

SPECIFICATION

Dental preparations

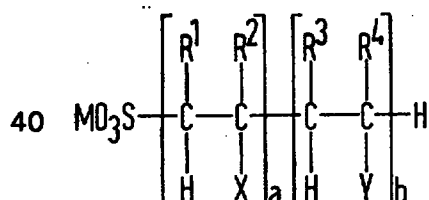
- 5 This invention relates to dental preparations comprising a stable aqueous composition which is effective to remineralize carious lesions in dental enamel. 5

It is known that dental caries begin with lesions or so called "white spots," which are demineralized areas below the surface of intact dental enamel. If unchecked, surface enamel above a sub-surface lesion eventually collapses, leading to cavitation and subsequent loss of tooth structure. 10

Various compositions have been proposed in order to arrest demineralization, and, indeed, in order to remineralize "white spots". For instance, U.S. Patent No. 3,679,360 to Rubin et al discloses deposition of calcium phosphate from a gel onto a tooth surface. This, however, does not reach the sub-surface area where demineralization initially occurs. Further, because of the difficulty of maintaining both calcium ions and phosphate ions available without precipitating a calcium phosphate material, two part kits have been proposed in which a calcium component and a phosphate component are sequentially applied to the oral cavity as in British Patent No. 1,408,922 to Raff et al and British Patent No. 1,452,125 to Grabenstetter et al or mixed together shortly before such application to form a metastable system with temporary stability as in U.S. Patent 4,080,440 to DiGiulio et al and British Patent No. 1,509,977 to Levine. Another metastable solution has been described in U.S. Patent No. 4,097,588 to Levine. Even this solution, however, is not substantially permanent and precipitation can occur, particularly when fluoride ions are present. 15 20

It is an advantage of this invention that a one-part stable aqueous remineralizing solution is suitably prepared as a dental mouthrinse and also can be incorporated into other dental preparations or dentifrice compositions such as dental creams or gels, mouth sprays, troches, chewable tablets, or lozenges. 25

In accordance with certain of its aspects, this invention relates to a stable aqueous composition comprising water having dissolved therein a source of calcium ions and a source of phosphate ions, the amount of calcium ions and phosphate ions being sufficient to effect remineralization of dental enamel; a compound which provides a fluoride anticaries agent; and an antinucleating agent consisting of diamine tetramethylenephosphonic acids of the formula $(M_2O_3PH_2C)_2N(CH_2PO_3M_2)_2$, wherein n is an integer from 1 to 10; phosphonoacetic acids of the formula $M_2O_3PCH_2COOM$; peroxydiphosphates of the formula $M_4P_2O_8$; or oligomers of the formula: 30 35



- 45 in which M represents a hydrogen atom or an orally acceptable cation, R^1 , R^2 , R^3 and R^4 are independently a hydrogen atom, or a methyl or ethyl group, Y is at least one hydrophilic member of the group consisting of COOM, $-CONH_2$ and CH_2OH , X is at least one hydrophobic member of the group consisting of $-CN$, $-COOR$, $-COOR^5OR$, $-CONHR$ and $COONHR^5COR$, where R is a C_{1-8} alkyl group; R^5 is a C_{1-4} alkylene group; a is 0 to 7 and $a + b$ is 4 to 15; the antinucleating agent being in the form of an acid or an orally acceptable water-soluble salt thereof; the solution having a pH of 5 to 9; and the mole ratio of calcium ions to phosphate ions being from 0.01:1 to 100:1. 50

The antinucleating properties of the agents employed in the present invention appear to be effective to prevent precipitation from the solution of calcium and phosphate ions even when fluoride ions are also present. As described in Ciba Foundation Symposium, "Hard Tissue Growth, Repair and Remineralization (Elsevier), Associated Scientific Publishers, New York, 1973 in the article by Francis et al, "Chemical Agents in the Control of Calcification Processes in Biological Systems", pages 57-83, particularly at pages 75-78, an antinucleating agent (e.g. a diphosphonate) can in a sufficient quantity at a physiological pH completely absorb onto a spherical nucleated particle of hydroxyapatite as it forms and entirely block crystal growth. In this way, the formation of large insoluble crystals of apatite is prevented and coated small hydroxyapatite crystals of higher water solubility are attained. 55 60

It has been found that not all antinucleating agents can successfully stabilize calcium ions and phosphate ions in solution against precipitation to form large insoluble apatite crystals. For instance, such insoluble crystals form when it is sought to use antinucleating agents such as 65

sodium hexametaphosphate, sodium pyrophosphate, sodium phytate and mellitic acid as well as disodium phosphonoethane-1,2-dicarboxylate, 1,1-diphosphonopropane-2,3-dicarboxylic acid monohydrate, 3-amino-1-hydroxypropane-1,1-diphosphonic acid and imino-di-acetic-N-methylene phosphonic acid. On the other hand, the antinucleating agents of the present invention

5 successfully stabilize the calcium ions and phosphate ions against precipitation as large insoluble apatite crystals in solution at a pH between 5 and 9. Preferably, the pH is adjusted to about 6.8 to about 7.5, which approximates to usual human physiological conditions and is suitable for effecting remineralization. Desirably, the antinucleating agent of the invention is present in an amount of about 1 to 500 ppm (1×10^{-8} M to 1×10^{-3} M) of the solution, preferably about 25 to 250 ppm (5×10^{-8} M to 5×10^{-3} M), for example at about 225 ppm (5×10^{-4} M).

10 The antinucleating agent of the invention is desirably a diamine tetramethylenephosphonic acid of the formula $(M_2O_3PH_2C)_2 N(CH_2)_n(CH_2PO_3M_2)_2$ wherein n is an integer from 1 to 10 and M is hydrogen or an orally acceptable cation such as an alkali metal (e.g. sodium or potassium), ammonium or C_1-C_{18} mono-, di or trisubstituted ammonium (e.g. mono-, di- or triethanolammonium) salt.

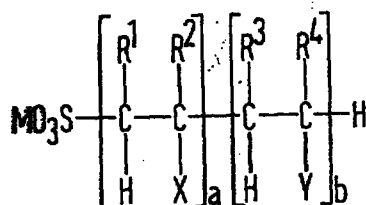
15 The polyamine polyphosphonic compounds which are most preferred are ethylenediamine tetra(methylenephosphonic acid), (hereinafter referred to as EDITEMPA) and its water-soluble orally acceptable salts, (e.g. sodium, potassium, and ammonium and other pharmaceutically acceptable salts; most preferably the tri-, tetra- or penta-sodium salts), other polyamine polyphosphonic compounds which can be used in the invention include for example: tetramethylenediamine tetra(methylenephosphonic acid), pentamethylene diamine tetra(methylenephosphonic acid), hexamethylenediamine tetra(methylenephosphonic acid) and the water-soluble salts of these acids, e.g. sodium, potassium, ammonium and other orally acceptable salts.

20 Phosphonoacetic acid (hereinafter referred to as PAA) and its water soluble orally acceptable salts are also desirable antinucleating agents. They are characterized by the formula $M_2O_3PCH_2COOM$, wherein M represents a hydrogen atom or an orally acceptable cation.

25 The peroxydiphosphate (hereinafter referred to as PODP) and particularly the alkali metal salts thereof (e.g. potassium or sodium) are likewise desirable antinucleating agents. They are characterized by the formula $M_4P_2O_8$ wherein M represents a hydrogen atom or an orally acceptable cation.

30 The desirable oligomer antinucleating agents and methods for their preparation are described in U.S. Patent Nos. 3,646,099 and 3,859,260.

They have the formula:



wherein M represents a hydrogen atom or a water soluble orally acceptable cation; R^1 , R^2 , R^3 and R^4 are independently a hydrogen atom, or a methyl or ethyl group; Y is at least one hydrophilic member of the group consisting of $-COOM$, $-COHN_2$ and $-CH_2OH$; X is at least one hydrophobic member of the group consisting of $-CN$, $-COOR$, $-COOR^5OR$, $-CONHR$ and $-COONHR^5COR$; R is a C_{1-8} alkyl group; R^5 is a C_{1-4} alkylene group; a is 0 to 7; and $a + b$ is 4 to 15.

45 The conventional free radical redox polymerization is conducted with an oxidative initiator such as hydrogen, alkyl, or acyl peroxides, persulphates or hydroperoxides in relatively large amounts and a reductive activator such as sodium bisulphate ($NaHSO_3$), sodium persulphate ($Na_2S_2O_8$) or sodium formaldehyde sulfoxylate in relatively low amounts generally added subsequently to the polymerization medium. The oligomers referred to above are anionic and of relatively low and accurately regulated degree of polymerization. In contrast to conventional free radical redox polymerisation these oligomers are prepared by a reductive polymerization in which a much larger amount of a bisulphite salt, e.g. $NaHSO_3$ (sodium bisulphite, sodium acid sulphite), a reducing agent, is added as the initiator charge initially with the monomer, and an oxidizing agent is added in smaller amounts as the activator during progress of the polymerizing or oligomerizing process.

50 Subscript a in the formula represents the number of moles of hydrophobic groups, and subscript b the number of moles of hydrophilic groups, in the oligomer molecule. The proportion of X (i.e. the value of a) must be small enough, or even zero, to avoid the production of a too large, sticky and hydrophobic polymer molecule, and will of course be dependent for the most part in any particular instance on the identity of the X and Y groups, i.e. the hydrophobic-containing and hydrophilic containing monomeric reactants. Mixtures of such oligomers may of

course also be employed.

Examples of monomers containing a hydrophilic Y group are acrylic acid, methacrylic acid, alpha-ethylacrylic acid, beta-methylacrylic acid, alpha, beta-dimethylacrylic acid, orally acceptable salts of these acids, for example those containing such cations as alkali metal (e.g. sodium and potassium), ammonium, C₁₋₁₈ mono-, di- and tri-substituted ammonium (e.g. alkanol substituted such as mono-, di and triethanolammonium), acrylamide, methacrylamide, ethacrylamide, and alkyl alcohol.

Examples of monomers containing hydrophobic X groups are acrylonitrile, methacrylonitrile, ethacrylonitrile, methyl, ethyl and octyl acrylate and methacrylate, methoxyethyl acrylate, octoxyethyl methacrylate, ethoxybutyl methacrylate, propoxymethyl acrylate, N-ethylacrylamide, N-isopropylacrylamide, N-methylacrylamide, N-propylethacrylamide, vinyl acetate, propionate and octanoate and diacetone acrylamide.

The oligomerization is carried out in water in the presence of a relatively large amount of the bisulphite reducing initiator, which, expressed in mols of monomer/gram formula weight (gFW) of reducing initiator, is about 4 to 15, this ratio determining the degree of oligomerization.

The reductive initiator is preferably a water soluble bisulphite salt (M in the formula), especially an alkali metal salt such as sodium or potassium, but bisulphite salts containing other orally acceptable cations of the type referred to above may be employed.

In practice, enough oxidative activator is used to effect 100% conversion of the monomers to oligomers. The amount of such activator, expressed as gFW activator/gFW initiator may range from 0.0001 to 0.1 but usually is from about 0.001 to 0.1. Examples of these oxidative activators are ammonium, sodium, or potassium persulphate, hydrogen peroxide and other water soluble oxidants commonly employed in the polymerization art.

Following completion of the oligomerization reaction, any free carboxylic acid groups in the oligomer molecules may, if desired be partially or completely neutralized, preferably at least 60% neutralized, by treating the aqueous oligomer solution with a suitable base to convert such groups to their salts with orally acceptable cations as referred to above. These aqueous oligomer solutions have a highly desirable low viscosity, and low molecular weight range depending on the monomer units in the oligomer.

It will be understood that the oligomer formula above is not intended to depict the actual structure of the oligomer molecule, the bracketed units of which formula are randomly distributed in the molecule with the -SO₃M group being normally bonded to a terminal carbon atom in the oligomer chain devoid of X and or Y substituents. In the oligomers preferred for use herein, a is zero, Y is -COOM, R¹ 6R⁴ are hydrogen atoms and M is an alkali metal, e.g. sodium, b being about 10, as derived from acrylic acid. An oligomer of the formula above in the form of its sodium salt, with a molecular weight of about 1,000, containing about 10 acrylic acid monomeric units, is commercially available under the trade name ND-2 (a product of Uni-Royal).

The effective antinucleating agents render the remineralizing solution stable at normally occurring temperatures, e.g. about 15°C-40°C. The remineralizing agents can diffuse effectively through an intact enamel surface in order to act on sub-surface lesions.

The stability provided by the effective antinucleating agents prevents spontaneous precipitation on enamel surfaces and thereby permits diffusion of the remineralizing components to sub-surface lesions.

One or more sources of each of calcium ions and of phosphate ions may be employed. When the source is normally insoluble such as a calcium phosphate, it is solubilized during preparation of the solution, by maintaining an acid pH of about 6 or less (e.g. about 2.5 to 6) during preparation of the remineralizing solution, particularly before the effective antinucleating agent is added.

The insoluble sources of calcium and phosphate ions may be a single compound such as tricalcium phosphate (which substantially corresponds to hydroxyapatite), Ca₅(PO₄)₃OH or 3Ca₃(PO₄)₂Ca(OH)₂, bone meal or dicalcium phosphate (dihydrate or anhydrous). In solution, particularly in the presence of fluoride ions, formation of hydroxyapatite, fluorohydroxyapatite and fluoroapatite occurs.

Examples of other normally water-soluble or normally water-insoluble (but soluble at pH of about 6 or less) sources of calcium ions, but not phosphate ion, which can be used in the remineralizing solution of the invention include calcium acetate, gluconate, nitrate, stearate, lactate, formate, molybdate, tungstate, sulphate, alkyl sulphonate (e.g. lauryl sulphonate), oleate, tartrate, sorbate, iodate, silicate, aluminate, benzoate, citrate, fumarate, butyrate, isobutyrate, malate, maleate, propionate and valerate. Mixtures of such calcium sources with each other or with calcium phosphate may also be employed.

Examples of sources of phosphate ion, but not calcium ion, which can be used in the remineralizing solution of the invention include the normally water-soluble or normally water-insoluble (but soluble at pH of about 6 or less) salts including alkali metal (e.g. sodium and potassium), ammonium, magnesium, barium and strontium orthophosphates and acid ortho-

phosphates, metaphosphates, pyrophosphates, as well as glycerophosphates, fructose-6-phosphate, sorbitol-6-phosphate, glucose-1-phosphate and glucose-6-phosphate. Mixtures of such phosphate sources with each other or with calcium phosphate may also be employed.

Tricalcium phosphate or the other sources of calcium and phosphate which together form hydroxyapatite in solution are employed with the mole ratio of calcium ion to phosphate ion being from 0.01:1 to 100:1, typically about 0.2:1 to about 5:1, preferably about 1.2:1 to 2:1, e.g. about 1.4:1 to about 1.7:1. A ratio of calcium to phosphate of 1.67:1 corresponds to the ratio of calcium to phosphate in dental enamel. The amount of calcium ion and phosphate ion in the composition is sufficient to effect remineralization, there being typically at least about 50 ppm of each of calcium ion and of phosphate ion. The maximum amount of calcium ion and phosphate ion desirable is that which would not result in precipitate formation. This could vary depending on the ion sources and the pH conditions. Typically, about 35,000 ppm of calcium ion and about 40,000 ppm of phosphate can be employed and precipitation still avoided.

In the prior art it has been difficult to maintain the solubility of calcium phosphate, particularly in the presence of a fluoride source. As previously indicated, this is overcome in the present invention when the effective antinucleating agents are employed. Examples of fluoride ion sources (including complex fluoride ions) include alkali metal (e.g. sodium, potassium lithium), ammonium, alkaline earth metal (e.g. calcium, barium, strontium, magnesium), aluminium, zinc, stannous, indium, zirconium, copper, nickel, palladium and organonitrogen such as alkylamine (e.g. hexylamine) compounds with fluoride ion sources. Sources of fluoride ions include fluoride, fluorophosphate (including monofluorophosphate, difluorophosphate and polyfluorophosphate), silicofluoride, fluorozirconate, fluoroborate and fluorostannite. Typical compounds are sodium fluoride, zinc fluoride, stannous fluoride and sodium monofluorophosphate. Sodium fluoride and sodium monofluorophosphate are preferred. The fluoride source compound is desirably present in an amount to provide about 1 ppm to 10,000 ppm (0.0001%–1%) fluoride to the remineralizing composition preferably from sodium monofluorophosphate and preferably about 5 ppm fluoride. The amount of the compound employed should not be sufficient to result in precipitate formation. For instance, in the case of a fluoride source of low solubility, such as calcium fluoride, the amount of the compound employed should not exceed 1500 ppm.

The stable remineralizing composition may be prepared by adding controlled amounts of the calcium ion and the phosphate ion sources to water and lowering the pH to keep the solution clear. The ion sources may be a single material, such as tricalcium phosphate, or may be a plurality of materials, such as calcium chloride and sodium dihydrogen orthophosphate. The ratio of calcium ion to phosphate ion may be from 0.01 to 100:1, but is desirably about 1.67:1 in order to readily form hydroxyapatite, for instance using about 1.5mM calcium ion and 0.9mM phosphate ion in solution. A preservative such as sodium benzoate or methyl-4-hydroxybenzoate may be employed to reduce bacterial growth. An electrolyte salt such as an alkali metal (e.g. sodium or potassium) chloride may be present (e.g. in an amount of 1 to 1000 ppm) in the stable remineralizing composition to further improve stability and diffusion of remineralizing material into sub-surface lesions.

Acidic materials are used to reduce the pH to about 2 to 4, typically about 2.8 to 3.8, in order to maintain clarity of the solution. Typical materials include phosphoric acid or hydrochloric acid.

The pH is then raised to a mildly acid level, such as about 5 to 6.5 e.g. about 6, with basic materials such as sodium hydroxide, potassium hydroxide or ammonium hydroxide.

The composition can be stabilized against precipitation by incorporating therein an effective antinucleating agent, such as ethylene diamine tetramethylenephosphonic acid, pentasodium salt. The antinucleating agent is added to the solution in amount of about 1×10^{-6} M to 1×10^{-4} M, typically about 3×10^{-4} M (300 ppm) and thoroughly mixed therein.

The pH can then be maintained or even raised to about 9, with the effective antinucleating agent preventing precipitation of hydroxyapatite. Preferably it is raised to a physiological pH in the range of about 6.8 to 7.5, typically about 7 to 7.5. Basic materials of the type indicated may be employed to raise the pH.

A fluoride ion source such as sodium fluoride or sodium monofluorophosphate is then added in the indicated amount and the composition can be diluted to a desired concentration. In the composition of the present invention the fluoride does not cause the hydroxyapatite to precipitate.

Thus, the composition can be maintained for a long period of time, remaining effective when brought into contact with dental material to remineralize sub-surface lesions. The composition can be used as such or incorporated into other dental compositions, such as mouth rinses, dental creams or gels or toothpastes; mouth sprays, troches, chewable tablets or lozenges.

The composition of the invention may be applied to dental surfaces as such, for instance, by rinsing the mouth therewith or it may be incorporated into a mouthwash, dental cream or other dental preparation such as a toothpaste. When incorporated into a mouthwash, the solution is typically about 20 to 80% by weight of the mouthwash, the mouthwash also including a non-toxic aliphatic alcohol, such as ethanol, N-propanol or isopropanol. A surface active agent about

1 to 5%) such as sodium lauryl sulphate, sodium N-lauroyl sarcosinate or polyoxyethylene-polyoxypropylene material, (e.g. Pluronic) and any one or more of a flavouring material, a sweetening material or an antibacterial agent may also be present.

When incorporated into a dental cream or gel, the solution is typically about 20 to 60% by weight of the cream or gel; such cream or gel also typically includes about 10 to 50% of a dentally acceptable polishing material such as a water insoluble phosphate e.g. insoluble sodium metaphosphate, hydrated alumina or silica (colloidal, precipitated or crystalline). Preferably polishing materials containing calcium orthophosphate moieties or both are not employed. The dental cream also generally contains an humectant such as glycerine, sorbitol, propylene glycol or polyethylene glycol such as polyethylene glycol 400 and a gelling agent such as sodium carboxymethyl cellulose or Irish moss. Also, a surface active agent, a flavouring or sweetening material or both, an antibacterial agent, an antibacterial preservative, (e.g. sodium benzoate or methyl-4-hydroxy benzoate), a silicone material, a chlorophyll compound or an ammoniated material may be present.

The invention may be put into practice in various ways and a number of specific examples will now be described. All parts, amounts and proportions are by weight unless otherwise noted.

EXAMPLE 1

A stock solution of hydroxyapatite (tricalcium phosphate) is prepared by adding hydroxyapatite to water to a final concentration of 1.5mM calcium and 0.9mM phosphate. 0.25 grams of sodium benzoate (from 0.05% solution thereof) are then added to the solution to minimize bacterial growth.

Phosphoric acid is then added to 500 ml of the stock solution to produce a clear solution at pH 3, after which the pH is raised to 6 with 1 N potassium hydroxide. Next EDITEMPA is added and mixed into the solution to a concentration of 1×10^{-5} M thereof, following which additional potassium hydroxide is added to produce a pH of 7. Sodium monofluorophosphate is then added to a concentration of 5 ppm fluoride in the stock solution following which sodium chloride is added to give an electrolyte concentration of 50mM and additional water is added to 1 litre.

The solution thus formed remains stable and clear upon storage. A similar solution without EDITEMPA and without fluoride containing compound results in precipitation within 10 seconds from the time of the final pH rise. When the fluoride containing compound is present and EDITEMPA absent, precipitation also occurs within 10 seconds from the time of the final pH rise. The solution remains clear when only sodium chloride is omitted.

EXAMPLE 2

Example 1 with EDITEMPA and sodium monofluorophosphate is repeated using dicalcium phosphate dihydrate in place of hydroxyapatite to give a final concentration of 60 ppm calcium and 400 ppm phosphate in the stock solution. The solution remains stable and clear.

EXAMPLE 3

Example 1 with EDITEMPA and sodium monofluorophosphate is repeated except that in place of hydroxyapatite, calcium chloride and sodium phosphate are each added to water to form the stock solution with a final concentration of 60 ppm calcium and 400 ppm phosphate. The solution remains stable and clear.

EXAMPLES 4A, 4B and 4C

Each of Examples 1, 2 and 3 are repeated except that in place of EDITEMPA, there is separately employed PAA (concentration 5×10^{-3} M), PODP (concentration 5×10^{-4} M) and UniRoyal Oligomer ND-2 (concentration 5×10^{-4} M) respectively. All solutions remain stable and clear.

EXAMPLES 5A, 5B, 5C, 5D, 5E and 5F

100 parts of each of the solutions of Examples 1-4A, 4B and 4C are incorporated separately into 100 parts of the following mouthwash:

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	PARTS	
Ethanol	6	
Pluronic (RTM) F-10 8 (polyoxyethylene-polyoxypropylene)	2	
5 Glycerin	15	5
Benzoic acid	0.01	
Sodium saccharin	0.02	
Flavouring	0.075	
Sodium benzoate	0.500	
10 Colouring	0.0006	10
Water	Q.S. to 100	

EXAMPLES 6A to 6F

1 part of each of the solutions of Examples 1-4A, 4B and 4C is mixed separately into 9 parts
 15 of the following dental cream formulation: 15

	PARTS	
Glycerine	10	
Sorbitol	17	
20 Water	13.70	20
Sodium benzoate	0.50	
Sodium saccharin	0.20	
Sodium carboxymethyl cellulose	1.10	
Precipitated silica	45.00	
25 Sodium lauryl sulphate	1.50	25
Flavouring	1.00	

The solutions of Examples 1 to 4A, 4B and 4C, the mouthwashes of Examples 5A to 5F and
 30 the dental cream of Examples 6A to 6F containing antinucleating agent all effectively
 remineralize sub-surface dental lesions when applied to dental surfaces in the oral cavity in a
 regimen manner. 30

CLAIMS

1. A stable aqueous composition comprising water having dissolved therein a source of
 35 calcium ions and a source of phosphate ions, the amount of calcium ions and phosphate ions
 being sufficient to effect remineralization of dental enamel, a compound which provides a
 fluoride anticaries agent, and an antinucleating agent consisting of diamine tetramethylenephos-
 phonic acids of the formula $(M_2O_3PH_2C)_nN(CH_2)_nN(CH_2PO_3M_2)_2$, wherein n is an integer from 1
 to 10; phosphonoacetic acids of the formula $M_2O_3PCH_2COOM$, peroxydiphosphates of the
 40 formula $M_4P_2O_8$, or an oligomer 40



50 in which M represents a hydrogen atom or an orally acceptable anion; R^1 , R^2 , R^3 , and R^4 are
 independently a hydrogen atom, or a methyl or ethyl group; Y is at least one hydrophilic
 member of the group consisting of $-COOM$, $-CONH_2$ and CH_2OH ; X is at least one hydrophobic
 member of the group consisting of $-CN$, $-COOR$, $-COOR^5OR$, $-CONHR$ and $-COONHR^5COR$,
 where R is a C_{1-8} alkyl group; R^5 is a C_{1-4} alkylene group; a is 0 to 7 and a + b is 4 to 15; the
 55 antinucleating agent being in the form of an acid or an orally acceptable water soluble salt
 thereof; said solution having a pH of 5 to 9 and the mole ratio of calcium ions to phosphate
 ions being from 0.01:1 to 100:1. 55

2. A stable aqueous composition as claimed in Claim 1 in which the pH of said solution is
 6.8 to 7.5.

60 3. A stable aqueous composition as claimed in Claim 1 or Claim 2 in which the
 antinucleating agent is present in an amount of 1 to 500 ppm. 60

4. A stable aqueous composition as claimed in Claim 1, 2, or 3 in which the antinucleating
 agent is diamine tetramethylenephosphonic acid or an orally acceptable salt thereof.

5. A stable aqueous composition as claimed in Claim 4 in which the antinucleating agent is
 65 ethylene diamine tetramethylene phosphonic acid or an orally acceptable salt thereof. 65



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	PARTS	
Ethanol	6	
Pluronic (RTM) F-10 8 (polyoxyethylene-polyoxypropylene)	2	
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Sodium saccharin	0.02	
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EXAMPLES 6A to 6F

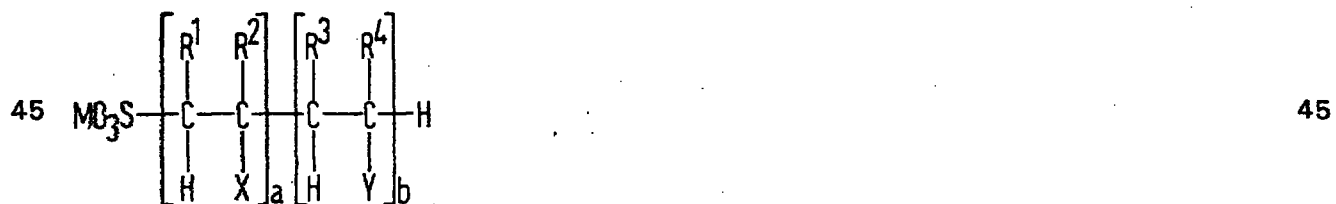
1 part of each of the solutions of Examples 1-4A, 4B and 4C is mixed separately into 9 parts
15 of the following dental cream formulation: 15

	PARTS	
Glycerine	10	
Sorbitol	17	
20 Water	13.70	20
Sodium benzoate	0.50	
Sodium saccharin	0.20	
Sodium carboxymethyl cellulose	1.10	
Precipitated silica	45.00	
25 Sodium lauryl sulphate	1.50	25
Flavouring	1.00	

The solutions of Examples 1 to 4A, 4B and 4C, the mouthwashes of Examples 5A to 5F and
the dental cream of Examples 6A to 6F containing antinucleating agent all effectively
30 remineralize sub-surface dental lesions when applied to dental surfaces in the oral cavity in a
regimen manner. 30

CLAIMS

1. A stable aqueous composition comprising water having dissolved therein a source of
35 calcium ions and a source of phosphate ions, the amount of calcium ions and phosphate ions
being sufficient to effect remineralization of dental enamel, a compound which provides a
fluoride anticaries agent, and an antinucleating agent consisting of diamine tetramethylenephos-
phonic acids of the formula $(M_2O_3PH_2C)_2N(CH_2)_nN(CH_2PO_3M_2)_2$, wherein n is an integer from 1
to 10; phosphonoacetic acids of the formula $M_2O_3PCH_2COOM$, peroxydiphosphates of the
40 formula $M_4P_2O_8$, or an oligomer 40



50 in which M represents a hydrogen atom or an orally acceptable anion; R^1 , R^2 , R^3 , and R^4 are
independently a hydrogen atom, or a methyl or ethyl group; Y is at least one hydrophilic
member of the group consisting of $-COOM$, $-CONH_2$ and CH_2OH ; X is at least one hydrophobic
member of the group consisting of $-CN$, $-COOR$, $-COOR^5OR$, $-CONHR$ and $-COONHR^5COR$,
where R is a C_{1-8} alkyl group; R^5 is a C_{1-4} alkylene group; a is 0 to 7 and $a + b$ is 4 to 15; the
55 antinucleating agent being in the form of an acid or an orally acceptable water soluble salt
thereof; said solution having a pH of 5 to 9 and the mole ratio of calcium ions to phosphate
ions being from 0.01:1 to 100:1. 55

2. A stable aqueous composition as claimed in Claim 1 in which the pH of said solution is
6.8 to 7.5.

60 3. A stable aqueous composition as claimed in Claim 1 or Claim 2 in which the
antinucleating agent is present in an amount of 1 to 500 ppm. 60

4. A stable aqueous composition as claimed in Claim 1, 2, or 3 in which the antinucleating
agent is diamine tetramethylenephosphonic acid or an orally acceptable salt thereof.

5. A stable aqueous composition as claimed in Claim 4 in which the antinucleating agent is
65 ethylene diamine tetramethylene phosphonic acid or an orally acceptable salt thereof. 65



6. A stable aqueous composition as claimed in Claim 1, 2 or 3 in which the antinucleating agent is phosphonoacetic acid or an orally acceptable salt thereof.
7. A stable aqueous composition as claimed in Claim 1, 2 or 3 in which the antinucleating agent is an orally acceptable peroxydiphosphate.
- 5 8. A stable aqueous composition as claimed in Claim 1, 2 or 3 in which the antinucleating agent is an oligomer or an orally acceptable salt thereof. 5
9. A stable aqueous composition as claimed in any one of Claims 1 to 8 in which an electrolyte salt is present.
- 10 10. A stable aqueous composition as claimed in any of the preceding claims in which the mole ratio of calcium ions to phosphate ions is 1.67:1. 10
11. A stable aqueous composition as claimed in any of the preceding claims in which at least 50 ppm of each of calcium ions and phosphate ions is present.
12. A stable aqueous composition as claimed in any of the preceding claims in which the source of calcium ions and of phosphate ions is hydroxyapatite.
- 15 13. A stable aqueous composition as claimed in any one of Claims 1 to 11 in which the source of calcium ions and of phosphate ions is dicalcium phosphate. 15
14. A stable aqueous composition as claimed in any of Claims 1 to 11 in which the source of calcium ions is calcium chloride and the source of phosphate ions is disodium phosphate.
15. A stable aqueous composition as claimed in any of the preceding claims in which the compound which provides the fluoride anticaries agent provides an amount of fluoride of from 1 ppm to 10,000 ppm. 20
16. A stable aqueous composition as claimed in any of the preceding claims in which the compound which provides the fluoride anticaries agent is sodium monofluorophosphate.
- 25 17. A stable aqueous composition as claimed in any one of the preceding claims substantially as specifically described herein with reference to any one of Examples 1 to 4A, 4B, or 4C. 25
18. A mouthwash comprising a non-toxic aliphatic alcohol carrier and incorporated therein a stable aqueous remineralizing solution as claimed in any one of Claims 1 to 17.
19. A mouthwash as claimed in Claim 18 substantially as specifically described herein with reference to any one of Examples 5A to 5F.
- 30 20. A dental cream or gel comprising water, a humectant, a gelling agent and a dentally acceptable polishing material and the stable aqueous composition as claimed in any one of Claims 1 to 17. 30
21. A dental cream or gel as claimed in Claim 20 substantially as specifically described herein with reference to any one of Examples 6A to 6F.