

1

3,544,678

ORAL COMPOSITIONS FOR CARIES PROPHYLAXIS
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8 Claims

ABSTRACT OF THE DISCLOSURE

Oral compositions such as dentifrice, mouthwash, chewing gum, prophylaxis paste, etc. containing a water-soluble fluoride salt, a water-soluble stannous compound, and a water-soluble source of a complexing anion of hydroxyethylnitrilodiacetic acid, m-hydroxybenzoic acid, 1,2,3-propanetricarboxylic acid, or itaconic acid, the stannous complexes of said acids providing a stable and dental enamel-reactive source of stannous tin.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a division of applicant's copending application, U.S. Ser. No. 546,535, filed May 2, 1966.

This invention relates to improved oral compositions useful in caries prophylaxis. More particularly, it relates to stable oral compositions for caries prophylaxis which contain a water-soluble source of fluoride ion, stannous tin, and certain complexing anions.

By the term "oral composition" as used herein is meant a product which in the ordinary course of usage is not intentionally ingested, but is retained in the oral cavity for a time sufficient to contact substantially all of the dental surface. Such products include, for example, dentifrices, mouthwashes, chewing gums, and dental prophylaxis pastes and topical solutions for application in the dental surfaces. Such products include, for example, dentifrices herein contemplated do not require ingestion for anticaries effect.

The efficacy of fluoride in caries prophylaxis is well established, to the extent that the topical application of aqueous solutions of various water-soluble fluorides has become a routine procedure in many dental offices and clinics. Moreover, toothpaste compositions containing certain fluorides have recently been recognized as effective against caries by the American Dental Association.

It is known that certain metallic ions can have a significant effect on the anticariogenic efficacy of fluorides. For example, a body of scientific literature shows that the use of a source of stannous ions in conjunction with fluoride gives a more effective anticariogenic product than is attained with fluoride alone (J. C. Muhler et al., J. A. D. A. 51, 665 (1955)).

One of the problems which has developed in the formulation of stable oral compositions containing stannous tin is the propensity of this metal to oxidize to its higher valence state, hydrolyze to stannous hydroxide and/or react with other constituents of the composition to form very stable complexes or highly insoluble compounds. The occurrence of any of the foregoing can render the tin non-reactive with dental enamel.

Various approaches have been used to maintain stannous tin in an available form. For example, Norris et al., U.S. Pat. 2,946,725, granted July 26, 1960 teach the use of a sparingly soluble stannous salt such as stannous pyrophosphate as a "reservoir" of stannous ion, to be used in conjunction with water-soluble stannous compounds such as stannous fluoride. As stannous ion de-

2

rived from the soluble salt becomes unavailable through hydrolysis, etc., the sparingly soluble stannous compound slowly dissolves to yield replacing stannous ion.

Holliday et al. in U.S. Pat. 3,105,798, granted Oct. 1, 1963, discloses an advance over Norris et al. involving the maintenance of available stannous tin by complexing this metal ion with an aldinate to form a water-soluble stannous aldinate. Such complexes are sufficiently stable to prevent inactivation by hydrolysis, and the like, but do not prevent reaction of the complexed stannous tin with the dental enamel.

Although both approaches to the problem provide oral compositions which are stable and effective, the Holliday et al. approach, i.e., provision of stannous tin in a water-soluble complex, is preferable because the preponderance of the total reactive stannous tin in the composition is then available to react with the dental enamel at any point in time during the shelf life of the composition.

Although the stannous aldinate complex of Holliday et al. is a satisfactory means of maintaining stannous tin in an available form, considerable difficulty has been experienced in flavoring dentifrice products containing such complexes. Stannous gluconate, for example, has an unpleasant burnt caramel flavor which places severe restrictions on the flavoring materials which can be used in formulations containing same. Indeed, only a relatively few flavoring oils serve to mask this flavor.

Stannous chelates of alkylene polyamine carboxylic acid chelating agents such as ethylenediaminetetraacetic acid are disclosed for use in oral preparations in British Pat. 92,385, published Mar. 27, 1963. Such chelates have been found to substantially impair the reactivity of stannous tin with dental enamel and are therefore of limited value in fluoride-containing oral compositions for caries prophylaxis.

It is an object of this invention to provide improved oral compositions for caries prophylaxis containing stannous tin in a form which resists hydrolysis and conversion to inactive species.

It is a further object of this invention to provide an oral composition which contains a high level of stannous tin in a form which is reactive with dental enamel throughout the life of the composition.

It is a still further object of this invention to provide oral compositions containing high levels of stannous tin in a stable and dental enamel-reactive form, which are adaptable to flavoring by a wide variety of flavoring oils.

These and other objects will become apparent from the following description.

It has now been discovered that stannous tin [Sn(II)] forms water-soluble complexes with certain complexing anions (as defined hereinafter) which are sufficiently stable to prevent hydrolysis and conversion of Sn(II) to inactive species, but which are highly reactive with dental enamel. These complexes are relatively flavorless; thus, oral compositions having excellent flavor characteristics can be prepared therefrom.

In general, this invention comprises an oral composition for caries prophylaxis containing a water-soluble fluoride, a water-soluble source of stannous tin, and a complexing anion of a member selected from the group consisting of hydroxyethylnitrilodiacetic acid, m-hydroxybenzoic acid, 1,2,3-propanetricarboxylic acid, and itaconic acid, the molar ratio of said complexing anion to stannous tin being in the range from about 10:1 to 1:100, the pH of said composition being from about 2.5 to 7.0.

A wide variety of fluorides can be used in the compositions of this invention. Specifically, any water-soluble fluoride 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	Lead fluoride
Sodium fluoride	Ferric fluoride
Potassium fluoride	Nickel Fluoride
Lithium fluoride	Palladium fluoride
Cesium fluoride	Silver fluoride
Ammonium fluoride	Zinc fluoride
Aluminum fluoride	Zirconium fluoride
Cupric fluoride	

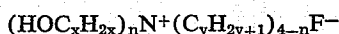
ORGANIC FLUORIDES

(I) Water-soluble amine hydrofluorides such as the following:

Hexylamine hydrofluoride
Laurylamine hydrofluoride
Myristylamine hydrofluoride
Decanolamine hydrofluoride
Octadecenylamine hydrofluoride
Myristoxylamine hydrofluoride
Diethylaminoethyloctylamide hydrofluoride
Diethanolaminoethyloleamide hydrofluoride
Diethanolaminopropyl-N'-octadecenylamine dihydrofluoride
1-ethanol-2-hexadecylimidazoline dihydrofluoride
Octylethanolamine hydrofluoride

Those compounds of this class which contain at least one hydrocarbon radical such as an alkyl, alkylol, alkenyl or alkylene radical having from 8 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. 3,083,143, granted Mar. 26, 1963.

(II) Compounds of the formula



wherein x and y are each integers from 1 to 4, and n is an integer from 1 to 3. Such compounds include, for example, dimethyldiethanol ammonium fluoride, trimethylethanol ammonium fluoride, and methyltriethanol ammonium fluoride. Further examples and methods of preparing these compounds are found in U.S. Pat. 3,235,459, granted Feb. 15, 1966.

(III) Water-soluble addition compounds of amino acids and hydrofluoric acid or fluorides.—Examples of this class of 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 Pat. 594,553, granted Mar. 15, 1960.

The quantity of fluoride salt employed in the compositions of this invention must be sufficient to provide at least about 25 parts of fluoride ions per million parts of the total composition. Extremely large amounts of fluoride ions do not appreciably enhance the desirable properties of the composition and may cause it to have toxic effects. Accordingly, the compositions of this invention do not contain a total of more than 4,000 parts fluoride ion per million parts of the total composition, and in the case of dentifrice compositions, preferably not more than about 3,000 parts per million.

Stannous tin can be provided as a complex of stannous tin and a complexing anion of the group herein defined, or by any water-soluble non-toxic stannous compound which will react with said complexing anions to form such stannous complexes. However, preferred sources of stannous tin for the purpose of this invention are stannous fluoride, stannous chloride, stannous hydroxyethylnitrilodiacetate, stannous *m*-hydroxybenzoate, stannous 1,2,3-propanetricarboxylate, and stannous itaconate. Mixtures of the foregoing stannous compounds can be used.

Preferably, stannous fluoride is used as a source of stannous tin, in a quantity sufficient to provide at least 300 p.p.m. of stannous tin and not more than 4,000 p.p.m. fluoride. In any event, the total stannous tin content must be from about 15 to about 10,000 p.p.m., the preferred range being from about 50 to about 8,000 p.p.m.

Complexing anions can be introduced into the compositions of this invention either in their free acid form or as a salt or complex of a cation having a stability constant which is less than the formation constant of the corresponding stannous complex, or as a stannous complex of the complexing anion. A preferred form for introducing the complexing anion is by way of the stannous complex, thereby providing two essential components with a single compound.

Among the salts of complexing anions which can be used in the compositions of this invention are the alkali metal (e.g., sodium and potassium), ammonium, and substituted ammonium (e.g., mono-, di- and triethanolammonium) salts of hydroxyethylnitrilodiacetic acid, *m*-hydroxybenzoic acid, 1,2,3-propanetricarboxylic acid, and itaconic acid. When combined with the other ingredients in the aqueous oral compositions of this invention, these water-soluble salts react with stannous tin to form the desired complexes of this metal in situ.

As hereinbefore disclosed, the quantity of complexing anion employed in the compositions of this invention must be sufficient to provide a molar ratio of complexing anion to total stannous tin of from about 10:1 to 1:100. If this ratio is less than about 1:100, adequate levels of protected stannous tin are not provided, even though high concentrations of stannous tin are used. Quantities of complexing anion greater than required to provide a 10:1 ratio, serve no useful purpose and can be detrimental to the physical properties and sudsing and flavor characteristics of the product. Preferably, the molar ratio of complexing anion to stannous tin ranges from about 2:1 to 1:3.

The pH of the compositions of this invention lies between about 2.5 and 7, the preferred range being from about 4.0 to 6.5. Above about pH 7 loss of stannous ions available for reaction with enamel can be too rapid, and, certain flavoring substances, especially esters, deteriorate rapidly. Too low a pH, below about 2.5, produces an astringent taste which is highly objectionable to most people. It also accelerates the hydrolysis of certain of the sudsing agents thereby producing an unpleasant "fatty acid taste" and reducing the amount of sudsing obtained in use. Furthermore, pH values below 2.5 tend to cause corrosion of metal tubes in which the composition may be stored, and tend to hydrolyze other ingredients such as condensed phosphates if used as abrasives. Such hydrolysis can decrease the availability of stannous ions by providing anions with which they can form very stable complexes or with which they can precipitate as highly insoluble compounds.

In addition to the essential ingredients described herein, the compositions of this invention can contain the usual dentifrice, mouthwash, etc., components. For example, toothpastes typically contain an abrasive material, sudsing agent, binders, humectants, flavoring and sweetening materials.

The abrasives preferably should be relatively insoluble and relatively stable at the pH ranges herein specified. They desirably should not be too abrasive so as to scratch

the surface of the teeth or unduly abrade the dentin, but they desirably should have just sufficient abrading power to clean the teeth. In the practice of this invention, any dental abrasives can be used which have these properties, and are sufficiently compatible with stannous ion and fluoride ions.

Preferred abrasives for use in the fluoride-containing dentifrices of this invention include the insoluble condensed phosphates and the water-impervious, cross-linked, thermosetting resins. Examples of such insoluble condensed phosphates include calcium pyrophosphate, insoluble highly polymerized calcium polyphosphate—sometimes called calcium polymetaphosphate, and insoluble highly polymerized sodium polyphosphate—sometimes called insoluble sodium metaphosphate. Examples of operable resin abrasives are the particulate condensation products of formaldehyde with melamine and/or urea, and others fully described in U.S. Pat. 3,070,510, granted Dec. 25, 1962. Mixtures of abrasives can be used.

The total amount of abrasive materials in dentifrices of this invention can range from 0.5% to 95% by weight of the dentifrice. Preferably, toothpastes contain from 20% to 60% by weight, and tooth powders contain from 60% to 95% by weight.

Dentifrices conventionally contain sudsing agents, although these are not critical in the practice of the present invention. Any of the commonly used sudsing agents can be used if they are reasonably stable and form suds within the pH range of the compositions of this invention. Examples of suitable sudsing agents include, but are not limited to, water-soluble alkyl sulfates having alkyl groups of from about 8 to 18 carbon atoms, such as sodium lauryl sulfate; water-soluble salts of sulfonated monoglycerides of fatty acids having from 10 to 18 carbon atoms, such as sodium coconut monoglyceride sulfonate; salts of fatty acid amides of taurines, such as sodium-N-methyl-N-palmitoyl tauride; salts of fatty acid esters of isethionic acid and substantially saturated aliphatic acyl amides of saturated aliphatic 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 also be used.

Sudsing agents can be used in the compositions of this invention in an amount of from 0.5% to 5.0% by weight of the total composition.

In preparing toothpastes, it is necessary to add some thickening material. Preferred thickening agents are 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 also can be used as thickeners, but may tend to cause undesirable odors or flavors in some formulations. Colloidal magnesium aluminum silicate or finely divided silica can be used as part of the thickening agent for improvement in texture. Thickening agents in an amount of from 0.5% to 5.0% by weight of toothpaste, can be used to form a satisfactory toothpaste.

Suitable humectants include glycerine, sorbitol, and other polyhydric alcohols. The humectants may comprise up to about 35% of the toothpaste composition.

Oral compositions additionally contain small amounts of flavorings, such as oil of wintergreen, oil of peppermint, oil of spearmint, oil of sassafras, and oil of anise. Small amounts of sweetening agents such as saccharin, dextrose, levulose, and sodium cyclamate are also conventionally added to such compositions.

The dental enamel reactivity of the stannous tin contained in an oral composition such as a dentifrice can be determined by measuring the amount of tin uptake by an enamel sample after exposure to the dentifrice according to the following procedure:

Tooth chips having a surface area of 25 to 35 mm.² are mounted on plastic rods and coated with a dental

plastic so that only the enamel surfaces are exposed. The surfaces are cleaned and polished and etched by immersion in a 2M solution of perchloric acid for one minute. The tooth chips are again cleaned and polished and placed in an agar-lactic acid decalcifying medium (comprised of 6% agar in .04N lactic acid at pH 6.1) for 48 hours at 5° C.

After exposure to the decalcifying medium, the tooth chips are cleaned and immersed in a slurry comprised of 1 part of the dentifrice to be tested and 3 parts of saliva, rotating the chips in the slurry at about 200 r.p.m. for 21 minutes. The treated chips are rinsed in distilled water, the dental plastic is removed and the dentin portion of the tooth chips is ground off from the underside of the chips so that only the treated dental enamel remains.

The dental enamel is analyzed for tin and this value is expressed hereafter in micrograms per/square centimeter ($\mu\text{g./cm.}^2$).

The stability of the dentifrice on storage with respect to supplying available stannous tin to react with dental enamel can be measured as a function of the age of the dentifrice in the following manner:

After specified intervals of time, soluble stannous tin is determined by mixing 1 part of the dentifrice with 3 parts of distilled water for 10 minutes. The solids are then removed by centrifugation for 30 minutes at 12,000 r.p.m. and the stannous tin concentration in an aliquot of the supernatant is determined iodimetrically. Results are reported as parts per million soluble stannous tin.

The following examples illustrate the invention with greater particularity.

EXAMPLE I

Stannous hydroxyethylnitrilodiacetate was prepared in the following manner:

40.0 g. of SnCl_2 was dissolved in 100 ml. of oxygen-free distilled water. The pH of this solution was adjusted to 8.0 with NH_4OH and the resulting precipitate $[\text{Sn}(\text{OH})_2]$ was removed by centrifugation. The precipitate was then washed in distilled water and added to a solution of 30.3 g. of hydroxyethylnitrilodiacetic acid in 600 ml. of distilled water and heated to a temperature of 85° C. The resulting solution was permitted to cool to room temperature stored in a nitrogen atmosphere overnight. The solution was then cooled in an ice bath to 5° C. and the resulting precipitate was filtered and dried. The remaining solution was concentrated to 100 ml. volume and again cooled to 5° C.; the resulting precipitate was filtered off, dried, and the remaining solution was concentrated to 50 ml. volume, cooled to 5° C. and the precipitate was removed by filtration a third time.

A total yield of 45 g. (approx. 90% of theoretical) of crystalline stannous hydroxyethylnitrilodiacetate was obtained. On analysis this compound was found to be comprised of equimolar quantities of stannous tin and hydroxyethylnitrilodiacetic acid anion.

EXAMPLE II

The following toothpaste composition was prepared by conventional methods and tested in the manner hereinbefore described for tin uptake and stability on aging.

	Percent by weight
Calcium pyrophosphate	40.00
Sorbitol (70% aqueous solution)	20.00
Glycerine	10.00
Sodium coconut monoglyceride sulfonate	0.81
Sodium lauryl sulfate	0.70
Sodium carboxymethylcellulose	1.00
Magnesium aluminum silicate	0.40
Saccharin	0.12
Flavor	0.85
Color	0.47
Stannous fluoride	0.40

7

8

Percent by weight
 Stannous hydroxyethylnitrilodiacetate (prepared
 in accordance with Example I) ----- 0.77
 Water ----- Balance
 Total Sn(II): 6000 p.p.m.
 Molar ratio of hydroxyethylnitrilodiacetic acid
 anion to total Sn(II) pH 4.8: 1:2
 Sn Uptake, $^{148.5}$ $\mu\text{g./cm.}^2$

STABILITY

Time interval:	Soluble Sn (p.p.m. in supernatant)
3 days -----	^{1725}
1 week -----	^{1725}
2 weeks -----	^{1660}
1 month -----	^{1615}
2 months -----	^{1570}
3 months -----	^{1540}
6 months -----	520
1 year -----	480

A similarly formulated toothpaste in accordance with U.S. Pat. 2,946,725, but containing stannous pyrophosphate rather than the stannous hydroxyethylnitrilodiacetate of the present invention (the above example) and containing 9,000 p.p.m. total Sn(II) yields approximately the same Sn uptake value when fresh as the formulation of Example II; however, the fraction of soluble Sn(II) contained in such toothpaste diminishes at a much more rapid rate on aging than in the toothpaste of this example.

The toothpaste of Example II has excellent flavor characteristics and is adaptable to formulation with a wide variety of flavoring oils. When diluted with water and brushed upon the teeth in the conventional manner, this composition substantially reduces enamel solubility and in this way produces substantial anticariogenic effects.

The stannous hydroxyethylnitrilodiacetate employed in this example can be replaced with equivalent amounts of stannous m-hydroxybenzoate, stannous 1,2 or stannous itaconate, with substantially equivalent results.

EXAMPLE III

A toothpaste having essentially the same composition as that of Example II, but containing 1.48% of the stannous hydroxyethylnitrilodiacetate of Example I was prepared. The toothpaste contained 8,800 p.p.m. of Sn(II), the molar ratio of total hydroxyethylnitrilodiacetic acid anion to Sn(II) being 2:3. The toothpaste of this example yielded a Sn uptake value of ^{42} $\mu\text{g./cm.}^2$. Stability on aging was established by the following results.

STABILITY

Time interval:	Soluble Sn (p.p.m. in supernatant)
3 days -----	^{1310}
1 week -----	^{1310}
2 weeks -----	1250
1 month -----	^{1150}
2 months -----	^{1160}
3 months -----	^{1080}
6 months -----	1060
1 year -----	^{1050}

^{1} Average of replicate runs.

This toothpaste has excellent flavor characteristics using a wide variety of flavoring oils. It can be seen that the stannous tin contained in this composition is highly reactive with dental enamel and high levels of soluble stannous tin are retained in the composition over a one-year period. The product is thereby effective in caries

prophylaxis for a long period of time when used in the conventional manner.

	Examples		
	IV	V	VI
	Percent by weight		
5	Calcium pyrophosphate -----	40.00	40.00
	Sorbitol (70% aqueous solution) -----	20.00	20.00
	Glycerine -----	10.00	10.00
	Sodium coconut glyceride sulfonate -----	0.81	0.81
10	Sodium lauryl sulfate -----	0.70	0.70
	Sodium carboxymethyl cellulose -----	1.10	1.10
	Magnesium aluminum silicate -----	0.40	0.40
	Saccharin -----	0.12	0.12
	Flavor -----	0.85	0.85
	Color (0.1% aqueous solution) -----	0.48	0.48
	Stannous fluoride -----	0.40	1.00
	Sodium fluoride -----		0.45
15	Stannous chloride -----	0.48	1.66
	m-Hydroxybenzoic acid -----	0.70	
	1,2,3-propanetricarboxylic acid -----		0.74
	Itaconic acid -----		0.82
	Water -----	Balance	Balance
	Total Sn(II) (p.p.m.) -----	6,000	10,000
	Molar ratio complexing anion to total Sn(II) -----	1.0	0.2
20	pH (adjusted with NaOH) -----	4.2	4.4
			4.6

Each of the dentifrices of Examples IV through VI contain effective levels of available Sn(II). These products are stable and can be satisfactorily flavored with a number of well-known flavoring oils.

EXAMPLE VII

A concentrated mouthwash in accordance with this invention is formulated as follows:

	Percent by weight
Ethyl alcohol (50% ethanol, 50% water) -----	83.38
Glycerine -----	12.00
Methyltriethanol ammonium fluoride -----	2.88
35 Stannous hydroxyethylnitrilodiacetate (prepared in accordance with Example I) -----	0.77
Flavoring -----	0.85
Saccharin -----	0.12
Total Sn(II): 3,000 p.p.m.	
Molar ratio of hydroxyethylnitrilodiacetic acid anion to total Sn(II): 1:1	
pH adjusted to 6.5	

Prior to use, this composition is diluted by adding 2 ml. of the concentrate to 20 ml. of water. This mouthwash contains high levels of enamel-reactive stannous tin over a long period of time and yields a significant reduction in enamel solubility, thus, providing an effective means for caries prophylaxis when used in the usual manner two or more times a day. The product has good flavor characteristics using several flavoring oils.

The stannous hydroxyethylnitrilodiacetate can be replaced with stannous m-hydroxybenzoate, stannous 1,2,3-propanetricarboxylate or stannous itaconate in quantities sufficient to provide an equivalent amount of Sn(II), with essentially the same results.

The methyltriethanol ammonium fluoride employed in this example can be replaced by ammonium fluoride, zirconium fluoride, zinc fluoride, or betaine hydrofluoride, in a quantity sufficient to provide an equivalent amount of fluoride ion, without substantial effect on the desired properties of the composition.

What is claimed is:

1. A dentifrice composition comprising (1) a non-toxic water-soluble fluoride salt in a quantity sufficient to provide from about 100 to about 4,000 p.p.m. of fluoride ion; (2) a non-toxic water-soluble stannous compound in a quantity sufficient to provide from about 50 to about 8,000 p.p.m. of stannous tin; and (3) hydroxyethylnitrilodiacetic acid or a non-toxic water-soluble salt thereof in a quantity sufficient to provide a molar ratio of acid anion to stannous tin in the range from about 2:1 to 1:3, the pH of said composition being in the range from about 4.5 to 6.5.

2. A dentifrice composition comprising (1) a non-

toxic water-soluble fluoride salt in a quantity sufficient to provide from about 100 to about 4,000 p.p.m. of fluoride ion; (2) a non-toxic water-soluble stannous compound in a quantity sufficient to provide from about 50 to about 8,000 p.p.m. of stannous tin; and (3) m-hydroxybenzoic acid or a non-toxic water-soluble salt thereof in a quantity sufficient to provide a molar ratio of acid anion to stannous tin in the range from about 2:1 to 1:3, the pH of said composition being in the range from about 4.5 to 6.5.

3. A dentifrice composition comprising (1) a non-toxic water-soluble fluoride salt in a quantity sufficient to provide from about 100 to about 4,000 p.p.m. of fluoride ion; (2) a non-toxic water-soluble stannous compound in a quantity sufficient to provide from about 50 to about 8,000 p.p.m. of stannous tin; and (3) 1,2,3-propanetricarboxylic acid or a non-toxic water-soluble salt thereof in a quantity sufficient to provide a molar ratio of acid anion to stannous tin in the range from about 2:1 to 1:3, the pH of said composition being in the range from about 4.5 to 6.5.

4. A dentifrice composition comprising (1) a non-toxic water-soluble fluoride salt in a quantity sufficient to provide from about 100 to about 4,000 p.p.m. of fluoride ion; (2) a non-toxic water-soluble stannous compound in a quantity to provide from about 50 to about 8,000 p.p.m. of stannous tin; and (3) itaconic acid or a non-toxic water-soluble salt thereof in a quantity sufficient to provide a molar ratio of acid anion to stannous tin in the range from about 2:1 to 1:3, the pH of said composition being in the range from about 4.5 to 6.5.

5. An oral composition for caries prophylaxis suitable for use in the oral cavity comprising (1) a non-toxic water-soluble fluoride salt in a quantity sufficient to provide from about 100 to about 4,000 p.p.m. of fluoride ion, and (2) stannous hydroxyethylnitrilodiacetate in a quantity sufficient to provide from about 50 to about

8,000 p.p.m. of stannous tin, the pH of said composition being in the range from 2.5 to 7.0.

6. An oral composition for caries prophylaxis suitable for use in the oral cavity comprising (1) a non-toxic water-soluble fluoride salt in a quantity sufficient to provide from about 100 to about 4,000 p.p.m. of fluoride ion, and (2) stannous m-hydroxybenzoate in a quantity sufficient to provide from about 50 to about 8,000 p.p.m. of stannous tin, the pH of said composition being in the range from 2.5 to 7.0.

7. An oral composition for caries prophylaxis suitable for use in the oral cavity comprising (1) a non-toxic water-soluble fluoride salt in a quantity sufficient to provide from about 100 to about 4,000 p.p.m. of fluoride ion, and (2) stannous 1,2,3-propanetricarboxylate in a quantity sufficient to provide from about 50 to about 8,000 p.p.m. of stannous tin, the pH of said composition being in the range from 2.5 to 7.0.

8. An oral composition for caries prophylaxis suitable for use in the oral cavity comprising (1) a non-toxic water-soluble fluoride salt in a quantity sufficient to provide from about 100 to about 4,000 p.p.m. of fluoride ion, and (2) stannous itaconate in a quantity sufficient to provide from about 50 to about 8,000 p.p.m. of stannous tin, the pH of said composition being in the range from 2.5 to 7.0.

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