-
Gantrez S-97	1.50	2.00	2.00
Water	26,107	26.657	28.657
NaOH(50%)	1.500	2.00	2.00
Zeodent 113(Silica Polishing Agent)	20.00	20.00	20.00
Sylodent 15 (Silica Thickener)	3.00	5.50	5.50
Flavor	1.10	1.10	1.10
Triclosan	0.50	0.50	0.50
Sodium Lauryl Sulfate	2.50	2.50	2.50
Ethanol	<u>-</u>	<u>1.00</u>	<u>1.00</u>
	pH 7.9	pH 7.0	pH 7.0

The uptake of triclosan from each of dentifrice A, B and (C) is determined on saliva coated hydroxyapatite disk (4 for each dentifrice) with slurries of 50% of dentifrice as indicated in Table 3 below:

<u>TABLE 3</u>	
<u>Dentifrice Slurry</u>	<u>Uptake of Triclosan</u> <u>Micrograms/Disk</u>
A	1.6 + 0.3
B	19.1 + 3
C	99.9 + 21

The foregoing results reveal improvements of about 11 and 61 times in triclosan uptake with anticalculus, antiplaque dentifrice B and antiplaque dentifrice C, each containing propylene glycol, over that achieved with dentifrice A containing no propylene glycol.

Additional experiments with a 50% slurry of dentifrice C to determine the retention of triclosan on the saliva coated hydroxyapatite disk over a period of time reveals retention of excellent levels of triclosan as shown in Table 4, below:

TABLE 4

Retention of Triclosan Adsorption

from Dentifrice C Slurry

<u>Time</u> <u>(in Minutes)</u>	<u>Uptake of Triclosan</u> <u>(Micrograms/Disk)</u>
0	70
30	60
60	70
120	65
180	57
240	59

EXAMPLE 4

An "in-house" study was conducted on a group of volunteers to assess the effects of particular toothpastes in influencing plaque regrowth in accordance with the method described by Addy, Willis and Moran, J. Clin. Paerio., 1983, Vol. 10, Pages 89-99. The toothpastes tested included a placebo control (1), a control containing 0.3% of triclosan and 1.5% of Gantrez S-97 with glycerine and sorbitol as humectant (2) and a toothpaste in accordance with this invention containing 0.3% of triclosan, 2% of Gantrez S-97 and humectant of propylene glycol and sorbitol. The formulas of toothpastes (1), (2) and (3) are as follows:

	Parts		
	(1)	(2)	(3)
	<u>Placebo</u>	<u>Control</u>	<u>Invention</u>
Polyethylene Glycol 600	3.00		
Glycerine	25.00	10.00	
Propylene Glycol			10.00
Sorbitol (70%)	41.617	30.00	25.00
Sodium Carboxymethyl Cellulose	0.35		
Iota Carrageenan		0.75	0.60
Sodium Benzoate	0.50		
Sodium Saccharin	0.20	0.30	0.40
Sodium Fluoride	0.243	0.243	0.243
Silica Polishing Agent			
(Zeodent 113)	18.00	20.00	20.00
Silica thickener			
(Sylox 15)	5.50		5.50
(Sylodent 15)		3.00	
Water	3.00	26.307	26.857
Gantrez S-97		1.50	2.00
Tetrasodium pyrophosphate		2.00	
Triclosan		0.30	0.30
Titanium Dioxide	0.50	0.50	0.50
Sodium Lauryl Sulfate	1.20	2.50	2.50
Flavor	0.89	1.10	1.10
Ethyl Alcohol			1.00
Sodium Hydroxide (50%)			2.00
pH		7.9	7.0

Sum 11,
N.W. 12.27.86
A.G.

With regard to plaque reduction, on the teeth of the volunteers, compared to placebo (1), toothpaste (2) provided only a non-significant reduction of 8% while toothpaste (3) provided a significant decrease of 20%.

Since lesser amounts of propylene glycol can dissolve the 0.3 parts of triclosan present in Toothpaste (3), similar results are expected when the amount of propylene glycol is reduced to 0.5 parts and the amount of sorbitol is increased to 39.5 parts. Likewise, propylene glycol can be replaced by any of dipropylene glycol, methyl cellosolve, ethyl cellosolve, olive oil, castor oil, amyl acetate, ethyl acetate, glyceryl tristearate or benzyl benzoate.

EXAMPLE 5

The mouthrinses below are effective in reducing plaque. Mouthrinse A is also effective in reducing caries and calculus.

	<u>A</u>	<u>B</u>
	<u>Parts</u>	<u>Parts</u>
Tetrasodium Pyrophosphate	2.00	-
Gantrez S-97	0.25	0.25
Glycerine	10.00	10.00
Propylene Glycol	5.00	5.00
Sodium Fluoride	0.05	-
Pluronic F108	2.00	2.00
(Polyoxyethylene/Polyoxypropylene Block Copolymer)		
Triclosan	0.10	0.10
Flavor	0.40	0.40
Water	Q.S. to 100.00	Q.S. to 100.00

In the foregoing examples, other antibacterial agents herein described such as 2-methyl phenol, methyl-p-chlorophenol and n-hexyl resorcinol may replace triclosan. Likewise, polymeric polycarboxylate other than Gantrez S-97, such as 1:1 copolymer of maleic anhydride and ethyl acrylate and sulfoacrylic oligomers, may be used.

2006719

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.

62301-1608

CLAIMS:

1. An oral composition comprising in an orally acceptable vehicle:

5 a water-humectant phase, in an amount of at least about 10% by weight based on the oral composition,

an effective antiplaque amount of a substantially water insoluble noncationic antibacterial agent selected from the group consisting of halogenated diphenyl ethers and phenolic compounds, and

10 about 0.005-4% by weight of a synthetic anionic linear polymeric polycarboxylate having a molecular weight of about 1,000 to about 1,000,000,

wherein the humectant includes a solubilizing humectant selected from the group consisting of propylene glycol, 15 dipropylene glycol, methyl cellosolve, ethyl cellosolve, olive oil, castor oil, amyl acetate, ethyl acetate, glyceryl tristearate and benzyl benzoate mixed with at least one of glycerine and sorbitol, the amount of the solubilizing humectant being sufficient to dissolve the antibacterial agent.

20 2. The oral composition claimed in Claim 1, containing about 0.5-50% by weight of propylene glycol.

3. The oral composition claimed in Claim 2, containing about 0.01-5% by weight of the antibacterial agent, wherein the antibacterial agent is a halogenated diphenyl ether.

25 4. The oral composition claimed in Claim 3, wherein the antibacterial agent is present in amount of about 0.1-0.5%.

62301-1608

5. The oral composition claimed in Claim 2 or 3, wherein the halogenated diphenyl ether is 2,4,4'-trichloro-2-hydroxy-diphenyl ether.

6. The oral composition claimed in Claim 1 or 2,
5 containing about 0.01-5% by weight of the antibacterial agent, wherein the antibacterial agent is a phenolic compound.

7. The oral composition claimed in any one of Claims 1 to 6, wherein the polymeric polycarboxylate is present in amount of about 0.1 to 2% and is a water soluble alkali metal or
10 ammonium salt of a copolymer of vinyl methyl ether and maleic acid or anhydride having a molecular weight of from about 30,000 to about 500,000.

8. The oral composition claimed in any one of Claims 1 to 7, containing an effective anticalculus amount of material
15 comprising at least one linear molecularly dehydrated polyphosphate salt as essential anticalculus agent.

9. The oral composition claimed in Claim 8, wherein the polyphosphate salt is present in amount of about 0.1-7% by weight and is tetrasodium pyrophosphate.

20 10. The oral composition claimed in Claim 8 or 9, wherein the composition contains an amount of fluoride ion source sufficient to supply 25 ppm. to 2,000 ppm. of fluoride ions.

11. The oral composition claimed in Claim 10 wherein the fluoride source is sodium fluoride.

25 12. The oral composition claimed in any one of Claims 1 to 7, wherein the composition contains an amount of fluoride ion source sufficient to supply 25 ppm to 2000 ppm of fluoride ions.

62301-1608

13. The oral composition claimed in any one of Claims 1 to 12, wherein the oral composition contains a dentally acceptable water-insoluble polishing agent and the oral compositions is a toothpaste or dentifrice.

5 14. The oral composition claimed in Claim 13, wherein the oral composition contains about 0.5-50% by weight of propylene glycol, about 0.1-10% by weight a gelling agent and about 10-75% by weight of the polishing agent; and the oral composition is a toothpaste or gel dentifrice.

10 15. The oral composition claimed in Claim 14, which comprises 0.3% by weight of the antibacterial agent, about 0.15-2% by weight of the polycarboxylate and about 0.5-1% by weight of propylene glycol.

15 16. The oral composition claimed in Claim 14 wherein the polishing material is a silica polishing material.

17. The oral composition claimed in any one of Claims 1 to 12, wherein the oral composition contains about 70-99.9% by weight of a mixture of water and alcohol in a weight ratio of from about 1:1 to about 20:1 and the oral composition is a
20 mouthrinse.

18. The oral composition claimed in Claim 17, wherein the alcohol is ethanol.

19. The oral composition claimed in Claim 17, wherein about 5-20% by weight of propylene glycol is present.

SMART & BIGGAR

OTTAWA, CANADA

PATENT AGENTS