

United States Patent

Widder et al.

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[54] ORAL COMPOSITIONS FOR CALCULUS RETARDATION

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[58] Field of Search 424/204, 52; 260/502.4 P

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[57]

ABSTRACT

Oral compositions, such as toothpaste, mouthwash, and the like, containing certain polyphosphonates as anticalculus agents, and a water-soluble source of fluoride ions to counteract the adverse effects of such polyphosphonates on post eruptive maturation of dental enamel.

13 Claims, No Drawings

ORAL COMPOSITIONS FOR CALCULUS RETARDATION

BACKGROUND OF THE INVENTION

The field of this invention is "oral compositions" which term is used herein to designate products which in the ordinary course of usage are retained in the oral cavity for a time and in a manner sufficient to contact substantially all of the dental surfaces, but are not intentionally ingested. Such products include, for example, dentifrices, mouthwashes, prophylaxis pastes and topical solutions.

A number of chemical and biological agents have been suggested in the art to retard calculus formation or to remove calculus after it is formed. Mechanical removal of this material periodically by the dentist is of course routine dental office procedure. The chemical approach to calculus inhibition generally involves chelation of calcium ion which prevents the calculus from forming and/or breaks down mature calculus by removing calcium. A number of chelating agents have been employed for this purpose. See, for example, British Patent 490,384, granted Feb. 15, 1937, which discloses oral compositions containing ethylenediaminetetraacetic acid, nitrilotriacetic acid, and related compounds as anticalculus agents; German Auslegeschrift Pat. No. 1,149,138, published May 22, 1963, which discloses certain water-soluble diglycolates as anticalculus agents; and U.S. Patent No. 1,516,206 which discloses oral compositions containing various sugar lactones for this purpose.

Although certain of the art-disclosed chelators are purportedly safe for use on dental enamel, the chemical similarity of calculus to the tooth structure limits the usefulness of the chelation approach since the more effective chelators can serious damage the tooth structure by decalcification. Thus, the development of oral compositions which effectively retard calculus by calcium chelation has been impeded by safety considerations.

Safe and effective oral compositions for calculus inhibition are disclosed and claimed in the copending application of Nathaniel B. Tucker and Homer W. McCune, Ser. No. 731,312 filed May 22, 1968, now U.S. Pat. No. 3,488,419. The polyphosphonate anticalculus agents of Tucker et al. inhibit calculus formation by interfering with the conversion of the calculus precursor, amorphous calcium phosphate, to crystalline calcium hydroxyapatite. Because these agents do not function by chelation of calcium, they do not demineralize or substantially alter the structure of mature teeth. It has been found, however, that the polyphosphonate anticalculus agents impede or prevent post eruptive maturation of dental enamel.

The maturation of dental enamel is characterized by the gradual influx of those mineral salts which are ultimately present in the mature enamel, followed by crystallization of these salts. Since crystallization is a first step in enamel maturation, the polyphosphonates impede or prevent maturation by interfering with calcium hydroxyapatite crystallization in much the same manner that they inhibit calculus formation.

Thus, the compositions of Tucker et al. are preferably employed by individuals over about thirteen years of age since dentition and post eruptive maturation of dental enamel is generally complete at that age.

SUMMARY OF THE INVENTION

It has now been discovered that a water-soluble source of fluoride ion can be used in conjunction with certain polyphosphonic acids and salts (referred to collectively hereinafter as "polyphosphonates") to provide effective anticalculus compositions which neither alter the structure of mature dental enamel nor interfere with post eruptive maturation.

Operable polyphosphonates for use in the compositions of this invention are characterized in that their molecular structure contains at least two gem- or at least three vicinal phosphono groups. Surprisingly it has been found that fluoride ion has no effect on the activity of such polyphosphonates in retarding calculus formation but does permit the post eruptive maturation of dental enamel to follow its normal course.

Unlike inorganic polyphosphates such as pyrophosphates, the polyphosphonates employed in the compositions of this invention resist hydrolysis in aqueous products and therefore remain in an active form throughout the normal shelf-life of such products.

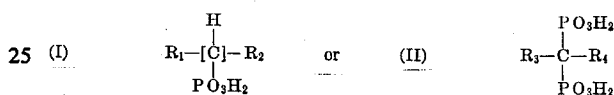
It is therefore an object of this invention to provide novel oral compositions which retard the formation of calculus without altering mature dental enamel or impeding post eruptive maturation of the tooth structure.

It is another object of this invention to provide an improved method for retarding the development of dental calculus.

Other objects will become apparent from the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

This invention is an oral composition effective in inhibiting the formation of dental calculus without adversely affecting the tooth structure or post eruptive maturation of dental enamel comprising (1) from about 0.01 percent to about 10 percent by weight of a polyphosphonate selected from the group consisting of those of the formulas:



wherein R_1 and R_2 are hydrogen or CH_2OH ; n is an integer of from 3 to 10; R_3 is hydrogen, alkyl containing from 1 to about 20 carbon atoms, alkenyl containing from 2 to about 20 carbon atoms, aryl (e.g., phenyl and naphthyl), phenylethenyl, benzyl, halogen (e.g., chlorine, bromine, and fluorine), amino, substituted amino (e.g., dimethylamino, diethylamino, N -hydroxy- N -ethylamine, acetylamine), $-\text{CH}_2\text{COOH}$, $-\text{CH}_2\text{PO}_3\text{H}_2$, $-\text{CH}(\text{PO}_3\text{H}_2)(\text{OH})$ or $-\text{CH}_2\text{CH}(\text{PO}_3\text{H}_2)_2$; R_4 is hydrogen, lower alkyl (e.g., methyl, ethyl, propyl and butyl), amino, benzyl, halogen (e.g., chlorine, bromine and fluorine), hydroxy, $-\text{CH}_2\text{COOH}$, $-\text{CH}_2\text{PO}_3\text{H}_2$, or $-\text{CH}_2\text{CH}_2\text{PO}_3\text{H}_2$; or a pharmaceutically acceptable salt thereof such as alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., calcium and magnesium), and ammonium or low molecular weight substituted ammonium (e.g., mono-, di-, and triethanolammonium) salts, and (2) a water-soluble source of fluoride ion in a quantity sufficient to provide a mole ratio of polyphosphonate to fluoride ion within the range from about 0.1 to 5.0, the pH of the composition being within the range from about 5.0 to about 11.0.

Operable polyphosphonates of the above formula (I) include propane-1,2,3-triphosphonic acid; butane-1,2,3,4-tetraphosphonic acid; hexane-1,2,3,4,5,6-hexaphosphonic acid; hexane-1-hydroxy-2,3,4,5,6-pentaphosphonic acid; hexane-1, 6-dihydroxy-2,3,4,5-tetraphosphonic acid; pentane-1,2,3,4,5-pentaphosphonic acid; heptane-1,2,3,4,5,6,7-heptaphosphonic acid; octane-1,2,3,4,5,6,7,8-octaphosphonic acid; nonane-1,2,3,4,5,6,7,8,9-nonaphosphonic acid; decane-1,2,3,4,5,6,7,8,9,10-decaphosphonic acid; and the pharmaceutically acceptable salts of these acids, e.g., sodium, potassium, calcium, magnesium, ammonium, triethanolammonium, diethanolammonium, and monoethanolammonium salts.

Propane-1,2,3-triphosphonic acid and salts thereof can be prepared by a process disclosed in the commonly assigned copending application of D. Allan Nicholson and Darrel Campbell, Ser. No. 694,002, filed Dec. 27, 1967.

Butane-1,2,3,4-tetraphosphonic acid and salts thereof can be prepared by a process disclosed in the commonly assigned copending application of D. Allan Nicholson and Darrel Campbell, Ser. No. 694,003, filed Dec. 27, 1967.

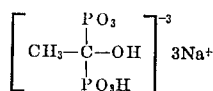
The higher aliphatic vicinal polyphosphonates and salts thereof can be prepared by the process disclosed in the commonly assigned copending application of D. Allan Nicholson and Darrel Campbell, Ser. No. 693,898, filed Dec. 27, 1967.

Among the operable polyphosphonates encompassed by the above formula (II) are ethane-1-hydroxy-1,1-diphosphonic

acid; methanediphosphonic acid; methanhydroxydiphosphonic acid; ethane-1,1,2-triphosphonic acid; propane-1,1,3,3-tetraphosphonic acid; ethane-2-phenyl-1,1-diphosphonic acid; ethane-2-naphthyl-1,1-diphosphonic acid; methanephenyldiphosphonic acid; ethane-1-amino-1,1-diphosphonic acid; methanedichlorodiphosphonic acid; nonane-5,5-diphosphonic acid; n-pentane-1,1-diphosphonic acid; methanedifluorodiphosphonic acid; methanedibromodiphosphonic acid; propane-2,2-diphosphonic acid; ethane-2-carboxy-1,1-diphosphonic acid; propane-1-hydroxy-1,1,3-triphosphonic acid; ethane-2-hydroxy-1,1,2-triphosphonic acid; ethane-1-hydroxy-1,1,2-triphosphonic acid; propane-1,3-diphenyl-2,2-diphosphonic acid; nonane-1,1-diphosphonic acid; hexadecane-1,1-diphosphonic acid; pent-4-ene-1-hydroxy-1,1-diphosphonic acid; octadec-9-ene-1-hydroxyl-1,1-diphosphonic acid; 3-phenyl-1,1-diphosphonoprop-2-ene; octane-1,1-diphosphonic acid; dodecane-1,1-diphosphonic acid; phenylaminomethanediphosphonic acid; naphthylaminomethanediphosphonic acid; N,N-dimethylaminomethanediphosphonic acid; N-(2-hydroxyethyl)-aminomethanediphosphonic acid; N-acetylaminomethanediphosphonic acid; aminomethanediphosphonic acid; and the pharmaceutically acceptable salts of these acids, e.g., sodium, potassium, calcium, magnesium, ammonium, triethanolammonium, diethanolammonium and monoethanolammonium salts.

Mixtures of any of the foregoing polyphosphonic acids and/or salts can be used in the compositions of this invention.

Ethane-1-hydroxy-1,1-diphosphonic acid, an especially preferred polyphosphonate, has the molecular formula $\text{CH}_3\text{C}(\text{OH})(\text{PO}_3\text{H}_2)_2$. (According to nomenclature by radicals, the acid might also be named 1-hydroxyethylidene diphosphonic acid.) The most readily crystallizable salt of the this acid is obtained when three of the acid hydrogens are replaced by sodium. Preferred salts for the purpose of this invention are the trisodium hydrogen salt which has the structure:



and the disodium salt.

The trisodium hydrogen salt normally crystallizes as the hexahydrate which loses some water during air-drying to yield a mixture of the hexa- and monohydrate averaging 3 to 4 molecules of water of hydration.

While any pharmaceutically acceptable salt of ethane-1-hydroxy-1,1-diphosphonic acid can be used in the practice of this invention, the tetrasodium salt, the trisodium hydrogen salt, the disodium dihydrogen salt, the monosodium trihydrogen salt, the monocalcium salt and the mixtures thereof are preferred. The other pharmaceutically acceptable salts and mixtures thereof are also suitable. These compounds can be prepared by any suitable method, however, an especially preferred method is disclosed in copending application Ser. No. 553,648, filed May 31, 1966, by Oscar T. Quimby et al, now U.S. Pat. No. 3,400,149.

Methanhydroxydiphosphonic acid and related compounds operable herein can be prepared, for example, by reaction of phosgene with an alkali metal dialkyl phosphite. A complete description of these compounds and the method for preparing same is found in copending patent application Ser. No. 517,073, filed Dec. 29, 1965, by Oscar T. Quimby, now U.S. Pat. No. 3,422,137.

Methanediphosphonic acid and related compounds useful herein are described in detail in U.S. Pat. No. 3,213,030, granted Oct. 19, 1965. A preferred method of preparing such compounds is disclosed in copending application Ser. No. 218,862, filed Aug. 23, 1962, by Clarence H. Roy, now U.S. Pat. No. 3,251,907.

Ethane-1,1,2-triphosphonic acid and related compounds which can be used in the compositions of this invention, as well as a method for their preparation are fully described in copending patent application Ser. No. 602,161, filed Dec. 16, 1966, by Oscar T. Quimby.

Propane-1,1,3,3-tetraphosphonic acid and related compounds useful herein, and a method for preparing same are fully disclosed in copending application Ser. No. 507,662, filed Nov. 15, 1965, by Oscar T. Quimby, now U.S. Pat. No. 3,400,176.

Pentane-2,2-diphosphonic acid and related compounds can be prepared in accordance with the method described by G. M. Kosolopoff in J. Amer. Chem. Soc., 75, 1500 (1953).

The concentration of polyphosphonate in the oral compositions of this invention can range from about 0.01 percent to about 10 percent by weight. Oral compositions which in the ordinary course of usage could be accidentally ingested should contain lower concentrations of polyphosphonate. Thus, a mouth wash in accordance with this invention preferably contains less than about 3 percent by weight of polyphosphonate. Dentifrice compositions, topical solutions and prophylaxis pastes, the latter to be administered professionally, can contain up to about 10 percent by weight, preferably from about 0.1 percent to about 5.0 percent by weight of polyphosphonate.

A wide variety of fluoride salts can be used in the compositions of this invention. Specifically, any water-soluble fluoride salt which is capable of providing at least 25 p.p.m. of fluoride ion in aqueous solution can be used to realize the benefits of this invention.

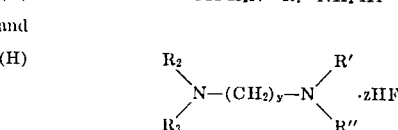
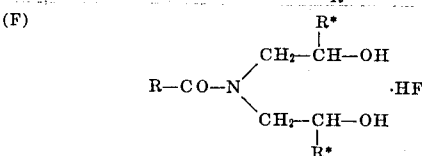
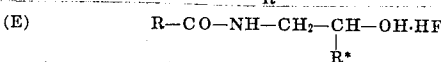
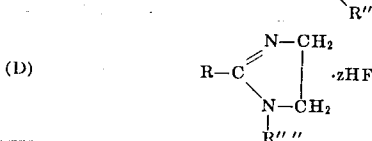
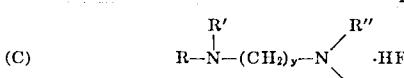
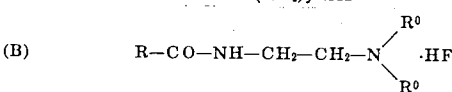
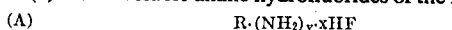
Among the fluoride salts contemplated for use in this invention are the following:

INORGANIC FLUORIDES

Stannous fluoride	Stannous fluorozirconate
Sodium fluoride	Lead fluoride
Potassium fluoride	Ferric fluoride
Lithium fluoride	Nickel fluoride
Cesium fluoride	Palladium fluoride
Ammonium fluoride	Silver fluoride
Aluminum fluoride	Zinc fluoride
Cupric fluoride	Zirconium fluoride
Indium fluoride	

ORGANIC FLUORIDES

(I) Water-soluble amine hydrofluorides of the formula:



wherein R is a member selected from the group consisting of alkyl, alkoxy, alkenyl, alkylol and aralkyl radicals of not more than 20 carbon atoms; x is a positive integer of at most three; y is a positive integer of at most three; R^o is a member selected from the group consisting of hydrogen, alkyl, alkenyl, alkylol, aralkyl and cycloalkyl radicals; each of R', R'', and R''' is a member selected from the group consisting of hydrogen, alkyl, alkoxy, alkylol, alkenyl, acyl, aralkyl, and cycloalkyl radicals; R'''' is a member selected from the group consisting of hydrogen, alkyl, acyl, alkenyl, alkylol, aralkyl and cycloalkyl radicals; R* is a member selected from the group consisting of hydrogen and lower alkyl radicals; R₁ is an alkylene radical of not more than 20 carbon atoms; R₂ is a member selected from the group consisting of alkyl and alkenyl radicals of not more than 20 atoms; R₃ is a member selected from the group consisting of alkyl, alkoxy, acyl, alkenyl, alkylol, aralkyl and cycloalkyl radicals; and z is a positive integer of at most two.

Examples of amine hydrofluorides which are encompassed by the above formulas and are suitable for use in the compositions of this invention are:

Hexylamine hydrofluoride
Laurylamine hydrofluoride
Myristylamine hydrofluoride
Decanolamine hydrofluoride
Octadecenylamine hydrofluoride
Myristoxyamine hydrofluoride
Diethylaminoethyloctoylamide hydrofluoride
Diethanolaminoethyloleylamide hydrofluoride
Diethanolaminopropyl-N'-octadecenylamine dihydrofluoride
1-ethanol-2-hexadecylimidazoline dihydrofluoride
Octoylethanolamine hydrofluoride

Those compounds of this class which contain at least one hydrocarbon radical such as an alkyl, alkylol, alkenyl or alkylene radical having from eight to 20 carbon atoms are especially preferred for use in the compositions of this invention because of their surface active properties. These and other operable amine hydrofluorides as well as a method for their preparation are disclosed by Schmid et al. in U.S. Pat. No. 3,083,143, granted March 26, 1963.

(II) Water-soluble quaternary ammonium fluorides having an atomic grouping of the formula:



where R represents an alkyl, alkenyl, alkylol, alkoxyalkyl, aryl, aryloxyalkyl, aralkyl, cycloalkyl, cycloalkenyl or heterocyclic radical, or an additional quaternary ammonium radical which may be attached to the nitrogen atom by a bridging group, or a radical of the formula -R₄CO-Y where Y represents OH, alkoxy, cycloalkoxy, aralkoxy or



where R₄ stands for an alkylene or arylenealkylene radical and each of the symbols R₅ and R₆ represents hydrogen, or an alkyl, alkenyl, alkylol, aryl, aralkyl, cycloalkyl or heterocyclic radical, or R₅ and R₆ form together with the nitrogen atom a heterocyclic nucleus, each one of the three free valences being satisfied by an alkyl, alkenyl, alkylol, alkoxyalkyl, aryl, aryl oxyalkyl, aralkyl, cycloalkyl, or heterocyclic, radical, or two of the free valences being satisfied by a group forming, together with the nitrogen atom, a saturated or unsaturated, unsubstituted or substituted heterocyclic nucleus. The following are specific examples of operable fluorides of this class:

Octyltrimethylammonium fluoride, dodecylethyldimethylammonium fluoride, tetraethylammonium fluoride, dilauryldimethylammonium fluoride, Δ^{8,9}-octadecenylbenzyl-dimethylammonium fluoride, dioctyldiethylammonium fluoride, cyclohexylcetyldimethylammonium fluoride, furfuryllauryldimethylammonium fluoride, phenoxyethylcetyldimethylammonium fluoride, N:N'-tetramethyl-N:N'-dilaurylene-diammonium difluoride, N-cetylpyridinium fluoride, N:N-dilaurylmorpholinium fluoride, N-myristyl-N-ethylmorpholinium fluoride, N-(octylaminocarbonyl)-N-benzyl-dimethylammonium fluoride, N-β-hydroxydodecyl-trimethylammonium fluoride, N-phenyl-N-hexadecyldimethylammonium fluoride, N-cyclohexyl-N-octadecyldimethylammonium fluoride, N-(2-carbomethoxyethyl)-N-benzyl-dimethylammonium fluoride, N-(2-carbocyclohexoxyethyl)-N-myristyldimethylammonium fluoride, N-(2-carbobenzoyloxyethyl)-N-dodecyldimethylammonium fluoride, N-[2-(N:N'-diethylaminocarbonyl)-ethyl]-N-dodecyldimethylammonium fluoride, N-carboxymethyl-N-eikosyldimethylammonium fluoride, etc. This class of compounds and methods for their preparation are disclosed in British Pat. No. 865,272.

Compounds of the formula

(HOC_xH_{2x})_nN+(C_yH_{2y+1})_{4-n}F- wherein x and y are each integers from 1 to 4, and n is an integer from 1 to 3, are encompassed by the above described class but have a greatly reduced tendency to cause sub-surface demineralization of dental enamel. These compounds, including, for example, dimethyldiethanolammonium fluoride, trimethylethanolammonium fluoride, and methyltriethanolammonium fluoride, can be used to special advantage in conjunction with the polyphosphonates in the compositions of this invention.

(III) Water-soluble addition compounds of amino acids and hydrofluoric acid or fluorides.

Examples of this class or fluorides include:

Betaine hydrofluoride
Sarcosine stannous fluoride
Alanine stannous fluoride
Glycine potassium fluoride
Sarcosine potassium fluoride
Glycine hydrofluoride
Lysine hydrofluoride
Alanine hydrofluoride
Betaine zirconium fluoride

Additional operable examples of this class of compounds as well as a method for their preparation are disclosed by Schmid in Canadian Patent No. 594,553, granted March 15, 1960.

The concentration of fluoride salt employed in the compositions of this invention will vary with the amount of fluoride ion provided by the particular salt and the concentration of polyphosphonate employed therein. It is essential that an amount of fluoride salt be employed which is sufficient to yield a mole ratio of polyphosphonate to fluoride ion within the range from about 0.1 to 5.0. If this ratio is greater than about 5.0, post eruptive maturation of dental enamel will be impeded. Toxicity considerations dictate the lower ratio limit inasmuch as the amount of polyphosphonate which can be employed to maintain a ratio below this limit while maintaining a safe level of fluorine in the composition is insufficient to provide the desired anticalculus effects.

The pH of the compositions of this invention is preferably maintained within the range from about 5 to 11. Below about pH 5.0 certain of the fluorides salts and/or polyphosphonates of this invention can damage dental enamel. Above about pH 11.0 the fluoride salts become less effective in promoting post eruptive maturation of dental enamel. A most preferred pH range is from about 6.0 to 7.5.

In addition to the essential components of the oral compositions of this invention as described in the foregoing, such compositions can also contain carriers suitable for use in the oral cavity. Such carriers include the usual components of

toothpaste, toothpowder, mouthwash, prophylaxis pastes and the like as more fully described hereinafter.

A dentifrice, especially toothpaste, containing a polyphosphonate is a preferred embodiment of this invention. Toothpaste compositions conventionally contain abrasive materials, sudsing agents, binders, humectants, flavoring and sweetening agents.

The abrasive materials and other adjuncts used in the practice of this invention are preferably not sources of much soluble calcium so that the crystal growth inhibiting capacity of polyphosphonate is not depleted to an extent that its anticalculus activity is impaired. Thus, conventional abrasives such as dicalcium orthophosphate and calcium carbonate are preferably not used. However, predominantly β -phase calcium pyrophosphate prepared in accordance with the teachings of Schweizer, U.S. Pat. No. 3,112,247, granted Nov. 26, 1963, which contains relatively little soluble calcium can be used. An especially preferred class of abrasives for use herein are the particulate thermosetting polymerized resins as described by Cooley et al. in U.S. Pat. No. 3,070,510, granted Dec. 25, 1962. Suitable resins include, for example, melamines, phenolics, ureas, melamine-ureas, melamine-formaldehydes, urea-formaldehydes, melamine-urea-formaldehydes, cross-linked epoxides, and cross-linked polyesters.

Other suitable abrasives include alumina and the insoluble non-calcium metaphosphates such as sodium metaphosphate. Mixtures of abrasives can also be used. In any case, the total amount of abrasive in the dentifrice embodiments of this invention can range from 0.5 to 95 percent by weight of the dentifrice. Preferably, toothpastes contain from 20 to 60 percent by weight of abrasive. Abrasive particle size preferably ranges from 2μ to 20μ .

Suitable sudsing agents are those which are reasonably stable and form suds throughout a wide pH range, preferably non-soap anionic organic synthetic detergents. Examples of such agents are water-soluble salts of alkyl sulfate having from 10 to 18 carbon atoms in the alkyl radical, such as sodium lauryl sulfate, water-soluble salts of sulfonated monoglycerides of fatty acids having from 10 to 18 carbon atoms, such as sodium monoglyceride sulfonates; salts of C_{10} - C_{18} fatty acid amides of taurine, such as sodium N-methyl-N-palmitoyl tauride; salts of C_{10} - C_{18} fatty acid esters of isethionic acid; and substantially saturated aliphatic acyl amides of saturated monoaminocarboxylic acids having two to six carbon atoms and in which the acyl radical contains 12 to 16 carbon atoms, such as sodium N-lauroyl sarcoside. Mixtures of two or more sudsing agents can be used.

The sudsing agent can be present in the dentifrice compositions of this invention in an amount from 0.5 to 5 percent by weight of the total composition.

In preparing toothpastes, it is necessary to add some thickening material to provide a desirable consistency. Preferred thickening agents are hydroxyethyl cellulose and water-soluble salts of cellulose ethers such as sodium carboxymethyl cellulose and sodium carboxymethyl hydroxyethyl cellulose. Natural gums such as gum karaya, gum arabic, and gum tragacanth can also be used. Colloidal magnesium aluminum silicate or finely divided silica can be used as part of the thickening agent to further improve texture. Thickening agents in an amount from 0.5 to 5.0 percent by weight of the total composition can be used.

It is also desirable to include some humectant material in a toothpaste to keep it from hardening. Suitable humectants include glycerine, sorbitol, and other edible polyhydric alcohols. The humectant can comprise up to about 36 percent by weight of the toothpaste composition.

Suitable flavoring agents include oil of wintergreen, oil of peppermint, oil of spearmint, oil of sassafras, and oil of clove. Sweetening agents which can be used include saccharin, dextrose, levulose and sodium cyclamate.

Several representative oral compositions illustrating this invention are set forth in the following examples.

EXAMPLE I

A toothpaste was prepared by conventional means formulated as follows:

Component	% By Weight
Calcium pyrophosphate	39.00
Sorbitol (70% aqueous soln.)	20.00
Glycerine	10.00
Sodium coconut alkyl sulfate	1.84
Sodium carboxymethylcellulose	1.30
Magnesium aluminum silicates	0.40
Flavoring	0.90
Sodium saccharin	0.18
Sodium cyclamate	0.30
Sodium hydroxide (5 N.)	1.28
Sodium fluoride	0.22
Disodium ethane-1-hydroxy-1,1-diphosphonate	3.00
Water	Balance
Mole ratio polyphosphonate/fluoride	2.32
pH	6.7

The toothpaste of this example was tested in the Rat Calculus Test conducted as follows:

Ten groups of 20 to 21 day old Rolfmeyer-Sprague-Dawley strain rats, each group comprising 20 animals, one from each of 20 litters, sex random, were employed in this test. Five groups served as control groups and the others as the test groups. All of the animals were placed on a calculus-inducing diet consisting of 50 percent cornstarch, 32 percent non-fat dry milk, 3 percent liver powder, 5 percent celluloflour, 1 percent cottonseed oil, 5 percent powdered sucrose, 1 percent $CaCl_2 \cdot 2H_2O$, 2.7 percent $NaH_2PO_4 \cdot H_2O$, and 0.3 percent $MgSO_4$. Topical applications of a 1:1 aqueous slurry of the test dentifrice were administered to the teeth of each of the animals in the test group with a cotton swab twice daily for 9 days over a fifteen day experimental period. Similar applications of water were administered to each animal in the control group of animals during the experimental period.

At three day intervals one test and one control group of animals were sacrificed and their molars were graded for severity of calculus formation by measuring the area and depth of accumulation on each of the 36 dental surfaces examined in each animal. Grading was made on a 0-3 scale for each surface, 0 being no detectable calcified deposits, 3 being coverage of 50-100 percent of the surface with a thick deposit, and intermediate values representing gradations between these extremes. The total calculus score for each animal was determined by adding the grades for each of the 36 surfaces. The results of this experiment are set forth in Table 1 below.

TABLE 1

Treatment	CSSI*	% reduction	CSI**	% reduction
Control (3 days)	23.7		21.8	
Test (3 days)	10.2	56.9	9.6	56.0
Control (6 days)	36.9		28.3	
Test (6 days)	10.3	72.0	9.4	66.8
Control (9 days)	40.2		28.8	
Test (9 days)	8.9	77.8	8.1	71.9
Control (12 days)	37.1		27.1	
Test (12 days)	14.3	61.5	12.5	53.9
Control (15 days)	49.6		30.1	
Test (15 days)	15.4	69.0	13.4	55.5

*Calculus Surface Index — the number of surfaces with calculus

**Calculus Surface Severity Index — the area and depth of calculus

Comparison of the control and test animals with respect to CSI reveals that the test composition inhibited deposition of

calculus at each time interval studied. Moreover, once the calculus was deposited, the test composition significantly decreased its rate of growth as indicated by the lower CSSI score for the test group of animals with each time interval.

Examination of the test and control groups of animals reveals no difference in the extent of maturation of the dental enamel.

EXAMPLE II

Another toothpaste composition was prepared having a formulation essentially identical to that of Example I. This composition was tested together with a control composition without fluoride in the Rat Calculus Test as described above. The results (after 14 days treatment) are set forth in Table 2 below.

Example.....	Percent by weight												
	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII			
Component:													
Glycerine.....	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0			
Ethyl alcohol.....	16.5	16.5	16.5	16.5	16.5	16.5	16.5	16.5	16.5	16.5			
Tween 80*.....	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12			
Sodium saccharin.....	.045	.045	.045	.045	.045	.045	.045	.045	.045	.045			
Sodium cyclamate.....	.074	.075	.075	.075	.075	.075	.075	.075	.075	.075			
Flavor.....	.088	.088	.088	.088	.088	.088	.088	.088	.088	.088			
Mg, propane-1,2,3,3-tetraphosphonate.....	0.5												
Na, propane-2,2-diphosphonate.....		1.0											
(NH ₄) ₂ ethane-2-carboxy-1,1-diphosphonate.....			1.5										
Nonane-5,5-diphosphonic acid.....				1.75									
n-pentane-1,1-diphosphonic acid.....					2.0								
Ethane-2-phenyl-1,1-diphosphonic acid.....						2.25							
Pent-4-ene-1-hydroxy-1,1-diphosphonic acid.....							2.5						
Octadec-9-ene-1-hydroxy-1,1-diphosphonic acid.....								3.0					
Methanedichlorodiphosphonic acid.....									3.5				
3-phenyl-1,1-diphosphonoprop-2-ene.....										5.0			
Sodium fluoride.....	0.4	0.2	0.5	0.1	0.6	0.3	0.8	0.22	0.22	0.22			
Water.....													
Polyphosphonate/fluoride ratio.....	0.15	0.86	0.42	2.64	0.60	1.15	0.53	1.35	2.76	3.38			

TABLE 2

Treatment	CSSI	% reduction	CSI	% reduction
Test Toothpaste	21.4	57.3	17.9	43.2
Control Toothpaste	25.5	51.6	23.2	26.1
Blank Toothpaste*	52.6		31.4	

*A placebo toothpaste similar in formulation to the test and control toothpastes but containing no polyphosphonate nor fluoride.

It can be seen from the above results that fluoride does not interfere with the anticalculus effects of the polyphosphonates.

Example III

Yet another toothpaste is prepared in accordance with this invention, having the following composition:

Component	% By Weight
Precipitated urea/formaldehyde condensate (abrasive)	31.00
Sorbitol (70% aqueous soln.)	6.25
Glycerine	18.00
Sodium coconut alkyl sulfate	0.40
Sodium coconut monoglyceride sulfonate	0.75
Sodium carboxymethylcellulose	1.15
Magnesium aluminum silicates	0.40
Sodium saccharin	0.12
Flavoring	0.95
Methanediphosphonic acid	1.50
Stannous fluoride	0.40
Water	Balance
Mole ratio polyphosphate/fluoride 1.64	
pH adjusted to 7.5 with 5N-NaOH	

This composition is effective in retarding the formation of dental calculus when used in the conventional manner. Post eruptive maturation is not impeded by this composition; nor is mature dental enamel adversely effected thereby.

Several additional toothpastes are prepared having essentially the same composition as the toothpaste of Example III, but using the tetrasodium salt of ethane-1,1,2-triphosphonic acid; the pentasodium salt of propane-1,1,3-triphosphonic acid; the pentasodium salt of ethane-1-hydroxy-1,1,2-triphosphonic acid; the pentasodium salt of ethane-2-hydroxy-1,1,2-triphosphonic acid; ethane-2-naphthyl-1,1-diphosphonic acid; propane-1,2,3-triphosphonic acid; butane-1,2,3,4-tetraphosphonic acid; and hexane-1,2,3,4,5,6-hexaphosphonic acid, respectively, rather than methanediphosphonic acid, in a quantity sufficient to provide an equivalent mole ratio of polyphosphonate to fluoride. Each of these toothpastes effectively retard dental calculus formation without damaging dental enamel or impeding its maturation.

Several mouthwash compositions illustrating this invention are set forth in the following examples:

EXAMPLE XIV

A toothpowder which constitutes yet another embodiment of this invention has the following formulation:

Component	% By Weight
Calcium pyrophosphate	94.00
Sodium lauryl sulfate	1.30
Sodium saccharin	0.25
Flavoring	1.45
Palladium fluoride	1.50
Trisodium ethane-1-hydroxy-1,1-diphosphonate	1.50
Ratio polyphosphonate/fluoride	0.55

When diluted with water and brushed upon the teeth in the conventional manner, this composition has a pH of approximately 7.0. The composition retards the formation of calculus without damaging dental enamel or interfering with its maturation.

Similar results are secured when ammonium fluoride, titanium fluoride, strontium fluoride, zinc fluoride, or silver fluoride are used in the above composition in place of palladium fluoride, in an amount sufficient to provide an equivalent polyphosphonate/fluoride ratio.

The trisodium ethane-1-hydroxy-1,1-diphosphonate employed in the above formulation can be replaced by an equimolar amount of dipotassium ethane-1-amino-1,1-diphosphonate; dimagnesium ethane-2-carboxy-1,1-diphosphonate; phenylaminomethanediphosphonic acid; or N,N-dimethylaminomethanediphosphonic acid with substantially equivalent results.

EXAMPLE XV

A prophylaxis paste for use in the dental office for removal of stains and polishing the tooth surface after mechanical removal of calculus is formulated as follows:

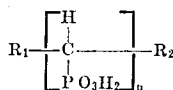
Component	Parts by Weight
Composition A:	
Navajo pumice	77.1
TiO ₂	4.0
Glycerine	17.757
Hydroxyethylcellulose	0.222
Sodium saccharin	0.326
Composition B:	
Methyltriethanolammonium fluoride	9.06
dodecyltrimethylammonium fluoride, lysine hydrofluoride, cetyl pyridinium fluoride, or laurylbenzyl dimethylammonium fluoride with substantially equivalent results.	0.255
Methanedibromodiphosphonic acid	87.00
Water	0.2
Ratio polyphosphonate/fluoride	

Immediately prior to use 5.5 gm. of composition A are mixed with composition B to attain the desired texture and adjusted to pH 7.0. The paste is then applied to the tooth surfaces with a rubber prophylactic cup in the conventional manner. This composition inhibits the reformation of calculus without adverse effects on dental enamel.

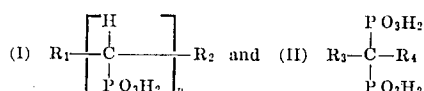
The methyltriethanolammonium fluoride employed in this example can be replaced by laurylamine hydrofluoride, dodecyltrimethylammonium fluoride, lysine hydrofluoride, cetyl pyridinium fluoride, or laurylbenzyl dimethylammonium fluoride with substantially equivalent results.

The methanedibromodiphosphonic acid of this example can be replaced by an equimolar amount of N-(2-hydroxyethyl)aminomethanediphosphonic acid; bis(triethanolammonium) N-acetylaminomethanediphosphonate; dicalcium aminomethanediphosphonate; diethanolammonium methanediethoxydiphosphonate; or tris(monoethanolammonium) nonane-1,1-diphosphonate with comparable results.

What is claimed is:



1. In an oral composition having a pH within the range from about 5.0 to 11.0 and containing from about 1.5% to about 3.0% by weight of an anticalculus agent which interferes with calcium hydroxyapatite crystal growth thereby impeding maturation of dental enamel, said anticalculus agent being selected from the group consisting of



wherein R₁ and R₂ are each hydrogen or CH₂OH; n is an integer of from 3 to 10; R₃ is hydrogen, alkyl containing from one to about 20 carbon atoms, alkenyl containing from two to about 20 carbon atoms, phenyl, naphthyl, phenylethenyl, benzyl, halogen, amino, dimethylamino, diethylamino, N-hydroxy-N-ethylamino, acetylaminomino, —CH₂COOH, —CH₂PO₃H₂, —CH(PO₃H₂)(OH) or —CH₂CH(PO₃H₂)₂; R₄ is hydrogen, lower alkyl, amino, benzyl, halogen, hydroxyl, —CH₂COOH, —CH₂PO₃H₂, or —CH₂CH₂PO₃H₂; or a pharmaceutically acceptable salt thereof, the improvement which comprises incorporating therein a non-toxic water-soluble source of fluoride ion in a quantity sufficient to provide a mole ratio of said anticalculus agent to fluoride ion within the range from about 0.1 to about 5.0, thereby promoting maturation of dental enamel and rendering said composition suitable for use by children.

2. An oral composition in accordance with claim 1 wherein the polyphosphonate is ethane-1-hydroxy-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof.

3. An oral composition in accordance with claim 1 wherein the polyphosphonate is methanediphosphonic acid or a pharmaceutically acceptable salt thereof.

4. An oral composition in accordance with claim 1 wherein the polyphosphonate is methanedichlorodiphosphonic acid or a pharmaceutically acceptable salt thereof.

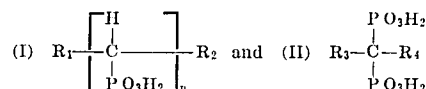
5. An oral composition in accordance with claim 1 wherein the polyphosphonate is methanediethoxydiphosphonic acid or a pharmaceutically acceptable salt thereof.

6. An oral composition in accordance with claim 1 wherein the polyphosphonate is phenylaminomethanediphosphonic acid or a pharmaceutically acceptable salt thereof.

7. An oral composition in accordance with claim 1 wherein the water-soluble source of fluoride ion is sodium fluoride.

8. An oral composition in accordance with claim 1 wherein the water-soluble source of fluoride ion is stannous fluoride

9. In a toothpaste composition having a pH within the range from about 5.0 to about 11.0 and containing from about 20 percent to about 60 percent by weight of a dentifrice abrasive and from about 1.5 percent to about 3 percent by weight of an anticalculus agent which interferes with calcium hydroxyapatite crystal growth thereby impeding maturation of dental enamel, said anticalculus agent being selected from the group consisting of

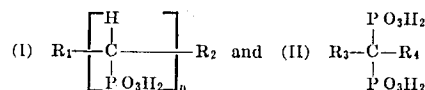


wherein R₁ and R₂ are each hydrogen or CH₂OH; n is an integer of from 3 to 10; R₃ is hydrogen, alkyl containing from one to about 20 carbon atoms, alkenyl containing from two to about 20 carbon atoms, phenyl, naphthyl, phenylethenyl, benzyl, halogen, amino, dimethylamino, diethylamino, N-hydroxy-N-ethylamino, acetylaminomino, —CH₂COOH, —CH₂PO₃H₂, —CH(PO₃H₂)(OH) or —CH₂CH(PO₃H₂)₂; R₄ is hydrogen, lower alkyl, amino, benzyl, halogen, hydroxyl, —CH₂COOH, —CH₂PO₃H₂, or —CH₂CH₂PO₃H₂; and the pharmaceutically acceptable salts thereof, the improvement which comprises incorporating therein a non-toxic water-soluble source of fluoride ion in a quantity sufficient to provide a mole ratio of anticalculus agent to fluoride ion within the range from about 0.1 to about 5.0, thereby promoting maturation of dental enamel and rendering said composition suitable for use by children.

10. A toothpaste composition in accordance with claim 9 wherein the polyphosphonate is ethane-1-hydroxy-1,1-diphosphonic acid or a pharmaceutically acceptable salt thereof.

11. A toothpaste composition in accordance with claim 9 wherein the water-soluble source of fluoride ion is sodium fluoride.

12. In a mouthwash composition having a pH within the range from about 5.0 to about 11.0 and containing water ethanol and glycerine and from about 0.1% to about 5.0% by weight of an anticalculus agent which interferes with calcium hydroxyapatite crystal growth thereby impeding maturation of dental enamel, said anticalculus agent being selected from the group consisting of



wherein R₁ and R₂ are each hydrogen or CH₂OH; n is an integer of from 3 to 10; R₃ is hydrogen, alkyl containing from one to about 20 carbon atoms, alkenyl containing from two to about 20 carbon atoms, phenyl, naphthyl, phenylethenyl, benzyl, halogen, amino, dimethylamino, diethylamino, N-hydroxy-N-ethylamino, acetylaminomino, —CH₂COOH, —CH₂PO₃H₂, —CH(PO₃H₂)(OH) or —CH₂CH(PO₃H₂)₂; R₄ is hydrogen, lower alkyl, amino, benzyl, halogen, hydroxyl, —CH₂COOH, —CH₂PO₃H₂, or —CH₂CH₂PO₃H₂; or a pharmaceutically acceptable salt thereof, the improvement which comprises incorporating therein a non-toxic water-soluble source of fluoride ion in a quantity sufficient to provide a mole ratio of said anticalculus agent to fluoride ion within the range from about 0.1 to about 5.0, thereby promoting maturation of dental enamel and rendering said composition suitable for use by children.

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13. In a toothpaste composition having a pH within the range from about 6.0 to 7.5 and containing from about 1.5 to 3.0 percent by weight of an anticalculus agent selected from the group consisting of ethane-1-hydroxy-1,1-diphosphonic acid and the pharmaceutically acceptable salts thereof, the improvement which comprises incorporating therein a non-

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toxic watersoluble source of fluoride ion in a quantity sufficient to provide a mole ratio of said anticalculus agent to fluoride ion within the range from about 0.1:1 to about 5.0 to 1.0, thereby promoting maturation of dental enamel and rendering said composition suitable for use by children.

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