United States Patent Office

3,737,522

Patented June 5, 1973

3,737,522

ORAL COMPOSITIONS FOR CALCULUS RETARDATION

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No Drawing. Filed June 30, 1970, Ser. No. 51,356
Int. Cl. A61k 7/16
U.S. Cl. 424—49 2 Claims

ABSTRACT OF THE DISCLOSURE

Oral compositions, such as toothpaste, mouthwash, and the like, containing certain carbonyldiphosphonates as herein defined which retard dental calculus formation without damaging tooth structure.

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 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.

Dental calculus, or tartar as it is sometimes called, is a deposit which forms on the surfaces of the teeth at the gingival margin. Supragingival calculus appears principally in the areas near the orifices of the salivary ducts; e.g., on the lingual surfaces of the lower anterior teeth and on the buccal surfaces of the upper first and second molars, and on the distal surfaces of the posterior molars.

Mature calculus consists of an inorganic portion which is largely calcium phosphate arranged in a hydroxyapatite crystal lattice structure similar to bone, enamel and dentine. An organic portion is also present and consists of desquamated epithelial cells, leukocytes, salivary sediment, food debris and various types of microorganisms.

As the mature calculus develops, it becomes visibly white or yellowish in color unless stained or discolored by some extraneous agency. In addition to being unsightly and undesirable from an aesthetic standpoint, the mature calculus deposits are constant sources of irritation of the gingiva and thereby are a contributory factor to gingivitis and other diseases of the supporting structures of the teeth, the irritation decreasing the resistance of tissues to endogenous and exogenous organisms.

A wide variety 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 Pat. 490,384, granted Feb. 15, 1937, which discloses oral compositions containing ethylenediaminetetraacetic acid, nitrilotriacetic acid and related compounds as anticalculus agents; German Auslegeschrift 1,149,138, published May 22, 1963, which discloses certain water-soluble diglycolates as anticalculus agents; and U.S. Pat. 1,561,206 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 seriously 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.

SUMMARY OF THE INVENTION

It has now been discovered that certain carbonyldiphosphonates possess the surprising capacity to retard the development of dental calculus without removing calcium from dental enamel or otherwise damaging the tooth structure when employed in oral compositions maintained within defined pH limits.

Unlike inorganic polyphosphates such as pyrophosphates, the carbonyldiphosphonates 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 otherwise affecting the tooth structure.

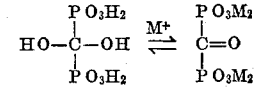
It is another object of this invention to provide an improved method for retarding the development of dental calculus.

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 comprising (1) from about .01% to about 10% by weight of a pharmaceutically acceptable carbonyldiphosphonate salt, such as alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., calcium and magnesium), non-toxic heavy metal (e.g., stannous and indium), and ammonium or low molecular weight substituted ammonium (e.g., mono-, di-, and triethanolammonium) salts; and (2) a carrier suitable for use in the oral cavity, the pH of said composition being in the range from about 5.0 to 11.0.

Upon neutralization, dihydroxymethanediphosphonic acid exists in equilibrum with the pharmaceutically acceptable carbonyldiphosphonate salt as follows:



When the salt-forming cation M replaces at least three of the acid hydrogens, the compound is predominantly in the carbonyldiphosphonate form. Unless otherwise specified, the term "carbonyldiphosphonate" as employed herein encompasses dihydroxymethanediphosphonic acid and salts as well as the carbonyldiphosphonate salts, collectively.

Carbonyldiphosphonates can be prepared in any convenient manner. A preferred method is disclosed by Oscar T. Quimby, U.S. Pat. 3,497,313, granted Feb. 24, 1970. The use of these compounds in inhibiting the anomalous deposition and mobilization of calcium phosphate by systemic administration is disclosed in the concurrently filed application of Marion D. Francis, Ser. No. 51,355, filed June 30, 1970.

The concentration of carbonyldiphosphonate in the oral compositions of this invention can range from about .01% to about 10% by weight. Oral compositions which in the ordinary course of usage could be accidentally ingested should contain lower concentrations of carbonyldiphosphonate. Thus, a mouthwash in accordance with this invention preferably contains less than about 3% by weight of carbonyldiphosphonate. Dentifrice compositions, topical solutions and prophylaxis pastes, the latter to be administered professionally, can contain up to about 10% by weight, preferably from about 0.1% to about 5.0% by weight of carbonyldiphosphonate.

The pH of the composition of this invention can range from about 5.0 to about 11. Below about pH 5.0 damage to the dental enamel can occur in spite of the relative safety of the carbonyldiphosphonates. Above about pH 11.0 difficulty is encountered in formulating products having satisfactory flavor and mildness. A preferred pH range is from about 7.0 to about 10. The pH of the composition, of course, is determinative of the predominant salt form of the carbonyldiphosphonates present therein.

While it is not intended that this invention be limited by a particular theory of operation, it has been observed that the carbonyldiphosphonates encompassed herein interfere with the progress of calculus formation by interfering with the conversion of amorphous calcium phosphate to crystalline calcium hydroxyapatite. Amounts of carbonyldiphosphonates which are much too small to chelate any appareciable quantities of calcium have been found to retard the formation of calcium hydroxyapatite. This selective action on the formative calculus deposits without demineralizing action on the dental enamel is surprising.

The efficacy of the compositions of this invention in calculus prophylaxis is demonstrated by the Rat Calculus and Crystal Growth Inhibition Tests which are conducted as follows:

Rat Calculus Study (Topical)

Two groups of 20 to 21-day old Holtzman-Sprague-Dawley strain rats, each group comprising one male and one female member of each of 10 litters, are employed in this test, one group serving as the control and the other serving as the test group. Both groups of animals are placed on a calculus inducing diet consisting of 63% cornstarch, 32% non-fat dry milk, 2% liver powder and 3% cellulflour. Topical applications of a 0.5% aqueous solution of the carbonyldiphosphonate to be tested, adjusted to pH 10,0, are made on the teeth of each of the animals in the test group for about one minute twice daily, five days per week for two weeks. Similar applications of water are made to each animal in the control group during the experimental period.

Three weeks after the commencement of the test, the animals are sacrificed and their molar are graded for severity of calculus by assessing the area and depth of accumulation on eacth of the 44 dental surfaces examined in each animal. Grading is made on a 0–3 scale for each surface, 0 being no detectable calcified deposits, 3 being coverage of 50–100% of the surface with a thick deposit and intermediate values representing gradations between these extremes. The total calculus score for each animal is determined by adding the grades for each of the 44 surfaces.

Substantial reductions in calculus formation are attained with topically applied compositions in accordance with this invention.

Crystal Growth Inhibition Determination

As hereinbefore stated, the carbonyldiphosphonates inhibit the growth of calcium hydroxyapatite crystals and in this way interfere with the normal formation of calcium hydroxyapatite from solution. The efficacy of carbonyldiphosphonates in inhibiting crystal growth was demonstrated by the Crystal Growth Inhibition Determination which was conducted as follows:

1 ml. of a 0.1 M stock solution of $NaH_2PO_4 \cdot H_2O$ was diluted with 22 ml. of distilled water. 1 ml. of an aqueous solution of tetrasodium carbonyldiphosphonate at a concentration sufficient to provide the desired ultimate concentration in the reaction mixture was added to the diluted NaH_2PO_4 solution and the solution was adjusted to pH 7.4 with sodium hydroxide. To this solution was added 1 ml. of a 0.1 M solution of $CaCl_2 \cdot 2H_2O$ preadjusted to pH 7.4 with sodium hydroxide. This mixture was held at a constant pH 7.4 throughout the reaction period.

After a sufficient reaction time as determined by the operator, generally within 90 minutes, the solution was filtered through a 0.45 Millipore filter pad. The precipitate was air-dried and analyzed by X-ray diffraction. The solid calcium phosphate precipitated from the above-described solution without a carbonyldiphosphonate gives a typical hydroxyapatite pattern, while the calcium phosphate precipitated under the same conditions but in the presence of small amounts of this representative carbonyldiphosphonate was amorphous to X-rays.

Those compounds which are effective in inhibiting the growth of hydroxyapatite crystals at concentrations of less than 1.5×10^{-3} M under the conditions of this test are found to inhibit anomalous mobilization and deposition of calcium phosphates in animal tissue, while several compounds outside the scope of this invention that have little or no effect in this test are ineffective in vivo.

When tested in the above-described manner carbonyldiphosphonate was found to inhibit crystal growth at a concentration of 2.3×10^{-4} M. Similar values are obtained when the other carbonyldiphosphonates encompassed by this invention are tested in like manner.

By way of comparison, ethylenediaminetetraacetic acid and nitrilotriacetic acid which have been suggested for use as anticalculus agents in the art fail to inhibit crystal growth at molar concentrations of 2.45×10^{-3}, respectively. At higher concentrations, these prior art compounds prevent precipitation of calcium phosphate in this test because of their powerful calcium sequestering properties.

A dentifrice, especially toothpaste, containing a carbonyldiphosphonate is 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 in the practice of this invention are preferably not sources of much soluble calcium so that the crystal growth inhibiting capacity of carbonyldiphosphonate 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. 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. 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% by weight of the dentifrice. Preferably, toothpastes contain from 20% to 60% 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 2 to 6 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% by weight of the total compositions.

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% 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% 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 of the following composition was prepared by conventional methods:

	Parts by weight
Water	31.58
Sorbitol	6.25
Saccharin	0.12
Calcium pyrophosphate [1]	39.00
Glycerine	18.00
Sodium alkyl (coconut) sulfate	0.40
Sodium coconut monoglyceride sulfonate	0.75
Sodium carboxymethyl cellulose	1.15
Magnesium aluminum silicates	0.40
Flavoring	0.85
Dihydroxymethanediphosphonic acid	1.50

pH 5.90.

[1] Prepared in accordance with U.S. Pat. 3,112,247, granted Nov. 26, 1963.

This composition effectively retards calculus formation without decalcifying dental enamel.

Toothpaste compositions substantially identical to the composition of Example I are prepared with tetrasodium carbonyldiphosphonate, tetrapotassium carbonyldiphosphonate, dimagnesium carbonyldiphosphonate, monocalcium disodium carbonyldiphosphonate and tetraammonium carbonyldiphosphonate, respectively, rather than dihydroxymethanediphosphonic acid, adjusting the pH to 5.9. These compositions substantially retard calculus formation and do not decalcify dental enamel.

EXAMPLE II

Yet another toothpaste was prepared having the following composition:

	Parts by weight
Water	39.58
Sorbitol	6.25
Saccharin	.12
Abrasive (precipitated urea/formaldehyde condensate)	31.00
Glycerine	18.00
Sodium alkyl (coconut) sulfate	.40
Sodium cococut monoglyceride sulfonate	.75
Sodium carboxymethyl cellulose	1.15
Magnesium aluminum silicate	.40
Flavoring	.95
Disodiumdipotassium carbonyldiphosphonate	1.50

pH 5.3.

When employed in the customary manner, this toothpaste retards the formation of dental calculus and no decalcification of dental enamel was observed after seven days' exposure.

Several additional toothpastes are prepared having essentially the same composition as the toothpaste of Example II, but using tetra(triethanolammonium)carbonyldiphosphonate, distannous carbonyldiphosphonate and diindium carbonyldiphosphonate, respectively, rather than disodium dipotassium carbonyldiphosphonate. The pH of these compositions is adjusted to 7.0. These toothpaste formulations effectively retard calculus formation on dental enamel without decalcifying same.

Several mouthwash compositions were prepared in accordance with this invention as follows:

	Parts by weight of example—			
Component	III	IV	V	VI
Glycerine	10.0	10.0	10.0	10.0
Ethyl alcohol	16.5	16.5	16.5	16.5
Water	67.172	67.172	67.172	70.192
Tween 80 [1]	.12	.12	.12	.12
Saccharin	.045	.045	.045	.02
Sodium cyclamate	.075	.075	.075	.04
Flavor	.088	.088	.088	.088
Carbonyldiphosphonate	[2] 3.0	[3] 3.0	[4] 3.0	[5] 1.0
pH [6]	7.0	8.5	10.0	10.0

[1] Polyoxyethylene (20 moles of ethylene oxide) sorbitan monooleate—a nonionic emulsifier supplied by Atlas Powder Company.
[2] Dihydroxymethanediphosphonic acid.
[3] Tripotassium carbonyldiphosphonate.
[4] Tetrasodium carbonyldiphosphonate.
[5] Tetraamonium carbonyldiphosphonate.
[6] Adjusted to value indicated with base corresponding to salt form of carbonyldiphosponate.

When used in the same manner as conventional mouthwash, at least once daily, each of the above compositions materially reduces accumulation of calculus on the surfaces of teeth. No decalcification is observed after several days exposure of dental enamel to these compositions.

EXAMPLE VI

A prophylaxis paste for use by the dentist for removal of stains and polishing the teeth after mechanical removal of calculus deposits is formulated as follows:

	Parts by weight
Navajo pumice	77.10
TiO_2	4.00
Glycerine	17.75
Hydroxyethylcellulose	.22
Saccharin	.33
Tetrasodium carbonyldiphosphonate	8.0

pH 8.0.

When applied to the teeth with a prophylactic rubber cup in the conventional manner, this composition retards the development of new calculus deposits.

Toothpowders and the like can be prepared by conventional methods and containing, in addition to the usual ingredients, an amount of carbonyldiphosphonate within the ranges specified herein, to provide an effective means

of retarding calculus formation without damaging the tooth structure.

Those components other than carbonyldiphosphonates which were included in the foregoing examples and various mixtures of those components are illustrative of carriers suitable for use in the oral cavity.

In the reference to pH adjustments in the foregoing examples, it is to be understood that a base of a cation corresponding to the salt form of the carbonyldiphosphonate employed is used to adjust to higher pH values. In each case in which the carbonyldiphosphonate was added in its acid form to the example compositions, the pH was adjusted to the specified higher value with NaOH. Adjustments in pH to more acid levels is accomplished with HCl acid. It will be obvious to those skilled in the art that pH adjustments can be made with any acid or base suitable for use in the oral cavity.

What is claimed is:

1. An oral composition effective in inhibiting the formation of dental calculus without adversely affecting tooth structure, comprising (1) from about 0.01% to about 10% by weight of a member selected from the group consisting of alkali metal carbonyldiphosphonates and alkaline earth metal carbonyldiphosphonates; and (2) a carrier

suitable for use in the oral cavity, the pH of the composition being within the range from about 5.0 to about 11.0

2. A toothpaste composition comprising (1) from about 0.01% to about 10% by weight of a member selected from the group consisting of alkali metal carbonyldiphosphonates and alkaline earth metal carbonyldiphosphonates; and (2) a carrier suitable for use in the oral cavity, the pH of the composition being within the range from about 5.0 to about 11.0.

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