

"ANTICALCULUS ORAL COMPOSITION"

The present invention relates to oral compositions containing an anticalculus agent.

Calculus is a hard, mineralized formation which forms on the teeth. Regular brushing aids in preventing a rapid build-up of these deposits, but even regular brushing is not sufficient to remove all of the calculus deposits which adhere to the teeth. Calculus is formed on the teeth when crystals of calcium phosphates begin to be deposited in the pellicle and extracellular matrix of the dental plaque and become sufficiently closely packed together for the aggregates to become resistant to deformation. There is no complete agreement on the route by which calcium and orthophosphate ultimately become the crystalline material called hydroxyapatite (HAP). It is generally agreed, however, that at higher saturations, that is, above the critical saturation limit, the precursor to crystalline HAP is an amorphous or microcrystalline calcium phosphate. "Amorphous calcium phosphate" although related to hydroxyapatite differs from it in atomic structure, particle morphology, and stoichiometry. The X-ray diffraction pattern of amorphous calcium phosphate shows broad peaks typical of amorphous materials, which lack the long-range atomic order characteristic of all crystalline materials, including HAP. It is apparent therefore that agents which effectively interfere with crystalline growth of HAP will be effective as anticalculus agents. A suggested mechanism by which the anticalculus agents of the

present invention inhibit calculus formation probably involves an increase of the activation energy barrier thus inhibiting the transformation of precursor amorphous calcium phosphate to HAP.

Studies have shown that there is a good correlation between the ability of a compound to prevent HAP crystalline growth in vitro and its ability to prevent calcification in vivo, provided of course that such compound is stable in and inert to saliva and its components.

The prior art indicates that soluble pyrophosphate may be utilized to reduce calculus formation. For example, U.S. Patent No. 4,515,772 issued 7th May, 1985 to Parran et al refers to several prior art references disclosing oral compositions containing soluble pyrophosphate salts, including an article by Draus et al, Arch. Oral. Biol., 15, pp.893-896, (1970), which discloses the in vitro effectiveness of such salts against calculus. The article refers to possible inhibition of pyrophosphate by pyrophosphatase enzyme.

It is known that saliva contains acid phosphatase, alkaline phosphatase and pyrophosphatase enzymes. It is considered that any one of the three enzymes may adversely affect pyrophosphates as an inhibitor of HAP formation and calculus. It is accordingly apparent that an anticalculus pyrophosphate dentifrice composition, should inhibit, reduce or nullify the destructive activity of all three salivary enzymes.

The compositions of the aforementioned Parran et al patent are limited to a pH of 6.0 to 10.0 and comprise a fluoride and soluble dialkali metal pyrophosphates alone or admixed with tetraalkali metal pyrophosphates, but no more than 4.0% $K_4P_2O_7$ (tetrapotassium pyrophosphate). The patent omits any disclosure or even mention of effectiveness of the patented fluoride-pyrophosphate composition in vivo or saliva.

The present invention aims to provide an improved dentifrice composition containing one or a mixture of pyrophosphate salts as essential anticalculus (antitartar) agent.

The present invention also aims to provide such a composition containing one or more inhibitors against enzymatic hydrolysis of the said agent in saliva.

The present invention also aims to provide such a composition effective over a relatively wide pH range and/or with improved cosmetic properties.

The present invention further aims to provide such a composition which does not significantly erode tooth surfaces and which also exerts substantial and acceptable anti-carries effects.

Earlier in the development of the present invention, it was found that dentifrice compositions containing only tetrasodium pyrophosphate as anticalculus agent were gritty, and that the solid gritty particles were composed of undissolved $Na_4P_2O_7$.

The present invention is at least in part based

on our determinations or discoveries that fluoride ion inhibits hydrolysis of pyrophosphate by acid phosphatase and pyrophosphatase enzymes, that the synthetic anionic polymeric polycarboxylate salts inhibit hydrolysis of pyrophosphate by alkaline phosphatase, and that the occurrence of gritty particles in the oral compositions can be avoided by employing a predominant portion of the pyrophosphate in the form of the tetrapotassium salt.

According to one aspect of the present invention an anticalculus oral composition in the form of a toothpaste, dental gel, toothpowder, dental tablet, chewing gum or lozenge comprises an orally acceptable vehicle and,

A. a mixture of tetrasodium pyrophosphate and tetrapotassium pyrophosphate of which the tetrapotassium pyrophosphate is a predominant portion such as to avoid the occurrence of gritty particles in the oral composition; and

B. an amount of a fluoride ion source sufficient to supply 25 ppm to 5,000 ppm of fluoride ions.

According to another aspect of the present invention an oral composition comprises an orally acceptable aqueous vehicle and,

A. 4.3% to 7% of alkali metal pyrophosphates as essential anticalculus agent, comprising at least 4.3% of tetrapotassium pyrophosphate, alone or admixed with up to 2.7% of tetrasodium pyrophosphate, and

B. an amount of a fluoride ion source sufficient

to supply 25 ppm to 5,000 ppm of fluoride ions.

According to another aspect of the present invention an oral composition comprises an orally acceptable aqueous vehicle and,

A. 4.3% to 7% of a mixture of tetrasodium pyrophosphate and tetrapotassium pyrophosphate in a respective ratio ranging from 2.7:4.3 to 1:6 containing at least 4.3% tetrapotassium pyrophosphate to avoid the occurrence of gritty particles of tetrasodium pyrophosphate in the composition, and

B. an amount of a fluoride ion source sufficient to supply 25 ppm to 5,000 ppm of fluoride ions.

Preferably the composition contains as an inhibitor against enzymatic hydrolysis of the said agent in saliva a synthetic anionic polymeric polycarboxylate having a molecular weight of 1,000 to 1,000,000, preferably 30,000 to 500,000, e.g. in an amount of 0% to 3% e.g. 0.05 to 3%.

Synthetic anionic polymeric polycarboxy-

lates 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 and instant assignee, U.S. Patent No. 4,152,420 to Gaffar and instant assignee, U.S. Patent No. 3,956,480 to Dichter et al and instant assignee, U.S. Patent No. 4,138,477 to Gaffar and instant assignee, and U.S. Patent No. 4,183,914 to Gaffar et al. None of these patents however nor any other known prior art discloses use of such polycarboxylates alone for inhibiting salivary hydrolysis of the said linear polyphosphates, much less in combination with a compound providing a source of fluoride ion. It is to be understood that the synthetic anionic linear polymeric polycarboxylates disclosed in these patents are operative in the compositions and methods of the present invention and such disclosures are to that extent incorporated herein by reference thereto.

The synthetic anionic polymeric polycarboxylates optionally but preferably employed herein are, as indicated above 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. The term "synthetic" is intended to exclude known thickening or gelling agents comprising carboxymethylcellulose and other derivatives of cellulose and natural gums. The preferred class of synthetic polymeric

polycarboxylates are the synthetic linear polymeric polycarboxylates. The term "linear" is intended to exclude from this preferred class polycarboxylates having cross-linkages which reduce solubility such as the carbopols. Preferred are 1:4 to 4:1 copolymers

of maleic anhydride or acid with another polymerizable ethylenically unsaturated monomer, preferably methyl vinyl ether (methoxyethylene) having a molecular weight (M.W.) of about 30,000 to about 1,000,000. 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.

Other operative polymeric polycarboxylates include those disclosed in U.S. Patent No. 3,956,180 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 N. 1103, M.W. 10,000, and EMA Grade 61, and 1:1 copolymers of acrylic acid with methyl or hydroxyethyl methacrylate, 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 sulphoacrylic 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-chlorosorbic, cinnamic, beta-styrylacrylic, muconic, itaconic, citraconic, mesaconic, glutaconic, aconitic, alpha-phenylacrylic, 2-benzyl acrylic, 2-cyclohexylacrylic, angelic, umbellic, fumaric and 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 issued 14th September, 1976 to Choun et al, U.S. 3,935,306 issued 27th January, 1976 to Roberts et al, U.S. 3,919,409 issued 11th November, 1975 to Perla et al, U.S. 3,911,904 issued 7th October, 1975 to Harrison, and U.S. 3,711,604 issued 16th January, 1973 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 cross-linked with from about 0.75% to about 2.0% of polyallyl sucrose or polyallyl pentaerythritol as cross-linking agent.

The synthetic anionic polymeric poly-

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carboxylate component is mainly a hydrocarbon with optional halogen and O-containing substituents and linkages as present in for example ester, ether and OH groups, and is generally employed in the compositions of the present invention in approximate weight amounts of 0.05 to 3%, preferably 0.05 to 2%, more preferably 0.1 to 2%. Amounts in the upper portions of these ranges are typically employed in dentifrice compositions, meaning oral compositions generally containing a dental abrasive and used in conjunction with brushing of the teeth, e.g. tooth pastes, gels, creams and powders. Amounts in excess of these ranges may be employed for thickening or gelling purposes.

As indicated above, these polymeric polycarboxylates have been found to be effective inhibitors of alkaline phosphatase enzyme. Since this enzyme has little activity (for hydrolyzing pyrophosphate) at about pH 7.0 or below, the polymeric polycarboxylate component may, if desired, be omitted from oral preparations formulated to operate at such pH of 7.0 or below. Such omission however obviously reduces the versatility and effectiveness of the present oral compositions over the broad pH range of about 4.5 to about 10.

The source of fluoride ions, or fluorine-providing compounds, required according to the present invention as an essential component of the described inhibitor combination, are well known in the art as anti-carries agents and also act as such

agents in the practice of the present invention. These compounds may be slightly soluble in water or may be fully water-soluble. They are characterised 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 and alkaline earth metal salts, for example sodium fluoride, potassium fluoride, barium fluoride, or calcium fluoride and ammonium fluoride, or a copper fluoride such as cuprous fluoride, or zinc fluoride, sodium fluorosilicate, ammonium fluoro-silicate, sodium fluorozirconate, sodium monofluoro-phosphate, aluminium 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 nontoxic amount, generally about 0.005 to about 3.0% in the preparation. In a dentifrice preparation, e.g. gel, cream, toothpaste or tooth-powder, 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 about 2,000 ppm, more preferably

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about 800 to about 1,500 ppm of fluoride ion. Typically, in the cases of alkali metal fluorides and stannous fluoride, 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%.

In dentifrice preparations such as lozenges and chewing gum, the fluoride-providing compound is typically present in an amount sufficient to release up to about 500 ppm, preferably about 25 to about 300 ppm by weight of fluoride ion. Generally about 0.005 to about 1.0 wt % of such compound is present.

The preferred dentifrice compositions of the present invention achieve the desired anticalculus effect by mixing therein about 4.3% to about 7% of tetrapotassium pyrophosphate. Preferred ratios of the tetrapotassium:tetrasodium salts range from about 4.3:2.7 to about 6:1, especially a ratio of 4.5:1.5. Contrary to the disclosure in the aforementioned Parran et al patent, it is highly significant that these preferred compositions of the present invention have highly acceptable anticalculus and improved cosmetic properties while including more than 4.0% of the tetrapotassium pyrophosphate and without inclusion of any dialkali metal pyrophosphate, although small amounts thereof, such as about 0.1% to about 0.4% or about 1.0% may be so included if desired.

The pH of the dentifrice preparations of the invention is generally in the range of from about 4.5 to about 10 and typically from about 5.5 to 9. The pH is preferably in the range of from about 6 to about 8.0. It is noteworthy that the compositions of the invention may be applied orally at the said pH ranges 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 (e.g. such as with sodium citrate, benzoate, carbonate, or bicarbonate, disodium hydrogen phosphate, or sodium dihydrogen phosphate).

In certain desirable forms of the present invention, the oral composition may be substantially solid or pasty in character, such as toothpowder, a dental tablet, a toothpaste, gel or dental cream. The vehicle of such solid or pasty oral preparations generally contains 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, aluminium silicate, zirconium silicate, silica, bentonite, and mixtures thereof. Other suitable polishing materials include the particulate thermosetting resins described in U.S. Patent No. 3,070,510 of 15th December, 1962 such as melamine-, phenolic-, and urea-formaldehydes, and cross-linked

polyepoxides and polyesters. Preferred polishing materials include crystalline silica having particle sizes 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 cm²/gm, silica gel or colloidal silica, and complex amorphous alkali metal aluminosilicate.

When visually clear gels are desired, 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 and alkali metal aluminosilicate complexes are particularly useful, since they 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 about 1% of the material is larger than about 37 microns.

The polishing material is generally present in the solid or pasty compositions in weight concentrations of about 10% to about 99%. Preferably, it is present in amounts ranging from about 10% to about 75% in toothpaste, and from about 70% to about 99% in toothpowder.

In a toothpaste, the liquid vehicle may comprise water and humectant typically in an amount ranging from about 10% to about 90% by weight of the preparation. Glycerine, propylene glycol, sorbitol, polypropylene glycol and/or polyethylene glycol (e.g. 400-600) exemplify suitable humectants/carriers. Also advantageous are liquid mixtures of water, glycerine and sorbitol. In clear gels where the refractive index is an important consideration, about 3-30 wt % of water, 0 to about 80 wt % of glycerine, and about 20-80 wt % of sorbitol is 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, wt %. 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, 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 as finely ground Syloid (e.g. 244).

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 aluminium, 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

compositions of the present invention 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 deterative material which imparts to the composition deterative and foaming properties. Suitable examples of anionic surfactants are water-soluble salts of higher fatty acid monoglyceride monosulphates, such as the sodium salt of the monosulphated monoglyceride of hydrogenated coconut oil fatty acids, higher alkyl sulphates such as sodium lauryl sulphate, alkyl aryl sulphonates such as sodium dodecyl benzene sulphonate, higher alkyl sulphoacetates, higher fatty acid esters of 1,2 dihydroxy propane sulphonate, 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).

Various other materials may be incorporated in the oral preparations of the present invention such as whitening agents, preservatives, silicones, chlorophyll compounds, other anticalculus agents, 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.

Any suitable flavouring or sweetening material may also be employed. Examples of suitable flavouring constituents are flavouring 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, sorbitol, xylitol, sodium cyclamate, perillartine, APM (aspartyl phenyl alanine, methyl ester), saccharine and the like. Suitably, flavour and

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sweetening agents may together comprise from about 0.1% to 5% or more of the preparation.

In the preferred practice of the present invention an oral composition according to the present invention such as dentifrice containing the described polyphosphate and enzyme inhibitor in an amount effective to inhibit calculus on dental surfaces is preferably applied as by brushing regularly to dental enamel, such as every second or third day or preferably from 1 to 3 times daily, at a pH of about 4.5 to about 10, generally about 5.5 to about 9, preferably about 6 to 8, for at least 2 weeks up to 8 weeks or more up to lifetime. The dentifrice is typically removed by rinsing with water after each application.

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

The vehicle or carrier in a tablet or lozenge is a non-cariogenic solid water soluble polyhydric alcohol (polyol) such as mannitol, xylitol, sorbitol, maltitol, a hydrogenated starch hydrolysate, Lycasin, hydrogenated glucose, hydrogenated disaccharides, and hydrogenated polysaccharides, in an amount of about

90-98% by weight of the total composition. Solid salts such as sodium bicarbonate, sodium chloride, potassium bicarbonate or potassium chloride may totally or partially replace the polyol carrier.

Tableting lubricants, in minor amounts of about 0.1 to 5% by weight, may be incorporated into the tablet or lozenge formulation to facilitate the preparation of both the tablets and lozenges.

Suitable lubricants include vegetable oils such as coconut oil, magnesium stearate, aluminium stearate, talc, starch and carbowax.

Lozenge formulations contain about 2% gum as barrier agent to provide a shiny surface as opposed to a tablet which has a smooth finish. Suitable non-cariogenic gums include Kappa carrageenan, carboxymethyl cellulose, hydroxyethyl cellulose, Gantrez, and the like.

The lozenge or tablet may optionally be coated with a coating material such as waxes, shellac, carboxymethyl cellulose, polyethylene/maleic anhydride copolymer or Kappa-carrageenan to further increase the time it takes the tablet or lozenge to dissolve in the mouth. The uncoated tablet or lozenge is slow dissolving, providing a sustained release rate of active ingredients of about 3 to 5 minutes. Accordingly, the solid dose tablet and lozenge compositions of the present invention affords a relatively longer time period of contact of the teeth in the oral cavity with the active ingredients.

The invention may be put into practice in various ways and a number of specific embodiments will be described to illustrate the invention with reference to the accompanying examples. All amounts and proportions referred to herein and in the appended claims are by weight and temperatures are in degrees centigrade unless otherwise indicated.

EXAMPLE A

Effect of Salivary Enzymes on Inhibition of HAP Formation by tetrasodium pyrophosphate (TSPP)

The in vitro formation of HAP is measured titrimetrically via a pH stat procedure. Stock solutions of 0.1M CaCl_2 and 0.1M NaH_2PO_4 are prepared fresh in carbonate-free deionized distilled water. To 23 ml CO_2 -free deionized distilled water 1.0 ml of the stock phosphate solution and 1.0 ml of an aqueous solution of $1 \times 10^{-4}\text{M}$ of the anticalculus agent being tested are added followed by 1.0 ml of the stock calcium chloride solution which initiates the reaction. The reaction is conducted at pH 7.4 under a nitrogen atmosphere. Consumption of 0.1N NaOH is recorded automatically from which the time required for crystal formation is determined. Table A shows the results of this procedure.

TABLE A

<u>Time of Crystal Growth Inhibition (Hrs.)</u>				
<u>Anticalculus Agent</u>	<u>Water</u>	<u>Saliva</u>	<u>Pyrophos- phatase</u>	<u>Alk. Phos- phatase</u>
TSPP	0.8	0.4	0.3	0.0

Table A shows that in water TSPP significantly delays HAP formation. However, the effectiveness of this agent is drastically reduced when incubated with saliva as evidenced by the shorter delay time. This reduction in efficacy is due to the enzymatic hydrolysis of P-O-P bonds. Incubation of this agent with pyrophosphatase and alkaline phosphatase drastically reduces the delay period and indicates the the susceptibility of the P-O-P bond to hydrolysis by phosphatases. Substantially the same results are obtained using tetrapotassium pyrophosphate (TKPP) instead of TSPP, both having the same effective P-O-P bond-containing pyrophosphate ion.

EXAMPLE B

Stabilization of TSPP to Enzymatic Hydrolysis in Presence of Inhibitors

Enzymatic hydrolysis is conducted in 100 millimolar morpholinopropane sulphonic acid - NaOH buffer solution (pH 7.0) containing 1.3 mg/ml of TSPP. Inhibitors according to the present invention are added (except to the control) to a final concentration of 1,000 ppm fluoride ion (from NaF) and 0.5% of the sodium salt of hydrolyzed methoxyethylene-maleic anhydride (1:1) copolymer, M.W. 70,000 (Gantrez S-97 Pharmaceutical Grade). Equal activities of acid phosphatase, alkaline phosphatase, and inorganic pyrophosphatase are then added to yield a total phosphatase activity of 0.3 units/ml. Samples of each test solution are taken and total orthophosphate available in each sample

measured after 3 hours hydrolysis in 4N HCl at 100°C. The reaction mixtures are incubated at 37°C with shaking and aliquots taken at appropriate times through at least 90 minutes for orthophosphate determination. Table B shows the results expressed as percent orthophosphate released due to hydrolysis of the pyrophosphate.

TABLE B

<u>Anticalculus Agent</u>	<u>Percent Orthophosphate Release in 90 min.</u>		<u>Percent Relative Protection</u>
	<u>Control</u>	<u>With Inhibitors</u>	
TSPP	98	58	41

Table B shows that after 90 minutes incubation in the presence of enzyme 98% of the available orthophosphate is released from the TSPP in the absence of the inhibitors. With inhibitors, hydrolysis of P-O-P bonds in pyrophosphate (TSPP) is reduced by 41%. It should be noted that the enzyme activities used in this study are at least 2-3 fold greater than those normally found in saliva. These data indicate that the inhibitors of this invention significantly reduce enzymatic hydrolysis of TSPP. Substantially the same results are obtained when equivalent amounts of TKPP is substituted for the TSPP.

The following dental gel formations are representative of the invention. Example 1 is a white opacified gel, Example 2 is a blue transparent gel. The

ingredients and proportions are set out in Table 1 below.

TABLE 1

<u>Ingredients</u>	<u>Parts by Weight</u>	
	<u>Example 1</u>	<u>Example 2</u>
<u>Part 1</u>		
TSPP	1.500	1.500
TKPP	4.500	4.500
Sorbitol (70% Aqueous solution)	22.507	22.500
<u>Part 2</u>		
Polyethylene Glycol 600	5.000	5.000
Glycerine	10.750	15.000
IOTA Carrageenan Gum	0.500	0.450
Sodium Fluoride	0.243	0.243
Sodium Saccharin	0.300	0.300
Gantrez S-97	1.000	1.000
Titanium Dioxide	0.500	-----
Deionized Water	31.000	26.607
FD&C Blue No.1 (1% Solution)	-----	0.200
<u>Part 3</u>		
ZEO 49B (SiO ₂)	17.000	16.000
SYLOID 244 (Synthetic Silica)	3.000	4.500
<u>Part 4</u>		
Sodium Lauryl Sulphate powder	1.200	1.200
Flavour	1.000	1.000

The above formulations are prepared as follows:
 The components of Part 1 are mixed to solution form.
 Separately, the components of Part 2, except the water, are mixed to form a dispersion in the poly-

ethylene glycol/glycerin humectant, and the water then mixed in. Parts 1 and 2 are then combined, followed by consecutive addition, with suitable mixing, of Parts 3 and 4. These and the following formulations are designed to retain the anti-carries effect of the fluoride component substantially unaffected by the other components, and to produce no significant tooth erosion effects.

EXAMPLE 3

Employing the same procedure as in Examples 1 and 2, a toothpaste formulation is prepared in accordance with the present invention having the ingredients and proportions set out in Table 2 below.

TABLE 2

<u>Ingredient</u>	<u>Parts by weight</u>
Deionized water	37.578
Glycerin	25.000
Zeo 49B (Silicon Dioxide)	21.500
TKPP	4.500
TSPP	1.500
Syloid 244 (synthetic silica)	3.000
Sodium Lauryl Sulphate	1.200
Flavour	1.000
Gantrez S-97 Pharmaceutical Grade	1.000
Sodium Hydroxide (50% Solution)	1.000
Xanthan Gum	1.000
Sodium Benzoate	0.500
Titanium Dioxide	0.500
Sodium Saccharin	0.300
Sodium Fluoride	0.242

Examples 4 and 5 represent lozenge formulations according to the present invention.

EXAMPLE 4

Lozenge formulations are set out in Table 3 below.

TABLE 3

<u>Ingredients</u>	<u>Parts by Weight</u>
Sugar	75-98
Corn syrup	1-20
Flavour Oil	0.1-1.0
Tablet lubricant	0.1-5
TKPP:TSPP-3:1	3.5-8
Gantrez S-97	0.05-3
Sodium fluoride	0.01-0.05
Water	0.01-0.2

EXAMPLE 5

Lozenges are made up from the ingredients and proportions set out in Table 4 below.

TABLE 4

<u>Ingredients</u>	<u>Weight Percent</u>
Sodium saccharin	0.15
Flavour	0.25
Magnesium stearate lubricant	0.40
Colour	0.01
Emulsifying Agent ¹	1.00
Sodium fluoride	0.05
Gantrez S-97	0.30
TKPP:TSPP - 3:1	6.50
Sorbitol	Q.S. to 100

Note on Table 4

¹ PEG (40) Sorbitan Diisostearate.

EXAMPLE 6

Chewing gum formulations are set out in Table 5 below.

TABLE 5

<u>Ingredients</u>	<u>Parts</u>
Gum base	10 to 50
Binder	3 to 10
Filler (sorbitol, mannitol or combination thereof)	5 to 80
Artificial sweetener	0.1 to 5
TKPP:TSPP - 3:1	3.5 to 8
Gantrez S-97	0.1 to 1.0
Sodium fluoride	0.1-0.05
Flavour	0.1 to 5

All the above formulations have been designed to provide improved non-gritty and other cosmetic properties and to exert improved anticalculus effects in vivo.

The present 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.



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CLAIMS

1. An anticalculus oral composition in the form of a toothpaste, dental gel, toothpowder, dental tablet, chewing gum or lozenge comprising an orally acceptable vehicle and,

A. a mixture of tetrasodium pyrophosphate and tetrapotassium pyrophosphate of which the tetrapotassium pyrophosphate is a predominant portion such as to avoid the occurrence of gritty particles in the oral composition; and

B. an amount of a fluoride ion source sufficient to supply 25 ppm to 5,000 ppm of fluoride ions.

2. An oral composition comprising an orally acceptable aqueous vehicle and,

A. 4.3% to 7% of alkali metal pyrophosphates as essential anticalculus agent, comprising at least 4.3% of tetra potassium pyrophosphate, alone or admixed with up to 2.7% of tetrasodium pyrophosphate, and

B. an amount of a fluoride ion source sufficient to supply 25 ppm to 5,000 ppm of fluoride ions.

3. An oral composition comprising an orally acceptable aqueous vehicle and,

A. 4.3 to 7% of a mixture of tetrasodium pyrophosphate and tetrapotassium pyrophosphate in a respective ratio ranging from 2.7:4.3 to 1:6 containing at least 4.3% of tetrapotassium



pyrophosphate to avoid the occurrence of gritty particles of tetrasodium pyrophosphate in the composition, and

B. an amount of a fluoride ion source sufficient to supply 25 ppm to 5,000 ppm of fluoride ions.

4. A composition as claimed in Claim 1, 2 or 3 containing as an inhibitor against enzymatic hydrolysis of the pyrophosphate in saliva a synthetic anionic polymeric polycarboxylate having a molecular weight of 1,000 to 1,000,000, preferably 30,000 to 500,000.

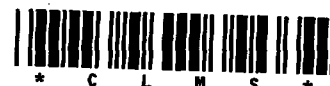
5. A composition as claimed in Claim 4 containing 0.05% to 3% of the said polycarboxylate.

6. A composition as claimed in any one of Claims 1 to 5 containing 4.5% tetrapotassium pyrophosphate and 1.5% tetrasodium pyrophosphate.

7. A composition as claimed in any one of Claims 4 to 6 containing 0.05% to 3% of the said polymeric carboxylate in the form of its water soluble alkali metal or ammonium salt.

8. A composition as claimed in any one of Claims 1 to 7 having a pH of 4.5 to 10.

9. A composition as claimed in any one of Claims 4 to 8 in which the said polymeric polycarboxylate is a linear polycarboxylate.



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10. A composition as claimed in Claim 9 in which the polycarboxylate is a copolymer of vinyl methyl ether and maleic acid or anhydride having a molecular weight of about 70,000.

11. A composition as claimed in any one of Claims 4 to 10 containing an amount of a fluoride ion source sufficient to supply 800 to 1,500 ppm of fluoride ions and 0.1 to 2% of the polycarboxylate.

12. A composition as claimed in any one of Claims 1 to 11 in which the said fluoride ion source comprises sodium fluoride.

13. A composition as claimed in any one of Claims 1 to 12 in the form of a toothpaste, gel or cream further containing a dentally acceptable polishing agent.

14. A composition as claimed in Claim 13 containing a dentally acceptable silica polishing agent.

15. A composition as claimed in Claim 1 substantially as specifically described herein with reference to any one of Examples 1 to 6.

16. A method of preparing a composition as claimed in any one of Claims 1 to 15 comprising mixing together the components specified in the said claims.
